BC CANCER
Provincial Health Services Authority

Does RT favor RP in long term Quality of Life?

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Disclosures

- Advisory Board/honoraria: Varian
- Advisory Board: Breast Microseed
- Speaker Honoraria: Abbvie
- Speaker Honoraria: Sanofi
- Research Funding: Ferring

Background Issues

- Non lethal prostate cancer is increasingly managed with surveillance
- Potentially lethal prostate cancer requires multi-modality treatment
  - RP +/- RT +/- ADT
  - RT + ADT +/- BT
- QOL depends on the combination and timing of modalities
- Patient-reported outcomes rare
- Variety of instruments available

Program

- Level One evidence from ProtecT
- Origin of tri-modality
- Level One evidence from Ascende RT
- Prospective data base comparing modalities

ProtecT: *Hamby et al, NEJM 2016*

- Prospective randomized trial comparing surgery, radiation and active monitoring
- 1999-2009
- 1643 men with screen-detected PCa
  - 77% GS 6, 76% T1c, median PSA 4.5
- RT 74 Gy/37 fractions + 3-6 months ADT
- 55% of AM patients ended up treated

ProtecT results *Hamby et al, NEJM 2016*

	AM	RP	RT	
PCSM	8	5	4	0.7/1000 pt-years
DM	33	13	16	6.3 vs. 2.4 vs.3.0 pt-yrs
Dis Prog	112	46	46	23 vs. 8.9 vs. 9 pt-yrs

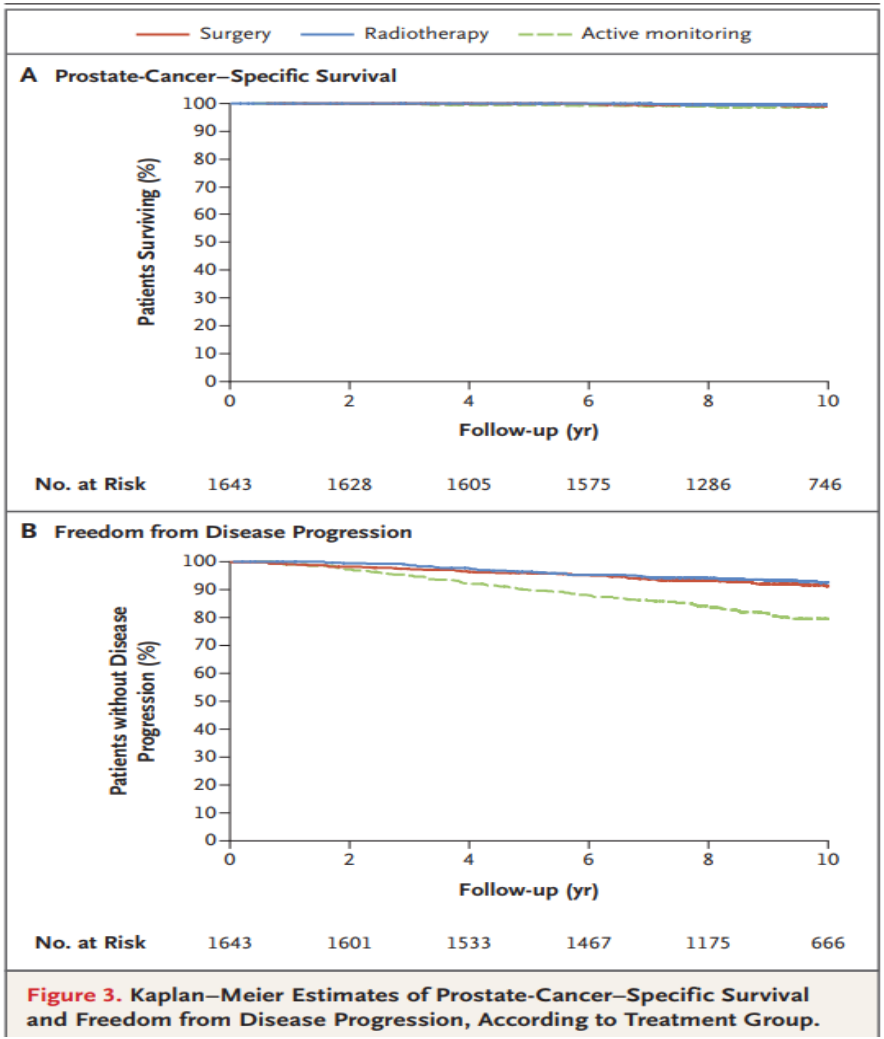


Figure 3. Kaplan–Meier Estimates of Prostate-Cancer–Specific Survival and Freedom from Disease Progression, According to Treatment Group.

PCSS

RP and EBRT
Active monitoring

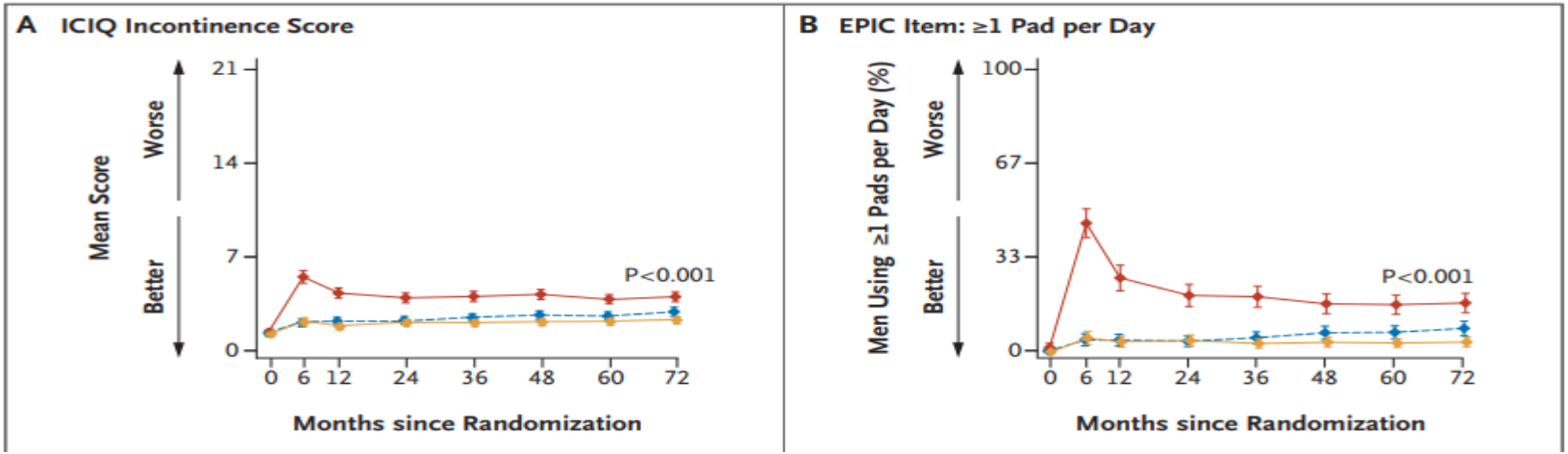
Freedom from Progression

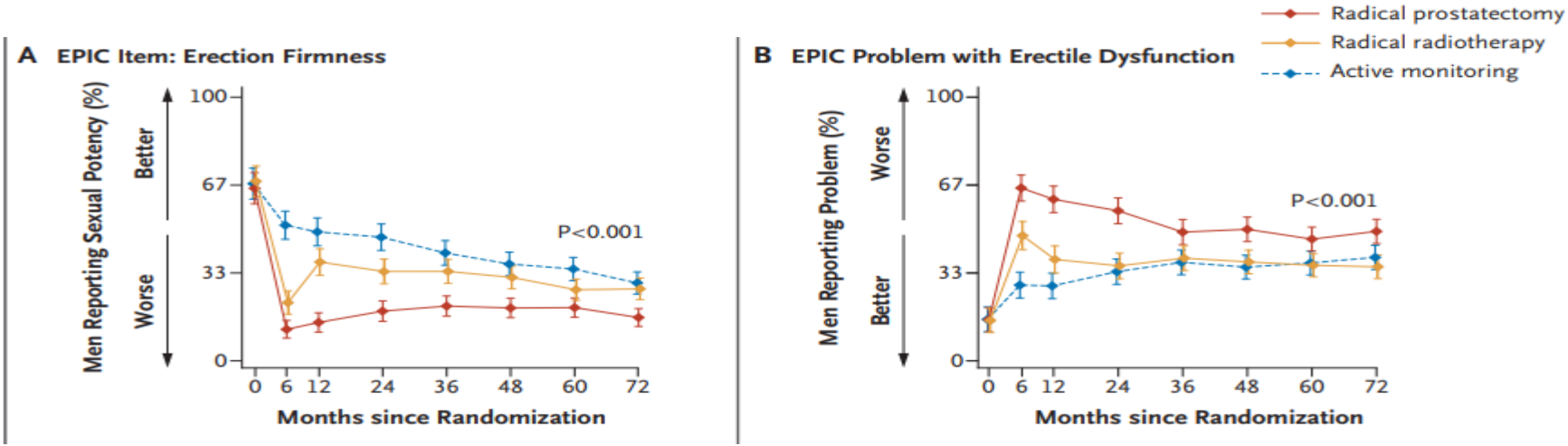
ProtecT QOL *Donovan et al NEJM 2016*

- Ca-related QOL @ 5 years
- Urinary Domain
  - EPIC and International Consultation on Incontinence Questionnaire (ICIQ)
- Sexual Domain: EPIC
- Bowel Domain: EPIC
- HR-QOL
  - SF-12, Anxiety and Depression (HADS), EORTC QLC-C30

