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Management of localized prostate cancer in men over 65 years

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Purpose of review

With the pervasive use of prostate-specific antigen-based screening, many men in the US are now diagnosed with prostate cancer in their 50s or earlier. However, the majority of tumors are still detected among men over 65-years-old. The appropriate management of localized disease among these older men is controversial.

Recent findings

The US Preventive Services Task Force recently strengthened its recommendation against screening men over 75 years old. To date, however, screening among older patients remains common, and does not adequately reflect patient life expectancy. Older men are more likely to be diagnosed with higher-risk tumors, but are less likely to receive curative local therapy, and are more likely to be managed with primary androgen deprivation therapy. Careful active surveillance is an increasingly viable option for selected older men with low-risk tumors; focal therapy and low-intensity medical therapy may be emerging alternatives in the near future.

Summary

Decisions regarding both screening and treatment should consider patient comorbidity, life expectancy, and treatment preferences rather than chronologic age. Treatment also must be tailored to the level of tumor risk. Increased use of active surveillance, together with diet and lifestyle intervention, is appropriate for many older men with lower-risk tumors. Conversely, those with high-risk disease should not be denied the opportunity for curative local therapy on the basis of age alone.

Keywords

aged, health services research, prostate neoplasms, screening

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Introduction

National screening efforts including prostate-specific antigen (PSA) measurement beginning at age 50 have effected a change in the US in the epidemiology and demographics of prostate cancer, such that the disease is increasingly one of middle as well as old age. Nonetheless, between 2001 and 2005 the median age at diagnosis in the US was 68 years; 62.8% of prostate tumors were diagnosed among men aged 65 years or older, whereas 91.6% of prostate cancer deaths occurred in this age group. The age-adjusted incidence per 100 000 of prostate cancers increases steadily from 136.4 for men aged 50–54, to a peak of 983.7 for those aged 70–74; for those over age 85, the incidence is 676.3. At all ages, the incidence is higher for black men than for white men, with greater differences at younger ages [1].

In the era of PSA screening, prostate cancer has become increasingly likely to be diagnosed early and with low-risk features [2]. Moreover, given the prolonged natural history of the disease, most men, even those diagnosed at younger ages, will survive for years or decades even in the absence of curative therapy [3]. Recent, large reviews commissioned by the American Urological Association [4] and the Agency for Healthcare Research and Quality [5••] were unable to find sufficient evidence supporting any one treatment approach over another for the management of localized prostate cancer at any level of risk, in terms of either oncologic or quality of life outcomes. These trends complicate decision making for older men diagnosed with localized prostate cancer.

Prostate cancer screening among older men

The US Preventive Services Task Force (USPSTF) recently published updated recommendations regarding prostate screening, for the first time advising explicitly against screening men over the age of 75 [6•]. This recommendation is on the basis of a conclusion that the harms of screening outweigh the benefits in this age group. However, age is an imperfect proxy for life expectancy, failing to account for health status and comorbidity. Many men under 75 have limited life

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expectancy given multiple cardiac and other risk factors, whereas a growing number of those reaching 75 may expect over a decade of further good health [7]. A recent review of four comorbidity indices noted that all were able to predict overall survival at 6 years (although only the Charlson score predicted local prostate cancer treatment in a population-based registry) [8]. Indeed, the American Urological Association's updated 2007 practice guideline for localized prostate cancer states explicitly that life expectancy, rather than chronological age, should be considered in making treatment recommendations and decisions [4].

Moreover, a general recommendation against screening fails to account for the considerable variation in prostate cancer aggressiveness. Albertsen *et al.* [3] demonstrated that with long-term follow-up, two-thirds of men with high-grade (Gleason score 8–10) prostate cancer died of their cancer, even among men aged 70–74 at diagnosis, the oldest group included in the study. Twenty-year cancer-specific mortality for men diagnosed at age 65 is estimated at 10, 40, and 70%, respectively, for men with Gleason score 2–6, 7, and 8–10 tumors; even for men aged 75 and older, the risk of cancer-specific mortality for a Gleason 8–10 tumor is approximately 25% [9]. Tewari *et al.* [10], Cowen *et al.* [11], and Walz *et al.* [7] have published nomograms predicting overall survival on the basis of a combination of cancer-specific and general health criteria; use of a more sophisticated model such as these seems better able to guide decisions regarding screening than a guideline based solely on age. Age-specific reference ranges for establishing normal values among older men may also be appropriate, although these are not without controversy [12•].

