International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Genitourinary Cancer

Health-Related Quality of Life After Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Results From a Multi-institutional Consortium of Prospective Trials☆

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Received Jun 25, 2013, and in revised form Aug 17, 2013. Accepted for publication Aug 19, 2013.

Summary

Self-reported quality of life (QOL) was prospectively measured from phase 2 trials of stereotactic body radiation therapy for prostate cancer. Transient decline in urinary/bowel domains within 3 months returned to baseline or better within 6 months and remained so. The same pattern was observed with good versus poor baseline function and was independent of early toxicities. Sexual QOL decline was predominantly observed within 9 months and not altered by androgen deprivation or age.

Purpose: To evaluate the early and late health-related quality of life (QOL) outcomes among prostate cancer patients following stereotactic body radiation therapy (SBRT).

Methods and Materials: Patient self-reported QOL was prospectively measured among 864 patients from phase 2 clinical trials of SBRT for localized prostate cancer. Data from the Expanded Prostate Cancer Index Composite (EPIC) instrument were obtained at baseline and at regular intervals up to 6 years. SBRT delivered a median dose of 36.25 Gy in 4 or 5 fractions. A short course of androgen deprivation therapy was given to 14% of patients.

Results: Median follow-up was 3 years and 194 patients remained evaluable at 5 years. A transient decline in the urinary and bowel domains was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years. The same pattern was observed among patients with good versus poor baseline function and was independent of the degree of early toxicities. Sexual QOL decline was predominantly observed within the first 9 months, a pattern not altered by the use of androgen deprivation therapy or patient age.

Conclusion: Long-term outcome demonstrates that prostate SBRT is well tolerated and has little lasting impact on health-related QOL. A transient and modest decline in urinary and bowel QOL during the first few months after SBRT quickly recovers to baseline levels. With a large number of patients evaluable up to 5 years following SBRT, it is unlikely that unexpected late adverse effects will manifest themselves.

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Conflict of interest: Aside from speaker honoraria for conference presentations, none of the authors have any conflict of interest regarding the content, treatment, drugs, or technology associated with this report.

Int J Radiation Oncol Biol Phys, Vol. 87, No. 5, pp. 939–945, 2013
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http://dx.doi.org/10.1016/j.ijrobp.2013.08.019

Introduction

The evolution of radiation therapy technology over the past 2 decades, which integrates 3-dimensional anatomy, conformal dose coverage, and image guidance combined with a deeper appreciation of the radiobiology of prostate cancer, has led to hypofractionated radiation therapy schedules. Consequently, substantial clinical data now exist from several studies including randomized trials using various moderately hypofractionated regimens, with dose-per-fraction ranging from 2.5 Gy per fraction for 70 Gy and 3.1 Gy per fraction for 62 Gy (1-9) and, more recently, extreme hypofractionation schemes of 7.25 Gy per fraction for 36.25 Gy to 10 Gy for 50 Gy (10-16) using stereotactic body radiation therapy (SBRT) approaches. Hypofractionation for prostate cancer, and in particular SBRT, results in a means of radiobiological dose escalation and potentially represents a therapeutic gain. It also affords a more economical course of definitive radiation therapy, improves patient access to care, and enhances patient convenience.

So far, data from published prostate SBRT trials have shown late grade 3 gastrointestinal and gastrourinary toxicities to lie within a 1%-3% range (10-16). Lacking, however, is an assessment of long-term quality of life (QOL) outcomes after prostate SBRT. In 2011, we formed a consortium for prostate SBRT with a 2-fold purpose: first to analyze all of the currently available clinical data and second to establish a centralized center for prospective data acquisition and analysis accessible to all current and future eligible centers. In an earlier report from this consortium based on 1100 patients (17), we showed 5-year prostate-specific antigen/relapse-free survival rates of 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively ($P<.001$). The current study from this consortium pools previously unpublished prospective data into a sufficiently large dataset and over a long enough follow-up period to provide a benchmark regarding the long-term health-related QOL outcomes following SBRT for prostate cancer.

