International Journal of Radiation Oncology biology • physics

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Clinical Investigation

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

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Received Aug 25, 2016, and in revised form Nov 12, 2016. Accepted for publication Nov 16, 2016.

Summary

The ASCENDE-RT trial (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation

Purpose: To report the primary endpoint of biochemical progression-free survival (b-PFS) and secondary survival endpoints from ASCENDE-RT, a randomized trial comparing 2 methods of dose escalation for intermediate- and high-risk prostate cancer. **Methods and Materials:** ASCENDE-RT enrolled 398 men, with a median age of 68 years; 69% (n = 276) had high-risk disease. After stratification by risk group, the subjects were

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The British Columbia Cancer Agency received unrestricted educational grants from Oncura Corporation, a Division of GE Healthcare, which manufactured the model 6711 ^{125}Iodine RapidStrand sources used in the trial, and Sanofi-Aventis Canada, the maker of the Suprefact and Eligard luteinizing hormone-releasing hormone depot injections used in the trial. Without these grants, ASCENDE-RT would not have been possible.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Acknowledgments—The authors acknowledge the members of the British Columbia Cancer Agency Provincial Prostate Brachytherapy Program and Genitourinary Radiation Oncology team who accrued patients and participated in the follow-up protocols. Without the efforts of Vincent Lapointe, who designed the ASCENDE-RT database, and the efforts of 3 consecutive data managers (Adam Kahnamelli, Devon Poznanski, and Lorenz Yeung), ASCENDE-RT would not have been possible.

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 275–285, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2016.11.026

Therapy) trial is a randomized comparison of 2 methods of dose escalation in the context of combined modality therapy for National Comprehensive Cancer Network high- and intermediate-risk prostate cancer that included 12 months of androgen deprivation therapy and whole pelvic irradiation to 46 Gy. Compared with a ^{125}I brachytherapy boost, men randomized to an external beam radiation therapy boost to a total of 78 Gy were twice as likely to have experienced biochemical failure at a median follow-up of 6.5 years.

randomized to a standard arm with 12 months of androgen deprivation therapy, pelvic irradiation to 46 Gy, followed by a dose-escalated external beam radiation therapy (DE-EBRT) boost to 78 Gy, or an experimental arm that substituted a low-dose-rate prostate brachytherapy (LDR-PB) boost. Of the 398 trial subjects, 200 were assigned to DE-EBRT boost and 198 to LDR-PB boost. The median follow-up was 6.5 years.

Results: In an intent-to-treat analysis, men randomized to DE-EBRT were twice as likely to experience biochemical failure (multivariable analysis [MVA] hazard ratio [HR] 2.04; $P = .004$). The 5-, 7-, and 9-year Kaplan-Meier b-PFS estimates were 89%, 86%, and 83% for the LDR-PB boost versus 84%, 75%, and 62% for the DE-EBRT boost (log-rank $P < .001$). The LDR-PB boost benefited both intermediate- and high-risk patients. Because the b-PFS curves for the treatment arms diverge sharply after 4 years, the relative advantage of the LDR-PB should increase with longer follow-up. On MVA, the only variables correlated with reduced overall survival were age (MVA HR 1.06/y; $P = .004$) and biochemical failure (MVA HR 6.30; $P < .001$). Although biochemical failure was associated with increased mortality and randomization to DE-EBRT doubled the rate of biochemical failure, no significant overall survival difference was observed between the treatment arms (MVA HR 1.13; $P = .62$).

Conclusions: Compared with 78 Gy EBRT, men randomized to the LDR-PB boost were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years.

Introduction

In multiple randomized studies, dose-escalated external beam radiation therapy (DE-EBRT) has been associated with improved biochemical progression-free survival (b-PFS) compared with standard dose EBRT using prostate-specific antigen (PSA) endpoints (1-5). However, randomized data comparing different methods of dose escalation are sparse, with just 2 randomized trials comparing EBRT plus a brachytherapy boost to EBRT alone (6, 7). Just as in ASCENDE-RT, both involved a brachytherapy boost and intermediate- and high-risk localized tumors. However, beyond these similarities, they differed fundamentally from ASCENDE-RT, because neither used DE-EBRT for the standard arm nor low-dose-rate prostate brachytherapy (LDR-PB) for the experimental arm. By randomizing men with National Comprehensive Cancer Network (NCCN) high- and intermediate-risk prostate cancer to receive either an LDR-PB boost or a DE-EBRT boost, the present trial is the only randomized comparison of LDR-BP with any other form of curative-intent radiation therapy for prostate cancer. This is important because LDR-PB has been widely used for localized prostate cancer with unfavorable prognostic features and there are, multiple retrospective studies demonstrating excellent rates of b-PFS when a LDR-PB boost was combined with modest doses of EBRT (8-10).

Methods and Materials

The ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation) study was a National Cancer Institute–registered trial (ClinicalTrials.gov identifier NCT00175396).

Protocol interventions

All trial subjects received androgen deprivation therapy (ADT) consisting of 12 months of luteinizing hormone-releasing hormone agonist using 3-month depot injections (either buserelin acetate [Suprefact Depot] 9.45 mg or leuprolide acetate [Eligard] 22.5 mg) given concurrent with 4 weeks of oral nonsteroidal antiandrogen (flutamide 250 mg every 8 hours or bicalutamide 50 mg daily; Appendix E3; available online at www.redjournal.org). After 8 months of neoadjuvant ADT, all trial subjects were to receive 46 Gy in 23 fractions of pelvic irradiation encompassing the prostate, seminal vesicles, and regional lymph nodes.

Directly after completion of pelvic irradiation, the DE-EBRT boost subjects (standard arm) received an additional 32 Gy in 16 fractions using a 2-phase 3-dimensional conformal boost (EBRT details provided in Appendixes E4-E6; available online at www.redjournal.org).

Two to 3 weeks after pelvic irradiation, the LDR-PB boost subjects (experimental arm) received a ^{125}I brachytherapy implant (minimal peripheral dose of 115 Gy). All implants used Oncura model 6711 sources (0.32-0.51 U) supplied as RapidStrand (Appendix E7; available online at www.redjournal.org).