ProtecT QOL results

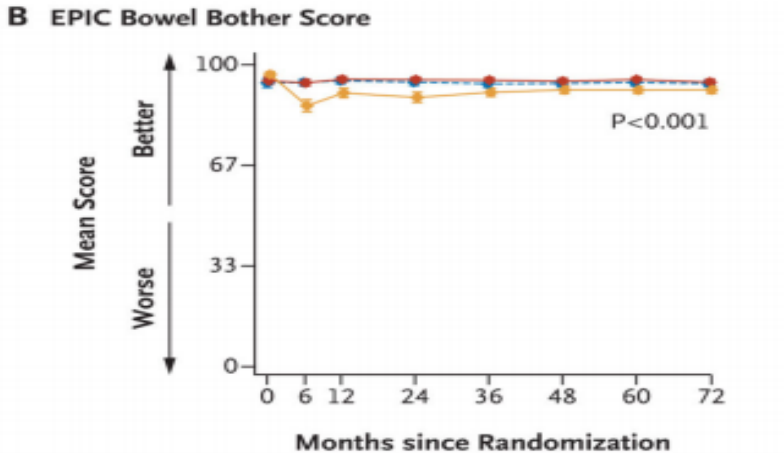
- RP greatest effect on sexual function and incontinence
- Remained worse throughout entire follow up period
- EBRT: sexual function worse at 6 months (all had ADT)
- AM: SF and UF both steadily decrease over time

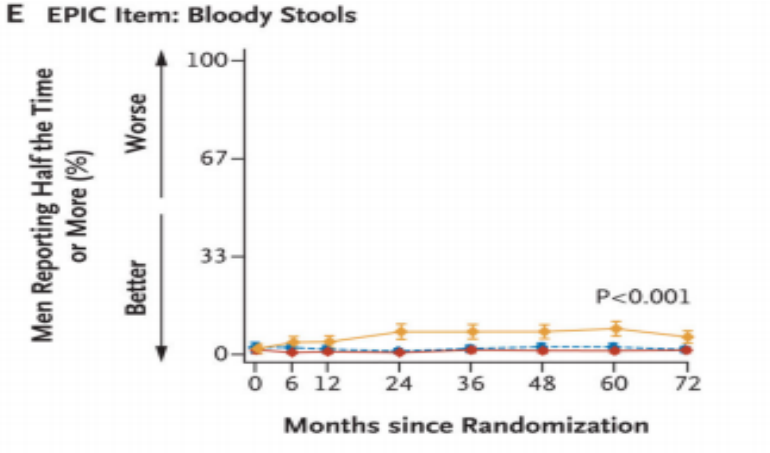

A ICIQ Incontinence Score
Mean Score
Worse
Better
21
14
7
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
B EPIC Item: ≥1 Pad per Day
Men Using ≥1 Pads per Day (%)
Worse
Better
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization


Radical prostatectomy
Radical radiotherapy
Active monitoring
A EPIC Item: Erection Firmness
Men Reporting Sexual Potency (%)
Better
Worse
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
B EPIC Problem with Erectile Dysfunction
Men Reporting Problem (%)
Worse
Better
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization

ProtecT QOL results, *Donovan et al, 2017*

- Bowel function:
  - Worst in RT patients at 6 months but recovered
  - Hematochezia continued to be a problem
  - Bowel bother and fecal incontinence recover and same in all modalities





But this is 74 Gy with short course ADT in a category of patients who mostly don’t need treatment

MULTI MODALITY REAL WORLD TREATMENT

High BED effect on outcome for Gleason 7-10 treated with BT *Stone et al IJROBP 2009*

- 1078 LDR BT (845 GS 7, 233 GS 8-10)
- Multi center: median follow up 46 months
- ADT in 62%: med duration 4 months
- EBRT in 58% (median BED 209 Gy vs. 155 Gy BT alone)

	<200 Gy	200-220	> 220 Gy	
n	645	199	234	
5-yr FFBF	76%	84%	88%	p<0.001
FFDM	92%		99%	
GS 8-10 FFBF	52%	86%	90%	p<0.001

Origin of trimodality

- Even with BED > 220 Gy, still need ADT for GS 8-10
  - 5-yr FFBF 96% with ADT vs. 78% without ADT p=0.001

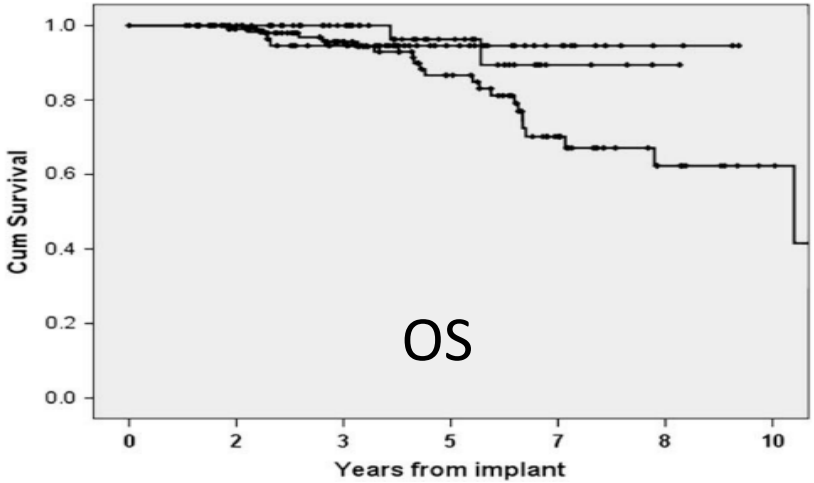


Fig. 3. Five-year survival by dose group for Gleason score 8–10: <200 Gy, 86.6%; 200–220 Gy, 89.4%; >220 Gy, 94.6% (p = 0.048). Cum = cumulative.

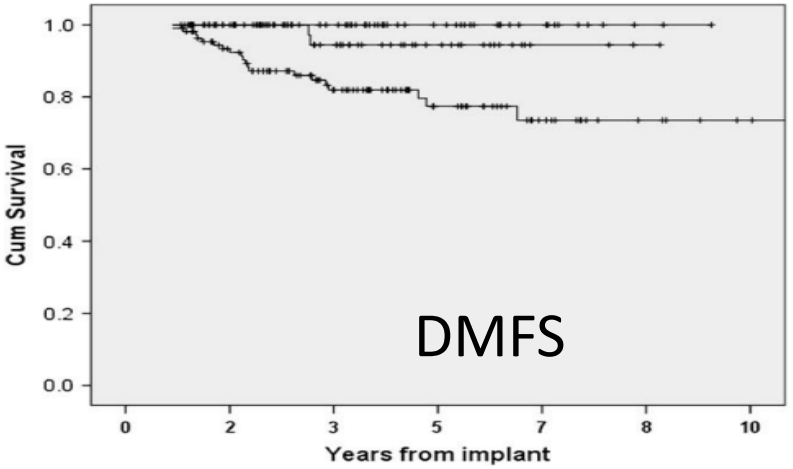


Fig. 2. Five-year freedom from metastases for Gleason score 8–10 by BED group (22 [9.4%] of 233 developed metastases): <200 Gy, 77.4%; 200–220 Gy, 94%; >220, 100% ($p < 0.001$). Cum = cumulative.

