Bladder | **2016** | Vol. 3(2) | e26
DOI: 10.14440/bladder.2016.89

REVIEW

Role of consolidative surgical therapy in patients with locally advanced or regionally metastatic bladder cancer

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Competing interests: The authors have declared that no competing interests exist.

Received May 3, 2016; Revision received July 21, 2016; Accepted August 11, 2016; Published August 31, 2016

ABSTRACT

The effect of radical cystectomy and extended pelvic lymph node dissection (RC/PLND) on the survival of patients with locally advanced and/or regionally metastatic bladder cancer is unknown. However, emerging evidence suggests that there may be survival benefit to a subset of select patients with this disease who demonstrate a response to chemotherapy. This article will review the current literature on the role of RC/PLND in the consolidative treatment of locally advanced and regionally metastatic bladder cancer.

Keywords: bladder cancer, consolidative surgery, cystectomy, metastatic

INTRODUCTION

In 2015, bladder cancer is estimated to be the sixth most common cancer and the seventh most common cause of cancer-related mortality in the US [1]. Approximately 25% of incident bladder cancers are muscle-invasive (T2) and approximately 25% of those will harbor metastatic disease at the time of cystectomy [2,3]. Unfortunately, metastatic bladder cancer remains, in the majority of cases, an incurable disease. There has been little progress in terms of survival since the introduction of platinum based combination chemotherapy regimens in the early 1980s. The combination regimen of methotrexate, vinblastine, doxorubicin and cisplatin, known as MVAC, is associated with an objective response rate of 39-65% and has long been regarded as the gold standard for first-line treatment of metastatic bladder cancer. In recent years, the combination regimen of gemcitabine and cisplatin (GC) has demonstrated equivalent efficacy as well as lower toxicity, and has become largely the regimen of choice, despite a slight trend toward greater efficacy with MVAC therapy [4]. Regardless, complete responses with either regimen are rare and progression to cancer-related death is all but inevitable for most patients with metastatic disease. Given the inability to cure metastatic bladder cancer with current chemotherapeutic regimens, the surgical resection of locally advanced and regionally metastatic disease has garnered renewed interest. In this review, we will discuss the role of radical cystectomy and extended pelvic lymph node dissection (RC/PLND) in the management of locally advanced and metastatic bladder cancer.

Survival outcomes after radical cystectomy

Survival after RC/PLND is driven by pathologic stage. For organ-confined, node-negative disease (T1 or T2, N0), RC/PLND results in a 5 year overall survival rate of 78% [3]. For patients with extravesical extension but negative nodes (T3, N0), the 5 year overall survival drops to 47%. Among all patients with lymph node metastasis, the 5 year overall survival is 31% compared to 69% for node negative disease [5-8]. However, a closer inspection of the data published by Stein *et al*. reveals that 23% of patients with node positive disease are alive at 10 years [3]. This increases to over 50% of patients in a subset of patients with T2 N1+ disease. These data suggest that appropriately selected patients may achieve a long-term cure from surgery even in the setting of locally advanced and/or regionally metastatic disease [9-11].

Survival outcomes after chemotherapy

Despite these promising results, the standard treatment for patients with locally advanced or metastatic bladder cancer remains upfront cisplatin-based combination chemotherapy. Most of these patients with a good performance status will be referred for systemic therapy, especially since the natural history of untreated bladder cancer is often dismal. Before the development of effective combination chemotherapy, the median survival for patients with inoperable locally advanced or metastatic bladder cancer was between 3 and 6 months [12]. However, with the advent of cisplatin-based combination chemotherapy regimens, the median survival has improved to approximately 15 months [13,14]. Interestingly, 15% of patients will achieve a durable, favorable survival result at 5 years indicating that systemic treatment may also offer a favorable oncologic result for a subset of highly selected patients [4,14]. Nonetheless, with an overall median survival of 15 months and a 5-year overall survival rate of 15%, there is substantial room for improvement in the care of these patients.

