Published in final edited form as:

J Urol. 2010 June ; 183(6): 2206–2212. doi:10.1016/j.juro.2010.02.013.

Health Related Quality of Life for Men Treated for Localized Prostate Cancer With Long-Term Followup

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Abstract

Purpose—Men who undergo primary treatment for prostate cancer can expect changes in health related quality of life. Long-term changes after treatment are not yet fully understood. We characterized health related quality of life evolution from baseline to 4 years after treatment.

Materials and Methods—We identified 1,269 men in CaPSURE™ who underwent primary treatment for clinically localized prostate cancer and completed followup health related quality of life questionnaires for at least 4 years. The men underwent radical prostatectomy, external beam radiotherapy, brachytherapy, combined external beam radiotherapy/brachytherapy or androgen deprivation therapy. Health related quality of life was measured using patient reported questionnaires. Effects of select covariates on quality of life were measured with a multivariate mixed model.

Results—Age at diagnosis, time from treatment and primary treatment were significant predictors of health related quality of life in all domains ($p < 0.05$) except primary treatment on sexual bother. Men who underwent radical prostatectomy experienced the most pronounced worsening urinary function but also had the greatest recovery. All treatments worsened urinary bother, and sexual function and bother. All forms of radiotherapy moderately worsened bowel function and bother after treatment but eventual recovery to baseline was noted.

Conclusions—Age at diagnosis, time from treatment and primary treatment type affect health related quality of life. Treatment has a greater impact on disease specific than general health related quality of life. All treatments adversely affect urinary and sexual function. Most adverse changes develop immediately after treatment. Recovery occurs mostly within 2 years after treatment with little change beyond 3 years.

Keywords

prostate; prostatic neoplasms; quality of life; questionnaires; treatment outcome

An array of treatments exists for clinically localized CaP, including RP, EBRT, BT, CRT and ADT. Men with clinically localized CaP who undergo surgery or radiotherapy can

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generally expect excellent long-term survival with 67% to greater than 95% 10-year disease specific survival.¹⁻³ Thus, consideration of HRQOL after treatment is particularly germane since patients often base therapeutic decisions on the side effect profiles of different treatments.⁴

A number of investigators have examined HRQOL after CaP primary treatment but almost all focused on HRQOL outcomes during early survivorship, ie the first 2 years after treatment.⁵⁻⁷ We sought to better understand the long-term evolution of HRQOL in patients who underwent treatment for clinically localized CaP using an ongoing, community based CaP registry.

Materials and Methods

Study Participants

CaPSURE is a longitudinal, observational study of men with biopsy proven prostate adenocarcinoma. The data registry contains demographic and clinical data on more than 13,000 patients from a total of more than 30 participating community based, academic and Department of Veterans Administration treatment sites. Detailed information on baseline and posttreatment general and disease specific quality of life is collected biannually via mailed questionnaires. Patients are recruited consecutively and treated according to the usual practices of their urologists. Patients are followed until death or study withdrawal. All men in the CaPSURE registry provided informed consent for participation. Institutional review board approval was obtained at each respective participating site. Additional project methodology details were reported previously.⁸

The study population was drawn from a pool of 13,124 men enrolled from 1995 to 2006. To be eligible for study inclusion participants must have had clinically localized disease and sufficient followup HRQOL assessment, defined by completion of a baseline questionnaire and at least 4 years of posttreatment followup. A total of 1,352 men were eligible for inclusion. Patients who underwent cryotherapy or active surveillance were excluded from study due to small sample sizes, resulting in a final study population of 1,269. Of the participants 757 (60%), 154 (12%), 219 (17%), 75 (6%) and 64 (5%) underwent RP, EBRT, BT, CRT and ADT, respectively. All patients who received ADT were treated with a luteinizing hormone-releasing hormone agonist as monotherapy or combined with an antiandrogen.

Outcome Measures

Baseline, treatment and subsequent followup clinical data were provided by participating urologists. HRQOL data were collected by patient completed questionnaires including elements from SF-36^{®9} and UCLA-PCI.¹⁰ Each HRQOL domain was scored from 0 to 100 with higher scores representing better outcomes. Questionnaires were completed by patients at baseline, then every 6 months thereafter.