The New York Mount Sinai experience by Stock and Stone was the basis for the definitive Canadian randomized trial

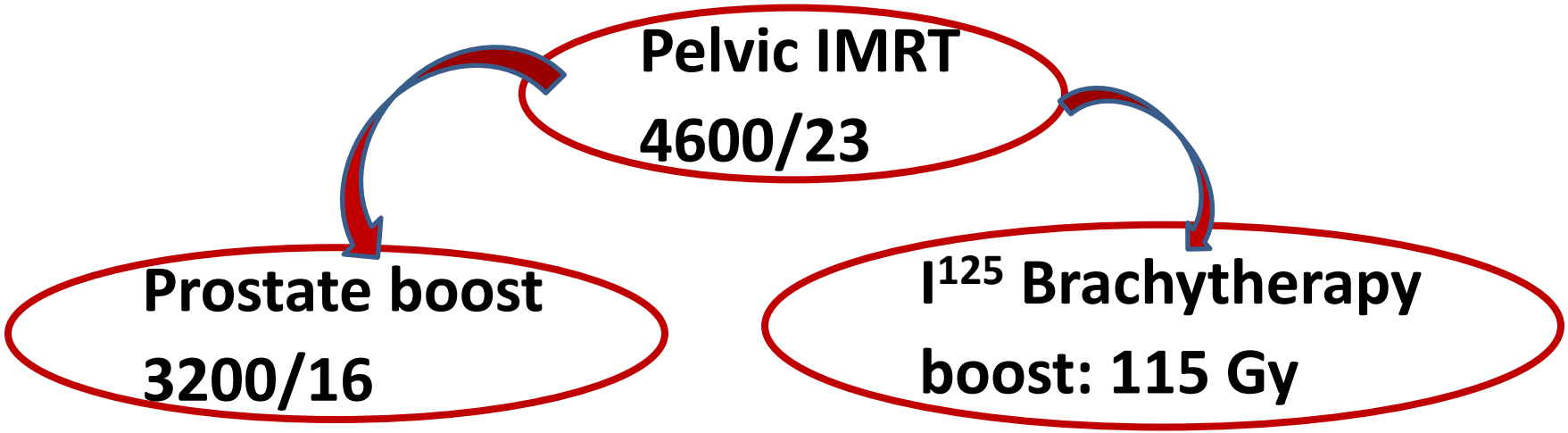
ASCENDE-RT

(ANDROGEN SUPPRESSION COMBINED WITH ELECTIVE NODAL DOSE ESCALATED RADIOTHERAPY)

Level One Evidence for benefit of Brachytherapy

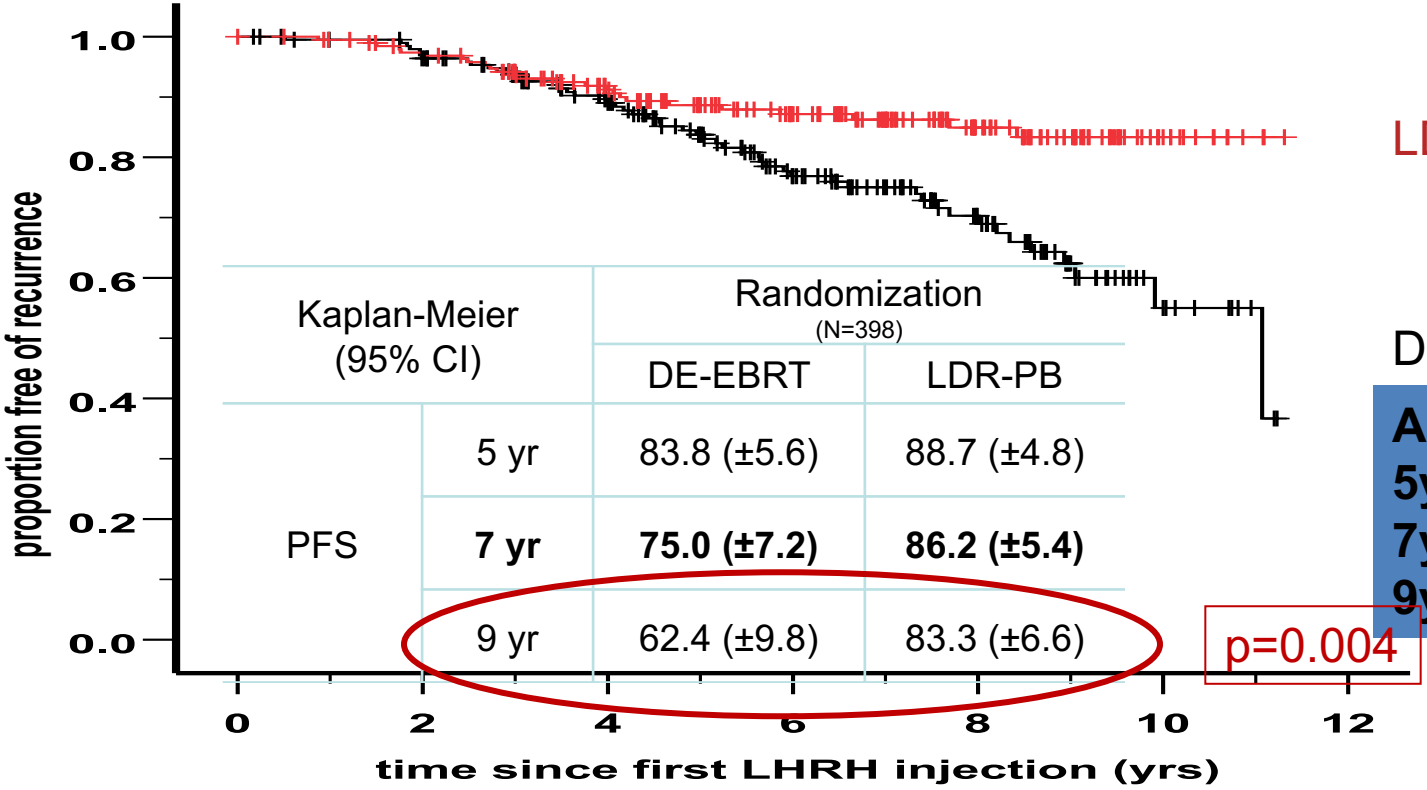
Canadian ASCENDE-RT *WJ Morris et al*

- Phase 3: 78 Gy vs. 46 Gy + LDR Brachytherapy
- n=398: follow up 5-11 years
  - High risk and high tier intermediate risk
  - 1 year ADT (8 month neoadj + 4 month concurrent/adjuvant)



Results: Biochemical PFS all patients

Intent-to-treat analysis of the primary endpoint



Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT	LDR-PB
PFS	5 yr	83.8 (±5.6)	88.7 (±4.8)
	7 yr	**75.0 (±7.2)**	**86.2 (±5.4)**
	9 yr	62.4 (±9.8)	83.3 (±6.6)

LDR-PB ARM

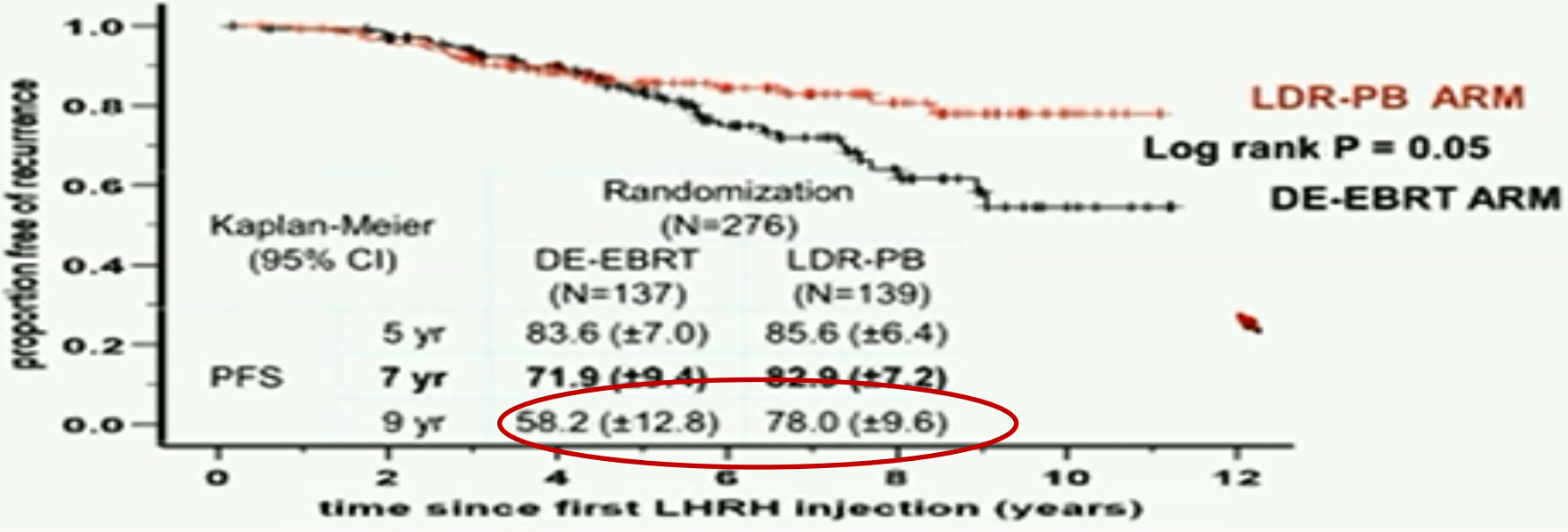
DE-EBRT ARM

Absolute difference
5y – 4.9%
7y – 11.2%
9y – 20.95%

p=0.004

PFS by NCCN Risk Group

High-risk stratum, N=276



9-year PSA Relapse Free Survival 58% vs.78%; p=0.05

Ascende Morbidity

- Randomization to 78 Gy vs. 46 Gy+brachy associated with 2X risk of BF at 6.5 yrs
- QOL data NOT collected after failure, so toxicity of salvage not considered when comparing the 2 arms
- 5-yr *cumulative* grade 3 GU 18% (RT+BT) vs. 5% (78 Gy)
- 5-yr *prevalence* of grade 3 GU toxicity 8.6% vs. 2.2%
- 5-yr prevalence of grade 3 GI 1%(RT+BT) vs. 2.2%
- 5-yr sexual function similar to baseline: 45% (RT+BT) vs. 37% (78 Gy)