Survival outcomes after chemotherapy and radical cystectomy

One possible strategy to enhance survival in locally advanced bladder cancer may be consolidative radical cystoprostatectomy (with a meticulous regional lymph node dissection [RC/PLND]) in select patients who have surgically resectable locally advanced and/or regionally metastatic disease, in addition to a favorable response to chemotherapy. Although the use of consolidative surgery is well defined in other cancers, it's role in bladder cancer is still unclear. Whereas, the role of salvage cystectomy has historically been limited, one rationale for consolidative surgery is the high incidence of relapse at the responding sites of disease [15]. Given the relative inaccuracy of current clinical assessments of complete responses to chemotherapy, as well as the apparent survival benefit of cystectomy in patients with loco-regional disease, a strong case could be made to proceed with cystectomy in select patients with favorable responses to chemotherapy [16,17].

To assess whether surgery after cisplatin-based combination chemotherapy is associated with a survival benefit, Dodd, *et al*. from Memorial Sloan Kettering Cancer Center (MSKCC) retrospectively evaluated their experience with post-chemotherapy surgery for locally advanced or metastatic bladder cancer [18]. Interestingly, of the patients who underwent complete resection of residual viable tumor, 33% were alive at 5 years. This compares favorably to the 41% of patients alive at 5 years who had a complete response to MVAC alone (no viable disease detected after post-chemotherapy cystectomy). Importantly, these data suggest that had the consolidative surgery patients not undergone extirpation, they would have likely succumbed to persistent viable disease—though admittedly this is an unobserved counterfactual outcome. Moreover, the receipt of combination chemotherapy and surgery resulted in a good long-term oncologic outcome for a significant proportion of patients. The methodological limitations of these comparisons notwithstanding, these data support the notion that appropriately selected patients with good performance status may derive survival benefit from surgical consolidation.

These authors followed this initial report with a larger, retrospective series of patients who underwent surgical consolidation [19]. In this update, the authors compared the survival of post-chemotherapy surgical patients to patients with a major response to chemotherapy and who ultimately refused to undergo surgery [19]. Similar to their prior experience, approximately 33% of the patients who underwent consolidative surgical therapy were alive at 5 years compared to only 8% of patients who had a major response to chemotherapy and were otherwise good candidates for surgery but refused a consolidative procedure. Notably, no patient who had a poor response to chemotherapy was alive at 5 years. While selection bias is undoubtedly a confounder in this series, these data build on the concept that surgery may have a therapeutic role in patients with locally advanced and/or regionally metastatic disease who respond to chemotherapy.

In a separate small, single institutional analysis of the role of consolidative surgery in patients with regionally metastatic bladder cancer, de Vries *et al*. also demonstrated that this approach can result in durable long-term survival for highly selected patients (24% at 5 years) [20]. Unlike the MSK series, this series also included patients who had supra-regional adenopathy suggesting an even more aggressive approach to patients with metastatic bladder cancer. In a separate phase II study exploring the potential benefit of retroperitoneal lymph node dissection in patients with bladder cancer in whom the disease showed a significant response to chemotherapy, Sweeney *et al*. reported 4 year disease specific and recurrence-free survival rates of 36% and 27% respectively [21]. One of the patients even had a retrocrural recurrence which responded to salvage chemotherapy and retroperitoneal lymph node dissection and was still living at the time of the publication (57 months). In a series reported by Meijer *et al*., the 5 year survival of node-positive disease treated with induction chemotherapy followed by surgery was 29% with a median cancer-specific survival rate of 20 months [22]. Most recently, Ho and colleagues at MD Anderson Cancer Center demonstrated that up to 66% of patients were alive at 5 years with chemotherapy followed by consolidative surgery, though questions remain whether many of these patients harbored clinically metastatic disease prior to initiation of therapy [23].

