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Prostate Cancer

Impact of Age on Quality-of-life Outcomes After Treatment for Localized Prostate Cancer

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Abstract

Background: Men aged >65 yr are less likely to receive local therapy for prostate cancer (PCa), perhaps because of concerns about quality-of-life (QOL) outcomes.
Objective: To describe QOL before and after PCa treatment in men of varying ages.
Design, setting, and participants: Participants enrolled in CaPSURE who underwent radical prostatectomy, brachytherapy, external beam radiation, androgen deprivation therapy, or active surveillance for localized PCa.
Outcome measurements and statistical analysis: QOL changes over time were assessed among age groups using repeated-measures mixed models adjusted for race, year, clinical risk, treatment, comorbidities, and an age-time interaction term. Differences are reported as adjusted least-square means and percentage decline. Secondary analyses evaluated age and QOL for local (prostatectomy, radiation) compared to nonlocal treatment (hormonal, surveillance).
Results and limitations: Older men had lower mean unadjusted pre- and post-treatment QOL scores for nearly all domains. Of the domains evaluated, adjusted mean sexual function, sexual bother, and urinary function showed greater declines from baseline to 2 yr. At 2 yr, more men <60 yr than those >70 yr experienced declines in urinary function (14% vs 9%) and sexual bother (39% vs 17%). Declines in these domains were also greater for local than for nonlocal treatment.
Conclusions: Definitive treatment for localized disease should not be deferred for older men because of fears regarding QOL declines. Younger men should be counseled about potential post-treatment declines in QOL despite higher absolute QOL scores. Communicating these differences to patients will facilitate more appropriate treatment decision-making in men of all ages.
Patient summary: In this study we evaluated quality of life before and after treatment for localized prostate cancer in a diverse patient population. Declines in quality of life after treatment varied according to age and treatment. We conclude that counseling about quality of life will help patients of all ages to make more appropriate treatment decisions.

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1. Introduction

Prostate cancer is the most common malignancy diagnosed in men of all ages in the USA, with 57.5% of new cases diagnosed in men aged ≥65 yr and a median age at diagnosis of 66 yr [1–3] At the time of diagnosis, considerable emphasis is placed on integrating health-related quality-of-life (QOL) considerations into treatment decisions, which may be even

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more important in older patients who may have lower baseline QOL [4,5]. Knowledge about the varied effects of prostate cancer treatment modality on QOL domains can help to inform patients about the potential impact of a given treatment type and may improve treatment decision-making by allowing the physician to uniquely personalize counseling to reflect each patient's treatment preferences and objectives [6–9].

It is known that patient age also strongly influences treatment decision-making. Studies have shown that older men are less likely to receive potentially curative local therapy at any level of disease risk, perhaps in part because of fears about QOL outcomes after treatment for older patients [10–12]. However, older men are more likely to be diagnosed with high-risk disease and these individuals face a higher risk of cancer-specific mortality in the absence of local therapy [13–15]. Despite this, older men have comparable outcomes and cancer control after treatment for localized disease [16,17]. Therefore, the potential impact of treatment on QOL must be measured against the individualized risk of progressive cancer.

The associations between age and QOL outcomes after treatment in contemporary practice are not well defined [10,18,19]. Our objective was to describe QOL in men before and after primary treatment for prostate cancer, examining the impact of age on QOL outcomes. We hypothesized that while older men may have lower absolute function and bother at baseline and follow-up compared to younger men, declines in QOL after treatment would be less meaningful to older men, particularly in regard to their bother scores. To investigate, we performed a retrospective review of a prospectively maintained, nationwide, largely community-based prostate cancer registry with longitudinal QOL follow-up.

2. Patients and methods

Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a prospective, longitudinal, observational study of men with biopsy-proven prostate cancer [1,3]. CaPSURE includes data on men treated at 43 community-based, academic, and veterans' practices nationwide. Participating urologists consent and enroll patients consecutively within 6 mo after diagnosis, treat according to their usual practices, and follow the patients until study withdrawal or death. Site urologists report clinical, treatment, and outcome data to the registry. Patients report demographic, comorbidity, and QOL data at diagnosis, and complete QOL questionnaires at regular intervals following treatment. Informed consent and data reporting are coordinated under central institutional review board supervision.