Statistical Analysis

We identified 7 categorical covariates that we hypothesized may impact posttreatment HRQOL, including primary treatment, age, time from treatment, race/ethnicity, marital status, secondary treatments and clinical risk defined by the modified D'Amico criteria.¹¹ Race/ethnicity, marital status and secondary treatments were not included in the final model due to the relative paucity of nonwhite men, single men and men requiring secondary therapy. We measured associations of clinical and sociodemographic factors by primary treatment received using the chi-square test. We analyzed baseline HRQOL among the 5 treatment groups using a multivariate model adjusted for age and clinical risk at diagnosis.

HRQOL modeling adjusted for primary treatment, age, clinical risk category, time from treatment, and interaction between primary treatment and time was done using a repeated measures mixed model. Repeated measures analysis considers the correlation of the recurring outcome in each individual, enabling it to account for missing and truncated data, and making it an optimal model for a longitudinal study. The adjusted mean domain scores of the general and disease specific HRQOL domains were the measured study outcomes. Independent variable statistical significance was considered at $p = 0.05$. All analysis was done SAS®, version 9.2.

Results

Baseline Characteristics

A total of 1,269 men underwent primary treatment for localized CaP. Table 1 lists clinical and sociodemographic characteristics by primary treatment. Significant differences in age, clinical risk, secondary treatments and relationship status were noted among the treatment groups (table 1). Significant differences in baseline PCS, urinary bother, sexual function, and bowel function and bother domains were noted among the treatment groups (table 2). Generally men who underwent RP had the highest baseline scores and those who underwent ADT had the lowest scores.

In the multivariate mixed model age at diagnosis and time from treatment were significantly associated with HRQOL in all domains. Primary treatment was significantly associated with HRQOL outcomes except sexual bother. No association was noted between clinical risk and HRQOL. Significant interaction was noted between primary treatment and time from treatment in all HRQOL domains. Table 3 lists multivariate mixed model p values.

HRQOL Evolution With Time by Primary Treatment

Mean summary scores in all 8 HRQOL domains with time were plotted for each treatment group after adjusting for the mentioned covariates (see figure).

General HRQOL (PCS and MCS)—Parts A and B of the figure show the evolution of general HRQOL during 4 years of followup. PCS remained stable in the RP, EBRT, BT and CRT groups throughout followup while a subtle gradual decrease was noted in the ADT group. No changes in MCS were noted with time.

Urinary function and bother—Worsening in the urinary function domain, which primarily assesses urinary incontinence, was noted immediately after treatment in the RP, BT and CRT groups. The initial decrease was greatest in men who underwent RP but subsequent recovery was also greatest. Beyond year 2 little change occurred in the surgery and radiotherapy groups. A subtle gradual decrease was noted in the ADT group. At the end of followup men who underwent RP had the greatest decrease relative to baseline (part *C* of figure). The urinary bother domain provides a more global assessment of urinary symptoms and is more likely to capture irritative and obstructive voiding symptoms aside from urinary incontinence. Notable decreases from baseline occurred in year 1 in all surgery and radiotherapy groups, followed by recovery between years 1 and 2. A subtle gradual decrease was again noted in the ADT group from baseline to year 4 (part *D* of figure).

Sexual function and bother—Significant worsening of sexual function was noted in all groups immediately after treatment with the greatest decrease for RP. The RP group experienced some recovery after year 1 while all other groups experience little or no recovery after the initial decrease (part *E* of figure). Sexual bother trends with time across all treatment groups were similar to those in the sexual function domain but recovery in men who underwent RP was more pronounced. Clear improvement was seen from years 1 to 2 with continued but more subtle improvement from years 2 to 4 (part *F* of figure).

Bowel function and bother—Men with RP experienced little change from baseline throughout followup. Men with all forms of radiation based therapy experienced slight worsening during year 1, followed by recovery almost back to baseline. Men with ADT also experienced a decrease until 2 years with no changes beyond 2 years (part *G* of figure). Bowel bother findings were similar to those of the bowel function domain (part *H* of figure).

