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Patient-Reported Quality of Life Progression in Men with Prostate Cancer following Primary Cryotherapy, Cyberknife, or Active Holistic Surveillance

Glenn T. Werneburg, PhD¹, Michael Kongnyuy, MD², Daniel M. Halpern, BS², Jose M. Salcedo, BBA², Kaitlin E. Kosinski, MS², Jonathan A. Haas, MD³, Jeffrey T. Schiff, MD^{1,2}, Anthony T. Corcoran, MD², and Aaron E. Katz, MD^{1,2}

¹Stony Brook University School of Medicine, Stony Brook, NY 11794

²Department of Urology, NYU Winthrop Hospital, Mineola, NY 11501

³Department of Radiation Oncology, NYU Winthrop Hospital, Mineola, NY 11501

Abstract

Background—Technological advancements have led to the success of minimally invasive treatment modalities for prostate cancer such as CyberKnife and Cryotherapy. Here, we investigate patient-reported urinary function, bowel habits, and sexual function in patients following CyberKnife (CK) or Cryotherapy treatment, and compare them with active holistic surveillance (AHS) patients.

Methods—An IRB-approved institutional database was retrospectively reviewed for patients who underwent CK, Cryotherapy, or AHS. Quality of life (QoL) survey responses were collected every three months and the mean function scores were analyzed in yearly intervals over the 4 years post-treatment.

Results—279 patients (767 survey sets) were included in the study. There was no difference among groups in urinary function scores. The CyberKnife group had significantly lower bowel habit scores in the early years following treatment (year two mean difference: -5.4 , $p < 0.01$) but returned to AHS level scores by year four. Cryotherapy patients exhibited initially lower, but not statistically significant, bowel function scores, which then improved and approached those of AHS. Both CyberKnife (year 1 mean difference: -26.7 , $p < 0.001$) and Cryotherapy groups (-35.4 , $p < 0.001$) had early lower sexual function scores relative to AHS, but then gradually improved and were not significantly different from AHS by the third year post-treatment. A history of hormonal therapy was associated with a lower sexual function scores relative to those patients who did not receive hormones in both CyberKnife (-18.45 , $p < 0.01$) and Cryotherapy patients (-14.6 , $p < 0.05$).

Conclusions—After initially lower bowel habits and sexual function scores, CyberKnife or Cryotherapy-treated patients had no significant difference in QoL relative to AHS patients. These

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Corresponding author: Glenn T. Werneburg, PhD, Stony Brook University School of Medicine, 100 Nicolls Rd, Stony Brook, NY 11794, Phone: 516 535 1900, Fax: 516 535 1905, glenn.werneburg@stonybrook.edu.

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results highlight the benefit of CyberKnife and Cryotherapy in the management of organ-confined prostate cancer.

Keywords

Quality of Life; CyberKnife; SBRT; Cryotherapy; Active Surveillance

INTRODUCTION

Prostate cancer is among the most common cancers in men and, over 80% of cases are clinically-localized¹. Patients with clinically-localized prostate cancer have extended life expectancy (99% survival at 5 years), and thus post-treatment quality of life (QoL) is often a central factor in the patient's choice of treatment modality¹. Conventional prostate cancer treatments are effective for cancer control, but have been associated with decreased post-treatment patient-reported QoL in terms of urinary, bowel, and sexual function²⁻⁶. Thus, efforts have been made towards the development of novel minimally-invasive treatment modalities with the goal of similar cancer-control rates to the conventional treatments, but with improved patient-reported QoL⁷⁻¹². Cryotherapy and CyberKnife (CK) (Accuray, Sunnyvale, CA) are two such minimally invasive treatment modalities. Additionally, many patients with early-detected and low-risk cancers may elect to follow a surveillance protocol wherein they are monitored for disease progression with the goal of delaying or avoiding definitive treatment^{13,14}. Our institution's active surveillance protocol is termed Active Holistic Surveillance (AHS), and employs regular follow-up exams, PSA draws, reviews of symptoms, digital rectal exams, and yearly MRIs, along with dietary and supplemental recommendations¹⁵.