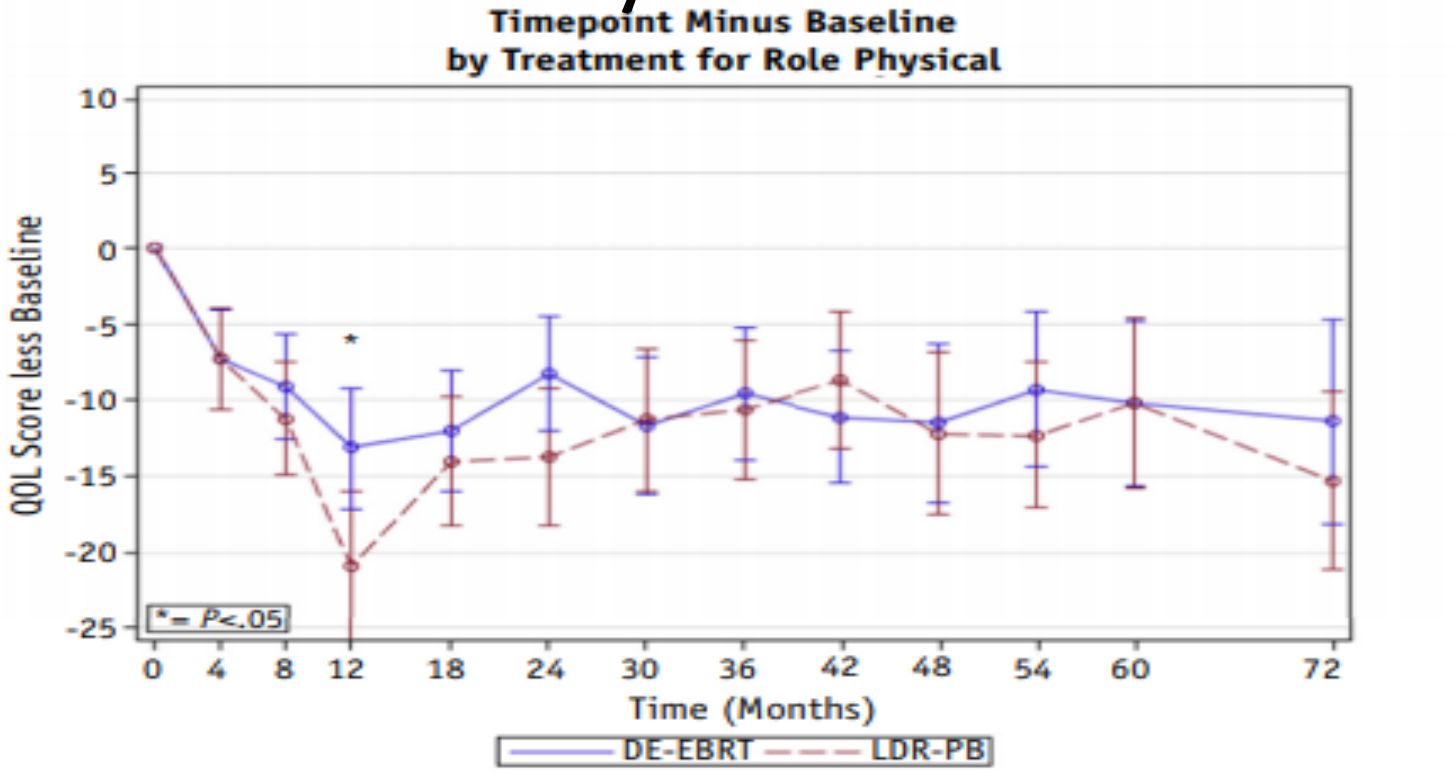
Ascende HRQOL: Patient reported outcomes: *Rodda et al IJROBP 2017*

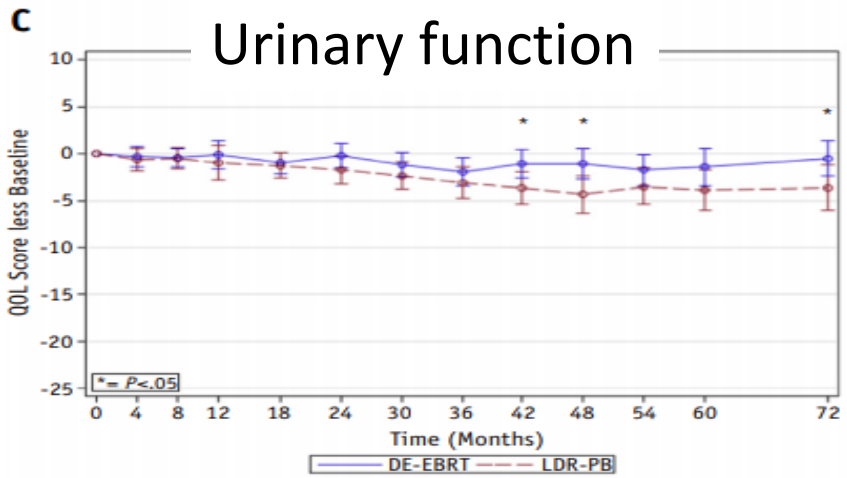
- Instrument: SF36 v2 plus urinary, bowel and SF domains
- Decline >10 points clinically significant
- Evaluated q4 months x 1 year then q6 months x 4 years then annually: 82-95% compliance
- @ 12 months larger drop in mean scores for RT+BT (~ 6 wks post implant)
- @ 6 years, sexual fn and urinary fn still worse for RT+BT, others similar.

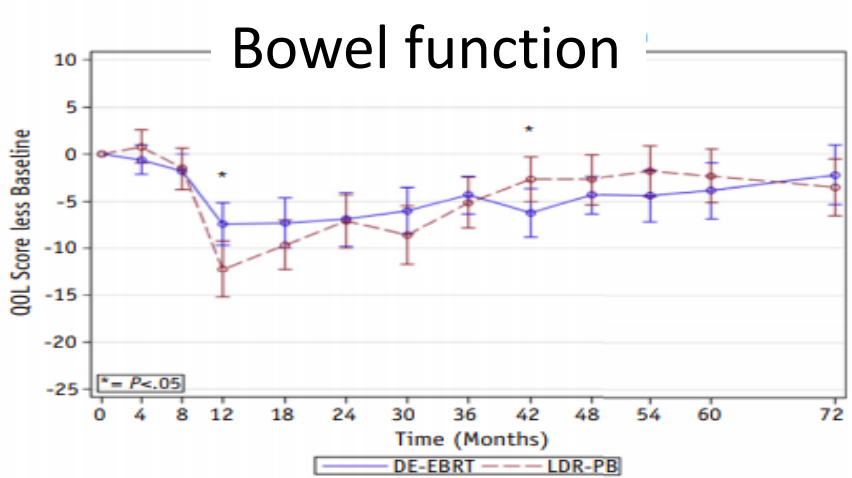
	12 mos*		5 years	
	78Gy	RT+BT	78 Gy	RT+BT
Physical fn	-7.4	-11.6	-7.7	-8.5
vitality	-7.5	-12.2	-2.2	-5.2
Physical role	-13.1	-20.9	-10.2	-10.2
General health	-0.9	-4.1	-0.9	-5.9
Social fn	-5.3	-8.0	-1.9	-1.9
Emotional role	-6.0	-6.2	-5.6	-2.9
Mental health	6.2	0.8	6.7	3.1

