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Definitive Radiation + /- ADT for Locally Advanced Prostate Cancer: What is the Optimal Treatment?

APCCC

**Friday March 10th, 2017
ST GALLEN, SWITZERLAND**

No relevant disclosures

Critical Review

Radical Prostatectomy vs Radiation and Androgen Deprivation Therapy for Clinically Localized Prostate Cancer: How Good is the Evidence?

Roach, Ceron-Liagarra, Lazar et al. IJROBP 93:1064-1070, 2015

International Journal of
Radiation Oncology
biology • physics

Purpose: ... We analyzed the available literature, to determine whether reliable conclusions could be made concerning the effectiveness of RP vs RT +/- ADT, assuming current Tx standards.

Results: ... 14 studies identified (one without CSS).

Median RS=12 (< or = “low” & > “high”)

Studies with RS \leq 12 10-yr OS & CSS Diff. 17% & 6%, respectively.

... RS >12 10-yr OS & CSS, Diff, 5.5% & ~1%, respectively.

Conclusions ... The most reliable studies suggest that the differences in 10 year CSS between RP and RT ... < or = 1%.

ORIGINAL ARTICLE

Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes.

Lennermas et al.

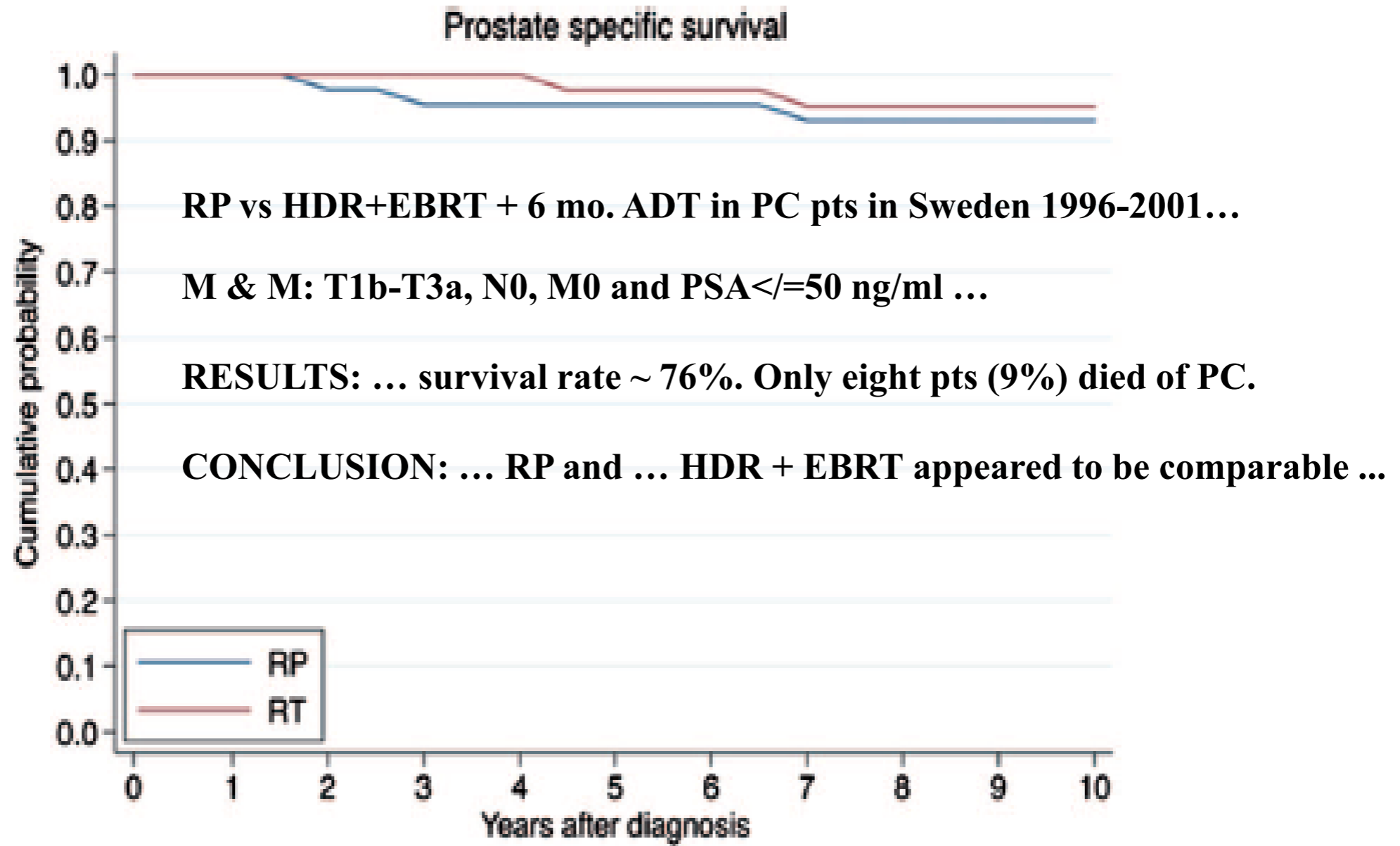
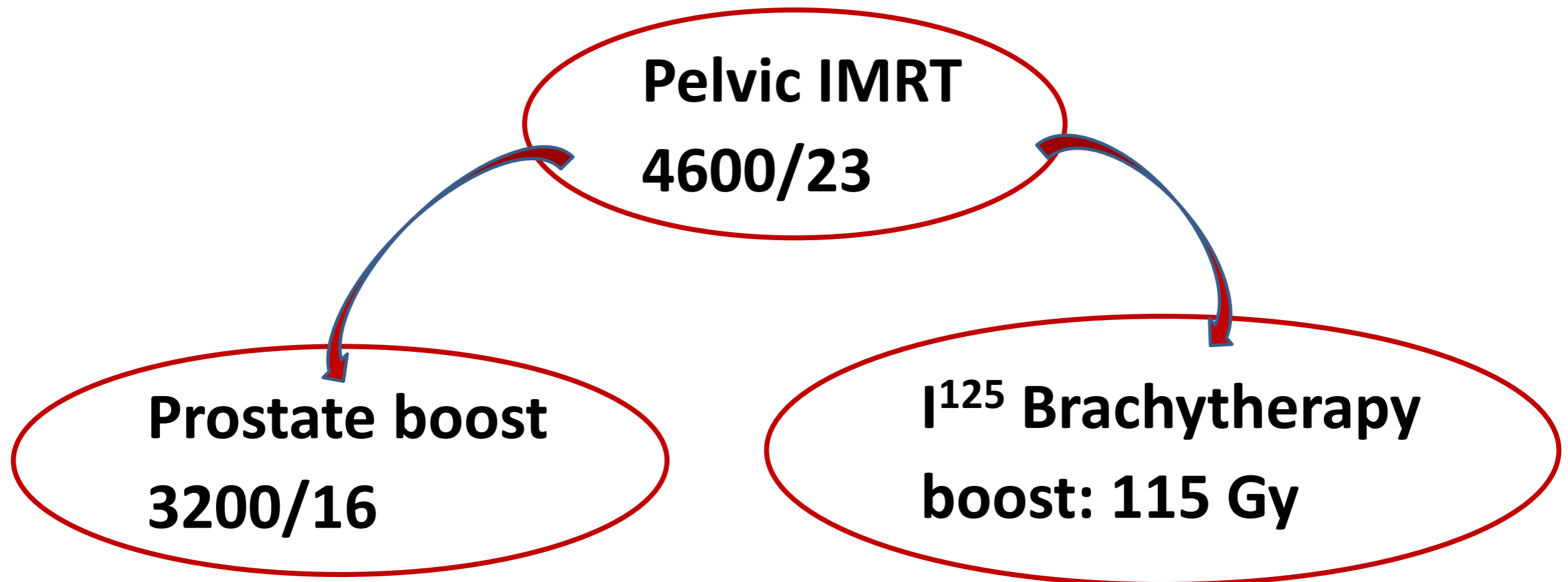