Cryotherapy is the controlled freezing of the prostate gland, wherein freeze-thaw cycles trigger protein denaturation, loss of blood supply, and apoptosis of prostate cells¹⁶. Cryotherapy is associated with an excellent biochemical recurrence-free survival rate – approximately 75% 2 years after treatment¹⁷. CK, precisely-targeted radiotherapy with large daily doses, also has a favorable biochemical recurrence-free survival – greater than 90% for low- and intermediate-risk prostate cancer at 5 years¹⁸. Both Cryotherapy and CK have been associated with a transient decrease in post-treatment QoL relative to baselines, particularly with regard to sexual function¹⁷⁻¹⁹. The extent and progression of this QoL decline remain unclear in each of these patient cohorts. Importantly, it is also unknown how these patients' QoL compares to that of patients who defer definitive treatment for an active surveillance protocol.

Here, we report the progression of patient-reported QoL in terms of urinary function, bowel habits, and sexual function in the four years following minimally-invasive treatment modalities. We compare QoL in Cryotherapy and CK patients relative to QoL of those who opted for AHS. Further, we examine the effect of hormonal treatment on the QoL of patients who underwent CK or Cryotherapy.

METHODS

Database maintenance

An IRB-approved institutional prostate cancer patient database is prospectively maintained. Included in this database are the results of patient-reported QoL surveys. These surveys include the Expanded Prostate Cancer Index Composite (EPIC), the International prostate symptom score (IPSS), and the International Index of Erectile Function Questionnaire (IIEF). These three questionnaires are valid and reliable standards for the assessment of QoL in patients with prostate cancer^{20–22}. The results of each of these surveys, stratified by domain, are tabulated and recorded in the database, along with various patient characteristics and disease and treatment factors.

Survey dissemination

Informed consent was obtained from prostate cancer patients who then received survey sets at three-month intervals after the initiation of treatment or enrollment in the AHS protocol. Each survey set consisted of EPIC, IIEF, and IPSS questionnaires, and were disseminated either at patient appointments or via postal mail every three months. Results of these questionnaires were deposited weekly in the database, as discussed above.

Design and patients

The database was reviewed retrospectively for patients who underwent Cryotherapy, CK, or AHS as primary prostate cancer treatment from February 2011 to March 2017. Patients who completed at least 1 survey within the four years following treatment or initiation of AHS protocol were included in our analysis. Additionally, patients who underwent CK boost were excluded, as were patients who underwent salvage Cryotherapy.

Cryotherapy procedure

All patients who underwent CK and Cryotherapy had a negative metastatic work-up with abdominal, pelvic imaging and bones scans. The Galil Cryotherapy Surgical System (Galil Medical, Inc., Arden Hills, MN) was used by a single surgeon²³. Briefly, the prostate gland dimensions as well as location of the urethra, peripheral zone, and the distance to the capsule were recorded via transrectal ultrasound (TRUS) to determine the optimal geometric placement of the 17-gauge (1.47 mm) cryoneedles or 2.4-mm cryoprobes, and thermocouples. Under TRUS guidance, cryoprobes/needles were inserted through the perineum into the prostate and each was placed approximately 10 mm apart and within 5 mm from the capsule, using a brachy-style grid. In individuals with pronounced or irregular resection defects, transverse and sagittal TRUS images were used to optimally place the probes away from the urethral lining while still providing effective cancer control. Prostate tissue was rapidly cooled to the target temperature of -40°C or below. The ice ball was clearly visible on TRUS as it formed and was monitored continuously throughout the procedure. Two freeze-thaw cycles were performed under TRUS guidance according to standard protocols. Temperatures were monitored with thermal sensors to ensure complete ablation of targeted tissue. Collateral damage to the nerves and urethra was minimized using color Doppler TRUS and warming catheter temperature respectively. Procedures were

performed in an outpatient setting, and patients were discharged with a temporary indwelling urethral catheter for 5 days ²⁴.

CyberKnife procedure

The CyberKnife system consists of a 6-MV linear accelerator mounted on a robotic arm. Two orthogonal kilovolt X-ray imagers allowed for real time imaging guidance with automatic motion correction. An MRI was obtained and fiducial markers were placed transperineally two weeks prior to the procedure, to help track motion during the procedure. Four fiducial markers were placed: two at the apex and two at the base. One week prior to the procedure a CT-scan (1.5 mm cuts) fused to MRI was used to check for possible fiducial migration. A gross target volume (volume of prostate plus one half of seminal vesicles) was generated. The gross target volume was used to determine the planning target volume. Bowel prep was achieved with Dulcolax (Boehringer, Germany) and a fleet enema. A radioprotectant (amifostine mixed with saline [MedImmune, LLC, Gaithersburg, MD, USA] was also given rectally prior to each treatment. Throughout the prostate, a margin of 5–8 mm (3 mm posteriorly by the rectum) on the involved side was obtained. Real time fiducial marker software registration using pre-treatment CT data was used to determine patient positioning and prostate targeting. After the registration, the robotic arm automatically adjusted the accelerators to account for rotation and translational movements of the patient and prostate during the procedure. Five consecutive treatments of 35–36.25 Gy fractions, were then delivered in a period of 5 days ²⁵.