Discussion

Similar to other published reports, we found that general HRQOL measured by SF-36 PCS and MCS changed little in men who underwent RP, EBRT or BT from baseline to year 2.^{5,12} We further noted that general HRQOL in these patients continued to remain unchanged at extended followup beyond 2 years. This finding agrees with 2 published reports of single institution data.^{13,14} The impact of CRT and ADT on general HRQOL has not been studied extensively. Our data indicate that, similar to the other primary treatments, neither CRT nor ADT significantly affected general HRQOL.

CaP primary treatments have been consistently shown to adversely impact disease specific HRQOL. Cross-sectional studies demonstrated that sexual and urinary function is adversely affected by surgery and radiotherapy compared to that in age matched controls.¹⁵ The Scandinavian Prostate Cancer Group Study indicated that urinary incontinence and erectile dysfunction were significantly more common after RP than in men treated conservatively with watchful waiting.¹⁶ Population based and multi-institutional studies showed that RP, EBRT and BT are associated with distinct patterns of change in urinary and sexual function.^{17,18} Our study, providing adjusted means summarized from patient reported HRQOL data during 4-year followup, confirms that RP and all forms of radiotherapy have clear negative impacts on urinary and sexual function.

RP is reported to be associated with a greater degree of urinary incontinence immediately after treatment than EBRT^{7,17} or BT,⁷ which we also noted. The degree of subsequent recovery was also greatest in our RP group but they experienced more residual urinary incontinence at the end of the 4-year followup. Men treated with CRT also experienced more severe incontinence than those treated with BT or EBRT.

The degree of incontinence alone does not correlate well with the degree of urinary bother,⁶ suggesting that irritative and obstructive voiding symptoms also contribute to bother. RP may cause more incontinence but radiotherapy may result in more severe irritative and obstructive symptoms.^{5,7,17} Our study shows that urinary bother worsened in the RP and in all radiotherapy treatment groups in year 1, followed by significant recovery in year 2 with little change thereafter. While men treated with RP generally experience worse residual incontinence at the end of 4 years, the degree to which they are bothered by urinary symptoms is remarkably similar to that in the EBRT and BT groups.

To our knowledge we report the first study of long-term HRQOL in men who underwent ADT for clinically localized CaP. Although ADT is no longer considered the standard of care for clinically localized CaP, it was historically used in this clinical setting. We were somewhat surprised by the subtle yet appreciable gradual decrease in the urinary function and bother domains in this group. To our knowledge the etiology of this decrease is unknown. It may be related to the physiological effects of androgen deprivation on the pelvic musculature and lower urinary tract in a manner analogous to the proposed role of estrogen in women with urinary incontinence.¹⁹ Further investigation is warranted to explore this hypothesis.

The greatest HRQOL decrease was observed in the sexual function domain. A large decrease was observed immediately after treatment in all groups with the largest for RP. Recovery was noted only in the RP group, mainly between years 1 and 2 after surgery. In contrast to 2 recent reports showing a sustained decrease beyond 2 years in men who underwent EBRT,^{13,17} we noted no further decrease after the initial decrease in year 1. The reasons for this discrepancy are unknown but may be related to differences in baseline sexual function between the study populations. Mean baseline sexual function was already low in all of our treatment groups.

Sexual bother domain results largely paralleled those of the sexual function domain but with a lesser decrease. This finding provides indirect evidence suggesting that while erectile dysfunction may be common, patients seem to adjust to these changes.

Bowel function and bother domain results were similar. Little change occurred with time in men treated with RP while all radiotherapy groups experienced a moderate decrease initially, followed by gradual recovery to almost baseline at 4 years. These results are similar to those in previous reports.^{14,17}

Our study has several limitations. Inherent selection bias due to the voluntary nature of the CaPSURE cohort may limit the generalizability of these data. Since followup is also voluntary, the possibility of nonrandom dropout must also be considered. However, when we compared men in the CaPSURE cohort with vs those without 4-year followup, we found

no difference in mean age and primary treatment between the 2 groups (Student's t test $p = 0.40$ and chi-square test $p = 0.80$, respectively).

