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CLINICAL INVESTIGATION

An Updated Analysis of the Survival Endpoints of ASCENDE-RT

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Purpose: Using the primary endpoint of time to biochemical progression (TTP), Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) randomized National Comprehensive Cancer Network patients with intermediate and high-risk prostate cancer to low-dose-rate brachytherapy boost (LDR-PB) or dose-escalated external beam boost (DE-EBRT). Randomization to the LDR-PB arm resulted in a 2-fold reduction in biochemical progression compared with the DE-EBRT group at a median follow-up of 6.5 years ($P < .001$). Herein, the primary endpoint and secondary survival endpoints of the ASCENDE-RT trial are updated at a 10-year median follow-up.

Methods: Patients were randomly assigned to either the LDR-PB or the DE-EBRT arm (1:1). All patients received 1 year of androgen deprivation therapy and 46 Gy in 23 fractions of pelvic RT. Patients in the DE-EBRT arm received an additional 32 Gy in 16 fractions, and those in the LDR-PB arm received an ^{125}I implant prescribed to a minimum peripheral dose of 115 Gy. Two hundred patients were randomized to the DE-EBRT arm and 198 to the LDR-PB arm.

Results: The 10-year Kaplan-Meier TTP estimate was 85% ± 5% for LDR-PB compared with 67% ± 7% for DE-EBRT (log rank $P < .001$). Ten-year time to distant metastasis (DM) was 88% ± 5% for the LDR-PB arm and 86% ± 6% for the DE-EBRT arm ($P = .56$). There were 117 (29%) deaths. Ten-year overall survival (OS) estimates were 80% ± 6% for the LDR-PB arm and 75% ± 7% for the DE-EBRT arm ($P = .51$). There were 30 (8%) patients who died of prostate cancer: 12 (6%) in the LDR-PB arm, including 2 treatment-related deaths, and 18 (9%) in the DE-EBRT arm.

Conclusions: Men randomized to the LDR-PB boost arm of the ASCENDE-RT trial continue to experience a large advantage in TTP compared with those randomized to the DE-EBRT arm. ASCENDE-RT was not powered to detect differences in its secondary survival endpoints (OS, DM, and time to prostate cancer–specific death) and none are apparent.

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Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Before the publication of the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy trial (ASCENDE-RT), there were no randomized prospective data regarding the efficacy of combining external beam radiation therapy (EBRT) with a low-dose-rate brachytherapy (LDR-PB) boost in the treatment of prostate cancer compared with dose- escalated EBRT (DE-EBRT) using a uniform regimen of androgen deprivation therapy (ADT), even though such protocols had been widely used for more than 2 decades. With a total accrual of 398 patients, randomization to LDR-PB boost was associated with a 2-fold risk reduction in biochemical failure compared with DE-EBRT.[1] Specifically, the 7-year Kaplan-Meier (K-M) time to first of biochemical, local, or distant progression (TTP) in the LDR-PB arm was 86% compared with 75% in the DE-EBRT arm. Consistent with previous randomized trials assessing dose escalation, other endpoints analyzed in ASCENDE-RT, including overall survival (OS), time to distant metastasis (DM), and time to prostate cancer specific death (PCSM), did not differ statistically between the 2 treatment arms.[1] The current publication presents the primary outcome of TTP and the secondary survival outcomes of ASCENDE-RT at a median follow-up of 10 years.

Methods and Materials

Patient recruitment, eligibility, and randomization

National Comprehensive Cancer Network (NCCN) patients with high- and intermediate-risk prostate cancer with Eastern Cooperative Oncology Group 0 to 2 performance status were eligible for the trial. As per NCCN, high-risk prostate cancer was defined as Gleason score (GS) 8 or higher, initial prostate-specific antigen (iPSA) greater than 20 ng/mL, or clinical stage T3a or higher disease.[2] Intermediate-risk prostate cancer was defined as having at least 1 of the following: T2b-T2c, iPSA 10 to 20 ng/mL, or GS 7.[2] Before randomization, patients with GS $\geq$8 or iPSA >20 ng/mL were required to have a computed tomography scan of the abdomen and pelvis and a bone scan to assess radiologic or scintigraphic evidence of nodal or DM. Men with iPSA level >40 ng/mL, T-stage $\geq$T3b, previous transurethral resection of the prostate, prior RT to the pelvis, pre-ADT prostate volume >75 cm^3, or ineligibility for anesthesia were excluded before randomization. After informed written consent, each man was stratified by NCCN group and randomly assigned to the treatment arm (1:1) using a computer-generated block randomization. Patients were accrued from November 2002 to December 2011. Two-hundred patients were randomized to the DE-EBRT arm, and 198 patients were randomized to the LDR boost arm. The study received approval from the appropriate institutional research ethics boards and is registered with the National Cancer Institute database (NCT00175396).

