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Using a surgical prostate-specific antigen threshold of >0.2 ng/mL to define biochemical failure for intermediate- and high-risk prostate cancer patients treated with definitive radiation therapy in the ASCENDE-RT† randomized control trial

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ABSTRACT

PURPOSE: To compare biochemical failure using a prostate-specific antigen (PSA) threshold of >0.2 ng/mL to that using Phoenix threshold (nadir+2 ng/mL).

METHODS AND MATERIALS: Androgen suppression combined with elective nodal and dose-escalated radiation therapy (the ASCENDE-RT trial) is a randomized control trial in which 276 high-risk and 122 intermediate-risk patients were randomized to (*1*) a standard arm with 12 months of androgen deprivation therapy, pelvic external beam radiation therapy (EBRT) to 46 Gy, and an EBRT boost (dose-escalated EBRT [DE-EBRT]) to 78 Gy, or (*2*) an experimental arm which substituted a low-dose-rate prostate brachytherapy boost (LDR-PB). The primary endpoint was biochemical progression-free survival (b-PFS) using the Phoenix threshold. In this reanalysis of ASCENDE-RT, the b-PFS using phoenix is compared to the surgical PSA threshold of >0.2 ng/mL.

RESULTS: Compared to nadir+2 ng/mL, the >0.2 ng/mL PSA threshold doubled the number of relapse events from 69 to 139. However, the increase was confined to the DE-EBRT subjects. The 7-year Kaplan-Meier b-PFS after DE-EBRT declined from 76% using nadir+2 ng/mL to 38% using the >0.2 ng/mL threshold ($p < 0.001$). Among the LDR-PB subset, there was no significant difference in b-PFS; the 7-year Kaplan-Meier b-PFS was 85% (>0.2 ng/mL) versus 88% (nadir+2 ng/mL) ($p = 0.319$).

CONCLUSIONS: Replacing Phoenix with a surgical threshold greatly increased biochemical failure after DE-EBRT boost but had no effect after LDR-PB. As a result of this finding, PSA outcomes after surgery or brachytherapy can be directly compared by using the surgical definition of PSA failure. In this context, a brachytherapy boost appears to produce superior b-PFS compared to contemporary surgical series.

Keywords: Prostate cancer; Brachytherapy; Surgical prostatectomy; PSA relapse

Introduction

Brachytherapy delivers high doses of ionizing radiation and extremely sharp dose gradients, which are intrinsic to brachytherapy and cannot be fully replicated with any known external beam technique. Thus brachytherapy offers a uniquely intense method of dose escalation that can combine high cure rates with acceptable normal tissue toxicity (1–4). The modern era of low-dose-rate prostate brachytherapy (LDR-PB) began in the 1980s with the utilization of transrectal ultrasound to plan and guide the placement of radioactive sources (5). Thirty years later, there exists a large body of evidence, showing generally excellent results for all prognostic strata (4,6–8).

Moreover, three randomized control trials (RCTs) have shown that a brachytherapy boost, when part of combined modality therapy, produces superior biochemical progression-free survival (b-PFS) compared to external beam radiation therapy (EBRT) alone, for men with National Comprehensive

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† ASCENDE-RT stands for androgen suppression combined with elective nodal and dose-escalated radiation therapy and is a National Cancer Institute registered trial (Clinical Trials.gov identifier NCT00175396).

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Cancer Network (NCCN) intermediate- and high-risk prostate cancer (6–8). If it is an established fact that brachytherapy is superior to EBRT (for biochemical endpoints), an important remaining question involves how brachytherapy compares to radical prostatectomy (RP) for similar unfavorable risk patients.