We found no clinical risk significantly associated with HRQOL, which may reflect the stratification schema used. More sensitive nomograms may have further stratified risk in this patient group.

Our results must also be interpreted with the recognition that patients in each treatment group were not treated in uniform fashion. We could not adjust for variations and evolutions in technique, eg nerve sparing surgery, or protocols, eg intensity modulated radiation therapy. We did not control for neoadjuvant or adjuvant ADT in men treated with RP, EBRT, CRT or BT. The study intent was to provide some insight into common community based treatments. The potential use of neoadjuvant or adjuvant androgen deprivation should therefore be considered in conjunction with the primary treatment. We also did not separately analyze the impact of secondary treatments, which have been shown to negatively impact HRQOL.²⁰

While HRQOL domain specific summary scores are useful for analytical purposes, they can be difficult to interpret clinically. A 5 to 10-point change in SF-36 or UCLA-PCI is generally accepted to denote a clinically significant change^{10,21} but the actual impact of this change on the individual remains hard to quantify.

Our focus was not to directly compare changes in HRQOL among different primary treatment groups. Rather, we focused on a descriptive approach to characterize HRQOL evolution in each treatment group. We believe that these data on long-term HRQOL outcomes in a community based setting can help guide clinical decision making in the pretreatment and posttreatment settings.

Conclusions

Primary treatment, age at diagnosis and time from treatment were significant predictors of HRQOL during 4-year followup in men with clinically localized CaP. All treatment types adversely impact urinary and sexual function but do not appear to significantly impact the overall sense of well-being. The degree to which patients are bothered is not entirely determined by urinary incontinence or erectile dysfunction. Most recovery occurs within 2 years after treatment with little change beyond 3 years.

Acknowledgments

Supported in part by National Institute of Health Grant R01CA114524-03 (DFP).

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
BT	brachytherapy
CaP	prostate cancer
CRT	combined EBRT and BT
EBRT	external beam radiotherapy
HRQOL	health related quality of life
MCS	mental composite score
PCS	physical composite score
RP	radical prostatectomy

Figure.

Longitudinal adjusted mean scores on patient reported questionnaires. Higher scores indicate better quality of life. *A* and *B*, general quality of life. *D* to *H*, CaP disease specific quality of life domains. *A*, PCS. *B*, MCS. *C*, urinary function. *D*, urinary bother. *E*, sexual function. *F*, sexual bother. *G*, bowel function. *H*, bowel bother. Blue curves indicate radical RP. Red curves indicate BT. Yellow curves indicate CRT. Green curves indicate EBRT. Purple curves indicate ADT.

Table 1
Clinical and sociodemographic characteristics by primary treatment

	No. RP (%)	No. EBRT (%)	No. BT (%)	No. CRT (%)	No. ADT (%)	p Value
Age at diagnosis:						
Less than 55	117 (15)	3 (2)	8 (4)	1 (1)	3 (5)	<0.01
55–64	355 (47)	21 (14)	51 (23)	16 (21)	4 (6)	
65–74	273 (36)	80 (52)	123 (56)	40 (53)	25 (39)	
75+	12 (2)	50 (32)	37 (17)	18 (24)	32 (50)	
Clinical risk:						
Low	337 (47)	37 (25)	134 (65)	6 (8)	17 (27)	<0.01
Intermediate	267 (38)	58 (38)	56 (27)	40 (55)	22 (35)	
High	106 (15)	56 (37)	15 (7)	27 (37)	24 (38)	
Secondary treatment:						
None/unknown	687 (91)	117 (76)	198 (90)	63 (84)	37 (58)	<0.01
Yes	70 (9)	35 (23)	21 (10)	12 (16)	27 (42)	
Race/ethnicity:						
Asian	24 (3)	3 (2)	4 (2)	3 (4)	2 (3)	0.30
Hispanic	11 (1)	0	8 (4)	2 (3)	0	
Black	27 (4)	11 (7)	10 (5)	3 (4)	3 (5)	
White	694 (92)	139 (90)	197 (90)	67 (89)	59 (92)	
Other/mixed/unknown	1 (0)	1 (1)	0	0	0	
Relationship status:						
In relationship	713 (94)	128 (83)	196 (89)	62 (83)	52 (81)	<0.01
Single	37 (5)	22 (14)	18 (8)	11 (15)	11 (17)	
Unknown/missing	7 (1)	4 (3)	2 (2)	2 (3)	1 (2)	

