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PHASE I TRIAL OF MRI-GUIDED PROSTATE CANCER LATTICE EXTREME ABLATIVE DOSE (LEAD) BOOST RADIOTHERAPY

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Abstract

Purpose: A phase I clinical trial was designed to test the feasibility and toxicity of administering high-dose spatially-fractionated radiotherapy to MRI-defined prostate tumor volumes, in addition to standard treatment.

Methods and Materials: We enrolled 25 men with favorable to high-risk prostate cancer and 1–3 suspicious multiparametric MRI (mpMRI) gross tumor volumes (GTVs). The mpMRI-GTVs were treated on day 1 with 12–14 Gy via dose cylinders using a Lattice Extreme Ablative Dose (LEAD) technique. The entire prostate, along with the proximal seminal vesicles (SVs), was then treated to 76 Gy at 2 Gy/fraction. For some high-risk patients, the distal SVs and pelvic lymph nodes received 56 Gy at 1.47 Gy/fraction concurrently in 38 fractions. The total dose to the LEAD dose cylinder volume(s) was 88–90 Gy (112–123 Gy in 2.0 Gy equivalents, assuming an α/β ratio of 3).

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Results: Dosimetric parameters were satisfactorily met. Median follow-up is 66 months. There were no grade 3 acute/subacute genitourinary (GU) or gastrointestinal (GI) adverse events. Maximum late GU toxicity was Grade 1 in 15 (60%), Grade 2 in 4 (16%), and Grade 4 in 1 (4%; sepsis after a post-treatment transurethral resection). Maximum late GI toxicity was Grade 1 in 11 (44%) and Grade 2 in 4 (16%). Two patients experienced biochemical failure.

Conclusions: External beam radiotherapy delivered with an upfront spatially-fractionated, stereotactic high dose mpMRI-GTV boost is feasible and was not associated with any unexpected events. The technique is now part of a follow-up Phase II randomized trial.

INTRODUCTION

Radiotherapy (RT) has been shown to be an effective treatment for prostate cancer (PCa) using contemporary doses of external beam radiotherapy (EBRT) in the 76–80 Gy range.[1,2] Such “escalated doses” have been supported by a series of randomized trials that have established the current standard of care. However, for intermediate and high-risk patients, there is evidence that doses equivalent to greater than 80 Gy in 2 Gy fractions (EQD_{2Gy} >80 Gy) result in additional gains,[3–5] with less need for the use of androgen deprivation therapy (ADT).[2,4,6] These findings, and that there is a late increase in metastatic disease at about 10 years after radiotherapy.[7] indicate that local persistence is a significant issue at whole prostate EDG_{2Gy} doses of 76–80 Gy.

Prostate cancer is hypothesized to respond to greater than 2 Gy fractional doses of radiation to a greater degree than surrounding normal tissue, which is partially explained by radiobiological data consistent with a low α/β ratio.[8,9] With extreme doses of 10 Gy and above, other mechanisms, such as endothelial cell death, appear to further enhance cell death.[10–12] For many years, extreme RT doses have been achieved using high-dose rate implants, typically given in combination with standard fractionation BRT.[13] The basis for the described Phase I clinical trial was the hypothesis that stereotactic delivery techniques targeting smaller multiparametric (mp) MRI-defined dominant tumor volumes are feasible and would not significantly add toxicity. A dominant mpMRI tumor targeted approach is supported by some findings of local persistence mainly in the dominant tumor lesion(s) seen on mpMRI.[14] The use of single fraction high dose targeted boosts is distinguished from simultaneous integrated boost methods[15–17] for boosting mpMRI- and/or PET-defined volumes that are becoming increasingly popular.

The Lattice Extreme Ablative Dose (LEAD) boost technique described herein is modeled after spatially-fractionated GRID EBRT (SPGRT),[18,19] as a conceptualized stereotactic at depth extension of the technique. SPGRT was initially developed to minimize skin and subcutaneous tissue reactions from orthovoltage treatment, with high doses of radiation (typically 10–20 Gy), given in a single fraction interspersed with blocked regions. Used as a standalone palliative treatment or as an adjunct to standard EBRT treatments, SPGRT is hypothesized to increase bystander and abscopal effects effects.[4] SPGRT has been adapted to IMRT[20] and more recently proton therapy.[21]

We report on the feasibility and toxicity results of treating 1–3 spatially separated high dose cylinders of 12–14 Gy into each mpMRI-defined GTV, followed by standard fractionated radiotherapy to the prostate and proximal seminal vesicles.