There is only one small RCT of RP versus LDR-PB, and, while it showed no difference in b-PFS at 5 years, the results are irrelevant because only NCCN low-risk patients were eligible (9). We must always be aware that comparisons across modalities, and especially those involving different institutions and investigators, suffer from several well-recognized limitations, and the authors contend that the case of prostate cancer has been uniquely challenging due to the fact that surgeons and radiation oncologists use very different prostate-specific antigen (PSA) thresholds to define biochemical failure, a fact that adds an unwieldy dimension to the problem of cross-modality comparisons. While a PSA threshold of >0.2 ng/mL is most often used when reporting biochemical relapse after RP (10), radiation oncologists most often use the Phoenix definition, with its 10-fold greater threshold of 2 ng/mL above the posttreatment nadir (11). Because EBRT typically leaves some PSA-secreting glands, Phoenix's high threshold value is necessary to avoid a host of "false positives." Nevertheless, any fair-minded assessment of the two definitions must conclude that Phoenix introduces a major lead time bias that favors radiation therapy in reporting actuarial results. The high Phoenix threshold has also been questioned by brachytherapists because, like RP, prostate brachytherapy often entirely ablates the glandular tissue, leaving undetectable PSA levels (8,12,13). In an effort to promote transparency and permit a more nearly fair, although still imperfect, comparison of biochemical failure rates between RP and radiation therapy, the authors have reanalyzed the androgen suppression combined with elective nodal and dose-escalated radiation therapy (ASCENDE-RT) data set using a surgical PSA threshold (>0.2 ng/mL) and compared it with the Phoenix (nadir+2 ng/mL) PSA threshold.

Material and methods

Eligibility, stratification, randomization, and treatment interventions

A complete description of the materials and methods, including a consort diagram, used in the ASCENDE-RT trial (NCI-registered trial number NCT00175396) is provided in the study by Morris et al (8). In brief, 398 men were accrued at six Canadian cancer centers over 81 months; 69% (n = 276) had NCCN high-risk disease, the remainder had NCCN intermediate-risk disease. The median age at registration was 68 years and the median followup was 6.5 years at data lockdown (September 30, 2014). After obtaining informed consent, trial subjects were stratified by risk group and randomized to a standard arm with 12 months of androgen deprivation therapy (ADT, 8 months was neoadjuvant), pelvic irradiation to 46 Gy, followed by a dose-escalated EBRT (DE-EBRT) boost to a total dose of 78 Gy, or an experimental arm that substituted an LDR-PB boost. Of the 398 trial subjects, 200 were assigned to DE-EBRT boost and 198 to LDR-PB boost.

Protocol violations—defining the denominators

The primary endpoint of ASCENDE-RT was an intent-to-treat analysis of b-PFS using the nadir+2 threshold and has been reported in Morris et al (8). For this study, the outcomes of the two arms were analyzed by the treatment actually received after accounting for 29 major protocol violations. Specifically, 15 subjects (seven assigned to DE-EBRT and eight assigned to LDR-PB) were excluded from analysis because they received neither of the two protocol interventions. In addition, there were 14 crossover events; six men assigned to DE-EBRT actually received the LDR-PB interventions, and eight crossed the opposite way. Correcting these crossover events and excluding the 15 men who received nonprotocol interventions leaves 195 men who received the DE-EBRT boost and 188 received the LDR-PB.

Defining biochemical failure

In ASCENDE-RT, b-PFS was defined as the absence of any biochemical, imaging, or clinical evidence of prostate cancer recurrence and no receipt of any form of secondary treatment for prostate cancer. PSA and testosterone were measured at baseline, every 4 months for the first year and 6 months thereafter. Patients were assessed for biochemical failure according to two definitions:

(1) Phoenix whereby a rise in PSA of at least 2 ng/mL above the posttreatment nadir indicates biochemical failure at the date of the PSA measurement (11).
(2) A surgical definition whereby biochemical failure is defined by a posttreatment PSA of >0.2 ng/mL on the date of the PSA measurement (14).

Statistical analysis

Descriptive statistics were used to compare the prognostic factors. Actuarial endpoints were calculated using the Kaplan-Meier (K-M) method. Statistical analyses were performed using SPSS, version 22 (IBM Corp., Armonk, NY).

Results

Table 1 lists the prognostic features: 69% had NCCN high-risk disease, 29% had clinical T3a disease, 41% had Gleason score ≥8, 19% had pretreatment PSA (iPSA) > 20 ng/mL, 68% had at least 50% of cores involved, and 49% had at least two of these high-risk features. Table 2 summarizes the 5-, 7-,