Analysis

Patient symptom scores in each of the EPIC domains (urinary function, bowel habits, sexual function), IIEF-erectile function domain, and IPSS were quantitated. Timing of the surveys was rounded to the nearest three months, severity score means and standard deviations were obtained, and data were plotted as a function of time following procedure or AHS enrollment. Statistical analysis was completed using two-tailed t-tests in Prism (GraphPad Software, Inc., La Jolla, CA), and results with p-values less than 0.05 were considered statistically significant. Overall curves were compared to one another using analysis of variance (ANOVA). A Bonferroni multiple comparison post-test was used to compare CK or Cryotherapy to AHS patients. Curves were then similarly compared at 12 month intervals: 0–12 months (post-procedural year 1), 13–24 months (post-procedural year 2), 25–36 months (post-procedural year 3), 37–48 months (post-procedural year 4). P-values were obtained and indicated with asterisks within their respective time intervals on the graphs. Data were smoothed for graphical representation. Similarly, a subset analysis was performed for patients who did or did not received hormone therapy. Patients who received Degarelix, Leuprorelin, or Bicalutamide prior to or after treatment, but before survey completion were placed in the hormonal therapy-treated group for analysis.

RESULTS

A total of 279 patients and 767 survey sets met the inclusion criteria. Yearly questionnaire numbers for CK, Cryotherapy, and AHS were for year 1: 86, 80, 17; year 2: 69, 96, 59; year 3: 52, 103, 71; year 4: 20, 52, 62 respectively. Patient demographics and mean quality of life

scores are indicated in Table 1. Briefly, overall median (range) age was 67 (46–85) years. Overall median PSA at time of treatment or AHS enrollment was 6.1 ng/ml. Both CK and Cryotherapy patients had a median pre-treatment Gleason score of 7, and AHS patients had a median Gleason score of 6 at time of enrollment. A significant difference ($p<0.05$) was observed among the three cohorts for all patient factors except prostate volume and urinary function scores. AHS patients had a median of 1.5 (range: 1–4) prostate biopsies during their active surveillance period.

Mean EPIC urinary function scores were 85.4, 87.9, and 87.1 for CK, Cryotherapy, and AHS patients, respectively ($p=0.073$). Mean EPIC bowel function scores were 88.9, 93.5, and 94.8 for CK, Cryotherapy, and AHS patients, respectively ($p<0.0001$). Mean EPIC sexual function scores were 40.6, 40.8, and 55.4 for CK, Cryotherapy, and AHS patients, respectively ($p<0.0001$).

Urinary function

Urinary function among CK, Cryotherapy, and AHS patients as determined by both EPIC ($p=0.82$) and IPSS surveys (0.08) exhibited no significant difference in the four years following treatment (Figure 1A). In EPIC, both CK and Cryotherapy patients exhibited an early trend toward lower initial urinary function scores. However, by 12 months, both groups had similar urinary function scores as compared to AHS patients. In IPSS, both CK and Cryotherapy urinary symptom scores initially declined. On a yearly basis, IPSS urinary symptom scores in Cryotherapy patients were significantly lower than AHS patients in year 2 (mean difference -2.2 , $p<0.01$), but returned to a similar level as AHS in years 3 and 4 post-treatment (Figure 2A).

When CK and Cryotherapy patients were stratified by whether or not they underwent hormonal therapy, there was no difference in urinary function between hormone-treated or non-hormone-treated patients compared to AHS patients. There was no significant difference between the urinary function scores of CK with or without hormones (mean difference: -2.8 , $p>0.05$) or between Cryotherapy with or without hormones (mean difference: -3.4 , $p>0.05$) (Figure 3A).

