

Treatment of localized prostate cancer in elderly patients

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Abstract: Prostate cancer is a disease of the elderly. According to National Cancer Institute, more than 56.7% of incident cases are diagnosed and more than 90% of cancer specific deaths occur in men greater than 65 years of age. Despite equivalent oncologic outcomes with treatment, primary local therapy is often deferred in elderly men with high-risk prostate cancer, in part due to concerns that post surgery quality of life (QOL) functional outcomes compare poorly to younger men. Our aim in this editorial is to discuss the functional and oncological outcomes in management of elderly with localized prostate cancer.

Keywords: Prostate cancer; local therapy; elderly patients

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Introduction

Treatment decisions for men newly diagnosed with localized prostate cancer are complex, and require careful consideration of the malignant potential of the primary tumor, patient life expectancy (LE), baseline quality of life (QOL), and expected change in QOL following definitive therapy. The purpose of the study by Hampson *et al.* (1) was to examine differences in QOL outcomes by age following treatment for localized prostate cancer.

Expert summary

Hypothesizing that declines in QOL after treatment would be less meaningful to older compared to younger men, Hampson *et al.* investigated changes in QOL outcomes over time by age using the CaPSURE database. CaPSURE is a longitudinal, observational cohort of approximately 15,000 men with all stages of biopsy proven prostate cancer enrolled at 43 community urology practices, academic medical centers, and VA Hospitals since 1995, and is unique in the fact that it predominantly represents outcomes for patients treated in community practice (2).

The analytic cohort included patients newly diagnosed with clinically localized (\leq cT3aN0M0) prostate cancer during 1999-2013 undergoing local treatment [radical

prostatectomy (RP), brachytherapy, EBRT] versus no local therapy [ADT, active surveillance/watchful waiting (WW)]. To meet inclusion criteria, all patients completed QOL questionnaires (RAND-36 short-form health survey, UCLA-Prostate Cancer Index) at the time of diagnosis and/or within 2 years after treatment. Following adjustment, QOL changes over time between age groups were compared using repeated-measures mixed models, utilizing an interaction term (age*time) to assess if the trajectory of QOL over time differed by age category. Secondary analyses adjusting for the same covariates were used to assess three-way interactions between age, time, and primary treatment.

Among 9,945 patients identified, 6,522 patients reported QOL data within 2 years meeting study criteria. Stratified by age (<60, 60-70, >70 years), older men had higher PSA at diagnosis, increased number of co-morbidities, higher clinical T-stage, higher biopsy Gleason Grade, and higher CAPRA clinical risk strata (all P values <0.01). A total of 44% of patients in the >70 years group underwent no local therapy compared to <5% in men <60 years of age and 11% in men 60-70 years of age (P<0.01).

Compared to younger men, men >70 years of age had lower baseline un-adjusted QOL scores in all domains (urinary function, urinary bother, sexual function, sexual bother, bowel function, bowel bother, physical function) except mental health. Over time, following adjustment for

clinical characteristics and treatment type, QOL differed by age group for all domains. For sexual and urinary domains, younger men had higher baseline scores, which declined at one year and then improved (but not to baseline values). Bowel function and bother domains were stable across age groups, except in men >70 years of age who reported less improvement in bother. At 2 years, declines in QOL were evident for sexual function, sexual bother, and urinary function regardless of age group, but the differences in QOL change were greatest in men <60 years of age.

Secondary analyses evaluating the impact of treatment type (local versus non-local) on change in QOL demonstrated that the largest differences in were noted in sexual function, sexual bother, and urinary function, most notably in those undergoing local treatment. At 2 years, more men <60 years experienced a decline in sexual function following local treatment (42% *vs.* 34%), whereas rates of decline in sexual function for men >70 years of age were similar between those undergoing local therapy and those who did not (43% *vs.* 45%). Adjusted scores for sexual bother and urinary function worsened after local versus no local therapy across age categories.

Summarizing these findings, the authors noted that older patients had lower unadjusted QOL scores both before and after treatment for all domains except mental health. However, in general, older and younger men experienced QOL declines in different ways. Men undergoing local therapy had lower post treatment urinary function scores compared to the no local therapy group regardless of age category. With respect to sexual outcomes, younger men had greater declines and better recovery in function, but experienced more bother over time when compared to older men. The authors concluded that age has a variable effect on QOL after treatment for localized prostate cancer, which has important implications for patient centered discussions regarding treatment options and patient's preferences regarding impact on QOL.

