Is ASCENDE-RT still pertinent?
Is LDR-PB obsolete?

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  - Oncura - a division GE Healthcare and the manufacturer RapidStrand® model 6711 125-Iodine
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- Speaking/travel fees from Varian corporation promoting RapidArc IMRT technology: 2008-2009
- PI for BC Cancer Foundation-sponsored Pilot Study of Focal LDR Brachytherapy: 2013-present

ASCENDE-RT

Androgen **S**uppression **C**ombined with **E**lective **N**odal and **D**ose **E**scalated **R**adiation **T**herapy

A RANDOMIZED TRIAL COMPARING LOW-DOSE-RATE BRACHYTHERAPY BOOST TO DOSE-ESCALATED EXTERNAL BEAM BOOST FOR HIGH- AND INTERMEDIATE-RISK PROSTATE CANCER

W. James Morris, Scott Tyldesley, Sree Rodda, Ross Halperin, Howard Pai, Michael McKenzie, Graeme Duncan, Mira Keyes, Gerard Morton, Jeremy Hamm, Nevin Murray

BC Cancer Agency: Vancouver, Vancouver Island, Southern Interior, and Fraser Valley Centres

Sunnybrook Cancer Centre and Princess Margaret Hospital, Toronto, Ontario

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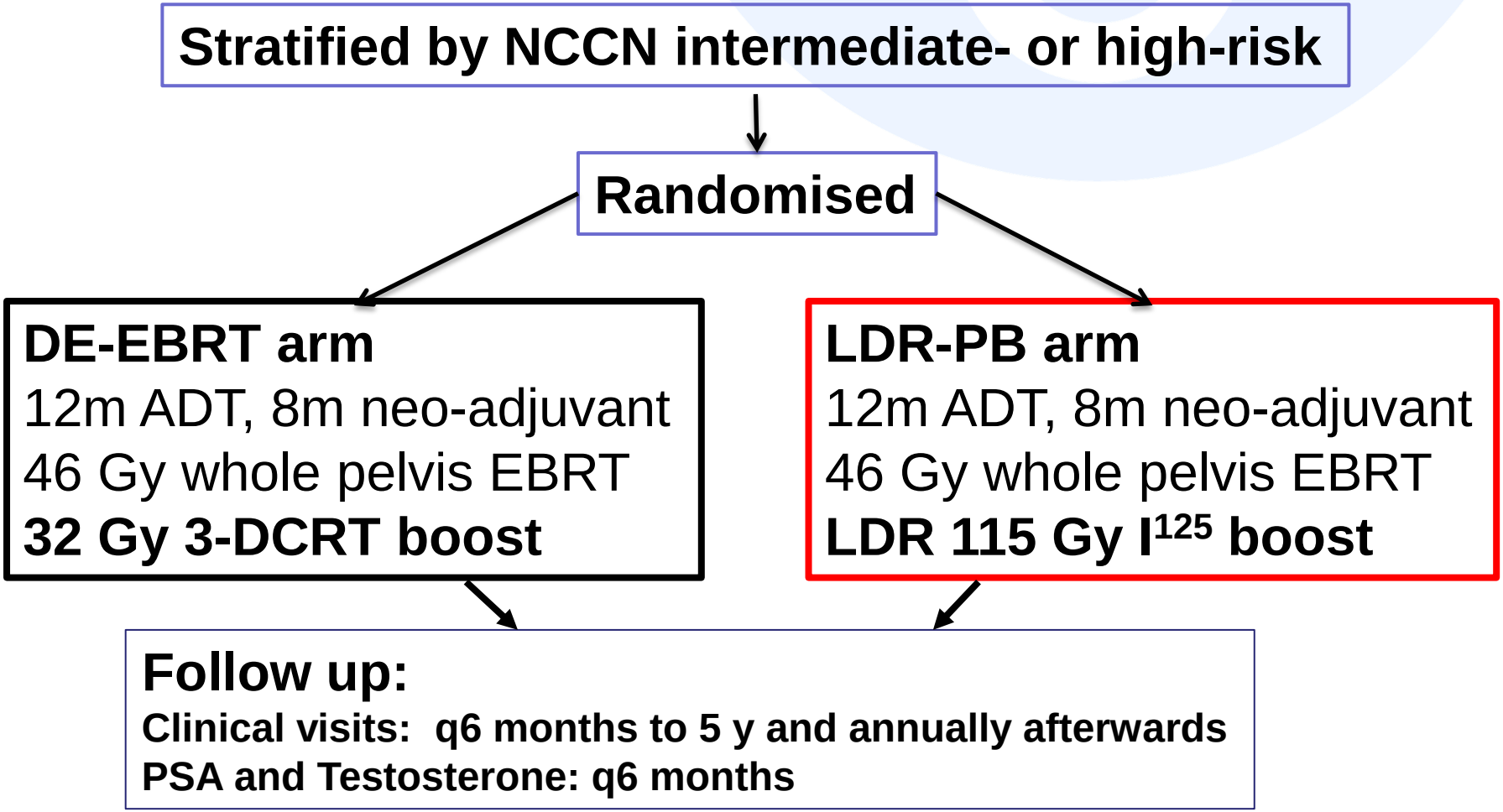
ASCENDE-RT

- Very short version
- Short version
- A slightly deeper dive

ASCENDE-RT simplified schema



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ASCENDE-RT: Very short version

- 6.5 yrs median FU
- DE-EBRT - twice as likely to have biochemical relapse
  - Cox MVA HR = 2.04 (95% CI 1.25-3.33; p=0.004)
- No significant difference in overall survival
  - nor in metastasis free or prostate cancer specific survival

ASCENDE-RT: Very short version

- LDR-PB - twice as likely to have **acute** Grade 2+ GU toxicity
  - 32.5% vs 16.3% (Chi square p<0.001)
- LDR-PB >3 times higher cumulative incidence of **late** grade 3 GU toxicity
  - 18.6% versus 5.2% (Log rank p <0.001)

Is ASCENDE-RT pertinent?

Some will dismiss ASCEND-RT as no longer pertinent because:

1. LDR is obsolete – HDR has a better therapeutic ratio
2. IGRT + dose painting is is[illegible]ctive and easier to learn/apply [illegible]stently
3. SABR will mak[illegible]ther forms of XRT obsolete
4. Surg[illegible] EBRT is at least as effective, a[illegible] harmful effects of XRT can be avoided in some patients

All four points are speculative at this juncture

Others will be tempted to dismiss ASCEND-RT as:

1. Underpowered
2. Uses an artificial endpoint (b-PFS)
3. The PSA threshold used (Phoenix or nadir + 2 ng/mL) prevents direct comparison with surgery

PSA endpoints are ideal

- PSA endpoints are objective, sensitive and reliable instruments
- Residual PSA is proportional to risk of relapse and therefore proportional to the biological dose delivered
- *And who says we can't compare to surgery?*

ASCENDE-RT: the short version

Prognostic features: summary

no significant differences between arms

- Median age: 68 years
- NCCN High-risk: 69%
- Gleason sum ≥8: 40%
- iPSA >20 ng/mL: 19%
- cT3a: 29%
- Positive cores ≥ 50% 68%

Endpoints

- Primary:
  - Biochemical Progression Free Survival (b-PFS) (Phoenix = nadir +2 ng/mL PSA threshold)
- Secondary:
  - Overall survival
  - The incidence and prevalence of treatment related adverse effects
  - Metastasis-free and prostate cancer specific survival
  - Erectile function
  - Quality of life

Accrual

- 398 accrued by 29 radiation oncologists working in 6 Canadian cancer centres
  - 93% from the four BCCA centres
- Open11/2002 to 8/2003 (feasibility phase)
- Reopened 8/2004 until completion December 2011
  - Open ~81 months

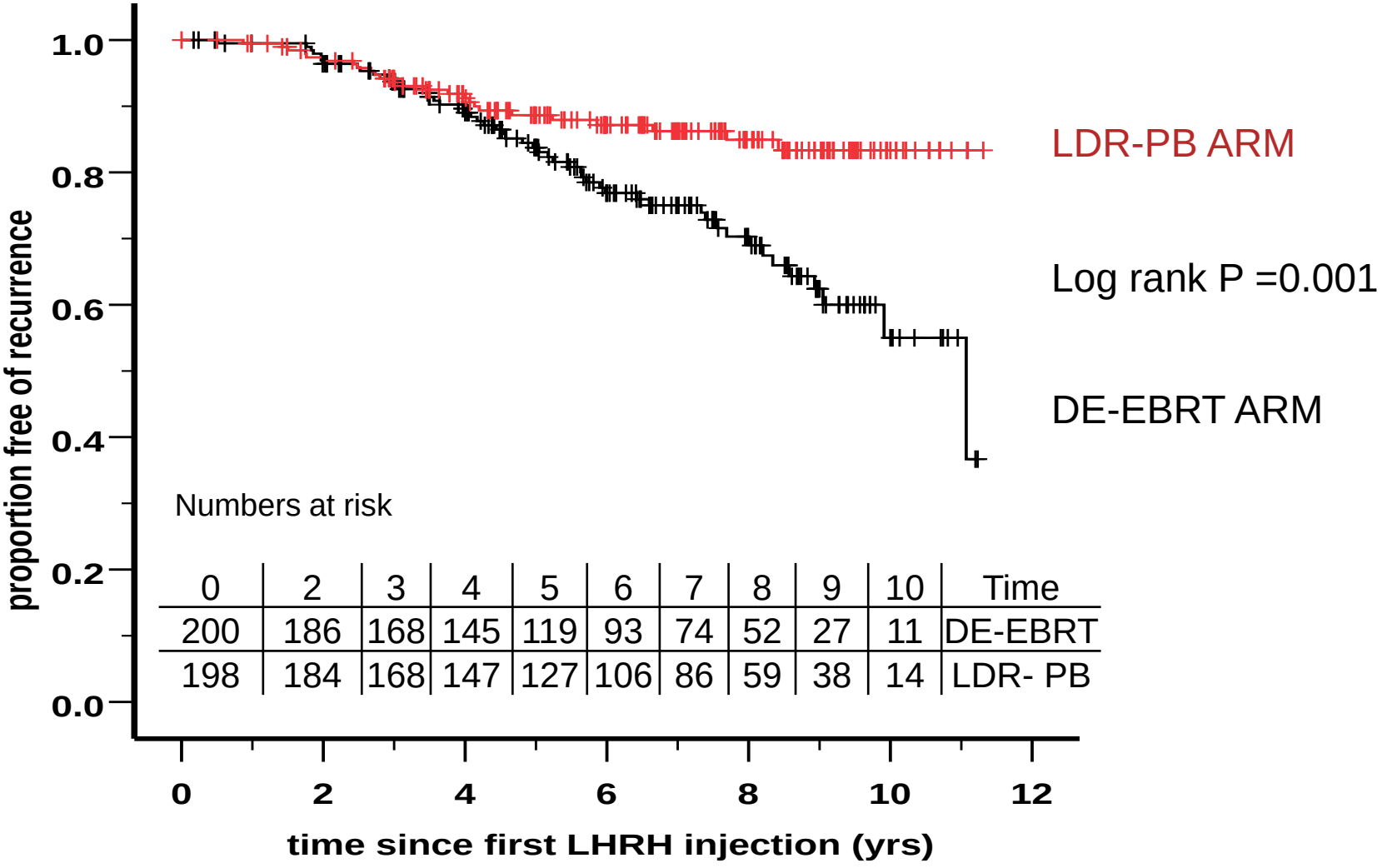
Protocol violations

- 29 (7%) major protocol violations including
  - 14 cross-over events
    - 6 men assigned to DE-EBRT received LDR-PB
    - 8 men assigned to LDR-PB received DE-EBRT
  - 15 received neither of the two protocol regimens