Figure 1. Cumulative probability of prostate-specific survival in RP, radical prostatectomy group compared to RT, radiotherapy group.

Level One Evidence for benefit of Brachytherapy

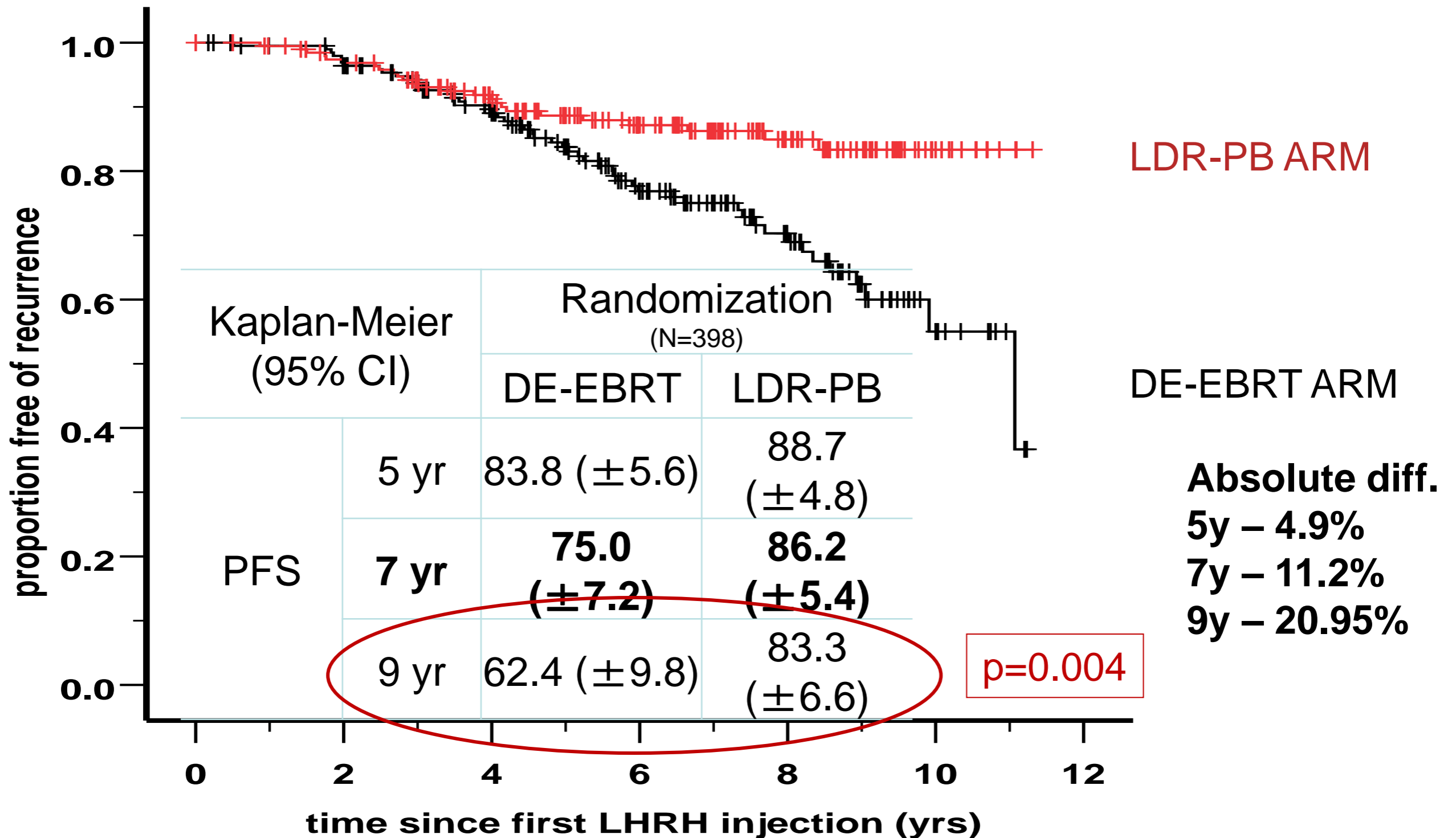
Canadian ASCENDE-RT *WJ Morris et al IJROBP 2016*