Table 1
Prognostic features including age and pretreatment tumor factors

Factor	All patients (N = 398)	Subset by treatment received		
		DE-EBRT N = 195	LDR-PB N = 188	[b]Neither N = 15
Age (y)				
Median	68	69	67	67
Mean (SD)	67.6 (7.5)	67.9 (7.5)	67.4 (7.5)	66.4 (8.1)
Range	45–86	45–86	50–85	49–78
NCCN risk stratum				
Intermediate	122 (30.7%)	64 (32.8%)	54 (28.7%)	4 (26.7%)
High	276 (69.3%)	131 (67.2%)	134 (71.3%)	11 (73.3%)
Clinical T-stage				
T1c–T2c	282 (70.9%)	137 (70.3%)	135 (71.8%)	10 (66.7%)
T3a	116 (29.1%)	58 (29.7%)	53 (28.2%)	5 (33.3%)
iPSA (ng/mL)				
<5	35 (8.8%)	17 (8.7%)	17 (9.0%)	1 (6.7%)
5–10	156 (39.2%)	74 (37.9%)	72 (38.3%)	10 (66.7%)
10–20	132 (33.2%)	66 (33.8%)	63 (33.5%)	3 (20.0%)
>20	75 (18.8%)	38 (19.5%)	36 (19.1%)	1 (6.7%)
Median	10.7	11.0	10.8	8.5
Mean (SD)	13.3 (8.2)	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	4.8–21.0
Gleason sum (GS)				
6	22 (5.5%)	11 (5.6%)	10 (5.3%)	1 (6.7%)
7	214 (53.8%)	109 (55.9%)	97 (51.6%)	8 (53.3%)
8–10	162 (40.7%)	75 (38.5%)	81 (43.1%)	6 (40.0%)
Percent positive cores (PPC)				
≤25%	57 (14.3%)	22 (11.3%)	31 (16.5%)	4 (26.7%)
25%–50%	142 (35.7%)	77 (39.5%)	61 (32.4%)	4 (26.7%)
50%–75%	84 (21.1%)	34 (17.4%)	48 (25.5%)	2 (13.3%)
≥75%	113 (28.4%)	60 (31.3%)	48 (25.5%)	5 (33.3%)
Data missing	2 (0.5%)	2 (1.0%)	0	0
Median	50	50	60	50
Mean (SD)	59.3 (26.9)	60.1 (26.9)	58.1 (26.4)	57.6 (28.4)
Range	7–100	9–100	7–100	17–100
[c]Number of high-risk features				
≤1	205 (51.5%)	100 (51.3%)	98 (52.1%)	7 (46.7%)
2	140 (35.2%)	66 (33.8%)	66 (35.1%)	8 (53.3%)
≥3	53 (13.3%)	29 (14.9%)	24 (12.8%)	0

None of the comparisons demonstrated a statistically[a] significant difference between the arms.

[a] χ^2 test was performed on categorical variables. Mann-Whitney-Wilcoxon test was performed on age variable to examine difference between the median values. T-tests were performed on iPSA and PPC.

[b] Of the 15 trial subjects who received neither treatment arms, nine received nonprotocol EBRT doses and/or non-protocol androgen deprivation therapy durations (three relapsed), three underwent radical prostatectomy (two relapsed), two had LDR-PB without pelvic EBRT (one relapsed), and one had high-frequency-focused ultrasound (relapsed).

[c] High-risk features include clinical T-stage = T3a, iPSA >20 ng/mL, GS ≥ 8, and PPC ≥50%.

and 9-year K-M b-PFS estimates and their respective 95% confidence intervals (CIs) according to treatment arm, NCCN risk group, and for both biochemical failure definitions.

Figure 1a shows b-PFS K-M curves using the nadir+2 ng/mL (Phoenix) threshold to define biochemical failure for all patients by treatment received. The K-M estimates do not differ significantly from those obtained in the intent-to-treat analysis of the primary endpoint (8). The two treatment arms diverge sharply at followup times greater than 4 years with LDR-PB subjects much less likely to experience biochemical failure (log rank $p = 0.001$).

As summarized in Table 2, when applying the nadir+2 ng/mL PSA threshold, the K-M b-PFS estimates are markedly superior for the LDR-PB arm compared to the DE-EBRT ARM (the 5-, 7-, and 9-year results are 90%, 88%, and 85% vs. 84%, 76%, and 63%). This relationship applies to both the intermediate-risk subset (N = 118; the 5-, 7-, and 9-years results are 96%, 93%, and 93% vs. 86%, 82%, and 72%) and for the high-risk subset (N = 265; the 5-, 7-, and 9-year results are 88%, 87%, and 84% vs. 84%, 73%, and 61%).

