## Clinical Investigation

# ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

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## Summary

This report concerns a randomized trial investigating 2 methods of dose escalation in the context of combined modality therapy for high- and intermediate-risk prostate cancer that included 12 months of androgen deprivation therapy and whole-pelvic irradiation to 46 Gy. Compared with an external beam boost to 78 Gy, the patients who received a brachytherapy boost had a significantly higher incidence and prevalence of LENT-SOMA grade 2 and 3 genitourinary morbidity.

**Purpose:** To report the genitourinary (GU) and gastrointestinal (GI) morbidity and erectile dysfunction in a randomized trial comparing 2 methods of dose escalation for high- and intermediate-risk prostate cancer.

**Methods and Materials:** ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) enrolled 398 men, median age 68 years, who were then randomized to either a standard arm that included 12 months of androgen deprivation therapy and 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. At clinic visits, investigators recorded GU and GI morbidity and information on urinary continence, catheter use, and erectile function. Exclusion of 15 who received nonprotocol treatment and correction of 14 crossover events left 195 men who actually received a DE-EBRT boost and 188, an LDR-PB boost. Median follow-up was 6.5 years.

**Results:** The LDR-PB boost increased the risk of needing temporary catheterization and/or requiring incontinence pads. At 5 years the cumulative incidence of grade 3 GU events was 18.4% for LDR-PB, versus 5.2% for DE-EBRT ($P<.001$). Compared with the cumulative incidence, the 5-year prevalence of grade 3 GU morbidity was substantially lower for both arms (8.6% vs 2.2%, $P=.058$). The 5-year cumulative incidence of grade 3 GI events was 8.1% for LDR-PB, versus 3.2% for DE-EBRT ($P=.124$). The 5-year prevalence of grade 3 GI toxicity was lower than the cumulative incidence for both arms (1.0% vs 2.2%, respectively). Among men reporting adequate baseline erections, 45% of LDR-PB patients reported similar erectile function at 5 years, versus 37% after DE-EBRT ($P=.30$).

**Conclusions:** The incidence of acute and late GU morbidity was higher after LDR-PB boost, and there was a nonsignificant trend for worse GI morbidity. No differences in the frequency of erectile dysfunction were observed. © 2017 Elsevier Inc. All rights reserved.

## Introduction

Dose escalation is associated with improved biochemical progression-free survival (b-PFS) using prostate-specific antigen endpoints in low-, intermediate-, and high-risk prostate cancer (1-7), with a trend toward increased toxicity (8-13). Two randomized studies reported improved b-PFS when combining external beam radiation therapy (EBRT) with a brachytherapy boost compared with EBRT alone (14, 15). However, in contrast to the ASCENDE-RT trial (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy), the previous 2 trials did not use dose escalated EBRT (DE-EBRT) in the standard arm or permanent low-dose-rate brachytherapy (LDR-PB) for the boost in the experimental arm.

A study reported by Stock et al (16) suggested that a higher biologically effective dose and improved b-PFS can result from combining modest doses of EBRT with an LDR-PB boost compared with EBRT alone. ASCENDE-RT was designed to test this hypothesis; however, the study was also designed to collect prospective data on the adverse effects associated with the treatment interventions. This report details the treatment-related morbidity; a companion article (17) reports the primary endpoint (b-PFS) and other survival endpoints.

## Methods and Materials

### Trial design

ASCENDE-RT is a 2-arm randomized comparison of 2 methods of delivering a boost to achieve prostate dose escalation. It accrued in 2 phases: a feasibility phase, open to accrual from November 2002 to August 2003, and a completion phase, open from August 2004 to December 2011. Target accrual was 400; a CONSORT diagram and further information on study design, eligibility, registration, stratification, and randomization can be found in our companion article (17).

The trial received approval from the appropriate research ethics board at each participating cancer center. W.J.M. designed and led the trial. N.M. chaired an independent Data Monitoring and Safety Committee with authority to suspend accrual; S.R., S.T., M.K., and J.H. performed data analysis.

### Defining the denominators for morbidity analysis

In total, 398 subjects were accrued; 200 were randomized to DE-EBRT, and 198 were randomized to LDR-PB. These

are the denominators used for the intent-to-treat analysis of the primary endpoint and secondary survival endpoints. For the morbidity analysis reported here, the denominators were adjusted by excluding 15 subjects who received neither treatment arm (7 were assigned to DE-EBRT, 8 to LDR-PB) and correcting 14 crossover events (6 men who were assigned to DE-EBRT actually received the LDR-PB interventions, and 8 men crossed the opposite way). The adjusted denominators of 195 for DE-EBRT and 188 for LDR-PB were chosen for this report because the authors have insufficient information on the treatment-related morbidity for the 15 excluded subjects (item 9 in the Supplemental Online Material; available at www.redjournal.org, details the 15 exclusions).

## Protocol interventions

All patients received luteinizing hormone—releasing hormone (LHRH) agonist injections using 4 3-month depot preparations; the first was given concurrently with 4 weeks of oral nonsteroidal antiandrogen (androgen deprivation therapy [ADT] details are in item 3, Supplemental Online Material; available at www.redjournal.org).