- **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

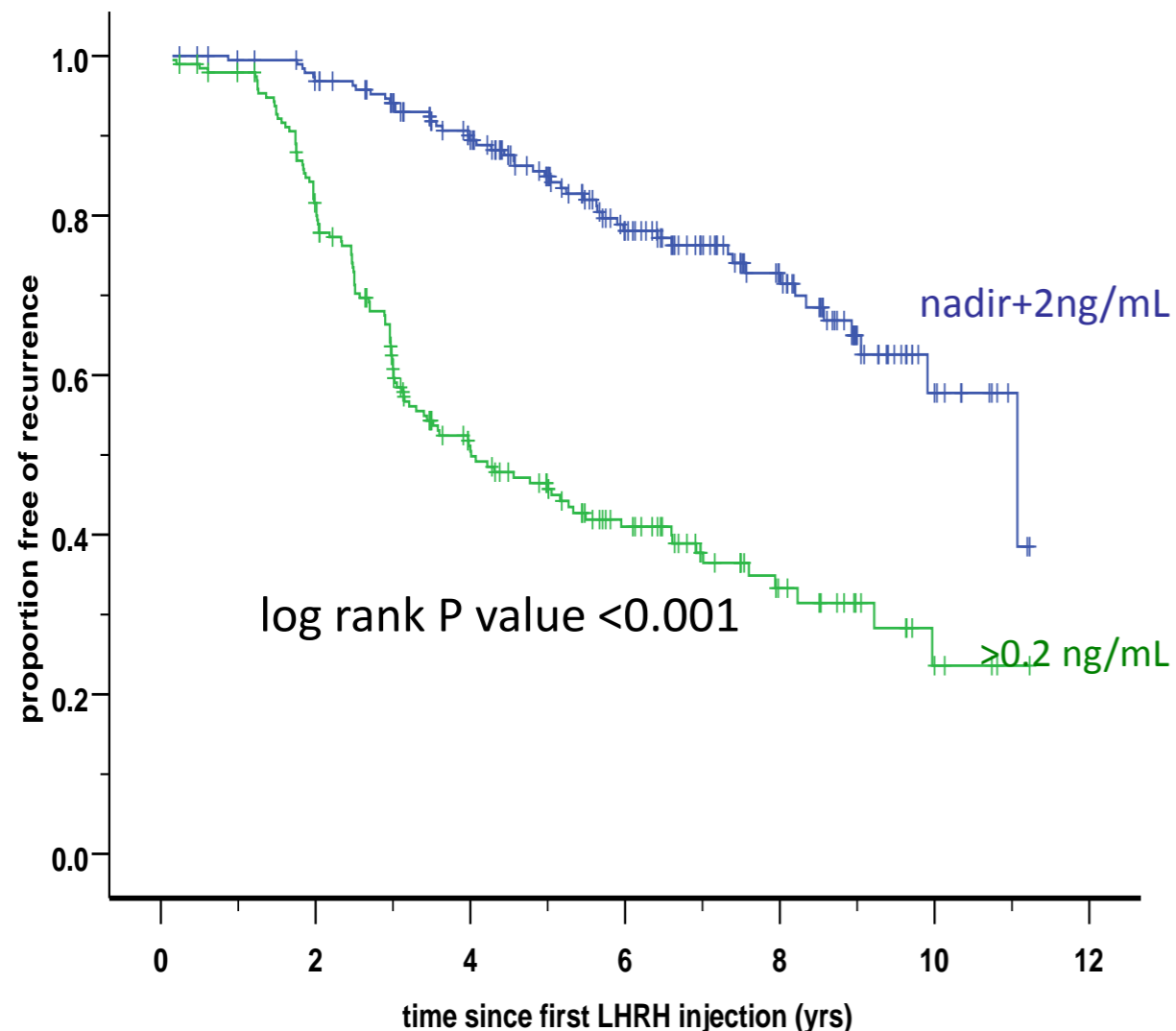
Intent-to-treat analysis of the primary endpoint



