Treating Elderly Patients With Muscle-Invasive Bladder Cancer

Elizabeth R. Kessler, MD^{1,2}; Janet B. Kukreja, MD, MPH^{2,3}; Christopher L. Geiger, MD^{1,2}; and Stacy M. Fischer, MD^{2,4}

ABSTRACT

Bladder cancer is an extremely common cancer that primarily affects individuals aged >65 years. In caring for patients with bladder cancer, clinicians must also consider care of older persons in general. Management of muscle-invasive bladder cancer (MIBC) involves multidisciplinary treatment planning, because curative-intent therapy includes either surgery or radiation, with consideration of the role of systemic therapy. As clinicians develop a treatment plan, considering a geriatric oncology perspective may enhance patient care and influence outcomes for this large and growing population. Similarly, treatment plan development must also consider aspects unique to an older patient population, such as altered organ function, increased comorbidity, decreased functional reserve, and perhaps altered goals of treatment. Thus a thorough evaluation inclusive of disease assessment and geriatric assessment is essential to care planning. Population-based data show that as patients with MIBC age, use of standard therapies declines. Given the complexities of coordinating a multidisciplinary care plan, as well the complexities of treating a heterogeneous and potentially vulnerable older patient population, clinicians may benefit from upfront assessments to inform and guide the process. This review highlights the unique treatment planning considerations for elderly patients diagnosed with MIBC.

J Natl Compr Canc Netw 2020;18(6):783–790
doi: 10.6004/jnccn.2020.7585

Bladder cancer is primarily seen among elderly individuals, with a median age at diagnosis of 73 years and most patients aged 65 to 85 years. It is the fourth leading cause of cancer-related death among men aged >80 years.¹ Thus, clinical care planning must include assessments and considerations unique to an older patient population. Bladder, or urothelial, cancer can be separated into 2 distinct stages: superficial and muscle-invasive. Management of muscle-invasive bladder cancer (MIBC) should include treatment planning from multiple disciplines, such as surgical urologic oncology, medical oncology, and radiation oncology. As clinicians develop treatment plans, considering a geriatric oncology perspective may enhance patient care and influence outcomes for this large and growing population.

MIBC includes stage II and III bladder cancer, including disease that invades the muscularis propria and can extend through the depth of the bladder and into the extravesicular tissue. Some patients may also have regional lymph node involvement. In general, this is a curable condition with the use of multimodal therapy. This includes treatment of the primary bladder tumor by either surgical removal of the tumor and bladder, or irradiation of the bladder. In addition, treatment includes an estimation of risk of recurrence or metastasis that may require intensification with systemic therapy to aid in management. The standardized approach, for patients with adequate fitness for therapy, includes neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and an extended lymph node dissection. In addition, trimodality therapy (TMT) including maximal transurethral resection of bladder tumor (TURBT) followed by combined chemotherapy and radiotherapy (RT) may be appropriate for select patients. Determination of TMT versus NAC followed by surgical resection is often dictated by patient health, frailty, and preferences.

Care planning is a complex process for patients with bladder cancer given their advanced age, increasing incidence of comorbid conditions, and functional decline. MIBC is a significant health condition associated with local symptoms and morbidity as well as a high

¹Division of Medical Oncology, University of Colorado School of Medicine;

²University of Colorado Cancer Center; and ³Department of Urology and

⁴Division of Internal Medicine, University of Colorado School of Medicine, Aurora, Colorado.

risk of mortality.² Population-based data show that as patients age, use of standard therapies declines in MIBC.³ Given the complexities of coordinating a multidisciplinary care plan, as well the complexities of treating a heterogeneous and potentially vulnerable older patient population, clinicians may benefit from upfront assessments to inform and guide the process. This review highlights the unique treatment planning considerations for elderly patients diagnosed with MIBC.

