Management of Prostate Cancer in the Elderly

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KEYWORDS

• Prostate cancer • Elderly • Geriatric • Localized • Metastatic • Oncology • Surgery • Radiation

KEY POINTS

- The impact of prostate cancer in the elderly depends largely on the aggressiveness of the disease and the time horizon over which prostate cancer morbidity and mortality may occur.
- Comorbidity and quality-of-life concerns are the key considerations when deciding whether treatment is necessary or the type of treatment modality to be used in prostate cancer in the elderly.
- In the elderly with metastatic prostate cancer, exercise and vitamin D serve to improve bone health and functional status to offset complications from hormonal therapy.

INTRODUCTION

Because of the stabilization of birth rates, better medical care, and improved living standards, the number of older persons worldwide tripled in the latter half of the twentieth century; this number is projected to triple again in the next 50 years.[1] In the United States, the proportion of the population aged older than 65 years has increased by 15% in the last decade alone.[2] Prostate cancer, currently the most incident cancer and the second highest cause of cancer death among men in the United States, is notably diagnosed in the later years of life.[3] The incidence of clinically detected prostate cancer in the United States between 2009 and 2011 was noted to be 1 in 304 for men younger than 49 years, 1 in 44 for men aged 55 to 59 years, 1 in 16 for men aged 60 to 69 years, and 1 in 9 for men 70 years and older.

Despite concerns regarding overdiagnosis of indolent disease, advanced and lethal prostate cancer are also more likely among older men.[4–6] The median age of death

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Clin Geriatr Med 32 (2016) 113–132

http://dx.doi.org/10.1016/j.cger.2015.08.001 **geriatric.theclinics.com**

0749-0690/16/$ – see front matter

from prostate cancer is 77 years, with men surviving to 90 years of age having a nearly 1 in 5 probability of dying of prostate cancer (Fig. 1). Although age definitions for the geriatric population may differ, it is clear that the prevalence of prostate cancer increases with age and older men are disproportionately affected by lethal prostate cancer. The authors discuss here the impact of prostate cancer and its treatment in the elderly and review the best available evidence with which clinicians may formulate management strategies.

CLINICALLY LOCALIZED PROSTATE CANCER

Deciding Who Needs to be Treated

Autopsy studies show that the prevalence of indolent prostate cancer is high and that this increases with age.[7] In 1997, Johansson and colleagues[8] reported on a 15-year follow-up of a Swedish cohort of 300 men with rectally detected early stage prostate cancer who were generally older than 60 years, finding a similar adjusted survival rate among men who received treatment and those who did not. These findings prompted controversy over the necessity for localized prostate cancer to be treated. With longer follow-up, however, it seems that the time horizon for disease progression is a critical factor. From follow-up reports at the 20- and 30-year intervals of the Johansson series, it has become apparent that local tumor progression and aggressive metastatic disease may occur in the long-term, even for men considered low risk at diagnosis.[9,10]

Two other natural history studies reported by Albertsen and colleagues[11] (767 men aged 55–74 years) and Cuzick and colleagues[12] (2333 men with a maximum age of 76 years) identified the Gleason score and prostate-specific antigen (PSA) as predictors

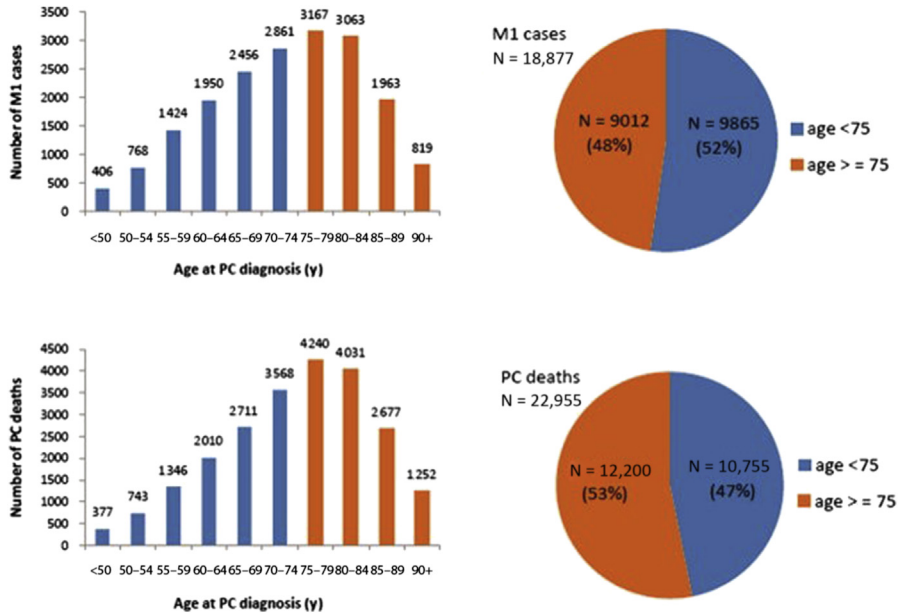

Fig. 1. The contribution of different age groups to the pool of patients who had prostate cancer (PC) with metastatic disease (M1) at diagnosis and PC deaths is illustrated. (*From* Scosyrev E, Messing EM, Mohile S, et al. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer 2012;118(12):3065; with permission.)