    (7 assigned to DE-EBRT 8 assigned to LDR-PB)

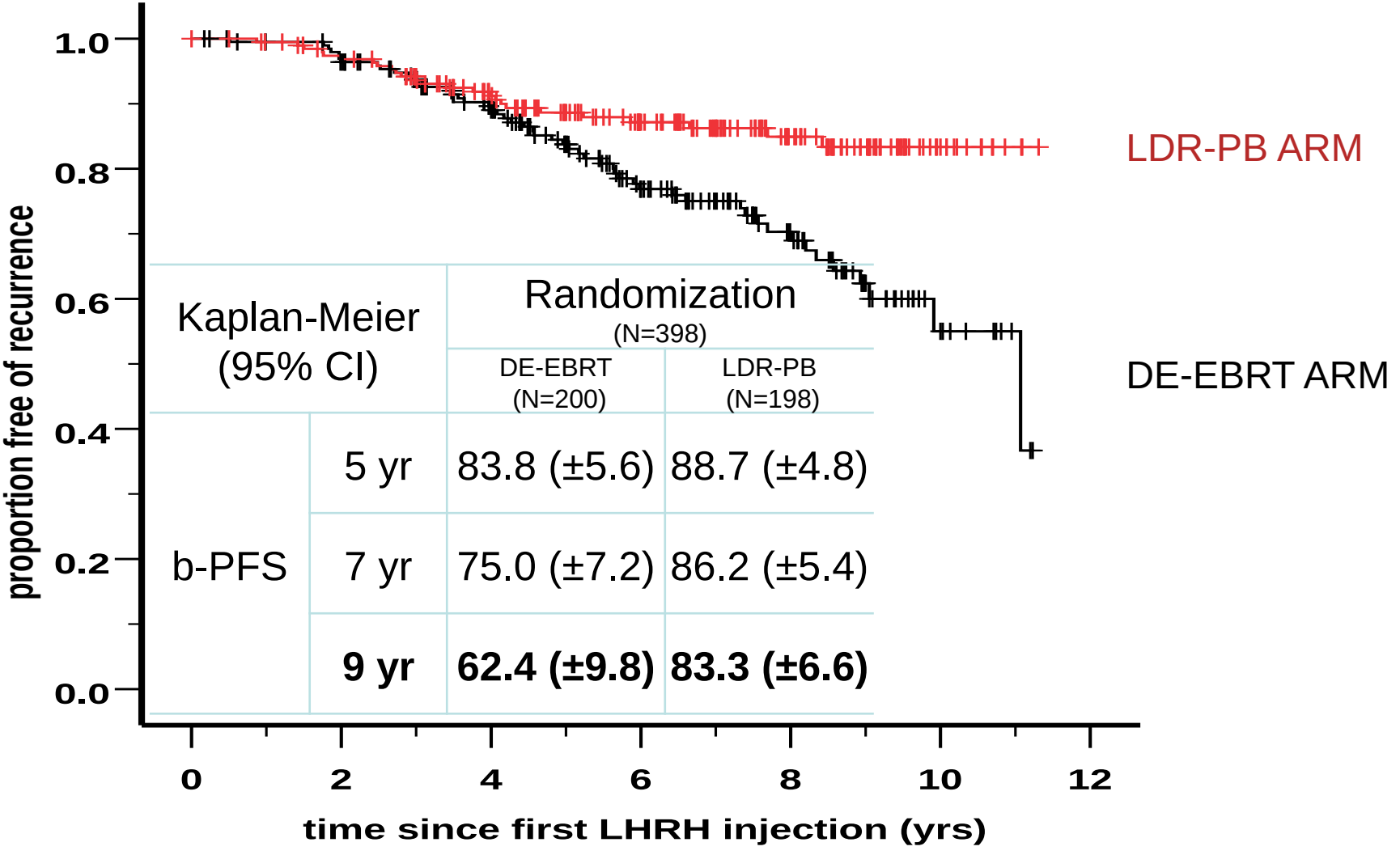
Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint



Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint



Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT (N=200)	LDR-PB (N=198)
b-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)**

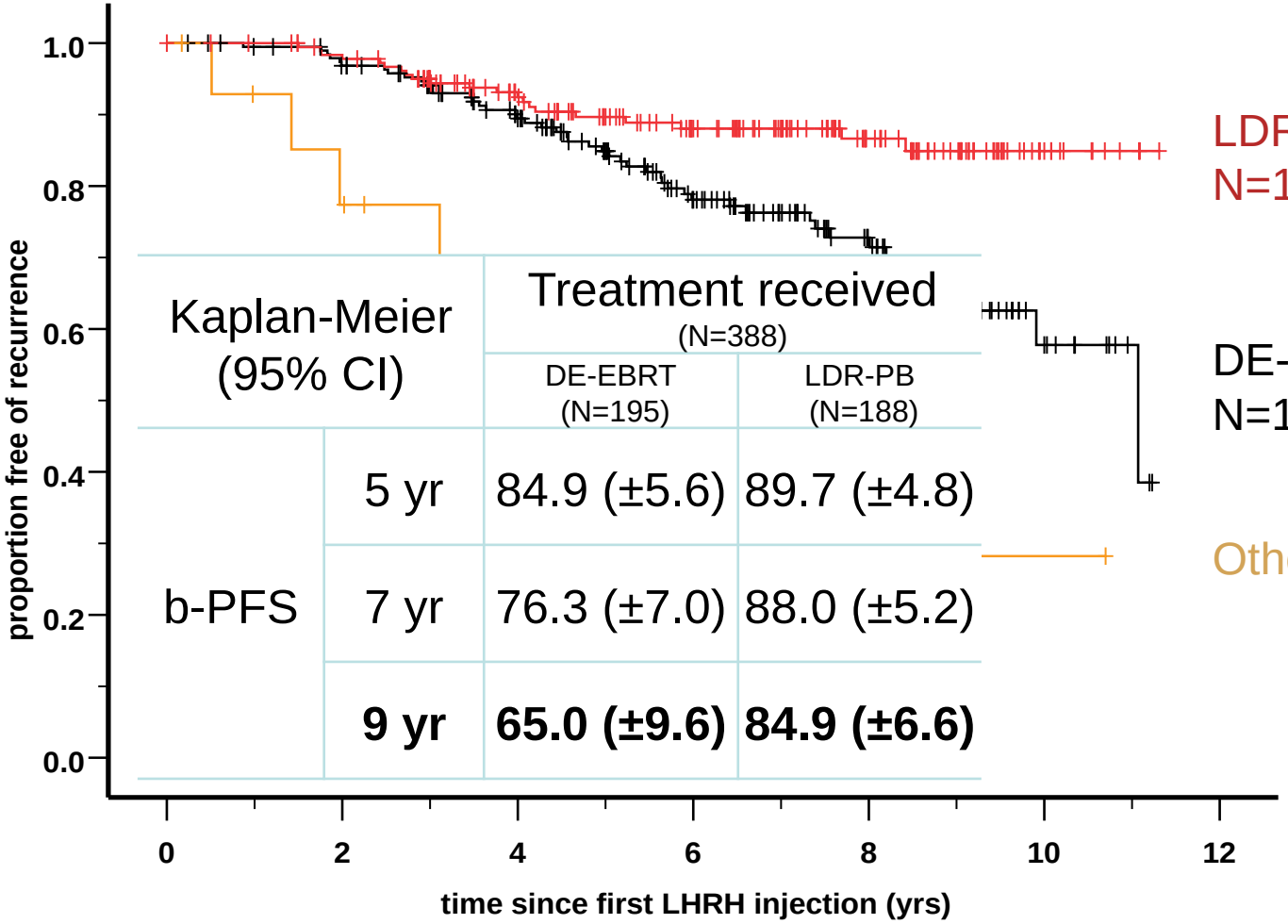
MVA analysis of biochemical failure:

(Backwards:Conditional Cox model, Intent-to-treat, N=398
Factors on UVA with p< 0.3 included)

Variable	HR	95% CI	P-value
Randomization arm (DE-EBRT vs LDR-PB)	***2.04***	***1.25 – 3.33***	***0.004***
PPC (unit = 1%)	***1.01***	***1.00 – 1.02***	***0.006***
Clinical T stage (T3a vs T1-T2)	***1.97***	***1.24 – 3.13***	***0.004***
Log iPSA (unit = 1 log)	***1.62***	***1.11 – 2.36***	***0.01***
Gleason Sum (8-10 vs ≤ 7)	1.38	0.87 – 2.19	0.17

b-PFS

by treatment actually received, N=383



Kaplan-Meier (95% CI)		Treatment received (N=388)	
		DE-EBRT (N=195)	LDR-PB (N=188)
b-PFS	5 yr	84.9 (±5.6)	89.7 (±4.8)
	7 yr	76.3 (±7.0)	88.0 (±5.2)
	9 yr	**65.0 (±9.6)**	**84.9 (±6.6)**

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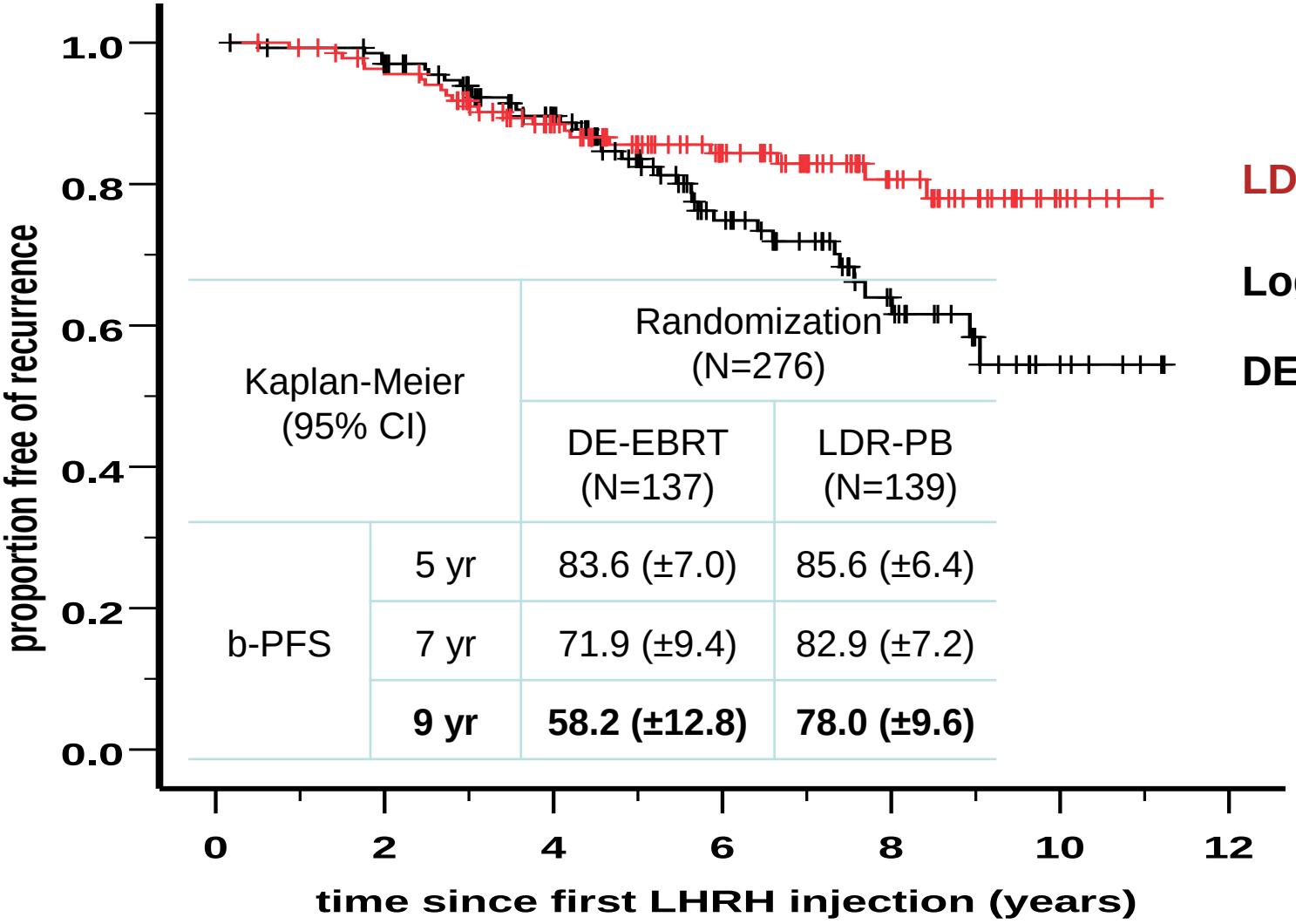
High-risk stratum, N=276 (intent to treat)