Geriatric Assessment

Clinicians must consider the significant risks associated with the treatment of muscle-invasive disease and the potential vulnerabilities that mount through the physiologic aging process in determining the appropriate treatment plan with patients. Each older patient with cancer should undergo a geriatric assessment to help determine a patient's functional age. Traditionally, candidacy for cancer treatment has been evaluated through a standard history and physical examination, assessment of comorbid medical conditions, and performance status based on ECOG score or the Karnofsky performance scale. However, a more detailed evaluation using the comprehensive geriatric assessment (CGA) can uncover underlying vulnerabilities that inform the potential risks of therapy. In addition to evaluating overall health, the CGA includes an assessment of cognition. Cognitive ability can predict whether a patient can engage in care planning and help understand noncancer life expectancy in the setting of multimorbidity. The CGA provides critical information to help ground the approach to treatment planning and has been shown to

improve satisfaction with communication for patients and families.⁴

The CGA evaluates functional status and fall history, comorbidity, cognition, depression, nutrition, social support, and additional geriatric syndromes using validated tools (Table 1). Multiple studies have found that the CGA is more sensitive than performance status in determining functional impairment and risks associated with chemotherapy or surgery.⁵ The CGA can uncover age-related issues in up to 50% of patients, including functional, cognitive, or nutritional deficiencies.⁶ As a result, the CGA can detect issues in the elderly population that may become increasingly significant during treatment, and are potentially modifiable in many instances. Multiple consensus groups, including NCCN, ASCO, and the International Society of Geriatric Oncology (SIOG), have recognized the utility of the CGA in gathering upfront information on the geriatric health of older patients.

Given the time-intensive nature of the CGA, physicians may start with simpler screening tools. For example, ASCO⁷ and the NCCN Clinical Practice Guidelines in Oncology for Older Adult Oncology⁸ recommend a minimum assessment of function, comorbidity, falls, depression, cognition, and nutrition, and delineates efficient and effective options for screening. Three initial tools include the Triage Risk Screening Tool (TRST), Geriatric 8 (G8), and Vulnerable Elders Survey-13 (VES-13).^{9,10} These brief questionnaires cover 5 to 13 items, take only minutes to complete in clinic, and have been used to uncover certain deficits associated with increased risk of morbidity and mortality in elderly patients receiving cancer treatment. Beyond the domains covered in a geriatric

Table 1. Geriatric Assessment Domains and Validated Tools

CGA Domain	Simplified Screening to Prompt Full Assessment	Examples of Validated Tools to Fully Assess Domain
Function	Dependence in 1 IADL ≥1 falls in the last 6 months	Reported function ADL and IADL Physical function Timed Get Up and Go ⁵⁹ Hand grip strength
Comorbidity	1 serious or 3 chronic medical problems	Charlson comorbidity index ⁶⁰ Cumulative Illness Rating Scale-Geriatric ⁶¹
Cognition	Zero words recalled on mini-cog	Mini-Mental Status Examination ⁶² Blessed Orientation-Memory-Concentration Test ⁶³
Depression	Score >5 on geriatric depression scale 15-item screen	Geriatric Depression Scale Patient Health Questionnaire-9 ⁶⁴
Nutrition	BMI <21 kg/m ² or 10% weight loss in 6 months	Mini Nutritional Assessment ⁶⁵ Simplified Nutritional Appetite Questionnaire ⁶⁶
Social support	Lives alone or without family in state	MOS Social Activity Survey ⁶⁷ MOS Social Support Survey
Polypharmacy	≥5 medications	AGS Beers Criteria ⁶⁸ STOPP/START criteria ⁶⁹

Abbreviations: ADL, activity of daily living; AGS, American Geriatrics Society; BMI, body mass index; CGA, comprehensive geriatric assessment; IADL, instrumental activity of daily living; MOS, Medical Outcomes Study; STOPP/START, screening tool of older people's prescriptions/screening tool to alert to right treatment.

screening tool, a measured functional assessment and chemotherapy toxicity tools enhance the ability to predict the risk of toxicity associated with therapy.^{11–13} Predicting complication risks from surgery is also important when considering multidisciplinary care, and evaluation of characteristics as simple as lean body mass may predict perioperative complications.¹⁴ Vulnerabilities uncovered through screening can then trigger the need for a CGA with interdisciplinary collaboration involving geriatrics, nutrition, social work, and rehabilitative specialists.

The CGA helps determine functional rather than chronologic age and can inform treatment decisions to avoid undertreatment or overtreatment. Cancer therapy may be altered in 25% to 50% of patients based on the CGA. Some deficits uncovered by the CGA may be modifiable or emphasize the need for additional support services. Patients can be stratified into 1 of 3 categories: fit, vulnerable, or frail (Figure 1). A better assessment of a patient's functional age and longevity can help direct more appropriate treatment on an individual basis.