Figure 1b shows that for all patients in the analysis (N = 383), substituting the >0.2 ng/mL threshold for the nadir+2 PSA threshold doubled the number of biochemical failures resulting in a crude relapse rate of 36% (139 events) instead of 18% (69 events). Moreover, when applying the >0.2 ng/mL PSA threshold, 79% of relapse events (110 of 139) were declared within 4 years of the first lutenizing

Table 2
The 5-, 7-, and 9-year K-M b-PFS estimates

Group	[a]Nadir+2 ng/mL (Phoenix) threshold			[d]>0.2 ng/mL (surgical) threshold		
	5-y K-M b-PFS[b]	7-y K-M b-PFS	9-y K-M b-PFS	5-y K-M b-PFS	7-y K-M b-PFS	9-y K-M b-PFS
[c]All patients (n = 383)	87% (83−91)	82% (78−86)	73% (67−73)	66% (61−71)	61% (56−67)	57% (51−63)
All DE-EBRT arm (n = 195)	84% (78−90)	76% (69−81)	63% (53−73)	46% (38−44)	38% (30−46)	31% (22−40)
All LDR-PB arm (n = 188)	90% (85−95)	88% (83−93)	85% (78−92)	88% (83−92)	85% (79−91)	82% (75−89)
IR subset (n = 118)	90% (84−96)	86% (82−90)	81% (72−90)	68% (59−71)	63% (53−73)	58% (47−69)
DE-EBRT IR subset (n = 64)	86% (77−95)	82% (72−92)	72% (58−86)	47% (34−60)	40% (26−54)	31% (13−49)
LD-PB IR subset (n = 54)	96% (90−100)	93% (86−100)	93% (86−100)	94% (87−100)	91% (82−100)	91% (82−100)
HR subset (n = 265)	85% (80−90)	79% (73−85)	71% (63−79)	64% (58−70)	58% (51−65)	54% (46−62)
DE-EBRT HR subset (n = 131)	84% (77−91)	73% (63−83)	61% (47−73)	44% (35−53)	34% (24−44)	32% (21−43)
LDR-PB HR subset (n = 134)	88% (82−94)	87% (81−93)	84% (76−92)	83% (76−90)	81% (74−88)	77% (68−86)

The results were calculated using the nadir+2 ng/mL (Phoenix) threshold, which are compared to those obtained using the >0.2 ng/mL (surgical) threshold. Outcomes are reported according to treatment arm, NCCN risk stratum, and the definition of biochemical failure applied. All values are rounded to the nearest integer for ease of comparison; the values in parentheses are the 95% confidence intervals.

b-PFS = biochemical progression-free survival; DE-EBRT = dose-escalated external beam radiation therapy; HR = NCCN high-risk disease; IR = NCCN intermediate-risk disease; K-M = Kaplan-Meier; LDR-PB = low-dose-rate prostate brachytherapy; PSA = prostate-specific antigen.

[a] Nadir+2 ng/mL threshold to define biochemical relapse (failure to maintain PSA at <the nadir+2 ng/mL. Because virtually all men in ASCENDE-RT achieved PSA nadirs of ≤0.02 ng/mL, this means that, effectively, any subject with a followup PSA ≥2 ng/mL was scored as biochemical failure).

[b] Progression-free survival (the absence of relapse) was defined as the absence of any biochemical (PSA), imaging, or clinical recurrence of prostate cancer and never having received any form of secondary treatment for prostate cancer after completion of the protocol interventions.

[c] Excludes 15 trial subjects who received neither of the two protocol treatments.

[d] >0.2 ng/mL threshold to define biochemical relapse (failure to maintain a PSA of ≤0.2 ng/mL).

hormone releasing hormone agonist injection compared to less than half when using nadir+2 ng/mL (46% or 32 of 69 events). As shown in Table 2, the 5-, 7-, and 9-year K-M b-PFS estimates are 66%, 61%, and 57% using the >0.2 ng/mL threshold compared to 87%, 82%, and 73% for the nadir+2 ng/mL threshold. At times greater than 4 years, however, the K-M curves become parallel and yield a relatively constant relapse rate of about 3% per year for years 4−9 inclusive (Fig. 1b).

Figure 2a compares the K-M b-PFS for LDR-PB arm (n = 188, Table 2) using both thresholds. The curves are statistically indistinguishable (log rank p = 0.319), with 5-, 7-, and 9-year b-PFS estimates of 88%, 85%, and 82% using the >0.2 ng/mL threshold versus 90%, 88%, and 85% for nadir+2 ng/mL threshold. Moreover, applying the >0.2 ng/mL threshold to the LDR-PB arm did not significantly increase the proportion of biochemical failures that were declared within 4 years, and the relapse rate is about 1% per year for years 4−9 inclusive.