Bowel habits

Bowel habit scores among CK, Cryotherapy, and AHS patients were statistically significantly different as analyzed over the four-year post-treatment time course ($p=0.001$) (Figure 1B). Particularly, within post-procedural years 2 and 3, CK patients exhibited lower bowel habit scores relative to AHS patients (mean difference year 2: -5.384 , $p<0.01$; mean difference at year 3: -5.198 , $p<0.05$). CK patients' bowel function improved over the time course, and by year 4 exhibited no significant difference relative to AHS (mean difference -1.97 , $p>0.05$). Cryotherapy patients showed a similar trend, but their bowel function showed no significant difference relative to AHS patients over each yearly follow-up interval.

When CK and Cryotherapy patients were stratified by whether or not they underwent hormonal therapy, there was a significant difference in bowel habits between CK patients who received hormones and AHS patients (mean difference -7.745 , $p<0.05$) (Figure 3B).

Sexual function

Cyberknife, Cryotherapy, and AHS patients differed with regard to sexual function in the four years post-treatment ($p < 0.001$). Specifically, in the first post-treatment year, both CK and Cryotherapy groups reported lower EPIC sexual function scores (mean difference -26.66 , $p < 0.001$; mean difference -35.41 , $p < 0.001$, respectively) relative to AHS (Figure 1C). Similarly, in the second post-treatment year, both CK and Cryotherapy patients' EPIC sexual function scores remained significantly lower than those of AHS patients, with mean differences of -13.99 ($p < 0.001$) and -10.00 ($p < 0.01$), respectively. By years 3 and 4, CK and Cryotherapy EPIC sexual functions scores returned to similar levels as AHS.

We then implemented the IIEF erectile sexual domain (the conventional erectile function questionnaire) score, which corroborated the EPIC questionnaire results, with a statistically significant difference among the CK, Cryotherapy, and AHS treatment groups over the 4 years post-treatment ($p < 0.0001$). With respect to the first year following treatment, Cryotherapy patients had a lower mean IIEF erectile function scores relative to AHS (mean difference -16.26 , $p < 0.001$) (Figure 2B). The difference decreased but remained significant during the second (mean difference -3.44 , $p < 0.05$) and third years (-5.05 , $p < 0.05$), but became insignificant in year 4 (-0.04 , $p > 0.05$). The CK patient population exhibited IIEF-erectile sexual domain scores that were stable but significantly lower only in year 2 relative to AHS patients (mean difference -3.98 , $p < 0.01$).

When CK and Cryotherapy patients were stratified by whether or not they underwent hormonal therapy, there was a significant difference in EPIC sexual function scores among hormone-treated patients, non-hormone-treated patients, and AHS patients ($p < 0.0001$). Particularly, CK patients who did not receive hormonal therapy reported better EPIC sexual function scores relative to those who received hormones (mean difference 18.45 , $p < 0.01$) (Figure 3C). Similarly, Cryotherapy patients who received hormonal therapy had better EPIC sexual function scores relative to those who did not receive hormones (mean difference 14.63 , $p < 0.05$). Cyberknife patients with or without a history of hormone therapy, had significantly lower EPIC sexual function scores relative to AHS (mean difference -32.45 , $p < 0.001$; -14.01 , $p < 0.05$, respectively). Also, Cryotherapy patients with or without a history of hormone therapy reported significantly lower EPIC sexual function scores (mean difference -28.67 , $p < 0.001$; -14.03 , $p < 0.05$, respectively).

DISCUSSION

Due to multiple management options and excellent disease control in prostate cancer, a strong emphasis is placed on post-treatment quality of life by patients, their partners, families, and physicians. Indeed, both the U.S. Preventive Services Task Force and the National Academy of Medicine indicated a need for the investigation of the harms and benefits of different prostate cancer treatment modalities^{26–28}. Our study is, to our knowledge, the first to compare QoL in CK and Cryotherapy patients with respect to active surveillance patients. Interestingly, we observe that in both CK and Cryotherapy patients, their QoL in terms of urinary, bowel, and sexual function, improves over time, approaching that of active surveillance patients. By four years after treatment, CK and Cryotherapy

patients had self-reported urinary, bowel, and sexual function no different from patients who underwent surveillance.

Recently, QoL after radiation therapy or radical prostatectomy was compared to active surveillance patients. Chen *et al.* observed a decrease in urinary and sexual function in the 3 months following treatment with radical prostatectomy, external beam radiotherapy, or brachytherapy as compared to active surveillance²⁹. At 24 months after treatment, nearly all symptom domains among the three treatment groups were similar to active surveillance patients. Barocas *et al.* reported similar QoL scores at 3 years for external beam radiation therapy but not radical prostatectomy, relative to active surveillance³⁰. At 3 years following treatment, there was a significant decrease in radical prostatectomy patients' sexual function and urinary continence relative to active surveillance. Our study sought to build on the insight provided by these studies and examine QoL in CK and Cryotherapy, emerging minimally invasive treatment modalities, as it compares with AHS.