Unfortunately, in practice it appears that age rather than life expectancy does in fact drive primary care provider decision making regarding PSA screening. A large study among men over 70 in the US Veterans Affairs population found that while screening rates fell with advancing age, from 64% for men 70–74 years old to 36% for men 85 years and older, comorbidity had a relatively minimal effect on screening. Among the whole cohort, 58% of the men in the best health were screened, compared to 51% of those in the worst health; among those over age 85, the respective screening rates were actually lower for those in the best health (34%) than for those in the worst health (36%) [13]. A set of recommendations, the Iowa Prostate Cancer Consensus, was recently released to help guide decision making among primary care providers regarding screening men over age 75 (reproduced in Table 1) [12•]. Promulgation of these guidelines, together with improved patient education, was able to reduce the likelihood of screening in this population by about 20% [14].

Prostate cancer diagnosed in older men tends to be higher risk than those detected earlier. Seventy-one percent of Gleason 8–10 tumors are diagnosed among men over age 65, and the proportion of tumors with low-risk features falls from over 50% among men diagnosed under age 50 to just over 30% among those in their 70s (Fig. 1) [9]. In a heavily screened population, such as US men, this phenomenon presumably reflects progression of disease among those who are not screened until later in life. In fact, the question of serial vs. de-novo screening among older men has been little studied or discussed in the recent literature. Nearly 10 years ago an analysis from the Baltimore Longitudinal Study of Aging found that of men with a PSA level of 1.0 ng/ml or less and 0.5 ng/ml or less at age 65, 93 and 100%, respectively, maintained a PSA level under 4 ng/ml over the next 10 years. The investigators thus estimated that 26–58% of PSA tests could be eliminated among the Medicare population if men with very low PSA levels at 65 were spared further screening [15]. It may well be the case, by extension, that screening can be safely stopped among men who have been serially screened and reach 75 years with a stable or slowly rising PSA, whereas men over 75 in good health who have never been screened or have had more rapidly rising PSA in the past should be offered the option, with the goal of detecting high-risk disease.

Prostate cancer treatment among older men

Overscreening and subsequent overdiagnosis of prostate cancer among older men is primarily a problem to the extent that treatment inexorably follows diagnosis, regardless of tumor or patient risk factors and comorbidities. An analysis from the CaPSURE national disease registry of patients treated in 1989–2001 found that even among men over 75 diagnosed with low-risk tumors (PSA $\leq$10 ng/ml, Gleason score $\leq$6, clinical stage T1c or T2a), watchful waiting/active surveillance was used relatively uncommonly, and most men received either radiation therapy or primary androgen deprivation therapy (PADT) given as monotherapy [16]. An analysis from Surveillance, Epidemiology and End Results (SEER) estimated that among those with low-risk disease (any patient with Gleason score 2–4 or a patient over 70 years old with Gleason score 2–7), 10% of those managed with radical prostatectomy and 45% of those receiving radiation therapy were potentially overtreated, with the greatest burden of overtreatment seen among those over 70. An important aspect of this analysis was the decision, on the basis of limitations of the data available in SEER, to include PADT with expectant management [17]. The true burden of overtreatment, then, may be even higher, especially among older men who are more likely to be managed with PADT alone [18].

