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Management of Prostate Cancer in Elderly Men

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Elderly men comprise a large percentage of men diagnosed with prostate cancer (PrCa). Although localized PrCa is often indolent, older men tend to be diagnosed with higher-stage disease and are more likely to die from PrCa than younger men. Multiple factors other than age play an important role in determining who will benefit from active treatment, such as comorbid conditions, life expectancy, and tumor characteristics. Careful consideration of such factors can help prevent the overtreatment of elderly men with low-risk disease and undertreatment of elderly men with high-risk disease. Management decisions should be individualized by weighing the benefits of treatment against potential risks and side effects pertinent to the elderly population, whether evaluating for surgery, radiation, or androgen deprivation.

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Prostate cancer (PrCa) is the most common malignancy and one of the leading causes of death in men aged >60 years. More than half of men diagnosed with PrCa are aged >65 years, and almost a quarter of men diagnosed with PrCa are aged >75 years (Fig. 1). The number of men aged >65 years is projected to more than double in the United States by 2050, rising to nearly 40 million.[1] As the elderly population grows, the number of men diagnosed with PrCa will increase accordingly.

The appropriate management of older men can be a challenge. Elderly men are more likely to be diagnosed with higher-grade PrCa and more likely to die from PrCa than younger men (Fig. 2). Many of these men would benefit from standard definitive therapies with proven survival benefits. By contrast, older men are also more likely to have comorbid medical conditions that put them at a greater risk of harm from the side effects of therapy. Also, if these comorbid conditions are severe, they may become competing causes of mortality, obviating the need for aggressive PrCa therapy.

The difficulty in management of this population lies in weighing the harms of definitive treatment against its survival and quality of life benefits, as these men are susceptible to both overtreatment and undertreatment of their disease. Tumor characteristics, comorbidity status, functional status, life expectancy (LE), patient preference, and specific side effects of treatment must all be considered to optimally manage older PrCa patients.

LE Estimates and Comorbidity Status

National Comprehensive Cancer Network (NCCN) guidelines emphasize estimating LE when considering treatment for localized PrCa.[2] The 10- and 20-year rules recommend active treatment for low- to intermediate-risk PrCa in those with greater than a 10-year LE and for very-low-risk PrCa in those with greater than a 20-year LE. Owing to the indolent nature of localized PrCa, patients who have less than a 10-year LE are more likely to die from other causes, and are unlikely to benefit from definitive cancer treatment. Consid-

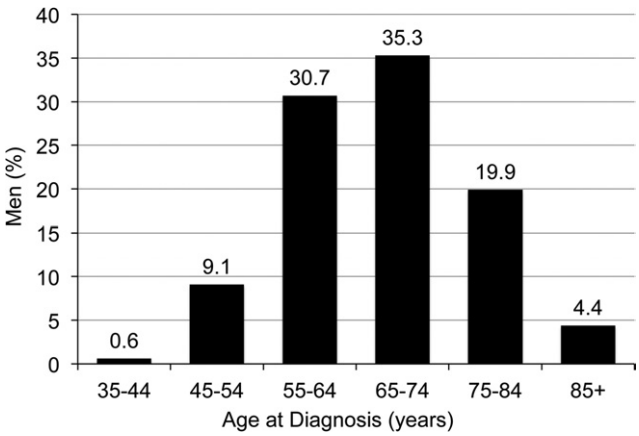

Figure 1 Age distribution of men diagnosed with prostate cancer in the USA. Adapted from SEER Cancer Statistics Review.[61]

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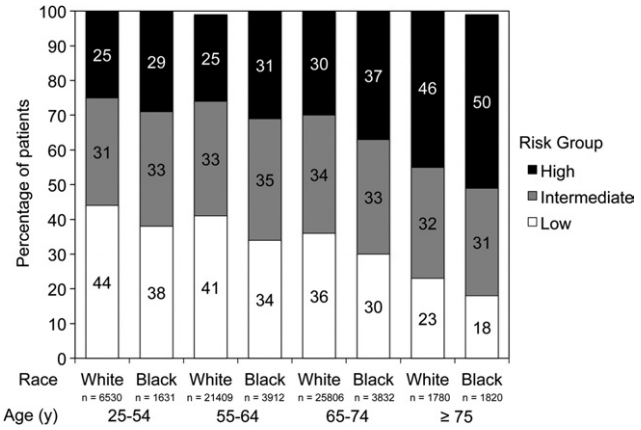