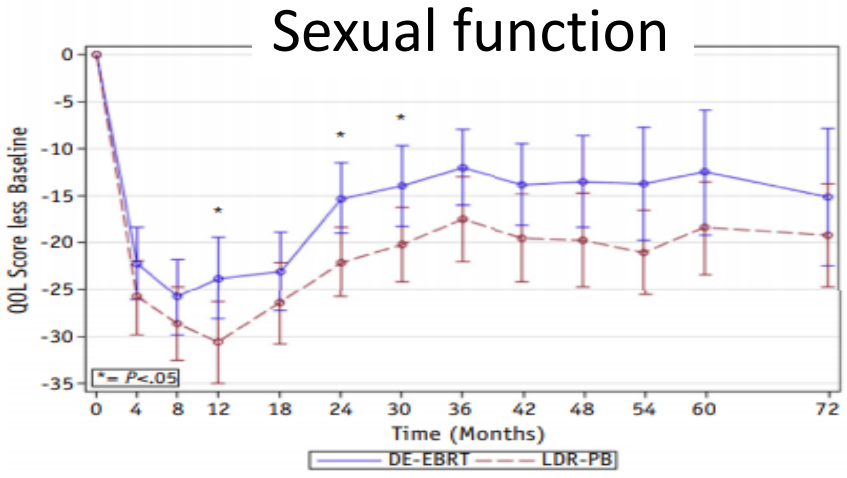
12 months is only 6 weeks after LDR BT

DE-EBRT vs. EBRT + BT
Physical role









PRO's for Ascende RT

LET’S BRING RP BACK INTO THE DISCUSSION

High Risk PCa

LDR+/-ADT, EBRT+/-ADT, RP+/-EBRT

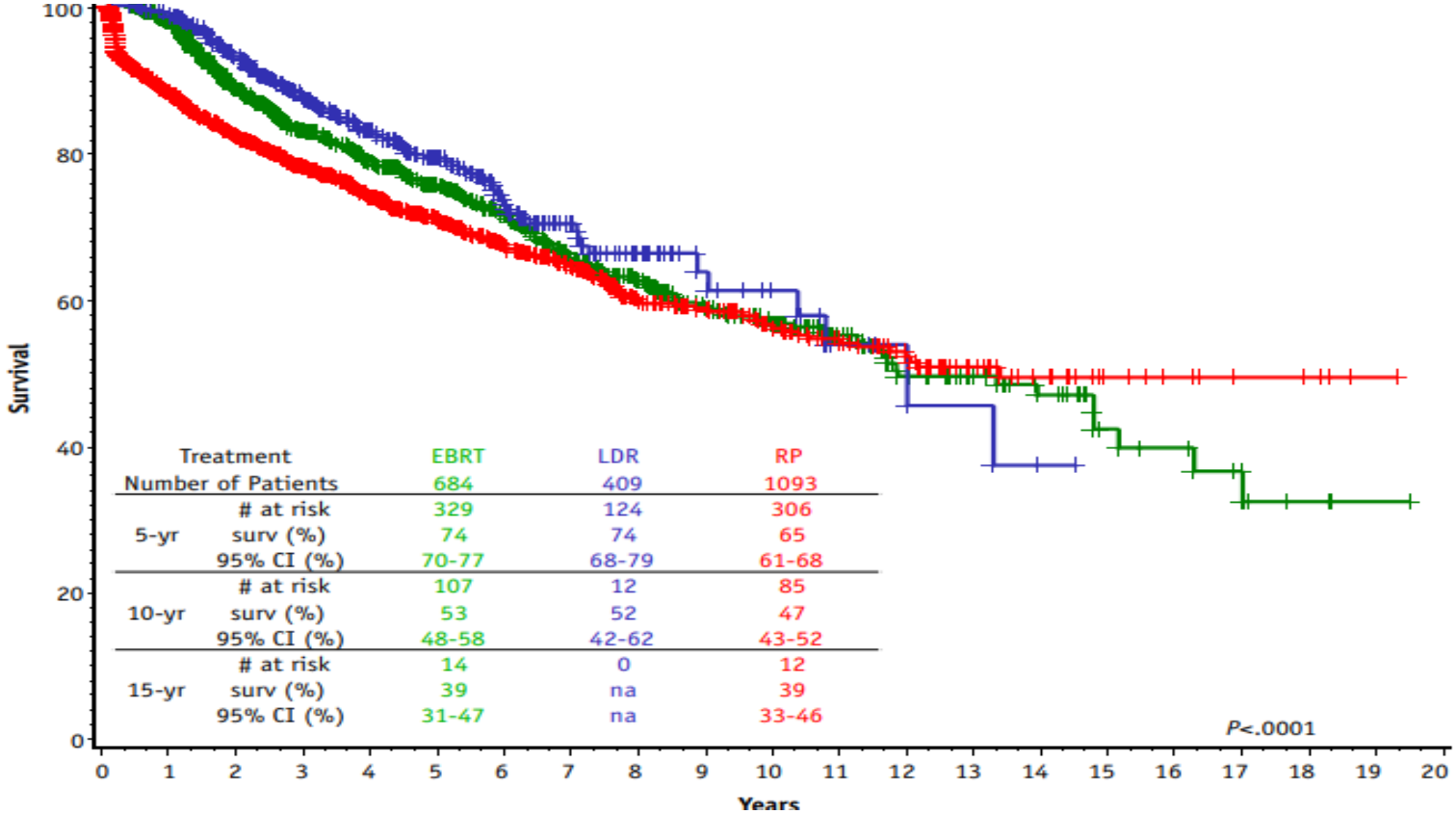
Ciezki et al IJROBP 2017

- Prospective data base 1996-2012
- n=2557, med follow up 63 months
- EBRT+/-ADT(n=734): 78 Gy/39 or 70 Gy/28
- RP+/-EBRT(n=1308): 56% open, 36% RARP (18% EBRT)
- LDR+/-ADT(n=515): 30-day D90 149 Gy (SD 21)

Baseline characteristics *Ciezki et al*

	EBRT	LDR	RP	
F-up	94	49	56	<0.0001
age	68	70	62	<0.0001
ADT	93%	53%	19%	<0.0001
PSA >20	36%	15%	15%	
T3	14%	0.4%	3%	<0.0001
GS 9-10	17%	11%	14%	<0.0001
2 IR	28%	48%	45%	<0.0001
≥ 1 HR	72%	52%	55%	