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Table 1 The Iowa Prostate Cancer Consensus for screening among older men

Screening	
	Initiation of screening for prostate cancer in men older than the age of 75 years should be undertaken with careful consideration.
	Patients with risk factors (positive family history, African-Americans) should be advised regarding the potential treatment options and relative benefits.
	Survival benefit from treatment for prostate cancer is unlikely to accrue in men with life expectancy of less than 10 years especially if they have low-stage (T1), low Gleason grade (6 or higher) disease.
	If patients are unlikely to pursue further therapy or are deemed unlikely to benefit from treatment of known prostate cancer, then obtaining a screening or diagnostic PSA should only be done selectively.
	Healthcare providers should reassess the benefits of initiating prostate cancer screening in men 75 years or older through discussion with the patient before proceeding.
	If screening is pursued, age-based PSA values can be used to determine normal levels.
Previously screened patients	
	Before continuation of routine screening in patients 75 years or older, healthcare providers should reassess the benefits of such continued screening through a discussion with the patient.
	The discussion should involve an outline of the risks and benefits of screening.
	There is currently no concrete evidence that prostate cancer screening prolongs survival, particularly in older men.
	Discontinuation of prior screening for prostate cancer can be considered particularly in men who have many comorbidities, are not likely to pursue therapy, or do not have a functional life expectancy of at least 5–10 years.
	Diagnostic PSA testing can be initiated or restarted in all patients if warranted by symptoms suggestive of prostate cancer that would include but are not limited to: hematuria, irritative or obstructive voiding symptoms, bone pain, back pain, and/or involuntary weight loss.
Diagnostic evaluation	
	In men who have never previously had a serum PSA or if the most recent prior PSA was more than 5 years prior, who are subjected to screening and are found to have an abnormal PSA (greater than 4 ng/ml) with a normal digital rectal examination (DRE), we recommend that the PSA be repeated after an interval of 4–6 weeks given that such a repeat test may demonstrate considerable variability in PSA values that can preclude further evaluation.
	If the repeat value is greater than 6.5 ng/ml, further evaluation for prostate cancer should be pursued.
	Further evaluation may also be clinically indicated in men with a rapidly rising PSA, that is increasing at a velocity of greater than 0.75 ng/ml per year based on comparison with at least two prior PSA values drawn at least 6 months apart.14
	All providers are encouraged to consider further evaluation for prostate cancer in symptomatic men with a serum PSA greater than 6.5 ng/ml
	In any of these instances, referral to an urologist is encouraged after assessment of functional status and patient comorbidity levels.
	Tools for functional assessment include: Easter Cooperative Oncology Group (ECOG) performance status (0–2 recommended); Karnofsky performance scale (70 or greater recommended); and Activities of Daily Living (ADL) or Instrumental Activities of Daily Living (IADL) scales.
	Recommend documentation in the patient chart of the clinical plan of action after obtaining a serum PSA.

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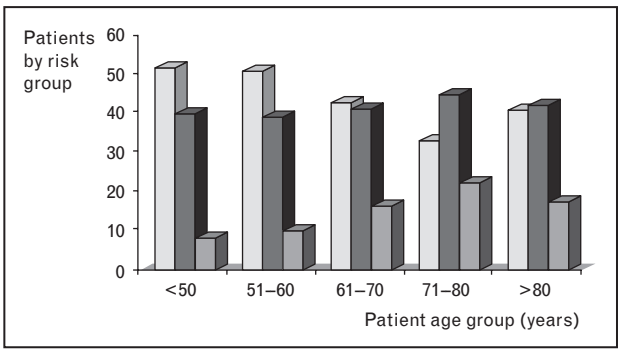
The issue of PADT monotherapy among older patients is an important one in light of growing awareness of the long-term side-effects of this modality – such as accelerated osteoporosis [19], cardiovascular disease [20], and cognitive decline [21] – which are particularly salient for the older population. Compared to men under 60, the likelihood of PADT rises with each subsequent decile: 1.2-fold, 3.0-fold, and 11.4-fold, respectively, among men in their 60s, 70s, and 80s [18]. Of note, a recent SEER-Medicare analysis of patients diagnosed in 1992–1999, of whom 31% received any androgen deprivation therapy within 6 months of diagnosis, found that the individual treating urologist accounted for 22.6% of the observed variation in use of androgen deprivation, compared to 9.7 and 4.3%, respectively, explicable by tumor or patient characteristics [22].

Figure 1 Distribution of men newly diagnosed with prostate cancer among low-risk, intermediate-risk, and high-risk groups, presented by age at diagnosis.



low risk; interm risk; high risk. Reproduced with permission [9].