Figure 2 Distribution of risk group at diagnosis by age and race among men in the SEER Cancer Registry. Reprinted with permission from Oxford University Press.[62]

eration of LE most commonly occurs within the elderly population. As a group, they indeed have a shorter LE than the general population; however, on closer examination, there is a great amount of variation in health status and longevity. In fact, many studies have shown comorbidity to be an indispensable component of LE predictions in addition to age.[3,4]

The NCCN guidelines for elderly cancer patients use a framework developed by Walter and Covinsky for understanding LE in the context of comorbidities.[5] For each given age, the average LE is obtained from social security life-tables. For men in the highest quartile of health, this number is increased by 50% and for men in the lowest quartile of health this number is decreased by 50%. Men in the middle 2 quartiles of health keep the average age-specific LE. Figure 3 illustrates the variability of the aging population with regard to LE for men aged 65-90 years. On one end, there are 65-year-olds with high comorbidity who, on average, survive <10 years, and on the other end, healthy octogenarians with almost a 12-year LE. Life tables such as these are often used for illustrating trends, but they do not provide individualized estimates. For evaluating comorbidity more specifically, the NCCN cites a few statistically validated comorbidity indexes, such as the Charlson comorbidity index (CCI), the adult comorbidity evaluation-27 index, the cumulative illness rating scale, and the Older Americans Resources and Services multidimensional functional assessment questionnaire. Metrics that have been used specifically in the setting of PrCa include the CCI, adult comorbidity evaluation-27 index, Kaplan–Feinstein index, and the total illness burden index.

Statistical nomogram models that take into account age, comorbidity data, and tumor factors have also been developed to predict LE. Notable models by Cowen[6], Tewari,[7] and Albertsen[8] have accuracies ranging from 69% to 72%. In Albertsen's model, 3 indexes of comorbidity (CCI, Kaplan–Feinstein index, and index of coexistent disease) were all shown to improve the prediction of LE significantly and independently when added to Gleason score. In 2007, Walz[9] used CCI and age to create a nomogram predicting the probability of death from non-PrCa causes within 10 years after definitive therapy. He reported a very high accuracy of 84.3%. There is not yet a standard method of predicting LE, but complex and comprehensive statistical models provide the most accurate individualized predictions for LE in PrCa patients.

Older men with localized PrCa are a heterogeneous group. It is important to consider all facets of health status in addition to chronologic age and disease characteristics when making treatment decisions in the elderly population. This includes, but is not limited to, comorbid conditions, functional status, cognitive function, and psychosocial issues. Not only do these factors influence LE but also tolerance of treatment, frequency of side effects, and treatment outcome.

