Grand Rounds in UROLOGY™

PRESENTS

Next Generation Brachytherapy for Ablation

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- None

Indisputable Truth #1 – For localized prostate cancer Higher radiation dose = better cancer outcomes

- Radiation dose escalation improves biochemical control (Level 1 – multiple RCTs), freedom from local recurrence (multiple RCTs), freedom from salvage therapy (multiple RCTs).

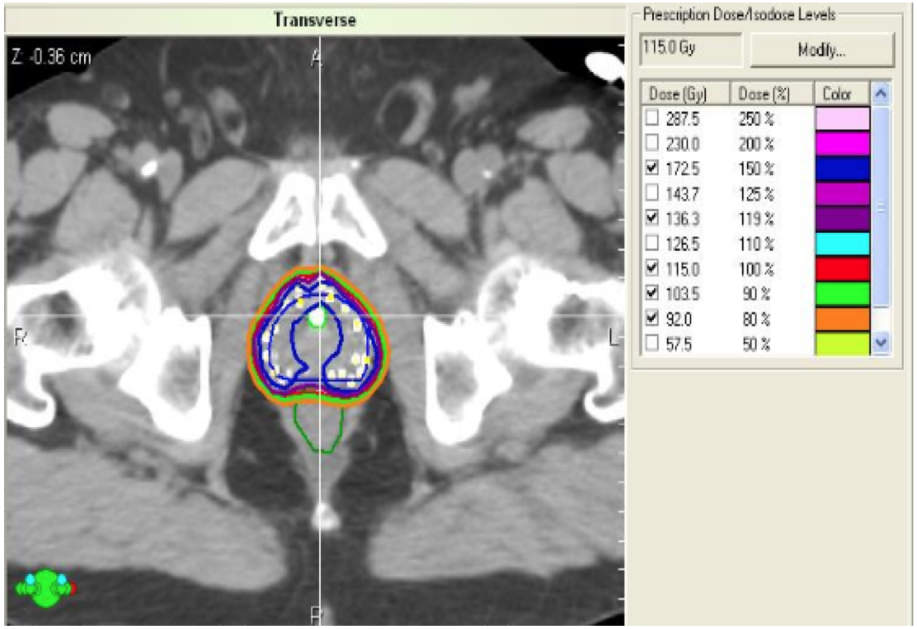
- Radiation dose escalation improves freedom from distant metastases (Level 1 – RTOG 0126)

- In select patients, dose escalation **may** also improve disease-specific and overall survival (prospective post-hoc and retrospective analyses).

- An upper limit to this effect has yet to be identified

Indisputable Truth #2

- Prostate brachytherapy is the most conformal and effective method for delivering dose-escalated radiation therapy to the prostate.

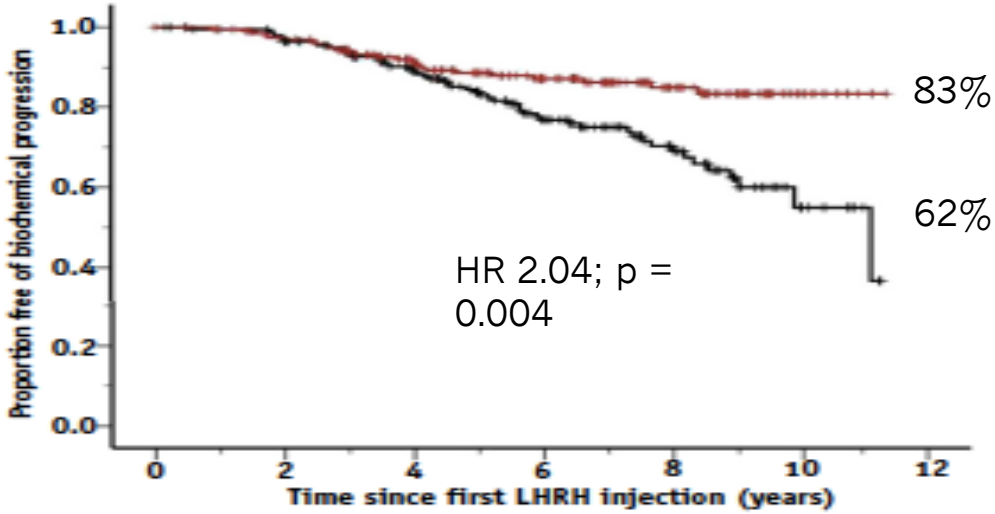


Cs-131 Monotherapy Post-Implant Dosimetry

Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) Trial

- Patients: NCCN intermediate or high risk prostate cancer
- Intervention:
  - All: 12 months LHRH agonist + 4-weeks oral antiandrogen (8-months neoadjuvant) → 46 Gy/23 pelvis
  - Randomized: External beam (32 Gy/16) vs. LDR brachytherapy (I-125 115 Gy) boost
- Endpoints
  - Primary: bPFS
  - Secondary: OS, prostate cancer specific survival, metastases-free survival, toxicity, QOL
- Statistics: Assume ≧ 15% improvement in bPFS (nadir PSA + 2 ng/ml) at 6.5 years from randomization. Target = 400 patients.

