



Patient reported outcomes for quality of life (QOL) by Expanded Prostate Cancer Index (EPIC) on average 15 years post treatment

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ABSTRACT

Objective/purpose: Previously patient reported quality of life (QOL) was reported in men with prostate cancer a mean 2 and 6 years post treatment with open radical prostatectomy (RP), 3D conformal radiation therapy (3D CRT), or ¹²⁵I low dose rate (LDR) brachytherapy (BT). Herein we update the results 15 years post-treatment QOL.

Materials/methods: The Expanded Prostate Cancer Index (EPIC) domains were scored with differences evaluated at a median 15.8 years follow up based upon mean EPIC summary domains by ANOVA with pairwise post-hoc comparisons adjusted for age. Patient differences of current survey from first cross-section are reported as median change in summary score for each treatment group at median of 2.2 and 6.0, and 15.8 years.

Results: Among men still alive response rate was 52% in BT, 60% in 3D CRT, and 62% in RP resulting in 30, 41, and 330 QOL questionnaires to evaluate for each corresponding modality at median follow up of 15.8 years. Men were a mean 75.3, 83.6, and 79.3 years of age after RP, 3DCRT, and BT, respectively.

At a median of 15.8 years, there were largely persistent differences in EPIC domains without substantial evolution in QoL from middle time points. Persistent worsening in urinary irritative and bowel domain with 3DRT or BT compared to RP. Trend towards worse urinary incontinence with RP were noted without statistical differences within radiotherapy options.

Conclusion: As the EPIC patient reported outcomes with the longest follow-up, these data uniquely reveal temporal trends from 2 to 15 years post treatment. However, the treatment modalities of open RP, 3D CRT without image guidance or intensity modulation, and BT without peripheral loading or MRI guidance may not reflect modern techniques.

Introduction

In the late 1990's, the importance of patient reported outcomes (PRO) started to gain appreciation. Increasing reports on short to middle-term health related quality of life (QOL) for all treatment modalities for prostate cancer are now within the literature of 2–5 years of follow up, but few have long-term data beyond that, and none up to 15 years [1–4].

In the era of less aggressive screening and active surveillance of prostate cancer (PCa), it still remains the most common malignancy among men within the United States with an estimated 233,000 new

case per year. [5,6] Given increasing longevity in the population with reductions in risk for death from other causes such as cardiovascular disease there is an increasing prevalence of prostate cancer and longer survival post-treatment. This combined with the long natural history PCa leads to a large cohort of patients who are at risk for the complications of treatment and the impact upon patient reported QOL, which is a more sensitive and valid indicator of patient satisfaction that physician-scored toxicity that may extend many years beyond their initial treatment decision. However, it is increasingly unclear what constitutes long term follow-up. Reports comparing treatment modalities with long-term data are sparse, especially analyses that include

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brachytherapy or stereotactic body radiotherapy (SBRT). [7–13] Most reports suggest the most dramatic changes in QOL occur within the first 2-years of therapy. However, fears of toxicity, such as early incontinence and impotence with prostatectomy and potential late urinary and rectal toxicity with radiotherapy, impact patients and practitioners in their clinical decision making albeit with limited data to inform these decisions.

Presented here is an analysis of late patient reported outcomes with median 15.8 years of follow-up from initial treatment for prostate cancer with either radical prostatectomy (RP), 3D conformal external beam radiotherapy (3D CRT), or permanent seed brachytherapy (BT).

Methods

A total of 1,014 men, including 902 consecutive patients treated with RP, 3DCRT, or BT as primary therapy for localized prostate cancer during the 4-year period from June 1, 1995, to May 31, 1999 from a single institution. The initial reports also included 112 prostate cancer-free control participants but these control patients were not assessed for this 15 year time point. The details of control group recruitment have been described previously and the control sample was frequency matched to the treatment group by decade of age [14,15].

Men treated with 3D CRT were simulated supine with CT based planning with customized foam devices without contrast. Doses utilized were 1.8 – 2 Gy daily fractions without daily image guidance for treatment planned 5 days per week for all dose levels. Initial treatment planning was completed to planning target volume which included prostate and seminal vesicles with planning margin of 1–1.5 cm with or without regional lymphatics. Total dose to the prostate and seminal vesicles was to a final prescribed dose of 66–80 Gy. Treatment plans were completed without inverse optimization utilizing either cerrobend blocks or multi-leaf collimation with variable margins to achieve the 95% coverage of the planning target at minimum.