of disease progression. Albertsen and colleagues[11] also reported that men with Gleason 8 to 10 prostate cancer were highly likely to die of prostate cancer within the first 10 years of cancer diagnosis. The prognostic factors of serum PSA, biopsy Gleason score, and clinical stage have since been validated as prognosticators for prostate cancer and are commonly grouped using the D'Amico risk classification system into low, intermediate, and high risk.[13]

The time horizon for morbidity and mortality to occur, or the life expectancy, thus, seems more important than chronologic age in dictating treatment of localized disease and, regardless of age, men with low-risk prostate cancer and a life expectancy of greater than 10 to 15 years and men with intermediate- to high-risk prostate cancer and a life expectancy of 5 to 10 years should be considered candidates for treatment. In the Scandinavian randomized trial on radical prostatectomy versus watchful waiting in prostate cancer (SPCG-4), which found a benefit with prostatectomy with a 44% relative risk reduction in deaths, the benefits were maximal in men younger than 65 years, illustrating the point that treatment advantages are apparent to those with a longer life expectancy.[14] On the contrary, the Prostate Intervention versus Observation Trial (PIVOT), randomizing men to radical prostatectomy or active surveillance, could not detect an overall survival benefit with prostatectomy, though a small advantage was seen in the intermediate-risk subgroup; this may be partly attributed to the fact that 40% of men in both arms died by the study conclusion date at 10 years, raising concerns that the group had an overall lower life expectancy than normal.[15] It is important to note that SPCG-4 was conducted in the pre-PSA screening era when most tumors, though localized, were clinically T2 and digitally palpable, whereas in PVIOT, most tumors were clinically T1c, impalpable, and detected by PSA screening, suggesting that with sufficient interval to overcome the lead time over the SPCG-4 cohort, the PIVOT group may have demonstrated a larger, detectable magnitude of benefit. Furthermore, in SPCG-4, though men older than 65 years did not have a survival advantage, they did experience a 32% relative risk reduction for the development of metastasis; in PIVOT, an overall 60% risk reduction in the development of bone metastasis was observed. In a paradigm of localized disease preceding metastasis and metastasis preceding death, this again emphasizes the chronologically distant impact of prostate cancer treatment.

The most favorable outcome for the elderly man can, thus, only be attained through balancing life expectancy and disease aggressiveness. In a decision-analytic Markov model, Alibhai and colleagues[16] showed that treatment of men up to 75 years old with moderately differentiated prostate cancers, and men up to 80 years old with poorly differentiated prostate cancers, produced gains in both life expectancy and quality-adjusted life expectancy.

Estimating Life Expectancy

Life-expectancy estimation is discussed by Li and colleagues, Dale and colleagues and, Wingfield and colleagues.[17–19] In short, according to the 2010 period actuarial life table published by the Social Security Administration, the average US man at 70 years of age has a 14-year life expectancy and at 80 years of age, an 8.1-year life expectancy.[20] Although national actuarial estimates alone remained the best estimators of life expectancy, predictive models co-opting a range of comorbidities may be more consistent and accurate than physician estimates.[21]

The competing risk of death conferred by comorbidities has been addressed elegantly by Daskivich and colleagues[22] in a report from the Prostate Cancer Outcomes Study, a cohort of 3183 men with localized prostate cancer. When men were classified by comorbidity count, older men were found to have a higher absolute

risk of other-cause mortality at the 14-year follow-up, with a proportional increase in other-cause mortality with the number of comorbidities present (Fig. 2). On the other hand, a higher D'Amico risk status was associated with a higher likelihood of dying of prostate cancer. One criticism of the study is the equal analytical weightage given to debatably less serious comorbidities, such as arthritis, inflammatory bowel disease, or Crohn disease, as more life-threatening comorbidities, such as stroke and myocardial infarction. Nonetheless, this study demonstrates that the number of comorbidities matter; their impact increases with age; and that these should be accounted for in clinical decision making around definitive therapy versus active surveillance in older men.

Beyond comorbidity, frailty is often subjectively assessed by clinicians using the eyeball test. The extent of independence in daily activities predicts survival in the elderly.[23] Cognitive impairment is also linked to shorter survival as well as worse postoperative outcomes, including complications and longer hospital stays.[23,24] The degree of frailty, when comprehensively measured by the geriatric status scale including independence in activities of daily living, bowel/urinary continence, and the presence of cognitive impairment, has also been found to impact survival.[25] Frailty and poor survival are in turn associated with poor nutritional status.[26,27] Incorporating these factors, the International Society of Geriatric Oncology Prostate Cancer Task Force has recommended that

