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Evaluation and Management of the Geriatric Urologic Oncology Patient

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Abstract

The geriatric population presents a unique set of challenges in urologic oncology. In addition to the known natural history of disease, providers must also consider patient factors such as functional and nutritional status, comorbidities and social support when determining the treatment plan. The development of frailty measures and biomarkers to estimate surgical risk shows promise, with several assessment tools predictive of surgical complications. Decreased dependence on chronologic age is important when assessing surgical fitness, as age cutoffs prevent appropriate treatment of many elderly patients who would benefit from surgery. Within bladder, kidney and prostate cancers, continued refinement of surgical techniques offers a broader array of options for the geriatric patient than previously available.

Keywords

Elderly; frailty; comorbidity; risk assessment; geriatric assessment; competing risks; active surveillance; prostate cancer; bladder cancer; kidney cancer

Introduction

Nearly two-thirds of all solid tumors are diagnosed in patients over 65 years of age, and these patients comprise 70% of cancer deaths.¹ Urologic malignancies (prostate, bladder, and kidney) are the second, sixth, and ninth most common malignancies in the US, respectively.² Management of elderly urologic oncology patients differs from that of younger patients, as life expectancy is more influential in determining whether a given treatment is life-lengthening and whether treatment risks and potential complications are acceptable. Researchers have traditionally excluded geriatric patients, but an increasing number of recent studies have focused on the geriatric population, providing a stronger

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Compliance with Ethics Guidelines

Conflict of Interest

Maxim J. McKibben declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

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evidence base supporting treatment decisions in this challenging (and growing) population. In this review, we aim to review the literature regarding surgical risk assessment in the elderly, and discuss evaluation and management of elderly patients with prostate, bladder and kidney malignancies.

Surgical Risk Assessment in the Elderly

Historically, decisions regarding a patient's fitness for surgery were primarily determined by subjective assessment by the surgeon. This method has obvious shortcomings; for example, significant inter-physician variation in estimates of ten-year life expectancy may affect treatment choices.³ Several studies have demonstrated that healthy elderly patients are less likely to receive guideline-concordant oncologic screening or treatment due to chronologic age.^{4,5} Traditional risk assessment tools, such as the American Society of Anesthesiologists' Physical Status (ASA) classification system, the Charlson Comorbidity Index (CCI) and the Eastern Cooperative Oncology Group performance status (ECOG) system, were developed for accurate data collection but not to quantify risk and are also subject to inter-observer variability and lack prospective validation.⁶⁻⁸ These measures capture medical comorbidities, but not sub-clinical physiologic deficits, nutritional status and cognitive disability. Surgeons need a standardized, validated risk assessment tool for the elderly in order to appropriately counsel and choose treatments, both for healthy and high-risk elderly patients.

In recent years, multiple risk assessment tools for the elderly have been developed, including the Comprehensive Geriatric Assessment (CGA) and the Preoperative Assessment of Cancer in the Elderly (PACE). The CGA has been validated to identify treatable health problems that may produce better health outcomes.⁹ In the surgical setting, the CGA has been found to be more predictive than the ASA in predicting one-year mortality and post-surgical disposition (home versus nursing facility), but may not accurately predict complications.¹⁰ The PACE uses elements of the CGA to evaluate comorbidities, physical activity, psychological state, social support and other metrics. Many PACE elements were found to be predictive of post-operative complications in a study of 460 patients over 70 years of age.¹¹ While geriatric assessments can be useful, a drawback is the significant time commitment in the busy preoperative clinic setting.

An additional element of geriatric assessment includes frailty. Frailty represents a patient's ability to withstand physiologic stressors and is being increasingly studied as a predictor of perioperative outcomes. The Fried frailty criteria assesses weight loss, decreased grip strength, exhaustion, low activity and slowed walking speed, all of which may underlie decreased reserve in multiple organ systems.¹² The Fried assessment can be performed in approximately 10 minutes, and yields a score from 0 (not frail) to 5 (frail).¹³ The relationship between frailty and outcomes were examined in a study of 594 patients 65 years and older undergoing elective surgery.¹³ Those patients who were "intermediately frail" (2-3) or "frail" (4-5) had significantly worse perioperative outcomes, including complications, length of stay (LOS) and discharge to assisted living or skilled nursing facilities.¹³ Similarly, in a study of 189 patients undergoing major abdominal surgery (primarily urologic), patients who scored "intermediately frail" or "frail" were more likely to

experience postoperative complications.¹⁴ Frailty provides a fast, simple measure of physiologic reserve that appears to predict perioperative risk. Currently, the role of frailty in the surgical setting remains limited, but this area should continue to evolve.