BT was performed with permanent seed implantation of Iodine-125 with treatment pre-dating routine use of peripheral loading or routine rigid urethral dose constraint. Prior to implantation a pre-treatment transrectal ultrasound was obtained for treatment planning purposes. Patients treated with either BT alone were prescribed to 160 Gy or those treated with BT boost to 80 Gy for the permanent seed implant (with 45 – 50.4 Gy of 3D CRT treatment as otherwise treated per external beam planning described above to the prostate and seminal vesicles with or without regional lymphatics) were considered to have BT as their primary modality of treatment.

Patients treated with RP, the treatment consisted as an open radical prostatectomy with removal of entire prostate with the seminal vesicles by a lower midline incision and then indwelling foley catheter was used to stent the urethrovesicular anastomosis for up to 3 weeks post-operatively.

Inclusion criteria for the follow-up assessment described herein include patient participation in the prior 1999 cross-sectional evaluation and survival at a sufficient state of health for the patient to be able to provide informed consent for participation for the current study. With IRB approval men were contacted by mail or phone. At 6-year time point, response rates were 73%, 77%, and 78% for patients in the RP, 3D CRT, and BT cohorts.

At time of 15-year assessment, 133, 79, and 23 patients had died in the RP, 3D CRT, and BT cohorts. In addition, 3 could not participate due to dementia or poor clinical condition, and 64 patients could not be reached due to incorrect contact information. A total of 401 surveys were received (330 RP, 41 3DCRT, and 30 BT) overall response rate was 62% with 62%, 60%, and 61% response rates in the RP, 3D CRT, and BT cohorts respectively. For evaluations across all three time points, 42%, 24%, and 33% of patients were available with QOL data at short, mid- and long-term periods, representing 2, 6, and 15 year evaluations, respectively.

Study measures

The initial QOL assessment instrument comprised measures that assess both general (RAND Corp Medical Outcomes Study 12-item short form [SF-12] physical and mental component scores [PCS and MCS, respectively]) as well as prostate cancer-specific (EPIC) QOL. For this long term EPIC instrument used for this assessment was limited to the 26-item version (EPIC-26) that had been derived by reducing the original 50-item EPIC by elimination of items that showed biometric or content overlap. The EPIC-26 instrument retains summary domain scores for urinary irritative-obstructive, urinary incontinence, bowel, sexual, and hormonal domains; the summary scores for the EPIC-26 instrument correlate strongly with the corresponding summary scores derived from the original 50-item EPIC (correlation coefficients 0.95 for each summary domain). EPIC-26 also retains internal consistency (Cronbach's 0.7 for each domain summary score) in item reduction analyses (conducted in the preceding validation cohort). Similar to the initial previous reports on EPIC and SF-12 instrument, the Likert responses for EPIC-26 are transformed to a 0 to 100 score, with higher values representing more favorable health status.

Meaningful Clinical Differences (MCD) for each aspect of the EPIC QOL questionnaire have been previously established as based on an anchor and distribution driven evaluation of EPIC data from 1200 patients. [16] A MCD for each domain would represent a 6 point reduction for urinary irritative, 7.5 point reduction for urinary incontinence, 5 point reduction for bowel, 5 point reduction for hormonal, and 11 point reduction for the sexual domain, respectively.

Statistical analyses

On return of completed questionnaires and consent forms, data were entered into a secure and confidential database wherein data stability and accuracy were verified by double data entry for a random sample of 10% of study participants.

Pairwise differences in demographic and response characteristics were compared between each of the three treatment groups among responders. Fisher's exact test was used to test for differences between the groups for categorical variables, including response rate, race or ethnicity (white v nonwhite), marital status (currently married v not currently married), relationship status (currently involved in a relationship v not currently in relationship), education (high school graduate v non-high school graduate), Gleason sum (<7, 7,>7), clinical tumor stage (T1, T2, T3), and exposure to androgen deprivation. Pairwise differences for age, follow-up time, and baseline prostate-specific antigen (PSA) were tested using the non-parametric Wilcoxon rank sum test. Long-term QOL domain scores were compared at each cross-sectional questionnaire time between each of the three treatment groups using analysis of covariance (ANCOVA) models, adjusted for age, including only the patients who responded to the final questionnaire. For comparisons between therapy groups, the Tukey-Kramer multiple comparison adjustment was used to preserve the overall significance level.