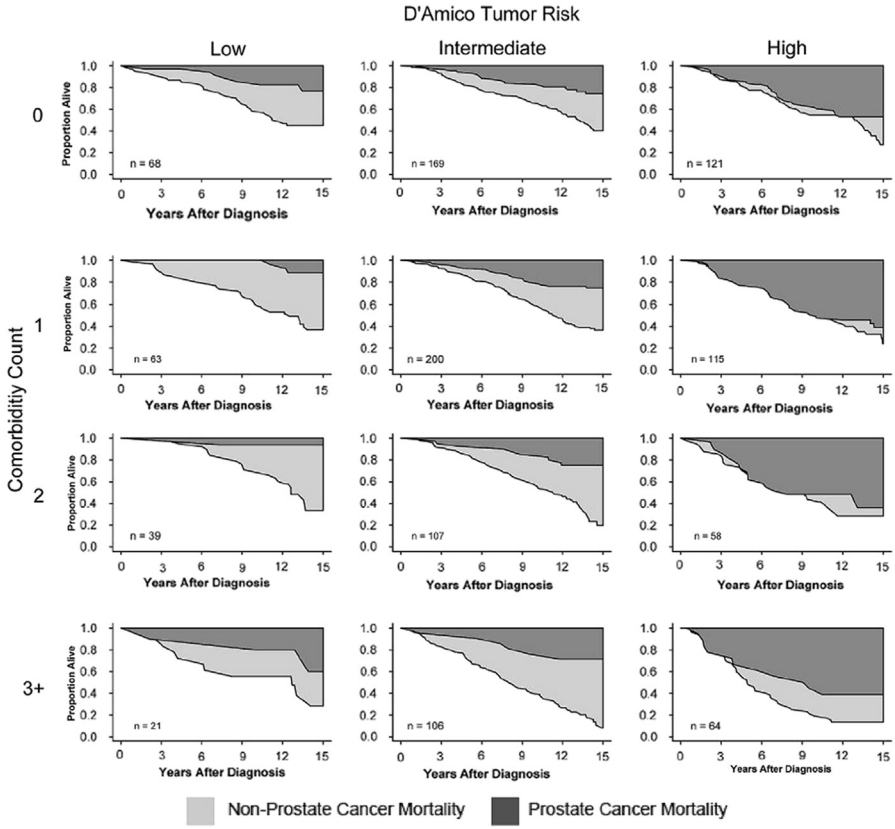

Fig. 2. Mortality by comorbidity count and D'Amico risk status in men aged greater than 70 years. (*From* Daskivich TJ, Fan KH, Koyama T, et al. Prediction of long-term other-cause mortality in men with early-stage prostate cancer: results from the Prostate Cancer Outcomes Study. Urology 2015;85(1):98; with permission.)

elderly men with prostate cancer undergo a comprehensive assessment for comorbidities using the cumulative illness score rating–geriatrics (CISR-G), dependence status, and nutritional status to determine whether they undergo oncologic treatment (Fig. 3).[28]

Ultimately, the aim of treatment of prostate cancer in the elderly man is to maintain a life free of the complications of local progression or systemic disease and avoiding prostate cancer–related mortality by obtaining oncological control *when necessary*. Solely relying on physician estimates may lead to an underestimation of life expectancy with resultant undertreatment of even high-risk categories of prostate cancer.[29] The use of geriatric assessment tools may better stratify elderly men for treatment or observation and reduce risks of therapy-associated morbidity.[30]

Expectant Management: Watchful Waiting or Active Surveillance?

Watchful waiting is a strategy of clinical observation, with interventions reserved for symptoms when they develop.[31] With this strategy, it is generally accepted that local progression and/or metastases may develop at some point and that these will be treated with palliative measures. Active surveillance, on the other hand, is a proactive process of close monitoring for disease progression over time with the aim of deferring but preserving the option for definitive therapy. Traditional surveillance regimes include men with low-risk cancer and recommend at least one rebiopsy within 12 to 18 months with subsequent biopsies dependent on PSA or other clinical triggers.[32] In a large cohort of men undergoing active surveillance, Klotz and colleagues[33] reported that 75.7% of men avoided intervention at 5 years, 63.5% at 10 years, and 55.5% at 15 years, with a metastasis rate of 2.8% and a prostate cancer–related mortality rate of 1.5%.

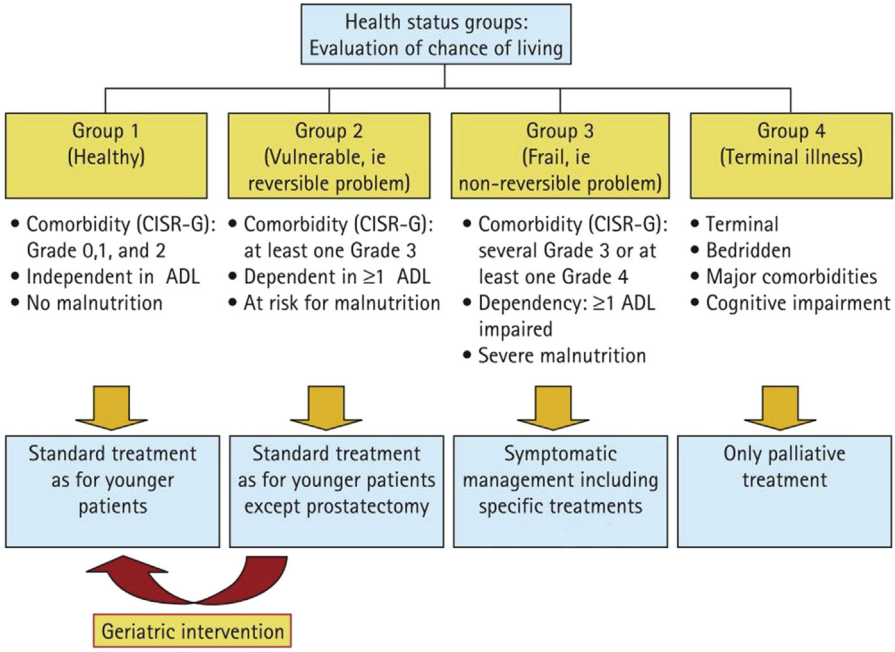

Fig. 3. A decision tree proposed by the International Society of Geriatric Oncology for treating patients with localized disease based on comorbidity and functional status. ADL, activities of daily living. (*From* Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int 2010;106(4):464; with permission.)

