Optimal Management of the Elderly Patient with Muscle-Invasive Bladder Cancer

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Abstract With the growing elderly demographic and the peak incidence of bladder cancer being approximately 70 years old, an increasing number of elderly patients will develop invasive bladder cancer. Several studies suggest that a survival gap exists between elderly patients with invasive bladder cancer and younger cohorts. Radical cystectomy is the standard of care that provides good cancer-specific survival, but few elderly patients are referred for cystectomy. This is likely, at least in part, due to concern with the morbidity associated with the operation. Cisplatin is the most effective chemotherapeutic agent used to treat invasive bladder cancer but some patients cannot receive it due to toxicity. There are few promising alternatives to cisplatin at this time. This review discusses opportunities for improved care, recent therapeutic advances, and future directions to improve the outcome for elderly patients with invasive bladder cancer.

Keywords Muscle invasive bladder cancer · Elderly · Radical cystectomy · Cisplatin · Cisplatin unfit · Urinary diversion · Bladder sparing · Bladder cancer · Urothelial carcinoma · Radical TURBT

Introduction

There were approximately 73,510 new cases of bladder cancer in the United States in 2012 [1]. With the incidence of bladder cancer increasing with age, it is most commonly seen in patients older than 70 years of age [1]. While bladder

cancer is the sixth most common cancer overall, it is the fourth most common in patients older than 85 years [2]. Fortunately, the vast majority of tumors will not invade into the muscle of the bladder wall. These non-invasive tumors can often be managed with conservative techniques, such as transurethral resection of the bladder tumor (TURBT) and intravesical therapies.

However, some of patients with non-muscle invasive tumors will progress to muscle invasive disease and approximately 20 % of patients will have invasive disease at initial presentation. Even with the best available treatments, the overall survival for muscle invasive bladder cancer (MIBC) is remains only 40–60 % at 5 years [3]. An estimated 14,880 patients died from bladder cancer in 2012 in the United States [1].

The peak age for MIBC is 70 years of age with 20 % of patients being over 80 years old [4]. As the United States' elderly population continues to grow at an unprecedented rate an increasing number of elderly will develop MIBC [2]. Similarly, elderly patients with non-muscle invasive tumors are less likely to respond to intravesical therapy, which puts them at greater risk of progression to MIBC [5].

Yet, several studies have shown a disparity in both cancer care and outcomes between elderly patients with MIBC compared to younger patients. There are multiple reasons for why these differences may exist. It is the objective of this review article to highlight areas that need most improvement in the care of elderly patients with MIBC and to discuss recent advances as well as future directions.

Radical Cystectomy in the Elderly: An Under-Utilized Standard of Care

Radical cystectomy with urinary diversion (RC) offers the best chance of survival for patients with MIBC and remains

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the gold standard for which alternative therapies are compared. The 10-year cancer-specific survival and overall survival for RC is approximately 70 % and 50 %, respectively, for organ-confined disease [6]. Patients over 75 and 80 years have been successfully treated with RC with similar cancer specific survival to younger cohorts [7, 8–11]. However, some studies have reported that older patients have more aggressive tumors than younger patients [12, 13]. However, when reviewing the care that elderly patients with MIBC receive, obvious disparities appear. For example, elderly patients with MIBC are less likely to receive aggressive treatments, even though aggressive treatment has been shown to improve survival in patients older than 80 years [13, 14, 15]. Similarly, elderly patients are less likely to get an extended lymph node dissection, which is also associated with improved outcomes [16, 17]. Lymphadenectomy in the elderly may be avoided by some surgeons due the increased time under anesthesia and concern about dissecting near atherosclerotic vessels. Although not yet proven in randomized controlled trials, retrospective studies suggest extended lymphadenectomy may have a therapeutic benefit and the number of lymph nodes removed may be an indicator of surgical quality [4, 18]. Surgical series have reported that when a similar number of nodes are removed from the elderly, there is comparable cancer specific survival to younger cohorts [17, 18].