After 8 months of ADT, patients received 46 Gy/23 fractions of pelvic irradiation encompassing the prostate, seminal vesicles, and regional lymph nodes. Directly after completion of pelvic irradiation, patients assigned to DE-EBRT received 32 Gy/16 fractions delivered as a 2-phase, 3-dimensional conformal boost (more EBRT details

| *Grade | 1 | 2 | 3 | 4 |
|--------|---|---|---|---|
| GU | Nocturia twice baseline. Microscopic hematuria. Light atrophy and minor telangiecta-sia. Occasional (< weekly) use of incontinence pads. | Moderate frequency. Nocturia more than twice baseline. Generalized telangiectasia. Intermittent macroscopic hematura. Two or fewer coagulations. Intermittent (< daily use of incontinence pads. Regular non-narcotic or occasional narcotic for pain. | Severe frequency and dysuria. Nocturia more frequent than once every hour. Minor surgical procedure (e.g. TURP, dilation). Reduction in bladder capacity (150 cc). Frequent hematuria requiring at least one transfusion. More than two coagulations for hematuria. Hyperbaric oxygen for bleeding/ulceration. Persistent use of incontinence pads/. Regular narcotic for pain. | Severe hemorrhagic cystitis or ulcerations with requirement for urinary diversion and/or cystectomy. |
| GI | Excess bowel movements at least twice baseline. Slight rectal discharge or blood. | More than 2 antidiarrheals/week Two or fewer coagulations for bleeding. Occasional steroids for ulcerations. Occasional dilations. Intermittent use of incontinence pads. Regular non-narcotic or occasion narcotic for pain. | More than 2 antidiarrheals/day. At least one blood transfusion or more than two coagulations for bleeding. Prolonged steroids per enema. Minor surgical procedure. Hyperbaric oxygen for bleeding/ulceration. Regular dilation. Persistent use of incontinence pads. Regular narcotic for pain. | Dysfunction requiring surgery. Perforation. Life-threatening bleeding. |

*Grade 0 = no adverse effects, Grade 5 corresponds to complications leading to death.

**Fig. 1.**    Modified LENT-SOMA (Late Effects of Normal Tissue—Somatic, Objective, Management, Analytic) scale used to score physician-reported genitourinary (GU) and gastrointestinal (GI) morbidity. *Abbreviation:* TURP = transurethral resection of the prostate.

in items 4-6, Supplemental Online Material; available at www.redjournal.org).

Two to 3 weeks after pelvic irradiation, the LDR-PB group underwent a $^{125}$I brachytherapy implant (LDR-PB details in item 7, Supplemental Online Material; available at www.redjournal.org).

## Reporting of adverse effects

Clinic visits occurred every 4 months for the first year, every 6 months for the next 4 years, and annually thereafter. Genitourinary (GU) and gastrointestinal (GI) morbidity were scored using the Late Effects of Normal Tissue−Somatic, Objective, Management, Analytic (LENT-SOMA) scale, shown in Figure 1. Scores of 3 and 4 represent moderately severe and severe adverse events, respectively; grade 5 refers to toxicity-related death. Acute GU and GI morbidity included events occurring within 6 months of starting pelvic irradiation; late morbidity occurred >6 months after that date.

For each follow-up visit there was a time-specific follow-up form, an example of which is provided as item 14 in the Supplemental Online Material (available at www.redjournal.org). Among other items, the investigator was required to sign-off on: (1) GU and GI morbidity according to the LENT-SOMA scale provided; (2) scoring urinary incontinence and recording the number of incontinence pads used per day; (3) whether the subject required artificial bladder drainage since the last visit, and for how long it was required; and (4) sexual activity, erectile function, and the use of aids for erectile function. Moreover, all grade ≥3 GU or GI events required the investigator to complete a special form that included a narrative description of the event. Thus, the protocol specified the method of toxicity data collection, the timing of data collection, and the instruments used. However, the statistical design of the trial was powered for the primary endpoint, and the protocol did not specify a plan for toxicity analysis. After data lockdown (September 30, 2014), but before analysis, a plan for the analysis of toxicity was designed by S.R., S.T., and J.H.

## Statistical analysis

For urinary and bowel events the start date of radiation was taken as t-0; for erectile dysfunction, t-0 corresponds to the first LHRH injection. Crude incidences of acute GU and GI events were compared using the $\chi^2$ test. Cumulative incidence for late GU and GI events, urinary incontinence, and late catheterization were analyzed using the Kaplan-Meier (K-M) method.

Cross-sectional analysis was done to obtain the prevalence figures at 2 and 5 years; the score recorded closest to the actual time point and within 3 months was used for calculation. Chi-squared tests were used to calculate the difference at 2 and 5 years as a priori times of interest.

Logistic regression was used in a post hoc analysis examining the association between patient/tumor variables and LDR-PB dose metrics and the probability of grade ≥2 GU morbidity. Variables used in this analysis included age, pretreatment International Prostate Symptom Score (IPSS), biopsy Gleason score, clinical T stage, and pretreatment prostate-specific antigen. For LDR-PB patients, the D90 and V100 were also included. Statistical analyses were done with SPSS version 22 (IBM, Armonk, NY) and SAS version 9.3 (SAS Institute, Cary, NC).