Next, data from the current assessment were combined with those from our earlier cross-sectional studies to calculate therapy specific changes in each of the QOL domains over time. ANCOVA models were created to determine treatment effect on the change in QOL scores between short-term (1999) and long-term (2003 and 2015) assessments. To adjust for differences between the therapy groups, age was included as a covariate in these models. Separate post-hoc tests were then performed to determine whether the age-adjusted change in QOL score for each treatment group was significantly different from zero.

Additionally, each EPIC question was dichotomized to report the proportion of patients at each cross-section who reported a significant "problem with...". All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The 5% significance level was used in all tests and comparisons.

Table 1
Patient Characteristics at 15 years.

Characteristic	RP	3D-CRT	BT	RP vs RT	RP vs BT	RT vs BT
Number of patients	330	41	30	p-values	p-values	p-values
Response rate, %	62.0%	60.3%	51.7%			
Median age, years	75.3	83.6	79.4	<0.0001	0.026	0.043
% white	95.1%	92.5%	96.7%	0.45	1.0	0.63
% married	83.2%	73.2%	76.7%	0.13	0.45	0.79
% involved in a relationship	90%	77.50%	83%	0.035	0.23	0.76
% high school education	95.4%	92.7%	93.3%	0.44	0.64	1.0
% hormonal therapy	28.8%	25.7%	46.4%	0.84	0.083	0.11
Median pre-treatment PSA, ng/mL	5.7	8.5	6.05	0.027	0.13	0.49
Biopsy Gleason Score distribution, %				0.35	0.12	0.067
2–6	59.0%	51.5%	75.0%			
7	38.4%	42.4%	21.4%			
8–10	2.6%	6.1%	3.6%			
Clinical T-Stage, %				0.018	0.019	0.89
T1	63.3%	44.1%	42.9%			
T2	36.4%	50.0%	50.0%			
T3	0.4%	5.9%	7.1%			

Results

Patients

A total of 401 QOL surveys were received with a median of 15.8 years of follow-up since prostate cancer therapy. Men who obtained RP remained significantly younger than either 3D CRT or BT cohorts.

Table 2
Age-Adjusted EPIC QOL Domain Summary Scores at a Median Follow-Up Time Among Men Treated for Cancer.

Questionnaire 1 Estimates at Median Follow-up time of 2.2 years (Min=0.33, Max=4.31)													
EPIC Domain	N	RP (N=330)			3D CRT (N=41)			Brachy (N=30)			p-values		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		RP vs RT	RP vs BT	RT vs BT
Urinary irritative	385	90.9	89.5	92.2	87.3	83.4	91.2	75.7	71.2	80.1	0.21	<0.0001	0.0003
Urinary incontinence	385	78.5	76.1	81.0	93.4	86.3	100.5	93.5	85.2	101.7	0.0004	0.0021	0.99
Bowel	396	94.9	93.5	96.2	86.5	82.4	90.6	74.0	69.6	78.5	0.0005	<0.0001	0.0002
Sexual	389	41.1	38.0	44.3	50.1	41.0	59.1	45.5	34.7	56.3	0.17	0.72	0.80
Hormonal/vitality	394	91.7	90.5	93.0	88.8	85.0	92.6	90.1	86.0	94.3	0.33	0.74	0.89

Questionnaire 2 Estimates at Median Follow-up time of 6 years (Min=4.01, Max=8.04)													
EPIC Domain	N	RP (N=276)			3D CRT (N=35)			Brachy (N=28)			p-values		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		RP vs RT	RP vs BT	RT vs BT
Urinary irritative	328	92.3	90.8	93.7	87.2	83.0	91.4	87.0	82.4	91.7	0.073	0.090	0.99
Urinary incontinence	331	79.9	77.2	82.7	90.2	82.3	98.0	83.1	74.4	91.7	0.044	0.78	0.44
Bowel	334	94.9	93.4	96.4	87.9	83.5	92.3	86.5	81.8	91.3	0.011	0.003	0.90
Sexual	321	41.3	37.7	44.9	43.8	32.8	54.8	41.7	30.3	53.1	0.90	0.99	0.96
Hormonal/vitality	327	92.5	91.3	93.8	93.3	89.6	97.0	91.6	87.7	95.6	0.92	0.91	0.81