Prostate Cancer

Overview

Prostate cancer (PCa) is the most commonly diagnosed malignancy in men, with annual incidence and mortality of about 230,000 and 30,000, respectively. Median age at diagnosis is 66, and median age of death is 80 years old, making it a common chronic malignancy of the elderly.² In young, healthy men, PCa screening, diagnosis and treatment are controversial due to high rates of indolent cancer detection and treatment with attendant morbidity. Advanced age presents other challenges for a provider.

Prostate cancer screening

Prostate-specific antigen (PSA) screening was approved by the Food and Drug Administration (FDA) in 1994 with the intent to detect PCa early and thus reduce the stage upon diagnosis. Recently, PSA screening has been under intense scrutiny for potential over-diagnosis of PCa and treatment of indolent disease. In 2012, the United States Preventive Services Task Force (USPSTF) recommended against the use of PSA screening for PCa based on the potential morbidity of treatment and the often indolent nature of low-grade PCa.¹⁵ Current AUA guidelines recommend shared decision-making regarding PSA screening in men aged 55–69, but not routine screening in men more than 70 years old, or those with less than 10 to 15 year life expectancy.¹⁶ A study using National Health Interview Surveys found that 41% of men 75 years or older with predicted life expectancy of less than 9 years were PSA screened in 2005 and 43% were screened in 2010, despite the 2008 USPSTF recommendation against screening in men older than 75 years.^{17,18} Discussion of the potential disadvantages of screening occurred with fewer than 25% of the patients.¹⁷ Compiling data from the U.S. Department of Veterans Affairs, another study revealed that 56% of men 70 years or older had PSA testing, and 35% of men 85 years or older also received the test, with no decrease in testing among men in poorer health.¹⁹ To realize the benefit of early detection of PCa, a life expectancy of ten or more years is required.²⁰ These studies suggest prevalent over-screening of the elderly, resulting in unnecessary anxiety and treatment.

Active surveillance

An increasingly utilized management option for low-risk PCa is active surveillance (AS). AS involves closely monitoring a patient's condition, but waiting to treat until clinical changes indicate a worsening disease condition. According to National Comprehensive Cancer Network (NCCN) guidelines, the ideal AS candidate is a man with PSA-detected PCa, a low volume Gleason score of 3+3, PSA<10 ng/mL, and PSA density <0.15 ng/mL/g, whose life expectancy is 10–20 years (very low-risk). For this patient, NCCN recommends *only* AS.²¹ AS is also recommended for low risk and some intermediate risk patients, especially as life expectancy decreases. A typical AS protocol includes a serum PSA every six months or less, an annual digital rectal exam (DRE) and confirmatory biopsy no more

than annually.²¹ Meanwhile, the decision for continued AS versus treatment is continually revisited.

For elderly patients considering treatment of PCa, the question of life expectancy and competing risks must be addressed. The association between mortality of men diagnosed with localized PCa and CCI was retrospectively evaluated.²² At 10 years, men with a CCI of 0 had a non-PCa mortality of 17% versus a non-PCA mortality of 74% in men with CCI of 3+.²² Many elderly men with newly diagnosed PCa have a life expectancy of less than ten years, so watchful waiting may be an option. However, men closer to age 65, elderly men in excellent health or men with intermediate or high-risk PCa should consider definitive treatment.