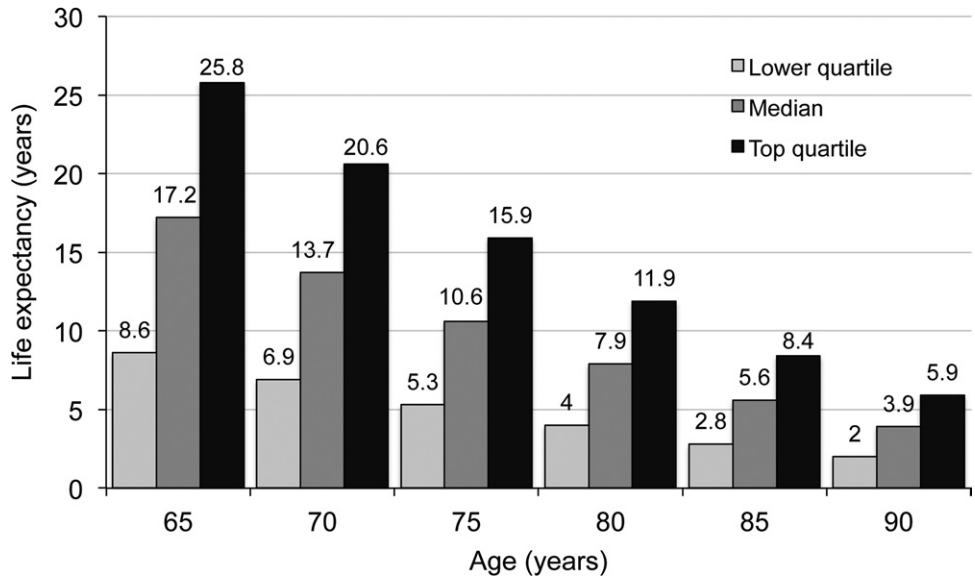

Figure 3 Estimated life expectancy for men in lower, median and upper quartiles of health, stratified by age based on 2007 Social Security Life Tables[63] and NCCN guidelines for estimating life expectancy.[5]

Overtreatment of Low-Risk PrCa

Active surveillance plays an important role in the management of elderly men with localized PrCa. PrCa is often an indolent process, and patients with multiple comorbidities and low functional status may be more likely to die from other medical causes, especially those with low- to intermediate-risk disease. NCCN guidelines recommend active surveillance for very-low-risk patients with LE <20 years, for low-risk patients with LE <10 years, and as an equal alternative to definitive radiation therapy (RT) for intermediate-risk patients with LE <10 years.[2] Active surveillance monitors the disease with prostate specific antigen (PSA) testing, digital rectal examination (DRE), and prostate biopsy, with the intent to deliver curative therapy if the cancer progresses.

Studies of active surveillance for low-risk PrCa have shown low mortality rates in the literature. Early results by Dall'Era[10] and Tosoian[11] showed that in cohorts of 321 and 769 very-low- and low-risk patients, respectively, PrCa specific survival was 100%. Median follow-up was 3.6 and 2.7 years, respectively. Similarly, Klotz's[12] prospective active surveillance trial followed 450 favorable-risk PrCa patients expectantly and offered treatment for clinical, pathologic, or PSA progression. He reported a 10-year PrCa actuarial survival of 97.2%, with 30% of patients eventually upstaging and receiving definitive treatment.

Others have reported similarly promising outcomes in the elderly population. Lu-Yao[13] used Surveillance, Epidemiology, and End Results (SEER) program Medicare data to analyze outcomes of men aged >65 years who underwent conservative management in the post-PSA era (1992 to 2002). Results showed a 10-year prostate-specific mortality rate of 6% in men aged 66-74 years with moderately differentiated PrCa: a large improvement compared with 15%-23% in the pre-PSA era (1949-1992). These results may be partially due to more widespread screening creating a lead-time bias, but they still illustrate the viability of active surveillance in the elderly population. A Scandinavian trial comparing watchful waiting with radical prostatectomy (RP) showed a survival benefit of RP in men aged <65 years but no difference in disease-specific survival, metastasis-free survival, or overall survival in men aged >65 years.[14] Low-risk PrCa is an indolent disease, and in elderly men with lower life expectancies, active surveillance should be an important consideration.

Although elderly men with low-risk PrCa and limited life expectancies are more likely than their younger counterparts to receive active surveillance, there is still a large percentage receiving aggressive treatment. Cooperberg's[15] analysis of treatment patterns in low-risk PrCa using the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database (1989-2001) showed that a minority of patients actually undergo active surveillance. In the subgroup of 556 men aged 70-79 years, he found that 58% received definitive local therapy (prostatectomy, external beam radiation therapy [EBRT], brachytherapy), 18% received primary androgen deprivation therapy (ADT), and only 24% received observation. In the 44 men aged >80 years, more received observation (38%), but a significant portion still received definitive therapy (25%) and ADT (36.4%). Similarly, in a SEER–Medicare study of 8323 men aged ≥75 years, 72% of men with low-risk PrCa received active treatment.[16] These data suggest an excess of definitive treatment in a population that does comparably well with active surveillance.

The same SEER Medicare study also looked at the influence of comorbidity on treatment selection and found that it had no effect; men with higher comorbidities were offered active treatment just as often as men with lower comorbidities. This trend was also supported by Daskivich[17] in a retrospective analysis of 509 men with low-risk PrCa. He found that age >75 years was a stronger clinical predictor of nonaggressive treatment than comorbidity status. Men with CCI scores of 3 or greater were treated aggressively in 54% of cases, whereas men aged >75 years were treated aggressively in 16%. However, men with CCI scores of 3 or greater had much higher 10-year other-cause mortality (70% vs. 24%).