Interventions

All patients in the trial were prescribed ADT for 1 year in total. ADT was administered every 3 months with either Buserelin acetate 9.45 mg SubQ (Suprefact Depot) or leuprolide acetate 22.5 mg SubQ (Eligard). They also received concurrent oral antiandrogen with either flutamide 300 mg tid or bicalutamide 50 mg daily for a minimum of 4 weeks beginning with the first injection. After 8 months of neoadjuvant ADT, 46 Gy in 23 fractions of pelvic RT was delivered using a 4-field technique encompassing the prostate, seminal vesicles, and regional lymph nodes. Subsequently, men in the DE-EBRT arm received an additional 32 Gy in 16 fractions of EBRT to the prostate immediately afterward, while patients in the LDR-PB arm received an ^{125}I implant (Oncura model 6711 sources as RapidStrand, prescribed to a minimum peripheral dose of 115 Gy) 2 to 3 weeks after the completion of pelvic RT.

Please refer to the initial ASCENDE-RT publication for details regarding statistical power, a consort diagram, follow-up procedures, randomization procedures, and protocol violations. Prostate specific membrane antigen (PSMA) or Axumin positron emission tomography scan were not routinely available for follow-up patients.[1]

Endpoints and analysis

The primary endpoint was TTP defined as the time from the first ADT injection to first progression, which in all cases was biochemical progression as per the Phoenix threshold of nadir PSA + 2 ng/mL. Secondary endpoints included OS, DM, and event free survival (EFS), defined as the time from the first ADT injection to any recurrence of cancer or death from any cause. Analysis of PCSM was based on a definition of prostate cancer death that included all deaths, regardless of apparent cause, if the death occurred after the initiation of systemic therapy for metastatic prostate cancer. Also included as prostate cancer−specific deaths are 2 treatment- related deaths in the LDR-PB arm who were not known to have cancer recurrence at the time of death.

The purpose of the current analysis is to update the primary endpoint and secondary survival endpoints. However, the justification for the timing of this reanalysis was based on a proposed hazard ratio for PCSM of 0.5 favoring the brachytherapy arm and all other-cause mortality being balanced. If this assumption were true, it was estimated that there would be sufficient statistical power to identify such a large effect on PCSM when 29 or more prostate- specific deaths occurred in the setting of fewer than 99 deaths from all other causes in both arms. These conditions were

satisfied as of July 2019, and the data were locked down and prepared for analysis.

In addition, 4 post hoc analyses are included in this update:

1. As per Lo and Crook et al,[3,4] the authors have included an analysis of "biochemical cure," namely the probability of having a residual PSA ≤0.2 ng/mL at 4-years follow-up from the date of brachytherapy. Briefly, ASCENDE-RT patients who had at least 4 years of follow-up from the date of treatment completion without biochemical progression as per Phoenix definition and who had a PSA value recorded between 3.5 to 4.5 years were stratified by whether they had PSA ≤0.2 at 4 years (or the closest time point to 4 years). We also investigated whether having a 4-year PSA >0.2 carried any implication for longer term TTP.
2. A second post hoc analysis assessed the subsequent use of systemic therapy for the LDR-PB and DE-EBRT arms for a subset (n = 356) of patients randomized in ASCENDE-RT with long-term population-based pharmacy data available up to June 2018.
3. Time to local failure (TTLF) was not reported in our previous publication. Of note, the original protocol included an ultrasound-guided sextant biopsy at 34 months (26 months post-RT) to assess local control, but this provision was formally removed from the protocol 4 years into accrual, because of the perception by some investigators of an unacceptable risk of infection/bleeding after such biopsies, which led to low compliance. Therefore, the TTLF reported in this post hoc analysis was generally restricted to the local failures that were identified only at digital rectal exam or imaging abnormality in follow-up and prompted a posttreatment biopsy.
4. EFS has been added to this analysis for direct comparison with other studies. EFS, unlike TTP, includes death from any cause (as well as biochemical, local, or distant relapses) as an event, with the patients censored at last follow-up only if they were both alive and free of any recurrence.

Statistical methods

K-M analyses were performed for TTP, OS, DM, TTLF, EFS, and PCSM to enable comparison with the prior publication. For OS, TTLF, DM, and TTP, patients were censored at last follow-up. Events in TTLF, DM, and TTP were local recurrence, metastatic recurrence, and any first progression (which was always biochemical progression as per the Phoenix definition), respectively. No metastatic events occurred before local recurrence events in the TTLF analysis. For PCSM, patients were censored at death from other cause or last follow-up. Events in PCSM were deaths as defined previously and included 2 treatment-related deaths in the LDR-PB arm, and all patients who died of any other cause were censored at last available follow-up before death. In addition, for TTP, DM, TTLF, and PCSM, Fine and Gray competing risk analyses were performed and are included in the Supplementary Materials (Figures E5-E8). Univariable analysis (UVA) and multivariable analysis (MVA) were undertaken using clinically relevant demographic and disease variables, including age, randomization arm, percent positive cores on biopsy (PPC), clinical T-stage, NCCN risk stratification, iPSA, number of high-risk features (T3a, iPSA >20 ng/mL, Gleason score ≥8, or >50 of cores positive [PPC]), and Gleason grade group (GGG), determined by the worst Gleason core from the reviewing pathologist. Randomization arm and the variables with P value < .3 on UVA were included in the MVA (conditional, backward). Binomial logistic regression analysis was performed to assess the factors associated with achieving PSA ≤0.2 at 4 years.