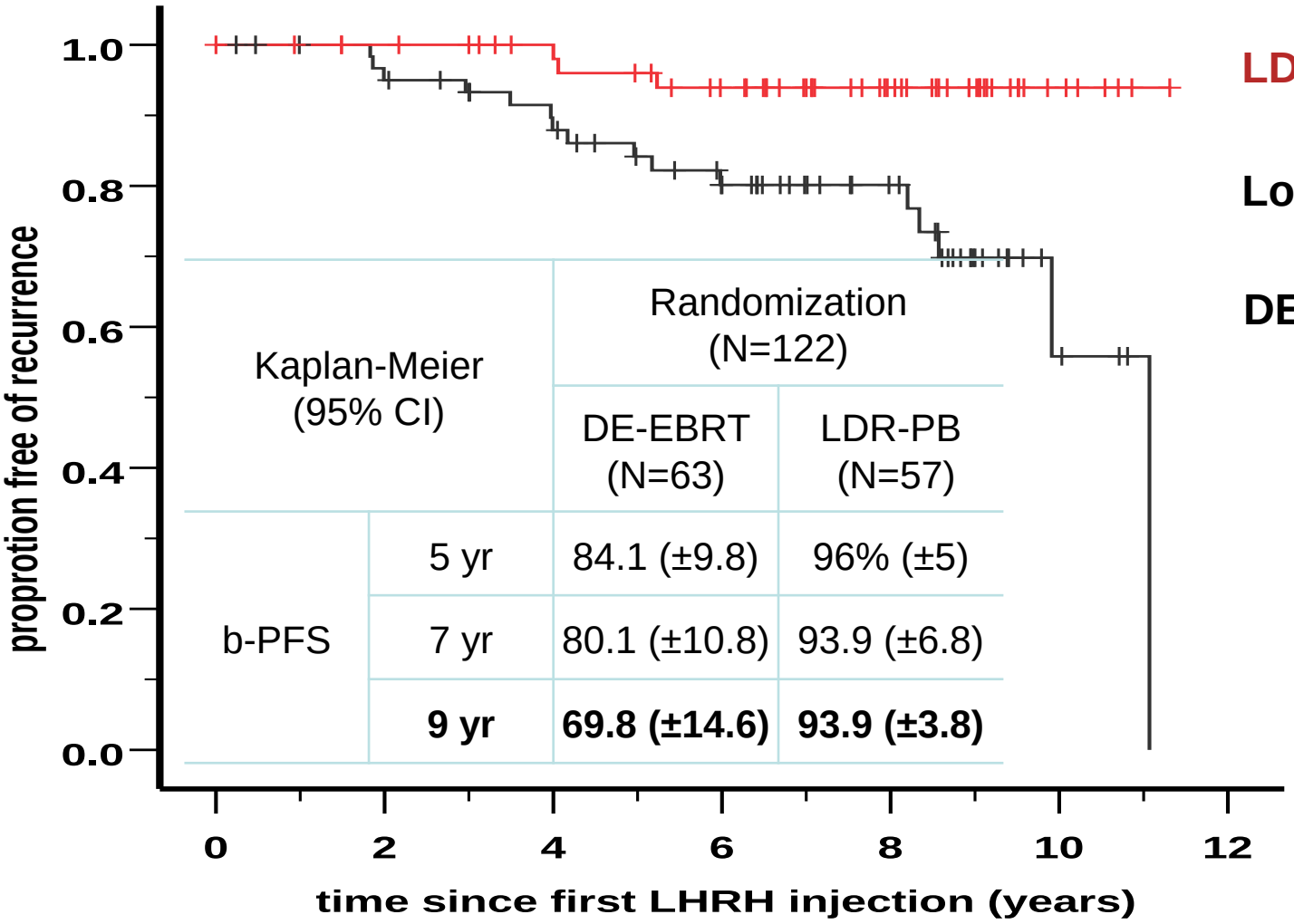
Kaplan-Meier (95% CI)		Randomization (N=276)	
		DE-EBRT (N=137)	LDR-PB (N=139)
b-PFS	5 yr	83.6 (±7.0)	85.6 (±6.4)
	7 yr	71.9 (±9.4)	82.9 (±7.2)
	9 yr	**58.2 (±12.8)**	**78.0 (±9.6)**

LDR-PB ARM

Log rank P = 0.05

DE-EBRT ARM

Intermediate-risk stratum, N=122 (intent to treat)



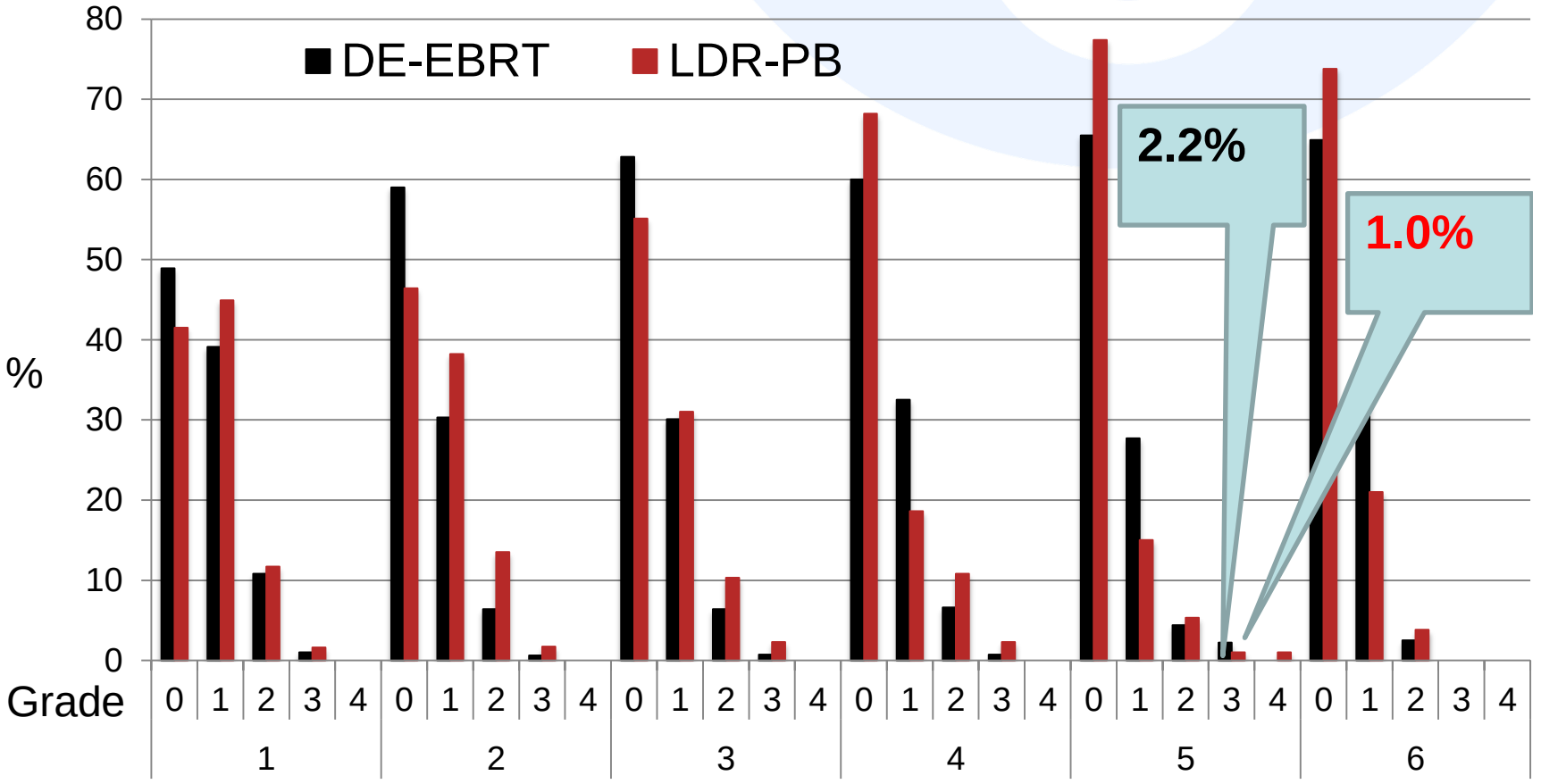
Kaplan-Meier (95% CI)		Randomization (N=122)	
		DE-EBRT (N=63)	LDR-PB (N=57)
b-PFS	5 yr	84.1 (±9.8)	96% (±5)
	7 yr	80.1 (±10.8)	93.9 (±6.8)
	9 yr	**69.8 (±14.6)**	**93.9 (±3.8)**