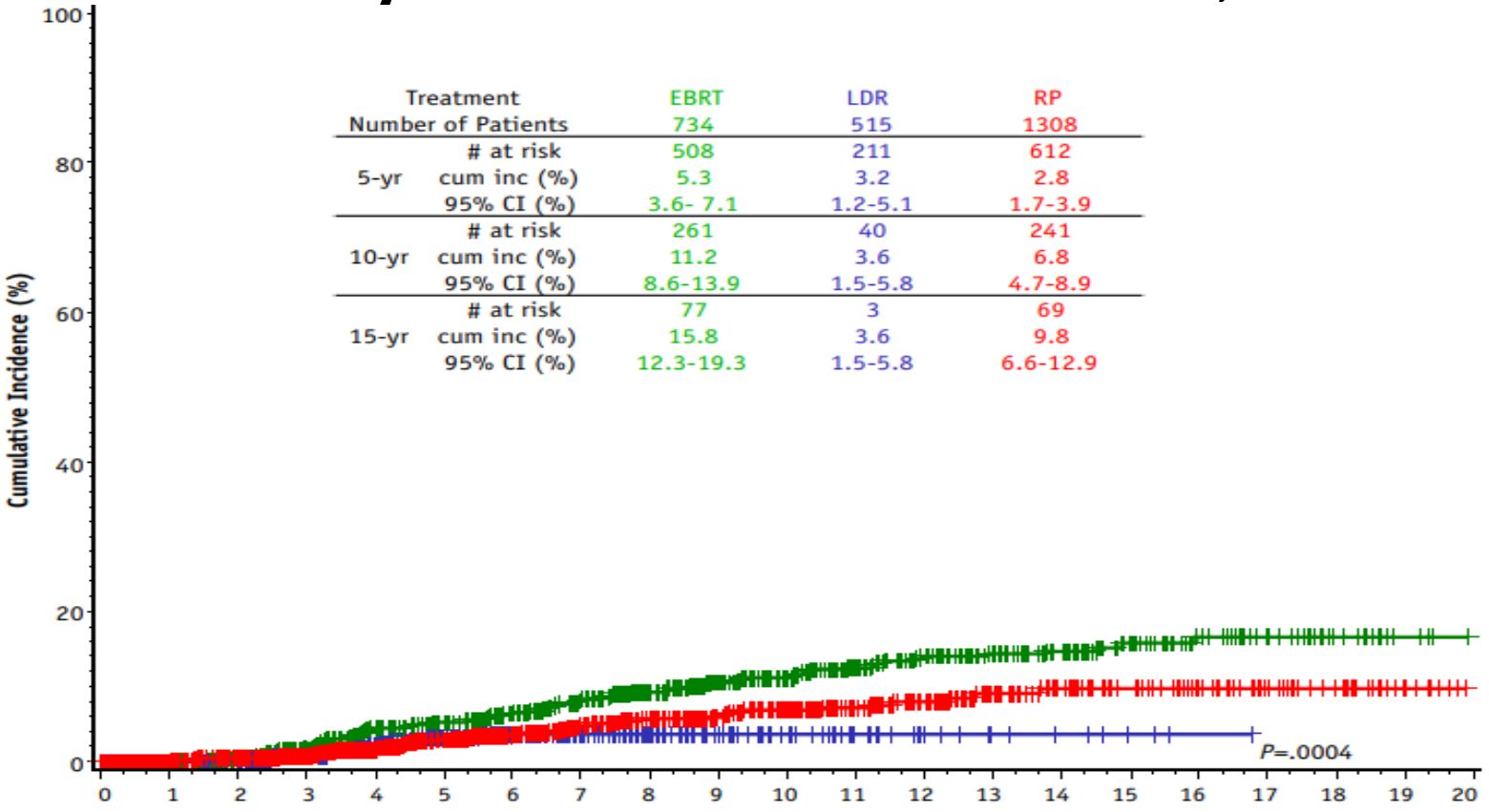
BRFS by treatment *Ciezki et al, 2017*



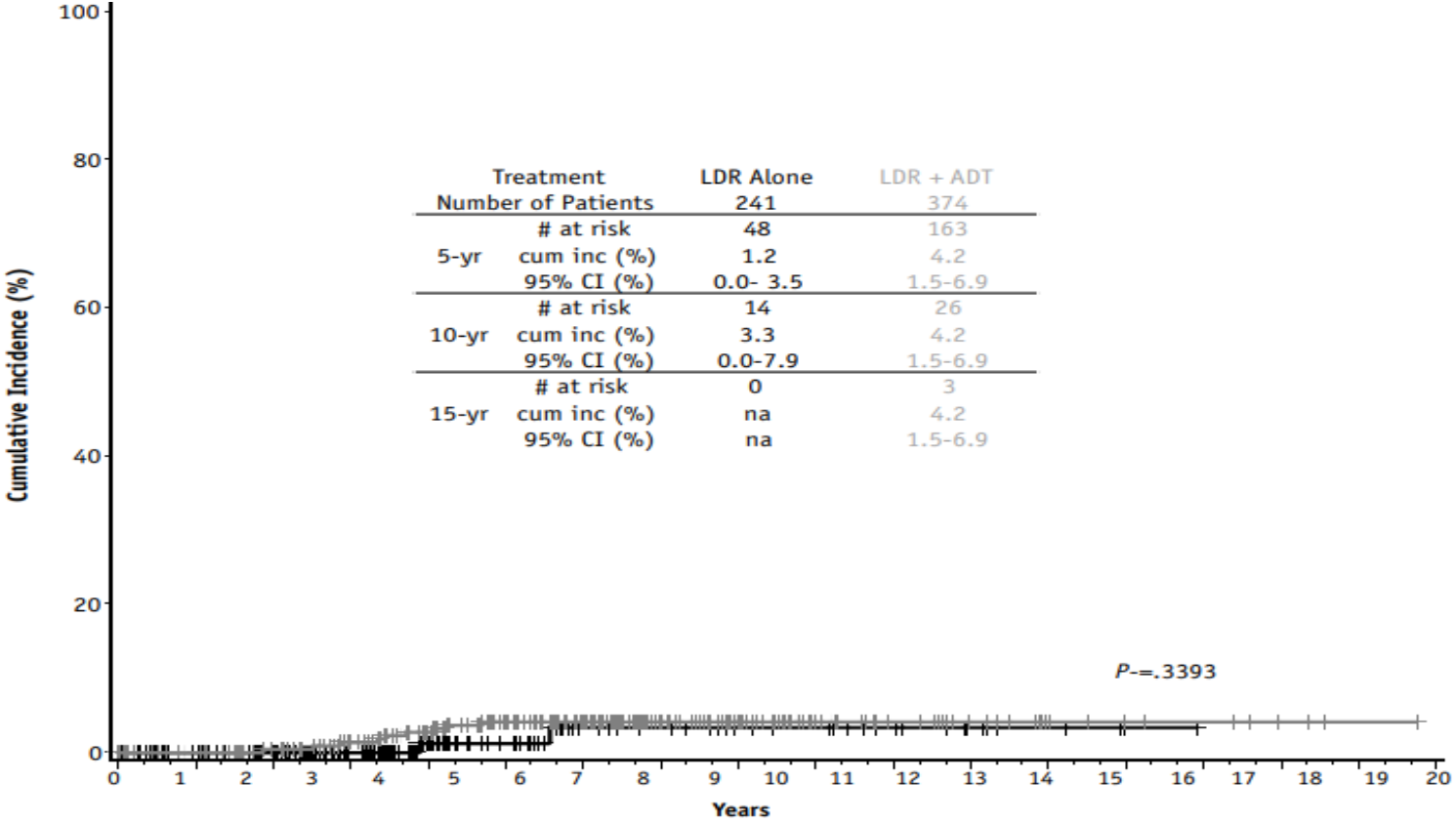
Treatment		EBRT	LDR	RP
Number of Patients		684	409	1093
5-yr	# at risk	329	124	306
	surv (%)	74	74	65
	95% CI (%)	70-77	68-79	61-68
10-yr	# at risk	107	12	85
	surv (%)	53	52	47
	95% CI (%)	48-58	42-62	43-52
15-yr	# at risk	14	0	12
	surv (%)	39	na	39
	95% CI (%)	31-47	na	33-46

PCSM by treatment *Ciezki et al, 2017*

Treatment		EBRT	LDR	RP
Number of Patients		734	515	1308
5-yr	# at risk	508	211	612
	cum inc (%)	5.3	3.2	2.8
	95% CI (%)	3.6- 7.1	1.2-5.1	1.7-3.9
10-yr	# at risk	261	40	241
	cum inc (%)	11.2	3.6	6.8
	95% CI (%)	8.6-13.9	1.5-5.8	4.7-8.9
15-yr	# at risk	77	3	69
	cum inc (%)	15.8	3.6	9.8
	95% CI (%)	12.3-19.3	1.5-5.8	6.6-12.9