Methods and Materials

Patients

In the present study, patients enrolled in separate Institutional Review Board-approved prospective phase 2 clinical trials and prospective protocols of prostate SBRT from 4 centers were pooled, yielding 864 patients treated between the years 2005 and 2012 (nb: this cohort is a subset of the 1100 patients of our publication on outcomes and is limited to those institutions with complete QOL data) (17). A separate Institutional Review Board for centralized data collection and analysis was obtained at this academic institution. Eligible patients had biopsy-proven newly diagnosed, nonmetastatic and untreated prostate cancer. For each trial, the endpoints included early and late urinary and rectal toxicities, questionnaire-based QOL measures with a validated instrument and prostate-specific antigen response.

Treatment

Fiducial-based image-guided SBRT was delivered with either the CyberKnife (Accuray Inc, Sunnyvale, CA) or with linac-based RapidArc technique on a Novalis Tx (Varian Medical Systems Inc, Palo Alto, CA). The treatment specifics from individual centers have been published previously (10-13). Differences among the 4 centers were relatively minor and primarily centered around dose, dosimetry, and dose fractionation. The course of radiation therapy consisted of a median homogeneous dose of 36.25 Gy (range 35-40 Gy) over 5 fractions for 84% of patients, and a median heterogeneous dose of 39 Gy in 4 fractions for the remaining 16%. For the homogenous planning, dose was normalized around the ~90% isodose line on average in order for the prescription dose to cover at least 95% of the planning target volume. Generally speaking, dose−volume histogram (DVH) goals for the rectum were such that the V50% <50% (ie, the volume receiving 50% of the prescribed dose was <50%), V80% <20%, V90% <10%, and V100% <5%. The bladder DVH goals were V50% <40% and V100% <10%. The femoral head DVH goal was V40% <5%.

A short course (median 4 months) of neoadjuvant and concurrent androgen deprivation therapy (ADT) was allowed at the discretion of the treating physician and given to 14% of patients.

Data collection, follow-up, and analysis

The Expanded Prostate Cancer Index Composite (EPIC) was used in each center (18). EPIC is a validated QOL instrument that consists of a set of 26 questions scoring urinary, bowel, and sexual domains. The resulting domain scores are then translated into a 0 to 100 scale, with higher values representing a more favorable health-related QOL or outcome satisfaction. Patient self-reported data were prospectively acquired at baseline and prospectively at 1, 2, and 3 months after SBRT and subsequently at 3- to 6-month intervals. A clinically relevant change in the QOL (or a minimum important change) was defined as a difference from baseline to follow-up that exceeded half a standard deviation of the baseline value as used in similar studies (19, 20). To compare the impact on QOL for patients with differing baseline characteristics a comparison was made between patients in the top 25th percentile versus the bottom 75th percentile for each domain. Similarly, to compare the impact on QOL for patients as a function of early toxicities (ie, within the first 3 months after SBRT), patients were stratified into quartiles based on the degree of their early decline in QOL for each domain. Lastly, to evaluate the outcomes on those patients with the poorest baseline function, the worst fifth percentile were identified and studied over time.

Results

The number of complete EPIC questionnaires available as a function of follow-up time is given in Table 1. The median follow-up for the 864 patients was 36 months, with 194 patients remaining evaluable out to 5 years. Median patient age was 69 ± 7.7 years. At baseline, the mean EPIC score for urinary and bowel domains revealed good baseline function with a narrow spread, 89 ± 12 and 95 ± 9, respectively, whereas for the sexual domain, it was consistent with the expectations for this age group, with a mean EPIC score 53 ± 28. Health-related QOL was evaluated as the change in score over time, stratified according to baseline function, use of ADT, or age at treatment. The mean change in EPIC scores

Table 1 Mean baseline Expanded Prostate Cancer Index Composite scores and change over time relative to baseline for all patients following prostate stereotactic body radiation therapy