Watchful waiting is, thus, considered suitable for elderly men with organ-confined prostate cancer when life expectancy is shorter than 5 to 10 years as they are unlikely to experience symptoms of disease progression or to die of prostate cancer.[8] Active surveillance is considered more appropriate in older men with prostate cancer when the disease is low risk and life expectancy is greater than 10 to 15 years.

However, both expectant management strategies are hampered by prostate cancer risk underclassification resulting from the use of random biopsies with high rates of sampling error. This underclassification, whereby intermediate- or high-risk cancers are erroneously classified as low risk, has been observed at a rate of 30% to 50% in prostatectomy studies, which, by avoiding sampling error, are the reference standard for accurate cancer risk classification.[34] In active surveillance series following men with biopsy-proven low-risk prostate cancer, up to 28% have a Gleason score upgrading at the first surveillance rebiopsy at 12 to 18 months, which is, arguably given the short time frame, a result of underclassification in the first place.[32] In elderly men older than 65 years, more pathologic upgrading and upstaging occurred compared with younger men in the Prostate Research International: Active Surveillance study.[35] Delaying treatment in such men with underclassified cancer results in adverse outcomes.[36] Indeed, in the Klotz series, those eventually subjected to treatment had post-treatment biochemical recurrence rates as high as 53%, highlighting the limitations of the current selection criteria.[33]

Furthermore, periodic rebiopsies during active surveillance are significant sources of morbidity with attendant risks of bleeding and urosepsis that may be amplified in the elderly.[37] Staging saturation biopsies may improve the accuracy of risk classification before embarking on active surveillance, but there are no long-term data to support reducing the number of subsequent biopsies during the course of active surveillance.[38] Similarly, outcomes of modern protocols using multi-parametric MRI, fusion biopsies, and molecular markers that may potentially reduce subsequent follow-up or biopsy intensity because of better initial risk classification are awaited.[34] Nonetheless, some form of surveillance that is more active than simply watchful waiting should be implemented in a healthy elderly man with ostensibly low-risk prostate cancer and a life expectancy of 10 to 15 years or more (**Table 1**). At some point during surveillance, it is reasonable to consider switching to a more passive form of expectant management as life expectancy reduces.

Table 1
Contemporary guideline recommendations for low-risk disease

Guideline	Condition	Recommendation
NCCN	Life expectancy $\leq$10 y	Observation
	Life expectancy >10 y	Active surveillance as an option
AUA	All men	Active surveillance as an option
EAU	Short life expectancy	Observation
	>10 y life expectancy and low volume disease ($\leq$2 cores positive cores, $\leq$50% core involvement)	Active surveillance as an option

Abbreviations: AUA, American Urological Association; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network.

Adapted from National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (Prostate Cancer) version 1.2015; American Urological Association Guideline for the Management of Clinically Localized Prostate Cancer (2007, up to date as of 2011); and European Association of Urology Guidelines on Prostate Cancer(updated March 2015).

Deciding on What Type of Treatment, If Treatment is Necessary

Treatment is necessary in the fit elderly man with high-volume intermediate- or high-risk disease and a life expectancy of more than 5 to 10 years. Although there are no randomized trials comparing the major treatment modalities of surgery or radiation, it is generally accepted that their efficacy is comparable across different risk groups. Compared with nonextirpative modalities, detection of recurrence after surgery is more well defined using PSA.[39] Data from the PCOS study suggest that both surgery and radiation are associated with a similar decline in sexual, urinary, and bowel symptom scores at the long-term 10- to 15-year follow-up, with most men experiencing erectile dysfunction.[40] Thus, treatment selection largely depends on the side-effect profile of each modality.

Radical prostatectomy in the elderly

Complete surgical extirpation is the gold standard for cure in clinically localized prostate cancer. Radical prostatectomy has undergone significant evolution in the last 2 decades with refinement of the original open techniques and the adoption of minimally invasive techniques. In particular, robot-assisted procedures in organ-confined prostate cancer have resulted in reduced blood loss while maintaining anatomic nerve and sphincter-sparing dissections through improved visualization and dexterity.[41,42] However, reduced cardiorespiratory reserves in the elderly raise concerns regarding the additional morbidity of pneumoperitoneum.[43,44] In general, perioperative mortality rates in prostatectomy cohorts have been less than 1% and complications rates less than 2%, though this may reflect a high degree of patient selection.[45]

Elderly men should be counseled that younger age is significantly associated with the return of continence and potency at 1 year after radical prostatectomy and men older than 70 years have a significantly longer time to reach continence.[46,47] On the other hand, the incidence of symptomatic bladder outlet obstruction increases with age; men with concurrent obstructive urinary symptoms benefit from both a better flow rate and cure of cancer with radical prostatectomy. An analysis of long-term functional outcomes in the SPCG-4 cohort showed that those undergoing radical prostatectomy had a 30% risk reduction in the incidence of poor flow and a 21% risk reduction in the incidence of nocturia at a median follow-up of 12 years.[48] It is also known that the degree of improvement in urinary symptoms is closely related to patient-perceived satisfaction with treatment.[49]

