INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

A Randomized Trial Comparing Quality of Life After Low-Dose Rate or High-Dose Rate Prostate Brachytherapy Boost With Pelvic External Beam Radiation Therapy

Juanita Crook, MD,* Nikitha Moideen, MD,† Greg Arbour, MSc,‡ Felipe Castro, MD,† Cynthia Araujo, PhD,§ Deidre Batchelar, PhD,§ Ross Halperin, MD,† Michelle Hilts, PhD,§ David Kim, MD,† David Petrik, MD,† Jim Rose, MD,‖ J.C. Cheng, MD,† and Francois Bachand, MD†

*Division of Radiation Oncology, Univeristy of British Columbia, Vancouver, British Columbia, Canada; †Radiation Oncology, BCCancer, Kelowna, British Columbia, Canada; ‡Department of Statistics, University of British Columbia, Vancouver, British Columbia, Canada; §Medical Physics, BCCancer, Kelowna, British Columbia, Canada; and ‖Radiation Oncology, BCCancer, Abbottsford, British Columbia, Canada

Received Dec 6, 2023; Accepted for publication Feb 10, 2024

Purpose: To compare health-related quality of life (QoL) in urinary, bowel, and sexual domains after combined external beam radiation therapy (EBRT) and either low-dose rate (LDR) or high-dose rate (HDR) prostate brachytherapy (BT).

Methods and Materials: Eligible men with intermediate or high-risk prostate cancer treated with combined pelvic EBRT and BT were randomly assigned to either HDR (15 Gy) or LDR (110 Gy) boost. International Prostate Symptom Score, Index of Erectile Function, and Expanded Prostate Cancer Composite were collected at baseline, 1, 3, 6, and 12 months, every 6 months to 3 years and then annually along with prostate-specific antigen/testosterone. Fisher's exact test compared categorical variables and the Mann-Whitney *U* test Expanded Prostate Cancer Index Composite (EPIC) domain scores.

Results: From January 2014 to December 2019, a random number generator assigned 195 men: 108 to HDR and 87 to LDR. Median age was 71 years. Risk group was high in 57% and unfavorable intermediate in 43%. Androgen deprivation (used in 74%) began with 3 months neoadjuvant and continued for median 12 months. Baseline EPIC scores were similar for the LDR/HDR cohorts: 89 and 88 respectively for Genito-urinary; 92 and 93 for Gastro-intestinal. EPIC urinary scores decreased at 1 month for HDR but recovered promptly to a steady state by 6 months. LDR scores reached a nadir at 3 months with slow recovery to 18 months, after which urinary QoL was similar for HDR and LDR. Bowel QOL scores fell in both cohorts reaching respective nadirs at 12 months. HDR patients recovered close to baseline and maintained higher scores than LDR patients to 5 years. The decline for LDR patients remained more than the minimum clinically important difference out to 5 years.

Conclusions: The patient experience for combined EBRT and prostate BT is improved with HDR BT. Urinary QoL improves over time to be equivalent between the 2 modalities after 18 months, but LDR patients report lasting bowel symptoms.

Corresponding author: Juanita Crook, MD; E-mail: jcrook@bccancer.bc.ca

This protocol is registered with ClinicalTrials.gov and may be viewed online at ClinicalTrials.gov (NCT 01936883).

Disclosures: The study is funded by BCCancer Foundation and Ride for Dad.

Data Sharing Statement: Research data to be shared when the efficacy endpoint is met.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2024.02.064.

Int J Radiation Oncol Biol Phys, Vol. 120, No. 1, pp. 59–68, 2024
0360-3016/$ - see front matter © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/)
https://doi.org/10.1016/j.ijrobp.2024.02.064

Introduction

Prostate brachytherapy (PBT) combined with pelvic external beam radiation therapy (EBRT) is the recommended standard of care for men with newly diagnosed nonmetastatic prostate cancer that is either upper tier intermediate risk or high risk.[1] This is associated with a long-term progression-free survival benefit compared with dose escalated (DE) EBRT alone.[2,3] PBT can be delivered using either low dose rate (LDR) or high-dose-rate (HDR) technique. LDR-PBT involves permanent placement of radioactive seeds, which deliver the required dose over the course of the isotope's natural decay. Conversely, HDR-PBT delivers the prescribed dose in a single treatment using a temporary source, which traverses a scaffolding of implanted hollow needles.

Despite the evidence in favor of combined PBT and EBRT, the use of this combination is still relatively infrequent.[4] This is in part due to concern about increased toxicity with PBT.[5,6] Nonetheless, PBT remains the most conformal and effective means of dose escalation,[7-9] and the superior outcomes of trimodality therapy (EBRT, brachytherapy, and androgen deprivation therapy [ADT]) strongly support this approach in unfavorable prostate cancer.[2,3]

Given the excellent survival outcomes in prostate cancer, emphasis is being placed on reduction of treatment-related side effects and improvement of quality of life (QoL). Reports of HDR-PBT boost efficacy appear comparable with that of the combination of LDR PBT and EBRT.[10,11] HDR-PBT boost is generally delivered in a single treatment over a matter of a few minutes. This eliminates uncertainties associated with seed movement or migration, which can occur with an LDR implant, or changes in the juxtaposition of organs due to variations in bladder and rectal filling over time during the prolonged period of treatment delivery with LDR. This should provide more reliable target coverage and sparing of adjacent organs. However, there have been no randomized trials comparing treatment efficacy or QoL for patients treated with combined EBRT and HDR or LDR PBT. As our team was equally skilled in both techniques, we initiated a randomized trial to compare acute and late urinary, bowel and sexual QoL associated with LDR and HDR PBT boost.

Methods and Materials

Patients

Eligible patients had a histologic diagnosis of prostate adenocarcinoma, either upper tier intermediate risk (at least 2 of: cT2b-c, Gleason Score 7, prostate-specific antigen [PSA] >10 ng/mL, or >50% cores positive) or high risk (cT3a and/or Gleason Score 8-10 and/or PSA>20 ng/mL). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and were suitable for anesthesia. Prostate volume was <60 cc, and voiding function was adequate with an international prostate symptom score (IPSS) <16 and/or adequate urinary voiding studies (peak flow rate >10 mL/s and post void residual < 20% of voided volume).[12-14] Men with previous pelvic/prostate radiation, prostatectomy, cryotherapy, or high intensity focused ultrasound for prostate cancer were ineligible, as were those with a prior invasive malignancy within 3 years. Pathology underwent central review through British Columbia Cancer genitourinary pathology. PSA was required within 3 months of registration and staging included computed tomography (CT) of the abdomen and pelvis, and Tc99 bone scan within 120 days with no evidence of metastases. As accrual began in 2014, magnetic resonance imaging (MRI) was not mandated in the protocol. Patients were high risk by virtue of Gleason score, PSA and/or palpable T-stage. No patients were included who were high risk based only on multiparametric MRI evidence of extraprostatic extension.