B-PFS using nadir + 2 vs. PSA > 0.2 ng/ml

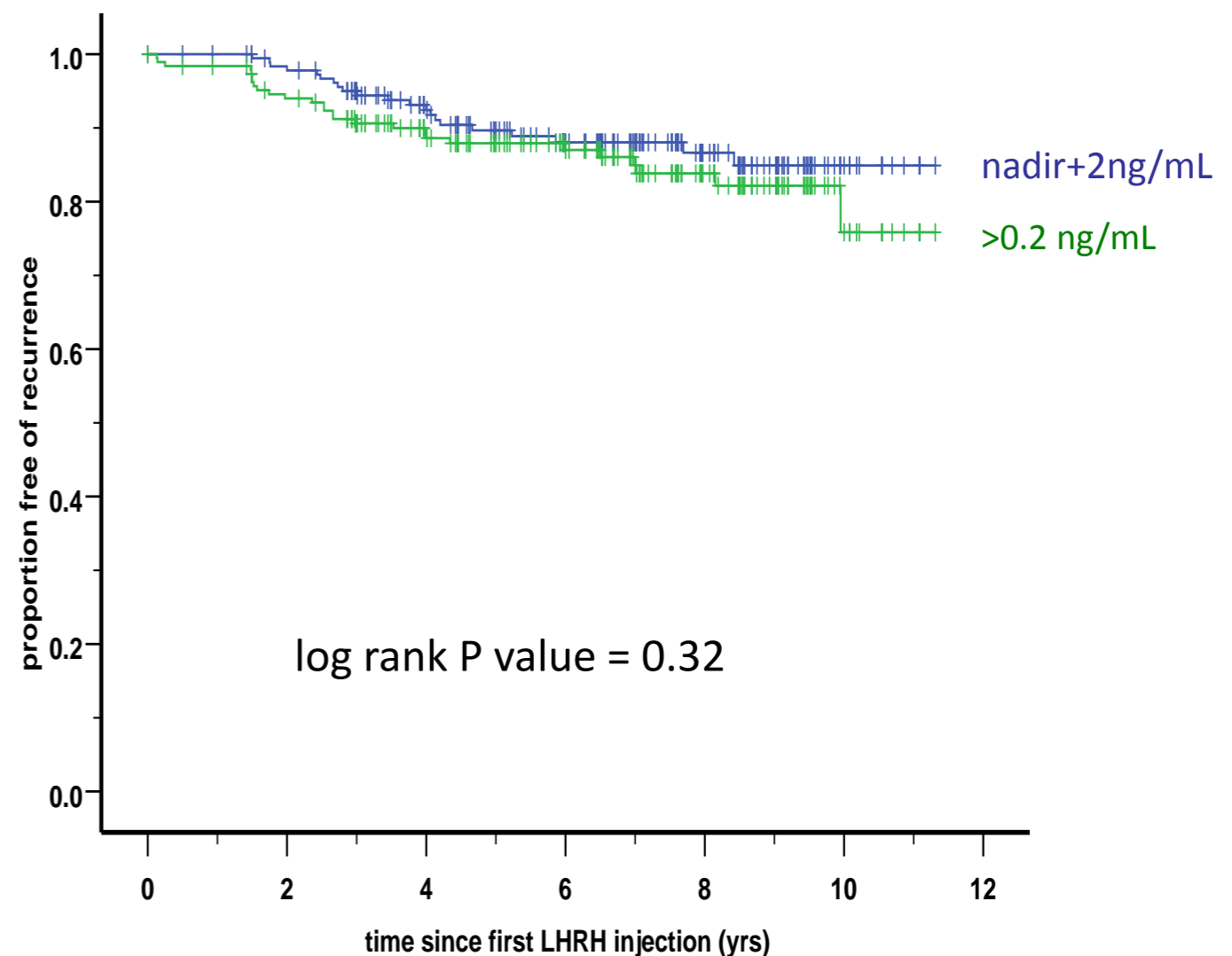
DE-EBRT (n=195)