Radiation therapy in the elderly

Radiation therapy has been the mainstay of definitive prostate cancer treatment in the elderly, particularly in those deemed requiring treatment but unfit for surgical intervention. External beam radiation therapy has evolved to boost delivery and minimize collateral damage culminating in modern intensity-modulation (intensity-modulated radiation therapy [IMRT]), stereotactic (stereotactic body radiation therapy), and proton beam techniques. IMRT, the workhorse of radiation therapy, typically involves 8 to 9 weeks of daily Monday-to-Friday fractionation schemes, delivering doses of 78 Gy. The effects of collateral radiation remain the main concern following radiation therapy. Although high-grade early rectal and urinary radiation toxicity are rare, the incidence of late toxicity is notable for urinary frequency, diarrhea, radiation cystitis and proctitis, urethral strictures, and a small long-term risk of secondary malignancy.[50] Wallis and colleagues[51] showed in a propensity-matched analysis that the complication rates of radiation are similar to prostatectomy at 1 year but diverge at 3 years, with radiation having twice the complications. In an elderly man, the probability of suffering these consequences would increase with the length of life expectancy.

On the other hand, interstitial brachytherapy using radioactive iodine or palladium isotopes seek to overcome the problems of collateral radiation by achieving cell-kill through gradual emission of low-penetrance alpha radiation. The main toxicity is to the urethra, with almost all patients experiencing some form of urinary irritation in the early post-treatment period and some early series reporting a urethral stricture rate of up to 10% to 12%.[52,53] Careful dosimetric considerations can reduce the risk of acute urinary toxicity, and contemporary stricture rates are closer to 5% to 6%.[52,54]

In men with high-risk prostate cancer, Jones and colleagues[55] showed that short-term androgen deprivation therapy (ADT) combined with radiation improved overall survival compared with radiation alone in a cohort of men with a median age of 71 years. Bolla and colleagues[56] demonstrated that 3 years of ADT was better than 6 months when combined with radiation therapy in men with a median age of 70 years. On the other hand, D'Amico and colleagues[57] showed that the beneficial effect of adjuvant ADT was not seen in men with moderate to severe comorbidities. In particular, one brachytherapy study showed that adjuvant ADT increased mortality in men with underlying cardiovascular disease.[58] These factors should be taken into account before subjecting the elderly man with high-risk prostate cancer to radiotherapy. In high-risk localized disease, successful surgical resection may help men avoid ADT. One alternative to addition of ADT to external beam radiation is a 2-fraction high-dose–rate radiation boost.

Thermal ablation in the elderly

Thermal ablation with high-intensity focused ultrasound (HIFU) and cryotherapy has been used as a minimally invasive method to treat prostate cancer. Many studies have been done in older men, and thermal ablation is limited by the need for downsizing with ADT in large prostates. Crouzet and colleagues,[59] reporting on a cohort of 1002 men with a mean age of 72 years undergoing primary whole-gland HIFU, found the biochemical recurrence-free rate at 8 years to be 76%, 63%, and 57% for low-, intermediate-, and high-risk men, respectively, with an early complication rate of up to 18.0% and a late complication rate of 9.4%.

Cryotherapy is another form of thermal ablation with advantages of better estimation of treatment extent by visualizing the edge of the expanding ice ball. In an analysis by Dhar and colleagues[60] on 860 men aged greater than 75 years from the Cryo On-Line Data registry, the biochemical recurrence-free survival rate at 5 years was found to be 82.4%, 78.3%, and 77.6% for low-, intermediate-, and high-risk prostate cancer. Early complications were seen in 6% and late complications in 0.1%. Incontinence was noted in 0.9% of patients. Similar to other contemporary cryotherapy reports, the rate of potency after treatment was low at 11%.

Focal therapy

Focal therapy is an experimental treatment in prostate cancer.[61] In the elderly, selective ablation of one or 2 lesions that are intermediate or high grade, may down-classify men back into the active surveillance or conservative management pool.[62] Although this is an attractive proposition, the feasibility and long-term outcomes of this strategy are unknown and represent an active area of research.

ADVANCED PROSTATE CANCER

Locally Advanced Prostate Cancer: Sequencing Multimodality Treatment in Elderly Patients

Men with locally advanced prostate cancer are at high risk of positive surgical margins and nodal and systemic microdissemination and are likely to require multimodality treatment, encompassing various combinations of surgery, radiation, and hormonal

therapy.[63] In very fit elderly men, the advantage of surgery in this setting is to preserve radiation and hormonal therapy as subsequent salvage options in view that salvage prostatectomy has markedly more complications and poorer functional outcomes than primary prostatectomy.[64] Radiation with adjuvant hormonal therapy is otherwise a reasonable therapeutic strategy. In men who are unfit even for radiation, hormonal therapy, discussed in detail later, may be used to palliate symptoms as a monotherapy.