Study design

This was a single institution, prospective phase 2 randomized trial. The sample size (n = 192) was adequate for a QOL endpoint but insufficient to compare efficacy definitively. Randomization was performed using a random number-generated list, applied in a 1:1 ratio between HDR and LDR brachytherapy arms. All participants provided written, informed consent. Ethics review board approval was obtained from the University of British Columbia and BC Cancer (H13-02139) and the trial was registered with ClinicalTrials.gov (NCT01936883).

External beam radiation therapy

All patients received pelvic EBRT, 46 Gy in 23 fractions, 5 days per week, using either a 3-dimensional (3D) conformal, intensity modulated (IMRT), or volumetric modulated arc (VMAT) technique. Patients were simulated supine, with a leg rest for stability, on a Siemens CT scanner with 2.5 mm slices, and instructed to have a comfortably full bladder and an empty rectum (<4 cm diameter) for simulation and for each treatment. Although for intermediate-risk disease the clinical target volume (CTV) for EBRT could be reduced to the prostate plus 1.5 to 2 cm of seminal vesicles, the CTV generally included pelvic lymph nodes for high-risk disease. The EBRT planning target volume included a 10-mm margin on the prostate, except posteriorly where it was reduced to 7 mm. The nodal CTV was expanded by 7 to 8 mm to create the nodal PTV. Treatment was delivered with mega voltage photon beams, 15 MV for a 4-field conformal technique, or 6MV for both IMRT and VMAT. Image guidance was provided by either prostate fiducials using KV imaging, or daily pretreatment cone beam computed tomography (CBCT). See Table 1 for external beam dosimetric constraints.

Table 1 External beam radiation dose constraints

Structure	Standard goal	Acceptable if standard goal not met
PTV_ low	V95% >99%	
	D_{min} >90%	
	D_{mean} >99%	
	D_{max} <110%	
CTVp (prostate)	D_{min} >95%	
Bowel bag	D_{max} <47.3 Gy	
	V40 Gy <100 cc	V40 Gy <250 cc
	V30 Gy <350 cc	V30 Gy <500 cc
Rectum	V40 Gy <80%	
	D_{max} <47.3 Gy	
Bladder	V45 Gy <35%	V45 Gy <70%
		V30 Gy <85%
	D_{max} <47.3 Gy	

Abbreviations: CTVp = clinical target volume (prostate); PTV = planning target volume; VxGy = volume enclosed by the xGray isodose.

Androgen deprivation

Patients received 0 to 12 months of ADT at the discretion of the treating oncologist, generally 0 to 6 months for intermediate risk and 12 months for high risk.

LDR brachytherapy

LDR brachytherapy was performed using permanent implantation of peripherally loaded Iodine-125 seeds (activity 0.329-0.422 U), 1 to 4 weeks after completion of EBRT, with a prescribed peripheral dose of 110 Gy. Implants were preplanned using BK FlexFocus US (BK Medical) and Variseed (version 9.0, Varian). For planning, the prostate was contoured with a margin of 3 to 5 mm but with no margin posteriorly. The desired V150 was 56% to 65% (% of prostate volume receiving 150% of prescribed dose) and V200 ≤22%. Urethral maximal dose (UD max), or central sparing if urethra not opacified at time of prostate mapping, was ≤130%.

LDR implant quality was assessed 4 weeks after the implant using both CT and MRI, performed sequentially on the same day. Before coregistration by seed-to-seed match, contouring was defined on the MRI and seed identification was defined on the CT scans for dose calculation.

HDR brachytherapy

Patients in the HDR arm began radiation with a single fraction of 15 Gy using an Iridium-192 source (Varian GammaMed afterloader). Implantation and treatment were completed as an outpatient in a single procedure under anesthesia with no patient transfers. Needle insertion for the HDR procedure was ultrasound-guided and treatment was ultrasound-planned using Vitesse 4.0 (Varian). Under ultrasound guidance, 16 needles (±2) were inserted using a template, advanced to the base of the prostate, and individually locked into the template. The urethra was opacified with aerated gel in the catheter before acquiring US images for treatment planning. The prostate ± the base of the seminal vesicles was contoured and a custom margin of 1 to 5 mm added according to the site of disease, tumor stage and bulk. Prostate constraints were V100 ≥98%, and V125 55% to 65%, urethral UDmax was 115% and rectal RD 1 cc ≤9.5 Gy. The urethral and rectal constraints were followed for all patients. Treatment was delivered with the US probe in the rectum to maintain the distance between the posterior prostate and the rectum. Three fiducial gold seeds were inserted in the prostate after completion of treatment delivery for subsequent EBRT image guidance. CT simulation for EBRT occurred the following morning and EBRT commenced 5 to 7 days later.

Follow-up

Patients were seen in follow-up at 1, 3, and 6 months, then every 6 months to year 3, and annually thereafter. PSA and serum testosterone were measured at each visit, and patients completed the International Index of Erectile Function (IIEF), the IPSS, and EPIC scores at each visit.

Statistical analysis

The primary study endpoint was comparison of urinary QoL in the 2 arms at 6 months after initiating treatment, measured using the EPIC questionnaire. The hypothesis was that HDR patients would recover more rapidly due to the faster time course of radiation delivery. The secondary endpoints were comparisons of acute (≤6 months) and late (12-60 months) urinary and bowel QoL and sexual function between the 2 arms using EPIC summary domain scores, IPSS and IIEF questionnaires.[15-17] Efficacy outcomes, including biochemical disease-free survival, cancer specific survival, and overall survival are currently being analyzed as a minimum 5-year follow-up has been reached. Results are planned to be submitted to American Society for Radiation Oncology 2024.