Surgical Treatment

RC has long remained the principal treatment of MIBC.¹⁵ RC includes bladder removal along with the prostate or female reproductive organs and pelvic lymph nodes with creation of a urinary diversion. RC is well-known to be associated with frequent complications (60%)

and readmissions (30%).¹⁶ There is a relatively low risk of death due to the surgery itself, yet patients face a prolonged recovery period of months. In addition, there is an increased risk of geriatric events (falls, continence changes, delirium) in any patient admitted to the hospital for a surgical procedure requiring weeks of recovery.¹⁷ Although RC in the elderly is associated with significant morbidity, a long recovery, and reported worse overall and cancer-specific survivals, these are seen more frequently in patients aged >80 years.¹⁸ Despite the associated morbidity, RC is still a reasonable option in properly selected patients who have undergone preoperative counseling and geriatric screening.¹⁹ In a recent systematic review, Fonteyne et al¹⁸ evaluated overall survival (OS), cancer-specific survival, and morbidity after curative treatment in patients with MIBC aged >70 years. They noted a decrease in OS after RC in association with advancing age, yet attributed this to the overall limited life expectancy and general frailty of the population rather than the surgical procedure. The cancer-specific survival in patients aged >80 years was also worse than in younger patients, suggesting that in the very old it may be a combination of age and disease itself that contribute to worse outcomes. The authors of this review concluded that the risk of dying from bladder cancer often outweighs the risks of treatment.¹⁸ However, treatment with RC should be more discerning for those aged >80 years and considered in conjunction with objective data, such

Figure 1. Algorithm for treatment of muscle-invasive bladder cancer in elderly patients.

Abbreviations: NAC, neoadjuvant chemotherapy; RT, radiotherapy; TURBT, transurethral resection of bladder tumor.

^aBladder-preserving trimodality therapy is not recommended for patients with hydronephrosis, extensive/multifocal carcinoma in situ, or tumor >6 cm. The tumor should be amenable to visually complete/maximal TURBT. Intensity of trimodality therapy may be altered based on patient functional status.

as CGA findings and life expectancy estimates.^{18,20} These data highlight the need for a CGA, because it has been shown to independently influence cancer treatment plans,²¹ with prospective studies evaluating the impact on outcomes still needed.

Localized MIBC is associated with a risk of progression to more advanced life-limiting disease as well as significant symptoms of primary tumor growth. This is a high-risk condition that can cause multiple symptoms if left untreated. Without definitive therapy, patients may only have 2 years of life expectancy. TURBT remains integral for the diagnosis of bladder cancer. In addition, it is often part of a comprehensive management strategy for MIBC. Reduction in tumor burden and aggressive TURBT can be key in TMT as well as palliative management for older adults not able to tolerate additional treatments.²² TURBT is often performed without general anesthesia and under local spinal blocks by the anesthesia team. This remains an option for patients who are too frail for definitive surgery, have a life expectancy <2 years and are thus more likely to die of an illness other than their cancer, or have decided to forego definitive therapy for personal decisions. The decision for localized therapy in MIBC is complex. This is a high-risk cancer with high-risk treatments, and thus the CGA and preoperative assessment are important to inform these discussions.

It is important to recognize that available data support the acceptability of RC in terms of safety and efficacy in properly selected older patients cared for at high-volume centers.^{23–25} Robotic surgery and the adoption of enhanced recovery after surgery (ERAS) principles continue to improve the postoperative recovery and quality of life in patients undergoing RC, and will remain key in perioperative management of the older surgical patient.²⁶

Robot-assisted laparoscopic RC (RARC) is an evolving technology, but may aid in the surgical management of older patients undergoing RC and ultimately their recovery.^{27,28} RARC has become an acceptable alternative to open surgery. Two randomized controlled trials have demonstrated no difference in oncologic outcomes.^{29,30} Specifically, RARC may benefit older patients compared with open RC, because RARC may be associated with an easier recovery with less pain, less blood loss, and shorter hospital stays.^{31–33} Open cystectomy is also a reasonable option, especially if the primary tumor may be removed without an extended surgery requiring prolonged anesthesia. Ultimately, patients will be fit for surgery or not, and the exact technique can be discussed within the high-volume center.