Urinary function was measured in our study using both the EPIC and IPSS questionnaires, which address both irritative and obstructive urinary symptoms, as well as continence and hematuria. In the year immediately following treatment, both CK and Cryotherapy patients were observed to have a lower, though not statistically significant, EPIC urinary function scores relative to AHS. This is a classic post-treatment finding that has been shown in major studies comparing radiation therapy QoL to active surveillance^{29,30}. The urinary function scores for both CK and Cryotherapy patients then increased over the following years and became similar to the AHS cohort. These data suggest minimal difference in decline of urinary symptoms in CK or Cryotherapy patients in the four years following treatment relative to AHS.

Bowel habits following treatment were similarly monitored using scores in the bowel domain of the EPIC survey, which addresses rectal urgency, fecal incontinence, hematochezia, frequency, and caliber of stools. The initial significant post-treatment decline in bowel habit scores observed in CK patients may be attributed to radiation toxicity, and was consistent with the results for external-beam radiation therapy reported by Barocas *et al.* and Donovan *et al.*^{30,31}. CK toxicity is usually of lower grade compared to other radiation modalities and most patients progress to normal bowel function with time^{32,33}. Cryotherapy patients had no statistically significant difference in bowel habit scores relative to AHS patients in the four years following treatment. However, Cryotherapy patients had an early trend of lower scores, which then improved and approached AHS patient scores. These data suggest that following CK treatment, patients initially have more severe bowel symptoms relative to AHS patients, but these symptoms remit in the years following and become indistinguishable from those of active surveillance patients. Given the resolution of the bowel symptoms, our patient cohort does not appear to be subject to chronic radiation damage such as stricture, diminished rectal compliance, or decreased storage capacity³². Also, the difference in severity of bowel function between CK and Cryotherapy relative to AHS may be due the differences in underlying mechanism of action of these treatment modalities^{16,34}.

Sexual function was monitored using both the EPIC sexual domain and the IIEF-erectile function domain scores. In the EPIC, a lower sexual function following each treatment relative to AHS was initially observed, but a progressive increase was observed over the ensuing four years. Donovan *et al.*, reported similar outcomes in their patient cohort that received external beam radiotherapy³¹. The erectile function domain of the IIEF questionnaire corroborated these results, showing a similar trend in Cryotherapy patients. Our results suggest a significant recovery in sexual function following CK or Cryotherapy, with no difference between either definitively-treated group and AHS by the fourth year of post-treatment follow-up. Improvements in procedure and imaging technology (smaller gauge needles, thermocouples for temperature monitoring, multiparametric MRI, color Doppler TRUS) as well physician experience may minimize collateral damage to neurovascular bundles imparting favorable sexual function over time. Sexual function has been defined and studied independent of whether or not patients made use of sexual aids^{35,36}. Thus, we chose not to distinguish between patients who used PDE5 inhibitors in our analysis of sexual function. However, we note that approximately 25% of patients in each of the three treatment groups reported use of a PDE5 inhibitor. With or without the use of sexual aids, our results in sexual function are encouraging, as patients' subjective measure of this domain is a critical metric. Our data also reveal a trend of slowly decreasing sexual function in the AHS cohort over the four years after the onset of AHS. This observation may be attributed to age-related declines in sexual function. Some of our AHS patients had repeat biopsies, which may also have contributed to the slow and minimal decline of sexual function scores in this cohort, as has been suggested in the literature³⁷.

Katz *et al.* monitored patient quality of life following CK through analysis of EPIC questionnaires in a five year post-treatment follow-up, wherein they observed an initial one year decrease in each of the domains relative to baseline, but a subsequent increase and stabilization over the ensuing four years¹⁸. However, differences in QoL of these patients were compared to baseline scores, and not an active surveillance cohort. Our study demonstrates that these symptoms are no different from patients who opt for active surveillance by the fourth post-treatment year. In a study that analyzed patient-reported QoL after Cryotherapy, Robinson *et al.* reported initial declines in urinary, bowel, and sexual function, followed by an improvement toward patient baselines¹⁹. This study also analyzed patients only relative to their baseline scores, and our study corroborates and builds on these results, confirming that Cryotherapy patients have QoL scores not significantly different from AHS patients by the fourth post-treatment year.