Time	Number of patients	Urinary domain	Bowel domain	Sexual domain
Baseline	864	89 ± 12	95 ± 9	53 ± 28
1-3 mo	826	−8.7 [−9.5 to −7.8]	−12 [−13.1 to −11]	−5.1 [−6.5 to −3.7]
6 mo	500	−0.95 [−1.9 to 0.01]	−3.5 [−4.5 to −2.5]	−4.2 [−5.8 to −2.5]
9 mo	388	−2.9 [−4.1 to −1.7]	−4.0 [−5.1 to −2.9]	−6.1 [−8.1 to −4]
12 mo	658	−2.5 [−3.4 to −1.6]	−3.2 [−4.2 to −2.3]	−5.5 [−7 to −4]
24 mo	489	−0.6 [−1.5 to 0.3]	−1.1 [−2 to 0.2]	−6.1 [−7.9 to −4.4]
36 mo	388	0.4 [−0.6 to 1.3]	−0.85 [−2.2 to 0.5]	−7.3 [−9.3 to −5.3]
48 mo	271	1.9 [0.9 to 2.8]	0.6 [−0.3 to 1.4]	−10.6 [−12.4 to −8.7]
60 mo	194	1.8 [0.7 to 2.9]	0.9 [0 to 1.9]	−13.1 [−14.9 to −11.3]
72 mo	63	2.3 [0.9 to 3.7]	1.8 [0.6 to 3]	−13.7 [−16.2 to −11.1]

Negative values indicate a decline and positive values indicate an improvement over baseline scores. The 95% confidence interval is given in brackets.

over time for each domain for all patients is given in Table 1. For urinary and bowel QOL, a decline was most notable within the first 3 months, which had mostly recovered by 6 months, remained stable and actually showed improvement over baseline starting at around 3 years. For the sexual domain, the observed decline remained stable out to 2 years and thereafter declined progressively for the duration of follow-up. Graphically, change in QOL is shown in Figure 1 for the domains of urinary, bowel, and sexual function. A significant but modest decline in urinary QOL is observed within the first 3 months after SBRT, which had nearly returned to baseline approximately 6 months after treatment. For those patients with poorer function at baseline (in lower 25th percentile), a gradual improvement in urinary QOL was in fact observed beginning 6 months after treatment and progressing to better than baseline function over the 6 years spanned by the available data. No differences were seen with the addition of ADT or as a function of patient age. A similar trend was seen for bowel QOL, where a significant decline occurs within the first 3 months after SBRT that subsequently returned to baseline levels approximately 6 months after. A gradual improvement over baseline was also observed for those patients who start off with poorer baseline QOL (in lower 25th percentile). Again, there was no impact from the addition of ADT nor with age.

For patients reporting good baseline function (in the top 75th percentile with a mean EPIC sexual QOL score of 66), sexual QOL is observed to decline predominantly within the first 9 months and subsequently at a steadily slow rate out to 6 years. For patients with the poorest baseline function (in lower 25th percentile with a mean EPIC score of 13), there is little significant change in their poor baseline sexual QOL over time. The impact of ADT on sexual QOL occurs primarily within a 3- to 9-month timeframe after SBRT, returning to baseline by 12 months after treatment, which is likely a consequence of testosterone recovery. The rate of subsequent decline parallels that of patients who did not receive ADT. Age at treatment does not appear to have an impact on the effect of SBRT because the 2 curves remain parallel out to 6 years.

The degree to which "early" QOL decline (ie, defined as 1- to 3-months post-SBRT) influences the time to recover or the late function for each domain was studied by stratifying the early response into 4 distinct quartiles. The results are shown in Figure 2. For the urinary and bowel domains, those patients with the worst early problems (in lower 25th and 25th-50th percentile groups) recovery to near baseline levels was seen within 9 to 12 months. Thereafter, all groups converge to their baseline levels. For the sexual QOL domain, early response identifies those patients who will continue to experience issues long term, and the 4 quartile groups remain separate throughout the 6 years of follow-up.