Lastly, there are several institutional series that note improved survival for those patients that underwent visceral metastectomy after prior treatment for muscle invasive bladder cancer. Siefker-Radtke *et al*. note median overall survival (OS) of 23 months and 33% 5-year survival for a select group of 31 patients with a variety of metastatic sites that underwent subsequent metastectomy [24,25]. Additionally, Abe and colleagues demonstrate median OS survival of 42 months for 12 patients that underwent metastectomy at sites including lung, as well as cervical and abdominal lymph nodes [26]. These series are consistent with responses noted in other consolidative surgical series and further suggest a potential role of surgical extirpation for highly select patients with locoregional or oligometastatic disease.

These studies make important contributions for several reasons. First, they externally validate the survival metrics observed in the MSK series [18,19]. This is an important point because reported survival rates may vary widely by institution based upon patient case-mix and experience. Second, they potentially broaden the generalizability of consolidative surgery, as outcomes are similar across institutions, including international sites. Lastly, they confirm the potential beneficial effect of surgery for those patients with a good initial response to chemotherapy. Moreover, each of these studies similarly find, for those patients who do not achieve a good response to chemotherapy or patients who progress while on chemotherapy, they do not seem to benefit from consolidative surgery as the 5-year survival rate in this cohort is essentially 0% [18,19].

Accurately assessing clinical response

Although the clinical response to chemotherapy appears to be an important predictor for clinical outcomes, the accurate measurement of the clinical response using conventional imaging modalities remains a challenge [27-31]. In many of these studies, discrepancies between clinical and pathological staging exceeded 30% [7,18,19,21-23,32]. Since one rationale for consolidative surgical therapy in this setting is the removal of clinically undetectable microscopic disease, an imaging modality that allows for better patient selection would be of great value.

^{18}F-fluorodeoxyglucose-positron emission tomography/computerized tomograph (PET/CT) is one such imaging modality that has been studied for the detection of lymph node metastasis in bladder cancer patients [33-37]. The overall sensitivity and specificity of PET/CT for the detection of nodal lesions harboring bladder cancer is approximately 82% and 89% respectively. While it appears that PET/CT may be more accurate than CT or MRI alone for staging bladder cancer, it is still associated with a nonzero rate of false positives and false negatives. Because of that, it's utility in this setting is not yet clearly defined.

A word of caution

While these data are certainly compelling, several important methodological limitations of these studies should temper a wholly enthusiastic interpretation. First, for the most part, these are single institution, retrospective case series without sufficient controls. Drawing causal inferences in this setting is difficult. Therefore, the observed survival rates for surgical patients may be solely a reflection of selection bias or confounding by indication. Second, these series are comprised of small sample sizes from high-volume academic centers and may not be generalizable to routine practice. Third, patients who undergo consolidative surgical therapy should only do so within the setting of a clinical trial with appropriate informed consent and full disclosure of the morbidity of radical cystectomy and urinary diversion. While a randomized trial would ideal, large multicenter prospective observational studies would help define the effect of consolidative surgery as well. Lastly, it is unclear what role, if any, consolidative surgery would play before a trial of Atezolizumab. Atezolizumab is a fully humanized engineered monoclonal antibody against the programmed cell death-ligand 1 (PD-L1) and has demonstrated promising results [38]. Undoubtedly, this agent will be upstream to consolidative surgery for most patients but further study is required.

CONCLUSION

Nevertheless, surgical consolidation for locally advanced or regionally metastatic bladder cancer may result in improved survival in carefully selected patients with surgically resectable disease, particularly for those who respond favorably to upfront cisplatin-base combination chemotherapy. When surgery is considered, careful patient selection is paramount and treatment must be individualized. The potential value of consolidative surgery must be weighed against several factors such as known harms of surgery, palliative benefit, pace of disease progression, previous treatment response, patient age and comorbidity, health-related quality of life and, most importantly, the desires of the patient. Further research is needed to fully characterize the effect of surgery in this population.

Acknowledgments

This work was in part supported by the National Cancer Institute, Grant 5T32CA106183 (Mark D. Tyson).

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