Our cohort included men who were newly diagnosed with prostate cancer during 1999–2013, prospectively enrolled in CaPSURE, underwent primary treatment with radical prostatectomy (RP), brachytherapy (BT), external beam radiation (EBRT), primary androgen deprivation therapy (ADT), or active surveillance/watchful waiting (AS/WW), and completed QOL questionnaires at baseline and/or within 2 yr after treatment. Baseline QOL was reported before treatment for all but the AS/WW group. Men enrolled in AS/WW received no active treatment within 6 mo after diagnosis, so the baseline for this group was set to the diagnosis date plus 6 mo. Localized disease was defined as $\leq$cT3aN0M0 disease. Clinical risk at diagnosis was defined according to the University of California, Los Angeles (UCLA) Cancer of the Prostate Risk Assessment (CAPRA) score (0–10 scale). Validated CAPRA groups are classified as low (0–2), intermediate (3–5), or high (6–10) risk [4]. Age at diagnosis was categorized into three subgroups ($<$60, 60–70, $>$70 yr) for assessment. Prior studies have used similar age groupings to assess the impact of age on QOL [6] and have identified the $\leq$60-yr age group as a population at high risk of treatment-related effects on QOL [10], prompting our evaluation for these age categories.

General QOL outcomes were assessed using the mental health and physical function scales from the RAND 36-item short-form health survey (SF-36), a well-validated, widely used measure of physical and mental well-being [13]. Treatment-specific QOL was reported via the UCLA Prostate Cancer Index (PCI), which measures function and bother for urinary, sexual, and bowel domains [20]. Scores for all SF-36 and PCI domains range from 0 to 100, with higher scores representing better QOL. Outcomes were defined as changes in QOL scores over time from baseline up to 2 yr after treatment.

Demographics, clinical characteristics, and QOL scores were compared between age groups using the Mantel-Haenszel χ^2 test for trends for categorical variables. QOL changes over time between age groups were assessed using repeated-measures mixed models in which the independent variables included race, year of diagnosis, CAPRA score, type of primary treatment, number of comorbidities, age group, time, and time-age interaction. Least-square means for the age-time interaction term were used to assess whether the trajectory of QOL over time differed by age category, indicating whether younger men experienced the same pattern of change over 2 yr as older men. A set of secondary models with the same covariates addressed three-way interactions among age, time, and primary treatment. The five primary treatment types were regrouped as local (RP, BT, EBRT) versus nonlocal treatment (ADT, AS/WW) for these additional models. We performed pairwise comparisons using the Tukey-Kramer method to adjust for multiple statistical testing. Least-square means with confidence intervals from the mixed models were graphed to illustrate adjusted changes over time. We explored both continuous differences and the amount of decline for ease of clinical interpretation. Model covariates were selected a priori and assessed for interitem correlations. A p value <0.01 was considered significant. Analyses were performed using SAS 9.4 for Windows (SAS, Cary, NC, USA) and R statistical software (R Foundation, Vienna, Austria).

3. Results

Among 9945 men newly diagnosed with prostate cancer and enrolled prospectively in CaPSURE during 1999–2013, 8069 were diagnosed with localized disease and treated with RP, BT, EBRT, ADT, or AS/WW. Of those, 6522 (81%) reported QOL data within 2 yr and formed the study cohort (Fig. 1). Among the study cohort, 5362 men had multiple QOL assessments within 2 yr and were included in repeated-measures analyses. Men who were excluded from analysis owing to a lack of QOL data had a similar age distribution, but fewer were Caucasian (76% vs 90%), clinical CAPRA risk was higher (14% vs 10% CAPRA $\geq$6), and fewer underwent RP (56% vs 44%) in comparison to the final analytic group (all $p < 0.01$; Supplementary Table 1).