Clinicians' overtreatment of the elderly population is exacerbated by the tendency to emphasize patient age more than comorbidity status when making treatment decisions. The decision to proceed with definitive treatment in low-risk PrCa in the elderly population should be carefully contemplated, especially in the context of higher comorbidity and lower LE.

Undertreatment of High-Risk PrCa

Although watchful waiting and active surveillance are important aspects of PrCa treatment, there is a significant portion of elderly men who would benefit from definitive treatment. The natural history of PrCa differs between younger and older men. Older men are more likely to be diagnosed with higher-grade PrCa, are less likely to receive definitive treatment, and are more likely to die from PrCa. Figure 4 illustrates the high number of PrCa deaths in elderly men. Treatment decisions would ideally minimize the number of PrCa deaths by identifying and treating men with longer life expectancies, while at the same time avoiding the overtreatment of men who will die of other causes before the progression of their PrCa.

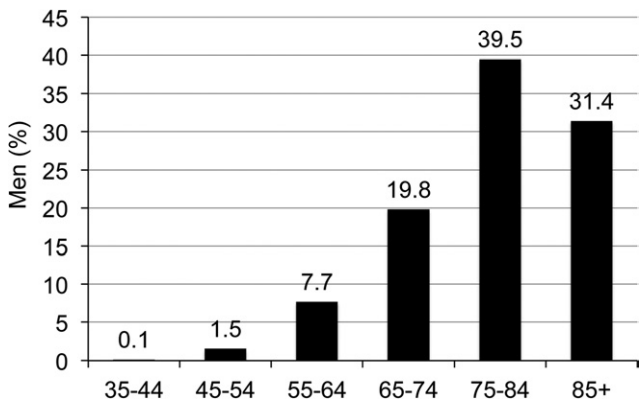

Figure 4 Distribution of age at time of death from prostate cancer in the USA. Adapted from SEER Cancer Statistics Review.[61]

Contrary to low-risk PrCa, prostate-cancer-specific mortality is extremely high in older men with higher-risk disease who are treated conservatively. Albertsen[18] reported 20-year outcomes for 767 patients with localized PrCa treated with either observation or ADT alone. Men with Gleason 8-10 disease had a 66% PrCa-specific mortality within 20 years of diagnosis. A similar risk of 64% was found in the oldest subset of men aged 70-74 years. This was in sharp contrast with the 20-year PrCa-specific mortality rates in men with Gleason 2-6 disease, ranging from 7% to 27%. Although the subjects were diagnosed in the pre-PSA era and have higher mortality rates than contemporary studies, this study continues to illustrate the relative risk of conservatively managing men with high-risk localized PrCa. Similarly, in Lu-Yao's[13] aforementioned analysis of patients aged 65-74 years with localized PrCa receiving conservative treatment in the post-PSA era, patients with Gleason 8-10 disease had a 10-year PrCa-specific mortality of 20%-54%, compared with 4%-8% in Gleason 5-7 disease. Owing to the high disease-specific mortality rates, conservative management alone is not adequate in the treatment of high-risk PrCa in healthy older men.

However, men with high-risk disease often do not receive definitive treatment. An analysis of patients with localized PrCa from the CaPSURE database by Bechis[19] looked specifically at how age influenced disease-specific survival. Men aged ≥75 years were shown to be more likely to be diagnosed with high-risk PrCa, more likely to be treated conservatively, and more likely to die from PrCa. Disease risk was divided into low, intermediate, and high based on the previously validated Cancer of the Prostate Risk Assessment scoring system. Men aged ≥75 years were more likely to receive ADT monotherapy over definitive local treatment within each risk group. Also, men aged ≥75 years with high-risk disease were more likely to receive ADT monotherapy than their age-matched low-risk counterparts. After adjusting for treatment modality and disease risk, age no longer had a significant effect on PrCa mortality. These data suggest that treatment decisions in elderly men are based more on age than disease factors and may account for the high proportion of PrCa-specific deaths in the elderly population.