Metastatic Prostate Cancer in the Elderly

Elderly men may be susceptible to more aggressive prostate cancer. A Surveillance, Epidemiology, and End Results database study spanning 1998 to 2007 found that men older than 75 years were more likely to present with metastatic disease than their younger counterparts and had a greater risk of death of prostate cancer despite having higher death rates from competing comorbidities.[6] The mainstay of treatment of metastatic prostate cancer is ADT.[65] Additionally, particularly fit elderly men with high-volume metastatic prostate cancer may benefit from an induction regime of 6 cycles of docetaxel for a survival benefit of 13 to 17 months as found in the ECOG CHAARTED trial (the Eastern Cooperative Oncology Group Chemo-Hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer).[66]

Androgen deprivation therapy

Early androgen deprivation is recommended for men with asymptomatic M1 disease based on findings from the UK Medical Research Council trial that men with ADT deferred until symptomatic were twice as likely to develop pathologic fractures, spinal cord compression, ureteric obstruction, and extraskeletal metastasis.[67] Before starting ADT, though, one should be cognizant that it has not been shown to improve cancer-specific survival and only impacts overall survival marginally at 10 years.[68]

ADT can be achieved using medical or surgical means. Surgical castration with bilateral orchiectomy results in the most rapid reduction in serum testosterone.[69] It results in better quality of life and is particularly useful in elderly men who are unlikely to be compliant to follow-up.[70] On the other hand, medical castration, typically with a luteinizing hormone-releasing hormone (LHRH) agonist, allows for the use of intermittent ADT and is suitable for men who are reluctant for orchiectomy.[71] Although several types and formulations of LHRH agonists (1, 3, and 6 monthly depot injections) exist, their clinical efficacy is considered to be similar.[72] At initial administration, LHRH agonists may produce a surge in testosterone resulting in a clinical flare in patients with extensive metastasis.[73] To prevent this, a peripheral antiandrogen is usually used in combination for 1 to 4 weeks during the first dose of the LHRH agonist.[74] Degarelix, currently the only Food and Drug Administration–approved LHRH antagonist, does not have the flare problem but may cause more hot flashes and is available only in 1-month depot formulations. Combined androgen blockade with the long-term addition of an antiandrogen to medical or surgical castration has not been found to have a meaningful impact on overall survival and cannot be recommended in the elderly man.[75]

ADT is associated with significant morbidities that may be exacerbated in elderly men.[76] These morbidities include fatigue, anemia, sexual dysfunction leading to loss of sexual intimacy, increased insulin resistance, and an increased risk of diabetes mellitus by 16% to 44%, increased arterial stiffness, increased triglycerides, and the eventual development of metabolic syndrome. ADT has been inconsistently linked to an increase in cardiovascular events; but in these studies, other traditional risk factors have been significant confounders, and a link to cardiovascular *mortality* remains elusive. The further implications of metabolic changes in body fat composition, reduced muscle mass, and bone mineral density loss are a decrease in physical strength and

endurance. In a group of men older than 70 years on ADT for 3 months, a 56% reduction in physical function and a 22% incidence of falls were reported.[77] Although the subsequent fates of these men are unknown, falls are generally linked to a high subsequent readmission rate and a 1-year mortality rate of 33%.[78] ADT has also been linked, albeit inconsistently, to cognitive decline, which is pertinent to the elderly man.[79]

There are several strategies to ameliorate these adverse effects. Intermittent ADT improves quality of life with reported benefits in vasomotor symptoms, sexual function, physical well-being, and weight management.[80] A systematic review of 7 phase III randomized trials with 4675 cumulative patients indicates that it is oncologically noninferior to continuous ADT.[81] A nadir PSA of less than 4 ng/mL after initiation of ADT has been found to identify a group of men with a longer survival during which the adverse effects of ADT may be experienced.[82] Intermittent ADT may thus be suited to the educated elderly man with a good prognosis, advanced or low-volume metastatic prostate cancer, and a desire for a break from therapy with the caveat that he is compliant to follow-up and recognizes the potential for a small increased risk of cancer progression and death. Close monitoring with resumption of ADT based on an increase in PSA to 10 to 20 should mitigate this risk in most men.

Vitamin D and calcium are commonly recommended for use in men on ADT based on their benefits in bone mineral density preservation and fracture risk reduction in trials of patients with osteoporosis. Fracture risk can be calculated using the FRAX risk calculator in order to provide an individual assessment of risk. Bisphosphonates have been shown to significantly improve lumbar and femoral bone mineral density, reduce osteoporosis by 61%, and reduce the risk of fractures by 20%.[83] However, bisphosphonates are not without adverse effects themselves and have been commonly reported to cause bone pain, fatigue, and anemia.[84] These effects depend on renal clearance, which is often decreased in the elderly. The most serious complication of bisphosphonate, osteonecrosis of the jaw, is thought to be related to dental caries, another significant risk in the elderly, and may be reduced by the use of dental preventative measures.[85] Denosumab, a monoclonal antibody that inhibits osteoclast maturation, has been shown to improve bone mineral density and reduce the vertebral fracture rate by 62% in men with nonmetastatic prostate cancer on ADT when given every 6 months.[86] In a trial evaluating denosumab against zoledronic acid in men with castrate-resistant prostate cancer, although denosumab was superior in the prevention of skeletal-related events, it also resulted in a greater incidence of hypocalcemia, which may produce nonspecific symptoms in the elderly.[87]