Lastly, we examined whether patients with the poorest baseline function were more susceptible to lasting negative impact on their QOL from SBRT. The results are shown in Figure 3 in which we compare patients within the worst fifth percentile group at baseline relative to all other patients. For urinary and bowel domains, this worst fifth percentile group actually showed improvement above their baseline QOL, peaking around 6 months after SBRT, and thereafter becoming stable out to 6 years. For the sexual domain, there was initial improvement above the baseline EPIC score for this group (with scores near zero) that peaked around 12 months after SBRT (EPIC score ~20) and thereafter remained stable.

Discussion

The health-related QOL data accumulated thus far on 864 patients from 4 prospective trials allows for the reporting of the long-term clinical outcomes following prostate SBRT. The principal conclusions were as follows: *(1)* the transient decline in the urinary and bowel domains observed within the first 3 months following SBRT returned to baseline status or better within 6 months and remained so long term; *(2)* the same pattern was observed among patients with good versus poor baseline function and was also independent of the degree of early toxicities; *(3)* neither a short course of ADT nor age had an impact on urinary or rectal QOL; and *(4)* for those patients experiencing sexual QOL decline, it was predominantly observed within the first 9 months, subsequently stabilized and declined naturally with aging, a pattern not altered by the use of ADT nor patient age at treatment.

Several key studies have prospectively examined the importance of health-related QOL after definitive treatment for prostate cancer (20-23). A recent comprehensive study was that of Sanda et al (20) reporting EPIC-based QOL after prostate IMRT, brachytherapy, or surgery. That study, which followed patients out to 2 years posttreatment, showed patterns of urinary and bowel decline in scores after IMRT of a magnitude range of 10-15 EPIC score points, occurring at approximately 2 months post-treatment and returning to baseline scores at approximately 6 months. Those results are consistent with our analysis after SBRT. Similar to our study, that study also showed that the addition of ADT was not