Patient characteristics are listed in Table 1. Of the patients, 27% were younger than 60 yr, 44% were 60–70 yr, and 29% were older than 70 yr. Older men tended to have higher biopsy Gleason grade, PSA at diagnosis, and clinical CAPRA scores (all $p < 0.01$). Of the cohort, 44% underwent RP (of whom 2% had RP + EBRT), 29% received radiotherapy (of whom 48% had BT, 38% had EBRT, and 14% had BT + EBRT), 18% had primary ADT (of whom 68% were treated

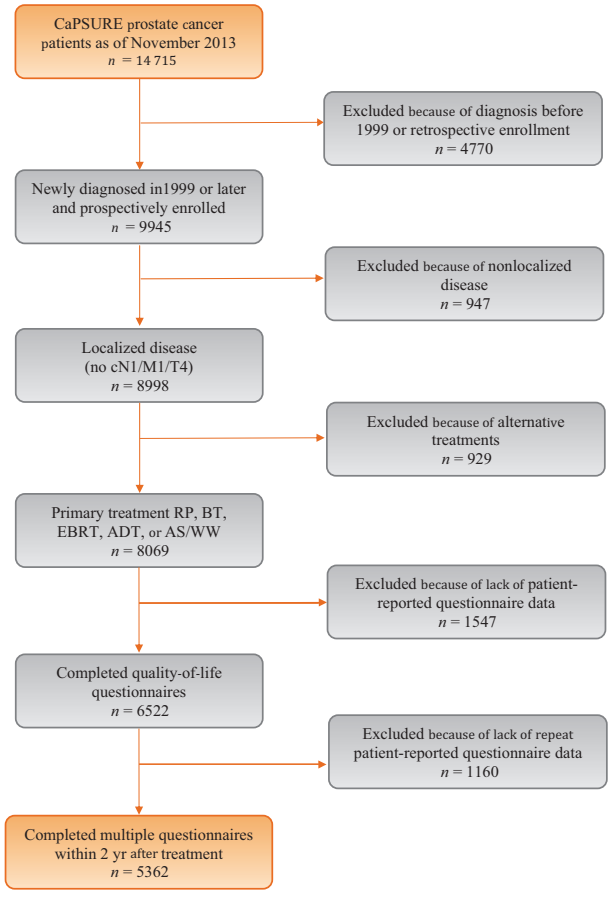

Fig. 1 – Cohort selection of men with prostate cancer enrolled in CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor). RP = radical prostatectomy; BT = brachytherapy; EBRT = external-beam radiation; ADT = androgen deprivation therapy; AS = active surveillance; WW = watchful waiting.

with a luteinizing hormone–releasing hormone agonist and 32% with an anti-androgen), and 10% enrolled in AS/WW (73% AS and 27% WW). Younger men underwent RP at a higher rate, whereas the oldest cohort of men more commonly underwent ADT or AS/WW.

At baseline, mean unadjusted physical function, urinary, and bowel scores were all ≥85, higher than the scores for mental health (79), sexual function (52), and sexual bother (61) for all ages combined (Table 2). Age was associated with all QOL scores ($p < 0.01$), with younger patients reporting higher scores for all domains except mental health. Baseline sexual, urinary, and physical outcomes differed across age groups by more than 10%. Treatment type was associated with all QOL measures except mental health ($p < 0.01$), but only sexual function, sexual bother, and physical function differed by more than 10% across treatment groups. Men who underwent RP (mean age 61 yr, standard deviation [SD] 6.9 yr) had better baseline scores in these domains than the other treatment groups (combined mean age 71 yr, SD 7.9 yr).

Over time, QOL differed by age group for all domains (all $p < 0.01$) in multivariate analyses adjusted for age at diagnosis, time since baseline, age-time interaction, race, number of comorbidities reported at diagnosis, clinical CAPRA score, year of diagnosis, and type of primary treatment (Fig. 2). For sexual and urinary outcomes, younger men had higher baseline scores, which declined at 1 yr, and then recovered somewhat better by 2 yr, although not to baseline levels. Bowel function and bother remained relatively stable for patients of all ages, except for the >70-yr age group, who reported less improvement in bother. Mental health scores started and remained highest for the >70-yr age group, but overall there was little change over the 2-yr period across all age groups. By contrast, baseline scores for physical function were lowest for the >70-yr age group and decreased at 2 yr in this group, but increased slightly for the other age groups.