METHODS AND MATERIALS

Protocol design

The feasibility and safety of the LEAD approach was tested in a phase I clinical trial of men with prostate cancer who had at least one DCE-MRI identifiable lesion (Figure S1). The LEAD technique involved placing 1–3 dose cylinder(s) in mpMRI-defined GTVs, wherein each dose cylinder was treated to 12–14 Gy on day 1. Standard fractionation of the planning target volumes (PTVs) was started on day 2 with treatment of the prostate and proximal seminal vesicles (SVs) at 2.0 Gy per day for 38 fractions to 76 Gy. The pelvic lymph nodes were treated in two patients. The total absolute dose for all treatments was 88–90 Gy to the LEAD dose cylinders or an EQD_{2Gy} of 112–123 Gy, assuming an α/β ratio of 3.0, which was used as a conservative estimate. The dose cylinders were limited initially to 7 mm diameter; however, an amendment allowing for up to 12 mm was active for the last 17 patients to allow for greater GTV coverage.

The trial was approved by the Institutional Review Board at the University of Miami (ClinicalTrials.gov: NCT01411319). All patients were provided with written informed consent.

Classification of risk, eligibility, and stratification

Men with Stage T1-T3a adenocarcinoma of the prostate and Gleason score 6–10 with favorable to high-risk features (Table 1) were eligible. Patients were able to refuse or accept up to 6 months of ADT that was not started more than 2 months prior to signing consent. High-risk patients who refused long term ADT were eligible (see Supplementary Methods for protocol risk classification).

Pre-enrollment multiparametric MRI:

All patients in the study received a diagnostic mpMRI at 2.5 mm slice thickness consisting of: T2, T1 non-contrast, T1 dynamic contrast-enhanced (DCE) MRI, and diffusion weighted imaging (DWI) with the generation of an Apparent Diffusion Coefficient (ADC) map (see Supplementary Methods). Patients were asked to have a moderately full bladder and empty rectum (bowel preparation procedure). The DCE-MRI scans were obtained pre-contrast and at ~30 sec intervals post-contrast, for a minimum of 10 scans, as described previously.[22,23] The GTVs were estimated using DCE-MRI with consideration of the volume of pixels on the ADC map with values of <1000. About a week prior to simulation, four fiducial markers placed in the prostate, with two at the base and two near the apex.

MRI and CT-Simulation

After fiducial marker placement and typically on the same day as CT-simulation, a second limited non-contrast prostate simulation MRI study that included T2w and T2* sequences was done to visualize the fiducial markers (see Supplementary Methods). Using rigid fusion

based on the fiducial markers, the simulation MRI was fused to the simulation CT. The diagnostic mpMRI was then fused to the simulation MRI. The GTVs and LEAD dose cylinders were referenced to the fiducial markers.

LEAD planning and acceptance

The LEAD RT dose plan involved the placement of 1–3 cylinders of ~7–−12 mm diameter spaced approximately 1.5 – 2.0 cm apart and extending for the length of the mpMRI GTV volume plus up to 6 mm above and below the GTV. The desired placement of the cylinders was through the center of the GTVs, although off center placement was used to respect OAR constraints. The GTV included the mpMRI-defined suspicious lesions recognized by early phase contrast enhancement on DCE-MRI or by water restriction on the Apparent Diffusion Coefficient (ADC) maps, along with abnormalities on T2-weighted imaging. For anterior lesions in the transition zone, an abnormality based solely on DCE-MRI was insufficient and had to be associated with ADC point value clusters of <1000. The LEAD dose cylinder volume(s) were planned to receive >90% (exact percentage not specified in the protocol) of a planned 12 Gy (14 Gy was allowed, but never prescribed), with a maximum dose of <20 Gy. A variation was considered to be maximum doses ≥20 Gy to 23 Gy, with a protocol violation defined as above this limit.

The organ at risk (OAR) contour definitions are similar to those described in the control arm of the Fox Chase hypofractionation trial[24] and are described in the Supplementary Methods. For the LEAD RT day 1 plan, the V_{3Gy} for the anorectum, bladder, and penile bulb were <8% (4.0 Gy Dmax). Protocol variations were V_{3Gy} of 8–10% with a Dmax of 4.5 Gy and a protocol violation being any value above these limits. For the urethra, the V_{3Gy} was <10% with a protocol primary variation 10–20% with a Dmax of 6.0 Gy and a secondary variation for any dose above these limits; there were no specified protocol deviations for the urethral dose. The LEAD dose distribution was delivered by Cyberknife® (Accuray Inc, Sunnyvale, CA) for all patients. The rest of the treatment was carried out either on Cyberknife (n=2) or a standard linear accelerator-based machine (Varian, Palo Alto, CA) (n=23).