Another recent SEER-Medicare study found that among this older population (median age 77), 41% of those diagnosed in 1992–2002 and not receiving local therapy were managed with PADT as opposed to surveillance/watchful waiting. Among this cohort of over 19 000 men, cancer-specific mortality was higher among men receiving PADT compared to those followed conservatively

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[hazard ratio 1.17, 95% confidence interval (CI) 1.03–1.33], and no difference was seen in overall survival. Among those with poorly differentiated cancer (Gleason 8–10), men receiving PADT had improved cancer-specific survival (hazard ratio 0.84, 95% CI 0.70–1.00) compared to those under conservative management, but no difference was seen in overall survival. The primary analysis in this study used an instrumental variables approach to adjust for unmeasured confounding in the large SEER-Medicare dataset; in a traditional Cox proportional hazards analysis, PADT patients overall had higher cancer-specific and overall mortality, and no benefit was seen for PADT even among those with high-grade cancer [23•].

The potential benefit of local therapy for older patients is no less controversial. A randomized trial comparing radical prostatectomy to watchful waiting found that patients undergoing surgery had a significant reduction in cancer-specific mortality, with a 5.4% absolute mortality reduction and a relative risk of 0.65 (95% CI 0.45–0.97) with a median follow-up of 10.8 years. However, a post hoc age-stratified subgroup analysis (prespecified but not stratified for in randomization) found that there was no benefit for surgery in terms of metastases, cancer-specific mortality, or overall mortality for men over 65 years of age at the time of diagnosis. It should be noted that over 40% of the tumors in this trial were symptomatic at the time of diagnosis, and just over 5% were detected following PSA screening [24•].

A utility-based analysis has found that for well differentiated tumors, prostatectomy or radiation therapy improved life expectancy, but not quality-adjusted life expectancy, at any age up to 75 years. Local therapy improved both life expectancy and quality-adjusted life expectancy for patients up to ages 75 and 80, respectively, with moderately and poorly differentiated tumors [25]. Of note, whereas the risk of complications following prostatectomy does rise approximately two-fold with every additional decade of age, the absolute risk remains low – under 1% – even for men in their 70s; as with oncologic survival outcomes, comorbidity rather than age is a more important consideration in predicting surgical complications [26].

Active surveillance and novel minimal-impact strategies

As noted above, conservative management, while elected as first-line management more commonly for older men than for younger men, is still underused for older men with low-risk disease. However, the current decade has witnessed a shift in the paradigm of conservative management from watchful waiting – implying deferring treatment (typically hormonal therapy) until clinically significant local progression and/or metastases are manifested – to active surveillance, denoting close monitoring with serial PSA measurements and repeat biopsies, and local treatment with curative intent applied if and when disease progression appears more likely [27•]. Indeed, recent data suggest that use of surveillance, while still relatively uncommon, is slowly rising [2].

Over 1000 patients followed with active surveillance at major centers have now been reported; while these reports confirm the feasibility of surveillance for selected patients, they have also highlighted the important problem that even extended-template biopsies will undergrade and/or understage a substantial proportion of tumors [27•]. A recent analysis of the various criteria used to define eligibility for surveillance across several large-reported series found that rates of undergrading ranged from 39 to 56%, and understaging in 13 to 26% among those expected to be good-surveillance candidates [28]. Awareness of this suboptimal accuracy of prostate biopsy in grading and staging tumors is a source of substantial anxiety for patients considering or attempting surveillance; indeed, anxiety has been found to be a strong predictor of ultimate treatment among those initiating conservative management [29].

Multivariable models have been proposed to predict 'indolent' prostate cancers [30]; although these have recently been validated [31], they are based on an accepted but relatively untested pathologic definition of indolence – an organ-confined tumor with Gleason score 3+3 and tumor volume of 0.5 cm^3 or less – which has not been demonstrated actually to predict the behavior of untreated cancer. Indeed, no existing model has in fact been validated to predict progression among surveillance patients. Given the relatively poor performance of existing models on the basis of clinical criteria alone in predicting outcomes on surveillance, it is hoped that emerging imaging strategies [32] and biomarkers [33] will facilitate improved risk stratification of the apparently low-risk population, and moreover that better risk assessment will produce better confidence and less anxiety on the part of both patients and clinicians, leading in turn to better acceptance of and adherence to surveillance protocols.