Prostate cancer treatment

Once diagnosed with PCa, elderly men are more likely to have an aggressive or metastatic disease. According to the Surveillance, Epidemiology and End Results (SEER) program, men older than 75 comprise 26% of overall Pca cases, but 52% of metastatic cases, and 47% of all PCa deaths.²³ In a study of men 70 years or older with localized PCa, 46.7% of men with Gleason score of 5–7 and 72.7% of men with a Gleason score of 8+ received suboptimal treatment.²⁴

Determining which men would benefit from treatment depends not only on chronologic age, but rather overall health. The International Society of Geriatric Oncology (SIOG) compiled consensus guidelines for the management of elderly men with PCa.²⁵ Using a combination of comorbidity, assessment of activities of daily living and nutrition status, they recommend classifying men into 4 groups; “healthy;” “vulnerable;” “frail;” and “terminal.” Men in the “healthy” and “vulnerable” groups (after intervention for any reversible problems) should be offered the standard treatment, regardless of chronologic age.²⁵ Another study of 770 men 70 years and older with low risk PCa (Gleason 6, PSA <10, T1–2a) revealed that 25% underwent radical prostatectomy (RP), 33% had external beam radiation, and 42% underwent observation, although 34% eventually received therapy.²⁶ There were no significant differences in age, comorbidities, or clinical stage between the cohorts. Men in the observation group had significantly decreased biochemical recurrence-free survival and overall survival (OS) compared to the RP group, suggesting a possible benefit of treatment in this elderly cohort.

The gold standard surgical treatment for clinically-localized PCa is RP. In elderly patients, RP remains a valid surgical option, as refinements in technique (nerve-sparing) and minimally-invasive approaches (robotics) may decrease morbidity. A clinically-matched retrospective cohort analysis comparing patients greater than 70 years of age to those less than 70 found no difference in pathologic or oncologic outcomes, and no difference in five-year OS.²⁷ RP demonstrated improved life expectancy and quality-adjusted life expectancy compared to watchful waiting in men up to 75 years of age in cases of a moderately-differentiated disease, and up to 80 years in poorly differentiated disease.²⁸ The most common side effects of RP are erectile dysfunction and urinary incontinence, and increased age is an independent predictor of both.^{29–31} Although associated with increased treatment-

related morbidity in the elderly, RP should be considered in selected healthy elderly men based on life expectancy rather than chronologic age.

Radiotherapy is another definitive treatment option for localized PCa. External beam radiation therapy (EBRT) with adjuvant androgen deprivation (ADT) has demonstrated improved five- and eight-year survival in patients with T3/T4 disease, and no differences in survival among those with T1/T2 disease.³² As with RP, age was an independent predictor of worse treatment-related urinary, bowel and sexual symptoms.³⁰ The SIOG task force recommends combined EBRT + ADT for intermediate and high risk elderly PCa patients with low comorbidity burdens.³³ Brachytherapy is indicated in men with low risk PCa with a small gland and minimal lower urinary tract symptoms; however, long-term outcomes in elderly men treated with brachytherapy are poorly studied. Therefore, no consensus guidelines exist.³³

ADT is the first-line treatment for metastatic PCa. In patients with a PSA >50 and a PSA doubling time of less than 12 months, there was a modest survival benefit to ADT alone, but, otherwise, ADT demonstrates no survival benefit.³⁴ Potential side effects of ADT include osteoporosis and bone fractures, diabetes and cardiovascular events, all of which may be amplified among older men, emphasizing the need to counsel patients regarding these risks when initiating treatment.²⁵ Baseline bone mineral density should be tested and at-risk men could consider therapy with bisphosphonates or other agents. A prospective observational study examined the health-related quality of life (HRQoL) in men 75 years or older with PCa who initiated ADT, finding a significant decrease in sexual activity and function at three to six months, but otherwise no change in HRQoL.³⁵

Bladder cancer

Overview

Bladder cancer (BCa) is the sixth most commonly diagnosed malignancy in the US, with an incidence of about 75,000 new cases and 16,000 deaths annually.² BCa is a disease of the elderly, with the median age of diagnosis being 73 years, the median age of death at 79 years and peak incidence occurring at 85 years of age or later.^{2,36} Treatment of low- and high-grade non-muscle invasive bladder cancer in the elderly mirrors treatment of younger patients: local tumor control using trans-urethral resection (of a bladder tumor) (TURBT) and intravesical agents such as mitomycin C or bacillus Calmette-Guérin (BCG) to reduce the risk of recurrence.³⁷

Approximately 20% of patients will initially present with muscle-invasive BCa (MIBC), and even with aggressive treatment, five year survival remains approximately 50%.^{38,39} Radical cystectomy (RC) with pelvic lymphadenectomy is the gold standard treatment for MIBC, but this morbid surgery has historically been avoided in elderly patients. Increasing evidence suggests that with proper pre-operative evaluation and risk stratification, appropriate elderly patients likely benefit from this surgery. Alternatives to radical surgery, such as bladder-sparing trimodal therapy (TMT), are also available.

