

Review article

# Treating octogenarians with muscle-invasive bladder cancer: Preoperative opportunities for increasing the benefits of surgical intervention

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Received 27 November 2012; received in revised form 4 March 2013; accepted 4 March 2013

## Abstract

The question posed to the authors is whether surgery is the best treatment option for octogenarians with invasive bladder cancer. Herein, we detail the rationale in favor of radical cystectomy and opportunities for improvement in the processes of care for those who may be surgical candidates. © 2014 Elsevier Inc. All rights reserved.

*Keywords:* Bladder cancer; Radical cystectomy; Octogenarian

## 1. Introduction

In the United States, the preferred treatment for muscle-invasive bladder cancer (MiBC) remains radical cystectomy (RC) with urinary diversion (UD). Surgical removal of the bladder and its associated organs (the prostate, seminal vesicles, and distal ureters in men; the uterus, ovaries, anterior vagina, and distal ureters in women) confers the most durable advantage in disease-specific and overall survival, particularly when combined with neoadjuvant platinum-based chemotherapy [1–4]. Bladder-preserving protocols combining transurethral resection of the bladder tumor(s), external-beam radiation, systemic chemotherapy, and salvage cystectomy for recurrences demonstrate non-inferiority in selected patients [5,6]. However RC with UD remains the “gold standard.”

### 1.1. What then is the best treatment for octogenarians with MiBC?

In general, surgical outcomes in octogenarians can be inferior relative to younger counterparts. Ninety-day mortality is often higher, 6.8% and 7.7% for those  $\geq 80$  years of age vs. 2.2% and 3.4% for those  $< 80$  years of age in 2 recently reported large series, respectively [7,8]. Elderly patients often experienced a higher number or severity of

complications, contemporary series using the Martin criteria for reporting complications consistent with earlier studies [7,9]. Advanced age has also shown to be an independent risk factor of decreased disease-specific and overall survival among those undergoing RC [10–13].

Although comparison of octogenarians to those of a younger age is instructive and worthy of further investigation, it is not the correct point of reference for determining the best treatment. Outcomes for octogenarians who undergo RC for MiBC should be appreciated in the context of age-matched cohorts who receive alternative treatments or nontreatment. The relevant question is not how outcomes compare between age groups, but what treatment strategy optimizes octogenarians' outcomes. Acknowledging the absence of level 1 data and surgical selection bias, comparisons of survival outcomes in octogenarians with MiBC demonstrate an advantage for RC relative to alternative treatment modalities, including radiation, chemotherapy, aggressive transurethral resection, and surveillance [14,15]. As such, RC should be the preferred treatment option for octogenarians in whom surgery is reasonable and survival is the primary objective.

Treatment decisions for MiBC with those in their ninth decade of life require a complex assessment of survival benefit, the morbidity of treatment vs. nontreatment, quality of life implications, and patient preferences [16]. Although we, along with others, have published on the safety of operating on carefully selected elderly patients with multiple comorbidities [7,17], extirpative surgery is not always

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possible or advisable. For the octogenarian with extensive comorbid conditions or poor performance status, the perioperative risk of mortality and significant morbidity may outweigh the risks; combined chemoradiotherapy is the remaining curative treatment option, particularly for those who are completely resected at initial transurethral resection of bladder tumor and who demonstrate complete response to induction chemoradiotherapy [6,18]. In addition, longevity may not be paramount. For octogenarians whose treatment goals include keeping their native bladder or avoidance of surgical convalescence, bladder preservation protocols are in accord with these preferences and may result in equivalent oncologic outcomes.

Yet, even the most conservative interpretation of the benefits of surgery suggests that RC is underutilized in octogenarians with MiBC. Octogenarians are less likely to undergo RC than those in their seventh or eighth decade of life, with best estimates suggesting that a mere 10% to 20% are undergoing this treatment [13–15,19,20]. The reasons for underutilization are multifactorial, but at least on some level reflect the perceived availability and effectiveness of RC relative to alternative treatments or nontreatment. As such, efforts to encourage greater utilization should increase the proportion of octogenarians evaluated for RC and improve the outcomes in those who opt for surgical intervention.

Opportunities to improve outcomes for octogenarians with MiBC exist in each phase of the perioperative period. Here we have chosen to focus on 2 topics whose processes are germane to the preoperative phase, reducing pathologic upstaging and optimization of surgical candidacy. In addition, we briefly address health-related quality of life (HRQOL) measurement in the MiBC population.

## 2. Reducing pathologic upstaging

Clinical staging in octogenarians is more likely to underestimate the burden of disease relative to their younger counterparts; a higher proportion of octogenarians with clinical organ-confined disease are upstaged to locally invasive and lymph node positive disease after RC [12]. Upstaging independently predicts survival; octogenarians upstaged from clinical T2 disease to pathologic T3, T4, and N+ disease are less likely to demonstrate improved survival [12,21].

Postulates for increased upstaging in octogenarians include delay in initial diagnosis, longer intervals between diagnosis and RC, increasing immunocompromise, and less receipt of neoadjuvant chemotherapy. Delay in initial diagnosis and subsequent time to RC may be related to tardy recognition of warning signs and symptoms, the effect of functional status on access to care, less aggressive transurethral resection of the incident lesion(s), workup of coexisting medical conditions prior to surgery, and regionalization of RC to high volume centers. Age-related

declines in immune function may have negative implications for tumor progression directly, via altered cancer immunosurveillance, or indirectly, decreasing efficacy of intravesical Bacille Calmette Guerin and interferon- $\alpha$  [22]. Similarly, octogenarians' decreased receipt of systemic chemotherapy is attributable at least in part to the challenges of delivering chemotherapy in the elderly, particularly in those with compromised renal function [23,24].

In the absence of technologies that improve clinical staging irrespective of age, efforts to affect pathologic upstaging in octogenarians could begin by examining known quality indicators. What role does presumed urinary tract infection as the etiology for gross hematuria play in delayed diagnosis of MiBC? What proportion of octogenarians experience a delay from diagnosis of MiBC to RC, a delay beyond 90 days associated with increased disease-specific and overall mortality [25]? Should the decreased efficacy of Bacille Calmette Guerin in octogenarians prompt earlier consideration of RC in those with high-risk nonmuscle invasive bladder cancer who are good surgical candidates? In what percentage of appropriate neoadjuvant candidates is chemotherapy considered, compromised renal function only partly explaining current utilization patterns [26]?

Identification of process-driven measures for improvement, when approached scientifically and in the spirit of collaboration, has resulted in improved care [27]. Similar efforts to facilitate earlier recognition of bladder cancer's warning signs and symptoms, expedite definitive surgical treatment, and overcome the barriers to appropriate use of neoadjuvant chemotherapy might serve to reduce the pathologic burden of disease and improve survival outcomes in octogenarians considering RC.

## 3. Optimizing surgical candidacy

Inherent in the clinical observation that a patient appears younger or older than his or her stated age is an acknowledgment that chronologic age has its limitations. For octogenarians in whom RC is an option, physiologic capacity and functional reserve to absorb the stresses of surgery and its convalescence are more relevant considerations than chronologic age.

Efficient and effective translation of the clinical gestalt of apparent age should attempt to incorporate coexisting medical conditions, performance status, nutritional status, cognition, and network(s) of social support. Comprehensive assessment tools for elderly patients considering surgery have demonstrated predictive value and feasibility [28,29]. Formal assessment may add layers of complexity to determine the appropriate treatment strategy, and could prompt as many questions as answers. Which medical conditions are of the greatest relevance, and how should severity be qualified? What relative role should decreased functional status, cognitive deficits, recognition of dementia, and the absence

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