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



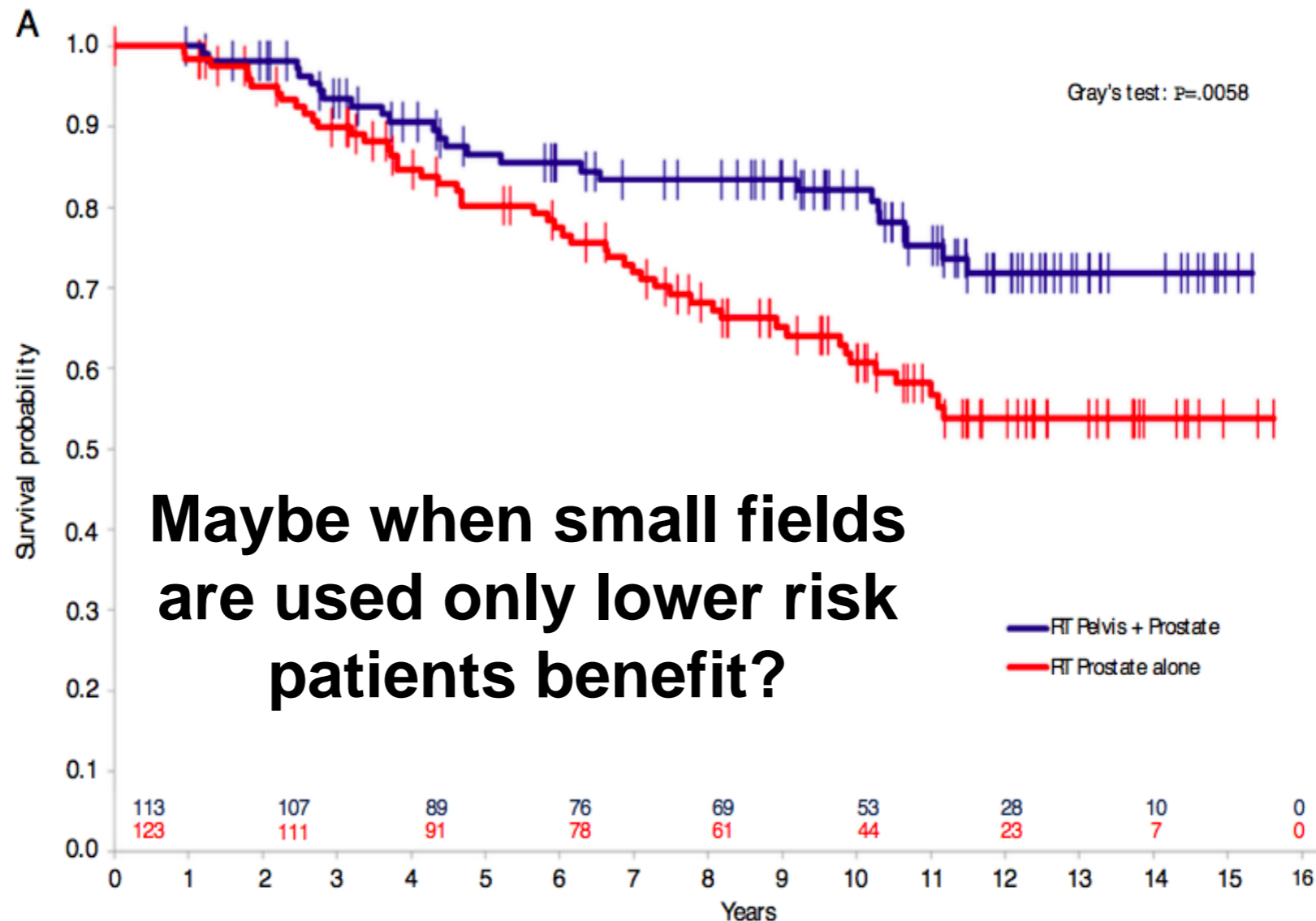
Status of WPRT for Prostate Cancer

- **Why Important?:**
 - **Small field vs Big Field?**
 - PORT (e.g. CHHiP Trial) thru SBRT or HDR monotherapy
 - **Potential Morbidity**
 - **Cost (time & money)?**
 - **Opportunity to improve outcomes!**
- **Why So Challenging?:**
 - e.g. 1200 pts with 1/3rd (33%) having + nodes
 - ... then study really based on n=400 pts
 - ... if disease beyond pelvis in 25% down to n=300 pts
 - ... and local failures 1/3rd to n=200 pts
 - ... competing causes of death (e.g. 50%) n=100
 - ... “optimal size of trial to answer questions of WPRT?”

RTOG 0924: n=2580 “big enough?”

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Update of the Long-Term Survival Results of the GETUG-01 Randomized Study

Pommier et al. IJROBP 96, 2016



Maybe when small fields are used only lower risk patients benefit?