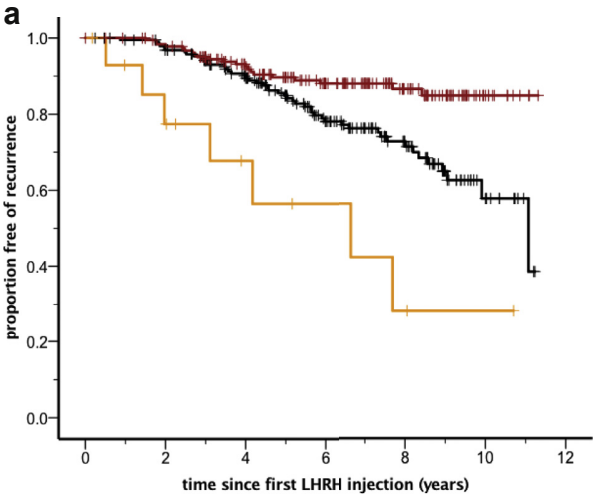
In sharp contrast, Fig. 2b compares the b-PFS K-M curves for DE-EBRT arm (N = 195) using both PSA thresholds. In this case, the use of the >0.2 ng/mL threshold resulted in a large increase in crude biochemical failure from 25% (48 events) using nadir+2 ng/mL to 57% (112 events). Furthermore, applying the >0.2 ng/mL PSA threshold to the DE-EBRT subset resulted in more than 80% of relapse events (90 of 112) being declared within 4 years compared to just 40% (19 of 48 events) using nadir+2 ng/mL. And the 5-, 7-, and 9-year b-PFS estimates have dropped to just 46%, 38%, and 31% when applying the >0.2 ng/mL PSA threshold versus 84%, 76%, and 63% using nadir+2 ng/mL. Of note, however, at times greater than 4 years, the K-M plots are parallel yielding a constant relapse rate of about 5% per year over years 4−9 inclusive independent of the PSA threshold applied (see Fig. 2b).

Figures 3a and 3b show the K-M b-PFS plots for the intermediate-risk (n = 118) and high-risk (n = 265) subsets, respectively, using the >0.2 ng/mL (surgical) threshold, and directly compares the DE-EBRT and LDR-PB arms. The 5-, 7-, and 9-year b-PFS rates are 47%, 40%, and 31%, respectively, for the DE-EBRT intermediate-risk subset versus 94%, 91%, and 91% following LDR-PB (log rank $p < 0.001$). For the high-risk subset, the 5-, 7-, and 9-year b-PFS rates are 44%, 34%, and 32% for DE-EBRT versus 83%, 81%, and 77% after LDR-PB (log rank $p < 0.001$).

Discussion

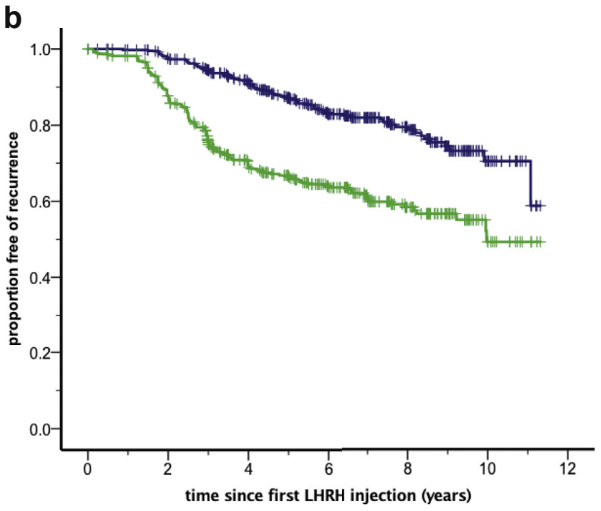
The optimal management of unfavorable localized prostate cancer

In an intent-to-treat analysis of all 398 subjects in the ASCENDE-RT trial, randomization was highly predictive of biochemical relapse using the nadir+2 ng/mL threshold with a multivariable hazard ratio of 2.04 (95% CI = 1.25−3.33, p = 0.004) and 9-year K-M b-PFS failure rates of 62% for those randomized to DE-EBRT versus 83% for the LDR-PB arm (8). ASCENDE-RT joins two previous RCTs all demonstrating the superiority of brachytherapy boost over EBRT alone in preventing biochemical relapse in NCCN intermediate- and high-risk prostate cancer. This leaves unsettled the equally important question of how the efficacy of the ASCENDE-RT treatment arms compares to a management strategy based on an up-front RP for patients with similar pretreatment risk factors.