Undertreatment is most pronounced in the subset of healthy older men with high-risk disease. In Roberts'[16] SEER analysis of men older than 75 years with localized PrCa, less than half of men in the high-risk disease group received definitive local therapy, even though two-thirds had no comorbidities. Furthermore, Schwartz's[20] analysis of treatment patterns in 276 men with localized PrCa used a Markov model to estimate the optimal treatment for each patient taking into account age, Gleason score, and comorbidity. He found that the largest proportions of suboptimal treatment occurred in the subsets of healthy men aged ≥70 years with Gleason 5-7 or 8-10 disease, with 46.9% and 72.7% receiving suboptimal management respectively.

The undertreatment of men with lower comorbidity further contributes to the high PrCa mortality in the elderly population. These otherwise healthy men are being overlooked solely based on their age and may lose valuable years that could have been preserved with definitive local therapy. It is therefore important to take multiple factors into account, including disease risk and comorbidity status, in addition to age when evaluating elderly patients.

Who Benefits From Active Treatment

Definitive local treatment of both intermediate- and high-risk PrCa has been shown to benefit healthy elderly men. Alibhai[21] developed a Markov state transition model to evaluate the LE and quality-adjusted life expectancy (QALE) in men aged >65 years with localized PrCa in response to 3 treatment options: RP, EBRT, and watchful waiting. For moderately differentiated tumors (Gleason 5-7), RP and EBRT resulted in improvements in LE and QALE up to age 75. For poorly differentiated tumors (Gleason 8-10), curative therapy resulted in improvements in LE and QALE up to age 80. Benefits of potentially curative therapy were restricted to men with no or mild comorbidity.

Wong[22] showed benefit of active therapy versus observation for localized low- and intermediate-risk disease in a SEER analysis of 44,630 men aged 65-80 years with localized PrCa. Men who underwent active treatment with RP or RT within 6 months of diagnosis had a 31% reduction in mortality with 12 years of follow-up. This benefit also extended to men aged 75-80 years at diagnosis and men with no comorbidities at diagnosis, with reductions in mortality of 27% and 29%, respectively.

Adjuvant ADT therapy in addition to EBRT or brachytherapy has been shown to be superior to RT alone in select elderly populations. In a post-hoc analysis of the Dana Farber Cancer Institute (DFCI) randomized trial comparing EBRT plus 6 months of ADT with EBRT alone for intermediate- to high-risk PrCa, combined therapy was associated with a decrease in all-cause mortality from 41% to 17% in older men with no or minimal comorbidity.[23] Similarly, in a large retrospective trial of men with high-risk PrCa, brachytherapy plus ADT showed improved PrCa-specific mortality compared with brachytherapy alone in men without active cardiovascular disease.[24]

Side Effects of Treatment

The harms of therapy such as surgery, radiation, or androgen deprivation may be more pronounced in the elderly population, especially those with lower functional status, increased comorbidities, and, thus, impaired ability to recover. It is important to weigh the specific benefits and risks for each treatment modality as they apply to the elderly.

The complications following RP have been shown to be more severe in the elderly. A study by Walz[25] showed 30-day postoperative mortality to be modulated independently by age, comorbidity status and tumor volume. Additionally, Alibhai[26] found comorbidity status to be more predictive than age in almost all categories of early complications, including death following prostatectomy. In the cohort of 11,010 men,

20% experienced complications and 0.5% died within 30 days, which is consistent with other large series.

Data regarding long-term postoperative outcomes, such as continence, erectile function, and further intervention also predominantly report worse outcomes in the older population. In a 20-year series of 3447 men, Kundu found that after at least 18 months follow up after RP, adequate erectile function, urinary continence, and postoperative complications were significantly decreased in men younger than 70 than in men 70 and older.[27] Similarly in the PrCa Outcomes Study, including 1291 men with up to 24 months follow up, urinary and sexual function were significantly worse in older men.[28] With follow-up of at least 18 months, men under 60 and men age 75-79 and older had potency rates of 39% vs 19% and incontinence rates of 0.5%-4% vs 14%, respectively. A nationwide Austrian study of 16,524 men also found that the rate of post operative urinary strictures requiring additional intervention incrementally increased from 5.8% in the youngest group age 44-49-10.8% in the oldest group age 70-74.[29]