One important area that warrants further investigation is that although cancer specific outcomes appear similar between older and younger cohorts, the overall survival is usually significant worse for elderly patients. This may result from competing risks due to differences in comorbidity and age-related changes. However it could be related to the impact that RC has on the elderly. RC is a major surgery with multiple suture lines, an intestinal anastomosis, abdominal incisions, and urinary diversion required for this operation. RC may result in a physiologic insult that could worsen or expose frailty within an individual [19].

Despite recent advances in surgical technique and peri-operative management that have substantially reduced the mortality associated with the operation, the morbidity rate remains alarmingly high 19–64 % [20, 21–23]. Those at greatest risk for morbidity and mortality after RC are those with multiple co-morbid conditions as well as the elderly [24, 25]. The risk of death within 90 days from RC is far greater in those >80 years old [26]. However, multiple studies contest that it is not chronologic age, but physiologic age that matters most. It may simply be that older patients have had more time to compound comorbidities and if properly controlling for comorbidities, elderly patients will have similar outcomes to younger patients. Unfortunately, it is often difficult to adjust for comorbid conditions in studies.

For example, the commonly used Charlson Comorbidity score does not account for severity of comorbid conditions and the American Society of Anesthesia (ASA) score may not be sensitive enough to properly discriminate differences [27, 28].

Elderly patients being considered for RC should undergo an individualized assessment of life expectancy, comorbidities, and functional status [29]. Various competing risks for the patient should also be considered. Chronologic age should be factored in to a lesser extent, as age often does not accurately predict ability to tolerate treatments [29]. Using an assessment tool designed specifically for elderly cancer patients may be most appropriate, albeit, also time consuming. Use of the preoperative assessment in elderly cancer patients (PACE) or the Comprehensive Geriatric Assessment should be considered before surgery as properly selected elderly patients are able to tolerate RC as well as younger patients [30, 31].

Considering that RC is the standard of care for MIBC, it is considerably under-utilized [16, 32]. Studies show that approximately half of patients between the ages 55–59 years with MIBC undergo RC, and those numbers rapidly decrease with increasing age [33]. For patients ages 85 years and older, only 4 % will undergo a RC. When looking at only those with few comorbidities (ASA score ≤ 2), only 9 % will receive a RC [33]. Under-utilization is not necessarily because surgeons are declining to perform the operation in this older cohort, as less than 5 % of patients referred for cystectomy are considered unfit by experienced surgeons [34].

The low referral rate of MIBC patients may reflect a bias in primary care providers against aggressive treatment in elderly patients. Primary care providers, including primary urologists, often influence the decision for an elderly patient to undergo RC, but often underestimate the patient's willingness to undergo aggressive treatment [35, 36]. While this is well intentioned, it can result in a significant delay in definitive treatment. Delays of over 12 weeks from diagnosis to RC have been shown to be detrimental to outcomes [37]. This delay may partially explain the worse pathological findings seen in some elderly patients undergoing RC [12, 13].

Future efforts are needed to focus on facilitating referral of elderly patients with MIBC to high volume tertiary care centers. A volume–outcome relationship has been demonstrated for RC with high-volume centers providing superior outcomes [20, 38]. Academic centers are also able to provide multi-disciplinary care, which is of increasing importance in this disease. A noted barrier for a patient undergoing RC is long distances from a cancer center [39]. This is an important consideration in the elderly, as they may depend on others for transportation to physician appointments.

Optimizing Radical Cystectomy Outcomes in Elderly Patients

As previously mentioned, the morbidity associated with RC is high and potentially worse for elderly patients. A prolonged postoperative ileus (PPOI) is the most common complication following RC [22]. Although, there is no standardized definition for PPOI and the pathophysiology contributing to this process is rather complex, several attempts have been made at decreasing the incidence of PPOI, ranging from pharmacologic agents to gum chewing [40, 41]. PPOI has previously been shown to be a common cause of a prolonged length of hospital stay (LOS) following RC. When we evaluated our RC experience of 330 consecutive patients for perioperative risk factors associated with a prolonged LOS ≥ 12 days, only older age and female gender were statistically significant on multivariate analysis [42]. Those with a prolonged LOS had significantly similar cancer specific outcomes but worse overall survival [42].