Questionnaire 3 Estimates at Median Follow-up time of 15.8 years (Min=13.77, Max=18.0)													
EPIC Domain	N	RP (N=330)			3D CRT (N=41)			Brachy (N=30)			p-values		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		RP vs RT	RP vs BT	RT vs BT
Urinary irritative	387	90.1	88.6	91.6	80.2	75.7	84.6	82.2	76.9	87.4	0.0001	0.013	0.83
Urinary incontinence	388	72.8	69.9	75.7	83.1	74.4	91.8	70.4	60.1	80.6	0.072	0.90	0.14
Bowel	393	92.9	91.4	94.4	84.9	80.5	89.3	82.0	76.7	87.4	0.002	0.0004	0.69
Sexual	375	31.1	28.1	34.2	27.0	18.2	35.9	34.5	24.4	44.6	0.67	0.81	0.51
Hormonal/vitality	386	90.3	88.8	91.8	89.0	84.7	93.3	85.7	80.8	90.6	0.84	0.19	0.58

RP = radical prostatectomy, 3D CRT = 3D conformal radiotherapy, Brachy = brachytherapy.

Responding men were more likely to be involved in relationships at the time of survey completion. Also men obtaining prostatectomy were associated with lower T-stage than 3D CRT and BT, while men who received BT had lower Gleason grade than men receiving 3D CRT. Patient characteristics see [Table 1](#).

Short and middle-term QOL assessment

Irritative symptoms were more pronounced at 2.2 years with BT compared to RP or 3D CRT with mean differences between modalities at that of a MCD and for BT the MCD was also beyond the 95% confidence interval ([Table 2](#)). Also noted at this early time point was urinary incontinence domain for RP compared to either BT or 3D CRT and mean differences were at the level of a MCD without differences between the radiotherapy options. The bowel domain also showed reductions in radiotherapy options compared to RP and with 3D CRT reporting better QOL than BT and with each difference reaching the mean level of a MCD and the BT reaching beyond the 95% confidence interval. No statistical differences between treatments were noted for either hormonal or sexual domains.

In the middle time point of 6.0 years of follow-up, irritative QOL improved for men treated with BT such that there were no substantial differences between RP and radiotherapy with trends noted for more urinary irritation but meeting neither statistical or a clinically important differences ([Table 2](#)). Statistically and the mean difference representing a MCD within the 95% confidence interval was still noted for more urinary incontinence with RP compared to 3D CRT but not BT. Bowel declines in RP were still less statistically that that with either radiotherapy modality with a mean difference of a MCD but falling within the confidence interval. No statistical differences were noted for either hormonal or sexual function domains.

Evaluating within patients and between questionnaires at 2.2 and 6.0 years ([Fig. 1a](#)), BT patients were likely to improve in terms of urinary irritative symptoms relative to either RP or 3D CRT suggesting middle