Prostate, SV and pelvic lymph node IMRT planning and acceptance

The CTV1 included the prostate and the proximal seminal vesicles (about 10 mm), with an extra 1–2 mm beyond known bulky disease and/or suspected extracapsular extension. The primary planning target volume (PTV1) was 3–5 mm around the CTV1 in all dimensions. For tumors at the base, a margin of 5 mm on the proximal seminal vesicles was recommended. Pelvic lymph node treatment was allowed and was done in two high risk patients. The pelvic lymph nodes (CTV2) were contoured per standard published guidelines;[25] however, there was no expansion for the secondary planning target volume (CTV2=PTV_{nodes}) to keep bladder toxicity at a minimum.[26]

The plans were evaluated by dose-volume histogram analysis based on prior established criteria.[27] The PTV1 was planned to receive ≥95% of the prescription dose of 76 Gy in 38 fractions ($V_{100\%}$ of ≥95% of the prescription dose); a minor variation was <95% to ≥90% and a violation was <90% of the prescription dose. Assuming an α/β ratio of 3.0, the cumulative EQD_{2Gy} to the LEAD RT dose cylinder with a prescription of 12 Gy would be

112 Gy. PTV_{nodes}, when given, received 56 Gy in the same 38 planned fractions. The objective was that the plan sum of the LEAD stereotactic and standard fractionation treated PTVs would meet the OAR dose limits used previously for a standard fractionation 76 Gy in 38 fraction plan described previously[24] (see Supplementary Methods).

Endpoint and statistics

The primary endpoint of the study is to determine the feasibility and toxicity in a Phase I clinical trial. The early and late side effects using the Common Terminology Criteria for Adverse Events (CTCAE) version 4 (NCI, Bethesda, MD) are described. Secondary endpoints include the Phoenix nadir+2 definition of biochemical failure[28] and prostate biopsy results 2.0–2.5 years after completion of all treatment.[29,30] Continuous variables and categorical variables were compared by using Student's t-test and Fisher's exact test, respectively. All tests were two-sided and $P<0.05$ was considered statistically significant. All analyses were conducted using the SAS software (version 9.4).

RESULTS

Patient enrollment and characteristics

Figure S2 shows a CONSORT diagram outlining patient eligibility, enrollment, and follow-up. The trial was initially planned for 20 patients, but with 19 patients accrued and low toxicity, the trial was expanded to 25 patients on 10/16/2013. One patient was noncompliant and lost to follow-up. Table 1 shows the baseline patient characteristics and disease characteristics for the 25 men enrolled. Mean age was 66.8 years. There were 14 (56%) patients who received short term ADT via an LHRH agonist (leuprolide). Bicalutamide was started a median of 7 days prior to the start of leuprolide injection and was given for a median of 4 months. Of note, one patient received only bicalutamide, and one patient, because of cirrhosis, was treated only with leuprolide. When given, leuprolide was administered for a median of 6 months. Median follow-up time was 66 months (range 21 – 71 months). All patients completed treatment without interruption. Men treated with ADT were significantly older than those who did not receive ADT (Table 1).

Feasibility

Table 2 summarizes the number of GTVs, the GTV volumes, and dose cylinder volumes, and maximum diameters. The mean GTV1 (n=25) volume was 2.5 cc, GTV2 (n=13) − 0.96 cc, and GTV3 (n=4) − 0.82 cc.

A summary of dosimetric parameters for the LEAD boost administered on day 1 is displayed in Table 3. There were no coverage specifications for the dose cylinder targets in the protocol, but, a prescription dose to 90% of the cylinders ($D_{90\%}$) was attempted. The mean cylinder $D_{90\%}$ was 11.1 Gy (range 7.7–13.4Gy). In terms of maximum doses to the cylinders (Dmax of <115%), there were no protocol deviations. There were no OAR violations.

Table 4 displays a summary of the dosimetry for the 38 fraction conventional plans alone and with the LEAD cylinder plans added. There were no target or OAR dosimetric protocol violations. Table 4 lists the variations.

Genitourinary (GU) adverse events (AEs)

The details of maximum GU toxicity at baseline and at various times after the completion of RT are summarized in Table 5. Toxicity details are subdivided by attribution code. Only toxicity events with attribution codes of “definite,” “probable,” and “possible” were included; events likely unrelated to treatment are not shown. Any prescribed use of a medication, such as tamsulosin 0.4 mg (most frequent alpha blocker used) was coded as a grade 2 reaction when symptoms of frequency/nocturia were present, as per CTCAEv4.0 guidelines. Table 5 shows that all but one patient had preexisting urinary symptoms and this was reflected in the baseline International Prostate Symptom Score (IPSS)[31] summarized in Supplementary Table 1. Only one patient had a greater than grade 2 event, which was related to a transurethral resection for urinary obstructive symptoms post-RT that was complicated by sepsis.