Eligibility, accrual, registration, stratification, and randomization

A CONSORT (Consolidated Standards of Reporting Trials) diagram is shown in Figure 1. The appropriate institutional research ethics board at each participating cancer center approved the present study. Only NCCN high- and intermediate-risk patients were eligible; those

with Gleason sum (GS) ≥8 or pretreatment PSA (iPSA) >20 ng/mL required a bone scan and computed tomography scan of the abdomen and pelvis to confirm image-based N0M0 status. Men with an iPSA level >40 ng/mL, T stage ≥T3b, previous transurethral resection of the prostate, pre-ADT prostate volume >75 cm^3, and those not fit for anesthesia were ineligible (details on eligibility provided in Appendix E2; available online at www.redjournal.org).

Eligible men who provided written informed consent were centrally registered, stratified by NCCN risk group, and randomly assigned to the treatment arms (1:1) using a computer-generated block randomization (n=4), with allocation concealed in opaque, sequentially numbered, and sealed envelopes before beginning therapy. Randomization occurred after establishing eligibility and obtaining consent; the subjects were informed of the treatment arm to which they were assigned.

The trial had 2 stages: a feasibility phase, open to accrual from November 2002 to August 2003, and a completion phase, open from August 2004 to December 2011. A total of 398 men were accrued by 29 investigators at 6 centers (Appendix E1; available online at www.redjournal.org).

WJM designed and led the trial (ASCENDE-RT); NM chaired an independent data monitoring and safety

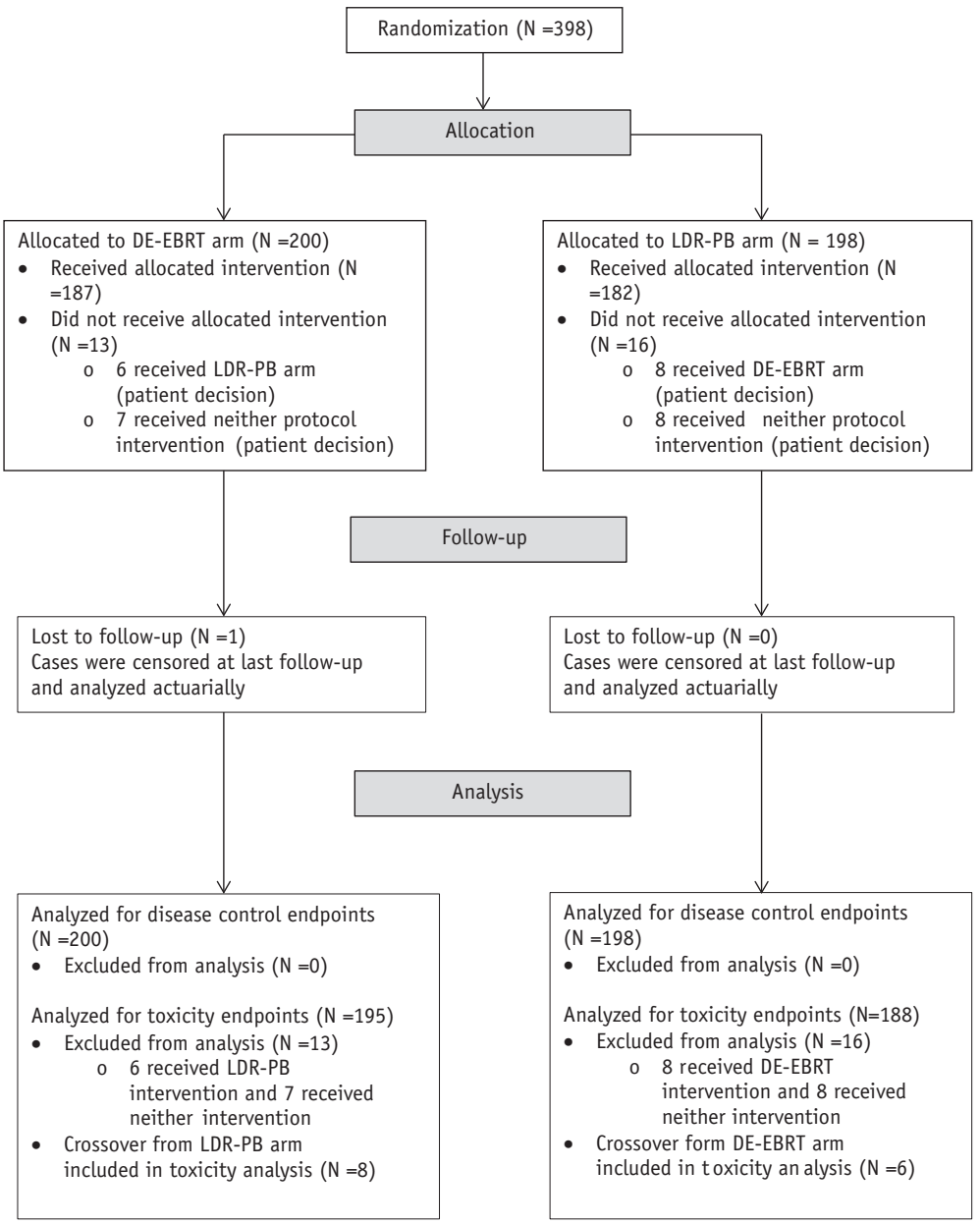

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. No attempt was made to track screened cases. *Abbreviations:* DE-EBRT = dose-escalated external beam radiation therapy; LDR-PB = low-dose-rate prostate brachytherapy.

committee with authority to suspend accrual; and WJM, SR, ST, and JH performed the data analysis.

Primary endpoint and trial design

The primary endpoint was b-PFS, determined using the nadir + 2 ng/mL PSA threshold. The target accrual was 400; the a priori statistical model assumed a 6.5-year b-PFS of 60% in the worse arm, such that a $\geq$15% difference between the arms should be detectable when the number of biochemical failure events reached 130 (2-tailed, β of 0.8, α of 0.05). However, the primary endpoint was defined as b-PFS at a median follow-up period of 6.5 years, regardless of the number of events recorded; 6.5 years was chosen according to previous institutional experience using 12 months of ADT and was regarded as equivalent to 5 years from the average time required for testosterone recovery sufficient to stimulate any residual, hormone-sensitive cancer cells. Specifying the analysis at 6.5 years satisfied a practical consideration; namely, if a brachytherapy boost did not significantly improve b-PFS by 6.5 years, adopting a LDR-PB boost as the standard of care would be logically excluded by the added complexity and potential morbidity. At data lockdown (September 30, 2014), only the median follow-up length and the total number of biochemical relapse events (n = 76) were known to the trial investigators.