As stratification arm did not satisfy proportionality assumptions in the Cox model for the primary endpoint of TTP, hazards are presented as both averaged hazard ratios and time- dependent hazard ratios for completeness. Five-year time interval was chosen a priori based on a clinical rationale that the early biochemical relapses due to occult metastatic disease would tend to occur within 5 years, in contrast to the biochemical relapses due to local failure, which would typically occur in the 5- to 10-year interval. In the 10- to 15-year interval, there was less than 25% of the original trial participants who remained at risk of biochemical progression, limiting the interpretability.

Results

Primary endpoint (time to progression)

In total, 95 patients had biochemical progression (Table 1). By randomization, the 10-year K-M TTP was 67% for the DE-EBRT arm compared with 85% for the LDR-PB arm (Fig. 1; log rank P < .001). Within the NCCN intermediate-risk group, the 10-year K-M TTP was 73% for the DE-EBRT arm compared with 90% for the LDR-PB arm (log rank P = .02; Fig. E4A). Within the NCCN high-risk group, the 10-year K-M TTP was 64% for the DE-EBRT arm compared with 81% for the LDR-PB arm (log rank P = .006; Fig. E4B). In the MVA, randomization arm, PPC, T-stage, and iPSA were associated with TTP (Table 2). The 10-year cumulative incidence of biochemical progression in the DE-EBRT arm was 30% compared with 15% in the LDR-PB arm (P = .0006; Fig. E5).

Overall metastatic relapse (nodal and/or distant recurrence)

Combining both nodal and distant recurrences, 50 (13%) patients had metastatic relapse: 27 in the DE-EBRT (14%) and 23 (12%) in the LDR-PB arm by randomization (Table 1). Ten-year K-M DM was 86% and 88% for DE-EBRT and LDR-PB, respectively (Fig. 2A; P = .56). On UVA, PPC, clinical T-stage, NCCN risk stratification,

Table 1 Disease status at data lockdown (July 1, 2019) by randomization and actual treatment arm received

		By randomization		By actual treatment received		
Analysis	All patients (n = 398)	DE-EBRT (n = 200)	LDR-PB (n = 198)	DE-EBRT (n = 195)	LDR-PB (n = 188)	Neither (n = 15)
Relapsed*	95 (23.9)	63 (31.5)	32 (16.2)	60 (30.8)	28 (14.9)	7
Nonrelapsed	303 (76.1)	137 (68.5)	166 (83.8)	135 (69.2)	160 (85.1)	8
Metastatic disease	50 (12.6)	27 (13.5)	23 (11.6)	26 (13.3)	21 (11.2)	3
Alive	281 (70.1)	138 (69.0)	143 (72.2)	131 (67.2)	140 (74.5)	10
Deceased	117 (29.4)	62 (31.0)	55 (27.8)	64 (32.8)	48 (25.5)	5
ANED	221 (55.5)	99 (49.5)	122 (61.6)	94 (48.2)	121 (64.4)	6
DNED	83 (20.9)	39 (19.5)	44 (22.2)	42 (21.5)	39 (21.3)	2
AWD	60 (15.1)	39 (19.5)	21 (10.6)	37 (19.0)	19 (10.1)	4
DOWD	34 (8.5)	23 (11.5)	11 (5.5)	22 (11.3)	9 (4.8)	3
Died of prostate cancer†	30 (7.5)	18 (9.0)	12 (6.1)	18 (9.2)	10 (5.3)	2
K-M estimates +/− 95% CI						
TTP (%)						
10 y	76 ± 5	67 ± 7	85 ± 5	68 ± 7	86 ± 5	
OS (%)						
10 y	77 ± 4	75 ± 7	80 ± 6	73 ± 7	82 ± 6	
DM (%)						
10 y	87 ± 4	86 ± 6	88 ± 5	86 ± 5	88 ± 4	
PCSM (%)						
10 y	93 ± 3	92 ± 4	95 ± 3	92 ± 4	95 ± 3	

Abbreviations: ANED = alive, no evidence of disease; AWD = alive with disease; DE-EBRT = dose-escalated external beam radiation therapy; DM = time to distant metastasis; DNED = dead, no evidence of disease; DOWD = dead of/with disease; K-M = Kaplan-Meier; LDR-PB = low-dose-rate prostate brachytherapy; OS = overall survival; PCSM = time to prostate cancer specific death; TTP = time to progression.

* TTP was defined as the absence of any biochemical (nadir prostate-specific antigen level plus 2 ng/mL threshold), imaging, or clinical recurrence of prostate cancer and no receipt of any form of secondary treatment for prostate cancer after completion of protocol interventions.

† Patients undergoing systemic treatment for metastatic prostate cancer at death were scored as having died of prostate cancer, regardless of the proximate cause of death.

number of high-risk features, and GGG were associated with DM (Table E6). On MVA, PPC, clinical T-stage, and GGG continued to remain significant (Table E6). The 10-year cumulative incidence of metastatic failure in the DE-EBRT arm was 13% compared with 12% in the LDR-PB arm (P = .61; Fig. E6).

OS

In total, 117 patients have died. Of the 117 deaths, 34 men died with evidence of recurrent prostate cancer; the remaining 83 deaths occurred in men without evidence of recurrence (Table 1). Median survival was not reached, and the 10-year K-M OS estimate was 77%. OS did not differ significantly between the arms, with 10-year K-M of 80% for LDR-PB versus 74% for DE-EBRT (P = .51; Fig. 2B). Only age at randomization and biochemical relapse status were significantly associated with OS in MVA (Table 3).