## Results

### Prognostic features

Table 1 shows patient and prognostic features, LDR-PB dose metrics, and baseline values of IPSS, urinary continence, and erectile function (a more comprehensive list of prognostic features is shown in Table 1 of our companion article [17]). There were no significant differences between the treatment arms. Median age was 68 years; the median baseline IPSS was 6 (75th percentile = 12). More than 95% had normal baseline urinary continence, and >60% had baseline erections adequate for penetration. The median follow-up was 6.5 years from the date of the first LHRH injection.

### Acute GU and GI morbidity

Table 2 shows the incidence of acute GU and GI morbidity; acute grade 2 GU morbidity was higher for LDR-PB versus DE-EBRT (P<.001), and 5 men treated with LDR-PB (2.5%) experienced acute grade 3 GU events: 1 with urinary frequency more often than hourly, 1 with severe dysuria, 1 who developed urge incontinence, and 2 subjects who required bladder drainage, initially Foley catheters but later replaced by suprapubic drainage in 1 patient and by intermittent self-catheterization in the other. Acute grade 3 GU morbidity occurred in 1 patient (0.5%) on the DE-EBRT arm; he developed lumbar plexopathy and a neurogenic bladder, thought to be secondary to Zoster reactivation. No acute grade ≥4 GU events were recorded in either arm. The incidence of acute grade 0 to 2 GI morbidity did not differ between the arms (Table 2), and there were no acute grade ≥3 acute GI events.

### Late GU morbidity

Figure 2A is a K-M plot of late grade ≥3 GU adverse events, showing a significantly higher cumulative incidence for men receiving LDR-PB (log-rank P<.001). The cumulative incidence of late grade 3 GU morbidity at 2 and 5 years was 7.7% and 18.4% for LDR-PB, versus 3.4% and 5.2% for DE-EBRT, respectively (log-rank

**Table 1**    Age, NCCN risk stratum, and postimplant dose metrics, as well as baseline IPSS scores, urinary continence, and erectile function

| | | By randomization | | By actual treatment received | | |
|---|---|---|---|---|---|---|
| Factor | All patients (N=398) | 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) |
| D90%* | | | | | | |
| Median | - | - | - | - | 108.7 | - |
| Mean (SD) | - | - | - | - | 109.6 (12.8) | - |
| Range | - | - | - | - | 81-154.3 | - |
| V100† | | | | | | |
| Median | - | - | - | - | 94.4 | - |
| Mean (SD) | - | - | - | - | 93.1 (5.2) | - |
| Range | - | - | - | - | 69.9-100 | - |
| Normal baseline urinary control, n (%) | 390 (97) | 196 (98) | 194 (97.9) | 190 (97.4) | 185 (98.4) | 15 (100) |
| Baseline IPSS, median (75th percentile) | 6 (12) | 6 (12) | 7 (12) | 7 (12) | 6 (12) | 9 (14) |
| Baseline erectile function,‡ n (%) | 248 (62.9) | 123 (61.5) | 125 (63.1) | 119 (61.0) | 120 (63.8) | 5 (55.5) |

*Abbreviations:* DE-EBRT = dose-escalated external beam radiation therapy; IPSS = International Prostate Symptom Score; LDR-PB = low-dose-rate prostate brachytherapy; NCCN = National Comprehensive Cancer Network.

Full information on the pretreatment prostate-specific antigen values, biopsy Gleason scores, clinical T stage, and percent positive cores are provided in a companion article (17). Numbers in parentheses are percentages unless otherwise noted. None of the comparisons demonstrated a statistically significant difference between the arms. The $\chi^2$ test was performed on categorical variables. The Mann-Whitney-Wilcoxon test was performed on the age variable, to examine difference between median values.

\* D90 is minimum dose in grays received by 90% of the postimplant, computed tomography—based prostate volume.

† V100 is the percentage of the postimplant, computed tomography—based prostate volume that received the prescription dose of 115 Gy or higher.

‡ Defined as erections adequate for penetration.

*P*<.001) The 5-year cumulative incidence, their respective hazard ratios, and the 95% confidence intervals for all grades of late GU morbidity are shown in Table 3.

**Table 2**    Crude incidence of acute GU and GI morbidity

| | By treatment received | | |
|---|---|---|---|
| Grade | DE-EBRT (n=195) | LDR-PB (n=188) | $\chi^2$ *P* |
| Acute GU morbidity | | | |
| 0 | 79 (40.5) | 36 (19.1) | <.0001* |
| 1 | 70 (35.8) | 75 (39.8) | .562 |
| 2 | 31 (15.8) | 64 (30.0) | <.0001* |
| 3 | 1 (0.5) | 5 (2.5) | .121 |
| 4-5 | 0 | 0 | N/A |
| Acute GI morbidity | | | |
| 0 | 88 (45.1) | 87 (46.2) | .961 |
| 1 | 65 (33.3) | 74 (39.3) | .271 |
| 2 | 28 (14.3) | 17 (9.0) | .090 |
| 3-5 | 0 | 0 | N/A |

*Abbreviations:* GI = gastrointestinal; GU = genitourinary. Other abbreviations as in Table 1.

Values are number (percentage).

\* Statistically significant.