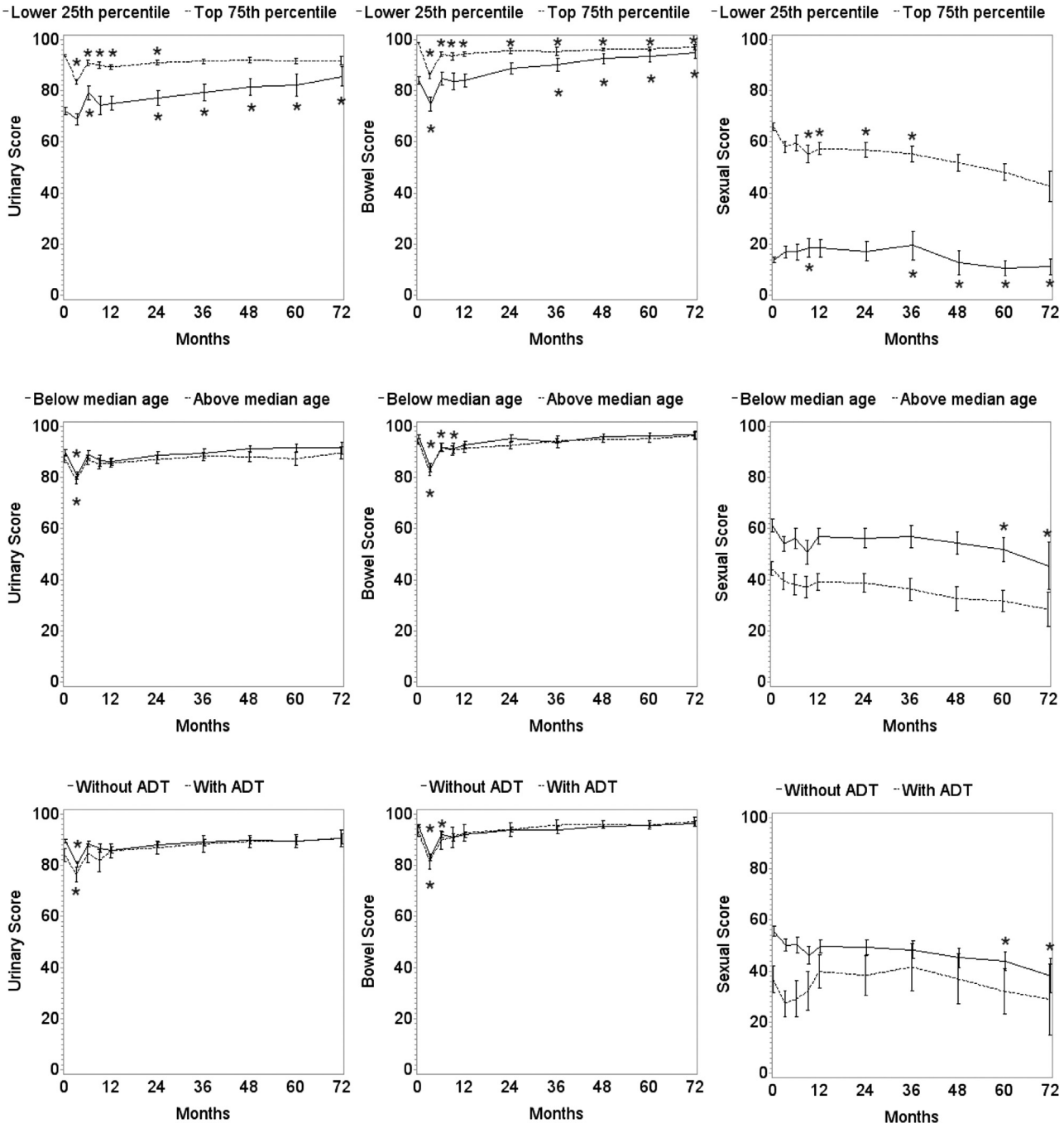

Fig. 1. The graphs show unadjusted mean quality of life scores over time for each domain stratified according to baseline level (top 25th percentile vs lower 75th percentile), use of androgen deprivation therapy (ADT), or age (younger vs older than median age). Scores from the Expanded Prostate Cancer Index Composite domains range from 0 to 100, with higher values representing a more favorable health-related quality of life. Asterisks (*) designate time points at which scores were clinically significantly different (either worse or better) from those at pretreatment baseline. Error bars represent 95% confidence intervals.

exacerbating. For the sexual QOL domain, that study showed decline of approximately 10 EPIC score points, peaking at around 2 months, again similar to our data after SBRT. In the Sanda study, the addition of ADT exacerbated sexual QOL long term, but in that study, the duration of ADT was not reported raising the possibility that prolonged ADT contributed to long-term sexual dysfunction. In the Pardo et al study (21), also using EPIC-based QOL to compare radical prostatectomy (RP), external beam radiation therapy to low-dose-rate brachytherapy without use of ADT, greater deterioration of urinary incontinence and sexual scores but better urinary irritative-obstructive results were observed with RP, whereas worse bowel symptoms were observed with external beam radiation therapy. Similarly, the Katz et al study (22) using EPIC-based QOL to compare RP with SBRT showed that largest differences in QOL occurred within the first 6 months after treatment, with larger declines following surgery in