Secondary endpoints

The secondary endpoints included overall survival (OS), metastasis-free survival (MFS), and prostate cancer-specific survival (PCSS). The incidence and prevalence of treatment-related adverse effects are reported in a companion report (11). The trial also included a longitudinal health-related quality of life study, which is in the final stages of preparation.

Patient monitoring

PSA, testosterone (TTT), and a complete blood count were recorded at baseline (t0) and at t+2, t+4, t+8, t+12, t+15, and t+18 months, and every 6 months thereafter. The clinic visits occurred at t+4, t+8, t+12 and t+18 months, every 6 months for 5 years, and annually thereafter.

Defining prostate cancer death

Two investigators (WJM and SR) independently reviewed the medical records of all deceased patients. Men treated with systemic agents for metastatic prostate cancer at or before their death date were scored as having died of prostate cancer, regardless of the proximate cause.

Statistical analysis

This was an intent-to-treat analysis of the primary and secondary survival endpoints. A parallel analysis of these endpoints according to the treatment actually received is also provided. Descriptive statistics were used to compare the prognostic factors. The actuarial endpoints were calculated using the Kaplan-Meier (K-M) method. Cox regression analysis was used for univariate analysis (UVA) and multivariable analysis (MVA). For the b-PFS endpoint, the UVA included age, randomization arm, T stage, GS, iPSA, percentage of positive cores (PPC), NCCN risk stratum, and the number of high-risk features. For OS, biochemical failure status was included as a time-dependent variable. Variables with $P \leq .3$ on UVA were included in the MVA (backwards: conditional). The NCCN risk strata and the number of high-risk features were excluded from the MVA models, because they were composites of other variables. Statistical analyses were performed using SPSS, version 22 (IBM Corp., Armonk, NY) and SAS, version 9.3 (SAS Institute Inc, Cary, NC).

Results

Patient accrual and protocol violations

This was an intent-to-treat analysis; 200 men were randomized to the DE-EBRT arm and 198 to the LDR-PB arm. The median follow-up for the primary endpoint at data lock down (September 30, 2014) was 6.5 years. Of the 29 major protocol violations, 14 were crossover events; 6 men assigned to DE-EBRT received LDR-PB, and 8 crossed from LDR-PB to DE-EBRT. The remaining 15 violations (7 assigned to DE-EBRT and 8 to LDR-PB) received neither protocol treatment (Appendixes E8 and E9; available online at www.redjournal.org).

Prognostic features

The prognostic features did not differ significantly between treatment arms (Table 1); 276 (69%) met the NCCN high-risk criteria, 41% had GS 8 to 10, 19% had an iPSA >20 ng/mL, 29% had T3a tumors, and 68% had cancer found in $\geq$50% of the biopsy cores. Nearly one-half (48%) had $\geq$2 high-risk features.

Testosterone recovery

The baseline TTT level was available for 334 trial subjects. The median baseline TTT was 13.8 nmol/L, and 99% (n = 330) had a baseline TTT level >5 nmol/L; the TTT level of 96% of these men recovered to >5 nmol/L. The median interval between the first luteinizing hormone-releasing hormone injection and TTT recovery to

Table 1 Prognostic features, including age, pretreatment tumor factors, and postimplant dose metrics (for LDR-boost patients only)*

Factor	All patients (n=398)	By randomization		By actual treatment received		
		DE-EBRT (n=200)	LDR-PB (n=198)	DE-EBRT (n=195)	LDR-PB (n=188)	Neither (n=15)
Age (y)						
Median	68	69	67	69	67	67
Mean ± SD	67.6 ± 7.5	67.9 ± 7.5	67.4 ± 7.4	67.9 ± 7.5	67.4 ± 7.5	66.4 ± 8.1
Range	45-86	45-86	49-84	45-86	50-85	49-78
NCCN risk stratum						
Intermediate	122 (30.7)	63 (31.5)	59 (29.8)	64 (32.8)	54 (28.7)	4 (26.7)
High	276 (69.3)	137 (68.5)	139 (70.2)	131 (67.2)	134 (71.3)	11 (73.3)
Clinical T stage						
T1c-T2c	282 (70.9)	143 (71.5)	139 (70.2)	137 (70.3)	135 (71.8)	10 (66.7)
T3a	116 (29.1)	57 (28.5)	59 (29.8)	58 (29.7)	53 (28.2)	5 (33.3)
iPSA (ng/mL)						
<5	35 (8.8)	18 (9.0)	17 (8.6)	17 (8.7)	17 (9.0)	1 (6.7)
5-10	156 (39.2)	76 (38.0)	80 (40.4)	74 (37.9)	72 (38.3)	10 (66.7)
10-20	132 (33.2)	66 (33.0)	66 (33.3)	66 (33.8)	63 (33.5)	3 (20.0)
>20	75 (18.8)	40 (20.0)	35 (17.7)	38 (19.5)	36 (19.1)	1 (6.7)
Median	10.7	11.0	10.1	11.0	10.8	8.5
Mean ± SD	13.3 ± 8.2	13.4 ± 8.3	13.2 ± 8.1	13.4 ± 8.3	13.5 ± 8.3	9.9 ± 4.6
Range	2.4-40.0	2.7-39.1	2.4-40.0	2.7-39.1	2.4-40.0	4.8-21.0
Gleason sum						
6	22 (5.5)	10 (5.0)	12 (6.1)	11 (5.6)	10 (5.3)	1 (6.7)
7	214 (53.8)	110 (55.0)	104 (52.5)	109 (55.9)	97 (51.6)	8 (53.3)
8-10	162 (40.7)	80 (40.0)	82 (41.4)	75 (38.5)	81 (43.1)	6 (40.0)
PPC						
≤25%	57 (14.3)	23 (11.5)	34 (17.2)	22 (11.3)	31 (16.5)	4 (26.7)
25%-50%	142 (35.7)	79 (39.5)	63 (31.8)	77 (39.5)	61 (32.4)	4 (26.7)
50%-75%	84 (21.1)	36 (18.0)	48 (24.2)	34 (17.4)	48 (25.5)	2 (13.3)
≥75%	113 (28.4)	60 (30.0)	53 (26.8)	60 (31.3)	48 (25.5)	5 (33.3)
Data missing	2 (0.5)	2 (1.0)	0	2 (1.0)	0	0
Median	50	50	61	50	60	50
Mean ± SD	59.3 ± 26.9	60.2 ± 26.9	58.3 ± 26.8	60.1 ± 26.9	58.1 ± 26.4	57.6 ± 28.4
Range	7-100	9-100	7-100	9-100	7-100	17-100
High-risk features† (n)						
≤1	205 (51.5)	101 (50.5)	104 (50.5)	100 (51.3)	98 (52.1)	7 (46.7)
2	140 (35.2)	72 (36.0)	68 (34.3)	66 (33.8)	66 (35.1)	8 (53.3)
≥3	53 (13.3)	27 (13.5)	26 (13.1)	29 (14.9)	24 (12.8)	0 (0)
D_{90}						
Median	NA	NA	NA	NA	108.7	NA
Mean ± SD	NA	NA	NA	NA	109.6 ± 12.8	NA
Range	NA	NA	NA	NA	81-154.3	NA
V_{100}						
Median	NA	NA	NA	NA	94.4	NA
Mean ± SD	NA	NA	NA	NA	93.1 ± 5.2	NA
Range	NA	NA	NA	NA	69.9-100	NA