Thirty-one patients in the LDR-PB boost arm experienced a late grade 3 GU event: 16 of them developed urethral strictures requiring dilatation, 4 required transurethral resection of the prostate (TURP), 5 developed severe urinary incontinence, 3 experienced urinary frequency more often than hourly, 2 required hyperbaric oxygen for radiation cystitis, and in 1 the nature of the event was not specified. In contrast, 10 DE-EBRT boost patients experienced a grade 3 GU event: 4 of them required TURP for obstructive symptoms, 2 developed urethral strictures requiring dilatation, another required hyperbaric oxygen for radiation cystitis, 1 developed total urinary incontinence after salvage prostatectomy, and 1 patient required ureteroscopy and lithotripsy for stone evulsion of distal ureter. The nature of the grade 3 event was not recorded in one individual. In addition, 1 individual in each treatment arm developed grade 4 hematuria requiring transfusion/hospitalization.

Figure 2B shows the prevalence of late GU morbidity at a priori—defined time points of 2 and 5 years. Because many of the late grade 3 GU events were temporary or resolved with treatment, the prevalence of grade 3 GU toxicity was less than half the cumulative incidence. However, the relative difference between treatment arms
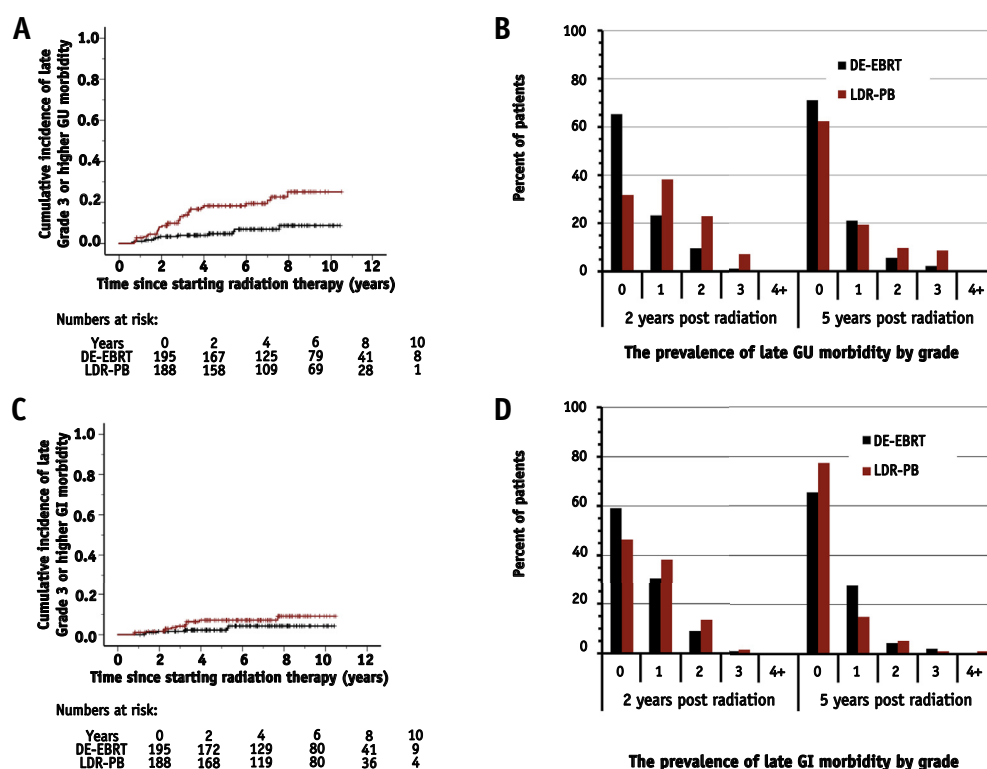
**Fig. 2.** The cumulative incidence and prevalence of late genitourinary (GU) and gastrointestinal (GI) morbidity. Black line and markers represent dose-escalated external beam radiation therapy (DE-EBRT); red line and markers represent low-dose-rate prostate brachytherapy (LDR-PB). (A) Kaplan-Meier plot of the cumulative incidence of grade 3 or higher late GU morbidity (log-rank $P<.001$). (B) The prevalence of late GU morbidity at 2 and 5 years after the start of radiation therapy. (C) Kaplan-Meier plot of the cumulative incidence of grade $\geq 3$ late GI morbidity (log-rank $P=.127$). (D) The prevalence of late GI morbidity at 2 and 5 years after the start of radiation therapy. (A color version of this figure is available at www.redjournal.org.)

was constant: the prevalence of grade 3 GU morbidity after LDR-PB was 7.0% at 2 years and 8.6% at 5 years, compared with 1.1% at 2 years ($P=.005$) and 2.2% at 5 years ($P=.058$) for those who received DE-EBRT. Of the patients with at least 1 grade 3 or 4 toxicity in the LDR boost arm, 13 had multiple GU toxicity events over time, and 3 patients had more than 2 GU toxicity events. Although the sequence of events varied, more frequent combinations were as follows: a procedure for obstruction/stricture followed by incontinence (8 patients), and a