LDR-PB ARM

Log rank P <0.001

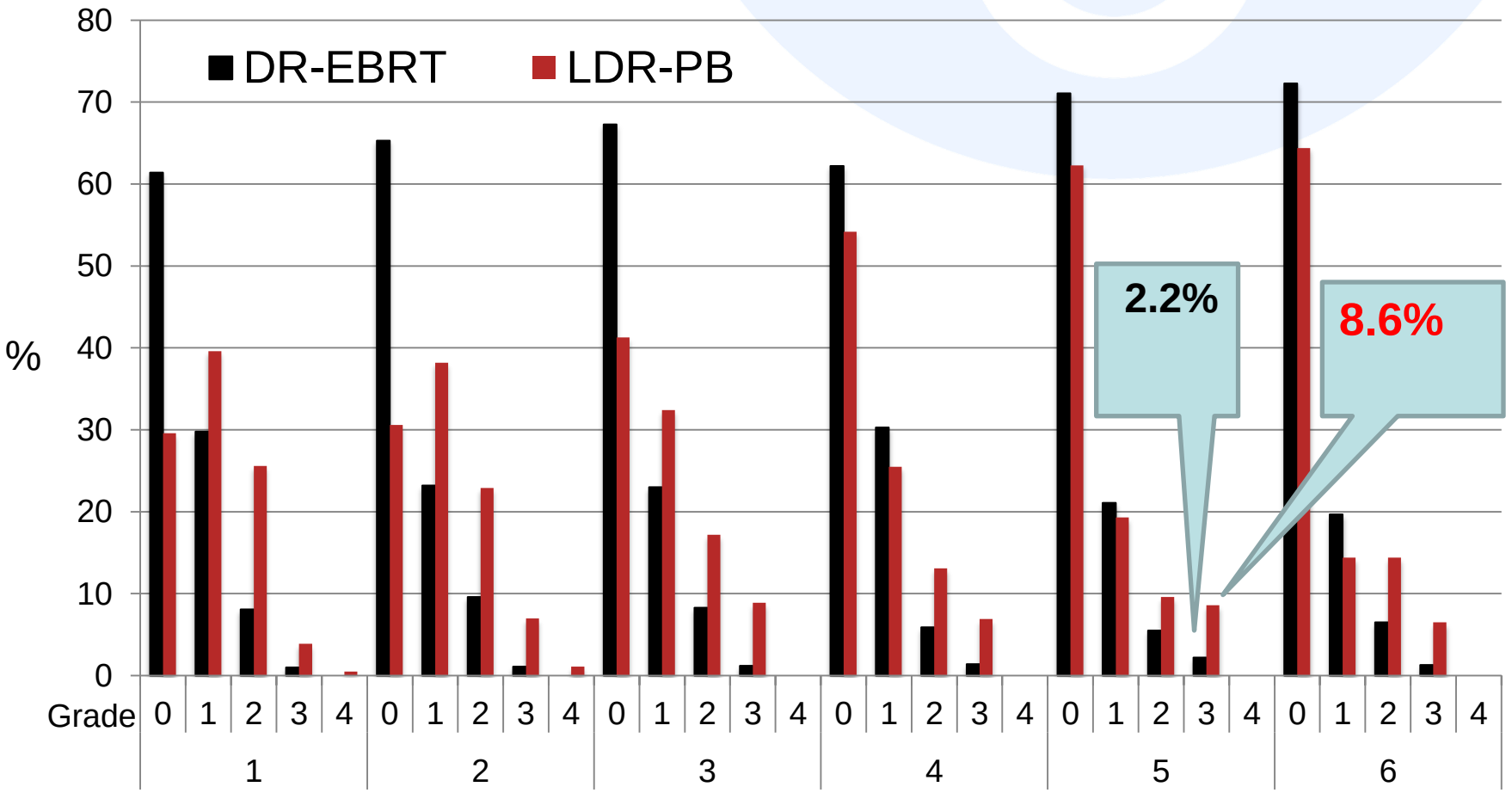
DE-EBRT ARM

Prevalence of Late GI toxicity
LENT-SOMA scale, (prospective, physician-graded)



Years after start of EPNI

Prevalence of Late GU toxicity LENT-SOMA scale, (prospectively physician-graded)



Summarizing Late toxicity

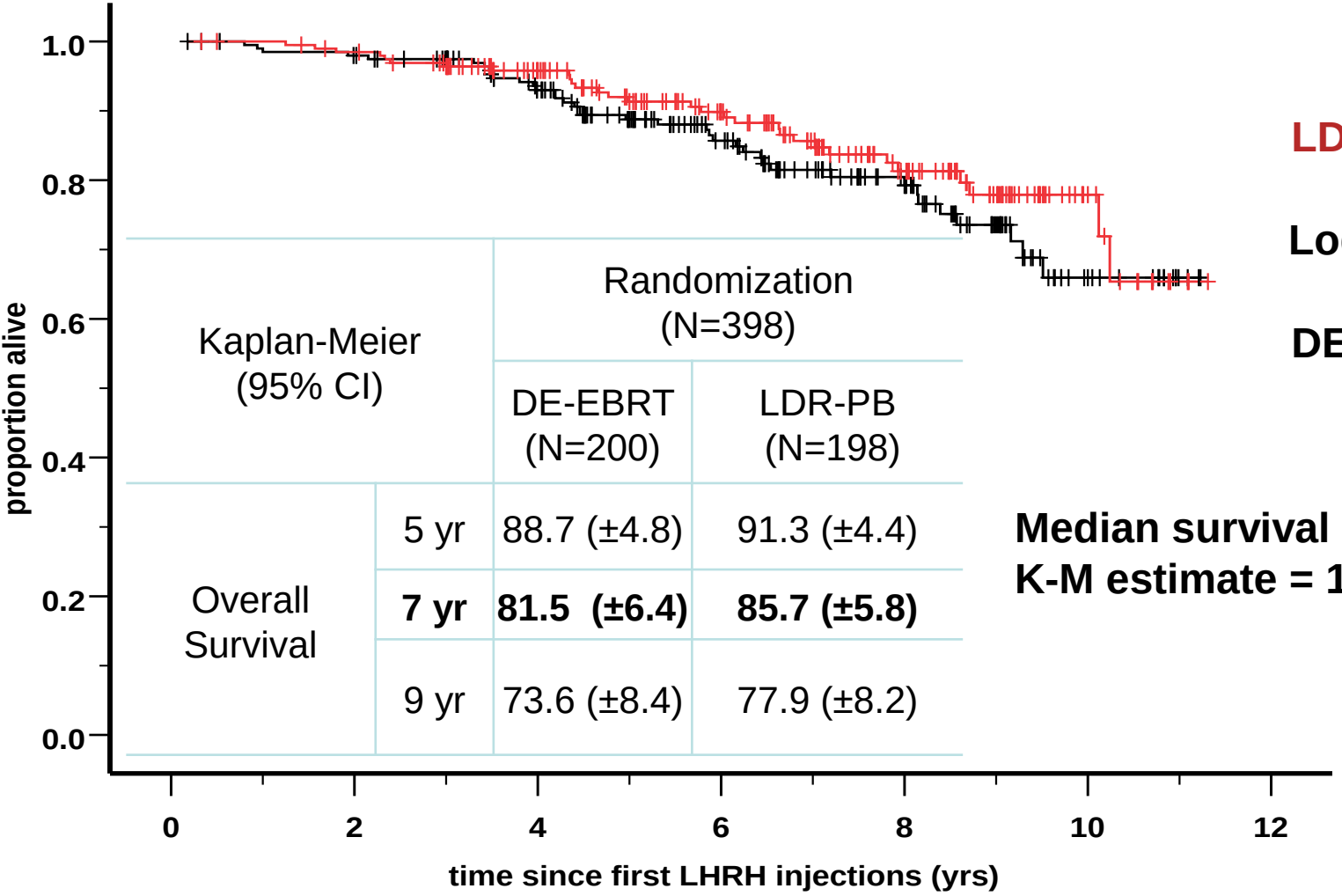
- At 6 years, minimal or no toxicity (G0-1)
  - GI: 95% of patients in both arms
  - GU: 90% in DE-EBRT arm vs 80% in LDR-PB arm

Overall survival

- 68 deaths in total
- At 18 events, prostate cancer is the most common cause of death among trial patients (responsible for 26% of all deaths)
- There have also been 15 cardiovascular deaths
- And 26 from other cancers
  - 7 lung, 5 pancreas/bile duct, 3 TCC of bladder/ureter, 3 colon, 3 with primary unknown, and 1 each; stomach, oesophagus, meningioma, metastatic melanoma, and a head and neck primary).
- 9 additional deaths
  - including one man treated on the LDR-PB arm who died at T+8y from Fournier's gangrene secondary to complications related recto-urethral fistula repair

Overall survival

Intent-to-treat analysis, N=398 (68 events)



Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT (N=200)	LDR-PB (N=198)
Overall Survival	5 yr	88.7 (±4.8)	91.3 (±4.4)
	7 yr	**81.5 (±6.4)**	**85.7 (±5.8)**
	9 yr	73.6 (±8.4)	77.9 (±8.2)

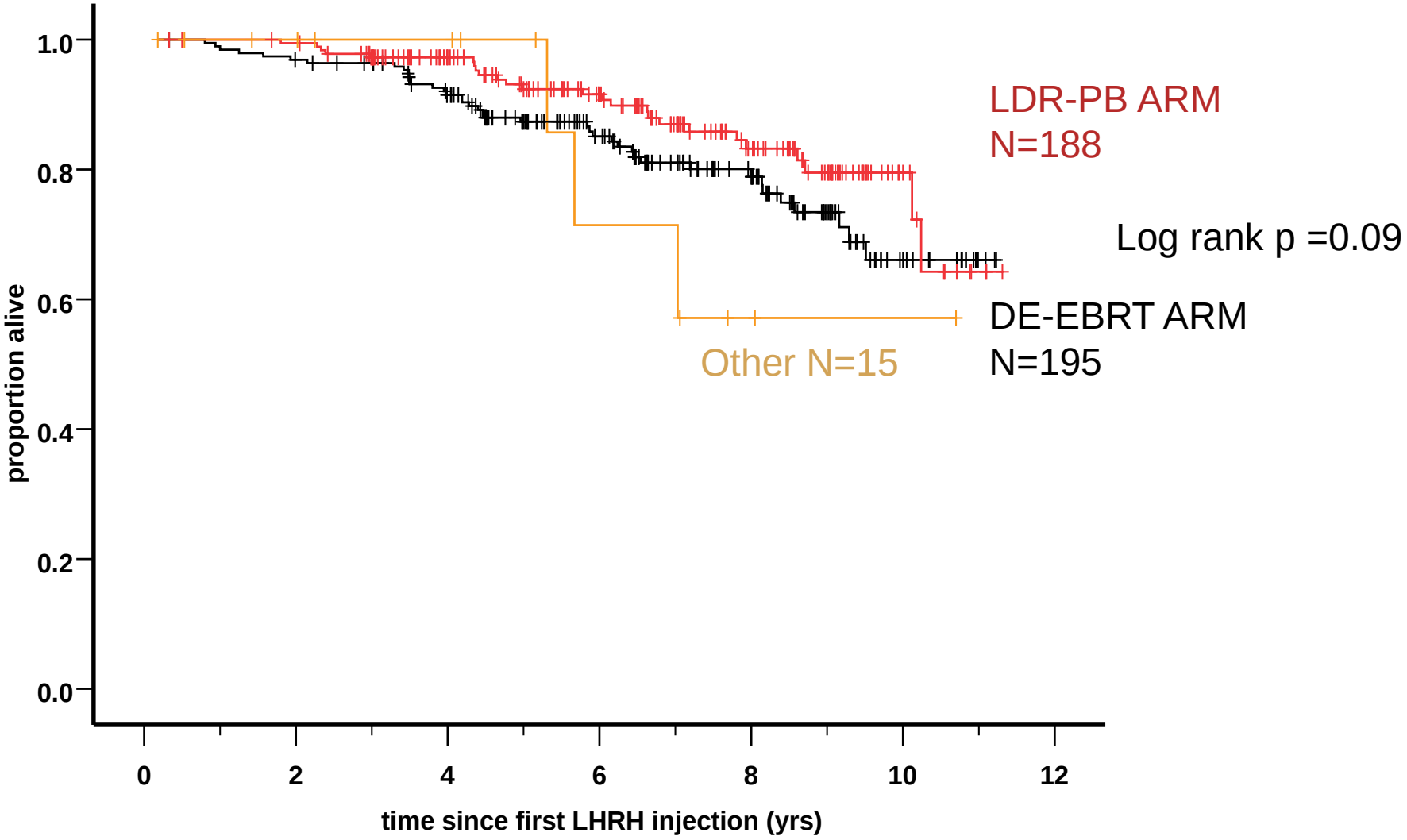
LDR-PB ARM

Log rank P = 0.29

DE-EBRT ARM

Median survival not reached
K-M estimate = 13 years

OS by treatment received

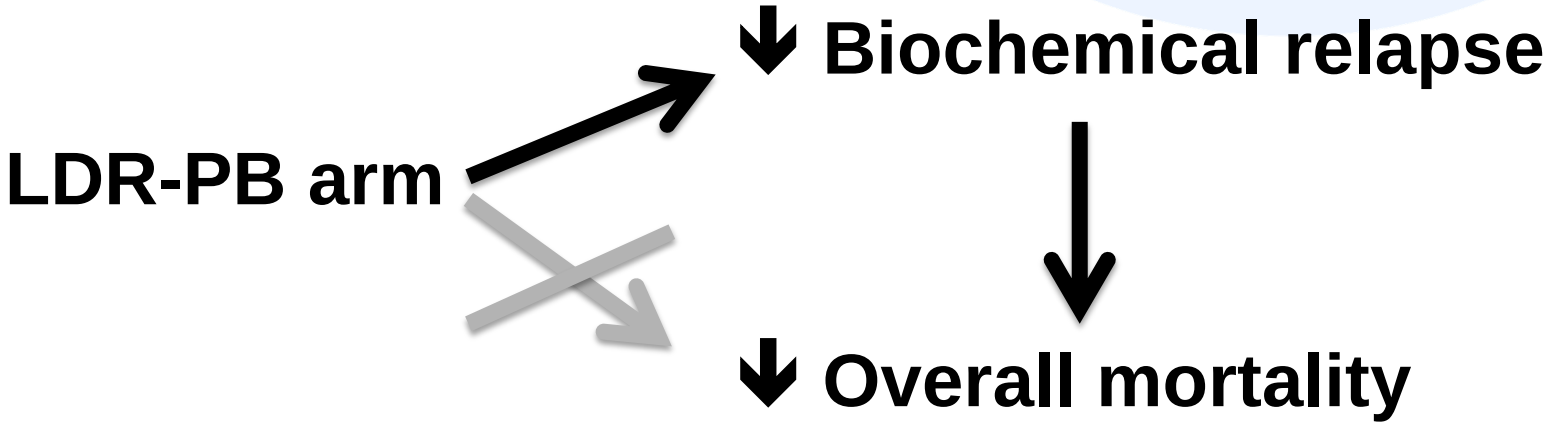


MVA analysis of overall survival:

(Backwards:Conditional Cox model, Intent-to-treat, N=398

Variable	HR	95% CI	P-value
Randomization arm (LDR-PB vs DE-EBRT)	0.84	0.51 – 1.38	0.49
Disease status (relapse vs no relapse)	***1.96***	***1.14 – 3.38***	***0.015***
Age (unit = 1 year)	***1.06***	***1.02 – 1.10***	***0.004***
Log iPSA (unit = 1 log)	1.30	0.87 – 1.95	0.20

Will OS advantage emerge with further FU?



ASCENDE-RT: a deeper dive

Residual PSA is proportional to risk of relapse and therefore proportional to the biological dose delivered

IJROBP

Prostate-Specific Antigen at 4 to 5 Years After Low-Dose-Rate Prostate Brachytherapy Is a Strong Predictor of Disease-Free Survival

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Predictive capacity of the 48-month PSA value

- 48mPSA ≤0.2 ng/mL — 10 yr K-M b-PFS = 98.5%
- 48mPSA 0.2 – 0.4ng/mL — 10 yr K-M b-PFS = 89.7%
- 48mPSA 0.4 – 1.0 — 10 yr K-M b-PFS = 70.9%
- If 48mPSA >1.0 — 10 yr K-M b-PFS = 0%

- No safe threshold – the lower the better

Residual PSA value (for non-relapsed patients)

DE-EBRT ARM

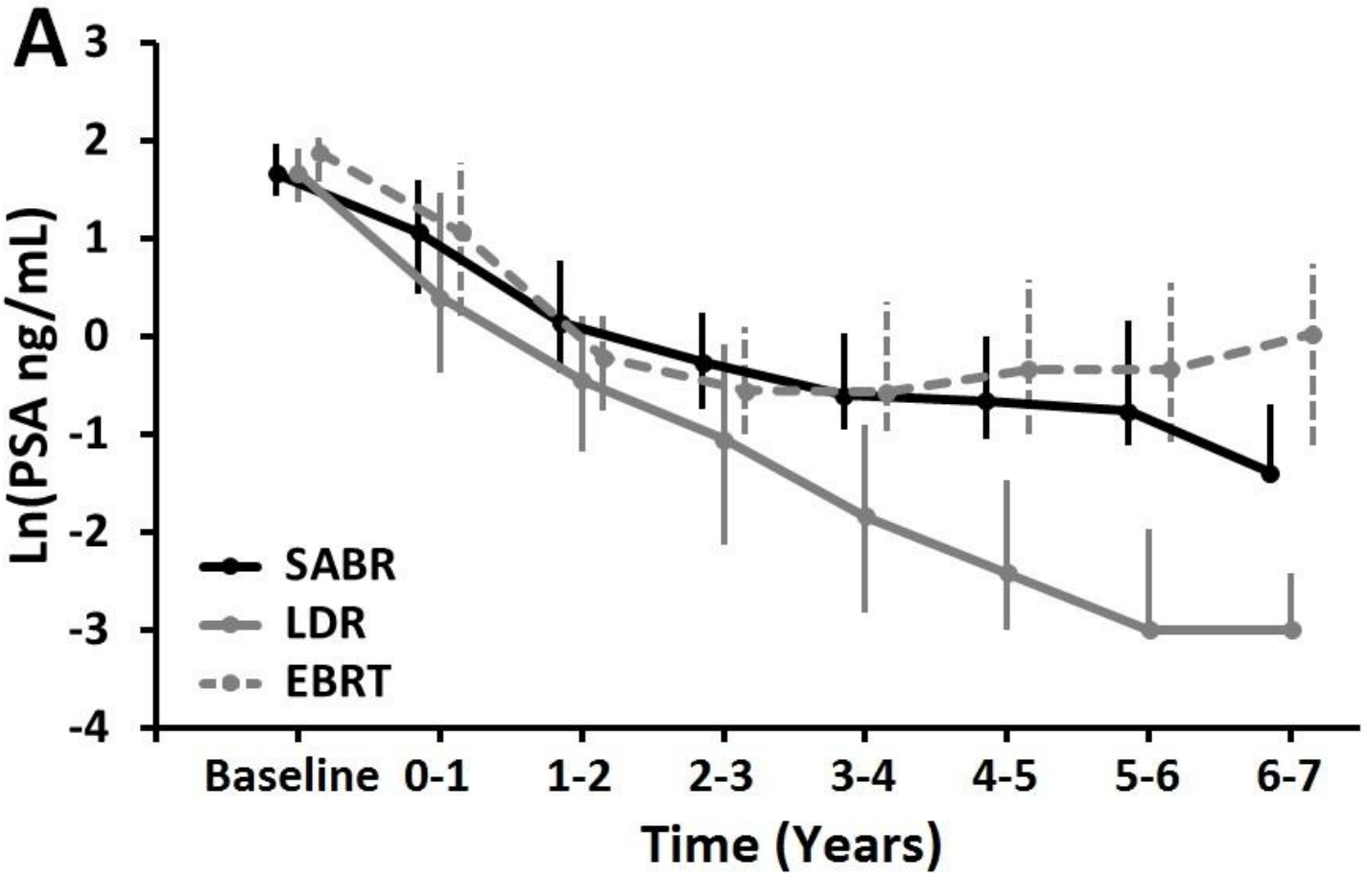
- Median = 0.22 ng/mL
- Mean = 0.32 (SD = 0.32)
- 9% are undetectable

LDR-PB ARM

- Median = 0.03 ng/mL
- Mean = 0.09 (SD = 0.20)
- 44% are undetectable

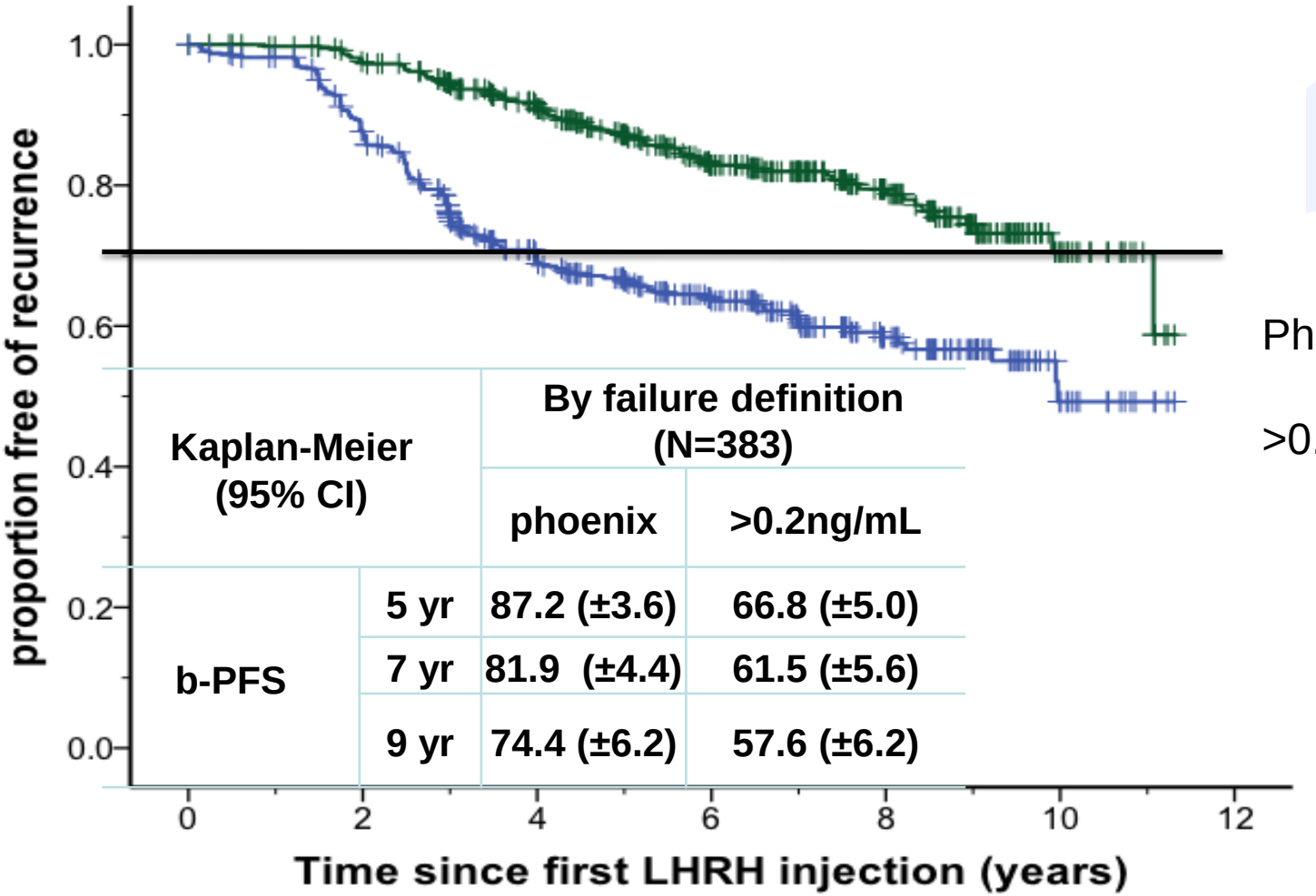
These differences are even larger if analysis is restricted to those with > median FU where 67% of the LDR-PB patients have undetectable PSA and the DE-EBRT median rises to 0.31 ng/mL

Unpublished data (courtesy of Andrew Loblaw)



What can be learned by using a **surgical** definition of biochemical recurrence: failure to maintain a PSA of ≤0.2?