Abbreviations: D_{90} = minimum dose received by 90% of the postimplant, computed tomography–based prostate volume; DE-EBRT = dose-escalated external beam radiation therapy; iPSA = pretreatment prostate-specific antigen; LDR-PB = low-dose-rate prostate brachytherapy; NA = not applicable; NCCN = National Comprehensive Cancer Network; PPC = percentage of positive cores; V_{100} = percentage of postimplant, computed tomography–based prostate volume that received the prescription dose of 115 Gy or more.

Data in parentheses are percentages.

* None of the comparisons demonstrated a statistically significant difference between the treatment arms; χ^2 test was performed to compare categorical variables, and the Mann-Whitney-Wilcoxon test was performed on the age variable to examine differences between the median values; *t* tests were performed on iPSA and PPC.

† High-risk features included clinical T stage T3a, iPSA >20 ng/mL, GS ≥8, and PPC ≥50%.

>5 nmol/L was 21.4 months. The treatment arms did not differ in either the rate or the extent of TTT recovery.

Primary endpoint (b-PFS)

The disease status of all trial subjects as of data lockdown (September 30, 2014) is listed in Table 2, which also lists the 5-, 7-, and 9-year K-M estimates (and 95% confidence intervals) for b-PFS, OS, MFS, and PCSS. Table 3 summarizes the UVA and MVA results for the primary endpoint (b-PFS). Compared with men randomized to LDR-PB, those randomized to DE-EBRT were twice as likely to experience biochemical failure (MVA hazard ratio 2.04; $P=.004$). Clinical T stage ($P=.004$), iPSA ($P=.01$), and PPC ($P=.006$) were also independent predictors of b-PFS. The 5-, 7-, and 9-year K-M b-PFS estimates were 89%, 86%, and 83% for those randomized to LDR-PB versus 84%, 75%, and 62% for men randomized to DE-EBRT (log-rank $P<.001$; Fig. 2a). LDR-PB improved b-PFS in the both the intermediate-risk ($P=.003$; Fig. 2b) and the high-risk ($P=.048$; Fig. 2c) subsets.

Post-treatment PSA values in nonrelapsed subjects

Among the 137 nonrelapsed LDR-PB subjects with ≥4 years of follow-up data available, the median PSA level was 0.01 ng/mL (mean 0.08, SD 0.23), and 54% had undetectable PSA levels using ultrasensitive assays. In contrast, the median PSA level for the equivalent DE-EBRT subjects (n=114) was 0.25 ng/mL (mean 0.35, SD 0.37), and 8% had an undetectable PSA level.

Table 2 Disease status at data lockdown (September 30, 2014) by randomization (intent-to-treat) 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)
Patients						
Relapsed*	76 (19.1)	51 (25.5)	25 (12.6)	48 (24.6)	21 (11.2)	7 (46.7)
Nonrelapsed	322 (80.9)	149 (74.5)	173 (87.4)	147 (75.4)	167 (88.8)	8 (53.3)
Metastatic disease	35 (8.8)	18 (9.0)	17 (8.6)	18 (9.2)	14 (7.4)	3 (20.0)
Alive	330 (82.9)	162 (81.0)	168 (84.8)	155 (79.5)	163 (86.7)	12 (80.0)
Deceased	68 (17.1)	38 (19.0)	30 (15.2)	40 (20.5)	25 (13.3)	3 (20.0)
ANED	274 (68.8)	124 (62.0)	150 (75.8)	120 (61.5)	148 (78.7)	6 (40.0)
DNED	48 (12.1)	25 (12.5)	23 (11.6)	27 (13.8)	19 (10.1)	2 (13.3)
AWD	56 (14.1)	38 (19.0)	18 (9.1)	35 (17.9)	15 (8.0)	6 (40.0)
DOWD	20 (5.0)	13 (6.5)	7 (3.5)	13 (6.7)	6 (3.2)	1 (6.7)
Died of prostate cancer†	18 (4.5)	11 (5.5)	7 (3.5)	11 (5.6)	6 (3.2)	1 (6.7)
K-M estimates +/− 95% CI						NA
b-PFS						
5 y	86.2 ± 3.8	83.8 ± 5.6	88.7 ± 4.8	84.9 ± 5.6	89.7 ± 4.8	
7 y	80.7 ± 4.6	75.0 ± 7.2	86.2 ± 5.4	76.3 ± 7.0	88.0 ± 5.2	
9 y	72.7 ± 6.2	62.4 ± 9.8	83.3 ± 6.6	65.0 ± 9.6	84.9 ± 6.6	
OS						
5 y	90.0 ± 3.2	88.7 ± 4.8	91.3 ± 4.4	87.4 ± 5.0	92.4 ± 4.2	
7 y	83.6 ± 4.4	81.5 ± 6.4	85.7 ± 5.8	81.1 ± 6.2	87.0 ± 5.8	
9 y	75.8 ± 5.8	73.6 ± 8.4	77.9 ± 8.2	73.4 ± 8.2	79.5 ± 8.4	
MFS						
5 y	92.9 ± 2.8	92.5 ± 4.0	93.3 ± 3.8	92.6 ± 4.0	94.1 ± 3.6	
7 y	91.7 ± 3.0	92.5 ± 4.0	91.0 ± 4.6	92.6 ± 4.0	91.6 ± 4.6	
9 y	86.8 ± 4.6	84.8 ± 7.6	88.6 ± 5.6	85.2 ± 7.4	90.1 ± 5.4	
PCSS						
5 y	97.1 ± 1.8	97.5 ± 2.4	96.8 ± 2.8	97.0 ± 2.6	97.1 ± 2.8	
7 y	95.1 ± 2.6	94.1 ± 4.2	96.0 ± 3.2	94.4 ± 4.0	96.2 ± 3.4	
9 y	93.5 ± 3.4	92.1 ± 5.6	94.8 ± 4.0	92.5 ± 5.4	95.0 ± 4.2	

Abbreviations: ANED = alive, no evidence of disease; AWD = alive with disease; b-PFS = biochemical progression-free survival; CI = confidence interval; DE-EBRT = dose-escalated external beam radiation therapy; DNED = dead, no evidence of disease; DOWD = dead of/with disease; K-M = Kaplan-Meier; LDR-PB = low-dose-rate prostate brachytherapy; MFS = metastasis-free survival; NA = not applicable (because of insufficient cases in protocol violation group for meaningful actuarial analysis); OS = overall survival; PCSS = prostate cancer–specific survival.