The standard deviation for the baseline urinary domain of the EPIC score was 11 for LDR and 8 for HDR. The minimum clinically important difference (MCID) in the EPIC score was considered to be half (0.5) of the standard deviation.[18] Furthermore, 172 patients were required to detect a difference using a 2-sided alpha of 0.05 and power of 90%.[19] Assuming 10% were lost to follow-up, the final sample size was chosen to be 192. The nonparametric Mann-Whitney *U* test was used to compare the mean domain scores between the trial arms. Categorical

variables were compared using the Fisher's exact test. Linear regression models were fit to gain an estimate of the effect size. Multivariate linear regression models were fit to test if the reported univariate effect continued in the presence of confounding variables. Insufficient responses from 32 patients resulted in their removal from the analysis. "Insufficient" was considered to be missing a baseline value or not having at least 2 data points at least 1 year apart in the 12- to 60-month period. It was assumed that they were missing at random and therefore their exclusion would not bias the results of the study.

Results

From January 2014 to January 2022, 195 patients were randomized: 108 to the HDR arm, and 87 to the LDR arm. The unexpected imbalance in numbers was found to be due to the use of a random number generator for randomization. Three patients were excluded, 2 from the HDR arm and one from LDR as they did not receive brachytherapy: one died before starting treatment, one became unsuitable for anesthesia due to cardiac issues, and the other was unsuitable for brachytherapy due to poor voiding. One additional HDR patient with severe chronic obstructive pulmonary disease crossed over to LDR due to advantages of the shorter anesthetic, and 2 others crossed over from LDR to HDR because of more advanced local disease detected on MRI (cT3b) felt to be better covered using HDR. All patients were analyzed according to treatment received, 107 HDR and 85 LDR. See Figure 1 for a Consort diagram.

The median age was 71 years. T stage was T1c: 14.9%, T2a/b: 47.2%, T2c/T3a: 34.9%, and T3b:2.1%. Gleason score was 7 in 57% and 8 or 9 in 43% (Table 2). Unfavorable intermediate risk comprised 43% of the study population and high risk, 57%. ADT was used in 74.8% of patients for a median duration of 12 months (IQR, 12 months), with at least the first 3 months completed before starting radiation. Baseline testosterone was available for 82% of the patients (n = 159) with a mean of 13.4 nmol/L (range, 2.5-29.4 nmol/L). The baseline IIEF score pre-ADT was available for 65% of the patients (n = 126). The median was 12 (of a maximum 25 points). The median follow-up is 61 months (range, 3-113 months). Day 0 was the first day of any radiation, either EBRT for the LDR patients, or brachytherapy for the HDR patients. The median interval from the final fraction of EBRT to LDR brachytherapy was 13 days (IQR, 14 days). The EBRT technique was IMRT or VMAT in 68% of patients (HDR 74%; LDR 61%; P = .06), with the remainder having 3D conformal. Image guidance by either KV matching to fiducials or CBCT was used in all patients. Because fiducials could be inserted under anesthesia at the end of the HDR procedure, HDR patients were more likely to have image guidance using fiducials (98%) and LDR patients were more likely to have cone beam CT (55%).

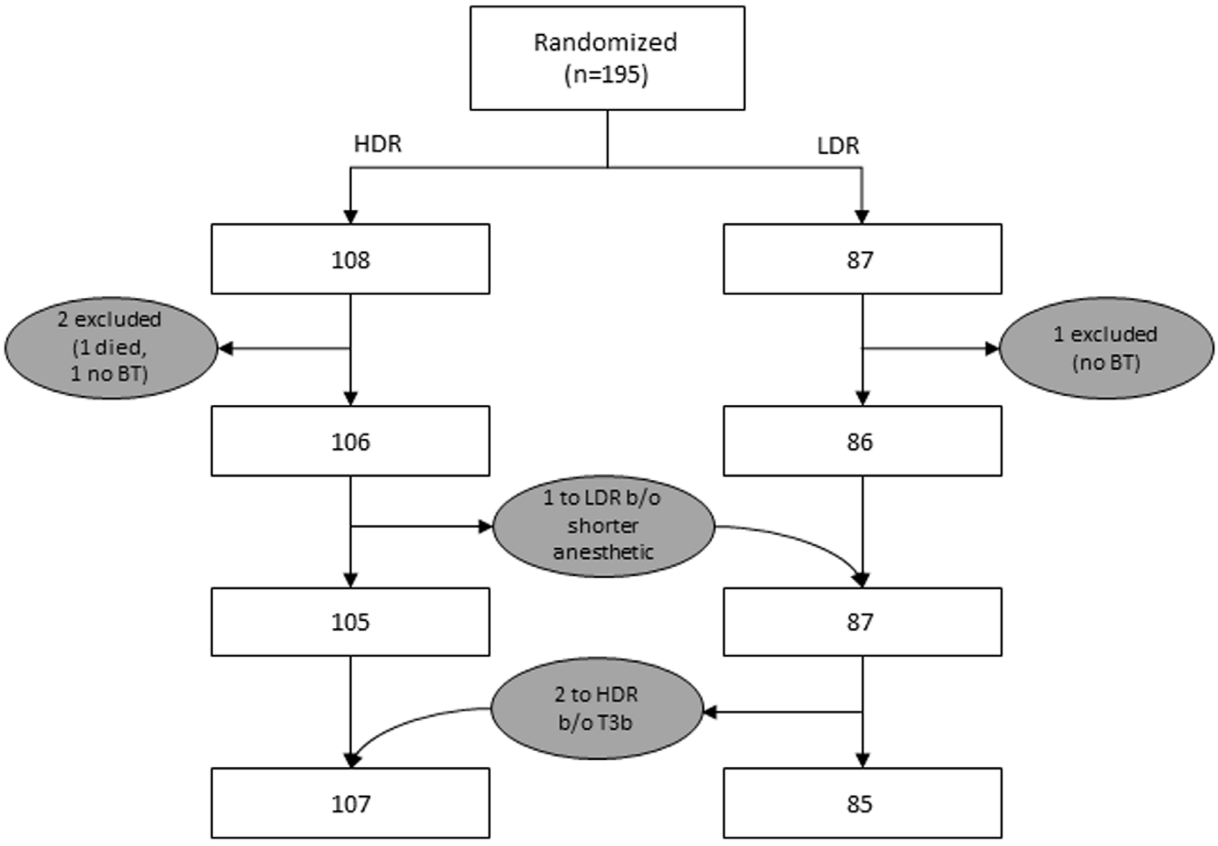

Fig. 1. Consort diagram.