Prevalence for GU toxicity (Figure 1A) revealed that many of the grade 2+ events were transient. The prevalence plot displays the possibly, probably, and definitely related adverse events, as well as any symptoms not considered related (e.g., no change from baseline). Distinguishing treatment related from pre-existing symptoms was not always clear; the bias was to code as treatment related when uncertain. For example, all patients at 3 months were coded as having treatment related increased symptoms, even if the grade was the same as baseline. There was a maximal increase in grade 2 GU symptoms at 3 mo and a trend for a gradual reduction and stabilization after 27 months. Cumulative incidence rates of grade 2+ toxicities for GU and GI after RT are presented in Figure S3.

Gastrointestinal AEs

The grade and attributions of maximum CTCAEv4.0 GI toxicities are displayed in Table 6. Baseline symptoms were minimal. There were 4 patients with maximal late grade 2 events. No adverse events above grade 2 were seen. The prevalence plot for GI events (Figure 1B) reveals a maximal increase in events at 3 months with some increased above baseline grade 1 and grade 2 AEs thereafter. Two grade 2 events for rectal bleeding/proctitis continued after 30 months post-RT; of these, one resolved to a grade 1 after successful minor cauterization and one did so spontaneously.

DISCUSSION

The LEAD technique was designed based on supportive evidence that (i) dose escalation beyond 80 Gy in 2 Gy fractions results in improved freedom from failure and lessens the impact of androgen deprivation therapy; (ii) extreme hypofractionation doses to tumor region(s) improve tumor cell killing through additional cell death mechanisms, bystander effects, and abscopal effects; and (iii) limiting the extreme doses to tumor areas with strict OAR constraints will keep grade 3 side effects lower than previously reported rates from whole prostate dose escalation above 80 Gy.

Contemporary prostate EBRT doses of 76–80 Gy have been considered radiotherapy "dose escalation." However, there is a dose-response above 80 Gy[3,5,32,33] and local persistence of disease is a strong predictor of eventual failure and distant metastasis.[34,35] Prostate biopsies at 2–3 yr after ≤80 Gy EBRT doses reveal that 30–40% of cases have suspicious atypical cells or adenocarcinoma with or without treatment effect;[30,36–38] about 50% of such cases experience biochemical failure over the next 10 years.[38] Levagrun et al[37] have described a dose response using prostate biopsy positivity as an endpoint, showing that the TCD50 for high risk patients is approximately 77 Gy. These results are an underestimate because ultrasound sextant template biopsies were used, and, based on MRI-guided biopsy data,[39] over 30% of tumors would be missed. Likewise, defining prostate cancer dose response using biochemical failure at a specific point in time, say 5 years, have been underestimates because failures typically continue to occur.[3,32]

The best tumor control rates in intermediate and high risk patients have been achieved using a combination of EBRT and brachytherapy that have included whole prostate high dose rate and low dose rate methods.[32] Along the lines of several retrospective series, the randomized ASCENDE-RT trial reported by Morris et al[5] is a clear illustration of the benefit of dose escalation, achieved using EBRT plus brachytherapy, in terms of reducing biochemical failure, the primary endpoint. Biochemical failure at 7 years was 25.0% in the EBRT alone arm and 14% in the EBRT plus brachytherapy arm.

The LEAD approach directs dose escalation to the dominant tumor lesion(s) using mpMRI and biopsy information, instead of treating the entire prostate to very high doses. Rodda et al[40] reported that grade 3 toxicity in the ASCENDE-RT patients who received EBRT plus brachytherapy was substantially higher than those who received EBRT alone. In contrast, only 1 grade 3+ complication attributable to radiotherapy was identified in the LEAD cohort. Our findings are in line with the reported results from the randomized FLAME trial in which the experimental arm used an MRI-guided simultaneous integrated boost technique, although only one dominant GTV was boosted in the FLAME trial.[17]

Large single radiation doses, such as that used on day 1 of treatment (12 Gy) is hypothesized to cause intratumoral bystander and abscopal effects,[41–43] induce more tumor endothelial cell death (doses above 8–11 Gy),[10] increase host T-cell priming,[44] and enhance treatment response in heterogeneous tumors containing cells with varying radiosensitivity.[45] We chose to administer the stereotactic boost up front for several reasons, including that the MRI boost target(s) is well-defined at this point, that biological data have historically shown that high-dose RT prior to standard RT doses results in significantly greater tumor regression overall,[46,47] and that giving a boost at the end of treatment could add to the uncertainty of focused targeting. An open question is whether a stereotactic boost timed after the conventional fractionation portion and the consequent reduced hypoxia at that point, would outweigh the hypothesized benefits from the other mechanisms at play from an upfront boost.