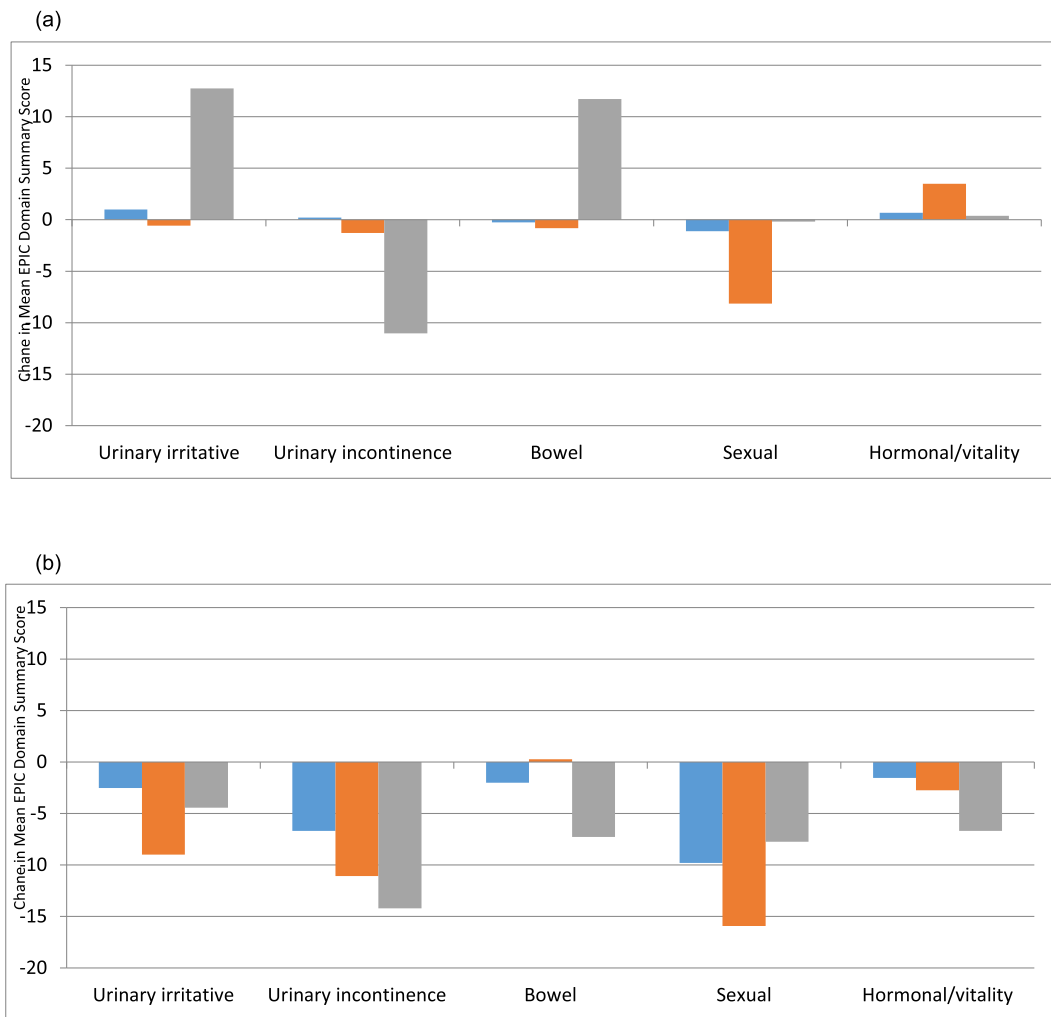


Fig. 1. Mean change in each EPIC domain between Questionnaires 2.2 and 6.0 years post treatment (a) and 6.0 and 15.8 years post treatment (b) by radicle prostatectomy (Blue), 3D CRT (orange), and BT (grey). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

term recovery of irritative symptoms. However, this was balanced by a decline in urinary incontinence of similar magnitude in patients treated with BT compared to RP and with worsening trends compared to 3D CRT. In addition, patients treated with BT were more likely to experience declines in the bowel domain compared to RP and even early compared to 3D CRT with perhaps some modest recovery in the middle term.

Long-term QOL assessment

With longer follow up, greater declines in urinary irritative QOL were observed in both 3D CRT and BT cohorts compared to RP with these declines statistically significant. The mean differences were beyond the threshold for the MCD, but again falling within the 95% confidence interval (Table 2).

Urinary incontinence was not statistically different between modalities with only a trend to worse incontinence with RP than 3D CRT but not BT. Bowel differences were again statistically significant for reduced QOL with both radiotherapy options but again fell within the confidence interval for a difference of a MCD. As in the earlier follow up period, no differences were observed within the hormone or sexual domains between modalities.

Comparing within patients between 6.0 and 15.8 years of follow up, there were no statistically significant differences suggesting a greater

decline in any domain between the middle-term of follow up and the late-term of follow up in one treatment modality over another (Fig. 1b). The only appreciable trend was potentially continued decline in the bowel domain with BT compared to RT. All unadjusted reported QOL with a proportion of patients reporting a significant “problem with...” by question within the EPIC form across domains is within Table 3.

Discussion

Overall this report supports the findings of patient reported QOL for patients treated with radiotherapy and prostatectomy for prostate cancer without substantial change in disease specific QOL metrics between middle-terms of 2–6 years and long-term periods beyond 10 years. With continued follow up the QOL remains very reasonable across treatment modalities with some caveats for specific differences that are most likely to be experienced within short to middle terms post-treatment.

The differences between modalities even where statistically different often did not statistically meet MCD thresholds. While these differences are present numerically, the actual differences between modalities was limited with further follow up without successive change within patients. The only area of continued evolution appeared in patients treated with BT which noted middle-term improvement in irritative QOL balanced by substantial worsening in urinary incontinence and bowel QOL which may be progressive in this cohort. Not only were differences

Table 3
Patient reporting “problem with” by question within EPIC.