Table 2 Baseline comparison of LDR and HDR cohorts

	HDR n = 106	LDR n = 84	Overall n = 190	*P* value
Age median [IQR], y	71.5 [66-74.8]	70.0 [67-73]	71.0 [66-74]	.32
Baseline prostate volume				
Median [IQR]	34.0 [24-46]	33.0 [24.8-42]	34.0 [24-43.8]	
Missing	0 (0%)	1 (1.4%)	1 (0.6%)	.95
EBRT volume				
Mini pelvis	33 (31.1%)	30 (35.7%)	63 (33.2%)	
Whole pelvis	73 (68.9%)	54 (64.3%)	127 (66.8%)	.54
ADT used				
No	23 (21.7%)	22 (26.2%)	45 (23.7%)	
Yes	83 (78.3%)	62 (73.8%)	145 (76.3%)	.50
NCCN risk group				
High risk	66 (62.3%)	46 (54.8%)	112 (58.9%)	
Intermediate risk	40 (37.7%)	38 (45.2%)	78 (41.1%)	.30
Clinical stage				
T1c	16 (15.1%)	13 (15.5%)	29 (15.3%)	
T2a/T2b	52 (49.1%)	39 (46.4%)	91 (47.9%)	
T2c/T3a	35 (33%)	31 (36.9%)	66 (34.7%)	
T3b	3 (2.8%)	1 (1.2%)	4 (2.1%)	.86
Gleason score				
7	57.4%	56.3%	56.9%	
8	13.9%	10.3%	12.3%	
9	28.7%	33.3%	30.8%	.66
IPSS baseline mean (SD)	7.3(5.9)	7.0(4.8)	7.2(5.5)	.67

Comparisons of continuous variables Mann-Whitney Wilcoxon test (age and prostate volume) and comparison of categorical variables by Fisher's exact test.

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; HDR = high-dose-rate; IPSS = International Prostate Symptom score; LDR = low dose rate; NCCN = National Comprehensive Cancer Network.

Higher HRQOL scores demonstrate better QoL. One month after the start of radiation, the HRQOL urinary domain score was higher for the LDR patients, (80.7 vs 73.6, $P = .001$, Table 3). At that time, LDR patients were receiving pelvic EBRT but had not had their brachytherapy, and the HDR patients had received their HDR brachytherapy and were part way through EBRT. However, by 3 months, the situation had reversed, with HDR patients now having a

Table 3 Mean EPIC domain summary scores ± standard deviation for GU and GI

Domain mean ± SD	Baseline	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48	Month 60
GU										
HDR	88 ± 12	73 ± 15	79 ± 15	84 ± 13	83 ± 14	84 ± 13	84 ± 15	84 ± 13	84 ± 13	85 ± 17
LDR	89 ± 10	81 ± 11	69 ± 16	77 ± 14	82 ± 12	84 ± 12	79 ± 15	85 ± 11	82 ± 15	83 ± 16
P value	0.72	.001	.001	.001	.51	.89	.05	.62	.48	.55
GI										
HDR	93 ± 8	78 ± 17	87 ± 14	89 ± 12	86 ± 16	90 ± 11	90 ± 10	91 ± 13	89 ± 14	91 ± 12
LDR	92 ± 11	80 ± 13	82 ± 15	83 ± 16	81 ± 18	85 ± 16	84 ± 16	86 ± 15	84 ± 17	86 ± 14
P value	.29	0.34	.04	.02	.08	.03	.007	.06	.07	.07

Abbreviations: GU = urinary; GI = bowel; HDR = high-dose-rate; LDR = low-dose rate.

higher mean urinary domain score (79.0 vs 69.4; $P = .001$) and better urinary QoL than the LDR patients whose urinary symptoms were approaching their peak after the LDR implant. Better acute urinary QoL was sustained through to the 6-month assessment in the HDR patients (84.0 vs 76.9; $P = .001$; Fig. 2). However, by 12 months after the start of radiation, the HRQOL urinary domain score was similar between the 2 arms and remained so through to the final evaluation at 60 months. Analysis of EPIC subscales scores for urinary bother and irritative/obstructive symptoms again showed the HDR patients to be more symptomatic at 1 month in both scales (68.4 vs 75.0; $P = .018$ and 70.2 vs 77.5; $P = .005$, respectively; Table 4). However, both the urinary bother subscale scores and the irritative and obstructive symptom subscale scores became worse at 3 months and 6 months for the LDR arm ($P = .001$ for all). IPSS scores (higher values indicate worse symptoms) confirmed what was seen with the EPIC scores with HDR patients being more symptomatic at 1 month 1 (13.7 vs 10.5; $P = .002$) but recovering quickly with fewer symptoms than LDR patients at 3 months (9.4 vs 14.9; $P < .001$) and 6 months (8.0 vs 11.8; $P = .0002$), coinciding with the ongoing radiation from the natural decay of I-125 LDR implant. There was no significant difference in the IPSS score from month 12 to 60 months in the 2 arms (Fig 3).

In the bowel domain, the HDR arm demonstrated better bowel QoL with higher bowel domain scores at 3 months (87.0 vs 82.1; $P = .005$) and 6 months (88.7 vs 82.8; $P = .023$). HDR patients maintained higher scores than the LDR patients throughout follow-up, with the difference being statistically significant at 18 and 24 months, and trending to significant through 3 to 5 years ($P = .06$ and 0.07). Although, neither cohort ever returned to baseline, bowel QoL for LDR patients showed more of a detriment with the difference from baseline being greater than the MCID up until the 5-year assessment. In contrast, the decrease in bowel QoL scores for the HDR patients was less than the MCID at all assessments after 12 months (Fig. 4). This was confirmed in the EPIC bowel bother subscale score with LDR patients experiencing greater degree of bowel bother from 3 to 36 months (Table 4). Neither EBRT field volume nor modality (VMAT/IMRT or 3DcRT) had a statistical influence on EPIC bowel score (data not shown).

There were no statistically significant differences in acute or late EPIC sexual domain or the IIEF scores for the 2 arms between 0 to 60 months. Testosterone recovery to the lower end of the range of normal for this age group (7 nmol/L) occurred in 46% by 12 months, 74% by 24 months, and 82% by 36 months. Sixteen percent of men had still not recovered to this minimal physiological level by 5 years.