Elderly patients have significantly greater risk in both short and long-term postoperative complications and mortality following prostatectomy especially if they suffer from other comorbidities. Therefore, RP is not routinely performed in this population.[16]

RT is more commonly used among the elderly as it is less invasive and does not carry the anesthesia associated risks of surgery. However, radiation is not without its side effects, especially for those with higher comorbidity. The most prominent side effects after RT include gastrointestinal (GI) toxicity, genitourinary (GU) toxicity, and erectile dysfunction (ED). Prior studies have conflicting data regarding whether age is a predictor of increased side effects in RT. Some studies have found equal rates of both acute and late side effects in all age groups,[30,31] while others have found older age to be associated with faster onset and more frequent side effects.[32]

The GI toxicity of RT is proportional to the volume of bowel irradiated. GI complications of grade 2 or greater were 16% when <25% of the bowel was treated, compared to 46% when the volume treated exceeded 25%.[33] A recent critical review cites age as an established risk factor for acute and late GI toxicity after RT along with larger rectal volume irradiated, prior abdominal surgery, concomitant ADT, diabetes, hemorrhoids and inflammatory bowel disease.[34] Because of the potential increased GI toxicity, radiation treatment plans for elderly men should minimize rectal dose, particularly when treating men with multiple comorbidities.

GU toxicity is generally limited to mild acute irritative symptoms. Incontinence and other severe urinary symptoms are rare following RT.[34] Because measurement of RT dose to the bladder is difficult, there is no good model for predicting the relationship between RT and GU complications. Pre-existing symptoms and previous transurethral resection of the prostate (TURP) have been shown to be risk factors for increased GU morbidity but a significant correlation between age and GU morbidity has not yet been shown.

ED develops gradually following RT. A prospective trial evaluating patients more than one year following 70-72 Gy RT treatments found that a higher patient age and diabetes were predictive of both pre-existing ED and post-RT acquired ED.[35] The greatest predictor for return of sexual function following RT was the presence of nighttime or early morning erections before treatment. Other studies have also shown sexual function before RT predicts sexual function after treatment.[36]

Studies of brachytherapy also show a relationship of complications with age and comorbidity. In a SEER Medicare analysis of 5621 men who underwent brachytherapy, increased bowel and urinary toxicity were both associated with older age, and higher CCI.[37] Urinary toxicity was also associated with additional treatment with EBRT or ADT and previous transurethral resection of the prostate, while bowel toxicity was also associated with inflammatory bowel disease.

Comorbidity and age are both important predictors of health related quality of life (HRQOL) following all modalities of PrCa therapy. In a CaPSURE database study of men who underwent RP, men who were younger than 65 were more likely to return to baseline urinary, sexual and physical health on multivariate analysis.[38] Furthermore, patients with good or excellent baseline health were more likely to return to baseline physical and mental health independent of other factors. Similarly in another CaPSURE database study of men with PrCa treated with RP or RT, severe comorbidity was predictive of significant declines in HRQOL, including mental, physical, sexual, urinary and bowel function, at 6, 12, 18, and 24 months after treatment.[39] Overall decline rates were similar across all comorbidity groups; men with more severe comorbidity started at a lower baseline HRQOL before treatment and thus experienced poorer outcomes after treatment.

When discussing anticipated side effects from treatment regimens with elderly patients, clinicians should take into account age, functional status, and baseline urinary, bowel, and sexual function.

Treatment With ADT

ADT is commonly used in the elderly population for both recurrent PrCa and as an adjunct to definitive treatment. ADT has a clear benefit in patients with high-risk PrCa. Multiple randomized controlled trials comparing adjuvant ADT with RT to RT alone have found a significant benefit in both PrCa specific survival and overall survival with combined treatment.[40-44] These studies enrolled mostly healthy men, with Karnofsky performance scale ratings greater than 60-70 or WHO performance status of 0-2, and median ages ranging from 69 to 70. Because a significant number of elderly men were included in these studies, the findings can be reasonably applied to healthy elderly men. Additionally in the TROG 96-01 trial, 6 months of ADT in addition to RT was shown to improve PrCa specific mortality in both men under age 70 and men 70 and over with locally advanced disease.[45] This trial was also limited to men without significant comorbidity and further illustrates the potential benefit of ADT in healthy elderly men.