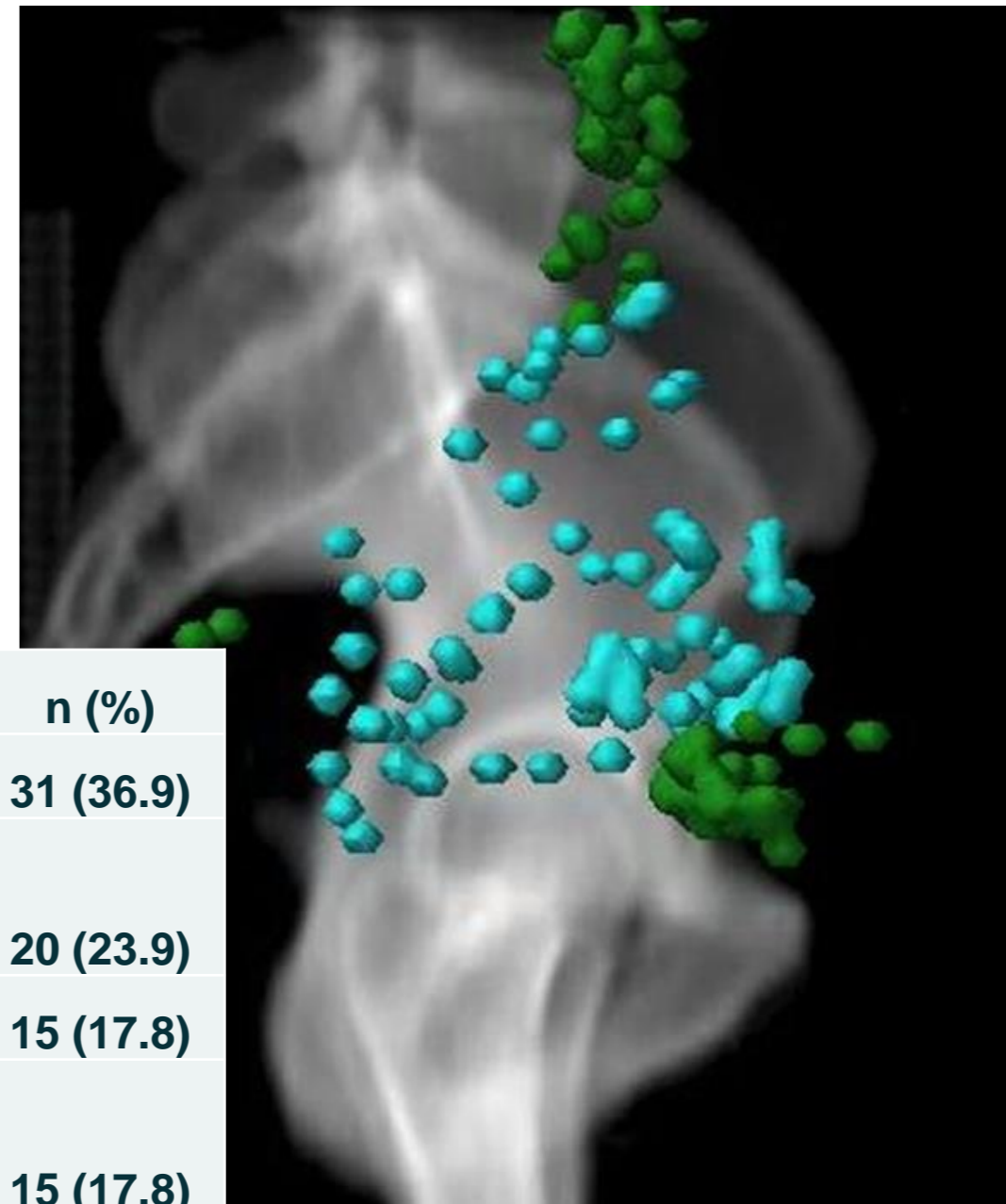
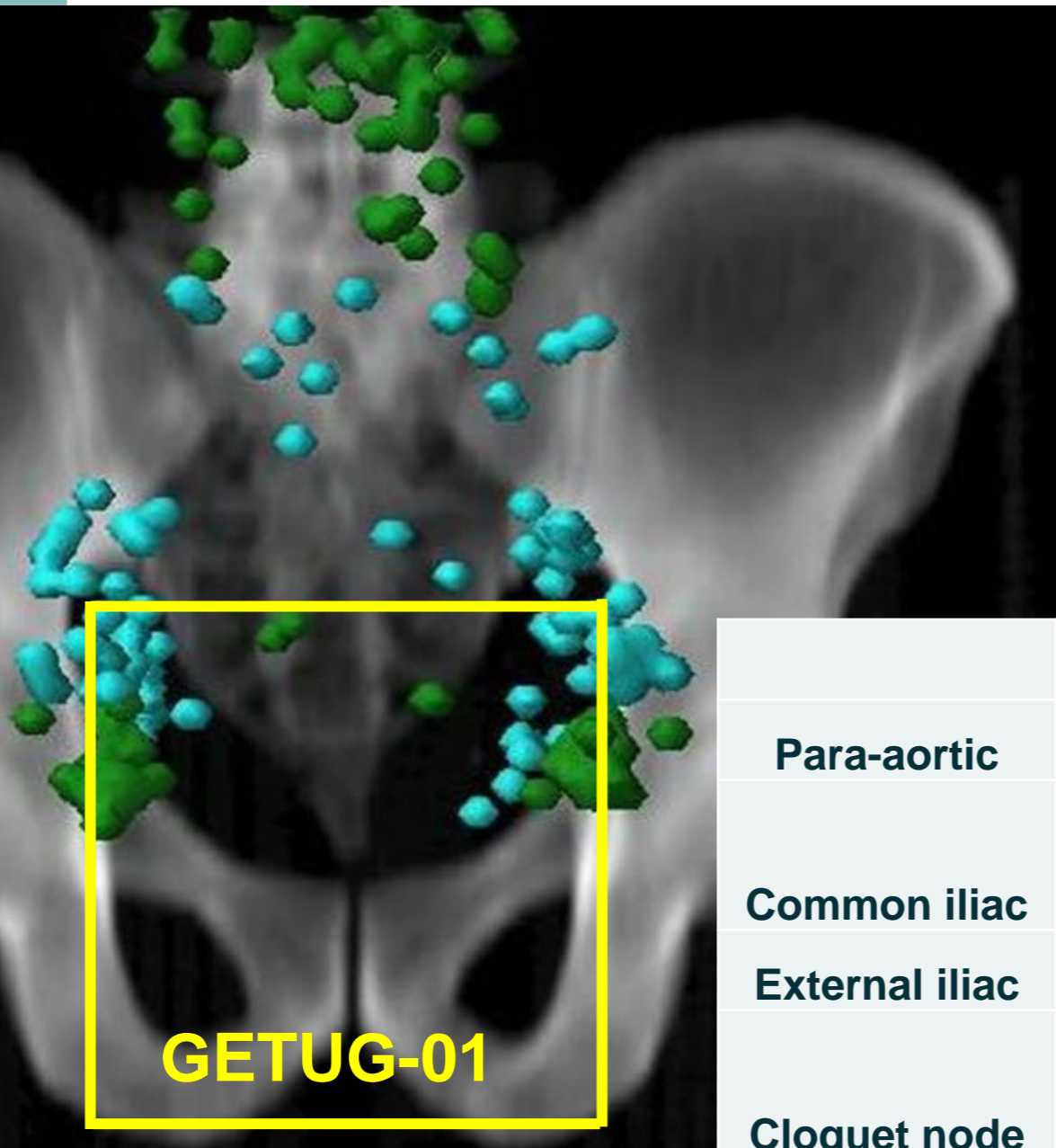
“Negative Trial”
but with issues:

1. Small (n=446)
2. Lower risk
3. Smaller fields
4. Variable ADT

Event-free survival (EFS) subset with risk of + nodes <15%

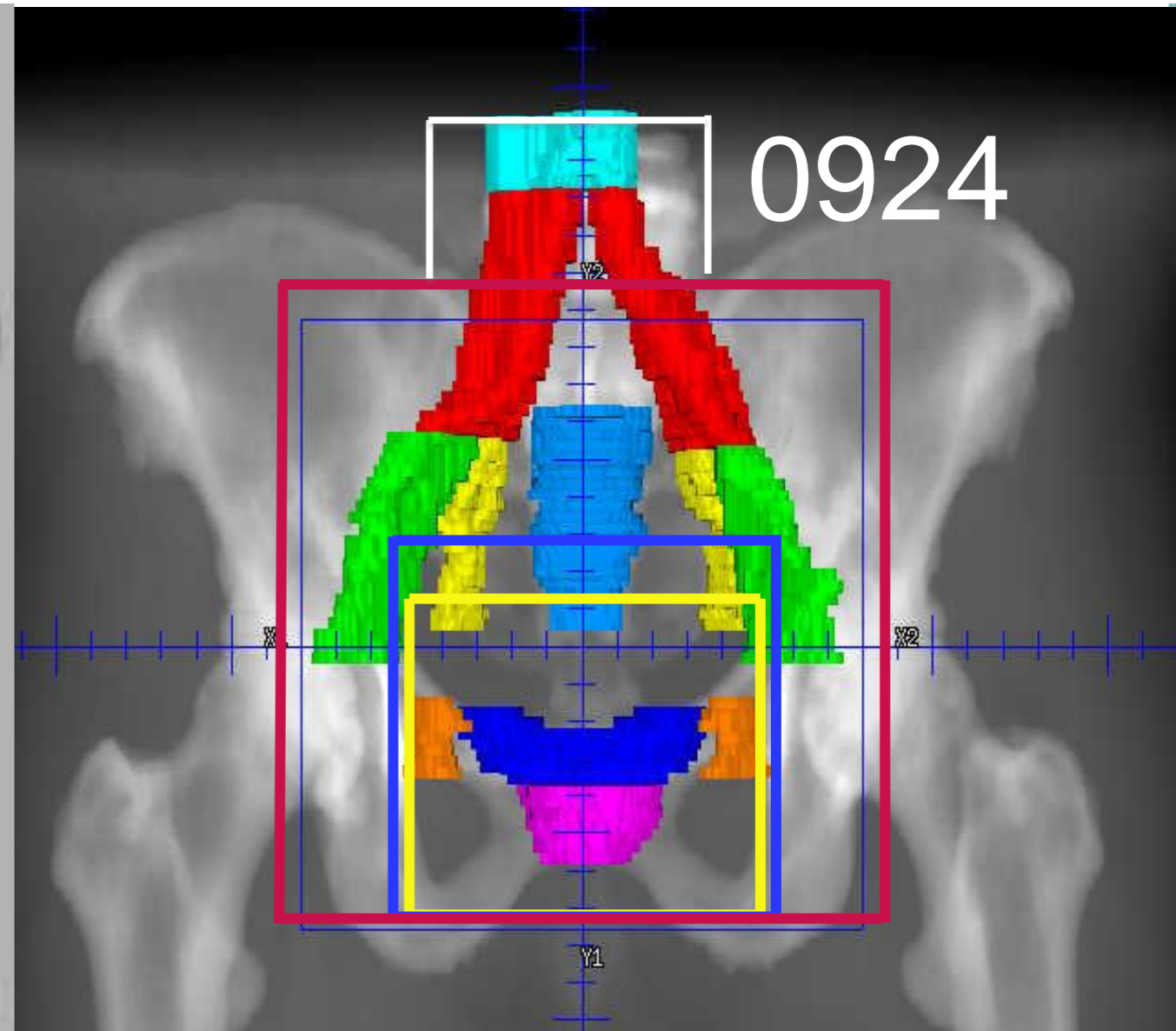
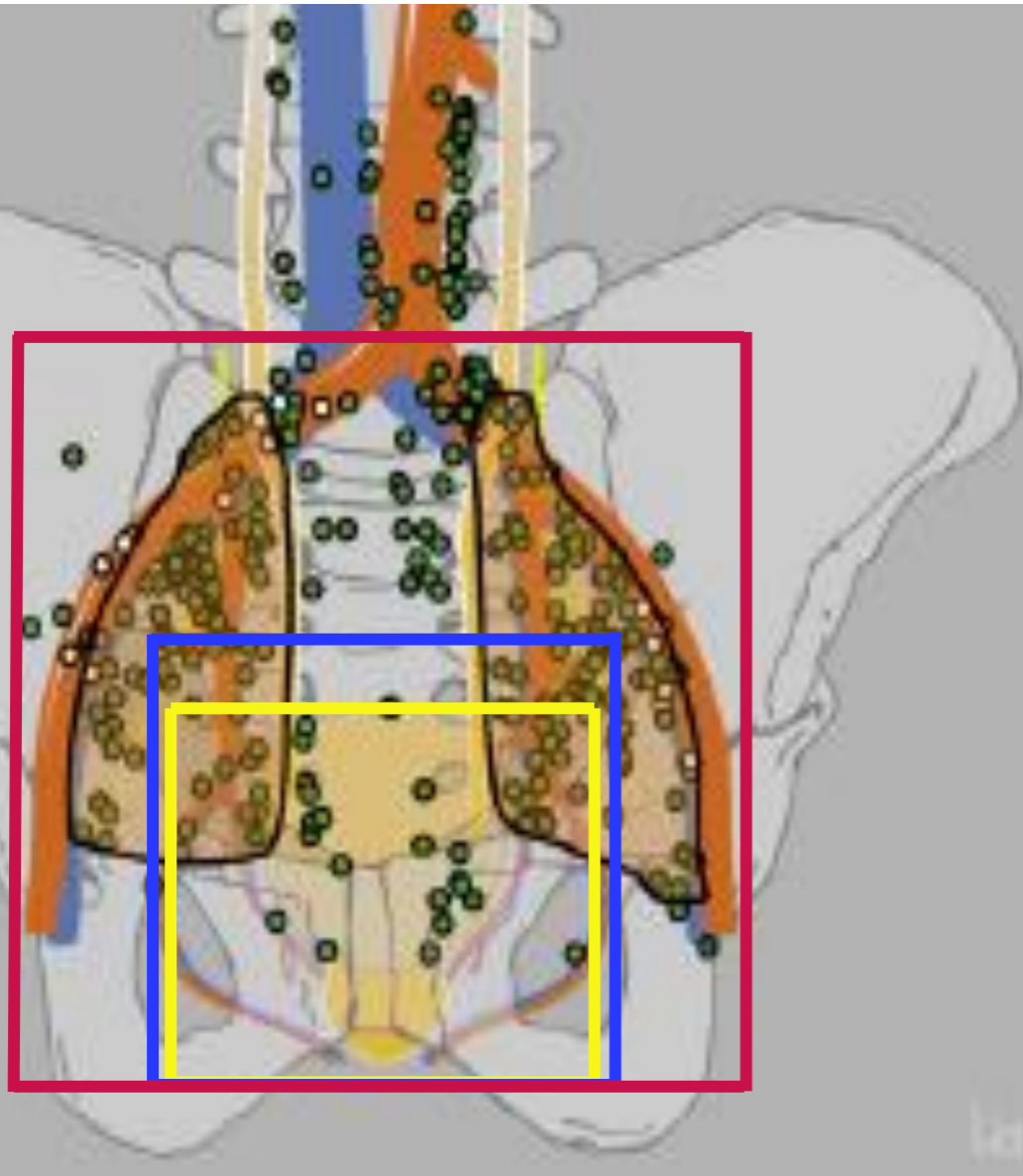
Patterns of Lymph Node Positivity on ^{11}C -acetate PET Imaging in Correlation to the RTOG Pelvic Radiation Field for Prostate Cancer.