Time to prostate cancer–specific death

Using a definition established before unlocking the data for analysis, 30 trial subjects died of prostate cancer (Table 1): 18 were randomized to the DE-EBRT and 12 to the LDR-PB arm, which included 2 deaths that have been assigned to toxicity from treatment. One patient developed debilitating pelvic pain that required inpatient management and died of an acute myocardial infarction and pulmonary embolism, and another patient died after receiving major pelvic surgery because of Fournier gangrene after brachytherapy. There were no deaths attributable to DE-EBRT toxicity. The 10-year K-M PCSM estimate was 93% for the entire study cohort. Analyzed by randomization, the 10-year K-M PCSM was 95% for the LDR-PB arm versus 92% for the DE-EBRT arm (P = .26, figure not shown). Ten-year cumulative incidence of PCSM was 5.5% for the LDR-PB arm and 8.5% for the DE-EBRT arm (P = .286; Fig. E7). In MVA (Table E7), only PPC was associated with PCSM. There were no statistical differences in

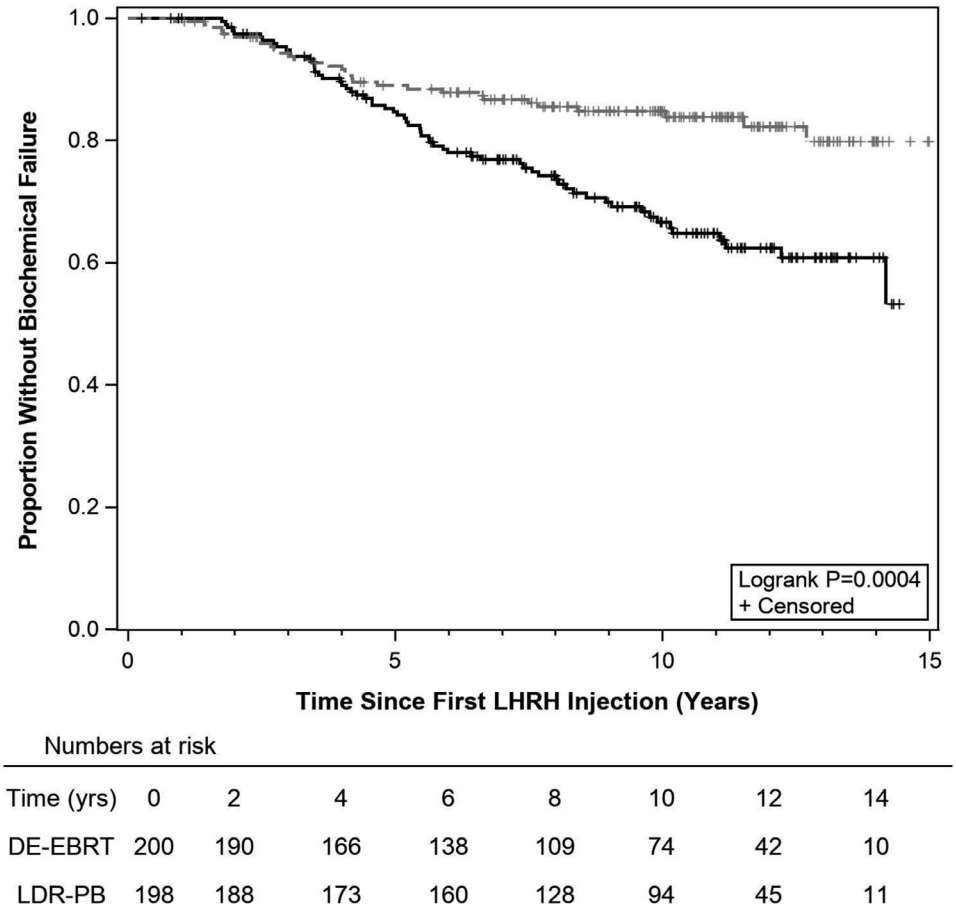


Fig. 1. Time to biochemical progression (TTP) by randomization arm. Black: Dose-escalated external beam radiation therapy (DE-EBRT). Gray: Low-dose rate prostate brachytherapy (LDR-PB).

Table 2 UVA and MVA for biochemical failure* (Cox model; backward: conditional)

Variables	UVA			MVA		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Randomization arm (DE-EBRT vs LDR-PB)[†,‡]	2.12	1.39−3.25	< .001	2.05	1.33−3.14	.001
0-5 y	1.39	0.79−2.43	.26	1.33	0.76−2.34	.32
5-10 y	4.71	2.06−1.079	< .001	4.81	2.10−11.01	< .001
10-15 y	2.35	0.59−9.41	.23	2.37	0.59−9.55	.22
PPC (unit = 1%)[†]	1.02	1.01−1.02	< .001	1.01	1.01−1.02	.001
Clinical T-stage (T3a vs T1-T2b)[†,‡]	2.05	1.37−3.08	< .001	2.09	1.38−3.16	< .001
Risk code (high vs intermediate)[‡,§]	1.47	0.91−2.23	.11	NA	NA	NA
Log iPSA (unit = 1 log)[†]	2.58	1.18−5.66	.02	3.01	1.38−6.57	.006
Number of high-risk features (≥3 vs ≤2)[‡,§]	3.04	1.92−4.81	< .001	NA	NA	NA
Gleason grade group (4-5 vs 1-3)[‡]	1.12	0.74−1.69	.59	NA	NA	NA
Age (unit = 1 y)	0.99	0.97−1.02	.66	NA	NA	NA

Abbreviations: DE-EBRT = dose-escalated external beam radiation therapy; HR = hazard ratio; iPSA = initial prostate-specific antigen; LDR-PB = low-dose-rate prostate brachytherapy; MVA = multivariable analysis; PPC = percent positive cores on biopsy; UVA = univariable analysis.