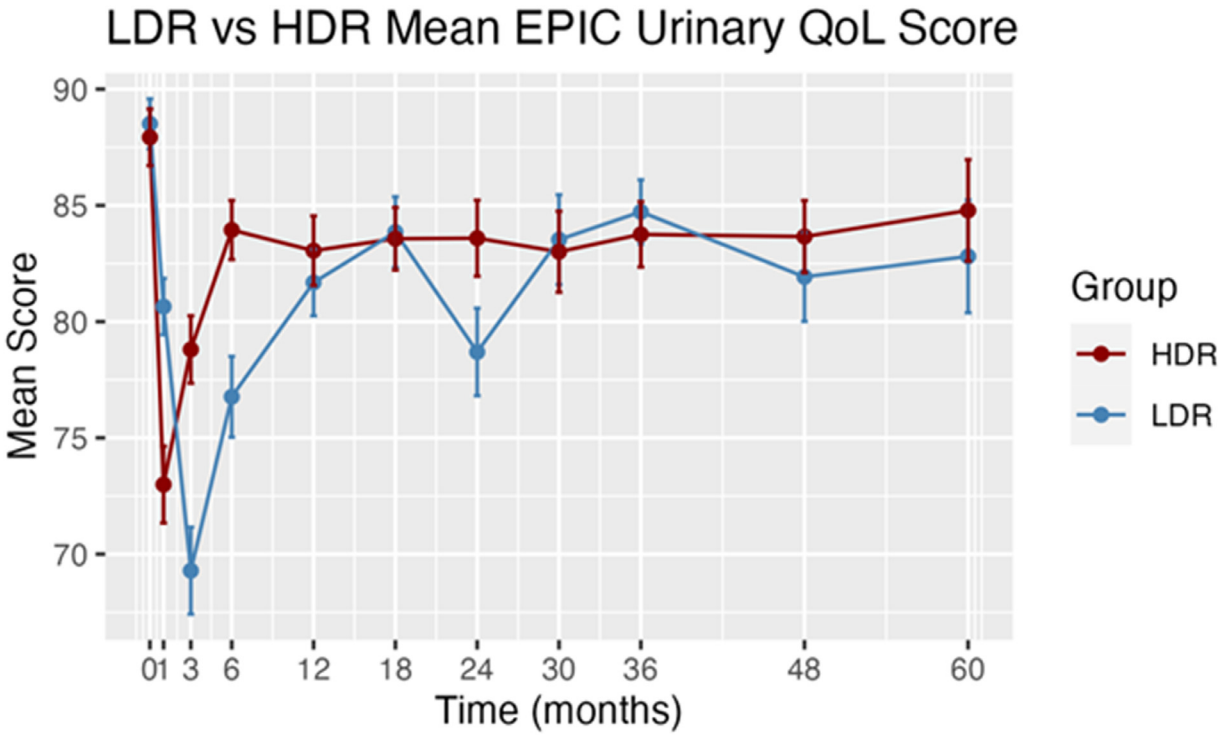

Fig. 2. Changes in mean Expanded Prostate Cancer Composite score for the urinary domain for high-dose rate (HDR) prostate brachytherapy and low-dose rate (LDR) prostate brachytherapy from 0 to 60 months. Note sharp decrease at 1 month for HDR with a later decline at 3 months for LDR. High-dose rate patients have recovered by 6 months to maintain less than the minimum clinically important difference for the duration of follow-up. LDR patients undergo more prolonged recovery to 18 months and then, except for temporary decline at 24 months, maintain less than the minimum clinically important difference from baseline. Note: A higher score indicates better quality of life. *Abbreviations:* EPIC = Expanded Prostate Cancer Composite score; LDF = low-dose rate; QoL = quality of life.

Table 4 Mean EPIC domain summary scores ± standard deviation for the urinary bother, urinary irritation/obstruction subscale, bowel bother subscale

Domain	Baseline	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36	Month 48	Month 60
Urinary Bother										
HDR	84 ± 14	68 ± 17	75 ± 15	81 ± 14	80 ± 16	81 ± 14	81 ± 16	83 ± 14	83 ± 18	81 ± 21
LDR	85 ± 12	75 ± 13	63 ± 17	72 ± 17	78 ± 14	80 ± 14	74 ± 19	81 ± 13	78 ± 14	85 ± 15
P value	.80	.01	<.001	<.001	.16	.69	.02	.20	.05	.67
Urinary irritation/ obstruct										
HDR	87 ± 12	70 ± 17	78 ± 14	84 ± 12	84 ± 13	86 ± 11	85 ± 15	88 ± 11	88 ± 12	87 ± 16
LDR	87 ± 10	77 ± 13	67 ± 17	77 ± 15	81 ± 13	83 ± 13	78 ± 17	85 ± 10	84 ± 10	89 ± 9
P value	.41	.005	<.001	<.001	.11	.49	.004	.12	.06	.98
Bowel bother										
HDR	95 ± 9	77 ± 19	86 ± 16	88 ± 14	85 ± 19	90 ± 13	89 ± 13	90 ± 16	89 ± 18	89 ± 19
LDR	91 ± 14	77 ± 16	81 ± 16	80 ± 20	78 ± 23	83 ± 19	81 ± 20	82 ± 20	80 ± 23	86 ± 19
P value	.17	.57	.03	.01	.03	.04	.02	.004	.06	.18

Abbreviations: EPIC = Expanded Prostate Cancer Composite score; HDR = high-dose-rate prostate brachytherapy; LDR = low-dose rate prostate brachytherapy.

Late toxicity was not required to be prospectively collected in the protocol, but guided by individual EPIC scores, patient charts were reviewed for clarification of symptoms and procedures and toxicity was graded according to Common Terminology Criteria for Adverse Events V5. Late urinary toxicity included one grade 3 event in each cohort, requiring Visual Internal Urethrotomy for the HDR patient and suprapubic catheter for the LDR patient, although the latter had a dysfunctional bladder and no evidence of stricture. Grade 2 urinary toxicity manifested in 7 HDR patients (6.7%) and 2 LDR patients (2.4%), all undergoing cystoscopy ± single dilatation. There was one LDR patient with