ERAS pathways for cystectomy have become gradually more popular to aid in patient recovery after surgery.²² Important components of ERAS for patients undergoing RC include patient education, prehabilitation, carbohydrate loading, maintenance of euolemia, maintenance

of normothermia, early enteral feeding, early mobilization, opioid avoidance, multimodal pain control, and venous thromboembolism prevention.²⁶ The components aim to help alleviate the physical and psychologic stress associated with RC.²⁶ A recent meta-analysis of ERAS pathways reported a reduction in complications and length of hospital stay.³⁴

Incorporation of upfront risk assessment specific to older patients, surgical techniques tailored to older patients, and enhanced recovery pathways allow clinicians to tailor care for this vulnerable population, which may prolong survival and improve quality of life.

Perioperative Chemotherapy

Most older patients with MIBC do not receive NAC despite strong recommendations from expert consensus panels, such as the NCCN Bladder Cancer Guidelines Panel.³⁵ An analysis of patients with stage II–IV MIBC in the National Cancer Database (NCDB) from 2003 through 2007 showed that only 34% of these patients receive any chemotherapy, and that the rates decline as age increases.³ A SEER database analysis of patients aged ≥66 years from 1992 through 2002 also demonstrated low rates of chemotherapy administration; only 18% to 22% of patients with invasive and resectable disease received chemotherapy within 6 months of diagnosis.³⁶ Older patients are underrepresented in clinical trials, and thus application of trial data to elderly patients with bladder cancer is inherently limited. It is unclear whether these low rates of treatment reflect age bias or concern for toxicity. However, a retrospective analysis performed in the United Kingdom from 2005 through 2012 suggests that patients aged >70 years treated with NAC and RC had similar disease-free survival (DFS) compared with their younger counterparts.³⁷ Patients should be assessed based on physiologic rather than chronologic age, with use of the CGA to determine candidacy for chemotherapy.

A seminal prospective, randomized clinical trial demonstrated the benefit of cisplatin-based combination NAC over surgery alone. Grossman et al³⁸ examined 317 patients (median age, 63 years) from 1987 through 1998 in a multicenter trial comparing MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) NAC versus RC alone, and found a significant improvement in median OS for MVAC + RC (77 months) versus RC alone (46 months). Given the toxicity of conventional MVAC, a dose-dense regimen (ddMVAC) with growth factor support has been developed and has demonstrated similar or better response rates with a more tolerable side-effect profile.³⁹ A retrospective analysis of 656 patients with a median age of 63 years examined gemcitabine and cisplatin (GC) versus MVAC⁴⁰ and found that pathologic complete response and OS were not significantly different

between the regimens. Although these regimens have not been compared prospectively in the neoadjuvant setting, both ddMVAC and GC are widely recommended and accepted options for patients.

In older patients, the toxicity of chemotherapy must be considered in terms of decreased marrow reserve and altered organ function. The backbone of therapy is treatment with cisplatin, which is reliant on adequate organ function—especially renal function. Carboplatin is not equivalent to cisplatin in bladder cancer and should not be used in perioperative chemotherapy.⁴⁰ Consensus criteria for cisplatin ineligibility are available to guide clinicians considering cisplatin therapy (Table 2).⁴¹ Whether based on cisplatin ineligibility or other vulnerabilities, many older patients do not receive NAC despite evidence supporting its role in improvement of disease control.⁴² However, data would suggest similar efficacy of platinum-based chemotherapy in a properly selected population.³⁷ Through patient discussion and geriatric-specific assessment, the rates of NAC may better align with the true goals and fitness of this population. If patients are considering curative-intent cystectomy, are eligible for cisplatin chemotherapy based on the criteria, and are generally fit for chemotherapy based on a geriatric health screen, then NAC should be offered. If patients are at risk for considerable toxicity with chemotherapy, based on a chemotherapy toxicity calculator, then they may opt for surgical resection and discussion of the role of adjuvant therapy based on the pathologic risk identified at the time of surgery.