* Biochemical failure was the first or concurrent sign of recurrence in all patients.

† Entered into MVA model if univariate $P < .3$.

‡ Categorical variable.

§ Composite variables not entered into MVA.

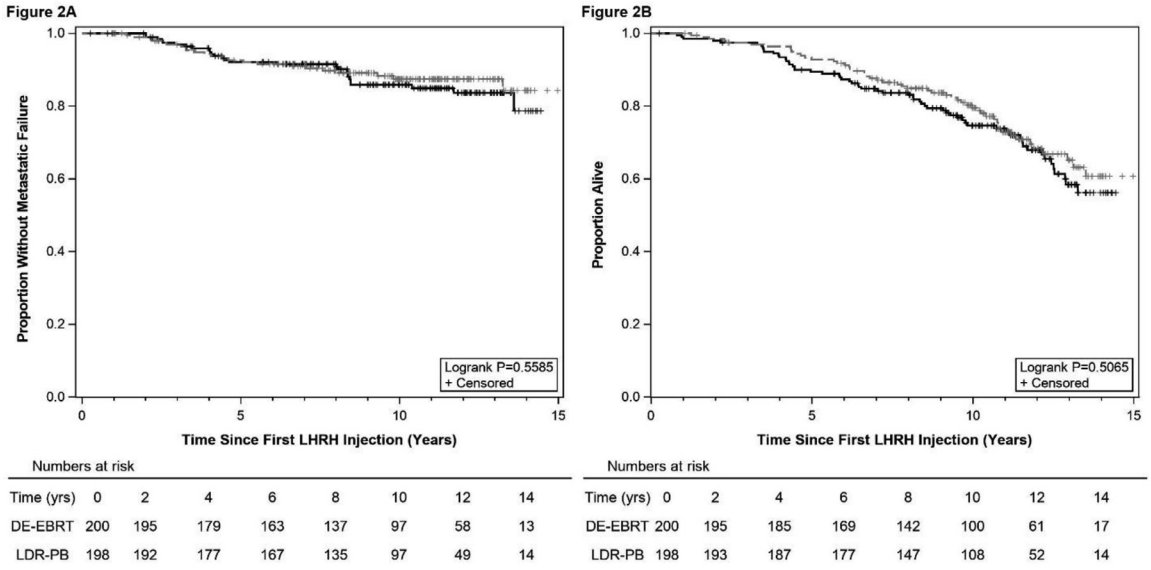


Fig. 2. (A) Time to distant metastasis (DM). (B) Overall survival (OS) by randomization arm. Black: Dose-escalated external beam radiation therapy (DE-EBRT). Gray: Low-dose rate prostate brachytherapy (LDR-PB).

the frequency of other causes of death such as intrapelvic or extrapelvic malignancy or cardiac death.

Post hoc analyses

Three-hundred and twenty patients had at least 4 years of follow-up, a PSA value measured between 3.5 and 4.5 years, and no evidence of biochemical failure to that point. In this subset, there were 94 patients in the DE-EBRT arm and 19 patients in the LDR-PB arm with PSA >0.2 at the 4-year follow-up. Of those who had a 4-year PSA ≤0.2, the subsequent 10-year TTP was 97% compared with 60% in those who had PSA >0.2 at 4 years ($P < .001$; Fig. E8). On MVA binomial logistic regression analysis, randomization arm (DE-EBRT vs LDR-PB: odds ratio [OR], 13.32; 95% confidence interval [CI], 7.22-24.58; $P < .001$), as well as log iPSA (OR, 3.88; 95% CI, 1.32-11.43; $P = .014$) and age (OR, 0.94; 95% CI, 0.91-0.98; $P = .003$) were associated with residual PSA >0.2 at 4 years (Table E4).

Table 3 UVA and MVA for overall survival (Cox model; backward: conditional)