Another important consideration in the elderly is the rate of delirium following RC. It has recently been shown to be 29 % following RC in patients older than 65 years [43]. Delirium is associated with an increased risk of morbidity and mortality after many surgical procedures [44]. Unfortunately, it is often under detected by health care providers. Evidence suggests that the involvement of geriatricians with in-patient care after surgery may decrease the risk of postoperative delirium [45].

With recent changes in the United States health care system, there has been a well-documented shift toward earlier discharges from the hospital after RC by discharging to skilled care facilities [23, 46]. However, patients discharged to a skilled care facility are at much greater risk of morbidity and mortality after RC as well as many other surgeries [47]. It should not come as a surprise that elderly patients are more likely to be discharged to a skilled care facility after RC and further research in this area is needed to more clearly define the role of such facilities following RC in elderly populations [48].

The readmission rate after RC is approximately 20–30 % within the first 90 days. In fact, RC has higher readmission rates than esophagectomy and pancreatectomy [49]. Those with comorbidities are at increased risk for readmission after RC [22]. Dehydration and failure to thrive are a common cause of readmission [22]. With greater attention being paid to the concept of frailty and geriatric failure to thrive, preemptive action may decrease hospital admission rates in this population [19]. Family involvement in the care of elderly patients after RC will also play a role in decreasing the risk of readmission. When planning to discharge an elderly patient from the hospital after RC, level of social support should be considered. For example, elderly

widowed men are at an increased risk for worse outcomes after RC [50].

It is important to remember that it could take several months for an elderly patient to recover from major abdominal surgery, both cognitively and physically [51]. RC is no different in this regard, with losses of lean body mass and strength seen up to 6 months later [52]. A target area for improving outcomes following RC is nutritional support. Approximately 20 % of patients undergoing RC have evidence of malnourishment [53, 54]. Although, not entirely specific for malnourishment, low serum albumin levels is one of strongest predictors of morbidity and mortality [55]. This is also true in the RC literature [26]. Seven to ten days of preoperative oral nutritional supplementation has shown to benefit gastrointestinal cancer patients undergoing surgery [56]. Peri-operative nutritional support will likely have a future role in optimizing outcomes for RC, particularly in the elderly and malnourished.

Additional future directions for improving RC outcomes will focus on reducing the morbidity of the procedure. The major contributor to morbidity is the use of bowel in the urinary diversion. One consideration is the use of cutaneous ureterostomies, which had fallen out of favor, but may have an increasing role with improvements in surgical techniques to help avoid bowel work [57]. Ultimately, the future of urinary diversion will likely be in tissue engineering [58–60]. The use of robotic assisted surgery is also gaining popularity, which may potentially decrease morbidity. Early reports suggest that robotic cystectomy is safe in elderly patients with similar short-term oncologic outcomes with a reduction in operative blood loss and a shorter LOS [61–63]. A combination of robotic assisted surgery and tissue engineered urinary diversions has the potential to markedly reduce the morbidity of RC [58].

Urinary Diversions: Considerations for Elderly Patients

Although continent diversions and orthotopic neobladders are increasingly being used at high volume centers, the most common diversion remains a non-continent diversion [64]. This is holds true in the elderly population [11, 64]. There has yet to be a well documented major difference in quality of life between the various urinary diversion types [65]. However, either a continent diversion or an orthotopic neobladder is a safe and reasonable option for carefully selected elderly patients [66].