For patients who do not receive NAC, adjuvant therapy is occasionally considered. Studies examining adjuvant chemotherapy for bladder cancer have been limited by failure to accrue patients, and are thus underpowered for any definitive recommendations. These trials failed to fully accrue partly because patients experienced difficulty in recovering completely from cystectomy in order to initiate adjuvant therapy in a timely manner. However, an updated systemic review and meta-analysis in 2013 that analyzed data from 9 trials with a total of 945 patients suggested an improvement in OS and DFS.⁴³ Finally, an observational NCDB study

demonstrated a potential OS benefit for adjuvant chemotherapy.⁴⁴ Currently, no prospective studies have compared neoadjuvant versus adjuvant chemotherapy. Despite the lack of strong evidence, it is reasonable to consider adjuvant chemotherapy in patients with lymph node involvement, or at least T3 status, who did not receive NAC but are felt to be cisplatin candidates after surgery. This is likely a small population of elderly patients, given the changes in health status that occur postoperatively in a population with less functional reserve. Therefore, NAC should be recommended whenever possible, although adjuvant cisplatin-based therapy is a reasonable option in older patients with MIBC, adequate organ function, sufficient functional status, and an interest in maximal curative-intent therapy.

Combined Modality Therapy

An alternative therapy with curative potential is TMT with a maximal TURBT, and RT with concurrent chemotherapy (CRT). Because bladder cancer is a disease of older patients, and patients may have additional cardiopulmonary conditions, there is a significant risk of perioperative morbidity and mortality associated with RC. Even at high-volume centers this risk is not trivial, with a 2.5% risk of mortality.^{45,46} High-level data for TMT and associated outcomes are lacking for a consistent radiation delivery method, radiosensitizer, and comparison groups. However, pooled analysis from the Massachusetts General Hospital and NCI cooperative group setting shows a 69% complete response rate and 5-year disease-specific survival rate of 71%.^{47,48} A multi-institutional retrospective evaluation of CRT or RC in patients aged ≥ 80 years treated in 1988 through 2015 showed that survival rates were similar for the 2 treatment groups, with disease progression primarily influencing survival.⁴⁹ Institutional knowledge and experience with TMT cannot be discounted, given that $<10\%$ of patients with MIBC receive RT.²² Yet experts in the field recognize the utility of TMT in patients who desire bladder preservation and/or are medically unfit for surgery.³⁵ Notably, there are particular disease features that limit the effectiveness of TMT, such as diffuse carcinoma in situ, a bulky primary tumor, bladder dysfunction, and hydronephrosis. In addition, the comparable outcomes were based on the fact that 10% to 15% of patients may still require salvage cystectomy.⁵⁰ Thus, patients who opt for this approach as an alternative to surgery with similar disease-control rates must understand that these data are most comparable in patients who are cystectomy candidates. One must also consider that postradiation cystectomy is feasible yet potentially more morbid than cystectomy alone.

When offered with curative intent, TMT is quite intensive. Use of RT in MIBC can be adapted to a

Table 2. Criteria for Cisplatin Ineligibility

Performance status	ECOG ≥ 2 ; KPS $\leq 60\%$ – 70%
Renal function	Creatinine clearance <60 mL/min
Hearing	Hearing loss of 25 dB at 2 contiguous frequencies; CTCAE grade ≥ 2
Neuropathy	CTCAE grade ≥ 2
Heart function	NYHA class $\geq III$

Abbreviations: KPS, Karnofsky performance status; NYHA, New York Heart Association.

palliative approach, which may be more applicable in an older patient population with identified vulnerabilities requiring therapy modification. Such considerations include a hypofractionated course of RT and a more tolerable radiosensitizer, such as gemcitabine or paclitaxel. In a population with competing comorbid conditions, this may offer disease control for those with shorter life expectancy overall. This modified therapy may improve progression-free survival and offer palliation of local symptoms; without direct comparison, we cannot comment on its efficacy compared with true TMT. A CGA and patient discussion are essential when deciding on surgical resection versus irradiation of a muscle-invasive tumor. Understanding local symptom control, long-term prognosis, and patients' values and concerns can help guide physicians and patients in this shared decision.