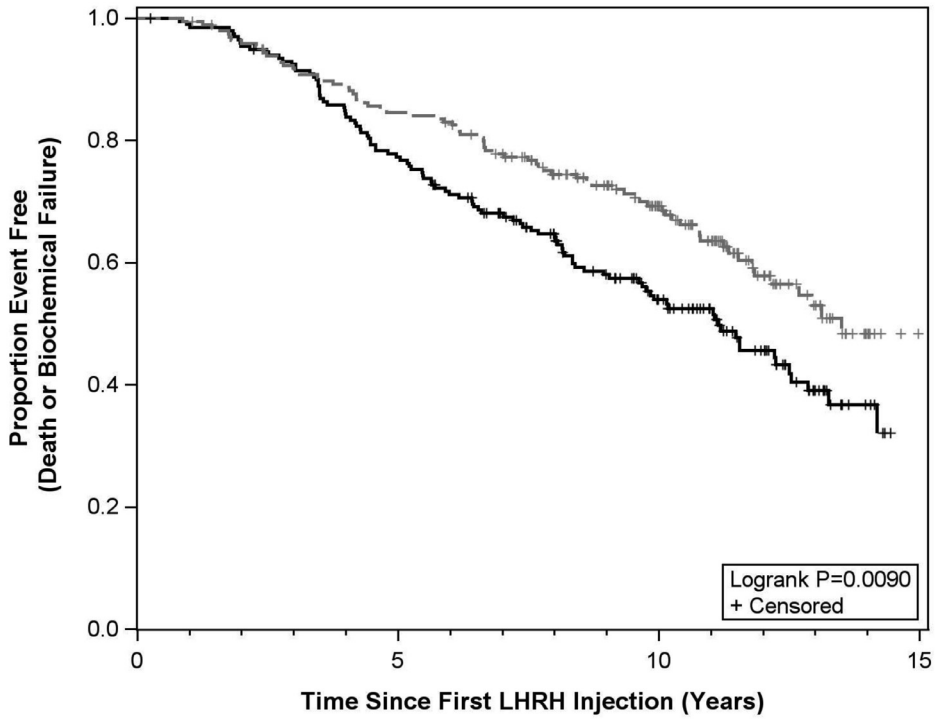
Variables	UVA			MVA		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Randomization arm (DE-EBRT vs LDR-PB)*	1.13	0.79−1.63	.51	1.04	0.72−1.50	.84
PPC (unit = 1%)†	1.01	0.99−1.01	.09	1.01	0.99−1.01	.12
Clinical T-stage (T3a vs T1-T2b)*,†	1.23	0.84−1.80	.29	1.11	0.75−1.66	.60
Risk code (high vs intermediate)*,‡	1.25	0.84−1.86	.27	NA	NA	NA
Log iPSA (unit = 1 log)	1.22	0.61−2.44	.58	NA	NA	NA
Number of high-risk features (≥3 vs ≤2)*,‡	1.34	0.82−2.19	.24	NA	NA	NA
Gleason grade group (1-3 vs 4-5)*	1.18	0.81−1.71	.39	NA	NA	NA
Age (unit = 1 y)†	1.07	1.04−1.10	< .001	1.07	1.04−1.10	< .001
Disease status (relapse vs no relapse)*,†	2.18	1.44−3.30	< .001	2.15	1.41−3.29	< .001

Abbreviations: DE-EBRT = dose-escalated external beam radiation therapy; HR = hazard ratio; iPSA = initial prostate-specific antigen; LDR-PB = low-dose-rate prostate brachytherapy; MVA = multivariable analysis; PPC = percent positive cores on biopsy; UVA = univariable analysis.

* Categorical variable.

† Entered into MVA model if univariate $P < .3$.

‡ Composite variables not entered into MVA.



Numbers at risk

Time (yrs)	0	2	4	6	8	10	12	14
DE-EBRT	200	190	166	138	110	74	42	10
LDR-PB	198	188	173	160	128	94	45	12

Fig. 3. Event-free survival (EFS) by randomization arm. Black: Dose-escalated external beam radiation therapy (DE-EBRT). Gray: Low-dose rate prostate brachytherapy (LDR-PB).

Three-hundred and fifty-six patients (177 in DE-EBRT and 179 in LDR-PB arms) had population-based pharmacy data available after the completion of protocol treatment. There were 48 (24%) patients in the DE-EBRT arm and 26 (13%) patients in the LDR-PB who received ADT at relapse. Overall, there were 644 and 468 prescriptions for systemic therapy (chemotherapy, antiandrogen, or lutenizing hormone-releasing hormone agonist) for prostate cancer recurrence or progression in the DE-EBRT and LDR-PB arms, respectively.

There were 19 (4.8%) local prostate relapses recorded; 17 were in men who received DE-EBRT and 2 in men who received LDR-PB. The apparent 10-year K-M TTLF was 99% in the LDR-PB arm compared with 91% in the DE-EBRT arm (log rank $P < .001$; figure not shown). Ten-year cumulative incidence of LF was 1.5% for the LDR-PB arm and 7.1% for the DE-EBRT arm ($P = .0006$; Fig. E9). On UVA, randomization arm and PPC were both statistically associated with TTLF, and both variables remained highly significant in MVA (Table E5).

For EFS, there were no local, regional, or distant recurrences before biochemical failure. By randomization, 10-year K-M EFS was 54% for the DE-EBRT arm compared with 69% for the LDR-PB arm (Fig. 3; log rank $P < .001$).

Discussion

Radiation dose escalation has been shown to reduce the incidence of biochemical relapse compared with conventional curative doses, particularly in men with unfavorable prognostic features.[5-7] ASCENDE-RT, which began accrual in 2002, took the next logical step and employed a rigorously designed randomized trial to compare the relative efficacy of 2 entirely different methods of achieving radiation dose escalation. Like other dose-escalation trials conducted at the time, pragmatic considerations, as explained in our original publication, led to the choice of TTP as the primary endpoint. In analyzing for TTP, deaths from unrelated causes were not scored as events; reporting TTP this way is consistent with our previous publication and reflects the probability of biochemical control for long-term survivors. In this update, the authors have also provided an analysis of EFS in which deaths from any cause are considered events to allow comparison with other contemporary studies.