Numbers at risk:

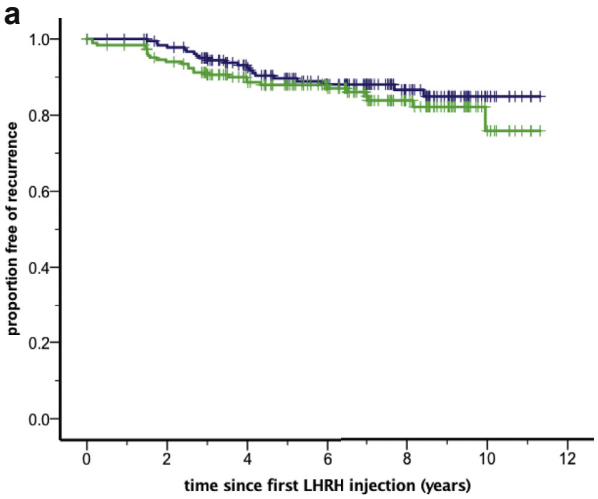
Time (yrs)	0	2	4	6	8	10
LDR-PB	188	177	137	98	54	11
DE-EBRT	195	182	147	95	54	11
neither	15	9	6	4	1	-



Numbers at risk:

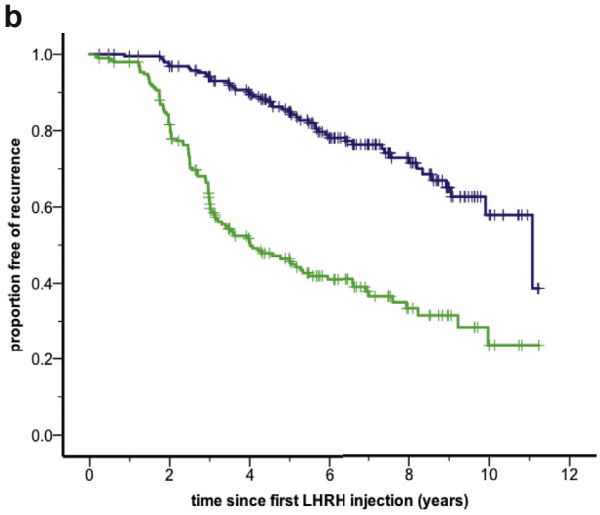
Time (yrs)	0	2	4	6	8	10
Nadir+2ng/mL	383	359	285	194	109	22
>0.2 ng/mL	383	322	207	142	72	16

Fig. 1. (a) All patients (N = 398): Kaplan-Meier plots comparing b-PFS for LDR-PB (upper [red] line), DE-EBRT boost (middle [black] line), and those who received neither of the two protocol interventions (lower [yellow] line) using the nadir+2 ng/mL (Phoenix) definition of biochemical failure. (log rank $p = 0.001$ comparing LDR-PB to DE-EBRT). (b) Kaplan-Meier b-PFS plots for all patients using two definitions of biochemical failure (upper [blue] line = nadir+2 ng/mL [Phoenix] definition, lower [green] line = > 0.2 ng/mL [surgical] definition) (log rank $p < 0.001$). b-PFS = biochemical progression free survival; LDR-PB = low-dose-rate prostate brachytherapy boost; DE-EBRT = dose-escalated external beam radiation therapy.



Numbers at risk:

Time (yrs)	0	2	4	6	8	10
Nadir+2ng/mL	188	177	137	98	55	11
>0.2 ng/mL	188	170	130	96	53	11

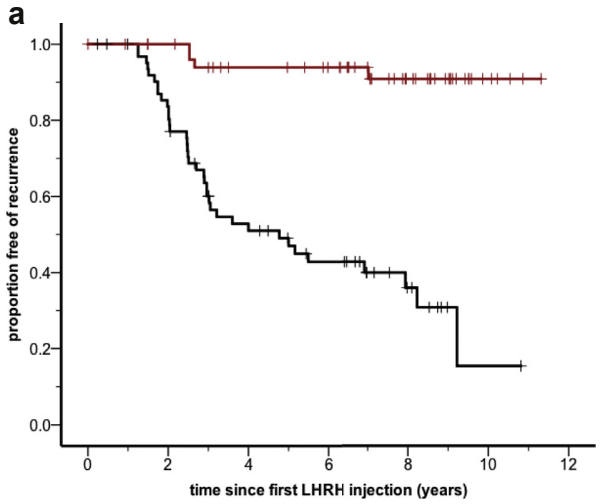


Numbers at risk:

Time (yrs)	0	2	4	6	8	10
Nadir+2ng/mL	195	181	141	95	53	11
>0.2 ng/mL	195	152	77	46	19	4

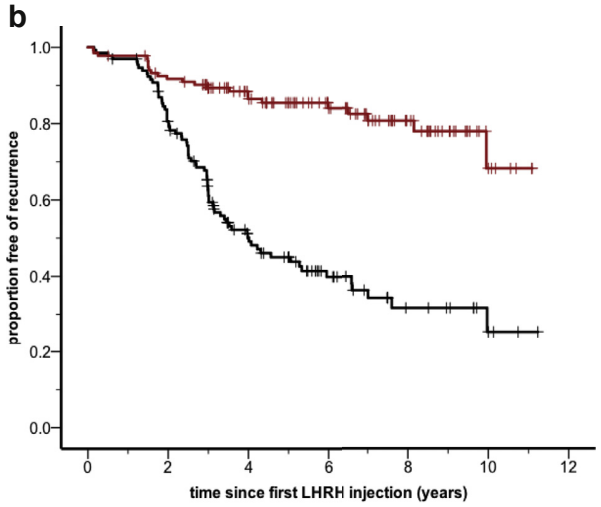
Fig. 2. (a) Kaplan-Meier b-PFS plots for the LDR-PB subset using two definitions of biochemical failure (upper [blue] line = nadir+2 ng/mL [Phoenix] definition, lower [green] line = > 0.2 ng/mL [surgical] definition) (log rank $p = 0.319$). (b) Kaplan-Meier b-PFS plots for the DE-EBRT subset using two definitions of biochemical failure (upper [blue] line = nadir+2 ng/mL [Phoenix] definition, lower [green] line = > 0.2 ng/mL [surgical] definition) (log rank $p < 0.001$). b-PFS = biochemical progression free survival; LDR-PB = low-dose-rate prostate brachytherapy boost; DE-EBRT = dose-escalated external beam radiation therapy.

This is important because the optimal management of men with unfavorable disease is controversial and expert opinion tends to divide along specialist lines (14−16). Most radiation oncologists are skeptical of up-front surgery in the high-tier intermediate and high-risk subsets because of the frequent need for adjuvant and salvage therapies (17). Surgeons, on the other hand, often advocate for RP as the best initial management for clinically unfavorable disease because of the prognostic value of postoperative pathology for guiding future management and the fact that some patients can be spared the



Numbers at risk:

Time (yrs)	0	2	4	6	8	10
LDR-PB	54	50	41	37	22	4
DE-EBRT	64	50	28	20	8	-



Numbers at risk:

Time (yrs)	0	2	4	6	8	10
LDR-PB	131	120	87	58	31	6
DE-EBRT	134	101	48	26	10	3

Fig. 3. (a) Intermediate-risk subgroup: Kaplan-Meier plots comparing b-PFS for LDR-PB boost (upper [red] line) with DE-EBRT boost (lower [black] line) using a surgical definition of biochemical failure of >0.2 ng/mL. (log rank $p < 0.001$). (b) High-risk subgroup: Kaplan-Meier plots comparing b-PFS for LDR-PB boost (upper [red] line) with DE-EBRT boost (lower [black] line) using a surgical definition of biochemical failure of >0.2 ng/ml (log rank $p < 0.001$). b-PFS = biochemical progression free survival; LDR-PB = low-dose-rate prostate brachytherapy boost; DE-EBRT = dose-escalated external beam radiation therapy.

additional side effects associated with multimodality therapy. Naturally, the argument supporting primary surgery is sound if, and only if, up-front RP (+/− adjuvant/salvage treatment) does not compromise the overall cure rate compared to up-front multimodality therapy. This is the crux of the controversy.

The data from the ASCENDE-RT trial is insufficient to resolve this controversy, but the authors submit that this re-analysis using a surgical PSA threshold allows a less confusing, if still imperfect, basis of comparison with RP for the risk strata examined. Fortunately, several large retrospective cohort studies have analyzed b-PFS following RP for high-risk patients and report actuarial 10-year values between 28% and 54% (18−25). As shown in Table 2, this range of results is inferior to both arms of ASCENDE-RT when the nadir+2 ng/mL PSA threshold is applied to the trial patients; but the DE-EBRT arm is numerically inferior to the range reported after RP when the >0.2 ng/mL threshold is applied (9-year K-M b-PFS = 31%: 95% CI: 22%−40%).