Expert comments

With the growing recognition that over diagnosis has resulted in the over treatment of early stage, screen detected prostate cancers, the dilemma of how best to treat an older patient with clinically significant prostate cancer has become over shadowed. However, as a gradual increase in the proportion of men presenting with locally advanced cancers is an anticipated consequence of the United States Preventive Services Task Force decision to

issue a Grade D recommendation against PSA screening in asymptomatic men (3), most experts agree that more focused recommendations for treatment of older men with high risk localized disease are needed.

It is an undisputable fact that elderly men with low risk disease and a limited LE are over treated with either RP or radiotherapy, and the most appropriate management strategy may be active surveillance (4). However, elderly patients show less effect from lead-time bias as they are screened and diagnosed at a later age and often present with more advanced disease compared to younger patients (5). High risk, clinically localized prostate cancers are not indolent and can have a significant deleterious effect on cancer specific survival in the absence of definitive local therapy. However, while RP and XRT are commonly employed for older patients with low and intermediate risk disease, older men with higher risk disease are less likely to be offered curative treatment (6), despite strong evidence to suggest a survival benefit with active treatment compared to conservative therapy or androgen deprivation alone (7-12). Although treatment decisions in elderly men are complex, reluctance to employ curative treatment in more elderly patients may be due to underestimation of LE, lack of definitive evidence demonstrating a survival benefit, and concerns regarding negative impact on QOL.

Estimating LE

Current guidelines are unclear when to offer primary treatment to elderly patients and likely impacts utilization of definitive therapy. The American Urological Association recommends RP or radiation therapy (RT) when the patient would have a reasonably long LE (13). "Reasonable" is left up to the discretion of the clinician. In comparison, the National Comprehensive Cancer Network guidelines recommend RP as a treatment alternative in men who have a LE of 10 years or more. RT is recommended as an acceptable strategy in patients with LE more than 20 years in low-risk, and an option in intermediate to high-risk regardless of LE (14). Although NCCN guidelines are more clearly defined, accurate LE calculations are still very difficult. Clinicians tend to grossly under-estimate LE and accuracy of clinician-predicted survival is limited (15-17). There is no definitive methodology of calculating accurate LE, which is based on both age and comorbidities. Life-tables themselves have a limited ability to predict LE in screened patients with prostate cancer, as healthier men than the general populations are usually screened (15).

Risk stratification and oncologic outcomes

Rather than relying on LE alone, prostate cancer risk stratification is paramount prior to offering treatment, as age may have less of an impact than tumor characteristics on mortality outcomes (18). Two randomized studies have showed a survival benefit from radiotherapy in combination with androgen deprivation therapy for men with high-risk prostate cancer, with a similar effect for men younger and older than 67 years of age (7,8). However, the comparative effective evidence base for RP in men with high-risk disease is lacking regardless of age.

The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a randomized clinical trial of RP and WW in men with localized prostate cancer diagnosed during the pre-PSA era, revealed a mortality benefit favoring surgery in men <65 years old and no benefit in men >65 years of age (19). However, application of the age cut-offs from SPCG-4 trial are challenging in the PSA era as these patients were not screened and therefore had a lower lead-time bias. While this trial demonstrated a survival benefit with treatment in patients with intermediate-risk prostate cancer, men with poorly differentiated prostate cancer on histology were excluded in the SPCG-4 study. As a result, it is very difficult to extrapolate these results to guide decisions in elderly men diagnosed in the contemporary PSA era with intermediate and high-risk disease. In comparison, the Prostate Cancer Intervention Versus Observation Trial (PIVOT), a trial randomizing men to RP or WW performed in the United States during PSA era, revealed no mortality benefit with RP at any age (20). In comparison to the SPCG-4 study, the PIVOT study included more men with cT1c disease with a PSA <10, and in post hoc analyses they observed that reductions in prostate-cancer mortality in the radical-prostatectomy group were more demonstrable in men with a PSA value that was greater >10 and in those with high-risk disease. In part due to misinterpretation of the existing evidence base, a recent study from Prostate Cancer Data Base Sweden (PCBaSe) illustrated that only 10% of men with high-risk prostate cancer aged 75-80 with Charlson Comorbidity Index (CCI) 0 received RT or RP despite 52% probability of 10-year LE, compared with approximately 52% of the men younger than 65 years with CCI 3 with similar 10-year LE (21).