Higher prostate doses are associated with greater risks of significant late side effects; however, the LEAD technique limits toxicity risk in several ways. In the LEAD trial, the MRI-defined GTV(s) were not covered completely by the LEAD boost on day 1 using dose cylinders of 0.6–1.2 cm diameter (mean diameter 0.9). Attention was paid to the dose to the

anorectum, positioning the dose cylinder such that point doses were kept below 4.5 Gy and the V3 Gy below 8% in all cases. We were more concerned with rectal doses because bladder constraints were easier to obtain. The doses to the OARs were, therefore, similar to that from our current standard course of 80 Gy in 40 fractions to the prostate and proximal seminal vesicles.

In summary, the integration of an upfront extreme single RT fraction dose to mpMRI-defined tumor volumes, with subsequent standard fractionation doses, is feasible and without untoward toxicity. The biochemical failure rate of 8% at a median follow-up of 66 months is encouraging. To facilitate broader use eventually, an automated workflow has been developed for prostate segmentation and pixel by pixel risk assignment (habitat risk score) based on quantitative mpMRI features.[48] The resultant workflow has been incorporated into a randomized phase II trial (NCT02307058; The BLaStM trial)[47]; the LEAD treatments in the BLaStM trial are administered on a standard linear accelerator, making the workflow more generalizable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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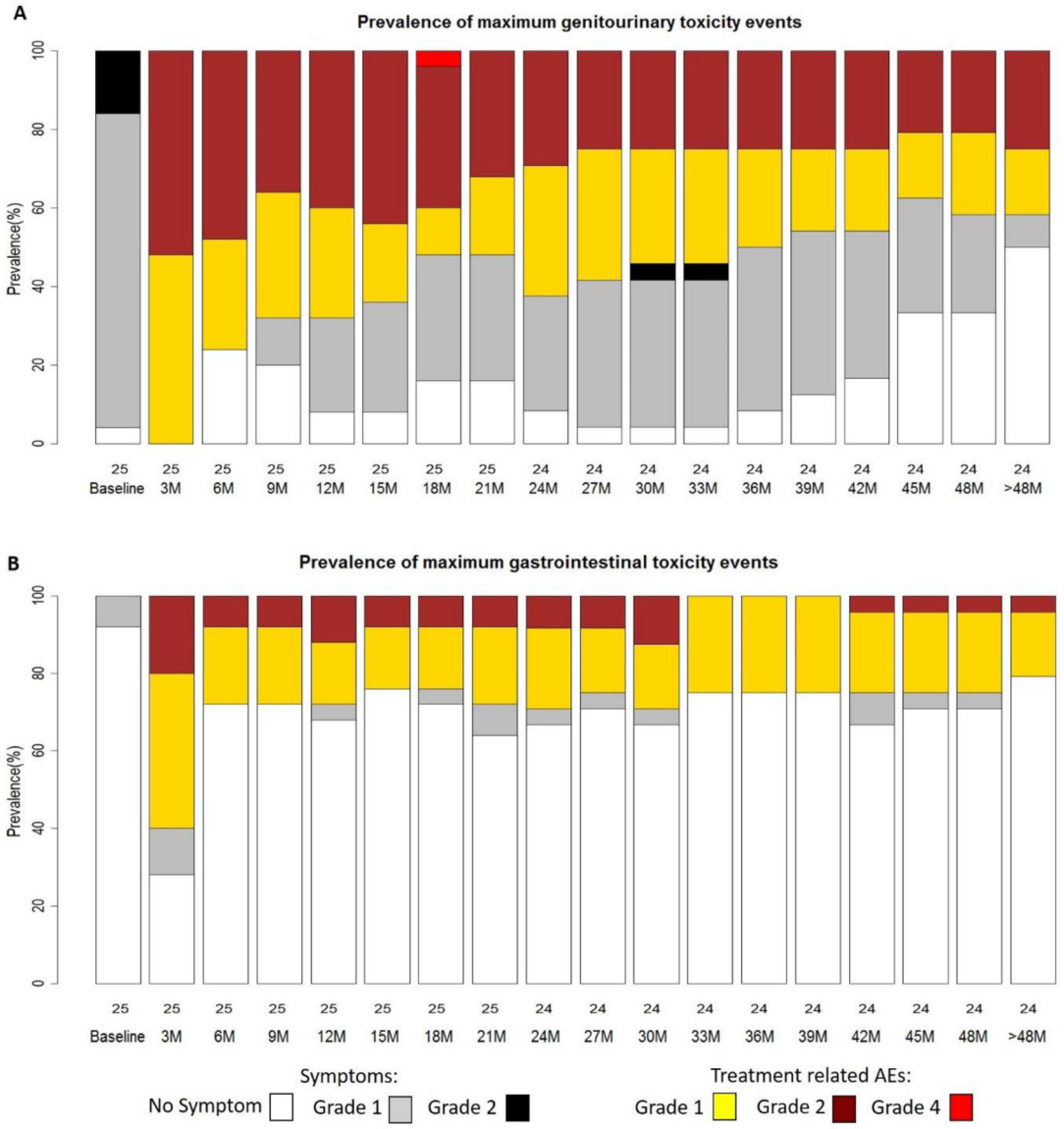