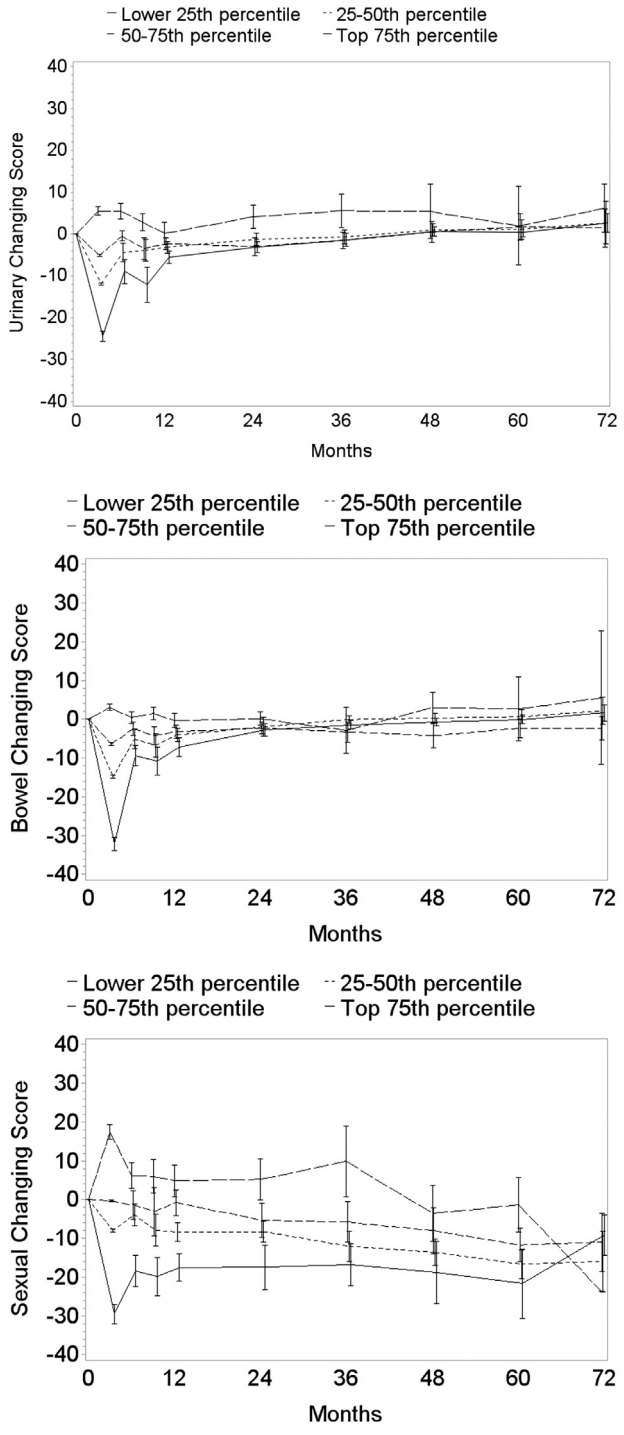

Fig. 2. The graphs show unadjusted changes relative to baseline mean quality of life scores over time for each domain (urinary, bowel, sexual) stratified into 4 quartile groups according to degree of initial decline in quality of life score within the first 3 months after stereotactic body radiation therapy. Error bars represent 95% confidence intervals.

urinary and sexual QOL compared with SBRT and a larger decline in bowel QOL following SBRT compared with surgery. Lastly, the Hoskin et al study (23) using the FACT-P (Functional Assessment of Cancer Therapy—Prostate) QOL instrument to compare EBRT alone or with high dose rate boost showed no differences in long-term QOL among patients randomly assigned to each treatment arm with up to 10-year follow-up. That study is particularly important in that it demonstrates a therapeutic advantage with hypofractionation because biochemical disease-free survival was superior with high dose rate boost compared with EBRT alone but did not result in worse sequelae.

Interestingly, our observations show that urinary, bowel, and sexual QOL recovers to better than baseline levels for the subset of patients with poorer baseline function (ie, worst 25th or fifth percentile). Naturally, this is not a beneficial consequence of SBRT but can be understood within the context of optimal management of those issues for trial patients with repeated access to physicians over a prolonged period. The current database did not document the use of alpha blockers, dietary modifications, or use of PDE5I phosphodiesterase-5 inhibitor during and after treatment, which would naturally yield improvements in QOL and is a limitation of this study. With respect to the sexual QOL for the age group represented by this study (median, 69 years), it is challenging to interpret because the prevalence of erectile dysfunction (ED) increases sharply between the ages of 60 and 70 years. In a large and recent epidemiologic study of US men, ED was present among approximately 15% of men 40-59 years of age, climbing to approximate 44% for men 60-69 years old, and approximate 70% for men aged >70 years (24). The incremental prevalence rate of ED is therefore on average 2%-3% per year. Consequently, longitudinal studies such as ours, which span ≥5 years, can expect to see an approximately 10% increase in ED measures simply from natural aging. Similarly, factors such as cardiovascular risk, hypertension, diabetes, and smoking were not specifically tracked in our study but are well-known factors affecting ED even after correcting for age (24). Nevertheless, our data clearly show that with judicious medical management the adverse effects resulting from SBRT can be overcome and compensated for, leading to an effective overall improvement in QOL relative to baseline. There did not appear to be a subset of patients in whom SBRT would be contraindicated because even those within the worst fifth percentile baseline urinary or bowel function were able to maintain, if not improve on, each QOL domain.