Functional outcomes and QOL

Oncologic outcomes aside, localized treatment for

prostate cancer can have effects on urinary, sexual, and bowel function even up to 15 years after RP or RT (22) and these effects can vary by age. Historically, it has been assumed that younger men had a quicker and more durable return to function following RP. Retrospective review of a large single surgeon series reported improved long-term continence and sexual function outcomes in men less than 60 years of age (23,24). A large study from Germany evaluating 8,295 patients with normal continence and International Index of Erectile Function (IIEF) >18 who underwent RP between January 2009 and July 2013 showed similar trends among the elderly. One-year continence rates were 93.2% in men <65 years of age compared to 86.5% in men >75 years of age. Additionally, 1 year potency rates were 59.3% in men <65 years of age versus 31.3% in men >75. In multivariate analysis, older age showed a significant negative effect in both functional outcomes (25). Other large series have similarly showed the negative effect of age on sexual and urinary function (26,27).

In comparison, a number of studies have demonstrated that functional decline following RP may not be age dependent. Namiki *et al.* evaluated QOL outcomes in 143 men >70 years of age undergoing RP, and demonstrated improved emotional, mental health, and social functioning post-surgery compared to pre-surgery (28). While only 25% of patients returned to baseline sexual function level, 83% had reached baseline sexual bother. Herkommer *et al.* conducted a prospective single-center study to evaluate QoL using EORTC QLQ-C30 questionnaire preoperatively and every 3 months postoperatively in 374 patients with localized prostate cancer undergoing RP (29). Sexual and urinary functions were not assessed but the group assessed global health, cognitive function, social function, emotional function, physical function and role functioning. Comparing patients <60 and >70 years of age, no differences were demonstrated post operatively with respect to global health and cognitive functioning. Physical function remained stable postoperatively in men >70 years while it declined at 3 months and then returned to baseline in men <60 years. Social functioning and emotional functioning scores were higher in patients >70 years of age both preoperatively and postoperatively.

The findings reported by Hampson *et al.* nicely illustrate that changes in functional status following prostate cancer treatment are strongly influenced by pre-treatment QOL, and that the absolute differences when comparing pre and post treatment may not be as large as previously assumed. It is clear that use of absolute or unadjusted post treatment

outcomes will favor younger patients with improved pre-treatment functional status, but when rigorously measured over time and adjusted appropriately, age alone does not predict decline in QOL in most cases.

While the effect of localized treatment on functional outcomes can be quantified, it is more difficult to assess the natural progression of functional outcomes after WW or non-localized treatment. Furthermore, secondary procedures such as channel TURP, ureteral stents, and nephrostomy tubes are commonly performed to relieve obstruction from advanced prostate cancer, and the total burden of these events is poorly described in the literature. In addition, an analysis of patients in SPCG-4 (both RP and WW arms) age-matched against a non-cancer control group revealed the prevalence of erectile dysfunction to be 84% in RP and 80% in men treated with WW compared to 46% in the control arm. Additionally, prevalence of urinary leakage was documented in 41%, 11% and 3% of patients treated in the RP, WW, and control group respectively (30). These results indicate that functional outcomes can also be negatively affected by progression of untreated local disease and it is very likely that these outcomes are underestimated.

Conclusions

To summarize, age should not be the primary motivator in driving the decision to undergo primary therapy in patients with localized prostate cancer. Treatment decisions for localized prostate cancer are complex, particularly in men with high-risk disease who are at significant risk for development of local symptoms and metastases. Discussions should be patient centered and focus on individualized assessment of malignant potential, baseline functional status, and estimation of LE. Careful elucidation of each and every patient's QOL priorities as well as understanding of expected changes to QOL should be an integral part of these discussions regardless of age.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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