Finally, we investigated the effect of hormonal treatment on QoL in men undergoing CK or Cryotherapy. Sexual function was appreciably lower in both groups who received hormones relative to those who did not undergo hormonal therapy, as was expected given the known effects of hormonal therapy including decreased libido and erectile dysfunction. We note that the hormonal treatment in each of these groups appears to play a larger factor in QoL than the treatment modality. For instance, both in terms of urinary function and bowel habits, patients who received hormones showed similar scores over the four post-procedural years in the CK or Cryotherapy groups. Similarly, patients who did not receive hormones showed similar scores, regardless of treatment modality.

Our analysis considered symptom scores following treatment, and did not compare post-treatment symptoms to patient baseline scores, a limitation of our study. Instead, our AHS cohort served as an internal standard against which comparisons were made over the course of the four initial post-treatment years, a strength of our study. Additionally, patients among the three studied cohorts were not randomized or matched, and thus initial urinary, bowel, and sexual characteristics may have differed among groups. Matching of our patient cohorts would have resulted in a small sample size, and as we continue to accrue data, a multi-institutional randomized, matched high-powered study will be performed. In spite of this limitation, this novel study provides the first post-treatment QoL comparisons of CK and Cryotherapy to AHS. The assumption of similar baseline scores among cohorts in our study is strongly supported by several reports in the literature – most recently, two prospective QoL comparisons of radiation, surgery, and active surveillance^{29,30}. These studies demonstrated no difference among their various cohorts' baseline QoL. Because this was a single-center study, its methodology was consistent, but its results may not be generalizable to other patient populations. Finally, this was a retrospective study that has inherent bias in patient selection.

Conclusion

This study provides critical insight as to the QoL outcomes of patients who have undergone CK or Cryotherapy relative to active surveillance patients. It is known that both CK and Cryotherapy have excellent biochemical recurrence-free survival. The current study demonstrates that they also have excellent self-reported QoL compared to active surveillance patients. These results underscore the utility of these minimally invasive modalities in the current and future treatment of prostate cancer.

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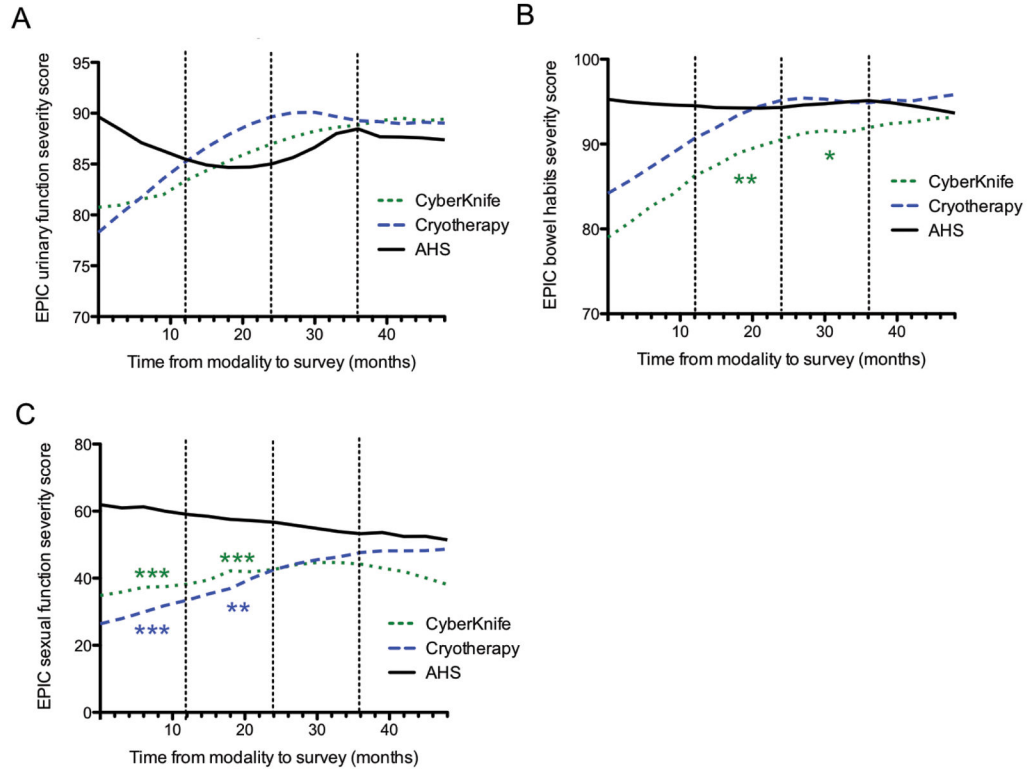