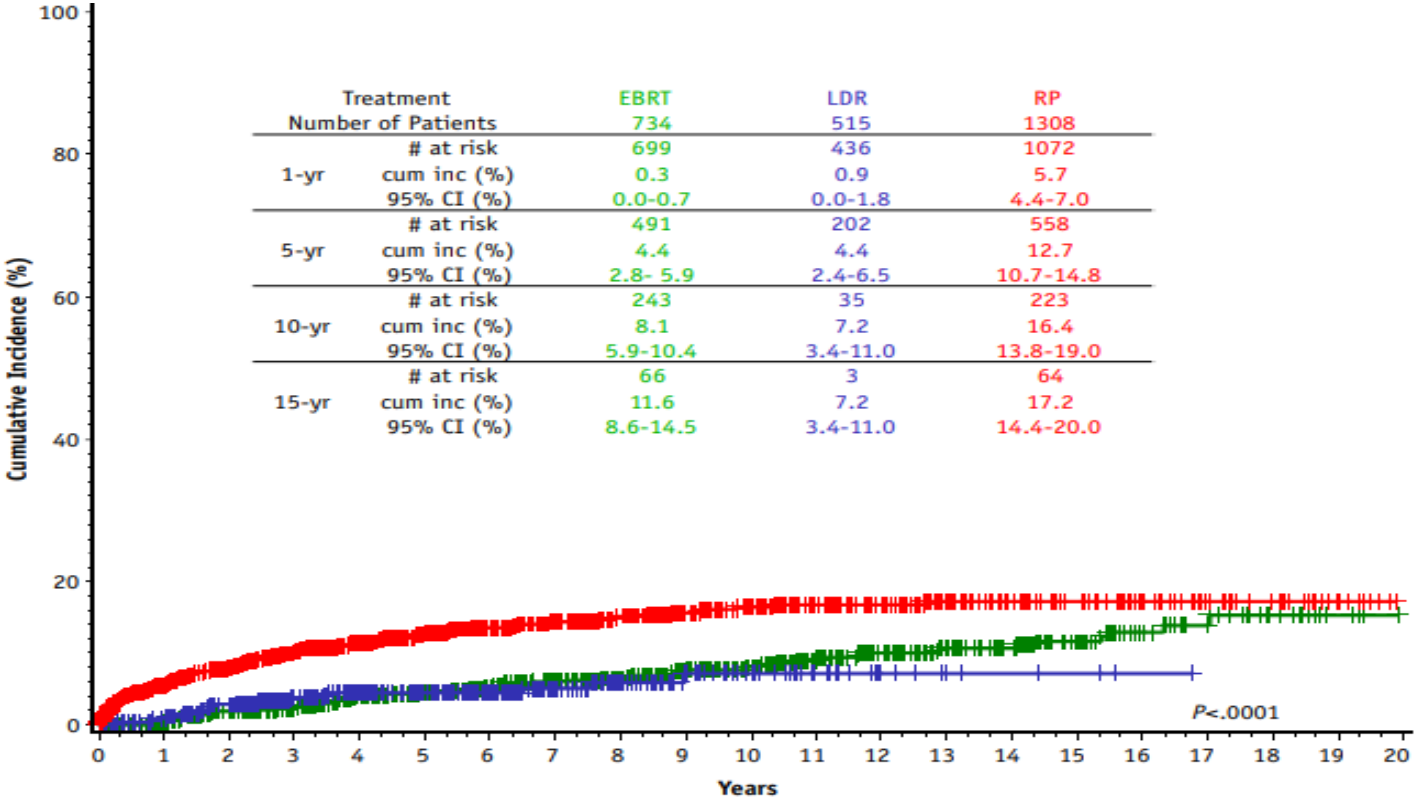


PCSM by use of ADT with BT *Ciezki et al, 2017*



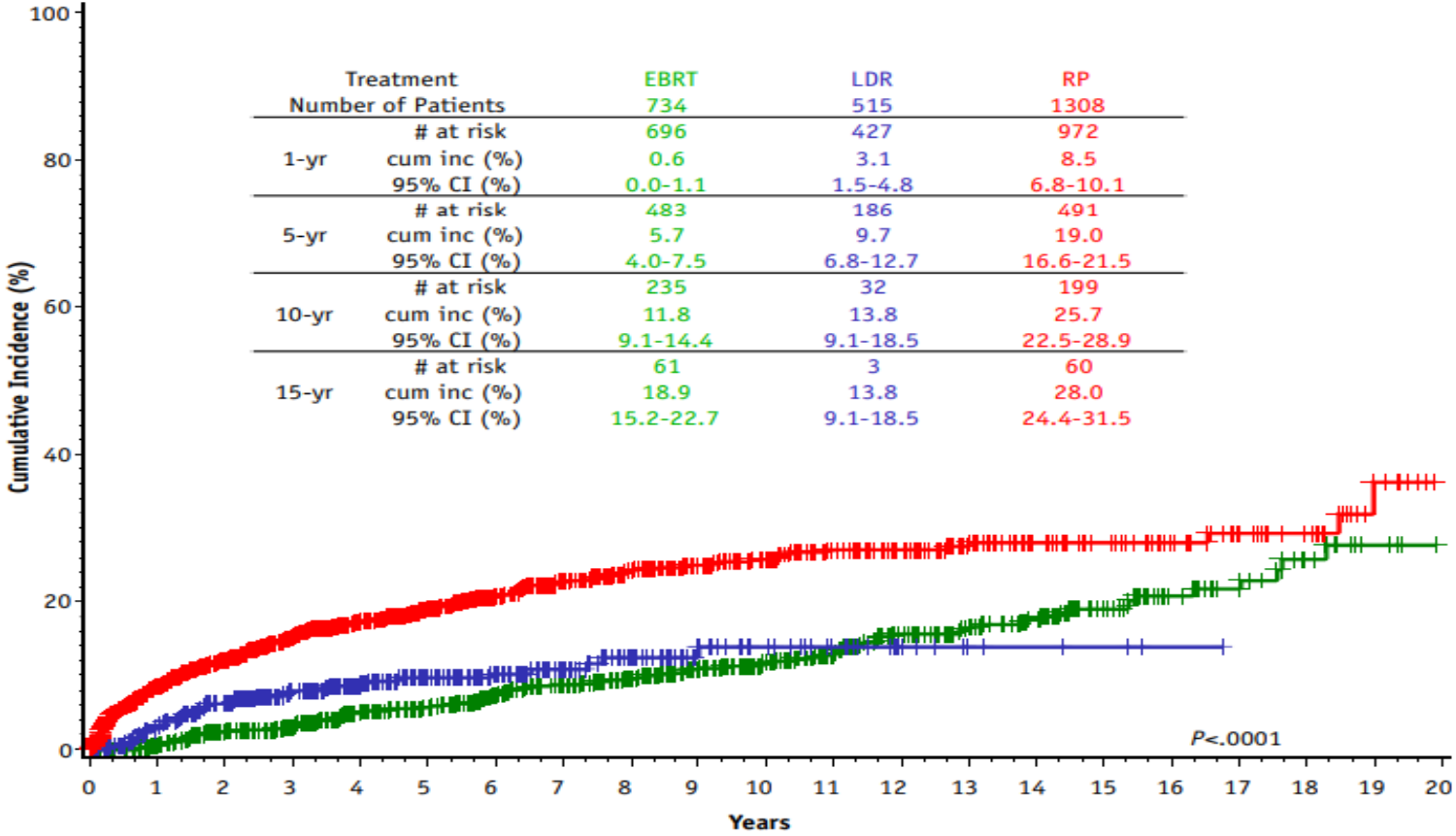
Treatment		LDR Alone	LDR + ADT
Number of Patients		241	374
5-yr	# at risk	48	163
	cum inc (%)	1.2	4.2
	95% CI (%)	0.0- 3.5	1.5-6.9
10-yr	# at risk	14	26
	cum inc (%)	3.3	4.2
	95% CI (%)	0.0-7.9	1.5-6.9
15-yr	# at risk	0	3
	cum inc (%)	na	4.2
	95% CI (%)	na	1.5-6.9