ASCENDE-RT: Brachytherapy improves bPFS compared to dose escalated EBRT

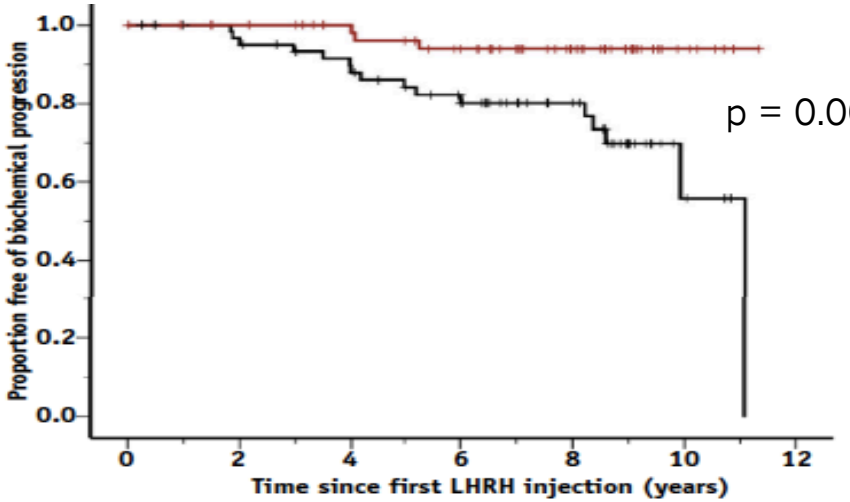


Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	186	168	145	119	93	74	52	27	11
LDR-PB	198	184	168	147	127	106	86	59	38	14

Morris et al. Int J Rad Bio Phys 2017

ASCENDE-RT: Brachytherapy improves bPFS compared to dose escalated EBRT – Intermediate Risk Subset

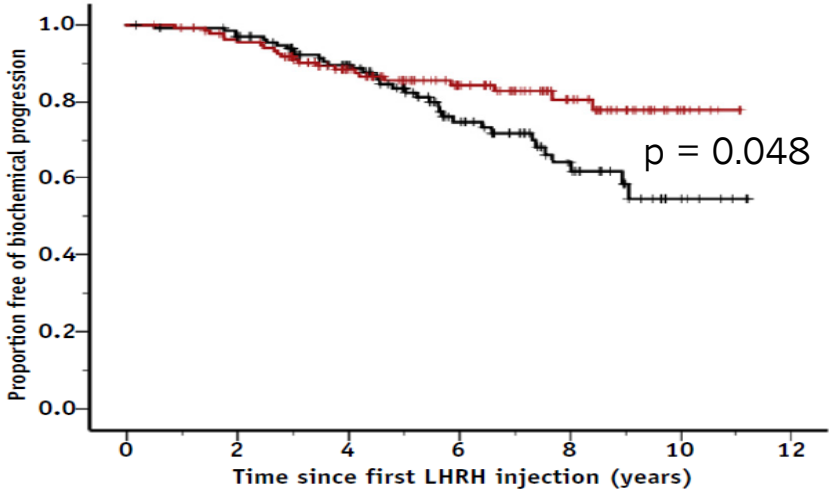


Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	63	57	54	49	43	38	30	25	12	4
LDR-PB	59	55	54	50	47	42	35	26	7	6

Morris et al. Int J Rad Bio Phys 2017

ASCENDE-RT: Brachytherapy improves bPFS compared to dose escalated EBRT – High Risk Subset



Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	137	129	114	96	76	55	44	27	15	7
LDR-PB	139	128	114	97	80	64	51	33	21	8

Morris et al. Int J Rad Bio Phys 2017

ASCENDE-RT: No statistically significant differences in Distant Metastases, Disease-Specific Survival, or Overall Survival

Analysis	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)
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)