Adjusted QOL means showed larger declines from baseline to 2 yr regardless of age group for the domains of sexual function (40–46%), sexual bother (17–39%), and urinary function (9–14%; Fig. 3 and Supplementary Table 2). More men aged <60 yr than men >70 yr experienced a decline at 2 yr in the domains of urinary function (14% vs 9%) and sexual bother (39% vs 17%). While a greater percentage of younger patients experienced a decline in sexual function at 1 yr (<60 yr 54% vs 60–70 yr 52% vs >70 yr 42%), fewer reported an overall decline in sexual function by 2 yr (<60 yr 40% vs 60–70 yr 44% vs >70 yr 46%).

Secondary analyses of treatment impact (local vs nonlocal treatment) on QOL demonstrated that the domains most affected were sexual function, sexual bother, and urinary function, with larger declines after local compared to nonlocal treatment, depending on age. At 2 yr, more men aged <60 yr experienced a decline in adjusted mean sexual function after local than after nonlocal treatment (42% vs 34%), while rates of decline for men aged >70 yr were similar for the treatment groups (43% vs. 45%). Adjusted mean scores for sexual bother worsened after local versus nonlocal treatment both for men aged <60 yr (41% vs. 25%) and men aged >70 yr (18% vs 12%). Declines in urinary function were also associated with local treatment, with men aged <60 yr, 60–70 yr, and >70 yr reporting declines of 15%, 14%, and 11%, respectively.

4. Discussion

We found that age was associated with sexual and urinary changes in QOL after treatment for localized prostate cancer. Previous studies have found that younger age at the time of treatment is associated with higher QOL function scores after treatment [21,22]. Indeed, our data confirm that older men had lower unadjusted QOL scores both before and after treatment for all domains except mental health. However, our results show that younger and older men did not necessarily experience QOL declines in the same ways. While fewer men aged <60 yr compared to men >70 yr reported adjusted QOL declines in sexual function at 2 yr after treatment (40% vs 46% decline), they were more prone to worsening sexual bother than older men at 2 yr (39% vs 17%). This may indicate that because older men start with lower baseline QOL scores, they have lower recovery expectations than younger patients, or that older patients have developed greater resilience to QOL fluctuations over time [23]. In the

Table 1 – Characteristics by age at diagnosis for 6522 men with prostate cancer [a]

Parameter	<60 yr (*n* = 1732)	60–70 yr (*n* = 2869)	>70 yr (*n* = 1921)	*p* value [b]
PSA at diagnosis, median ng/ml (IQR)	5.2 (4.2–7.2)	5.7 (4.5–8.0)	7.0 (5.0–11.1)	<0.01
Number of comorbidities, median (IQR)	1 (1–2)	2 (1–3)	2 (1–3)	<0.01
Race/ethnicity, *n* (%)				
Latino/Hispanic	32 (2)	45 (2)	17 (1)	<0.01
African American	147 (8)	213 (7)	85 (4)	
Caucasian	1526 (88)	2559 (89)	1789 (93)	
Other or mixed	27 (2)	52 (2)	30 (2)	
Clinical T-stage, *n* (%)				
T1	1108 (64)	1783 (62)	983 (51)	<0.01
T2	608 (35)	1061 (37)	899 (47)	
T3	15 (1)	25 (1)	39 (2)	
Biopsy Gleason grade, *n* (%)				
2–6	1218 (71)	1814 (64)	987 (52)	<0.01
7 (3 + 4)	290 (17)	525 (19)	384 (21)	
7 (4 + 3)	126 (7)	261 (9)	235 (13)	
8–10	84 (5)	218 (8)	257 (14)	
CAPRA clinical risk, *n* (%)				
Low (0–2)	1115 (68)	1610 (60)	783 (45)	<0.01
Intermediate (3–5)	422 (26)	843 (32)	668 (38)	
High (6–10)	93 (6)	214 (8)	305 (17)	
Primary treatment, *n* (%)				
Radical prostatectomy	1450 (84)	1826 (64)	285 (15)	<0.01
Radical prostatectomy + EBR	29 (2)	30 (1)	3 (<1)	
Brachytherapy	104 (6)	348 (12)	319 (17)	
Brachytherapy + EBR	28 (2)	101 (4)	105 (5)	
EBR	36 (2)	226 (8)	346 (18)	
LHRH agonist/antagonist	26 (1)	129 (4)	376 (19)	
Anti-androgen medication	15 (<1)	63 (2)	176 (9)	
Watchful waiting	14 (<1)	45 (1)	77 (4)	
Active surveillance	30 (2)	101 (4)	234 (12)	