When considering toxicities, it is challenging to separate differences resulting from technique, that is, 3D versus IMRT versus IGRT versus SBRT, from those resulting of dose escalation or dose fractionation. Therefore, caution should be exercised when comparing SBRT, which inherently adopts smaller planning target volume margins and provides intrafraction IGRT. Comparison with IMRT was briefly discussed earlier in the article. To date, outcome studies following proton beam therapy are limited in scope and duration of follow-up. A recent study from the University of Florida Proton Therapy Institute (25) based on 262 patients (aged ≤60 years) with a median follow-up of 2 years showed a decline in EPIC scores of approximately 5 points for urinary and bowel scores, and 13 points for sexual score at 2 years posttreatment, results that are quite similar to those presented for SBRT.

Conclusions

After a transient decline in the first few months, the urinary and bowel QOL following SBRT for prostate cancer quickly recovers back to baseline levels or better within 6 months and remains so long term. Age, use of ADT, and the degree of early toxicities had

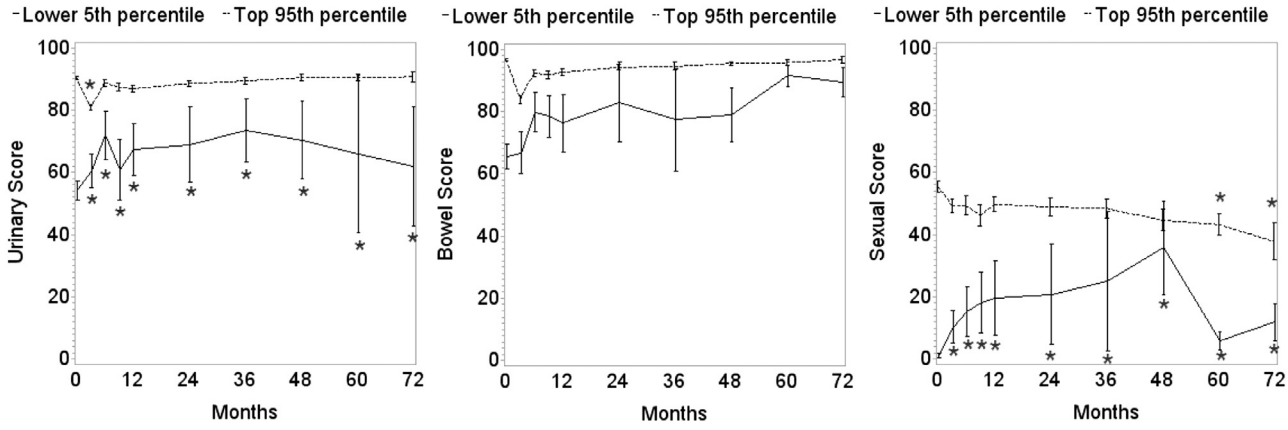

Fig. 3. The graphs show unadjusted mean quality of life scores over time for each domain (urinary, bowel, sexual) stratified according to patients with the worst baseline level (bottom fifth percentile) versus the remainder (top 95th percentile). Asterisks (*) designate time points at which scores were clinically significantly different from those at pretreatment baseline. Error bars represent 95% confidence intervals.

no impact on recovery. When present, most of the decline in sexual QOL is observed within the first 9 months. With such a large number of patients evaluable up to 5 years following SBRT, it is unlikely that unexpected adverse effects will manifest at later time periods. The current evidence regarding early and long-term health-related QOL supports consideration of SBRT among the definitive therapeutic options for localized prostate cancer.

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