Gabapentin and medroxyprogesterone have proven efficacy in treating vasomotor symptoms, and data from case series suggest that acupuncture may be helpful.[88–90] Resistance exercises improve upper- and lower-body strength.[91] A combination of metformin and aerobic exercise has been shown to reduce abdominal girth, weight, and body mass index.[92] Given the higher risk of falls in the elderly and the evidence of ADT-induced sarcopenia and muscle loss, regular exercise at least 30 minutes 3 to 5 times per week is recommended to all men undergoing ADT. Exercise may also maintain sexual activity in men undergoing ADT.[93] Finally, in men who are unable to tolerate the side effects of ADT, bicalutamide 150 mg monotherapy, which is less efficacious than castration but has a more acceptable side-effect profile, may be used after proper counseling.[94]

Castrate-Resistant Prostate Cancer

The morbidity of castrate-resistant prostate cancer (CRPC) is substantial except in the most infirm. The median disease-specific survival in the patients with CRPC is 12 to 15 months. The management of CRPC is both complex and costly.[95] In the elderly,

particular attention should be paid to underlying comorbidities, which place them at higher risk of adverse treatment effects, and financial toxicity, which may affect them disproportionately.

Secondary hormonal manipulation

Enzalutamide is a multistep inhibitor of the androgen receptor, from nuclear translocation to DNA binding and coactivator recruitment, thus increasing its potency over traditional antiandrogens. The efficacy of enzalutamide was demonstrated in 2 randomized controlled trials: first in the castration-resistant postchemotherapy setting (AFFIRM) and in then in the prechemotherapy setting (PREVAIL).[96,97] In both trials, diarrhea, fatigue, and hot flashes seemed to be the major adverse effects. Although there was an initial concern with seizures (0.6% incidence in AFFIRM [A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100]), the incidence was later found to be lower in PREVAIL (0.1%). A post hoc analysis in AFFIRM (median age 69 years) comparing those aged greater than 75 years with those younger showed a similar efficacy and side-effect profile.[98] However, emerging data suggest more falls in men older than 75 years, which may be related to the impact of potent AR blockade in muscular tissue.[99] This finding emphasizes the importance of exercise and conditioning during a potent hormonal therapy, such as enzalutamide, which is being further investigated in the ongoing EXTEND (Safety and Efficacy of EXercise Training in Men Receiving ENzalutamide in Combination With Conventional Androgen Deprivation Therapy for Hormone Naïve Prostate Cancer) trial (NCT02256111).

Abiraterone acetate is a CYP17 (Cytochrome P450 17alpha hydroxylase/17,20 lyase) inhibitor targeting adrenal androgen synthesis. In men with CRPC, abiraterone was shown in the COU-AA-301 trial after chemotherapy and in the COA-AA-302 chemotherapy-naïve trial to improve survival compared with placebo.[100,101] Side effects of abiraterone are largely secondary to its mechanism resulting in a secondary mineralocorticoid excess, which can be managed with a mineralocorticoid receptor antagonist.[102] In both trials, the median age of the participants was 69 to 72 years. Given that abiraterone is given together with prednisolone and both undergo hepatic metabolism, liver function should be monitored in elderly patients receiving them. Data to date have not suggested differential increased toxicity in elderly patients with abiraterone. However, long-term use of corticosteroids may impact bone mineral density and risk of infection with immunosuppression, induce steroid skin changes such as purpura, and cause metabolic syndrome and insulin resistance, which are adverse effects that may burden elderly men.

Immunotherapy

Sipuleucel T is an autologous cellular immunotherapy, whereby antigen-presenting cells are exposed to PSA and prostatic acid phosphatase fused to colony-stimulating factor before reintroduction into the patients. The IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment), involving 512 men at a median age of 71 years, demonstrated a 22% reduction in death, translating to a 4.1-month median survival benefit in the treatment arm.[103] Similar to findings from smaller, prior randomized trials, no improvement was seen in progression-free survival.[104,105] This finding was attributed to a delayed antitumor response relative to the progression, which was noted to be early in the entire IMPACT cohort. This lack of short-term benefit carries importance when considering treatment for palliative purposes in the elderly. The most common adverse events occurring in the treatment group compared with the control group were chills, fever, and headache. There are presently no data to suggest a differential efficacy or toxicity in elderly men, as overall this is a well-tolerated therapy that is completed in a 4-week

treatment period. However, there is a need for a central venous catheter in up to 25% of patients with poor intravenous access.

Radioisotopes

Radium 223 is a calcium-mimetic that is absorbed by osteoblasts in areas of high-bone turnover.[106] It then emits short-range alpha-radiation targeting areas of metastasis, while relatively sparing the bone marrow because of its limited penetration. The ALSYMPCA trial (Alpharadin in Symptomatic Prostate Cancer Patients) randomized men with CRPC who declined or were not eligible for docetaxel to radium 223 or placebo and best available care, finding a 3.6-month overall survival benefit and a 5.8-month longer time to first skeletal event with radium 223.[107] The median age in this cohort was 71 years, with less adverse events reported in the radium 223 group compared with placebo. Side effects include low risks of and gastrointestinal (GI) toxicity due to GI excretion. In addition to survival, secondary benefits may include pain response and delay in spinal cord compression over time. However, PSA declines are not commonly seen with this agent. Radium 223 is appropriate for symptomatic patients with metastatic CRPC who have bone metastatic-predominant disease, no liver metastases, and adequate bone marrow reserve but are too frail to receive docetaxel chemotherapy or who wish to receive docetaxel at a later time. Concurrent use of palliative radiation, hormonal therapy, corticosteroids, and ADT is permitted.