In the curative setting, cisplatin is the preferred radiosensitizer, yet many patients are cisplatin-ineligible. As stated earlier, there are clear criteria for cisplatin eligibility. Additional data support the use of mitomycin/5-FU, paclitaxel, and gemcitabine.^{51,52} These studies included older patients and had acceptable rates of toxicity. There is an ongoing prospective effort evaluating CRT with or without a checkpoint inhibitor, and will certainly contribute to the understanding of outcomes in this patient population (ClinicalTrials.gov identifier: NCT03775265). This trial allows for physician choice in radiosensitizer, and thus may be tailored to the heterogeneity of this patient population and potentially allow for enrollment of patients with demographics reflective of the true MIBC population.

Future Considerations

Improvements in proper assessment and support of patients with MIBC (such as preoperative physical therapy) may lead to better outcomes for these patients in the future. This includes ensuring that patients and their family and/or caregivers are able to participate in discussions of their goals and priorities and align these with the proposed treatment options. These discussions would be enhanced by trial data that are more applicable to the older patients seen most often in the clinic setting. Outcomes of trials inclusive of older patients should include measures beyond OS, as posited by many geriatric oncology experts.⁵³ Impairments identified through CGA place patients at higher risk for chemotherapy toxicity, further functional decline, increased mortality, and potentially burdensome healthcare utilization.^{54,55} Routinely communicating CGA results to oncologists has been shown to improve patient and caregiver satisfaction with the quality of communication in treatment planning.⁴ Data have shown that a CGA regularly results in an alteration of a treatment plan, yet how this affects

additional outcomes remains an area of scientific opportunity, with ongoing clinical trials examining this question.⁵⁶ As bladder cancer research expands, it is paramount to design research protocols allowing for altered organ function, comorbid conditions, and mildly reduced functional status if scientific understanding is to be applied to those most commonly affected by this important cancer. In addition, ongoing research into non-platinum-based perioperative therapy may also improve outcomes. Checkpoint inhibitors are approved for the treatment of metastatic bladder cancer based on survival benefits not previously seen in this population.⁵⁷ These agents have been shown to be generally safe and effective in the elderly, and may offer improved tolerability in vulnerable patients and a platinum alternative for those not otherwise eligible for perioperative therapy. Many ongoing trials are exploring the use of checkpoint inhibition based on early-phase studies that have shown promising results (ClinicalTrials.gov identifiers: NCT00362713, NCT02845323, NCT02365766, NCT02451423).⁵⁸ Further understanding of molecular and histologic subtypes of bladder cancer, and their potential prognostic and predictive outcomes, will improve discussions on the risks and benefits of therapeutic decisions.

Conclusions

Older persons with bladder cancer are a distinct and heterogeneous population requiring a tailored approach to care. Engaging in goals- and values-based care-planning discussions and assessing the geriatric health of a patient allow clinicians to determine a care plan that is most appropriate and possible. Older patients can be considered for NAC, RC, and TMT with the intent to cure their significant cancer. Additionally, through improved representation of this patient population in trials designed for patients with comorbid conditions, altered organ function, and decreased performance status, clinicians can engage in more informed discussions of the potential risks and benefits of therapy. To continue to advance the care of persons with bladder, or urothelial, carcinoma, we must advance the options for and representation of this large and growing population.

Submitted November 18, 2019; accepted for publication May 4, 2020.

Disclosures: Dr. Kessler has disclosed that she has received research funding from Astellas, Bristol Myers Squibb, and Pfizer. The remaining authors have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Elizabeth R. Kessler, MD, Division of Medical Oncology, University of Colorado School of Medicine, Mailstop 8117, 12801 East 17th Avenue, Aurora, CO 80045. Email: Elizabeth.kessler@cuanschutz.edu