All ASCENDE-RT patients analyzed by treatment received (N = 383) using two thresholds to define biochemical recurrence

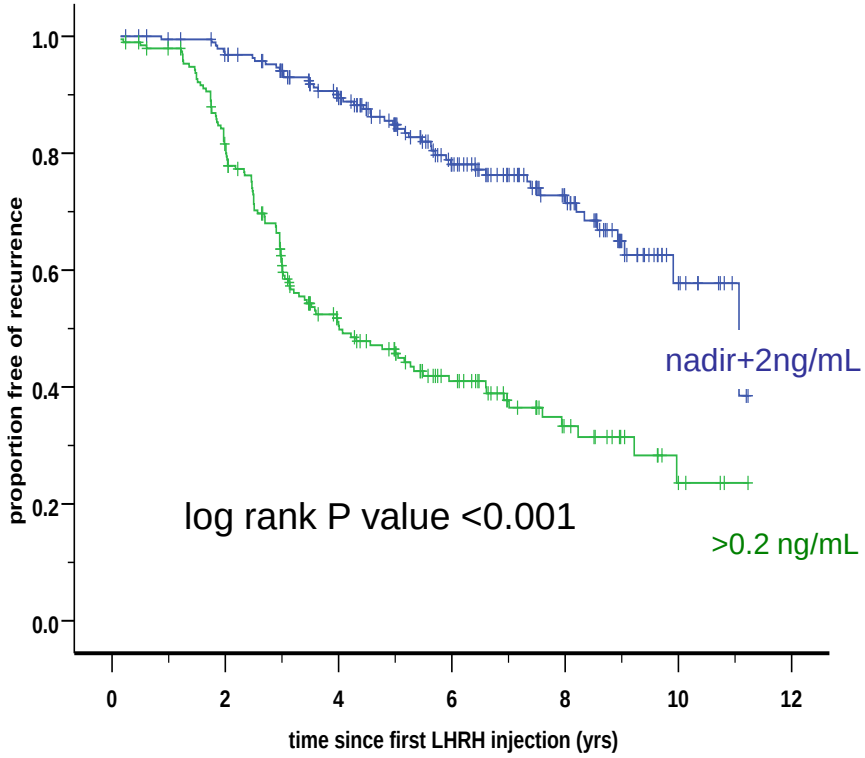


Kaplan-Meier (95% CI)		By failure definition (N=383)	
		phoenix	>0.2ng/mL
b-PFS	5 yr	87.2 (±3.6)	66.8 (±5.0)
	7 yr	81.9 (±4.4)	61.5 (±5.6)
	9 yr	74.4 (±6.2)	57.6 (±6.2)

b-PFS using two definitions of biochemical relapse

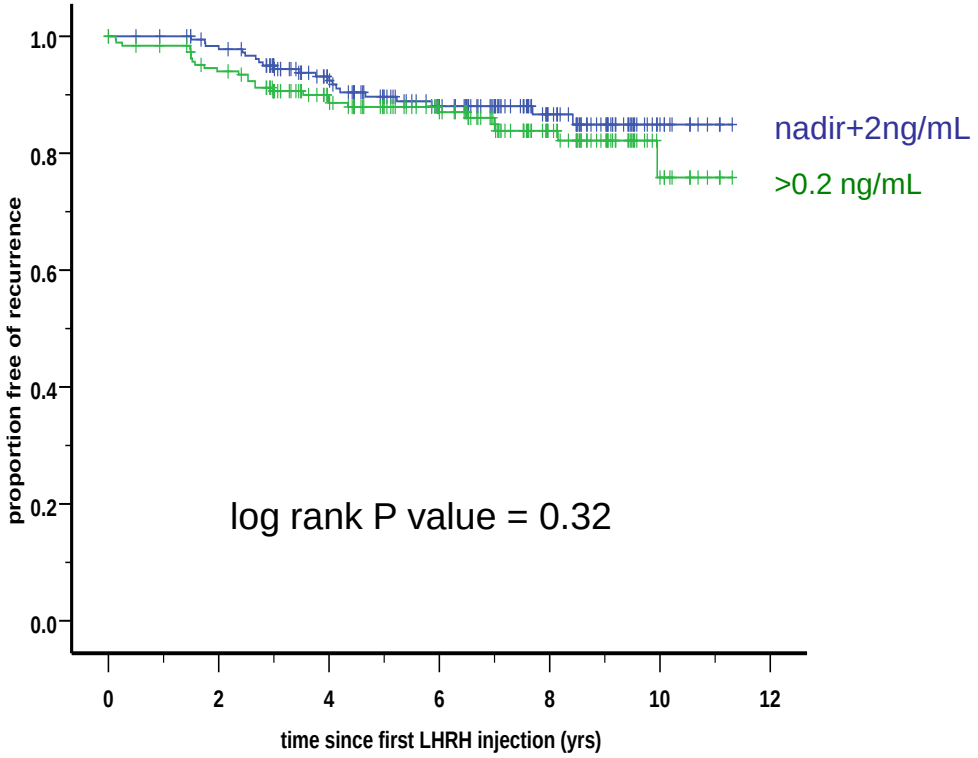
DE-EBRT (N=195)

9-year K-M PFS = 32% using >0.2 ng/mL

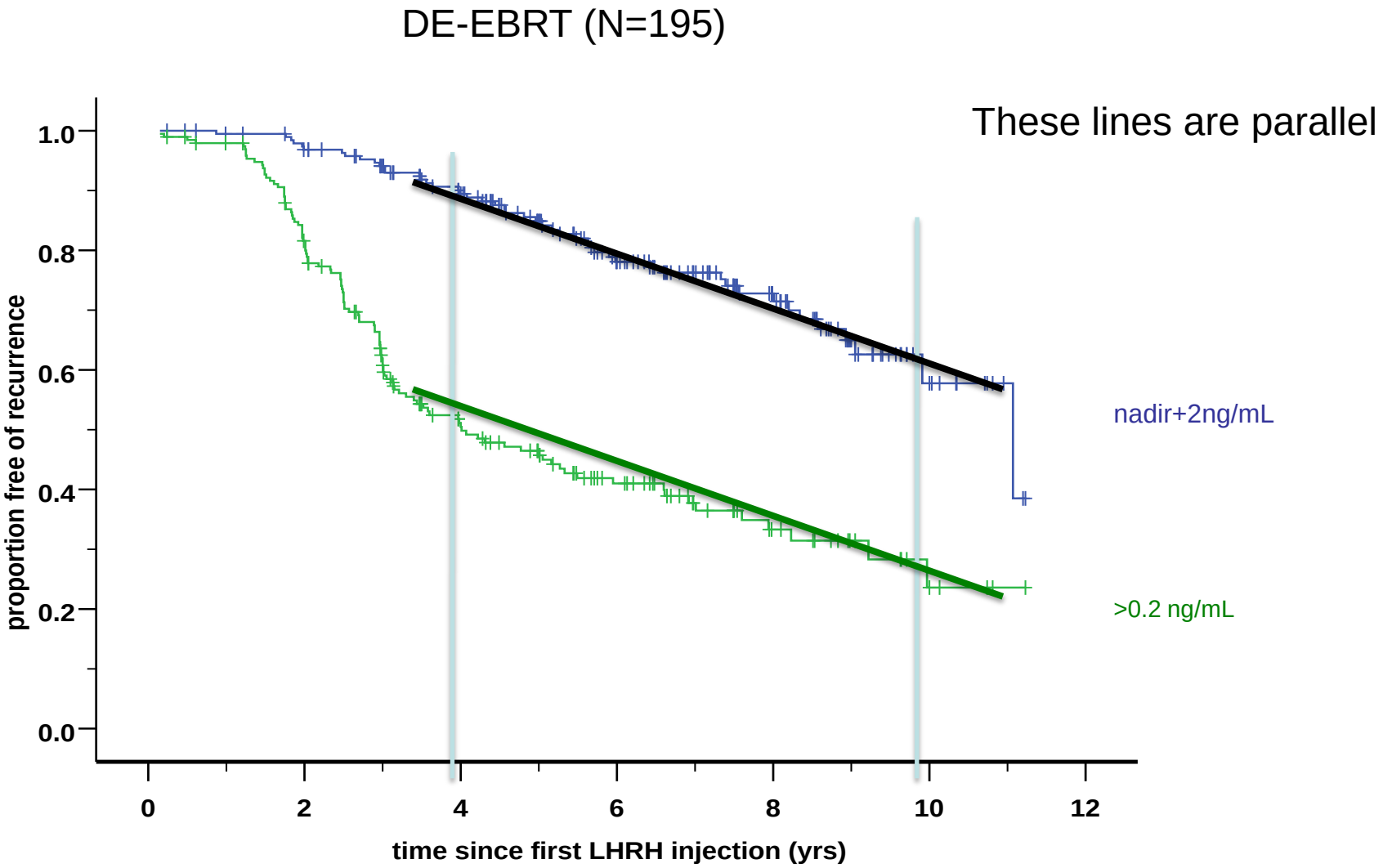


LDR-PB (N=188)

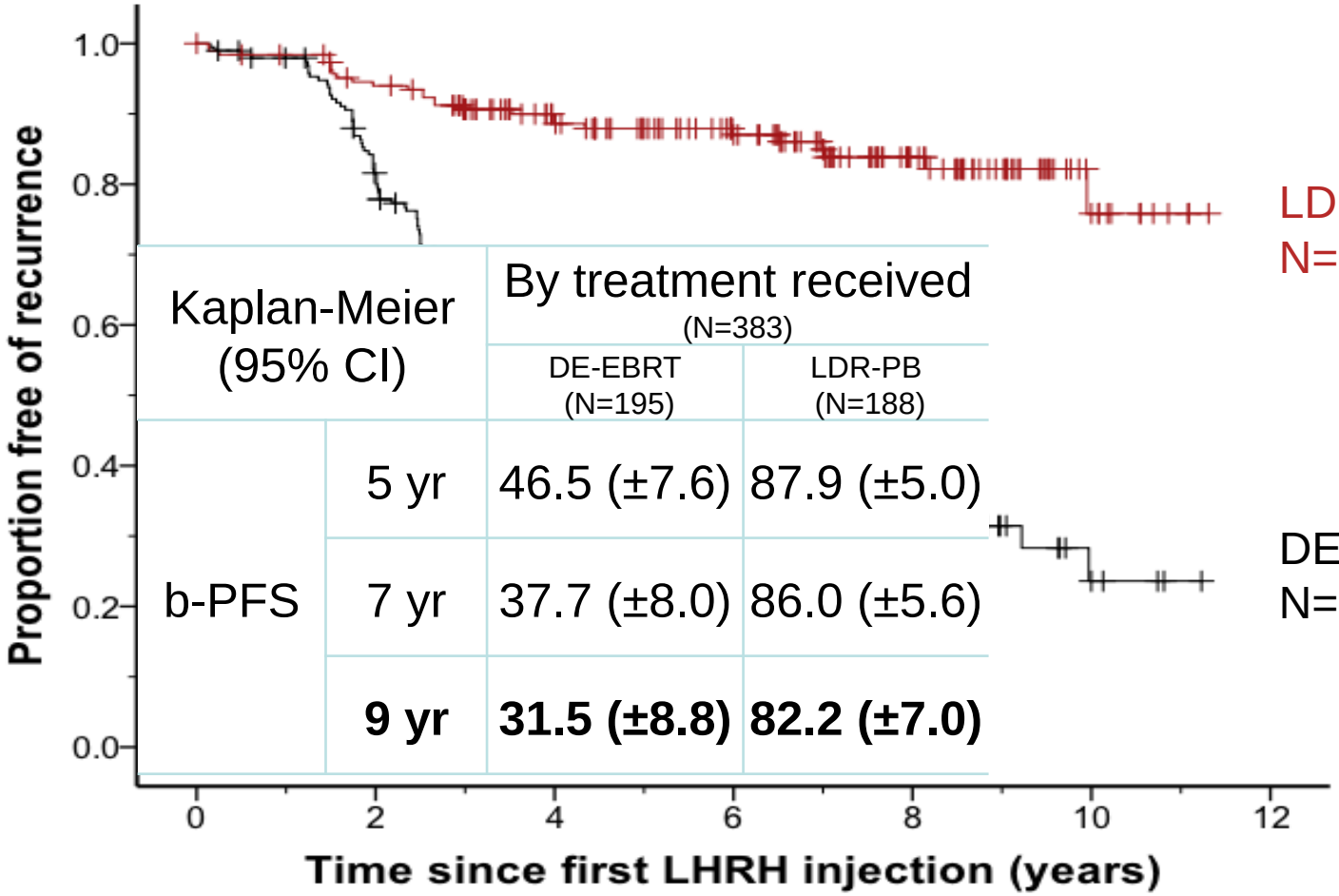
9-year K-M PFS = 82% using >0.2 ng/mL



DE-EBRT arm


DE-EBRT (N=195)
These lines are parallel
nadir+2ng/mL
>0.2 ng/mL
proportion free of recurrence
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
time since first LHRH injection (yrs)

b-PFS using a >0.2 ng/mL threshold (by treatment received N= 383)



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)**

LDR-PB ARM
N=188

DE-EBRT ARM
N=195

Is surgery equivalent?