There are several benefits to an ileal conduit diversion, which is likely the reason it is commonly used in the elderly population. The procedure has relative ease, shorter operative time, and more predictable functional outcomes [67]. The shorter length of contact time between urine and bowel results in less metabolic changes, although up to 10 % with

an ileal conduit will have some metabolic disturbances [67]. The most common metabolic disturbance is a hyperchloremic metabolic acidosis, which results from a chronic acid load and reduced renal function [67, 68]. This can result in muscle weakness, electrolyte abnormalities, and bone demineralization. The resultant bone demineralization is of particular concern in the elderly. It occurs from the effects of chronic acidosis on bone buffering, an impairment of renal activation of vitamin D, and an activation of osteoclasts [67]. To date there is no standardized way to follow or screen patients with urinary diversions for osteopenia [68, 69].

Another important consideration when selecting the type of urinary diversion in the elderly population is the individual's manual dexterity as well as their willingness and ability to properly maintain their diversion [70]. Early referral to a stoma care specialist is particularly important to optimize care and improve quality of life [68, 71]. Both family members and care providers should be encouraged to attend these appointments as many elderly patients will not independently care for their urostomy [72].

Chemotherapy in Muscle Invasive Disease

Cisplatin combination therapy remains the standard chemotherapeutic agent for urothelial cell carcinoma. Although initial trials used combination methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), more recently gemcitabine and cisplatin (GC) combination therapy has become the preferred regiment at many centers due to the similar efficacy to MVAC but with less toxicity [73•].

Neoadjuvant cisplatin combination therapy has a small but definite advantage in the treatment of MIBC with a 5 % improved overall survival [74]. The rate of pT0 disease at time of cystectomy also increases from 10–15 % with transurethral resection alone to 35–45 % with neoadjuvant chemotherapy [73•]. Although pT0 does not guarantee cure, these patients do have a more favorable prognosis [75]. These potential benefits of neoadjuvant therapy must be weighed against the delay to RC that may result from non-responder or toxicity from therapy.

Prospective trials evaluating adjuvant chemotherapy for bladder cancer have suffered from methodological flaws and are limited by small subject numbers due to poor accrual [76–78]. Adjuvant chemotherapy is typically reserved for patients with $\geq$ pT3 or positive nodes. This strategy may avoid overtreatment in pT0 disease patients and potentially pT2 patients. However, up to 17 % patients following their urinary diversion will no longer for eligible for cisplatin due to impair renal function [79]. Only one prospective randomized trial attempted to

compare neoadjuvant to adjuvant therapy, which showed no difference between them, but small subject numbers and study design limits interpretation [80].

Despite level one evidence demonstrating a benefit for neoadjuvant chemotherapy, only 1.2 % of patients with MIBC will receive preoperative chemotherapy and only 11.6 % of patients will receive any peri-operative chemotherapy [81]. Compounding this issue is that fact that approximately 40 % of patients with MIBC are not “eligible” for cisplatin and no alternative systemic agent has similar efficacy. Recently, a consensus criteria was published on “fitness” to receive cisplatin; ECOG performance status of ≤ 2 , glomerular filtration rate (GFR) ≥ 60 ml/min, minimal comorbidities, particularly heart failure [82••]. The elderly not only have an increased rate of comorbid conditions, but also GFR decreases roughly 1 % per year from about 30 years of age [82••]. Even if criteria for cisplatin are met by an elderly patient it is questionable as to whether the results of those clinical trials are generalizable to them as most trials limited enrollment to less than 70 years old. This is not a problem unique to bladder cancer as the elderly are frequently excluded from randomized control trials [83].

Finding an alternative therapy for cisplatin that is better tolerated and safe for “unfit” patients should be a top priority in bladder cancer. Carboplatin does have some activity against urothelial cell carcinoma but is far less effective and should not be considered a substitution for cisplatin. Carboplatin with gemcitabine may be the best option currently [84]. However, active investigation into alternatives is underway. Current trials are looking at various combination therapies, including the use of taxanes, novel microtubules inhibitors, folate synthesis inhibitors, and molecularly targeted agents [84, 85]. Future efforts will also need to focus on translational research into tumor genetics to predict chemotherapy responders and help guide more targeted therapies [73•].