**Table 3** Worst grade of late GU and GI toxicity experienced (5-year actuarial cumulative incidence and hazard ratios)

| Maximum grade | DE-EBRT (%) (n=195) | LDR-PB (%) (n=188) | Hazard ratio: LDR-PB vs DE-EBRT | P |
|---|---|---|---|---|
| Cumulative incidence of late GU side effects at 5 y | | | | |
| 0 | 29.6 (23-36) | 20.6 (9-32) | 0.51 (0.32-0.80) | .003* |
| 1 | 43.8 (36-51) | 33.7 (27-41) | 0.75 (0.54-1.04) | .088 |
| 2 | 20.6 (14-27) | 32.8 (26-40) | 1.97 (1.3-3.00) | .002* |
| 3 | 5.2 (1-8) | 18.4 (12-25) | 3.46 (1.7-7.07) | <.001* |
| 4/5 | 0.6 (0-2) | 2.1 (0-6) | 2.05 (0.19-22.6) | .559 |
| Cumulative incidence of late GI side effects at 5 y | | | | |
| 0 | 35.8 (28-42) | 31.3 (23-38) | 0.83 (0.56-1.23) | .343 |
| 1 | 48.2 (41-56) | 42.0 (35-49) | 0.86 (0.63-1.16) | .322 |
| 2 | 20.2 (14-26) | 31.3 (17-45) | 1.33 (0.86-2.08) | .205 |
| 3 | 3.2 (0-6) | 8.1 (3-13) | 2.16 (0.81-5.75) | .124 |
| 4/5 | 0 | 1.0 | N/A | N/A |

Abbreviations as in Tables 1 and 2.
Values in parentheses are 95% confidence intervals.
* Statistically significant.

procedure for obstruction/stricture followed by hematuria (5 patients). In most cases of multiple different events, the initial event was obstructive in nature.

## Urinary continence and pad usage

The cumulative incidence of any pad usage at 5 years was 16.1% for LDR-PB, compared with 6.3% for DE-EBRT ($P<.001$). After LDR-PB, 35 men (18.6%) required pads: 22 needed $\leq 2$ pads per day, 9 required $>2$ pads per day, and 4 had no bladder control.

After DE-EBRT, 12 men (6.1%) required pads: 7 required $\leq 2$ pads per day, 3 required $>2$ pads per day, and 2 had no bladder control. The 2 DE-EBRT patients who developed total incontinence did so after stricture dilatation in 1 case and salvage prostatectomy for local recurrence in the other.

In the LDR-PB arm, the prevalence of pad usage was 7.6% at 2 years and 6.5% at 5 years, compared with 1.1% ($P=.003$) and 1.1% ($P=.049$) for the DE-EBRT arm. Among those requiring them, the median time to pad usage was 2.5 years (range, 0.8-10.2 years) and did not differ between treatment arms.

## Late catheterization

Cumulative incidence of late catheterization at 5 years was 12% for LDR-PB, compared with 3% for DE-EBRT ($P=.001$). A total of 22 men (11.7%) in the LDR-PB arm needed late catheterization, which was required for $<5$ days in 8, 5 to 10 days in 2, 10 to 20 days in 2, and $>20$ days in 10 patients. Of the 10 who required a catheter for $>20$ days, 2 were catheter-free in 4 weeks, and 8 were not catheter-free at latest follow-up. After DE-EBRT, 6 men (3.0%) required late catheter insertion: for $<5$ days in 2 patients, for 5 to 10 days in 2, and $>20$ days in 2 patients, neither of whom was catheter-free at latest follow-up.

## Factors predicting grade ≥2 late GU toxicity

Age, Gleason score, and various IPSS cut points were each predictive of late grade $\geq 2$ GU events, whereas acute GU toxicity, pretreatment prostate-specific antigen, and clinical T stage, and in the LDR-PB subset, V100 and D90, were not predictive. In logistic regression, only increasing IPSS correlated with a higher risk of grade $\geq 2$ GU morbidity. A priori pretreatment IPSS cut points of $\geq 12$ (odds ratio 1.79, $P=.02$) and $\geq 16$ (odds ratio 2.02, $P=.03$) were associated with an increased risk. However, the link between GU toxicity and pretreatment IPSS seems to be confined to the LDR-PB subset in which an IPSS cut point of 16 yields an odds ratio of 2.57 ($P=.04$) for late GU (grade $\geq 2$), compared with 1.37 ($P=.56$) for DE-EBRT (further details regarding factors predicting grade $\geq 2$ GU morbidity can be found in item 13, Supplementary Online Material; available at www.redjournal.org).

## Late GI morbidity

Figure 2C is a K-M plot of late grade $\geq 3$ GI adverse events by treatment arm showing a nonsignificant trend with an increased incidence for LDR-PB boost (log-rank $P=.127$). The cumulative incidence of late grade 3 GI events at 2 and 5 years was 1.6% and 8.1% after LDR-PB boost, compared with 2.3% and 3.2% in the DE-EBRT boost arm ($P=.116$). The 5-year cumulative incidence, their respective hazard ratios, and the 95% confidence intervals for all grades of late GI morbidity are shown in Table 3.

Twelve patients (6.3%) in the LDR-PB boost arm experienced grade 3 GI toxicity: 7 with rectal bleeding requiring $\geq 2$ endoscopic plasma-argon coagulation procedures, 3 who developed fecal incontinence, and 1 with hemorrhoids requiring banding.

After DE-EBRT boost, 6 men (3.0%) developed late grade 3 GI toxicity: 5 had rectal bleeding requiring $\geq 2$ endoscopic plasma-argon coagulation procedures, and 1 developed fecal incontinence.

In addition, 2 individuals in the LDR-PB boost arm experienced very severe GI toxicity. One required subtotal colectomy for ischemic colitis (grade 4), and the other died 8 years after enrolling in the trial as a result of complications related to a radiation-induced recto-urethral fistula (grade 5).