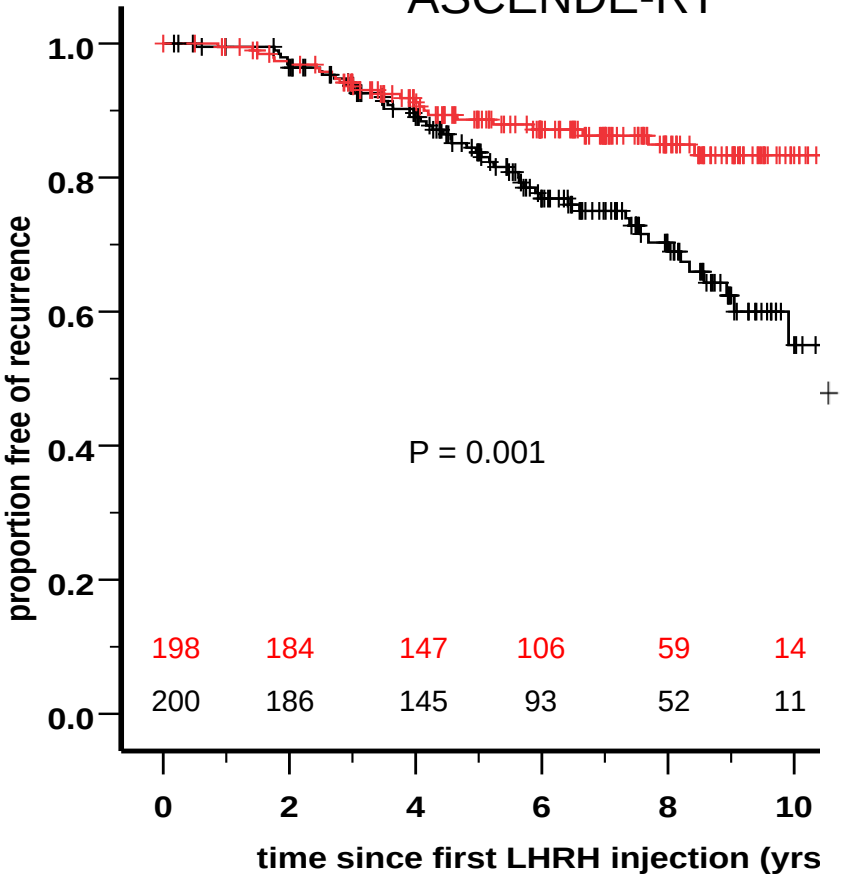
- After LDR-PB boost, the **10 year b-PFS** is ~80% using the surgical threshold of >0.2 ng/mL
- I'm unaware of any surgical results that come close – for example the **5 year rate*** after surgery for Gleason 4+3 =7 is 65.1%

*Pierorazio PM, Walsh PC, Partin AW, and Epstein JI. 2013 Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU International; 111(5):689–852

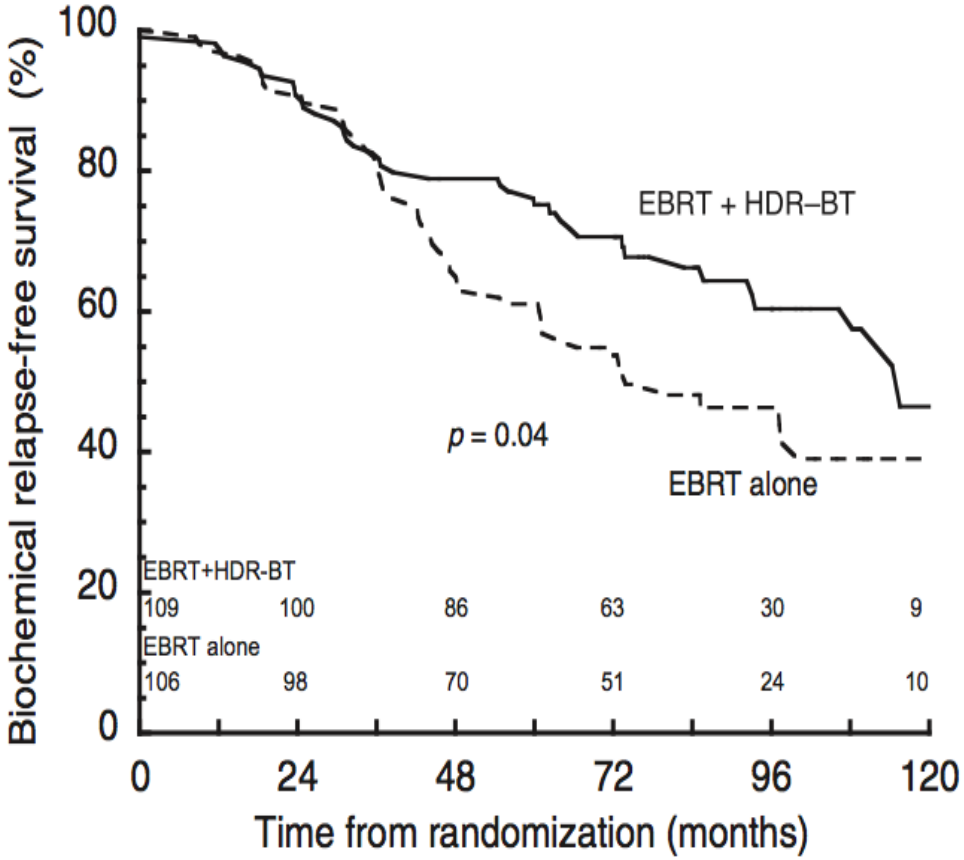
Are HDR and LDR iso-effective?

HDR vs LDR for unfavourable risk

ASCENDE-RT



Hoskins *et al*.



Local control

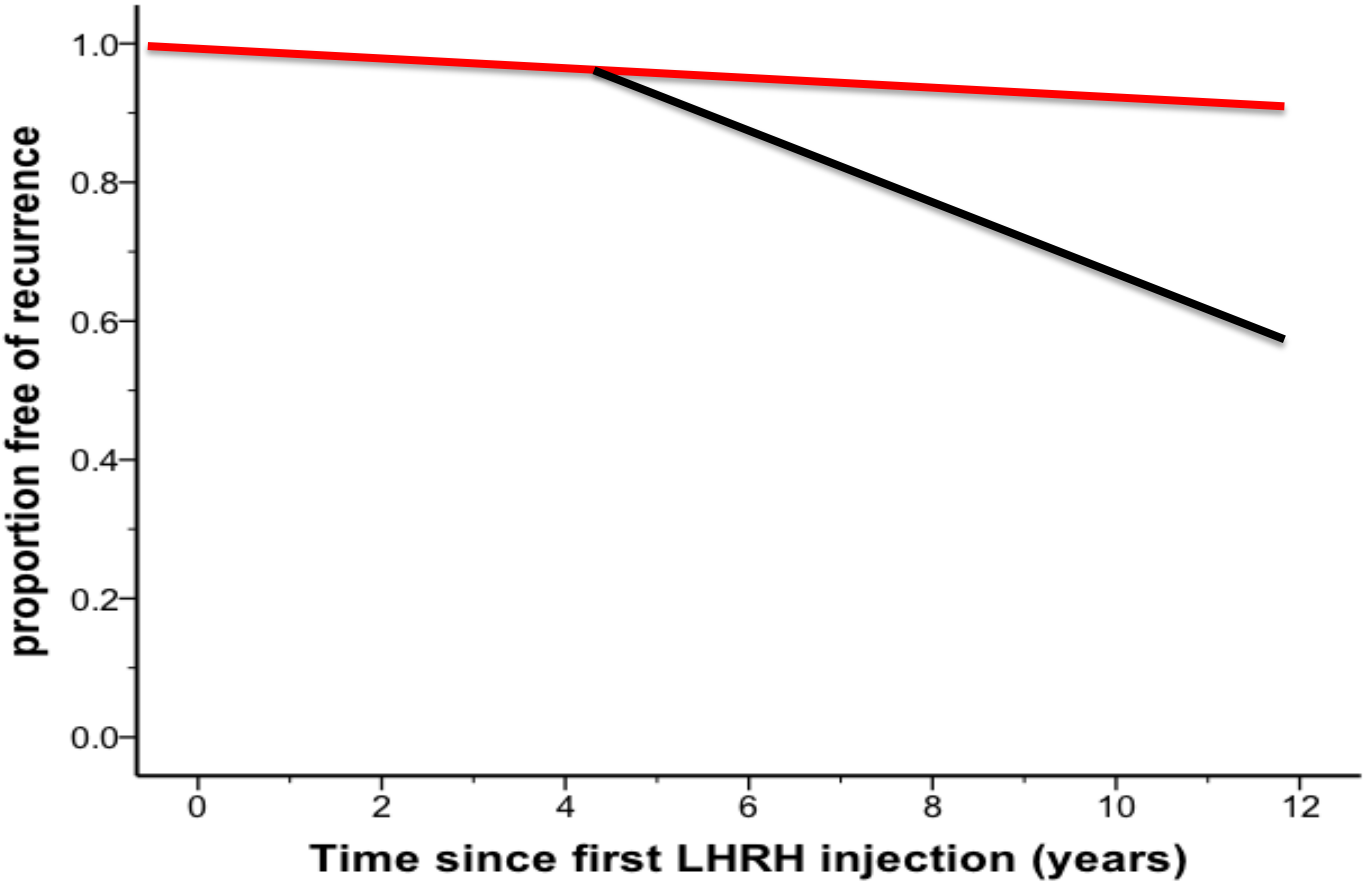
Local control

- 35 of 76 PSA recurrence events (46%) were metastatic
  - 17 LDR
  - 18 DE-EBRT
  - Presumably distributed evenly by randomisation
- 30 of 35 (86%) had evidence of mets <2 years from biochemical failure
  - Median interval = 4 months

Local control

- 46 biochemical relapses were not associated with early metastatic relapse
- 80% of these (N =37) were in the DE-EBRT arm

b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (Phoenix)