	RP (median age = 75.3, N = 330)		3-D CRT (median age = 83.6, N = 41)		BT (median age = 79.4, N = 30)	
	% Currently Reporting Function for EPIC item	% at 6.2 years Reporting Function for EPIC item	% Currently Reporting Function for EPIC item	% at 6.2 years Reporting Function for EPIC item	% Currently Reporting Function for EPIC item	% at 6.2 years Reporting Function for EPIC item
Urinary						
Irritative-obstructive						
Problem with pain or burning on urination	1.2	1.1	2.6	2.9	0	7.1
Problem with bleeding with urination	0.3	0.7	0	0	0	0
Problem with weak stream/incomplete emptying	4.9	4.5	20.5	2.9	18.5	7.4
Problem with need to urinate frequently	12.7	8.1	15.0	14.3	23.1	7.4
Incontinence						
Leakage of urine more than once a day	23.2	17.3	17.5	5.7	20.7	10.7
Frequent dribbling or no urinary control	13.5	7.7	12.5	5.7	25.0	7.1
Need for 1 or more pad per day	26.6	14.0	17.5	5.7	14.8	7.1
Problem with dripping or leaking urine	14.7	7.8	10.5	2.9	15.4	10.7
Overall urinary						
Problem with overall urinary function	10.1	6.5	12.2	2.9	20.7	7.4
Bowel						
Problem with urgency to have a bowel movement	5.2	3.6	4.9	15.6	17.9	11.1
Problem with increased bowel frequency	3.4	2.2	10.0	9.4	20.0	11.1
Problem with fecal incontinence	1.2	2.2	7.5	3.1	11.5	3.7
Problem with bloody stools	0	1.1	5.0	3.0	3.9	3.7
Problem with abdominal/rectal/pelvic pain	1.2	1.8	7.5	6.1	7.4	3.7
Problem with overall bowel habits	5.8	2.5	14.6	12.1	10.7	14.8
Sexual						
Poor to no ability to have an erection	25	59.4	13.2	61.3	20.7	67.9
Poor to no ability to reach orgasm (climax)	43.0	36.7	13.5	54.8	37.0	53.6
Erections not firm enough for intercourse	81.7	68.3	94.9	74.2	89.7	82.1
Erections achieved less than half the time desired	68.8	58.1	86.8	60.0	79.3	57.7
Poor to no ability to function sexually	67.0	53.3	89.7	63.3	75.0	66.7
Problem with sexual function	40.1	37.2	50.0	33.3	31.0	35.7
Hormonal/vitality						
Problem with hot flashes	1.6	1.5	0	0	6.9	3.7
Problem with breast tenderness/enlargement	1.6	1.9	0	3.2	3.5	0
Problem with feeling depressed	5.3	1.1	12.5	0	6.9	7.1
Problem with lack of energy	12.2	6.3	17.1	9.1	24.1	3.6
Problem with change in body weight	5.0	1.1	7.3	0	10.3	10.7

Outpoint for items reported as “Problem with...” was patients reporting moderate or worse problem in the HRQOL item response.

between modalities not different from a middle term of follow up of a median of 6.2 years, but the differences within patients did not meet a MCD across any EPIC domain. This included urinary incontinence which continued to decline in all patient groups and no group disproportionately so more than any other treatment cohort.

Effectively from 6 to 15-years post treatment most QOL changes were on average small without substantial worsening or improvement with either RP or 3DCRT. These data indicate that once patients have passed the initial 2–6 years after treatment there are no late dramatic changes in QOL based on their initial treatment for prostate cancer. This is reassuring that as survival after treatment for prostate cancer increases, our general appreciation for differences in QOL with different treatment modalities is not substantially changed beyond 6 years. This may place the emphasis on reducing toxicity and meaningful reductions in QOL in the short term. Therefore, utilization of resources for future prospective clinical studies are most likely best dedicated to QOL evaluation with short to middle-term follow up based on these findings and these findings potentially will function as surrogates for later QOL.