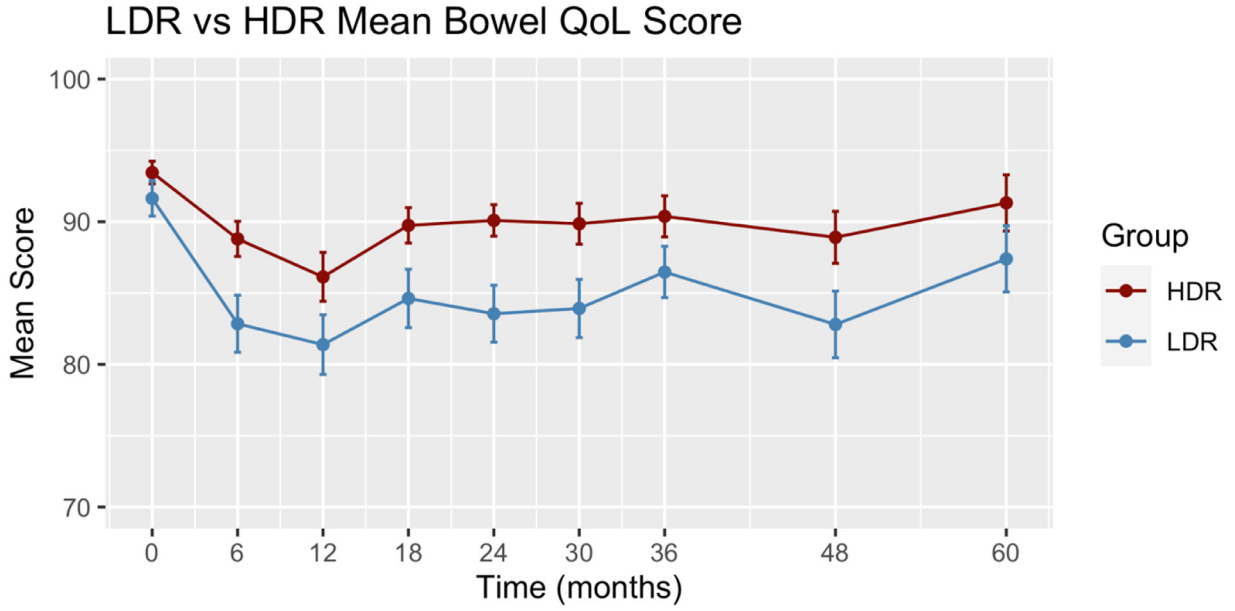

Fig. 3. Changes in mean Expanded Prostate Cancer Composite score for the bowel domain for high-dose rate (HDR) prostate brachytherapy and low-dose rate (LDR) prostate brachytherapy from 0 to 60 months. Neither cohort recovers to baseline but after the 12-month assessment, HDR patients maintain a less than the minimum clinically important difference from baseline, and LDR patients remain significantly more symptomatic than the HDR patients until 5 years (*P* values shown) and have a higher than minimum clinically important difference from their baseline for much of the time. Note: A higher score indicates better quality of life. *Abbreviations:* EPIC = Expanded Prostate Cancer Composite score; LDF = low-dose rate; QoL = quality of life.

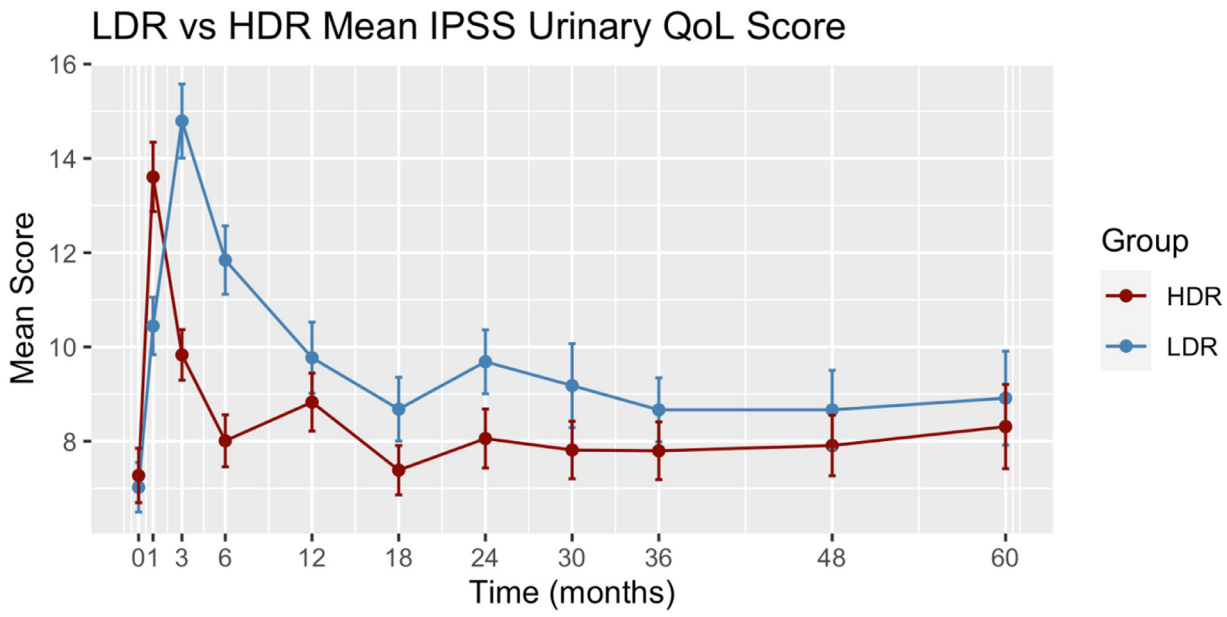

Fig. 4. Mean International Prostate Symptom Score for high-dose rate (red) and low-dose rate (blue) patients. Similar to the pattern for the Expanded Prostate Cancer Composite scores, the International Prostate Symptom Score for HDR patients peaks at 1 month but recovers rapidly, and LDR patients peak at 3 months and have a more prolonged recovery. Baseline scores shown in dotted lines. Note: A higher score indicates more severe symptoms. *Abbreviations:* EPIC = Expanded Prostate Cancer Composite score; HDR = high-dose rate; IPSS = International Prostate Symptom Score; LDF = low-dose rate; QoL = quality of life.

late grade 3 Gastro-intestinal (GI) toxicity (rectal hemorrhage with concurrent idiopathic thrombocytopenia), but no grade 3 rectal toxicity in the HDR cohort. Late grade 2 GI toxicity manifesting as intermittent rectal bleeding, was seen in 5 HDR patients (4.8%) and 9 LDR patients (10.8%). All cases were confirmed on colonoscopy, either mild or receiving a single cauterization.