* b-PFS 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.

Table 3 Univariate and multivariable analyses (Cox model; backwards: conditional) for biochemical failure

Variable	UVA			MVA Cox model		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Randomization arm*† (DE-EBRT vs LDR-PB)	**2.17**	**1.33-3.45**	**.002**‡	**2.04**	**1.25-3.33**	**.004**‡
PPC* (unit = 1%)	**1.01**	**1.01-1.02**	**.001**‡	**1.01**	**1.00-1.02**	**.006**‡
Clinical T stage*† (T3a vs T1-T2b)	**1.89**	**1.20-3.00**	**.006**‡	**1.97**	**1.24-3.13**	**.004**‡
Log iPSA* (unit = 1 log)	**1.60**	**1.10-2.34**	**.014**‡	**1.62**	**1.11-2.36**	**.01**‡
Risk code†§ (high vs intermediate)	1.66	0.99-2.80	.0557	NA	NA	NA
Number of high-risk features†§ (≥3 vs ≤2)	**2.60**	**1.60-4.33**	**<.001**‡	NA	NA	NA
Gleason sum*† (8-10 vs ≤7)	1.28	0.81-2.02	.29	1.38	0.87-2.19	.17
Age (unit = 1 y)	1.00	0.97-1.03	.99	NA		

Abbreviations: CI = confidence interval; DE-EBRT = dose-escalated external beam radiation therapy; iPSA = pretreatment prostate-specific antigen; LDR-PB = low-dose-rate prostate brachytherapy; MVA = multivariable analysis; NA = not applicable; PPC = percentage of positive cores; UVA = univariate analysis.

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

† Categorical variable.

‡ Statistically significant.

§ Composite variables not entered into MVA.

Overall survival

A total of 68 patients have died, with no significant difference in OS between the treatment arms ($P=.293$; Fig. 2d). The results of the UVA and MVA for OS in which biochemical failure (MVA HR 6.30; $P<.001$) and age (MVA HR 1.06/y; $P=.004$) were the only significant predictors of OS are listed in Table 4. The 5-, 7- and 9-year K-M OS estimates were 91%, 86%, and 78% for those randomized to LDR-PB and 89%, 82%, and 74% for those randomized to DE-EBRT (Table 2), respectively. The median OS was not reached and was estimated at 13 years on Cox regression (details on the causes of death are provided in Appendix E10; available online at www.redjournal.org).

Metastasis-free survival

Of the 76 trial subjects with biochemical failure, 35 (46%) developed metastatic disease; 17 were randomized to LDR-PB and 18 to DE-EBRT (Table 2). The 5-, 7-, and 9-year K-M MFS estimates were 93%, 91%, and 89% for those randomized to LDR-PB and 93%, 93%, and 85% for DE-EBRT, respectively (Table 2). On MVA, PPC ($P=.02$), T stage ($P=.02$), and GS ($P=.03$) were predictive of MFS (the MVA results for MFS are provided in Appendix E11; available online at www.redjournal.org). Of the 35 metastatic events, 12 (34%) were in subjects with ≥3 high-risk features, a subgroup that constituted only 13% of the subjects ($P=.002$).

Of the 35 metastatic events, 30 (86%) occurred within 2 years of biochemical failure, and the median interval for this subset was just 4 months. These 30 men with early metastatic relapse were distributed evenly between the 2 arms. In contrast, 37 of the remaining 46 men (80%) with biochemical failure that was not associated with early metastatic relapse had been randomized to DE-EBRT.

Prostate cancer-specific survival

Death from metastatic prostate cancer was the most common cause of death in the entire cohort (18 of 68; Appendix E10; available online at www.redjournal.org). No difference was found in PCSS between the treatment arms (the MVA results for PCSS are provided in Appendix E12; available online at www.redjournal.org). The number of prostate cancer deaths was 7 in the LDR-PB arm and 11 in the DE-EBRT arm, for a 5-, 7-, and 9-year K-M PCSS estimate of 97%, 96%, and 95% for LDR-PB versus 98%, 94%, and 92% for DE-EBRT, respectively (Table 2).

Discussion

Primary endpoint (b-PFS)

The 2 previous randomized trials comparing EBRT plus brachytherapy with EBRT alone (6, 7) differed from the present trial in 2 key features. First, neither used LDR-PB. Instead, the experimental arm in the study by Sathya et al (6) used a 35-Gy boost with a traditional temporary iridium-192 implant, and the study by Hoskin et al (8) used 2 high-dose-rate (HDR) iridium-192 implants of 8.5 Gy each. Second, neither used dose escalation for comparison. In the trial by Saytha et al (6), the standard arm was 66 Gy in 33 fractions, and the study by Hoskin et al (8) used a hypofractionated regimen of 55 Gy in 20 fractions (approximately equivalent to 64-66 Gy at 2 Gy per fraction). Despite these differences, the 3 trials shared a common outcome. In the study by Sathya et al (n = 104), the brachytherapy arm improved the 5-year b-PFS by 32% (71% vs 39%). In the larger study by Hoskin et al (8) (n = 215), the HDR-PB boost improved the 7-year b-PFS by 18% (66% vs 48%). In the present trial (n = 398), the LDR-PB boost improved the 7-year b-PFS by 11% (86% vs