Figure 2D shows the prevalence of late GI morbidity at a priori—defined time points of 2 and 5 years from the start of pelvic radiation. Because of successful interventions and spontaneous resolution, the prevalence of grade 3 GI morbidity was lower than the cumulative incidence. For the LDR-PB boost the prevalence of late grade 3 GI morbidity was 1.7% at 2 years and 1.0% at 5 years, compared with 1.1% and 2.2% after DE-EBRT boost.

## Erectile function

Before ADT, 120 LDR-PB subjects (63.8%) and 119 DE-EBRT subjects (61.0%) reported erections adequate for penetration; at 1 year these values had dropped to 5.2% and 7.1%, respectively (Fig. 3). At 5 years, 33.9% of LDR-PB and 30.6% of DE-EBRT subjects reported adequate erectile function ($P=.60$). Of those men who had adequate erections at baseline, 45.0% in the LDR-PB arm and 37.1% in the DE-EBRT arm retained (or recovered) similar erectile function at 5 years ($P=.30$).

## Discussion

Although at 5 years more than 80% of the LDR-PB subjects in ASCENDE-RT had minimal or no GU side effects (LENT-SOMA grade 0-1), the use of LDR-PB boost was associated with significantly more GU side effects than DE-EBRT boost, including the incidence and prevalence of moderate to severe late GU morbidity, the use of
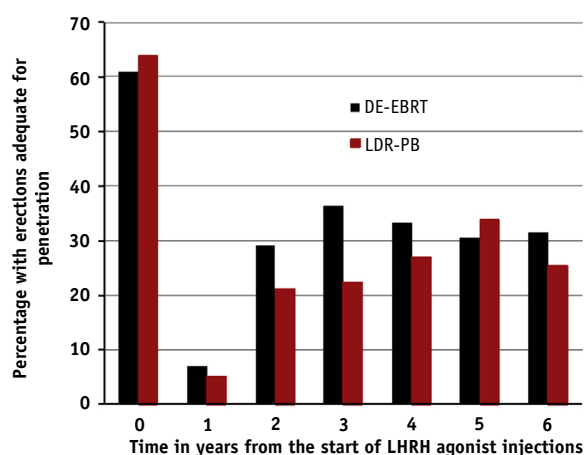
**Fig. 3.** Changes in the frequency of erectile function over time. *Abbreviation:* LHRH = luteinizing hormone—releasing hormone.

incontinence pads, and the need for catheterization. Approximately half of all grade 3 GU events in the LDR-PB boost arm resolved with procedures such as stricture dilatation or TURP, hence the prevalence of grade 3 GU morbidity at 5 years (8.6%) was much lower than the 5-year cumulative incidence of grade 3 GU events (18.4%).

Table 4 compares the frequency of adverse effects observed in the present study versus other studies of dose escalation, some of which involve EBRT only (1-4, 18); some involve combined EBRT with LDR-PB boost (8-12), and others report on combined EBRT and high-dose-rate prostate brachytherapy (HDR-PB) boost (13-15, 19, 20). As shown, the cumulative incidence of late grade 3 GU morbidity in the cited studies ranges enormously, from 1.4% to 31%, which parallels the large range in late grade 3 GI morbidity at 1.4% to 30%. Comparisons of GU and GI morbidity between ASCENDE-RT and these studies are limited by differences in morbidity scoring systems, length of follow-up, eligibility characteristics, the use of pelvic versus prostate-only EBRT, and the duration of ADT.

Hoskin et al (15), in a prospective randomized comparison of HDR-PB plus EBRT versus EBRT alone, reported a cumulative incidence of grade 3 events in the HDR-PB arm of 31%. However, these were often transient, with prevalence rates of 4% to 14%. There are 2 prospective studies (Table 4) that report variable toxicity outcomes in patients receiving an LDR-PB boost. The Cancer and Leukemia Group B 99809 study (11) reported only a 3% incidence of late grade 3 morbidity at 73 months, whereas Radiation Therapy Oncology Group protocol 0019 (12) reported a 15% grade $\geq 3$ GI/GU morbidity at 48 months. The GU morbidity after LDR-PB in this trial seems higher than in the latter 2 studies and is also higher than with LDR-PB monotherapy at our institutions (21).

A recent study, using the Surveillance, Epidemiology and End Results (SEER)—Medicare database, compared the incidence of grade 3 urinary adverse events (UAEs), in a large cohort of men treated with LDR-PB monotherapy (n = 12,801), LDR-PB + EBRT (n = 8518), HDR-PB