Table 2
Pretreatment mean HRQOL summary scores by treatment group

	Mean $\pm$ SD RP	Mean $\pm$ SD EBRT	Mean $\pm$ SD BT	Mean $\pm$ SD CRT	Mean $\pm$ SD ADT	p Value
Unadjusted:						
PCS	53.7 $\pm$ 7.3	48.6 $\pm$ 9.0	49.0 $\pm$ 9.8	50.5 $\pm$ 9.0	43.5 $\pm$ 11.2	
MCS	52.1 $\pm$ 9.1	52.9 $\pm$ 8.9	53.3 $\pm$ 8.3	50.7 $\pm$ 9.9	52.5 $\pm$ 9.0	
Urinary function	93.6 $\pm$ 12.1	89.7 $\pm$ 12.8	93.0 $\pm$ 11.7	90.5 $\pm$ 13.3	89.8 $\pm$ 17.0	
Urinary bother	88.4 $\pm$ 20.4	80.5 $\pm$ 26.4	85.3 $\pm$ 22.8	79.5 $\pm$ 24.4	78.5 $\pm$ 13.1	
Sexual function	59.5 $\pm$ 27.3	33.9 $\pm$ 27.6	48.8 $\pm$ 30.1	36.1 $\pm$ 30.0	33.2 $\pm$ 27.4	
Sexual bother	66.4 $\pm$ 35.6	51.2 $\pm$ 41.1	57.5 $\pm$ 39.2	58.0 $\pm$ 38.6	55.2 $\pm$ 40.3	
Bowel function	89.5 $\pm$ 12.8	87.1 $\pm$ 13.7	89.4 $\pm$ 13.1	85.0 $\pm$ 14.3	84.2 $\pm$ 17.7	
Bowel bother	92.1 $\pm$ 17.7	86.7 $\pm$ 22.5	89.7 $\pm$ 19.8	87.5 $\pm$ 17.4	81.6 $\pm$ 27.2	
Adjusted:						
PCS	53.1	49.5	49.2	51.5	44.9	<0.01
MCS	52.5	52.5	52.6	50.9	51.4	0.61
Urinary function	92.9	90.7	93.3	91.9	90.9	0.33
Urinary bother	87.2	82.4	86.3	81.4	79.8	0.04
Sexual function	55.5	41.9	51.7	43.8	42.4	<0.01
Sexual bother	63.6	58.0	59.3	62.8	61.9	0.48
Bowel function	89.5	87.4	89.2	85.9	84.1	0.02
Bowel bother	91.4	87.8	90.2	89.0	82.5	0.02

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Table 3
Association between select covariates and HRQOL in multivariate mixed model

	p Value					
	Primary Treatment	Time From Treatment	Primary Treatment + Time From Treatment	Interaction	Age at Diagnosis	Clinical Risk Group
PCS	<0.001	<0.001	<0.001	<0.001	<0.001	0.27
MCS	0.008	<0.001	<0.001	<0.001	<0.001	0.12
Urinary function	<0.001	<0.001	<0.001	<0.001	<0.001	0.71
Urinary bother	0.002	<0.001	<0.001	<0.001	<0.001	0.20
Sexual function	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sexual bother	0.16	<0.001	<0.001	<0.001	0.005	0.46
Bowel function	<0.001	<0.001	<0.001	<0.001	0.02	0.77
Bowel bother	<0.001	<0.001	<0.001	<0.001	<0.001	0.35