PSA = prostate specific antigen, CAPRA = Cancer of the Prostate Risk Assessment; EBR = external beam radiation; LHRH = luteinizing hormone–releasing hormone; IQR = interquartile range.
[a] Values might not sum to the total number of men because of missing data.
[b] Analysis of variance for PSA, comorbidities; Mantel-Haenszel χ^2 test for all other variables.

other QOL domains, however, there were only slight differences in the declines experienced between age groups.

Further exploration of all domains using three-way age-QOL-treatment interactions yielded data supporting previous studies that suggest that local treatments such as RP have an effect on QOL, depending on age [23–25]. Men undergoing local treatment tended to have lower QOL post-treatment scores and greater declines in terms of urinary function in comparison to the nonlocal treatment group across all age groups. However, differences in sexual outcomes were more age-specific; younger men had greater declines and better recovery in function but experienced more bother over time than older men. These results suggest that treatment modality should be selected for patients according to their individualized baseline characteristics, quality of life, and treatment objectives rather than merely their age.

This study has several limitations, such as its observational study design. Among 8069 men who were eligible for

Table 2 – Unadjusted quality-of-life scores at baseline for the whole population and by age at diagnosis for 6522 men with prostate cancer

Quality-of-life domain	All ages		<60 yr		60–70 yr		>70 yr		*p* value [a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
UCLA prostate cancer index									
Urinary function	92	13.3	94	12.1	92	12.7	90	15.8	<0.01
Urinary bother	85	23.4	89	19.7	85	23.1	80	25.9	<0.01
Sexual function	52	30.3	69	24.2	53	28.9	33	26.9	<0.01
Sexual bother	61	38.2	75	32.4	60	37.6	48	40.1	<0.01
Bowel function	88	13.6	89	13.4	89	13.2	86	14.3	<0.01
Bowel bother	89	20.3	92	17.6	90	19.0	85	23.5	<0.01
SF-36									
Physical function	85	21.4	91	18.6	87	19.5	76	23.8	<0.01
Mental health	79	15.9	76	16.9	80	15.9	81	14.6	<0.01

SD = standard deviation; UCLA = University of California, Los Angeles; SF-36 = 36-item short-form health survey.
[a] Analysis of variance.