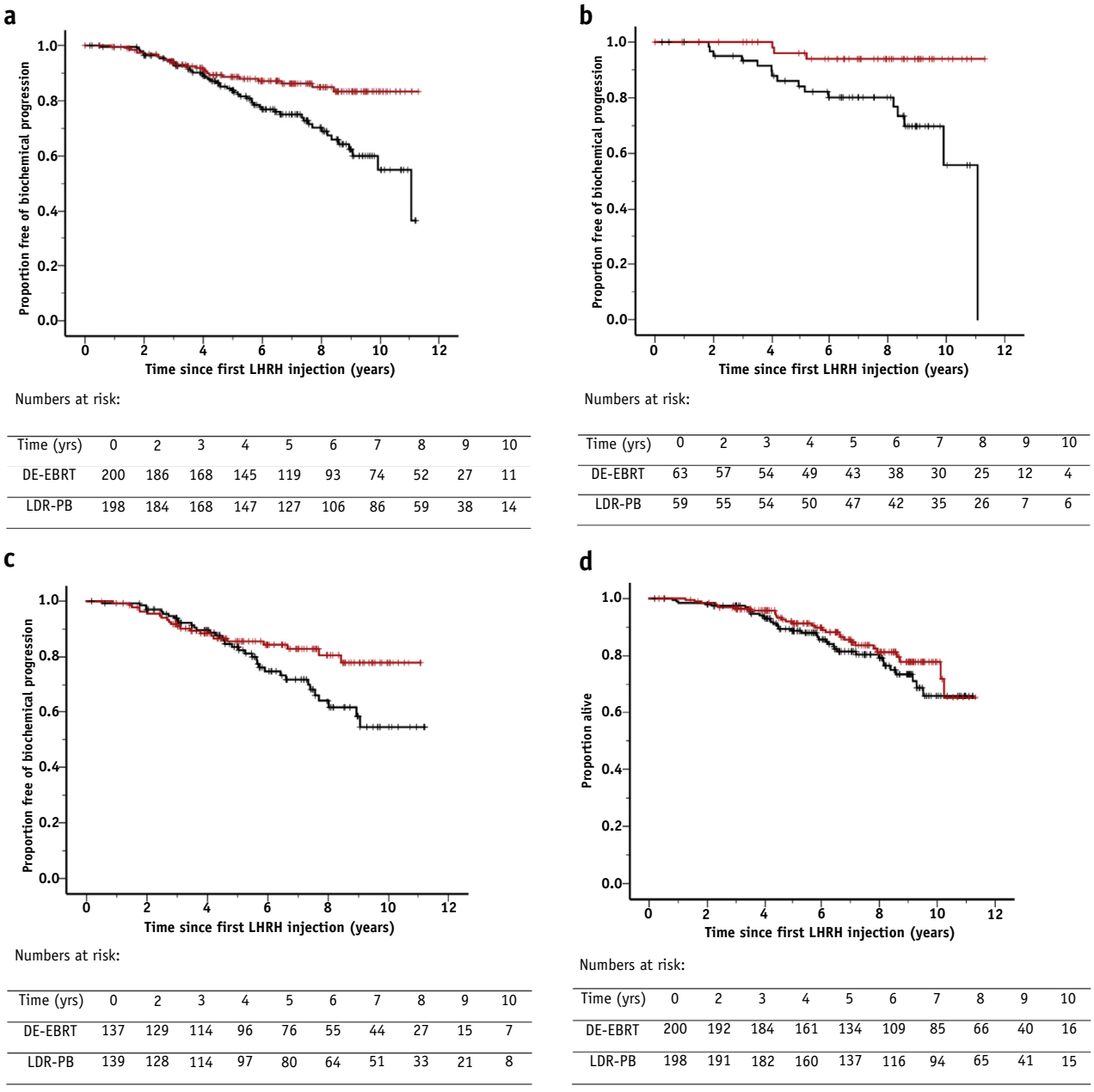

Fig. 2. Kaplan-Meier plots showing intent-to-treat analyses stratified by randomization arm. Black line and censor marks indicate dose-escalated external beam radiation therapy (DE-EBRT) arm; red line and censor marks indicate low-dose-rate prostate brachytherapy (LDR-PB) arm. (a) Biochemical progression-free survival (b-PFS) for all trial subjects stratified by randomization arm (n = 398, log-rank $P = .001$). (b) b-PFS for National Comprehensive Cancer Network (NCCN) intermediate-risk subset (n = 122; log-rank $P = .003$). (c) b-PFS for the NCCN high-risk subset (n = 276; log-rank $P = .048$). (d) Overall survival for all trial subjects stratified by randomization arm (n = 398; log-rank $P = .293$).

75%) and an estimated 21% by 9 years of follow-up (83% vs 62%; Table 2).

The 7-year b-PFS in the DE-EBRT arm of the present trial (75%) was consistent with the b-PFS outcomes for the dose-escalation arms comparing standard and dose-escalated EBRT regimens (1-5). Therefore, in ASCENDE-RT, the LDR-PB boost resulted in a b-PFS gain similar in magnitude to that seen when DE-EBRT was compared with standard-dose EBRT. Assuming the diverging K-M trajectories shown in Figure 2a are maintained, the relative advantage in b-PFS associated with the LDR-PB boost will increase with longer follow-up.

Overall survival

The findings of ASCENDE-RT align with other dose-escalation studies showing improved b-PFS but no

Table 4 Univariate and multivariable analysis (Cox model; backwards: conditional) for all-cause mortality

Variable	UVA			MVA Cox model		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Randomization arm*† (DE-EBRT vs LDR-PB)	1.29	0.80-2.08	.30	1.13	0.69-1.84	.62
PPC (unit = 1%)	1.00	0.99-1.01	.61	NA	NA	NA
Clinical T stage† (T3a vs T1-T2)	1.04	0.62-1.74	.89	NA	NA	NA
Log iPSA* (unit = 1 log)	1.28	0.86-1.89	.23	1.18	0.80-1.73	0.42
Risk code†‡ (high vs intermediate)	1.13	0.68-1.87	.64	NA	NA	NA
Number of high-risk features†‡ (≥3 vs ≤2)	1.30	0.68-2.49	.42	NA	NA	NA
Gleason sum† (8-10 vs ≤7)	1.23	0.76-2.01	.40	NA	NA	NA
Age* (unit = 1 y)	**1.05**	**1.02-1.09**	**.004**§	**1.05**	**1.02-1.09**	**.006**§
Disease status*‖ (relapse vs no relapse)	**6.60**	**3.80-11.4**	**<.001**§	**6.30**	**3.62-10.9**	**<.001**§

Abbreviations: CI = confidence interval; DE-EBRT = dose-escalated external beam radiation therapy; HR = hazard ratio; iPSA = pretreatment prostate-specific antigen; LDR-PB = low-dose-rate prostate brachytherapy; MVA = multivariable analysis; NA = not applicable; PPC = percentage of positive cores; UVA = univariate analysis.