Figure 1.

Prevalence of maximum (A) genitourinary (GU) and (B) gastrointestinal (GI) toxicity events (adverse effects). Prevalence plots display baseline, acute (≤3 months), and late reactions (> 3 months).

Table 1.

Patient characteristics for study cohort organized by whether androgen deprivation therapy (ADT) was administered.

	TOTAL	ADT[a]	NO ADT	
Variable	**N (%)**	**N (%)**	**N (%)**	***p-value*[b]**
No of Patients	25 (100)	14 (56)	11 (44)	
Age years, median (range)	67 (44–85)	67 (44–78)	71 (52–85)	0.026
Race/ethnicity				0.504
Non-Hispanic White	17 (68.0)	8 (57.1)	9 (81.8)	
Non-Hispanic Black	1 (4.0)	1 (7.1)	0 (0.0)	
Hispanic/Latino	7 (7.0)	5 (35.7)	2 (18.2)	
Gleason score: Grade Group				0.125
6: 1	3 (12.0)	0 (0.0)	3 (27.3)	
7 (3+4): 2	12 (48.0)	7 (50.0)	5 (45.5)	
7 (4+3): 3	7 (28.0)	4 (28.6)	3 (27.3)	
8–9:4–5	3 (12.0)	3 (21.4)	0 (0.0)	
T stage				1.000
T1	17 (68.0)	10 (71.4)	7 (63.6)	
T2	8 (32.0)	4 (28.6)	4 (36.4)	
PSA, ng/mL, median (range)	5.8 (3.1–18.9)	6.2 (3.1–12.8)	5.7 (3.8–18.9)	0.515
PSA groups, ng/mL				1.000
<10	17 (68.0)	10 (71.4)	7 (63.6)	
10–20	8 (32.0)	4 (28.6)	4 (36.4)	
Follow-up months, median (range)	66.2 (20.8, 71.1)	63.1 (20.8, 66.9)	66.7 (53.7, 71.1)	0.246
AJCC prognostic group[c]				0.203
I	2 (8.7)	0 (0.0)	2 (20.0)	
IIA	17 (73.9)	10 (76.9)	7 (70.0)	
IIB	4 (17.4)	3 (23.1)	1 (10.0)	
Biochemical failure[d]				1.000
Yes	2 (8.0)	1 (7.1)	1 (9.1)	
No	23(92.0)	13 (92.9)	10 (90.9)	
Endpoint biopsy				1.000
Negative	11	6	5	
Positive[e]	1	1	0	
Not performed	13	7	6	

Abbreviations: AJCC = American Joint Commission on Cancer; SD = standard deviation

[a] ADT was for a median of 6 months (range: 4 to 9 months);

[b] p-values from t-test for continuous variables or Fisher's exact test for categorical variables;

[c] AJCC 7th edition, Group I = favorable, Group IIA, intermediate, and Group IIB, high risk;

[d] Positive biochemical failure was determined by PSA > nadir plus 2 ng/mL;

[e] Adenocarcinoma with treatment effect.

Table 2.

Gross tumor volume (GTV) and dose cylinder size

Parameter	GTV1 (n=25) Mean ± SEM (range)	GTV2 (n=13) Mean ± SEM (range)	GTV3 (n=4) Mean ± SEM (range)	Total Mean (range)
GTV Volume (cc)	2.5 ± 0.37 (0.60 – 8.06)	0.96 ± 0.19 (0.19 – 2.21)	0.82 ± 0.33 (0.22 – 1.58)	3.26 (0.66 – 8.06)
Dose Cylinder Volume (cc)	1.44 ± 0.19 (0.49 – 4.59)	0.54 ± 0.07 (0.23 – 0.97)	0.46 ± 0.19 (0.21 – 1.01)	1.79 (0.66 – 4.59)
Dose Cylinder Diameter (cm)	0.95 ± 0.04 (0.60 – 1.40)	0.8 ± 0.05 (0.60 – 1.20)	0.8 ± 0.14 (0.60 – 1.20)	0.92 (0.60 – 1.40)

Abbreviations: SEM = standard error of the mean.