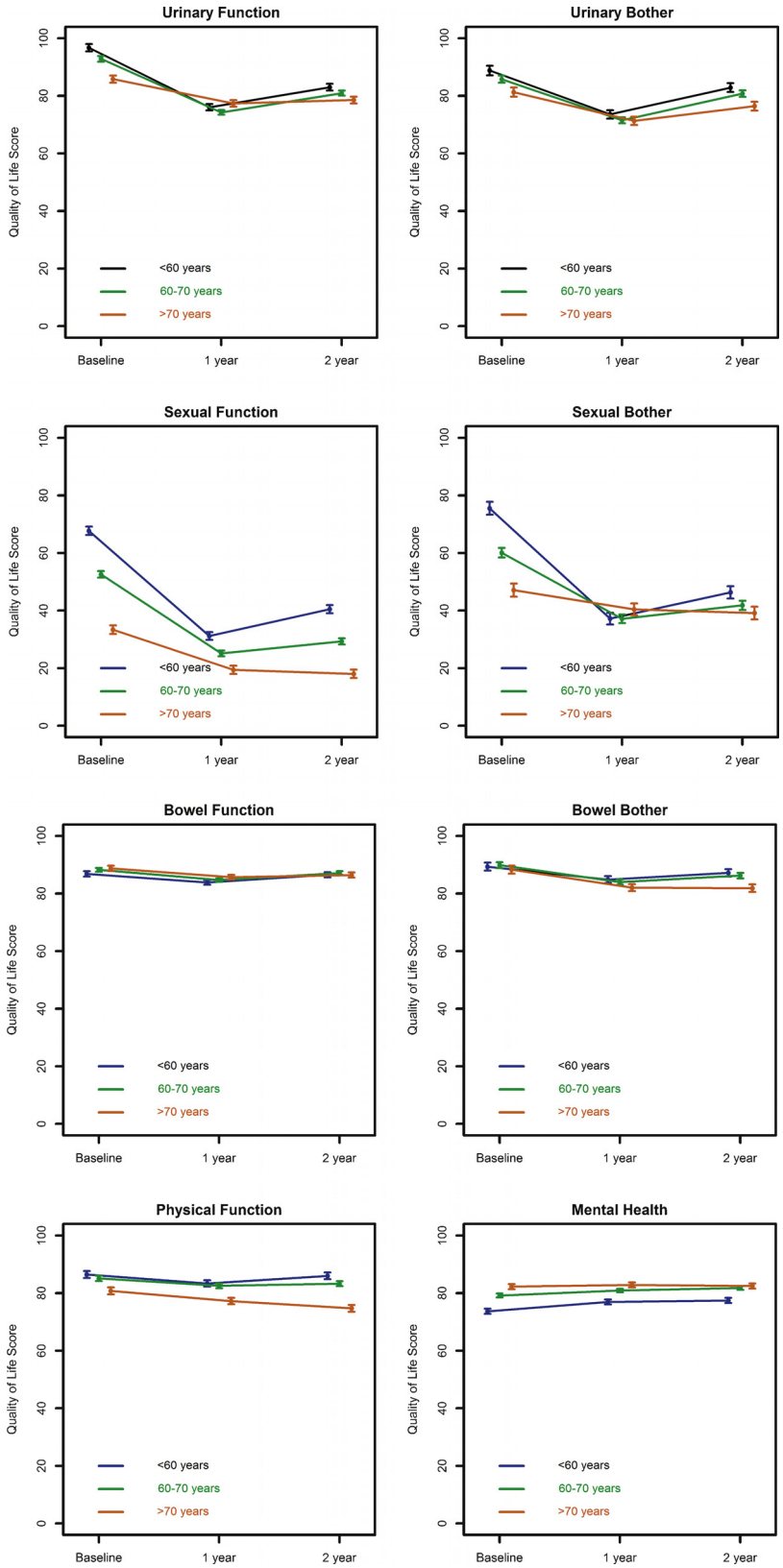

Fig. 2 – Adjusted least-square mean at baseline and 1 yr and 2 yr after treatment according to repeated-measures mixed-model results for quality-of-life outcomes for 5362 men who completed both baseline and post-treatment questionnaires. Error bars indicate confidence intervals.