Grade 3 GU toxicity by treatment

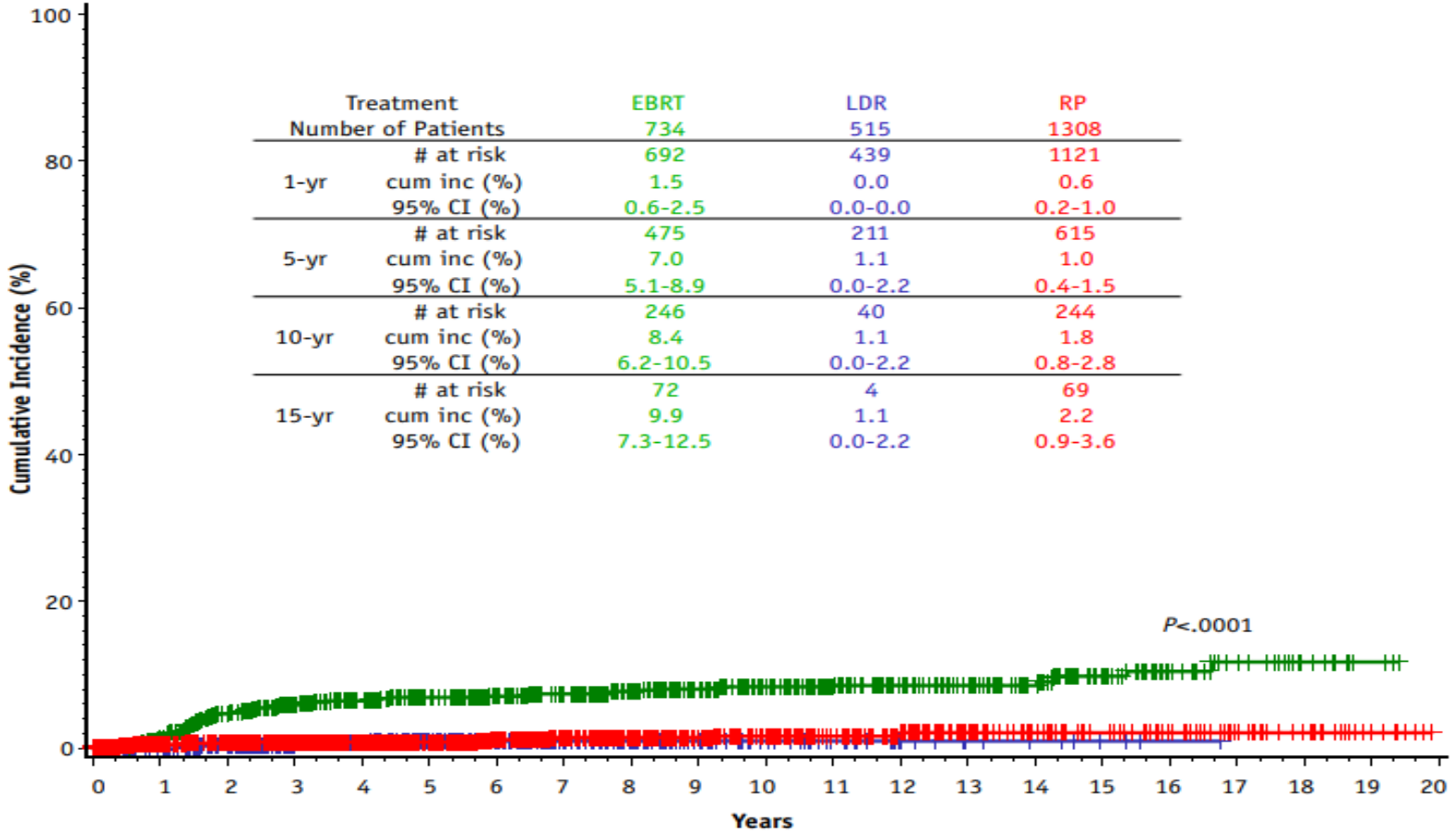


	Treatment	EBRT	LDR	RP
	Number of Patients	734	515	1308
1-yr	# at risk	699	436	1072
	cum inc (%)	0.3	0.9	5.7
	95% CI (%)	0.0-0.7	0.0-1.8	4.4-7.0
5-yr	# at risk	491	202	558
	cum inc (%)	4.4	4.4	12.7
	95% CI (%)	2.8- 5.9	2.4-6.5	10.7-14.8
10-yr	# at risk	243	35	223
	cum inc (%)	8.1	7.2	16.4
	95% CI (%)	5.9-10.4	3.4-11.0	13.8-19.0
15-yr	# at risk	66	3	64
	cum inc (%)	11.6	7.2	17.2
	95% CI (%)	8.6-14.5	3.4-11.0	14.4-20.0

Grade ≥ 2 GU toxicity by treatment



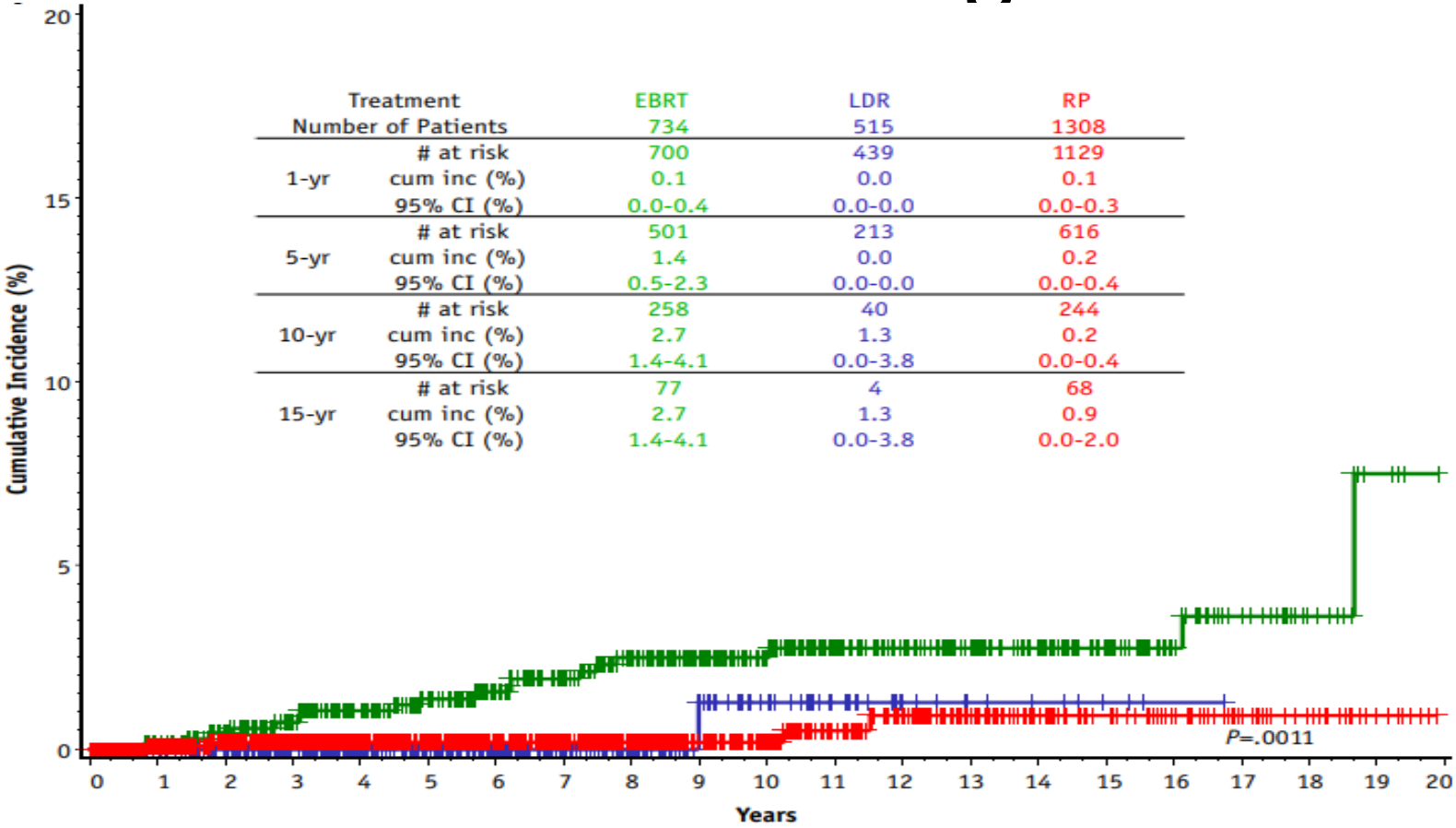
Grade ≥ 2 GI toxicity by treatment



	Treatment	EBRT	LDR	RP
	Number of Patients	734	515	1308
1-yr	# at risk	692	439	1121
	cum inc (%)	1.5	0.0	0.6
	95% CI (%)	0.6-2.5	0.0-0.0	0.2-1.0
5-yr	# at risk	475	211	615
	cum inc (%)	7.0	1.1	1.0
	95% CI (%)	5.1-8.9	0.0-2.2	0.4-1.5
10-yr	# at risk	246	40	244
	cum inc (%)	8.4	1.1	1.8
	95% CI (%)	6.2-10.5	0.0-2.2	0.8-2.8
15-yr	# at risk	72	4	69
	cum inc (%)	9.9	1.1	2.2
	95% CI (%)	7.3-12.5	0.0-2.2	0.9-3.6

Cumulative 2° malignancies

	Treatment	EBRT	LDR	RP
	Number of Patients	734	515	1308
1-yr	# at risk	700	439	1129
	cum inc (%)	0.1	0.0	0.1
	95% CI (%)	0.0-0.4	0.0-0.0	0.0-0.3
5-yr	# at risk	501	213	616
	cum inc (%)	1.4	0.0	0.2
	95% CI (%)	0.5-2.3	0.0-0.0	0.0-0.4
10-yr	# at risk	258	40	244
	cum inc (%)	2.7	1.3	0.2
	95% CI (%)	1.4-4.1	0.0-3.8	0.0-0.4
15-yr	# at risk	77	4	68
	cum inc (%)	2.7	1.3	0.9
	95% CI (%)	1.4-4.1	0.0-3.8	0.0-2.0



Efficacy/toxicity results *Ciezki et al, 2017*

	EBRT	BT	RP	p
BRFS-5 yr	74%	74%	65%	.0001
BRFS-10	53%	52%	47%	
cRFS-5 yr	85%	90%	89%	0.12
cRFS- 10	73%	76%	75%	
PCSM 5 yr	5.3%	3.2%	2.8%	.0004
PCSM 10	11.2%	3.6%	6.8%	
10 yr $\geq$ gr 3 GU	8.1%	7.2%	16.4%	<0.001
10 yr $\geq$ gr 3 GI	4.6%	1.1%	1.0%	<0.0001

Summary: Ciezki et al

- Not randomized
- BT group has shorter follow up (few beyond 10 years)
- BT alone not usually considered for HR
- GU toxicity for EBRT does not plateau and equals RP by 15 yrs

Conclusions

- Brachytherapy appears to be an ablative treatment equivalent to RP without as high a price of incontinence and sexual dysfunction
- Brachytherapy alone can’t do better than RP alone for HR disease
- For optimal results need the combination of ADT and EBRT with BT

Conclusions

- Tri-modality (ADT + EBRT + BT)is the most effective form of treatment for high risk prostate cancer
- When you add EBRT → increase bowel and GU effects (Ascende)
- Tri-modality may have a toxicity price: 5-8% persistent grade 3 GU with standard techniques
- Improve toxicity profile with improved technique: attention to sagittal imaging, MR planning, MR QA, HDR vs. LDR