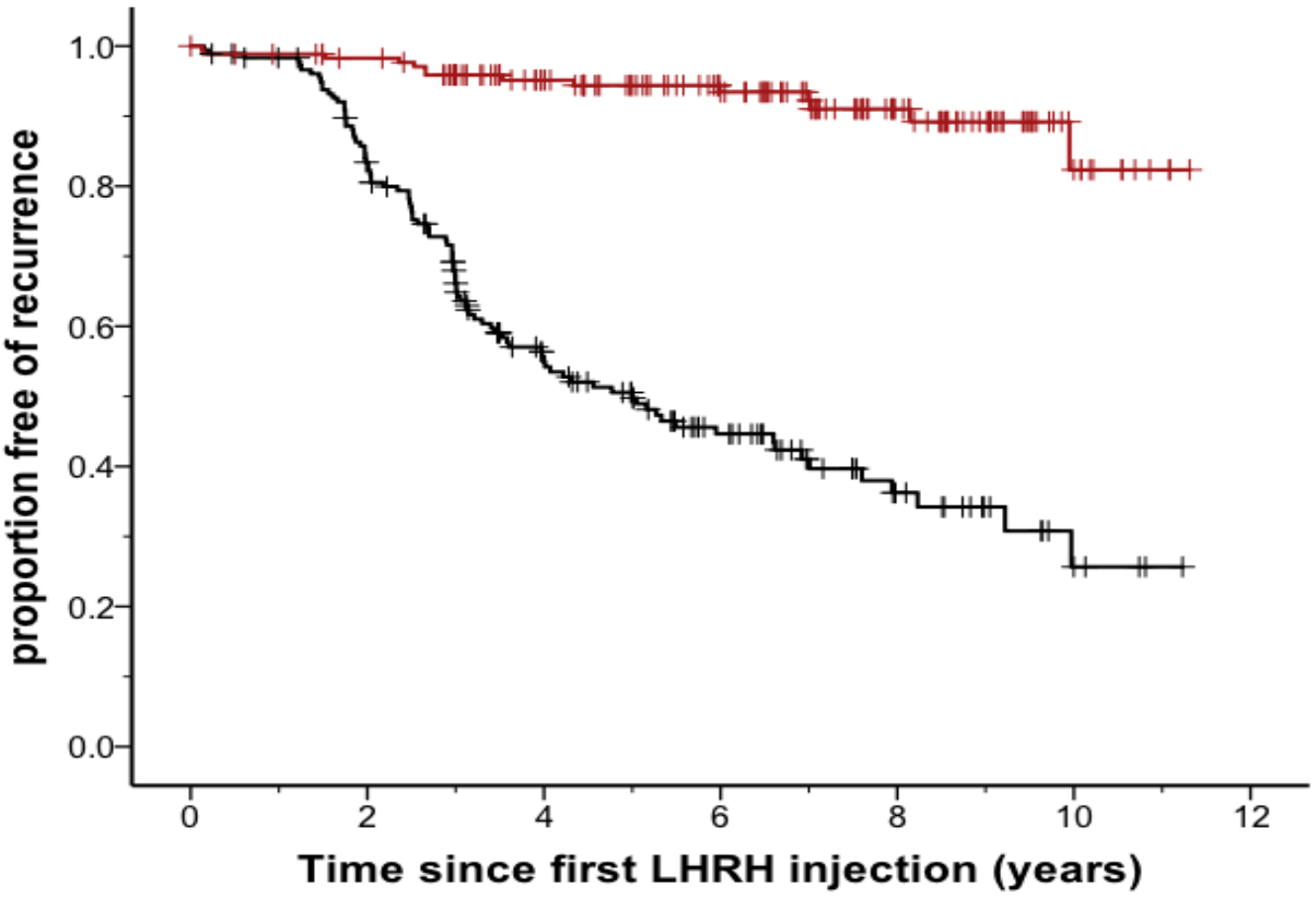


LDR-PB

Log rank p < 0.001

DE-EBRT

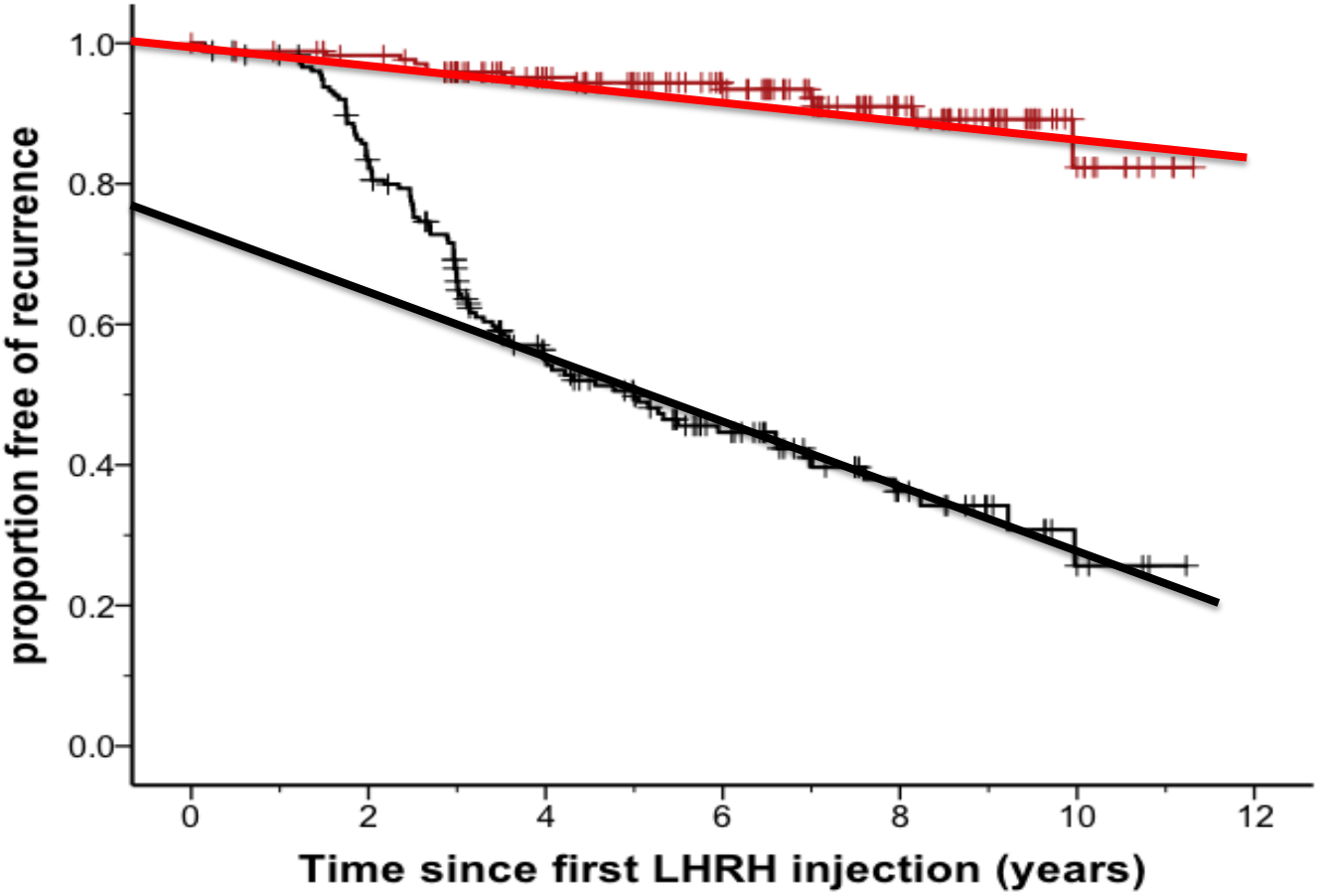
b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (>0.2 ng/mL)



LDR-PB

DE-EBRT

b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (>0.2 ng/mL)

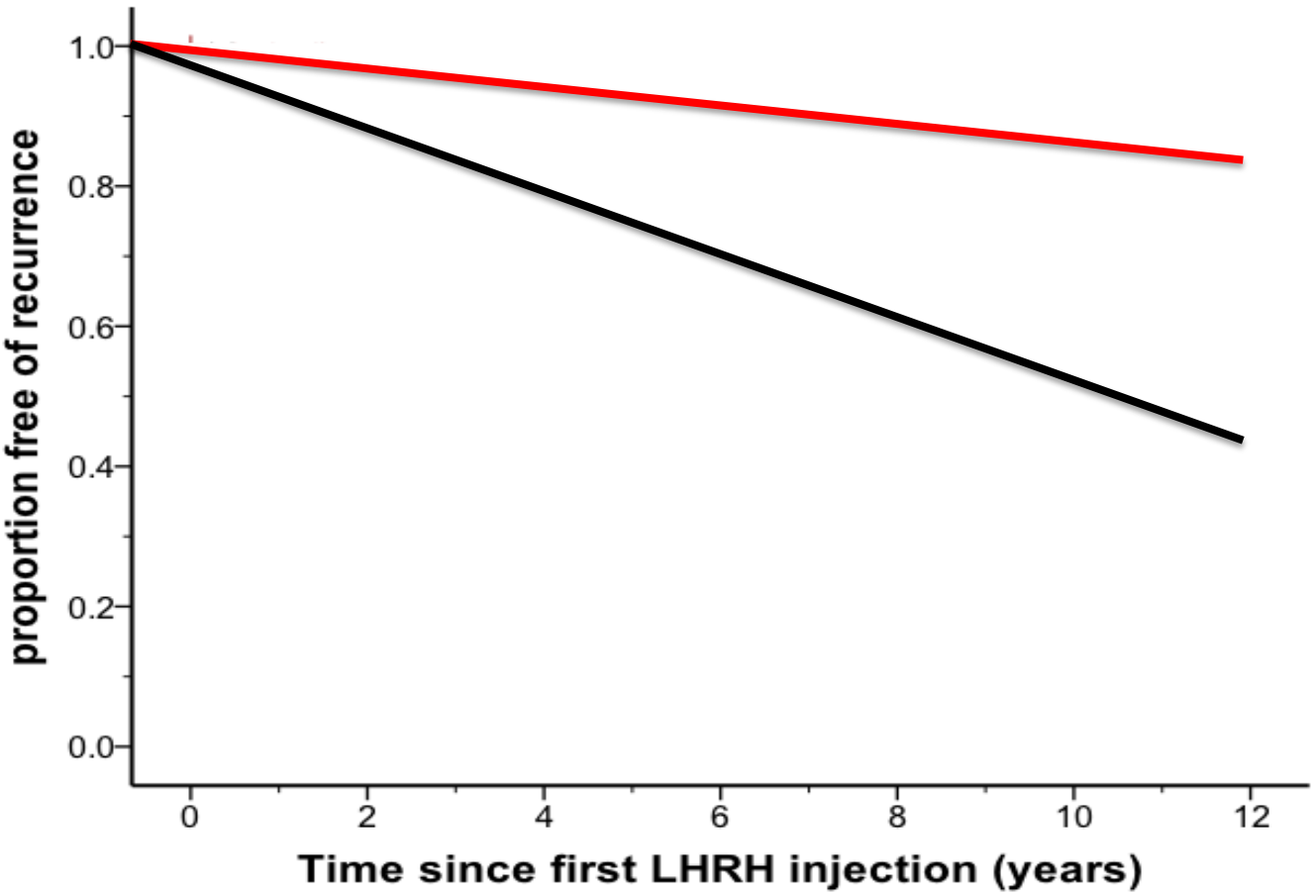


LDR-PB

DE-EBRT

*subset of men who received one of the two treatment regimens who **did not** have evidence of metastatic disease within 2 years of biochemical recurrence

Renormalize on 100% at Time 0



LDR-PB

DE-EBRT

Local control

- For DE-EBRT ~5% per year local recurrence rate
  - Constant from year 5-10
- For LDR-PB ~1% per year local recurrence rate
  - Constant from year 5-10

Why LDR-PB boost for high risk

- LDR-PB provides low residual PSA values leading to local recurrence rates of ~1%/year
- Using a > 0.2 ng/mL threshold results in the same b-PFS as Phoenix allowing comparison with surgery
- Increased GU toxicity in ASCENDE-RT may be related to BCCA dose planning and obsolete imaging technology

Why LDR-PB boost for high risk

- The purported equivalence or superiority of SABR, HDR and RP demand confirmation with long term multi-institutional studies, population-based outcomes analysis and/or randomised data

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  - Dana Matuszewski
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  - Ross Halperin
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- Winkle Kwan
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- Jennifer Goulart
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- Amy Hayden
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