Figure 1. Prostate cancer patient quality of life in the 4 years following CK, Cryotherapy, or AHS as quantitated by EPIC questionnaire

Urinary function (A), bowel habits (B), and sexual function (C) are shown as quantitated by the EPIC survey over the four years following CK (dotted line), Cryotherapy (dashed line), or AHS (solid line). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

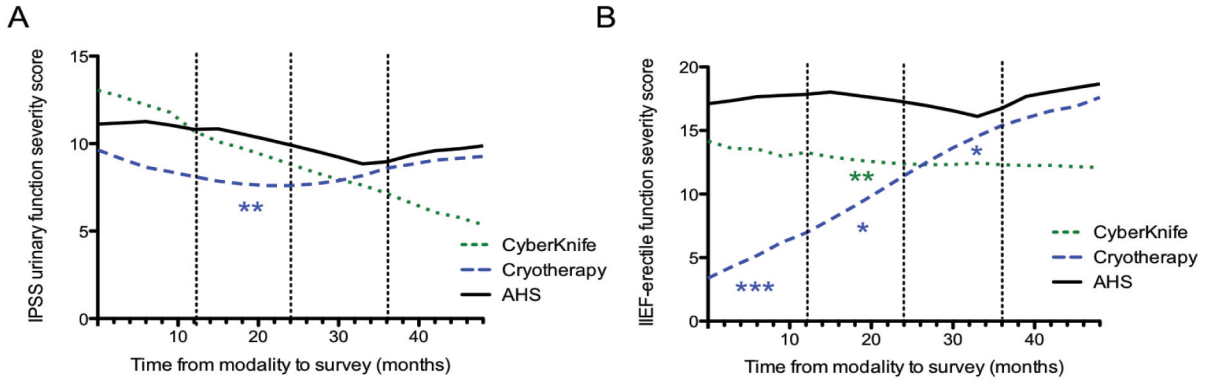


Figure 2. Prostate cancer patient quality of life in the 4 years following CK, Cryotherapy, or AHS as quantitated by IPSS and IIEF questionnaires

Urinary function (A) and sexual function (B) are shown as quantitated by the IPSS and IIEF-erectile questionnaires, respectively, over the four years following CK (dotted line), Cryotherapy (dashed line), or AHS (solid line). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