Discussion

In this randomized trial, men with unfavorable intermediate risk and high-risk prostate cancer receiving an HDR prostate brachytherapy boost recovered more rapidly from the urinary and bowel side effects of treatment. They reported less effect on urinary and bowel function between 3 to 6 months after initiation of radiation treatment compared with patients treated with LDR PBT. Although the LDR patients recovered their urinary QOL by 12 months and maintained that up to 5 years, they experienced a more prolonged course of bowel side effects between 12 and 48 months, marked by increase in bowel bother. Patient reported outcomes did not identify any differences in QoL for acute or late sexual metrics between the 2 cohorts.

The time course of brachytherapy treatment delivery is the main factor contributing to urinary symptoms and QoL. The urinary QoL for the HDR brachytherapy cohort at 1 month after initiation of treatment is affected by both the implant and the ongoing pelvic EBRT. At 1 month, the LDR patients are nearing the end of pelvic EBRT but have not yet had their LDR brachytherapy implant, thus their urinary QOL is not heavily affected. However, by 3 and 6 months, the HDR cohort has completed all radiation and has recovered from the acute treatment effects and report significantly better bowel and bladder function compared with LDR patients, who are still undergoing radiation from the LDR-PBT implant, given the 59-day half-life of I-125. This is clearly illustrated in Figure 2, which shows the rapid decline in urinary QOL for HDR patients at 1 month, and rapid recovery by 6 months.

Hathout et al investigated the inherent difference in the tolerance of HDR and LDR brachytherapy and time to recovery in a small, randomized phase 2 pilot study comparing HDR and LDR monotherapy, removing any potential effect from ADT or additional EBRT.[20] HDR (single 19 Gy) was compared with LDR (144 Gy) for 16 and 15 patients, respectively. EPIC and IPSS were recorded at 1, 3, 6, and 12 months. The primary endpoint was urinary HRQoL at 3 months. Both IPSS and EPIC urinary irritative scores were significantly worse for LDR patients at 3 and 6 months, with the difference diminishing over time to 12 months. There were no differences in continence, bowel, or sexual EPIC scores at any time point.

Randomized trials on dose escalation to the prostate gland using HDR or LDR brachytherapy have provided level 1 evidence of improved biochemical progression free survival compared with EBRT alone.[2,3] However, this came at a price. The cumulative incidence of late grade 3 urinary toxicity in patients treated with LDR brachytherapy boost in the Ascende RT trial was an unacceptable 18% versus 5%

for those treated with dose escalated EBRT ($P < .001$).[6] Urethral strictures dominated the grade 3 toxicities, many of which are correctable, resulting in a lower 5-year prevalence of late grade 3 urinary toxicity (LDR 8.6% vs DE-EBRT 2.2%, $P = .058$).[6] However, this is still considerably higher in LDR boost patients than for DE-EBRT and clearly a significant burden for patients to bear. The reported rates of acute and late Genito-urinary (GU) toxicity in Ascende RT have been attributed to generous inferior margins during brachytherapy planning, with resultant late urethral toxicity[11] from increased dose to the membranous urethra.[2]

The reported Ascende GU toxicity has generated a lot of discussion and concern. However, non-Ascende institutions have not validated similar toxicity rates. Spratt et al compared DE-EBRT using IMRT (86 Gy) to combined brachytherapy plus pelvic IMRT. There was no differences in late urinary toxicity (grade 2 urinary: 19% vs 21%, $P = .14$, grade 3: 3% vs 1.4%, 0 = 0.74), or in late bowel toxicity (grade 2 both <5% and grade 3 < 2%).[21] Furthermore, one of the centers contributing to the Ascende RT trial undertook an analysis of 99 patients treated consecutively with combined EBRT and LDR BT after Ascende closed to accrual.[22] Patient charts and hospital records were reviewed and the same assessment scale was used as in the Ascende analysis. The late grade 3 GU toxicity was only 3%. This lower rate was attributed to multiple factors: more experienced team, reduction of prescription dose from 115 Gy in Ascende to 110 Gy after toxicity was discovered, weekly brachytherapy quality assurance rounds, tighter apical margin, and post plan assessment incorporating MRI at 1 month for MR-CT fusion to improve soft tissue delineation for contouring.

Although concerns remain over the Ascende trial-reported GU toxicity, LDR prostate brachytherapy boost nonetheless remains an extremely effective treatment. With the present results, we can allay these concerns as we report no difference in urinary QoL from 1 to 5 years after treatment between HDR and LDR boost patients. The mean EPIC urinary QoL score was 83.3 for both cohorts from 12 to 60 months, compared with baseline scores of 88 for the LDR patients and 89 for HDR.

Dhere et al used PROs to compare LDR and HDR brachytherapy combined with EBRT in intermediate and high-risk prostate cancer.[23] Between 2012 and 2018, 106 men underwent either LDR (110 Gy) or HDR (15 Gy) with pelvic EBRT (37.5-45 Gy at 2.5 or 1.8 Gy/fraction respectively). They also found that LDR brachytherapy was associated with a greater change in IPS scores, but diminishing over time to 24 months, also seen in the EPIC irritative score. There was no difference between the 2 types of brachytherapy in continence, bowel function or sexual function.

Although Slevin et al[24] compared LDR boost (n = 116) to HDR boost (n = 171) in sequential cohorts and reported 5 year cumulative grade 3 GI toxicity in 5% of LDR boost patients and 1% of HDR boost patients, bowel function has not differed between HDR and LDR treatment cohorts in many prior reports, whether used in combination with EBRT or as monotherapy.[20,23] The prolonged decrease in bowel QoL for our LDR patients was not expected. A decline in bowel QOL score at 3 and 6 months could be explained for LDR patients by the time course of radiation delivery, but not in the 24- to 48-month follow-up assessments. A post hoc analysis of rectal dose for the LDR patients was undertaken to investigate this observation. The mean RD1 cc (dose received by 1 cc of rectal wall with rectal wall defined on MRI at 1 month) for the LDR patients was 82 Gy (SD 22 Gy), well within the accepted guidelines of RV100 (volume of rectal wall receiving 100% of prescribed dose, in this case 110 Gy) at 1 month <1.3 cc.[25-27] These guidelines from 2001 were designed to keep grade 2 rectal toxicity <5%. A patient-reported outcome such as EPIC QoL is clearly a more sensitive endpoint. Our median RV100 was 0.17 cc (IQR, 0.01-0.54). A multivariate linear regression model was used to investigate the dose response relationship between the EPIC bowel domain score and RD1 cc for LDR patients. In this range of rectal dose, a 20 Gy increase in RD1 cc was associated with a 1.5-point decrease in bowel QOL. This did not achieve statistical significance but may well be clinically significant and suggests that LDR patients may do better with a lower rectal dose as proponents of rectal spacers have suggested.[28,29] For the HDR cohort, the rectal dose constraint of RD1 cc <9.5 Gy was adhered to strictly. Delivery of treatment with the TRUS probe in situ was used to increase the rectal-prostate distance while planning images were acquired and during treatment delivery.