Cytotoxic chemotherapy

Docetaxel, a microtubule inhibitor, is the first cytotoxic agent to prolong survival in men with CRPC. Two randomized trials, SWOG 9916 (Southwest Oncology Group trial 9916) and TAX-327, compared docetaxel against the standard of care, mitoxantrone, and found a 1.8- to 2.4-month survival benefit.[108,109] TAX-327 (XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer) further established the superiority of docetaxel administered every 3 weeks versus a weekly dose.[109] The median age in the SWOG trial was 70 years and 68 years in TAX-327, with 20% of the patients aged 75 years and older. In both trials, the docetaxel arm experienced significantly more grade 3 to 4 neutropenic fevers, fatigue, neuropathy, stomatitis, and lower limb edema. In TAX-327, the docetaxel arm had fewer cardiovascular events, whereas, in the SWOG trial, the reverse was observed. This finding may be due to the combined use of estramustine in the latter trial. In subsequent analyses, the benefits of every-3-weeks docetaxel on survival was found to be independent of age, as men older than 65 years had a similar survival benefit as younger men, provided they had adequate functional status.[110] Secondary benefits of docetaxel include a high rate of PSA decline, radiographic responses, and preserved quality of life due to delayed disease progression and pain progression. Reduced dosing or use of alternative schedules may reduce adverse effects in the elderly.

Cabazitaxel, a taxane with similar mechanism of action to docetaxel, is approved for use in docetaxel-refractory tumors at 25 mg/m^2 every 3 weeks with prednisone. The TROPIC trial, comparing cabazitaxel with mitoxantrone in this setting, showed a 30% reduction in risk of death, translating to an overall survival advantage of 1.4 months.[111] Febrile neutropenia and diarrhea were the most common adverse events noted. These adverse events may be addressed with prophylactic use of granulocyte colony-stimulating factor (G-CSF) and dose reductions to 20 mg/m^2.

Sequencing treatments in castrate-resistant prostate cancer

The proliferation of novel agents in CRPC has led to much debate regarding the sequencing of treatments.[112] To further complicate matters, the overlap in targeting of the androgen receptor pathway by novel agents and taxanes could limit the efficacy

Table 2
Treatment options for CRPR

Agent	Benefit	Toxicity	Other Considerations	Cost[a]
Enzalutamide	Prechemotherapy: 2.2-mo median survival benefit, 70%–80% radiographic PFS, 17-mo delay to chemotherapy Postchemotherapy: 5.2-mo median survival benefit, better QOL and longer time to PSA/radiological progression	Falls (>75-year-old subgroup), diarrhea, fatigue, hot flashes, seizures (0.1%–0.6%)	An exercise/ physical conditioning program may be beneficial to reduce muscular effects of potent androgen suppression	$7500/mo
Abiraterone	Prechemotherapy: 3.9-mo survival benefit Postchemotherapy: 25% reduction in all-cause mortality	Hypertension, hyperkalemia, edema, side effects of prednisolone	Needs to be on prednisolone Hepatic metabolism Liver function monitoring recommended	$5800/mo
Sipuleucel T	4.1-mo survival benefit	—	No PSA response seen May need central venous access	$93,000 per course of 3 treatments
Radium 223	3.6-mo survival benefit, 5.8 mo longer to first skeletal event	Myelosuppression (<10%), GI toxicity (low-grade diarrhea/nausea)	Use in bone-predominant metastasis Hepatic metabolism	$75,000 per course of 6 treatments
Docetaxel	2-mo survival benefit	Neutropenic fever, neuropathy, fatigue, stomatitis, lower limb edema	Consider reduced dosing or alternative schedules to reduce adverse effects	$2300 per cycle[b]
Cabazitaxel	1.4-mo survival advantage	Neutropenic fever, diarrhea	Consider prophylactic G-CSF or dose reductions to reduce adverse effects	$50,000 per course of 6 cycles

Cost-benefit table for secondary agents in CRPC.
Abbreviations: PFS, progression-free survival; QOL, quality of life.
[a] Cost derived from Lew and colleagues,[95] in US dollars.
[b] Estimated cost based on docetaxel (Taxotere).

of treatments used later in the sequence.[113] Cross-resistance observed between enzalutamide and abiraterone acetate may also limit clinical benefit from sequential oral-oral therapy.[114] In the elderly, it is prudent to choose a treatment based on its side-effect profile and tolerability, accounting for comorbidity and physiologic reserves (**Table 2**). It is also important to note that the response to treatment may not be immediate, and sufficient time should be allowed to elapse before declaring a treatment inadequate.[115]

SUMMARY

The goal of treating prostate cancer in the elderly is to maximize survival and quality of life while minimizing treatment-related morbidity. Life expectancy, comorbid conditions, and physiologic reserve are critical considerations in choosing therapeutic modalities in order to achieve these goals.

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