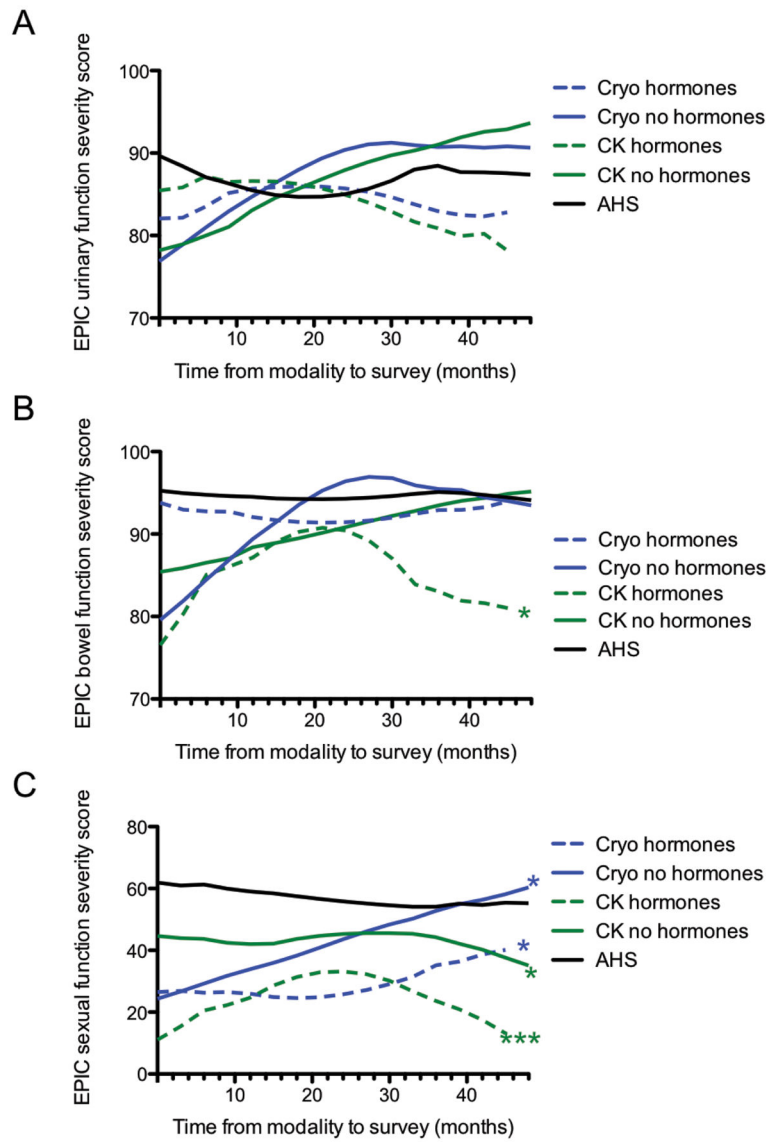


Figure 3. Hormonal treatment effect on QoL following CK, Cryotherapy, or AHS
 Urinary function (A), bowel habits (B), and sexual function (C) are shown as quantitated by the EPIC questionnaire over the four years following CK (green lines), Cryotherapy (blue lines), or AHS (black line), for patients who either received hormonal therapy (dashed lines) or did not receive hormonal therapy (solid lines). * $p < 0.05$, *** $p < 0.001$.

Characteristics of patients who underwent CyberKnife, Cryotherapy, or AHS as Primary Management for Prostate Cancer

Table 1

	CyberKnife (n=82)	Cryotherapy (n=129)	AHS (n=68)	Total patients (n=279)	p-value ¹
<i>Survey packets (EPIC/IIEF/IPSS) analyzed</i>	227	331	209	767	
<i>Median age</i>	66	69	66	67	0.02
<i>Race or ethnic group - no. (%)</i>					0.02 ²
White	73/82 (89.0)	99/122 (81.1)	63/66 (95.5)	235/270 (87.0)	
Black	8/82 (9.8)	15/122 (12.3)	3/66 (4.5)	26/270 (9.6)	
Hispanic	0/82 (0)	5/122 (3.6)	0/66 (0)	5/270 (1.9)	
Asian	1/82 (1.2)	1/122 (0.8)	0/66 (0)	2/270 (0.7)	
Other	0/82 (0)	2/122 (1.6)	0/66 (0)	2/270 (0.7)	
<i>Median PSA at treatment or initiation of AHS</i>	6.7	6.1	5.0	6.1	0.006
<i>Gleason score median (%)</i>	7	7	6	7	N/A ³
0-6	24/81 (29.6)	48/128 (37.5)	53/64 (82.8)	125/273 (45.8)	
7 (3+4, 4+3)	49/81 (60.5)	55/128 (43.0)	11/64 (17.2)	115/273 (42.1)	
8+	8/81 (9.9)	25/128 (19.5)	0/64 (0)	33/273 (12.1)	
<i>Prostate volume median (g)</i>	37.5	41	39	39	0.15
<i>EPIC</i>					
Urinary function mean (SD)	85.4 (14.8)	87.9 (11.6)	87.1 (12.5)	86.9 (12.9)	0.073
Bowel habits mean (SD)	88.9 (15.6)	93.5 (10.3)	94.8 (6.6)	92.5 (11.6)	<0.0001
Sexual function mean (SD)	40.6 (28.0)	40.8 (29.1)	55.4 (28.6)	44.8 (29.3)	<0.0001
<i>IIEF-erectile function mean (SD)</i>	12.8 (11.4)	11.5 (11.4)	17.0 (11.8)	13.6 (11.8)	<0.0001
<i>IPSS mean (SD)</i>	9.6 (7.5)	8.1 (5.4)	9.6 (7.1)	9.0 (6.7)	0.021

¹ p-values were obtained for mean differences among CyberKnife, Cryotherapy, and AHS groups

² p-value for race was determined in comparison of white versus black and other races/ethnicities combined

³ N/A, not applicable; p-value was not obtained due to the lack of AHS patients in AHS with Gleason scores greater than or equal to 8.