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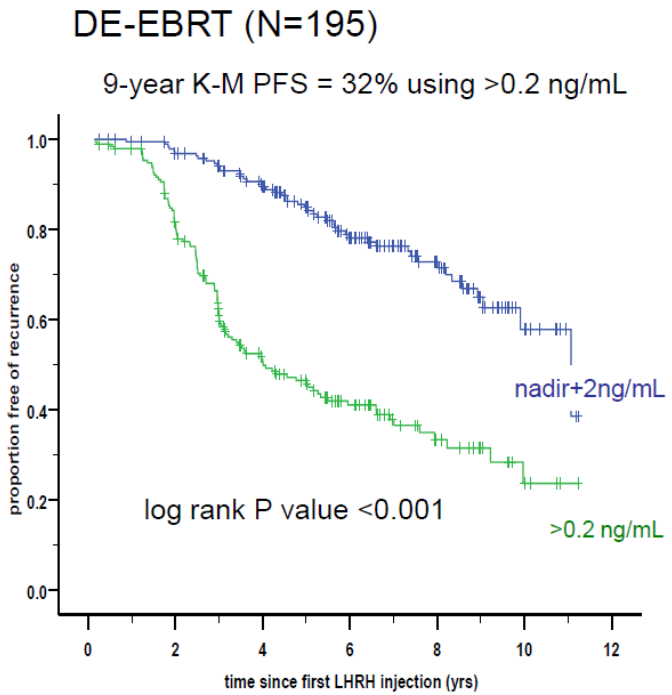
ASCENDE-RT: No difference in Distant Metastases, Disease-Specific Survival, or Overall Survival

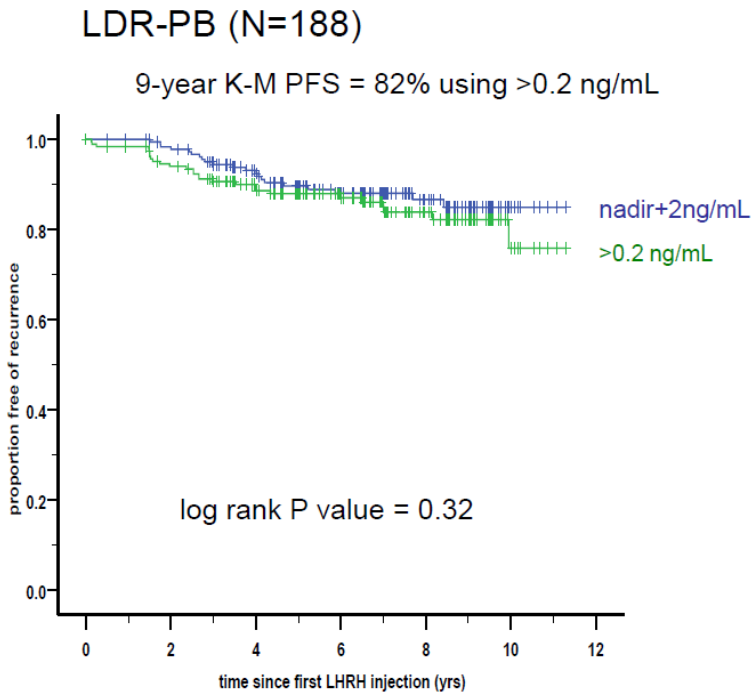
Table 4 Univariate and multivariable analysis (Cox model; backwards: conditional) for all-cause mortality

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**§

Morris et al. Int J Rad Bio Phys 2017

ASCENDE-RT: FFBF by PSA definition





ASCENDE-RT using PSA <0.2 ng/mL

Kaplan-Meier (95% CI)		By treatment received (N=383)	
		DE-EBRT (N=195)	LDR-PB (N=188)
b-PFS	5 yr	46.5 (±7.6)	87.9 (±5.0)
	7 yr	37.7 (±8.0)	86.0 (±5.6)
	9 yr	**31.5 (±8.8)**	**82.2 (±7.0)**

ARS Questions for Discussion

For locally advanced intact prostate cancer, prospective randomized trials have demonstrated the following benefits from dose-escalation:

A. Biochemical Control
B. Distant Metastases
C. Freedom from Salvage Therapy
D. Grade 3 or higher toxicity
E. Disease specific survival

ARS Question for Discussion

Which of the following might improve the therapeutic ratio when using prostate brachytherapy for prostate dose escalation?

A. Multi-parametric MRI integration
B. Advanced PET Radiotracer Imaging
C. Differential radiation dosing (focal therapy)
D. Intensification of anti-androgen therapy
E. All of the above