In this update with median follow of 10 years, a clear advantage in TTP and EFS for those subjects randomized to the LDR-PB arm persists. Although numbers are small at 15 years, it is estimated that only 20% of those in the LDR-PB arm will have experienced biochemical recurrence

compared with 47% of the patients in the DE-EBRT arm at that point. The TTP outcomes after LDR-PB boost in ASCENDE-RT are especially noteworthy because more than two-thirds of the trial subjects (276/398) were high risk (HiR) by NCCN criteria and nearly half (193/398) had 2 or more HiR features, which included PPC ≥50%, GGG 4 to 5, iPSA >20 ng/mL, or T3a stage. Even within HiR subset, fewer than 25% of the trial subjects assigned to the LDR-PB arm had a biochemical relapse.

Limitations of the ASCENDE-RT trial were discussed in the original publication and are not repeated in detail herein but remain relevant to the current analysis. It is possible that changes in clinical practice, such as adjuvant rather than neoadjuvant ADT, longer durations in ADT, changes in planning and prescribing external RT, newer staging modalities (eg, multiparametric MRI and PSMA positron emission tomography), changes in image guidance, and intensification of ADT (such as an addition of abiraterone), would alter the differences observed if this trial were repeated. Similarly, changes in brachytherapy practice and dose may alter the side effect profile previously described. Recent meta-analyses have suggested that adjuvant ADT may be superior to neoadjuvant ADT for DM in localized prostate cancer.[8,9] In addition, the Randomised Androgen Deprivation and Radiotherapy trial has suggested improvement in DM with 18 months compared with 6 months of ADT among those who received high-dose-rate (HDR) boost, although it consisted of nonrandomized radiation dosing, and younger men with higher risks were associated with HDR boost treatment.[10] ASCENDE-RT was not designed to assess the sequencing or duration of ADT, but each arm received the same ADT regimen to ensure that the assessment of the effect of LDR-PB could be isolated as much as possible. Some of the rationales for neoadjuvant ADT and the duration included in the original protocol, written more than 20 years ago, included early results of Radiation Therapy Oncology Group (RTOG) 9413 as well as surgical and preclinical literature that have suggested the benefit of neoadjuvant ADT.[11-13] A recent meta-analysis by Kishan et al[8] proposed that neoadjuvant ADT may not be necessary, although the study did not demonstrate inferiority of prolonged neoadjuvant ADT duration, and no trial included in the meta-analyses used neoadjuvant ADT as long as ASCENDE-RT.[9] It is possible that the trial subjects reported here may not have required or benefited from neoadjuvant ADT or that a similar or longer duration of concurrent and adjuvant ADT may have resulted in equivalent or even superior outcomes, particularly for the DE-EBRT arm. Data in this regard are lacking, and prospective randomized trials with prespecified duration and sequencing of ADT for both DE-EBRT and LDR-PB arms would be required to answer such questions. For TTLF post hoc analysis, patients were not censored at time of biochemical or distant metastasis (although no metastatic events occurred before local or regional relapse), which may have resulted in a bias that affected the local recurrence rate described.

As in the previous analysis, there was strong statistical correlation between biochemical failure and all-cause mortality.[1] We proposed that the observed reduction in OS among relapsed subjects was principally caused by a relatively small number of trial participants with occult metastatic disease that was present before registration and unrelated to the treatment arm, which was thoroughly discussed in the original ASCENDE-RT publication. Because these trial subjects would have been allocated evenly to each arm by the randomization process, OS was not correlated with treatment arm despite the relatively large difference in biochemical relapse rates observed. This interpretation is supported by the observed reduction in the HR comparing the current and previously published analyses: the relative risk of death among those with biochemical relapse was more than 6 times greater than those without relapse in the original analysis (HR of 6.3; 95% CI, 3.6-10.9; $P < .001$) compared with an HR of just 2.2 in the current analysis (95% CI, 1.4-3.3; $P < .001$) (Table 3). This reduction in HR suggests that deaths from prerandomization occult metastatic disease no longer dominate all-cause mortality because competing causes of death have become more common among the aging trial participants. The observation supports the efforts to better identify men with occult metastatic disease with more sensitive investigations such as PSMA scan to triage treatment plans and establish appropriate future clinical trial protocols.[14,15]

There were 19 (4.8%) documented local failures, which almost certainly underreports the true local failure rate because the plan for routine systematic biopsies at defined posttreatment intervals did not prove feasible (as described in the Methods and Materials section), and the sensitivity of digital rectal exam is poor in detecting persistent/recurrent local disease.[16,17] Thus, for most of the patients, unless there was locally aggressive recurrence or a clinical situation where local salvage was contemplated, posttreatment biopsies were not typically performed, therefore it is difficult to accurately estimate the true rate of local relapse. However, there remains a large disparity in the number of local failures, with only 2 recorded among the 188 subjects who received LDR-PB boost compared with 17 among the 195 men who received DE-EBRT. Furthermore, there were an additional 26 patients with biochemical relapses (1/4 of all biochemical relapses and which occurred disproportionally among those assigned to DE-EBRT) in which the site of relapse could not be identified despite a bone scan and computed tomography of chest/abdomen/pelvis.