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

† Categorical variable.

‡ Composite variables not entered into MVA.

§ Statistically significant.

‖ Time-dependent variable.

difference in OS. In this context, ASCENDE-RT demonstrated a statistical correlation between biochemical failure and increased all-cause mortality (MVR HR 6.30, $P<.001$; Table 4) and a major reduction in biochemical failure with an LDR-PB boost (MVR HR 2.04; $P=.004$; Table 3). However, no statistical correlation was seen linking LDR-PB to improved OS (MVR HR 1.13; $P=.62$; Table 4). Despite appearances, this is logically consistent because the 35 subjects with known metastatic disease were largely responsible for the correlation between biochemical failure and diminished OS. The observed correlation probably reflects diminished survival in a small subset of trial subjects with pre-existing, but occult, metastatic disease, because in 86% of metastatic events (30 of 35), evidence of metastatic disease was identified at or shortly after biochemical failure. The members of this subset were distributed evenly between the treatment arms, presumably by the randomization process.

In contrast, 37 of the remaining 46 men (80%) with biochemical failure that was not accompanied by early metastatic relapse were randomized to DE-EBRT, an observation consistent with the hypothesis that LDR-PB improved the b-PFS by improving local control. Although "second wave metastases" can seed from local failure, multiyear intervals often separate the 2 events, and the practice of prescribing systemic therapies for biochemical failure probably expands the interval further.

Thus, although longer follow-up might show an OS benefit with LDR-PB, that is far from certain. The present trial enrolled only 398 subjects with a median age of 68 years. The small sample size of (now) elderly subjects, combined with the long interval from local recurrence to life-threatening disease, means that competing causes of mortality will erode any potential survival benefit associated with improved local control.

Incidence of occult metastatic disease before treatment

Metastatic relapse occurred in <10% of the subjects (35 of 398; Table 2). This fact suggests that the incidence of occult metastatic disease was probably <15% at registration. This observation implies that for most prostate cancer patients, including many with multiple unfavorable prognostic features, sufficient local treatment can result in long-term biochemical and clinical remission.

Alternate treatments

Opinions vary regarding the best initial management for localized prostate cancer with unfavorable prognostic features. Some expert opinion urge the use of surgical prostatectomy (12-14), notwithstanding the absence of randomized data supporting this as a preferred approach and the common indications for adjuvant and salvage radiation because of adverse pathologic features and biochemical recurrence, respectively (15).

With respect to radiation therapy, randomized data have demonstrated the advantage of DE-BBRT (1-5) over conventional doses and have shown that combining EBRT with ADT is superior to either modality alone (16, 17). Hypofractionated DE-EBRT has been subjected to randomized comparisons with conventionally fractionated DE-EBRT,

with no consistent trends in b-PFS identified (18-20), although the most definitive study (20) demonstrated similar efficacy between 60 Gy in 20 fractions and 74 Gy in 37 fractions. Other investigators are exploring extreme hypofractionated EBRT (21) to take advantage of a purported low α/β ratio.

Including ASCENDE-RT, three randomized trials, each incorporating a distinct brachytherapy boost regimen, have demonstrated improved b-PFS compared with EBRT alone. In the ASCENDE-RT trial, an LDR-PB boost resulted in K-M b-PFS benchmarks of 83% for high-risk and 94% for intermediate-risk disease at a 6.5-year median follow-up (Figs. 2b and 2c). However, these 3 trials have only begun to explore the diversity of brachytherapy, with its pallet of isotopes, dose rates, and techniques. This diversity could prove problematic. For example, numerous dose/fractionation schemes have been used for HDR boosts, making it difficult to define an optimal regimen. Also, several less easily quantified, but potentially critical, differences exist in treatment planning and delivery for both HDR-PB and LDR-PB across institutions (22).

Residual PSA as a surrogate for biological effective dose

In ASCENDE-RT, the median PSA after LDR-PB was ~20 times lower than that after DE-EBRT (see Results section), and their respective K-M curves diverged sharply (Fig. 2a), suggesting that the long-term b-PFS after LDR-PB boost will be markedly superior to that after DE-EBRT. This observation is consistent with findings from other studies demonstrating a strong inverse correlation between the probability of long-term biochemical control and the residual PSA value in nonrelapsed subjects at 4 or 5 years after radiation therapy (23-25). Because radiation is a local therapy, this phenomenon is best explained if the residual PSA level is proportional to the effect of the radiation on normal prostate glands and the PSA-secreting cancers that arise from them, which constitutes a practical definition of the biological effective dose (BED).

Although a dose response must link BED and residual PSA level, researchers have not yet derived a quantitative model to describe it. However, multiple databases exist that contain pretreatment prognostic information, long-term b-PFS data, and serial PSA values and would probably be suitable for such an effort. If these data sets collectively span a sufficient range of radiation dose and fractionation, they could be used to derive and validate a quantitative dose response, construct an isoeffect curve, and derive the α/β ratio. Thus, the residual PSA level might become an objective surrogate for BED. Using BED to rank radiation prescription doses could help researchers evaluate novel regimens against known standards and permit comparisons of LDR-PB and HDR-PB protocols without recourse to mathematical formulas that contain multiple variables that are weakly constrained by empiric observations.

Study limitations

Centralized quality assurance procedures including real-time review of EBRT and postimplant dose metrics were not included in ASCENDE-RT. The optimal duration of ADT and the role of elective nodal irradiation are still not clearly defined (26-28) and might differ for intermediate- and high-risk disease (27, 28). Although placed in 40% of DE-EBRT boost subjects, fiducial markers for image guidance were not required. Notwithstanding the small number of patients available for the comparison, we did not observe a difference in biochemical failure in the DE-EBRT arm between those with or without the use of image guidance. Intensity modulated radiation therapy was not used (29). However, although intensity modulated radiation therapy might alter toxicity and facilitate safer dose escalation, its use is unlikely to alter tumor control in a manner independent of the prescribed dose. Of concern, 93% of trial subjects were accrued from 4 centers that shared a single LDR-PB planning/treatment algorithm, which differed in some potentially relevant details from those used by other high-volume LDR-PB programs, implying that the gain in b-PFS observed for the LDR-PB might not be generalizable (30, 31).

