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Platinum Priority – Review

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## The Role of Surgery in Metastatic Bladder Cancer: A Systematic Review

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### Abstract

**Context:** The role of surgery in metastatic bladder cancer (BCa) is unclear.

**Objective:** In this collaborative review article, we reviewed the contemporary literature on the surgical management of metastatic BCa and factors associated with outcomes to support the development of clinical guidelines as well as informed clinical decision-making.

**Evidence acquisition:** A systematic search of English language literature using PubMed-Medline and Scopus from 1999 to 2016 was performed.

**Evidence synthesis:** The beneficial role of consolidation surgery in metastatic BCa is still unproven. In patients with clinically evident lymph node metastasis, data suggest a survival advantage for patients undergoing postchemotherapy radical cystectomy with lymphadenectomy, especially in those with measurable response to chemotherapy (CHT). Intraoperatively identified enlarged pelvic lymph nodes should be removed. Anecdotal reports of resection of pulmonary metastasis as part of multimodal approach suggest possible improved survival in well-selected patients. Cytoreductive radical cystectomy as local treatment has also been explored in patients with metastatic disease, although its benefits remain to be assessed.

**Conclusions:** Consolidative extirpative surgery may be considered in patients with clinically evident pelvic or retroperitoneal lymph nodal metastases but only if they have had a response to CHT. Surgery for limited pulmonary metastases may also be considered in very selected cases. Best candidates are those with resectable disease who demonstrate measurable response to CHT with good performance status. In the absence of data from prospective randomized studies, each patient should be evaluated on an individual basis and decisions made together with the patient and multidisciplinary teams.

**Patient summary:** Surgical resection of metastases is technically feasible and can be safely performed. It may help improve cancer control and eventually survival in very selected patients with limited metastatic burden. In a patient who is motivated to receive chemotherapy and to undergo extirpative surgical intervention, surgery should be discussed with the patient among other consolidation therapies in the setting of multidisciplinary teams.

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## 1. Introduction

In Western countries, muscle-invasive disease accounts for about one-fourth of newly diagnosed urothelial bladder cancer (BCa) cases and approximately 10–30% of nonmuscle invasive BCa that have progressed. Nearly half of patients with muscle-invasive BCa will relapse despite intensive therapies, eventually succumbing to their disease [1–4]. Approximately, three-fourths of these patients relapse with distant failure, with the remaining one-fourth experiencing local recurrence [4,5]. In addition, somewhere between 5% and 15% of patients present with unresectable or metastatic disease at time of diagnosis [6]. When possible, for all patients with primary or secondary metastatic cancer, systemic platinum-based combination chemotherapy (CHT) is the standard treatment [2] resulting in initial response rates of 40–70%, but long-term survival of less than 15% within 5 yr [7,8]. In addition to the unfavorable response to systemic CHT, nearly half of patients are already unfit for this regimen due to renal and other comorbid conditions.

Surgical extirpation of the primary or metastases is part of a multimodal approach in various malignancies yielding potentially better survival and/or quality of life. This concept is increasingly being considered in urology from accepted entities such as testis and kidney cancers to more recently, prostate cancer [5,9]. Nevertheless, the role of surgery in metastatic urothelial carcinoma (UC) is not yet established with most of the experience being accrued from retrospective uncontrolled studies [2]. No pertinent prospective randomized trials have been published on this topic. Therefore, there is a need to better delineate the evidence-based potential oncological benefit of surgical extirpation of the primary in metastatic setting and of metastasectomy.

To address this need, we performed a systematic review of the role of surgery in patients with clinically node-positive BCa, distant metastasectomy, as well as cytoreductive radical cystectomy (RC).

## 2. Evidence acquisition

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols [10]. A systematic literature search of the PubMed-Medline and Scopus databases was performed on November 2016, including literature from 1999 through 2016. We included English language articles only. The search strategy included broad terms in isolation or in combination: “metastatic bladder cancer,” “metastatic urothelial carcinoma,” “locally advanced bladder cancer,” “lymph node positive bladder cancer,” “clinically node positive,” “radical cystectomy,” “cytoreductive radical cystectomy,” “metastasectomy,” and “aborted radical cystectomy.”

Relevant articles on surgical management of metastatic BCa were selected. Articles were considered relevant when they included urothelial BCa patients diagnosed with locally advanced disease or clinically evident lymph node metastasis or pulmonary metastasis who underwent RC with or without pelvic or retroperitoneal lymph node dissection or

metastasectomy with intention to treat. Review articles, editorials, case reports, comments, and meeting abstracts were excluded. Articles pertinent to the upper tract but not the lower tract were also excluded. If more than one report of the same study population existed, we selected the most recent one for qualitative evidence synthesis. Additional relevant articles were selected from authors' bibliographies. All studies of interest were obtained as full text articles. European Association of Urology Guidelines 2016 were also reviewed. Study eligibility was determined by two authors (S.F.S and M.A).

We used the MetaProp program (MetaProp NYC, New York, NY, USA) which incorporates the arcsine transformation of proportions in STATA 14.2 (Stata Corp., College Station, TX, USA) to pool the available clinical complete and partial response rates as well as the complete pathological response rates with computation of 95% confidence intervals.

## 3. Evidence synthesis

A total of 1430 unique articles were identified, of which 28 were selected and critically analyzed for evidence synthesis based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (Fig. 1) [11–38].

### 3.1. Surgery in patients with lymph node metastasis

#### 3.1.1. The role of surgery in patients with clinically positive lymph nodes

Patients with clinically positive lymph node (LN) disease are generally considered for induction systemic platinum-based CHT [39–41]. In the absence of visceral metastasis and despite CHT, the reported 5-yr overall (OS) rate was less than 20% [11]. Several groups evaluated RC and pelvic LN dissection (PLND) as a consolidative intervention in patients who experienced complete or significant response to induction systemic CHT [11–19] (Table 1).

The largest series was published by Zargar-Shoshtari et al [14] in which 304 patients received induction CHT. The rate of complete pathological response in LN and bladder specimens, combined, was 14.5%. This rate is lower than the 23–38% reported rates in neoadjuvant CHT series that had not included patients with cN1–3 [42,43]. Complete pathological response in LN (pN0), number of LNs removed ( $\geq 15$ ), negative soft tissue surgical margins, and cisplatin-based CHT were independently associated with better OS. Interestingly, there was no statistically significant difference in OS between cN1 and cN2–3. Likewise, there was no statistically significant difference between methotrexate, vinblastine, adriamycin, and cisplatin, and gemcitabine and cisplatin.

Similarly, Meijer et al [13] reported that clinical and pathological responses to CHT are predictive of better cancer-specific survival (CSS). Complete pathological response was achieved in about one-fourth of patients with a 5-yr CSS of 63.5%. Complete radiological response was documented in about one-third of patients with a

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