**Table 4** Comparing late grade 3 GU and GI toxicity reported for radiation dose-escalation studies for prostate cancer

| Study | Median follow-up (y) | Late GU toxicity grade 3 (%) | Late GI toxicity grade 3 (%) |
|---|---|---|---|
| EBRT + LDR-PB studies: combination arm | | | |
| Albert et al (8) | 2.8 | N/A | 30 (rectal bleeding) |
| Wong et al (9) | 4.8 | 18 | 5 |
| Spratt et al (10) | 5.3 | 1.4 | 1.4 |
| CALGB 99809 phase 2 study (11) | 6.0 | 3 | 0 |
| RTOG 00-19 phase 2 study* (12) | 8.2 | ~15 | ~15 |
| ASCENDE-RT (LDR-PB arm) | 6.5 | 18.4 | 8.1 |
| HDR + EBRT studies: combination arm | | | |
| Aluwini et al (13) | 6.2 | 4 | 1 |
| Sathya et al (14) | 8.2 | 13.7 | 3.9 |
| Hoskin et al (15) | 7.3 | 31 | 7 |
| Agoston et al (19) | 5.1 | 14 | 2 |
| Ghadjar et al (20) | 5.1 | 10.9 | 0 |
| EBRT alone dose-escalation studies: dose-escalation group | | | |
| M. D. Anderson (1) | 8.7 | 4 | 7 |
| MRC RT01 (2) | 5.2 | 4 | 10 |
| Dutch CKVO96-10 (3) | 5.8 | 13 | 5 |
| PROG95-09 (18) | 8.9 | 2 | 1 |
| ASCENDE-RT (DE-EBRT arm) | 6.5 | 5.2 | 3.2 |

*Abbreviations:* ASCENDE-RT = Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy; CALGB = Cancer and Leukemia Group B; HDR = high-dose-rate; MRC = Medical Research Council; RTOG = Radiation Therapy Oncology Group. Other abbreviations as in Tables 1 and 2.

Note that not all grading systems are the same.

* RTOG 00-19 reported the 8-year estimate of combined grade 3 or 4 GU and or GI toxicity being 15% (15 of the 19 events were GU events).

monotherapy (n=685), and HDR-PB + EBRT (n=2392) (22). The 4- and 8-year incidence of grade 3 UAEs was 15.4% and 22.2%, respectively, for the LDR-PB + EBRT group. The SEER-based study also demonstrated that the incidence of grade 3 UAEs was higher for combined LDR-PB + EBRT than for LDR-PB monotherapy. Moreover, the incidence of grade 3 UAEs in this SEER-based study did not differ significantly between those who received LDR-PB + EBRT and those who received HDR-PB + EBRT, for whom the 4- and 8-year incidence of grade 3 UAE was 15.4% and 26.6%, respectively.

In ASCENDE-RT, strictures accounted for approximately half of all grade 3 GU events in the LDR-PB boost arm, and many involved the membranous urethra. Relevant to this, the study protocol specified a generous inferior margin in defining the brachytherapy treatment volume because of uncertainty regarding the location of the prostatic apex on (previous generation) TRUS imaging, resulting in high doses being given to significant volumes of normal tissue inferior to the prostate. In addition, the inferior borders of the pelvic EBRT fields typically extended to the ischial tuberosities, thus a large proportion of the membranous urethra typically received the entire 46 Gy before implant.

## Potential mechanisms for improving the therapeutic ratio

Two important facts emerge from ASCENDE-RT: compared with an additional 32 Gy of EBRT, using an LDR-PB boost halved the rate of biochemical failure (see our companion article [17]) and increased the incidence of moderate and severe GU adverse effects. Both results are consistent with the hypothesis that an LDR-PB boost delivers a substantially higher biologically effective dose. Technical changes may have the potential to reduce the incidence and severity of adverse effects while maintaining the gain in b-PFS. Specifically, using magnetic resonance imaging (MRI) for treatment planning or exploiting the improved image quality of newer-generation ultrasound equipment should allow a reduction in dose to the membranous urethra. Reducing the prescription dose and/or reducing the proportion of the intraprostatic volume that receives ultra-high doses (>150% of prescription) may reduce the morbidity. Using multiparametric MRI to identify the dominant intraprostatic lesion and limiting ultra-high doses to the dominant intraprostatic lesion may also be helpful. The therapeutic ratio may also be improved by treating smaller volumes with EBRT or even omitting EBRT entirely, depending on risk factors.

Finally, although the therapeutic ratio of LDR-PB may be improved by better imaging and more refined dose distributions, there is some evidence that the use of an HDR-PB boost to provide dose escalation may provide similar efficacy with fewer adverse effects than an LDR-PB boost (23-25), although this latter conjecture is not

supported by the results of the large SEER-based study discussed above (22) and remains a subject for further investigation.

## Study limitations

Although baseline IPSS predicted for late GU toxicity, this result arises from a post hoc analysis and is prone to α error because several combinations of variables with a priori–defined cut points were included in the analysis. Erectile function and sexual activity were physician-reported in this trial, which is inferior to patient-reported outcomes for these endpoints. Centralized real-time review of radiation therapy was not included in the protocol. The optimal duration of ADT and the role of elective nodal irradiation are still not clearly defined and may differ for intermediate- and high-risk patients (26-28). Although encouraged, only 40% of DE-EBRT patients had fiducial markers placed for image guidance. Intensity modulated radiation therapy was not used, and it is possible that toxicity would have been lower if it had (29). Although this was a multicenter trial, 93% of trial subjects were accrued from 4 centers that share a single LDR-PB planning/treatment algorithm, which differs in some potentially relevant details from those used by other high-volume LDR-PB programs (30). This trial and the radiation therapy EBRT techniques it used were from the early 2000s, when the trial protocol was designed. The protocol specified many details in regard to technique and planning as outlined in the Supplemental Online Material (available at www.redjournal.org); however, specific dose-volume histogram criteria were not specified in the protocol with respect to the external beam component, because there was no local consensus at the time of the study design. The dose-volume histogram criteria for external beam were left to individual centers. Some prespecified anticipated toxicity outcomes, such as obstruction and catheterization, were collected as categorical variables (eg, catheter duration 5-10 days or 10-20 days), and as such could not be summarized as continuous variables for median and interquartile ranges.