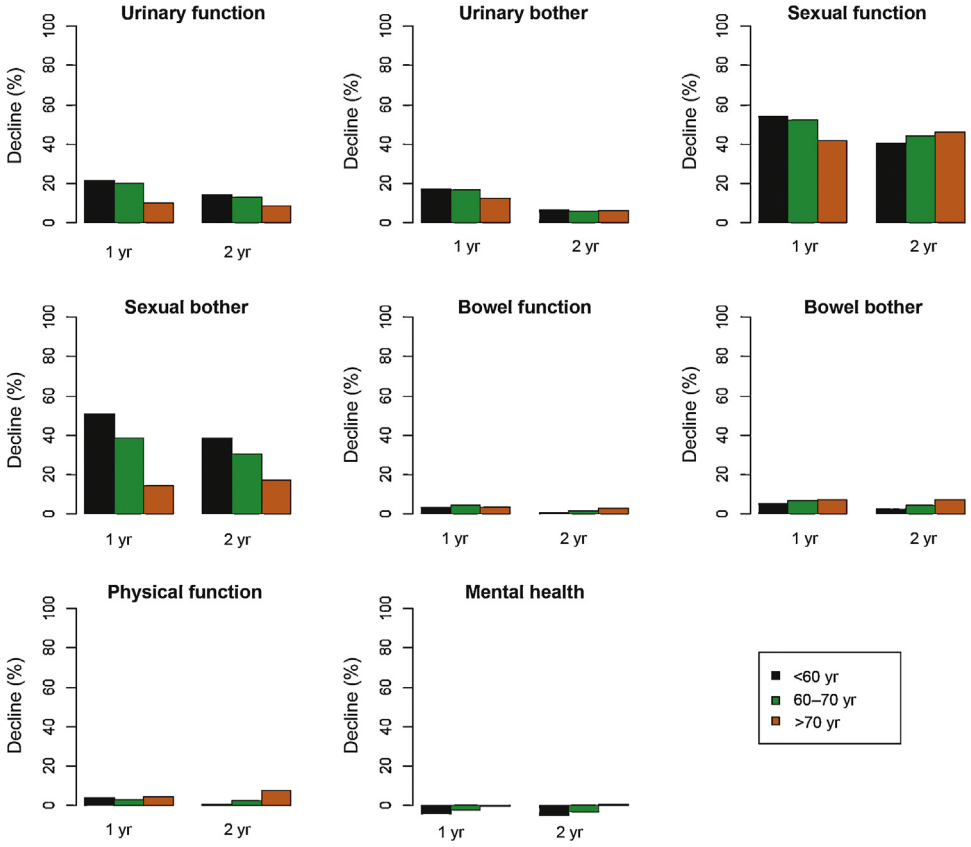

Fig. 3 – Adjusted percentage decline in least-square mean from baseline at 1 and 2 yr after treatment according to repeated-measures mixed-model results for quality-of-life outcomes for 5362 men who completed both baseline and post-treatment questionnaires.

inclusion, 66% completed pre- and postoperative QOL questionnaires necessary for analysis. However, men who were excluded from evaluation because of a lack of complete data had a similar mean age to our study population, differing only by the proportion of CAPRA $\geq$6 (14% vs 10%), race (76% vs 90% Caucasian ethnicity), and treatment type (56% vs 44% RP; all $p < 0.01$). Given that CAPRA risk and race are rarely be associated with risk of QOL declines, and that the mean age of the groups was similar, we feel that our analysis is representative of the larger cohort [26]. Our analysis used cutpoints to define categorical age groups. Age cutoffs can be difficult to determine, particularly when relying on chronologic age, but we selected these categories based on previous studies that have used similar groupings, and consider them to be representative of the population receiving treatment for localized prostate cancer. Finally, we were unable to reflect irritative and obstructive urinary symptoms using the UCLA PCI. Because the prevalence of benign prostatic hypertrophy increases with age and moderate to severe lower urinary tract symptoms are commonly identified in older men, the inability to evaluate these symptoms limited our conclusions for this domain [27].

The study also has a number of strengths, including the use of well-validated and widely used patient-reported surveys to assess QOL after treatment for prostate cancer. In addition, we used a large prostate cancer registry with 2-yr follow-up of more than 5000 men representing a wide array of practice types. Finally, we present our findings as both adjusted means and percentage change to enable readers to consider both statistical significance and clinical relevance.

The implications of these findings are significant; providers should use these data to better inform patients about treatment choices and to discuss the effect of age and type of treatment on future QOL. The data show that in most circumstances, age alone does not predict greater declines in QOL after treatment, and in some cases the opposite is the case. Therefore, treatment options for localized prostate cancer in older men should not be limited because of fears about declines in QOL after treatment. Regardless of chronological age, treatment decisions for men should be based on cancer risk, overall health, and life expectancy, as well as patient preferences for treatment characteristics and prioritization of QOL domains.

5. Conclusions

Age has a variable effect on QOL after treatment of localized prostate cancer according to the QOL domain and type of treatment. Understanding these nuances is important when discussing treatment options with patients. Determining a patient's own QOL priorities after treatment should be an integral part of this discussion to help in individualizing management choices. Ultimately, this approach necessitates taking QOL into account regardless of age, whether to

avoid deferring or delaying definitive treatment for older men whose age may have little effect on their QOL after treatment, or rushing to treat younger men with localized disease who may have more significant declines in QOL if treated at a younger age.

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Author contributions: Matthew R. Cooperberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hampson, Cowan, Cooperberg.
Acquisition of data: Cowan, Zhao, Cooperberg, Carroll.
Analysis and interpretation of data: Hampson, Cowan, Zhao, Cooperberg.
Drafting of the manuscript: Hampson.
Critical revision of the manuscript for important intellectual content: Hampson, Cowan, Cooperberg, Carroll.
Statistical analysis: Cowan, Zhao.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.01.008.

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