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
2. Cancer Stat Facts: Bladder Cancer. National Cancer Institute. Bethesda, MD. Accessed May 4, 2020. Available at: <https://seer.cancer.gov/statfacts/html/urinb.html>
3. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. *J Urol* 2011;185:72–78.
4. Mohile SG, Epstein RM, Hurria A, et al. Communication with older patients with cancer using geriatric assessment: a cluster-randomized clinical trial from the National Cancer Institute Community Oncology Research Program. *JAMA Oncol* 2020;6:196–204.
5. Repetto L, Frattino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002;20:494–502.
6. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol* 2013;24:1306–1312.
7. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *J Clin Oncol* 2018;36:2326–2347.
8. Dotan E, Walter LC, Baumgartner J, et al. NCCN Clinical Practice Guidelines in Oncology: Older Adult Oncology. Version 1.2020. Accessed May 19, 2020. To view the most recent version, visit NCCN.org.
9. Luciani A, Ascione G, Bertuzzi C, et al. Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and vulnerable elders survey-13. *J Clin Oncol* 2010;28:2046–2050.
10. Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. *J Clin Oncol* 2014;32:19–26.
11. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* 2012;30:1829–1834.
12. Hurria A, Mohile S, Gajra A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol* 2016;34:2366–2371.
13. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 2012;118:3377–3386.
14. Hornor MA, Ma M, Zhou L, et al. Enhancing the American College of Surgeons NSQIP Surgical Risk Calculator to predict geriatric outcomes. *J Am Coll Surg* 2019;229:S121–122.
15. Chang SS, Bochner BH, Chou R, et al. Treatment of nonmetastatic muscle-invasive bladder cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology Clinical Practice guideline summary. *J Oncol Pract* 2017;13:621–625.
16. Froehner M, Brausi MA, Herr HW, et al. Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol* 2009;56:443–454.
17. Tan HJ, Saliba D, Kwan L, et al. Burden of geriatric events among older adults undergoing major cancer surgery. *J Clin Oncol* 2016;34:1231–1238.
18. Fonteyne V, Ost P, Bellmunt J, et al. Curative treatment for muscle invasive bladder cancer in elderly patients: a systematic review. *Eur Urol* 2018;73:40–50.
19. VanderWalde NA, Chi MT, Hurria A, et al. Treatment of muscle invasive bladder cancer in the elderly: navigating the trade-offs of risk and benefit. *World J Urol* 2016;34:3–11.
20. Sikic D, Wach S, Taubert H, et al. How octogenarians with bladder cancer are treated in a maximum-care hospital: the real-life experience. *Urol Int* 2017;98:262–267.
21. Caillet P, Canoui-Poitaine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. *J Clin Oncol* 2011;29:3636–3642.
22. Chang SS, Bochner BH, Chou R, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol* 2017;198:552–559.
23. Gupta NP, Goel R, Hemal AK, et al. Radical cystectomy in septuagenarian patients with bladder cancer. *Int Urol Nephrol* 2004;36:353–358.
24. Zebic N, Weinknecht S, Kroepfl D. Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. *BJU Int* 2005;95:1211–1214.
25. Elting LS, Pettaway C, Bekele BN, et al. Correlation between annual volume of cystectomy, professional staffing, and outcomes: a statewide, population-based study. *Cancer* 2005;104:975–984.
26. Baack Kukreja JE, Kieman M, Schempp B, et al. Quality Improvement in Cystectomy Care With Enhanced Recovery (QUICCER) study. *BJU Int* 2017;119:38–49.
27. Erlich A, Zlotta AR. Treatment of bladder cancer in the elderly. *Investig Clin Urol* 2016;57(Suppl 1):S26–35.
28. Yasui T, Tozawa K, Ando R, et al. Laparoscopic versus open radical cystectomy for patients older than 75 years: a single-center comparative analysis. *Asian Pac J Cancer Prev* 2015;16:6353–6358.
29. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. *Lancet* 2018;391:2525–2536.
30. Bochner BH, Sjoberg DD, Laudone VP. A randomized trial of robot-assisted laparoscopic radical cystectomy. *N Engl J Med* 2014;371:389–390.
31. Winters BR, Bremjit PJ, Gore JL, et al. Preliminary comparative effectiveness of robotic versus open radical cystectomy in elderly patients. *J Endourol* 2016;30:212–217.
32. Hussein AA, May PR, Jing Z, et al. Outcomes of intracorporeal urinary diversion after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *J Urol* 2018;199:1302–1311.
33. Tzelves L, Skolarikos A, Mourmouris P, et al. Does the use of a robot decrease the complication rate adherent to radical cystectomy? A systematic review and meta-analysis of studies comparing open with robotic counterparts. *J Endourol* 2019;33:971–984.
34. Tyson MD, Chang SS. Enhanced recovery pathways versus standard care after cystectomy: a meta-analysis of the effect on perioperative outcomes. *Eur Urol* 2016;70:995–1003.
35. Flaig TW. NCCN Guidelines updates: management of muscle-invasive bladder cancer. *J Natl Compr Canc Netw* 2019;17:591–593.
36. Porter MP, Kerrigan MC, Donato BMK, et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol* 2011;29:252–258.
37. Chau C, Wheeler M, Geldart T, et al. Clinical outcomes following neoadjuvant cisplatin-based chemotherapy for bladder cancer in elderly compared with younger patients. *Eur J Cancer Care (Engl)* 2015;24:155–162.
38. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–866.
39. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol* 2001;19:2638–2646.
40. Galsky MD, Pal SK, Chowdhury S, et al. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. *Cancer* 2015;121:2586–2593.
41. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol* 2011;12:211–214.
42. Gray PJ, Fedewa SA, Shipley WU, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol* 2013;63:823–829.
43. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol* 2014;66:42–54.
44. Galsky MD, Stensland KD, Moshier E, et al. Effectiveness of adjuvant chemotherapy for locally advanced bladder cancer. *J Clin Oncol* 2016;34:825–832.
45. Longo N, Imbimbo C, Fusco F, et al. Complications and quality of life in elderly patients with several comorbidities undergoing cutaneous ureterostomy with single stoma or ileal conduit after radical cystectomy. *BJU Int* 2016;118:521–526.
46. Novotny V, Hakenberg OW, Wiessner D, et al. Perioperative complications of radical cystectomy in a contemporary series. *Eur Urol* 2007;51:397–401; discussion 401–402.

47. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol* 2014;32:3801–3809.
48. Efstathiou JA, Shipley WU, Zietman AL. Reply to Neeraj Kumar Goyal, Manish Garg, and Apul Goel's Letter to the Editor re: Jason A. Efstathiou, Daphna Y. Spiegel, William U. Shipley, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol* 2012; 61:705–11. *Eur Urol* 2012;62:E42.
49. Boustani J, Bertaut A, Galsky MD, et al. Radical cystectomy or bladder preservation with radiochemotherapy in elderly patients with muscle-invasive bladder cancer: Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. *Acta Oncol* 2018;57:491–497.
50. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: an updated analysis of the Massachusetts General Hospital experience. *Eur Urol* 2017;71:952–960.
51. Graham K, Williamson A, Lamb C, et al. Comparison of two palliative radiotherapy regimens in poor prognosis patients with glioblastoma multiforme. *Neuro-oncol* 2012;14:61–62.
52. Choudhury A, Swindell R, Logue JP, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol* 2011;29:733–738.
53. Lichtman SM. Geriatric oncology and clinical trials. *Am Soc Clin Oncol Educ Book* 2015;35:e127–131.
54. Hamaker ME, Te Molder M, Thielen N, et al. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients – a systematic review. *J Geriatr Oncol* 2018;9:430–440.
55. Puts MT, Santos B, Hardt J, et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology. *Ann Oncol* 2014;25:307–315.
56. Caillet P, Laurent M, Bastuji-Garin S, et al. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. *Clin Interv Aging* 2014;9:1645–1660.
57. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376: 1015–1026.
58. Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. *J Clin Oncol* 2018;36:3353–3360.
59. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. *J Geriatr Phys Ther* 2006;29:64–68.
60. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
61. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 1992;41:237–248.
62. Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the Mini-Mental State Examination and the standardized Mini-Mental State Examination: implications for clinical practice. *Appl Nurs Res* 2000; 13:209–213.
63. Katzman R, Brown T, Fuld P, et al. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *Am J Psychiatry* 1983;140:734–739.
64. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–613.
65. Kaiser MJ, Bauer JM, Ramsch C, et al. Validation of the Mini Nutritional Assessment Short-Form (MNA-SF): a practical tool for identification of nutritional status. *J Nutr Health Aging* 2009;13:782–788.
66. Wilson MM, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr* 2005;82: 1074–1081.
67. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30: 473–483.
68. By the American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2019;67:674–694.
69. Mahony DO, Sullivan DO, Byrne S, et al. Corrigendum: STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2018;47:489.