Radical cystectomy

In younger patients with MIBC, RC is the preferred treatment, with clear survival benefit when compared to TURBT, chemotherapy and radiation.⁴⁰ Currently the median age at RC is 69 years.⁴¹ RC is feasible and appropriate in selected patients older than 80 years, as demonstrated by multiple studies showing similar cancer-specific survival (CSS) compared to younger patients,^{42,43} and improved CSS and OS compared to age-matched patients.⁴⁴ However, elderly patients are far less likely to receive aggressive treatment. A population-based study of MIBC found that 55% of patients aged 55–59 years underwent RC, compared to only 4% of patients 85 or older, and 9% of healthy patients 85 with an ASA of 0–2.⁴⁵ Elderly patients are also more likely to have worse pathologic findings and pathologic upstaging after RC.⁴⁶

The reluctance to refer or perform RC in the elderly may be related to fear of complications. A retrospective review of perioperative complications comparing octogenarians to younger patients undergoing RC at a single institution found no difference in the rate of overall, major or minor complications, although the older cohort had more neurological complications.⁴⁷ The complication rate in the elderly following RC has been studied extensively, with heterogeneous results. Age appears to be associated with longer LOS and worse nighttime leakage after neobladder construction, but other associations are conflicting.⁴⁸ Overall 90-day mortality following RC in all patients is ~3.9% and varies significantly with age; 9.2% at older than 80 compared to 2% in those younger than 69 years.^{41,49} Referral of elderly RC candidates to tertiary centers is encouraged, as these centers demonstrate superior outcomes and provide access to multidisciplinary care.⁵⁰ An institutional minimum of ~10 RCs per year appears adequate, although this is debatable. The majority of these data are gleaned from open RC series with data regarding robot-assisted RC (RARC) outcomes being less mature. Small series in octogenarians undergoing RARC have demonstrated outcomes and complication rates comparable to open RC, possibly with less blood loss and shorter LOS.^{51,52}

The most common urinary diversion following RC is the ileal conduit, both in the young and old.⁵³ While continent diversions are feasible in select older patients, an ileal conduit is relatively simple to construct and requires less manual dexterity and maintenance for a patient than a continent diversion, with lower rates of metabolic disturbance.⁵⁴

Given the morbid nature of RC, risk stratification among patients with MIBC is critical. Preoperative albumin levels may be a surrogate marker for perioperative outcomes following RC⁵⁵, supporting perioperative nutritional optimization. Sarcopenia, or degenerative loss of skeletal muscle mass associated with aging, is also being actively researched as a predictive tool for post-operative outcomes. Sarcopenia can be easily measured by MRI or CT, which are routinely obtained for staging purposes in oncologic settings.⁵⁶ A recent series of 205 MIBC patients who underwent RC demonstrated worse CSS and OS in patients with sarcopenia compared to those without.⁵⁷ Sarcopenia has also been shown to be an independent predictor of major complications among women following RC.⁵⁸ Albumin levels and sarcopenia represent clinical markers of surgical risk that may be amenable to pre-operative optimization, but data regarding improved outcomes with

nutritional supplementation or exercise in the urologic oncology patient are currently lacking.