Table 3.

Dosimetric parameters for the LEAD boost (12 Gy in 1 Fraction)

Parameter (unit)	Mean ± SEM (Range)	Goal Constraints
Cylinder(s) V_{95} (%)	82.65 ± 2.84 (26.62 – 100)	NS*
Cylinder(s) V_{90} (%)*	88.83 ± 2.18 (42.91 – 100)	NS
Cylinder(s) D_{95} (Gy)	10.45 ± 0.24 (6.75 – 12.94)	NS
Cylinder(s) D_{90} (Gy)	11.10 ± 0.22 (7.68 – 13.42)	NS
Cylinder(s) Mean Dose (Gy)	13.42 ± 0.20 (10.40 – 15.79)	NS
GTV V_{95} (%)	58.69 ± 3.98 (6.56 – 99.83)	NS
GTV D_{95} (Gy)	7.62 ± 0.38 (1.69 – 12.58)	NS
Anorectum V_{3Gy} (%)	0.68 ± 0.21 (0 – 4.07)	<8%
Anorectum max dose (Gy)	3.86 ± 0.55 (3.86 – 4.70)	4.0 Gy#
Bladder V_{3Gy} (%)	0.22 ± 0.08 (0 – 1.58)	<8%
Bladder max dose (Gy)	3.10 ± 0.18 (1.06 – 4.44)	4.0 Gy#
Urethra V_{3Gy} (%)§	27.11 ± 4.63 (0 – 76.93)	<10%
Urethra max dose (Gy)	5.74 ± 0.51 (2.16–11.60)	6 Gy

Abbreviations: SEM = standard error of mean; GTV = gross tumor volume.

*NS = Not specified in the protocol, but D_{90} was used as the main measure;

§There was no defined protocol violation for urethral doses higher than the dose goal shown. There were 18 variations, 4 primary (10–20%) and 14 secondary (>20%);

#A variation was considered if the max dose was >4.0 Gy and ≤4.5 Gy. A violation was for >4.5 Gy. While there was no protocol violation in the max point dose on the treatment planning station in which the plans were generated, the calculated max point dose to the anorectum in MIM (used to generate the table) in one patient was 4.7 Gy, due to differences in contour interpolations on the two systems.

Table 4.

Dosimetric parameters for the conventional 38 fraction plans, with and without LEAD cylinder day 1 treatments included (Sum Plans).

PTVs	Prostate+ProxSVs Mean ± SEM (range)	Sum Plan Mean ± SEM (range)	Goal Constraints
PTV1 V_{100} (%) *	95.49 ± 0.20 (92.96 – 98.85)	97.20 ± 0.37 (91.43 – 99.01)	≥95% *
PTV1 D_{95} (Gy)	76.20 ± 0.05 (75.81 – 76.92)	77.28 ± 0.13 (74.95 – 78.62)	76 Gy
PTV1 Mean (Gy)	79.29 ± 0.21 (78.06 – 81.75)	81.73 ± 0.23 (80.35 – 84.29)	
PTV_{nodes} V100 (%) **	93.87 ± 0.09 (93.54 – 94.19)	93.99 ± 0.06 (93.99 – 94.19)	≥95%
PTV_{nodes} D_{95} (Gy)	55.73 ± 0.02 (55.70 – 55.75)	55.80 ± 0.00 (55.79 – 55.80)	56 Gy
OARs			
Anorectum V_{40Gy} (%)	19.87 ± 1.47 (6.42 – 31.70)	20.94 ± 1.57 (6.76 – 34.96)	≤35%
Anorectum V_{65Gy} (%)	6.59 ± 0.75 (2.23 – 17.00)	7.37 ± 0.83 (2.45 – 18.68)	≤17%
Bladder V_{40Gy} (%)	19.83 ± 1.85 (3.56 – 37.27)	20.33 ± 1.88 (3.73 – 38.33)	≤50%
Bladder V_{65Gy} (%)	7.62 ± 0.77 (1.28 – 13.72)	8.01 ± 0.83 (1.36 – 16.00)	≤25%
Bowel V_{45Gy} (cc) †	5.21 ± 3.81 (0.00 – 78.34)	5.50 ± 3.93 (0.00–79.07)	≤150 cc ≥45 Gy

Abbreviations: PTVs = planning target volumes; OARs = organs at risk; ProxSVs = proximal seminal vesicles; SEM = standard error pf the mean; GTV = gross tumor volume; Fx = fraction; NS = not specified in the protocol.