In addition to better markers for risk stratification, clinicians and patients need novel approaches for management of low-risk disease. One consequence of screening-driven downward stage migration has been the growing proportion of unifocal prostate cancers. Interest is therefore growing in the promise of focal therapy – the use of radiation or energy ablation targeted only to the area of the tumor as assessed by imaging or mapped biopsy results – to treat the cancer while minimizing morbidity and adverse quality of life effects. Several small series

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using cryoablation, and one using high-intensity focused ultrasound have been reported and recently reviewed [34]. Although they certainly require further prospective study, these emerging technologies may be particularly suitable for older men with low-risk tumors, for whom cancer control, as opposed to cure, may be sufficient.

The Prostate Cancer Prevention Trial has demonstrated the efficacy of finasteride in reducing the likelihood of diagnosis of prostate cancer. Given the known high-population prevalence of histologically detectable prostate cancer among older men, this agent could prove effective for secondary prevention of minimal burden disease; indeed a recent analysis of data from the study found that given its effectiveness across a range of risk strata, the agent likely exerts both preventive and treatment effects [35•]. Use of finasteride among men over 65 may have additional quality of life benefits given the high prevalence of symptomatic benign prostatic hyperplasia in this population.

Aggressive diet and lifestyle modification has been found effective in a small pilot study in effecting PSA decreases among men with low-risk tumors [36]. More recently, these interventions have further been shown consistently to modulate gene expression in a number of prooncogenic and antioncogenic signal transduction pathways [37•]. In considering the potential utility of these types of interventions, clinicians should remember that the leading cause of mortality of men of any age with prostate cancer remains cardiovascular disease, not prostate cancer [38]. The diagnosis of cancer is often a stimulus to patients to make lasting changes in diet and/or lifestyle; since the changes recommended for prostate cancer patients are largely consonant with those advised for improved cardiovascular health, interventions targeting improvements in these domains may in fact ameliorate the overall future burden of morbidity and mortality even for older men with lower-risk tumors [39].

Conclusion: is there, or should there be, an age bias in prostate cancer management?

As noted above, primary providers overall tend to overscreen older men for prostate cancer, and pay insufficient heed to comorbidity and life expectancy rather than age *per se*. Clinicians treating prostate cancer, for their part, appear to do little better in terms of tailoring treatments among newly diagnosed older men. An analysis from CaPSURE including over 2000 men over the age of 75 found that whereas older men were less likely overall to receive active treatment for prostate cancer compared to younger men, there was little evidence that either tumor-risk characteristics or patient comorbidities were adequately considered in decision making for patients in this age group [40]. Population-based data from Ontario, Canada likewise found evidence for an inappropriate age bias, demonstrating that age was a strong inverse correlation with likelihood of local treatment; in particular, radical prostatectomy was less likely to be offered to older men compared to younger men with a similar relative life expectancy, accounting for comorbidity and tumor characteristics [41].

Blanket recommendations against screening or treating men of a certain age, such as those released by the USPSTF, if widely adopted, would do a disservice to older men in otherwise good health who harbor high-risk tumors. These men account for a significant proportion of those diagnosed with high-risk disease annually, and face substantial tumor-related morbidity and mortality if undiagnosed and untreated. Older men with high-risk tumors appear to benefit from local therapy to the same extent as younger men, and should not be denied the option of curative treatment on the basis of age alone.

On the other hand, older men with significant comorbidity burdens should generally not be screened, in most cases should not be biopsied even if screened and found to have modestly elevated PSA levels, and should not be treated unless found to have high-risk disease. Even healthy older men with low-risk tumors generally will be excellent candidates for at least a trial of active surveillance, perhaps in combination with dietary and/or lifestyle interventions, and should be spared the potential morbidity associated with all currently available active therapies. If urologists and other clinicians cannot demonstrate that diagnosis will not always inevitably lead to treatment and that treatment can be used appropriately and selectively, it might be expected that public health policymakers will continue to attack the problem of overtreatment by discouraging screening. This trend would be a significant disservice to older men with high-risk disease.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 332).

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