Bladder Sparing Protocols

Bladder sparing as an alternative to RC has gone through an extensive evolution [3]. All modern bladder sparing protocols use a trimodal therapy (TMT) approach of radical TURBT, chemotherapy, and radiation. Any of those modalities as a monotherapy alone produce inferior results. However, long-term results for TMT have shown a complete response rate in 60–80 % of patients with a 5-year overall survival between 40–60 % [3]. Although these results are comparable to RC series, it must be remembered that patients enrolled in most bladder sparing protocols are highly selected patients. Patients who are the most optimal candidate for TMT do not have diffuse carcinoma in situ (CIS),

no hydroureteronephrosis, clinically negative lymph nodes, complete transurethral resection, minimal comorbidities, and enough renal function to tolerate cisplatin combination chemotherapy [3]. Many elderly patients will not be candidates for true TMT as they will not be cisplatin “fit”. To date, no randomized controlled trials exist comparing RC to TMT and it is unlikely that accrual numbers of such a trial would even be large enough to provide meaningful data. However, based on the best available data, TMT is a reasonable alternative to RC for select patients with the intention to perform a RC if there is no evidence of initial tumor response to TMT [3]. Patients considering TMT who desire to maintain a functional bladder, must accept that if they fail TMT, they will be far less likely to get either an orthotopic neobladder or continent diversion at time of salvage RC [86].

Patients with MIBC who are poor surgical candidates present a difficult management situation as their usually severe co-morbid conditions often prevent the usage of cisplatin required for effective TMT bladder sparing protocol. Several experimental protocols involving alternatives to cisplatin in combination with TURBT and radiation are underway [84]. Radical TURBT alone, or in conjunction with radiation, for MIBC patients unfit for surgery and cisplatin may have some success for those with a low tumor burden, no CIS, and no hydronephrosis. Patients with confirmed pT0 status on repeat TURBT within the first 3 months will likely have the most success.

Regardless, when comparing TURBT to RC in elderly patients, TURBT alone had a much worse cancer specific and overall survival [87]. Other retrospective series evaluating bladder preservation strategies have also shown worse cancer specific outcomes for elderly patients with MIBC compared to RC series [88, 89]. And even though a strategy of repeat radical TURBT is less morbid than RC, it still has some limitations in the elderly. It requires strict adherence to cystoscopic evaluation every 3 months, at least initially, which can be a burden to both patient and family. Furthermore, patients may also require multiple procedures with anesthesia which is associated with cognitive dysfunction in the elderly [90].

Although TURBT is a routine procedure with low morbidity, the elderly with MIBC are at higher risk for bladder perforation. This is particularly true for females with a low BMI, usually because of thin bladder walls [91]. Those with a large tumor burden, which is most muscle invasive tumors, are also at increased risk of perforation [91, 92]. Fortunately, most perforations are extraperitoneal and can be managed with extended Foley catheter drainage, however intraperitoneal perforations can occur which requires emergent open exploratory surgery and repair. Elderly patients are at the greatest risk for perforations that require open surgical repair [93].

Conclusion

Elderly patients with muscle invasive bladder cancer are a unique and growing population. Several challenges must be overcome to improve care. The most important of which is finding an effective alternative to cisplatin that is better tolerated and can be given to those with renal insufficiency. Radical cystectomy remains the standard of care and is safe in older patients. Attempts should be made to optimize perioperative management to reduce the morbidity of the procedure. Immediate referral of elderly patients with MIBC to high-volume RC centers will help improve outcomes. Bladder sparing protocols using combination radical TURBT and chemo-radiation are currently limited by the lack of a good alternative to cisplatin, however bladder sparing does have promise for carefully selected patients.

Conflict of Interest Eugene J. Pietzak declares he has no conflict of interest.

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- Of importance
- Of major importance

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