Chemotherapy

Neoadjuvant chemotherapy (NAC) with cisplatin and gemcitabine (GC) is currently the gold standard chemotherapeutic treatment for MIBC, with patients receiving NAC having a 5% survival advantage compared to those treated with RC alone.⁵⁹ A recent analysis suggests that about 20% of patients undergoing RC are now receiving NAC.⁶⁰ Exclusion criteria for cisplatin-based chemotherapy include an ECOG ≥ 2 , a GFR ≤ 60 ml/min, significant hearing loss or neuropathy, and NYHA class III heart failure.⁶¹ These conditions are more prevalent in the elderly, precluding many from receiving treatment. Much active research into alternative regimens to GC excludes older patients, and no alternative regimens have robust data yet.⁶¹

Bladder-sparing treatment

Trimodal therapy (TMT) with maximal TURBT followed by chemotherapy and radiation, has demonstrated superior outcomes compared to these modalities individually. The ideal patient for TMT is one with focal MIBC that can be completely resected, no high risk features, sufficient renal function to tolerate cisplatin, and who wishes to avoid RC.³⁸ A recent review of TMT literature suggests a 5-year OS of 48–60% in patients treated with TMT (with 25% rate of salvage RC).⁶² Five-year OS in MIBC patients treated with RC is 62–68%,⁶³ with 5-year CSS as high as 83.5% in patients with MIBC without high risk features.⁶⁴ In a small retrospective study of elderly patients undergoing TMT, there was a 61% and 71% OS and DFS at three years.⁶⁵ Survival comparisons between RC and TMT are difficult because there are no randomized trials and significant selection bias exists between the groups. In the elderly, bladder-sparing protocols do not typically include cisplatin, with many receiving TURBT alone or TURBT plus radiation, with poor CSS compared to RC.⁶⁶

Renal cell carcinoma

Overview

Renal cell carcinoma (RCC) is the ninth most common malignancy in the US, with about 64,000 new cases and 14,000 deaths annually. Median ages at diagnosis and death are 64 and 71 years, respectively.² The majority of tumors are detected incidentally at an early stage due to increased use of CT and ultrasound, and most have an organ-confined disease that can be definitively treated and cured with extirpative therapy, with a 91.8% five-year OS.² Radical nephrectomy (RN) and partial nephrectomy (PN) have lower morbidity than RC, but remain potentially morbid for elderly patients without significant physiologic reserve, especially those with pre-existing renal dysfunction. Other treatment modalities such as AS and cryoablation have emerged as potential options for elderly patients wishing to avoid traditional surgery.

Active surveillance

Over 50% of RCCs are now incidentally detected as small renal masses (SRMs), defined as solid, enhancing lesions ≤ 4 cm in maximal diameter detected on MRI or CT.^{67,68} However,

early detection and treatment with radical or partial nephrectomy have not resulted in a corresponding reduction in RCC mortality,^{2,69} which suggests treatment of a predominantly indolent process. In elderly patients with limited life expectancy, the question of whether or not to treat a SRM is paramount.

SRMs are amenable to AS in patients with limited life expectancy for several reasons.⁷⁰ First, most SRMs have low malignant potential, with 15–20% showing benign histology. Of the remaining ~80%, only about 25% have aggressive pathologic characteristics.^{71,72} Second, in elderly individuals, the risk of death from RCC is low compared to the risk of death from non-RCC causes. In patients older than 75 years of age with a SRM, surgical treatment did not improve survival over AS alone.⁷³ Using SEER data, a competing risks model in patients 66 years or older with clinically-localized RCC was constructed based on age, tumor size, race, gender and CCI to determine who would benefit from surgery.⁷⁴ They found that patients with localized, node-negative kidney cancer had a low risk of cancer-specific death compared to overall risk of death, with increased cancer-specific death to overall risk of death ratio increasing with a higher CCI. Third, AS does not preclude definitive treatment in the future, with no effect on outcomes.⁷⁵

Growth kinetics of SRMs vary significantly, but average about 0.3 cm per year in a linear fashion. Approximately one third of lesions may demonstrate no growth over several years of follow-up; however, a tumor's growth rate cannot accurately predict malignancy.^{76,77} Progression to a metastatic disease during AS is rare, occurring in 2.1% of patients in a pooled analysis, and risk factors for progression include an age greater than 75 years, an initial tumor diameter larger than 4.1 cm and a growth rate of 0.8 cm/year or more.⁷⁸