For locally advanced PrCa, longer courses of ADT have been shown to be more effective. The EORTC 22,961 trial compared RT plus 6 months of ADT with RT plus 3 years of ADT and found the 3-year course to be superior to the 6 month course with 5-year overall mortality rates of 19% and 15%, and PrCa specific mortality rates of 4.7% and 3.2%, respectively[46] Long-term ADT of 2-3 years yielded similar results in other randomized controlled trials, especially for Gleason 7-10 disease.[40,43]

The optimal time course of ADT for older men with clinically localized high-risk disease has not been studied specifically, although a reanalysis of the DFCI trial by risk group concluded that 6 months of ADT in addition to RT in intermediate and high-risk localized PrCa improved overall survival for men with no to mild comorbidity.[47] This benefit was not seen in either risk group with moderate to high comorbidity. These same findings were found to be applicable to the elderly population (greater than 72.4 years) in a separate postrandomization analysis stratified by age group and comorbidity.[23]

It has been postulated that shorter courses of ADT may be sufficient for older men due to the slower rate of testosterone recovery after ADT. Results from an additional postrandomization analysis of the DFCI trial linked slower testosterone recovery times to improved PrCa specific survival rates after undergoing 6 months of ADT in addition to RT.[48] Since a majority of men over 70 had testosterone recovery times >2 years, shorter ADT regimens may be an effective treatment option for older men, although additional prospective study is needed to determine if shorter course therapy provides equivalent outcomes for older patients.

The benefit of short-term ADT in patients with intermediate-risk PrCa was examined in a recent retrospective review from the University of Texas M D Anderson Cancer Center.[49] Six months of ADT in addition to RT was found to improve failure free survival (FFS) for men with unfavorable intermediate-risk disease (Gleason 4 + 3 = 7 or at least 50% positive biopsy cores) who had no or mild comorbidity but did not improve outcomes for men with moderate to severe comorbidity. A separate analysis stratifying the cohort by age found an FFS improvement in both men less than age 70 and men age 70 and older. Furthermore, in both age groups, this benefit was more pronounced in men with no or mild comorbidities.[50] This study and post-hoc analysis of the DFCI randomized trial suggest that although healthy older men with intermediate-risk PrCa benefit from ADT, men with moderate to severe comorbidities may not benefit from the addition of ADT to RT. The ongoing RTOG 0815 randomized trial evaluating the addition of ADT to dose-escalated RT stratifies men based on severity of comorbidities and will provide higher level evidence for the use of ADT in intermediate-risk PrCa.[51]

ADT is not recommended by the NCCN or the AUA 2007 guidelines as treatment for low-risk disease or as primary treatment for localized PrCa but men continue to be offered ADT in clinical practice. In large scale SEER and CaPSURE studies of treatment patterns in men over age 75, 27-43% of men with localized PrCa and 15% of men with low-risk PrCa received primary ADT treatment.[16,52] Considering the side effect profile of ADT especially in the elderly, clinicians should minimize the unnecessary usage of ADT.

Side Effects of ADT

ADT has a broad side effect profile that may be particularly harmful to elderly men with preexisting conditions. Side effects include decreased bone mineral density, increased lipid stores, decreased muscle mass, fatigue, loss of libido and exacerbation of cardiovascular disease.

GnRH agonists decrease bone mineral density steadily for the duration of treatment, significantly increasing the risk for fractures in men with PrCa.[53] Older men with baseline osteopenia or limited mobility may be at even a greater risk for falls after ADT administration and subsequent hospitalization, immobility and mortality. Attention to fall hazards, weight bearing exercise, calcium and vitamin D supplementation, and ambulation devices should be considered to prevent morbidity from ADT induced osteopenia.