* Minor variation for PTV1 was for any $V_{100\%}$ value between 90–95%; there was 1 patient at 92.96% with a minor variation that was related in part to treating for 9 fractions with a rectal balloon and then fusing to a plan for the remainder without a rectal balloon; this patient also had bilateral hip replacements.

** PTV_{nodes} is the same as the pelvic lymph node CTV2, for which there was no expansion. Two high risk patients had the pelvic lymph nodes treated.

† The potential space was contoured.

Table 5.

Maximum CTCAE V4.0 Genitourinary Toxicity

	BASELINE* SYMPTOMS			TOTAL AEs			CUTE/SUBACUTE[a] AEs								LATE[b] AEs							
	Grade			Grade			Grade 1				Grade 2				Grade 1				Grade 2+			
Symptoms/ Adverse events	***All***	***1***	***2***	***All***	***1***	***2***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***
No of patients	24	20	4	25	9	16	12				13				15				5			
All events	40	35	5	159	109	50	70	18	39	13	29	12	14	3	39	2	24	13	21	0	20	1
Cystitis, non-infective	0	0	0	22	17	5	15	3	9	3	2	0	2	0	2	0	2	0	3	0	3	0
Hematuria	0	0	0	6	6	0	2	0	2	0	0	0	0	0	4	0	3	1	0	0	0	0
Renal & urinary disorders, NOS	0	0	0	10	9	1	5	3	1	1	1	1	0	0	4	2	2	0	0	0	0	0
Urinary frequency	22	20	2	46	28	18	17	5	8	4	11	5	4	2	11	0	7	4	7	0	7	0
Urinary incontinence	1	0	1	6	4	2	3	1	1	1	1	0	1	0	1	0	0	1	1	0	1	0
Urinary retention	9	9	0	19	13	6	7	2	3	2	3	1	2	0	6	0	3	3	3	0	2	1
Urinary tract obstruction	1	0	1	6	3	3	3	0	3	0	2	1	1	0	0	0	0	0	1	0	1**	0
Urinary tract pain	0	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary urgency	7	6	1	43	28	15	17	3	12	2	9	4	4	1	11	0	7	4	6	0	6	0

[a] ≤90 days after RT;

[b] >90 days after RT;

* The baseline (before treatment on the protocol) symptoms were coded and are contrasted with the attribution of adverse events to protocol treatment (above the baseline);

** Includes a single grade 4 adverse event (only event above grade 2), related to sepsis after a transurethral resection post-RT for urinary obstructive symptoms.

Table 6.

Maximum CTCAE V4.0 Gastrointestinal Toxicity

	BASELINE* SYMPTOMS			TOTAL AEs			ACUTE/SUBACUTE[a] AEs								LATE[b] AEs							
	Grade			Grade			Grade 1				Grade 2				Grade 1				Grade 2			
Symptoms/ Adverse events	***All***	***1***	***2***	***All***	***1***	***2***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***	***All***	***Definite***	***Probable***	***Possible***
No. of patients	1	1	0	18	10	8	12				5				11				4			
All events	1	1	0	47	37	10	26	2	13	11	6	0	4	2	11	2	5	4	4	2	0	2
Abdominal pain	1	1	0	2	2	0	1	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0
Anorexia	0	0	0	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Bloating	0	0	0	2	2	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
Constipation	0	0	0	6	2	4	1	0	0	1	3	0	1	2	1	0	0	1	1	0	0	1
Dehydration	0	0	0	3	3	0	1	0	1	0	0	0	0	0	2	0	2	0	0	0	0	0
Diarrhea	0	0	0	17	16	1	14	1	8	5	1	0	1	0	2	0	1	1	0	0	0	0
Fecal incontinence	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Flatulence	0	0	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhoids	0	0	0	2	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	1	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Proctitis	0	0	0	3	2	1	1	0	1	0	0	0	0	0	1	1	0	0	1	1	0	0
Rectal bleeding	0	0	0	5	3	2	0	0	0	0	0	0	0	0	3	1	1	1	2	1	0	1
Rectal pain	0	0	0	4	3	1	3	1	0	2	1	0	1	0	0	0	0	0	0	0	0	0

[a] ≤90 days after RT;

[b] >90 days after RT;

* The baseline (before treatment on the protocol) symptoms were coded and are contrasted with the attribution of adverse events to protocol treatment (above the baseline)