In contrast, the b-PFS for the LDR-PB patients is statistically independent of the threshold used (Fig. 2a) with 9-year K-M b-PFS estimate of 77% (95% CI: 68%−86%) for the high-risk subset using > 0.2 ng/mL versus 84% (95% CI: 76%−92%) using nadir+2 ng/mL. Both values are obviously well above the range of values cited for RP. For example, in the largest of the studies cited, Ciezki et al. reported on 1308 high-risk patients treated with RP at the Cleveland clinic (25). Using Fine and Gray's competing risk analysis and a >0.4 ng/mL PSA threshold, the 5- and 10-year b-PFS estimates were 65% and 47%, respectively, which compares unfavorably with those for the high-risk subset of ASCENDE-RT who received the LDR-PB, where the 5- and 9-year rates were 83% (95% CI: 76%−90%) and 77% (95% CI: 68%−86%), respectively, although ASCENDE-RT used the more stringent PSA threshold of >0.2 ng/mL (Table 2). Similarly, Abdullah et al. published long-term outcomes in 1100 high-risk patients treated with robotic-assisted RP (23). Their 10-year b-PFS for entire group was 50%, once again comparing unfavorably with ASCENDE-RT LDR-PB subset, but apparently superior to DE-EBRT (Table 2). Moreover, Abdulla et al. subdivided their cohort into five risk subgroups, where subgroups 3−5 most closely resembled the ASCENDE-RT cohort. The 10-year b-PFS in these three subgroups was only 26%−35% despite the use of salvage therapies and demonstrated an ongoing failure rate of 3%−4% per year, which is much higher than the 1% per year seen in LDR-PB arm of ASCENDE-RT regardless of the threshold used (Fig. 2a).

Limitations of this study

The ASCENDE-RT trial was not designed for comparison with RP, but, like RP, patients did start with an undetectable PSA at treatment completion. To achieve this, however, ASCENDE-RT specified 12 months of ADT, which may have delayed biochemical failure in a manner that favors radiation therapy in the comparison because only a minority of men in the surgical series received ADT (22−25).

Patients treated in ASCENDE-RT had either (*1*) NCCN intermediate-risk (>90% of the intermediate-risk subjects in the trial had so-called high-tier intermediate-risk disease in which more than one risk factor was present) or (*2*) relatively favorable NCCN high-risk patients (iPSA ≤ 40 ng/

mL and clinical stage < T3b). As a result, it is unclear whether all high-risk patients would derive a similar benefit from an LDR-PB.

Although a sensitive measure of treatment success, biochemical failure often correlates poorly (or not at all) with overall, metastasis-free, and cause-specific survival (8,26–28). In ASCENDE-RT, biochemical failure was a strong predictor of diminished overall survival (OS) (multivariable hazard ratio = 6.3, $p < 0.001$) and randomization to LDR-PB substantially reduced biochemical failure, but no statistically significant difference in overall or cause-specific survival between the treatment arms has emerged thus far (8). Having said that, ASCENDE-RT was not powered for OS and the numbers favor the LDR-PB arm; the 9-year K-M OS = 73% (95% CI 65%–81%) for DE-EBRT arm versus 80% (95% CI 72%–88%) for LDR-PB arm (8). It is also noteworthy that the ASCENDE-RT subjects who received an LDR-PB boost had substantially more treatment-related genitourinary adverse effects and a slightly greater decline in patient-reported long-term quality of life compared to DE-EBRT (29,30). Of course, how these adverse effects might compare to policy of up-front RP has never been addressed in an RCT. Thus, the authors submit that this analysis adds usefully to the debate regarding the relative efficacy of the two main treatment strategies, but an important message is that the b-PFS rate is only one consideration in making management decisions.

Conclusions

The unusual circumstances of the ASCENDE-RT trial, in which all subjects had undetectable PSA values at the completion of radiation therapy, provide a unique opportunity to evaluate b-PFS after definitive radiation therapy using a surgical threshold (>0.2 ng/mL) to define biochemical relapse. The results suggest that combined modality therapy using a brachytherapy boost provides b-PFS outcomes for men with unfavorable risk disease that are at least as good as any published results for RP.

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