## Conclusions

The incidence and prevalence of moderate to severe GU morbidity, the frequency and severity of urinary incontinence, and the need for late catheterization were all higher in men treated with LDR-PB compared with DE-EBRT. On the other hand, men randomized to the DE-EBRT arm were also twice as likely to experience biochemical recurrence, and >80% of men who received LDR-PB reported minimal or no GU side effects at 5 years' follow-up.

Despite future efforts intended to reduce treatment-related adverse effects, an increased risk may necessarily accompany the reductions in treatment failure associated with delivering higher doses. Therefore, patient selection, particularly regarding life expectancy and pretreatment

urinary function, are important considerations when recommending a brachytherapy boost.

# References

1. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67-74.

2. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomized controlled trial. *Lancet Oncol* 2007; 8:475-487.

3. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-1996.

4. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. *JAMA* 2005;294:1233-1239.

5. Pollack A, Hanlon AL, Horwitz EM, et al. Prostate cancer radiotherapy dose response: An update of the Fox Chase experience. *J Urol* 2004;171:1132-1136.

6. 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.

7. 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.

8. Albert M, Tempany CM, Schultz D, et al. Late genitourinary and gastrointestinal toxicity after magnetic resonance image-guided prostate brachytherapy with or without neoadjuvant external beam radiation therapy. *Cancer* 2003;98:949-954.

9. Wong WW, Vora SA, Schild SE, et al. Radiation dose escalation for localized prostate cancer intensity-modulated radiotherapy versus permanent transperineal brachytherapy. *Cancer* 2009;115:5596-5606.

10. Spratt DE, Zumsteg ZS, Ghadjar P, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. *BJU Int* 2014;114:360-367.

11. Hurwitz MD, Halabi S, Archer L, et al. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: Long-term results of CALGB99809. *Cancer* 2011;117:5579-5588.

12. Lawton CA, Yan Y, Lee WR, et al. Long-term results of an RTOG phase II trial (00-19) of external-beam radiation therapy combined with permanent source brachytherapy for intermediate-risk clinically localized adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2012;82:e795-e801.

13. Aluwini S, VanRooij PH, Kirkels WJ, et al. High-dose-rate brachytherapy and external-beam radiotherapy for hormone-naïve low- and intermediate-risk prostate cancer: A 7-year experience. *Int J Radiat Oncol Biol Phys* 2012;83:1480-1485.

14. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing Iridium implant 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.

15. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103: 217-222.

16. Stock RG, Yalamanchi S, Hall SJ, et al. Impact of hormonal therapy on intermediate risk prostate cancer treated with combination brachytherapy and external beam irradiation. *J Urol* 2010;183:546-551.

17. Morris WJ, Tyldesley S, Rodda S, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;98:275-285.

18. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010;28:1106-1111.

19. Agoston P, Major T, Fröhlich G, et al. Moderate dose escalation with single-fraction high-dose-rate brachytherapy boost for clinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the first 100 consecutively treated patients. *Brachytherapy* 2011;10: 376-384.

20. Ghadjar P, Rentsch CA, Isaak B, et al. Urethral toxicity vs. cancer control—lessons to be learned from high-dose-rate brachytherapy combined with intensity-modulated radiation therapy in intermediate- and high-risk prostate cancer. *Brachytherapy* 2011;10:286-294.

21. Keyes M, Miller S, Pickles T, et al. Late urinary side effects 10 years after low-dose-rate prostate brachytherapy: Population-based results from a multiphysician practice treating with a standardized protocol and uniform dosimetric goals. *Int J Radiat Oncol Biol Phys* 2014;90: 570-578.

22. Tward JD, Jarosek RN, Chu H, et al. Time course and accumulated risk of severe urinary adverse events after high- versus low-dose-rate prostate brachytherapy with and without external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2016;95:1443-1453.

23. Martinez AA, Demanes J, Vargas C, et al. High-dose-rate prostate brachytherapy: An excellent accelerated-hypofractionated treatment for favorable prostate cancer. *Am J Clin Oncol* 2010;33:481-488.

24. Morton GC, Hoskins PJ. Brachytherapy: Current status and future strategies—can high dose rate replace low dose rate and external beam radiotherapy? *Clin Oncol (R Coll Radiol)* 2013;25:474-482.

25. Morton GC. High-dose-rate brachytherapy boost for prostate cancer: Rationale and technique. *J Contemp Brachytherapy* 2014;6: 323-330.

26. RTOG Foundation. 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: www.rtog.org/ClinicalTrials/ProtocolTable.aspx. Accessed February 18, 2015.

27. RTOG Foundation. 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: www.rtog.org/ClinicalTrials/ProtocolTable.asp. Accessed February 18, 2015.

28. Nabid A, Carrier N, Martin A. High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study. In: ASCO Annual Meeting Proceedings; 2013. February. Vol. 31, No. 6_suppl, p. 3.

29. Al-Mamgani A, Heemsbergen WD, Peeters ST, 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.