The metabolic effects of ADT may lead to increased fat mass and decreased muscle mass within months of initiating treatment and may lead to eventual dyslipidemia and reduced insulin sensitivity. In a SEER Medicare study, GnRH agonist use was associated with an increased risk of diabetes and coronary artery disease.[54] The American Heart Association and American Urological Association issued a statement in 2010 suggesting a relationship between ADT and cardiovascular risk.[5] Furthermore, D'Amico found that men over 65 who were randomized to ADT had a shorter time to myocardial infarction than those not receiving ADT (Fig. 5).[55] However, there is still controversy over the influence of ADT on cardiovascular mortality. A recent meta-analysis of 8 randomized trials found no association between ADT and increased risk of cardiovascular death in unfavorable risk PrCa, but a positive association with lower PrCa specific mortality and all-cause mortality.[56] When the trials were stratified by

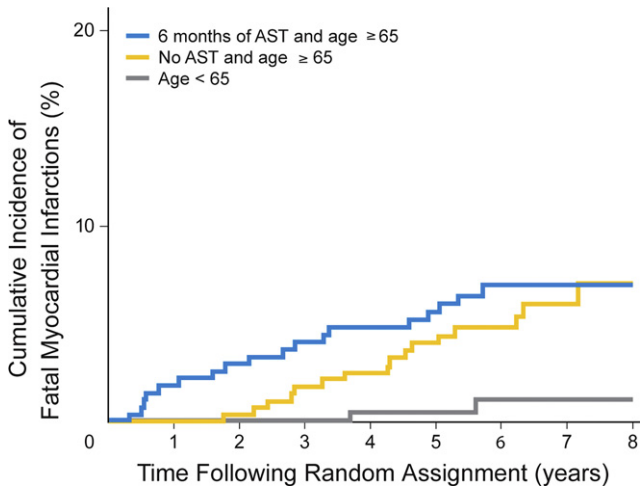

Figure 5 Shorter time to fatal myocardial infarction in men age 65 and older randomly assigned to receive androgen suppression therapy. Reproduced with permission from D'Amico et al.[55] (Color version of figure is available online.)

age, ADT did not increase cardiovascular death in either group. However, many of these trials excluded men with significant comorbidity and did not perform analyses stratified by comorbidity. Therefore, this study cannot definitively comment on the effect of ADT on patients with pre-existing cardiovascular comorbidity. Retrospective studies focusing on men with cardiovascular disease show poorer outcomes associated with ADT use. Multiple reports have found the addition of ADT to RT to be associated with increased all-cause mortality in men with a history CHF or MI than those with no comorbidity in both favorable and high-risk disease.[57,58]

ADT suppression of testosterone also results in loss of libido, fatigue and a general increase in frailty in older men. Frailty describes the limited physiological reserve that often accompanies aging, causing an inability to withstand and recover from physiological insults. Bylow's review article on older men with PrCa found that ADT can accelerate the development of frailty in vulnerable older men measured by the 5 frailty components of weight loss, weakness, exhaustion, slow gait, and low activity.[59] Although 95% of men over 65 do not meet the frailty criteria, ADT has the potential to induce frailty in men who are on the border.

Older men also return to baseline testosterone levels much more slowly than their younger counterparts. After at least 2 years of ADT, men over 67 were found to have significantly higher median testosterone recovery time of 15 months compared to 6 months in men less than 67.[60] Elderly men may experience the side effects of ADT long after their last administered dose. Considering the harms of ADT, and its long-lasting effects on the elderly, care should be taken when prescribing ADT to the elderly by taking into account comorbidity status and the impact of treatment on functional status and quality of life.

Conclusions

PrCa is a disease that has a significant impact on the elderly population. Elderly men have the highest prevalence of PrCa as well as the highest mortality rate from PrCa. Observational studies show that clinicians tend to overemphasize patient age when weighing active and conservative therapy. As a result, clinicians are in danger of overtreating unhealthy elderly men with low-risk disease and undertreating healthy elderly men with high-risk disease. LE estimates that guide treatment decisions should take into account comorbidity and functional status in addition to chronologic age and tumor characteristics. Conservative management should be considered in elderly patients with low-risk PrCa, particularly those with severe comorbidity and definitive therapy should be discussed with healthy elderly men with intermediate to high-risk disease.

ADT in addition to RT has proven benefits that extend to select elderly populations. However, the side effects of ADT may override its benefits for some elderly men, especially frail men and those with significant comorbidities.

The elderly population is a very heterogeneous group with regard to health status and LE. When evaluating an elderly patient with PrCa, comorbidity status, functional status, potential side effects of treatment and patient preference should augment age as factors that guide treatment decisions.

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