Both HDR and LDR cohorts reported poor sexual QoL in the short- and long-term intervals with no differences between the 2 arms. ADT is the major driver for this phenomenon. Notably, both groups reported baseline low sexual QoL, before the initiation of any radiation treatment. The baseline sexual function score was assessed at first consultation. At this time, some patients had already been started on ADT by their referring urologist, and a true baseline before any treatment is not available for these patients. Those who were not on ADT at referral had a better baseline sexual QoL (IIEF median, 12). Overall, 75% of patients received ADT for a median duration of 12 months. The long-term poor sexual QoL seen in both cohorts may be attributed to slow testosterone recovery after ADT. Nabid et al reported that after 18 months of ADT only 55% of men recovered a normal testosterone and the median time to recovery was 2.1 years after completion of treatment.[30] This is very similar to the current study where 65% recovered to a testosterone of 7 nmol/L by 18 months.

Conclusion

This is the first randomized control trial comparing QoL in men treated with HDR or LDR prostate brachytherapy combined with EBRT, with results demonstrating better patient-reported acute urinary and bowel QoL with HDR prostate brachytherapy boost compared with an LDR brachytherapy boost. LDR brachytherapy boost remains a very safe option

in experienced hands, but it is associated with longer and slower recovery than an HDR boost. These findings will aid informed decision-making and facilitate counseling patients on the expected duration of side effects in the context of multiple treatment options for unfavorable prostate cancer. Overall, the differences in patient-reported QOL are relatively small and the ultimate winner as "best boost" may well depend on relative efficacy. Additional analysis is underway for efficacy endpoints including overall survival, disease-free survival, and biochemical progression-free survival and will be reported later this year.

References

1. Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer Care Ontario joint guideline update. *J Clin Oncol* 2017;35:1737-1743.
2. Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:275-285.
3. Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. *Radiother Oncol* 2021;154:214-219.
4. Glaser SM, Dohopolski MJ, Balasubramani GK, Benoit RM, Smith RP, Beriwal S. Brachytherapy boost for prostate cancer: Trends in care and survival outcomes. *Brachytherapy* 2017;16:330-341.
5. Rodda S, Morris WJ, Hamm J, Duncan G. ASCENDE-RT: An analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:581-589.
6. Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:286-295.
7. Georg D, Hopfgartner J, Gòra J, et al. Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2014;88:715-722.
8. Spratt DE, Scala LM, Folkert M, et al. A comparative dosimetric analysis of virtual stereotactic body radiotherapy to high-dose rate monotherapy for intermediate-risk prostate cancer. *Brachytherapy* 2013;12:428-433.
9. Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer—between options. *J Contemp Brachytherapy* 2013;5:33-41.
10. Helou J, D'Alimonte L, Loblaw A, et al. High dose-rate brachytherapy boost for intermediate risk prostate cancer: Long-term outcomes of two different treatment schedules and early biochemical predictors of success. *Radiother Oncol* 2015;115:84-89.
11. Shahid N, Loblaw A, Chung HT, et al. Long-term toxicity and health-related quality of life after single-fraction high dose rate brachytherapy boost and hypofractionated external beam radiotherapy for intermediate-risk prostate cancer. *Clin Oncol (R Coll Radiol)* 2017;29:412-420.
12. Martens C, Pond G, Webster D, McLean M, Gillan C, Crook J. Relationship of the International Prostate Symptom score with urinary flow studies, and catheterization rates following 125I prostate brachytherapy. *Brachytherapy* 2006;5:9-13.
13. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012;11:6-19.
14. Yamada Y, Rogers L, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for high-dose rate prostate brachytherapy. *Brachytherapy* 2012;11:20-32.
15. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56:899-905.
16. Barry MJ, Fowler Jr FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148:1549-1557 discussion 1564.
17. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822-830.
18. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Med Care* 2003;41:582-592.
19. Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. *Health Qual Life Outcomes* 2020;18:136.
20. Hathout L, Mahmoud O, Wang Y, et al. A phase 2 randomized pilot study comparing high-dose-rate brachytherapy and low-dose-rate brachytherapy as monotherapy in localized prostate cancer. *Adv Radiat Oncol* 2019;4:631-640.
21. Spratt DE, Zumsteg ZS, Ghadjar P, et al. Comparison of high-dose (86.4 Gy) IMRT versus combined brachytherapy plus IMRT for intermediate-risk prostate cancer. *BJU Int* 2014;114:360-367.
22. Zheng J, Bachand F, Halperin R, Kim D, Petrik D, Crook J. After ASCENDE-RT: Outcomes of androgen deprivation, external beam radiation and LDR brachytherapy boost for high-tier intermediate and high-risk prostate cancer. *Radiother Oncol* 2021;163:32.
23. Dhere VR, Fischer-Valuck BW, Goyal S, et al. Patient-reported outcomes after low-dose rate versus high-dose rate brachytherapy boost in combination with external beam radiation for intermediate and high-risk prostate cancer. *Brachytherapy* 2021;20:1130-1138.
24. Slevin F, Rodda SL, Bownes P, et al. A comparison of outcomes for patients with intermediate and high-risk prostate cancer treated with low-dose rate and high-dose rate brachytherapy in combination with external beam radiotherapy. *Clin Transl Radiat Oncol* 2019;20:1-8.
25. Snyder KM, Stock RG, Hong SM, Lo YC, Stone NN. Defining the risk of developing grade 2 proctitis following 125I prostate brachytherapy using a rectal dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2001;50:335-341.
26. Keyes M, Spadinger I, Liu M, et al. Rectal toxicity and rectal dosimetry in low-dose-rate 125I permanent prostate implants: A long-term study in 1006 patients. *Brachytherapy* 2012;11:199-208.
27. Price JG, Stone NN, Stock RG. Predictive factors and management of rectal bleeding side effects following prostate cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2013;86:842-847.
28. Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: Dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;92:971-977.
29. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: Final results of a phase III trial. *Int J Radiat Oncol Biol Phys* 2017;97:976-985.
30. Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: A randomized phase III trial. *Eur Urol* 2018;74:432-441.