These findings seem supported by another cohort study of similar size and scope review of 15-year outcomes from Australia were patients including 333 with prostatectomy, 42 with external beam and/high dose rate brachytherapy and 25 with low dose rate brachytherapy along with 45 patients on androgen deprivation alone and 103 controls, were evaluated for long term QOL with EPIC as well as SF-12 domain as compared to baseline pre-treatment data [17]. Men treated with prostatectomy had persistent issues with urinary incontinence and sexual dysfunction. In that report, men treated with external beam radiotherapy and/or high dose rate brachytherapy along with hormonal therapy alone had decline over time in urinary continence as well as bowel bother as would be anticipated in an aging older baseline population. The strength of Mazariego *et al.*, in comparison to this paper is the presence of baseline pre-treatment data. However once one looks beyond the initial reduction in QOL, long term evaluation of QOL would have demonstrably changed initial statistical differences at shorter follow up periods with most differences within patients being well within a MCD at longer intervals of follow up.

Applicability of these results to current patient cohorts is limited for each modality as over the past 20 years each technique has experienced considerable improvements that could affect QOL in one or more domains. Surgery now has evolved to robotic assisted prostatectomy with the potential for nerve sparing and less decline in sexual domain and potentially even urinary continence which on meta-analysis has improved both outcomes [18,19].

Meanwhile, radiation therapy has experienced dramatic changes in both dose and technique. 3DCRT is no longer the standard of care for prostate external beam radiotherapy as both IMRT and IGRT have become standard and appear to decrease the rates of toxicity observed. Dose and volume do matter in terms of both toxicity and disease specific QOL. Dose has increased modestly that may increase the risk of reduce QOL after radiotherapy as toxicity has been shown to be increased especially when care is not made to maximize optimal sparing to adjacent structures [20–22]. However, at minimum this should be offset by advancement in treatment planning techniques, reduced margins, and improved alignment with daily image guidance. New forms of radiotherapy such as intensity modulated radiotherapy have also shown superiority in sparing organs at risk including bowel and rectum which may minimize these disease specific declines in QOL [23]. New dose-volume reports have shown that continued reduction of the volume of the rectum receiving 70 Gy, which is reduced with intensity modulation, improved bowel associated QOL [24]. Beyond sharper fall of dose with intensity modulation, image guidance has also allowed to limit planning target volume expansions to 5–10 mm for standard intensity modulated radiotherapy and this would have implications on reduced dose to bladder, rectum, and penile bulb [24]. Delivery is now faster such as with volumetric modulated arc delivery rather than step and shoot intensity modulation will minimize the risk of prostatic motion during

radiotherapy delivery. With more advanced image techniques these can be reduced to 2–3 mm with stereotactic delivery and imaging approximately every minute with excellent reported QOL with modest changes with dose-escalation within this modality [25–28]. Specifically as it relates to bowel-related QOL, rectal separation is feasible for favorable risk prostate cancer with substantial improvement of both physician reported toxicity and patient reported bowel QOL, as well as sexual QOL, relative to radiotherapy without rectal separation on a randomized control study [29,30].

The brachytherapy results may be the least applicable to modern series of the three modalities analyzed here. Continued radiation from permanent low-dose rate seeds may have continued deleterious effects and improvements in ultrasound guidance and peripheral loading technique may mitigate some of these findings. Beyond that, brachytherapy utilization has substantially reduced over the subsequent decades [31]. This has happened in spite of data on improved survival, including prostate cancer specific mortality for very high risk disease that appears at least on par with tri-modal of surgery, radiotherapy, and hormonal therapy in this population [32–34]. There has also been a shift at some centers towards high dose-rate brachytherapy as well competition from stereotactic body radiotherapy which has shown similar QOL, toxicity, and cancer specific outcomes. Toxicity has been shown to be reduced with early generations of high dose-rate brachytherapy compared to permanent-seed implantation, but movement to peripheral loading techniques and improved dose constraints may mitigate this advantage to some degree [35,36]. The temporal nature of toxicity and QOL with these newer techniques should be continued to be investigated to ensure that this pattern of stability holds true for differences at the extremes of hypofractionated radiotherapy. Effectively it may be that the results for RP, 3DCRT, and BT represent a worst case scenario compared to more modern deliveries for QOL estimates.

Conclusion

In this first report of long-term follow up of 15.8 years after treatment for prostate cancer with 3D CRT, BT, or RP, QOL was not substantially different than middle-term follow up of 6.0 years between modalities or within patients. Long term disease-specific QOL appears very reasonable across modalities but subtle differences between modalities should be discussed with patients at time of treatment decision making as these changes are often persistent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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