Conclusions

The initial management for high- and intermediate-risk prostate cancer usually involves surgery or some form of radiation therapy. At the very least, the findings from ASCENDE-RT provide benchmarks for future comparisons. The 6.5-year K-M b-PFS estimate was 83% for NCCN high-risk and 94% for NCCN intermediate-risk subjects randomly assigned to an LDR-PB boost. The results of the present trial indicate that most men with adverse prognostic features lack occult metastatic spread at presentation and can be cured by local tumor eradication. In marked contrast to those randomized to DE-EBRT, most nonrelapsed men assigned to the LDR-PB arm had undetectable PSA values when using ultrasensitive assays, implying that LDR-PB frequently provides gland-ablative doses of ionizing radiation, but that DE-EBRT rarely does.

However, as detailed in a companion report, the men who received an LDR-PB boost also had a significantly greater incidence of treatment-related genitourinary morbidity compared with those receiving DE-EBRT. Thus, the LDR-PB boost provided gland-ablative doses but produced more adverse events related to normal tissue effects. It is logical to connect these 2 facts through the common mechanism of an increased BED. Current efforts are directed at reducing toxicity by exploiting better image guidance and more accurate treatment delivery, and it is possible that technological solutions might provide the benefits of dose

escalation without its liabilities. It is also possible that major improvements in the therapeutic ratio might require more than image guidance, altered fractionation, and HDR-PB (collectively) have to offer, and arguments derived from radiobiological modeling are no substitute for phase III trials and data from large prospective cohorts. Until such data are available, incorporating an LDR-PB boost, or any method of dose escalation that can achieve gland-ablative doses, should be individualized and requires careful consideration of the potential risks and benefits.

References

1. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: The results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys* 1995;32:3-12.
2. Heemsbergen WD, Al-Mamgani A, Slot A, et al. Long-term results of the Dutch randomized prostate cancer trial: Impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol* 2014;110:104-109.
3. Beckendorf V, Guerif S, Le Prise E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-Year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011;80:1056-1063.
4. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: Long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;15:464-473.
5. Kuban DA, Levy LB, Cheung MR, et al. Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer: Who dies of disease? *Int J Radiat Oncol Biol Phys* 2011;79:1310-1317.
6. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implants plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192-1199.
7. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localized prostate cancer. *Radiother Oncol* 2012;103:217-222.
8. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low intermediate and high risk prostate cancer treatment by radical therapy: Results of the Prostate Cancer Results study group. *BJU Int* 2012;109(suppl 1):22-29.
9. Bittner N, Merrick GS, Galbreath RW, et al. Treatment outcomes with permanent brachytherapy in high-risk prostate cancer patients stratified into prognostic categories. *Brachytherapy* 2015;14:766-772.
10. Carpenter TJ, Forsythe K, Kao J, et al. Outcomes for patients with extraprostatic prostate cancer treated with trimodality therapy, including brachytherapy, external beam radiotherapy and hormone therapy. *Brachytherapy* 2011;10:261-268.
11. Rodda S, Tyldesley S, Morris WJ, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT trial): An analysis of treatment-related morbidity 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. *In J Radiat Oncol Biol Phys* 2016.
12. Eastham JA, Evans CP, Zietman A. What is the optimal management of high risk, clinically localized prostate cancer? *Urol Oncol* 2010;28:557-567.
13. Zelefsky MJ, Eastham JA, Cronin AM, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: A comparison of clinical cohorts adjusted for case mix. *J Clin Oncol* 2010;28:1508-1513.
14. Fradet Y. Radical prostatectomy is the most cost-effective primary treatment modality for men diagnosed with high-risk prostate cancer. *Can Urol Assoc J* 2012;6:396-398.
15. Tyldesley S, Peacock M, Morris WJ, et al. The need for, and utilization of prostate-bed radiotherapy after radical prostatectomy for patients with prostate cancer in British Columbia. *Can Urol Assoc J* 2012;6:89-94.
16. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-Year results of an EORTC randomized study. *Lancet Oncol* 2010;11:1066-1073.
17. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol* 2015;33:2143-2150.
18. Pollock A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;31:3860-3868.
19. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionated trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1172-1178.
20. Dearnaley D, Sydikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-Year outcomes of the randomized, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17:1047-1060.
21. Musunuru HB, Cheung P, Loblaw A. Evolution of hypofractionated accelerated radiotherapy for prostate cancer—The Sunnybrook experience. *Front Oncol* 2014;4:313.
22. Morton GC. High-dose-rate brachytherapy boost for prostate cancer: Rationale and technique. *J Contemp Brachytherapy* 2014;6:323-330.
23. Lo AC, Morris WJ, Lapointe V. Prostate specific antigen at 4 to 5 years after low-dose-rate prostate brachytherapy is a strong predictor of disease free survival. *Int J Radiat Oncol Biol Phys* 2014;88:87-91.
24. Ko EC, Stone NN, Stock RG. PSA nadir of <0.5 ng/mL following brachytherapy for early-stage prostate adenocarcinoma is associated with freedom from prostate-specific antigen failure. *Int J Radiat Oncol Biol Phys* 2012;83:600-607.
25. Yock TI, Zietman AL, Shipley WU, et al. Long-term durability of PSA failure-free survival after radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54:420-426.
26. RTOG 0924—Androgen deprivation therapy and high dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high risk prostate cancer: A phase III randomized trial. Disease Site Tables: RTOG Genitourinary Cancer Studies. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable.aspx. Accessed February 18, 2015.
27. RTOG 0815—A phase III prospective randomized trial of dose-escalated radiotherapy with and without short-term androgen deprivation therapy for patients with intermediate risk prostate cancer. Disease Site Tables: RTOG Genitourinary Cancer Studies. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable.asp. Accessed February 18, 2015.
28. Nabid A, Carrier N, Martin A, et al. High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study. *J Clin Oncol* 2013;31(suppl 6): abstract 3.
29. Al-Mamgani A, Heemsbergen WD, Peeters STH, et al. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73:685-691.
30. Morris WJ, Spadinger I, Keyes M, et al. Whole prostate D90 and V100: A dose-response analysis of 2000 consecutive 125I monotherapy patients. *Brachytherapy* 2014;13:32-41.
31. Morris WJ, Halperin R, Spadinger I. Point: the relationship between postimplant dose metrics and biochemical no evidence of disease following low dose rate prostate brachytherapy: is there an elephant in the room? *Brachytherapy* 2010;9:289-292.