Absolute PSA cutoff and relative PSA rise have both been used as surrogate endpoints for recurrence after definitive therapy in prostate cancer, mostly based on large retrospective studies.[18-20] A reanalysis of TTP in ASCENDE-RT using an absolute PSA cutoff of >0.2 ng/mL showed an even larger advantage for the LDR-PB boost arm.[21] In this update, we show that the probability of having a PSA >0.2 at 4 years is over 10 times more likely for trial subjects randomized to the DE-EBRT arm compared with those in the LDR-PB arm. In turn, PSA values ≤0.2 at 4 years after definitive RT are associated with a high probability of long-term biochemical control.[3,4] Recent analysis by Noble et al[22] has

also externally validated this surrogate outcome for long-term durable biochemical control, demonstrating that patients who achieved PSA ≤0.2 at 4 years after brachytherapy had greater than 97% 10-year disease-free survival. Among ASCENDE-RT participants, the 10-year TTP was only 60% for trial subjects with a 4- year PSA >0.2 versus 97% for those with ≤ 0.2, an observation that appears to apply to both treatments. However, we acknowledge that this PSA cut off has not been fully validated for DE-EBRT, and residual PSA at 4 years may reflect residual "healthy" prostate tissue that may or may not influence future prostate cancer outcomes.

Although TTP has not reliably served as a surrogate marker for OS in the randomized trials to date, biochemical relapse continues to have clinical relevance. In addition to being quantitative, objective, and minimally invasive, biochemical failure faithfully predicts eventual clinical recurrence and often signals the introduction of further treatment, including potentially morbid salvage therapies or the reintroduction of ADT, which is associated with multiple short- and long-term adverse effects. To date, there have been almost 40% more prescriptions for systemic agents for prostate cancer relapse in the DE-EBRT arm of ASCENDE-RT.[23-30]

Our results are similar to previously published brachytherapy boost studies. Hoskin et al[31] recently updated their analysis of relapse-free survival (equivalent to EFS as reported here), defined as the time to biochemical recurrence, clinical progression, or death, of the patients who had cT1-T3 prostate cancer and received HDR brachytherapy boost versus EBRT boost in addition to 6 to 36 months of ADT. The patients who had HDR brachytherapy boost continued to demonstrate relapse-free survival improvement at 12 years compared with the EBRT boost group, but there was no statistically significant difference in DM or OS.[31] Another study by Sathya et al demonstrated time to biochemical progression improvement in patients with cT2-T3 prostate cancer who received EBRT and iridium implant boost compared with those who received EBRT alone at a median follow-up of 8 years.[32,33] Subsequent 14-year follow-up study did not demonstrate a statistically significant difference between the 2 groups in PCSM, DM, or OS.[32] However, there were substantially more patients who died of other causes than prostate cancer, and potential OS benefit in a younger patient cohort therefore could not be completely excluded.[32]

Compared with those trial subjects who received DE-EBRT, the improvement in TTP enjoyed by the LDR-PB boost arm came at a price in terms of the severity and frequency of adverse urinary side effects and a statistically significant reduction in some quality of life domains.[34] There were 2 toxic deaths among trial participants and both were in the LDR-PB arm. As stated in our prior publication, it is possible, but not certain, that technical modifications may improve the therapeutic ratio of brachytherapy boosts, and such approaches should be investigated in future prospective studies.[34,35]

Since the design of the ASCENDE-RT trial other radiation treatment modalities, including HDR boost, salvage brachytherapy, focal external beam boost, and SABR have emerged and entered mainstream treatment protocols.[36-38] Although studies featuring these modalities seem promising, direct comparison to ASCENDE-RT is limited by the short follow-up or different inclusion criteria. To this date, there has not been a randomized prospective study with as many high-risk patients, as long of a follow-up, and as effective biochemical control as the ASCENDE-RT trial. It may be true that other modalities may demonstrate better therapeutic ratios in the future. However, it is premature to conclude that an LDR-PB boost necessarily has similar efficacy to or worse adverse effects than HDR-PB or ultrahypofractionation via stereotactic techniques until these modalities are compared directly in clinical trials in which the prospective collection of the primary outcome, toxicity, and quality of life data are collected using similar tools. Exploration of these modalities will hopefully provide more options for patients for the treatment of localized prostate cancer, incorporating disease characteristics and patient preference based on efficacy and toxicity.

Conclusions

LDR-PB boost continues to demonstrate superior and durable time to biochemical progression and EFS compared with DE-EBRT at 10 years for patients with intermediate- and high-risk prostate cancer. LDR-PB also results in substantially lower posttreatment (residual) PSA values and may be associated with less subsequent use of systemic therapy. The important balancing issue of treatment-related toxicity has been reported in detail in our previous publications. Although ASCENDE-RT was not designed for prolonged prospective toxicity analysis, differences in toxicity, whether transient or permanent, remain important considerations. Despite the differences observed, both treatment arms in ASCENDE-RT demonstrated high and equivalent rates of OS, time to DM, and prostate cancer−specific death among patients with unfavorable prognostic features.

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