Though lacking Level 1 evidence, AS represents a reasonable management option in selected elderly and/or frail patients with SRMs. AUA guidelines suggest cross-sectional imaging six months after initiation of AS to determine baseline lesion growth rate, renal biopsy for those considering extirpative therapy, and annual chest x-ray to evaluate for pulmonary metastases in those with biopsy-proven RCC.⁷⁹ Though there are no strict guidelines for intervention, criteria used in the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry suggest that linear growth of more than 0.5 cm annually, a symptomatic mass, or size 4 cm or larger should prompt intervention.⁸⁰ In a pooled analysis of patients undergoing active surveillance, 45.4% of patients underwent delayed intervention after a median of 30.5 months of follow-up, though intervention was due primarily to patient preference rather than tumor growth.⁷⁸

Surgical management

RN has long been the gold-standard treatment for RCC. However, with increased diagnosis of incidental SRMs, nephron-sparing surgery (NSS) such as PN has emerged. AUA guidelines currently recommend PN for T1 lesions with favorable anatomy.⁸¹ The advantages of PN over RN include avoidance of chronic kidney disease,⁸² decreased cardiovascular risk,⁸³ and improved OS.⁸⁴ In the recent European Organisation for Research and Treatment of Cancer (EORTC) study randomizing 541 patients with 5cm or less of a solitary renal masses to either RN or PN, there was an unexpected small, but significant, ten-year survival advantage in the RN arm (81.1% v. 75.7%, $p=0.03$). Critics of the study cite

heterogeneity between the two groups as an explanation for the unexpected results, and when adjusted, the significant survival advantage of RN disappears. While flawed, the study provides Level 1 evidence that NSS does not necessarily provide advantages over RN in all patient groups. Supporting this idea is a propensity-based matched analysis using SEER-Medicare data comparing other-cause mortality (OCM) after PN and RN. While there was an OS advantage for PN versus RN, in patients 75 years or older and/or two or more comorbid conditions, there was no difference in OCM.⁸⁵ For patients in whom the long-term benefits of PN are unclear, such as the elderly, and in whom surgery is indicated, RN may be at least an equivalent option.

Perioperative complications are generally higher following PN than RN, with major (Clavien Grade 3–4) complication rates for PN ranging from 6.4% for low-complexity renal masses to 21.9% for high complexity masses.^{86,87} Based on age >75 and CCI>2, 1,092 patients who underwent PN or RN were divided into high and low risk categories. The high risk group had a 1.9 times more overall complications compared to the low risk group when looking at PN and RN in aggregate, but there was no difference when comparing PN to RN. Risk status rather than surgery type appeared to be the major driver of complications.⁸⁸ Evaluation of competing risks in elderly patients is critical when determining surgical modality, as complications may have lasting consequences.

Minimally-invasive techniques for both RN and PN have largely supplanted open surgery for localized RCC, with less post-operative pain, shortened LOS, and equivalent oncologic outcomes.⁸⁹ Surgeons at high-volume PN centers are attempting maximal renal preservation with early vascular unclamping, or even zero-ischemia, though these patients are highly selected and the approach may not be applicable to the elderly population.⁹⁰ Other nephron-sparing options include cryoablation, radiofrequency and thermal ablation, providing important alternatives for patients ineligible for surgery. Ablation is performed either percutaneously or laparoscopically, with the advantages of lower complication rates, faster recovery, no ischemia and potential for outpatient management.⁹¹ While long-term oncologic data using ablative techniques are sparse, midterm outcomes are promising. A retrospective study of patients with solitary T1a tumors who underwent partial nephrectomy or RF ablation showed no difference in five year OS, CSS or recurrence between the cohorts.⁹²

Conclusions

Increasing life expectancy has seen an attendant rise in urologic malignancies in the elderly. Advanced knowledge regarding the natural history of urologic malignancies has led to an evolution of the management of these malignancies, with increased utilization of AS, especially in PCa and RCC. Surgical management is also being refined, with minimally-invasive options in a majority of the urologic oncology conditions being applied. In the elderly, competing risk analysis is essential in determining a patient's prognosis, both independent of and with a given urologic malignancy. Refined frailty measures and geriatric assessments can better characterize a patient's physiologic reserve, and nomograms provide an evidence base for our treatment recommendations. The provider should engage in shared

decision-making via open dialogue with the patient to discuss the potential burden of treatment versus the risks of AS or expectant management.

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