McClinton et al. ASTRO 2015



| | n (%) |
|----------------|-----------|
| Para-aortic | 31 (36.9) |
| Common iliac | 20 (23.9) |
| External iliac | 15 (17.8) |
| Cloquet node | 15 (17.8) |
| Pre-sacral | 2 (2.4) |
| Other | 1 (1.2) |

The Template of the Primary Lymphatic Landing Sites of the Prostate Should be Revisited: Results of a Multimodality Mapping Study. Mattei ... Studer. EAU 53:118-125, 2008



RTOG 9413 (UPDATED, 4-3-2016)

Progression-Free Survival Multivariate Analysis (Phoenix)

| Outcome | Stratified variables | Variable categories | HR* | 95% CI | p-value [†] |
|---------------|----------------------|---------------------|------|-------------|----------------------|
| PFS (Phoenix) | Treatment | NHT+WPRT | RL | -- | -- |
| | | NHT+PORT | 1.21 | (1.02,1.43) | 0.027 |
| | | WPRT+AHT | 1.21 | (1.02,1.43) | 0.025 |
| | | PORT+AHT | 0.93 | (0.78,1.10) | 0.39 |
| | Gleason | 2-6 | RL | -- | -- |
| | | 7-10 | 1.27 | (1.11,1.45) | 0.0006 |
| | PSA | ≤ 30 | RL | -- | -- |
| | | > 30 | 1.43 | (1.26,1.63) | <0.0001 |
| | T-Stage | T1c,T2a | RL | -- | -- |
| | | T1b,T2b | 0.96 | (0.76,1.20) | 0.71 |
| | | T2c-T4 | 1.05 | (0.90,1.21) | 0.54 |

*HR: hazard ratio, a risk ratio of 1 indicates no difference between subgroups.

[†] p-value is from Chi-square test using the Cox proportional hazards model

(Roach et al. unpublished data, 2017)

Basis of study design for RTOG 0924?

Table 12.6. 4-Yr PFS: Intermediate Risk (PSA <30 and GS 7-10 excluding Clinical Stages T2c-T4, or GS=6 with PSA <30, Gleason 2-6, and Clinical Stages T2c-T4, or PSA ≥30 and GS 2-6)

| Treatment Arm | Failures | N | 4-Yr Rate (%) [95% C.I.] | P-Value* |
|----------------------------------|----------|-----|-----------------------------|--------------|
| Hormones + RT Whole Pelvis+Boost | 35 | 125 | 68.1 [58, 78] | 0.027 |
| Hormones + RT Prostate Alone | 56 | 125 | 46.6 [36, 58] | |
| RT Whole Pelvis+Boost + Hormones | 44 | 113 | 53.8 [42, 65] | |
| RT Prostate Alone + Hormones | 50 | 118 | 49.8 [39, 61] | |

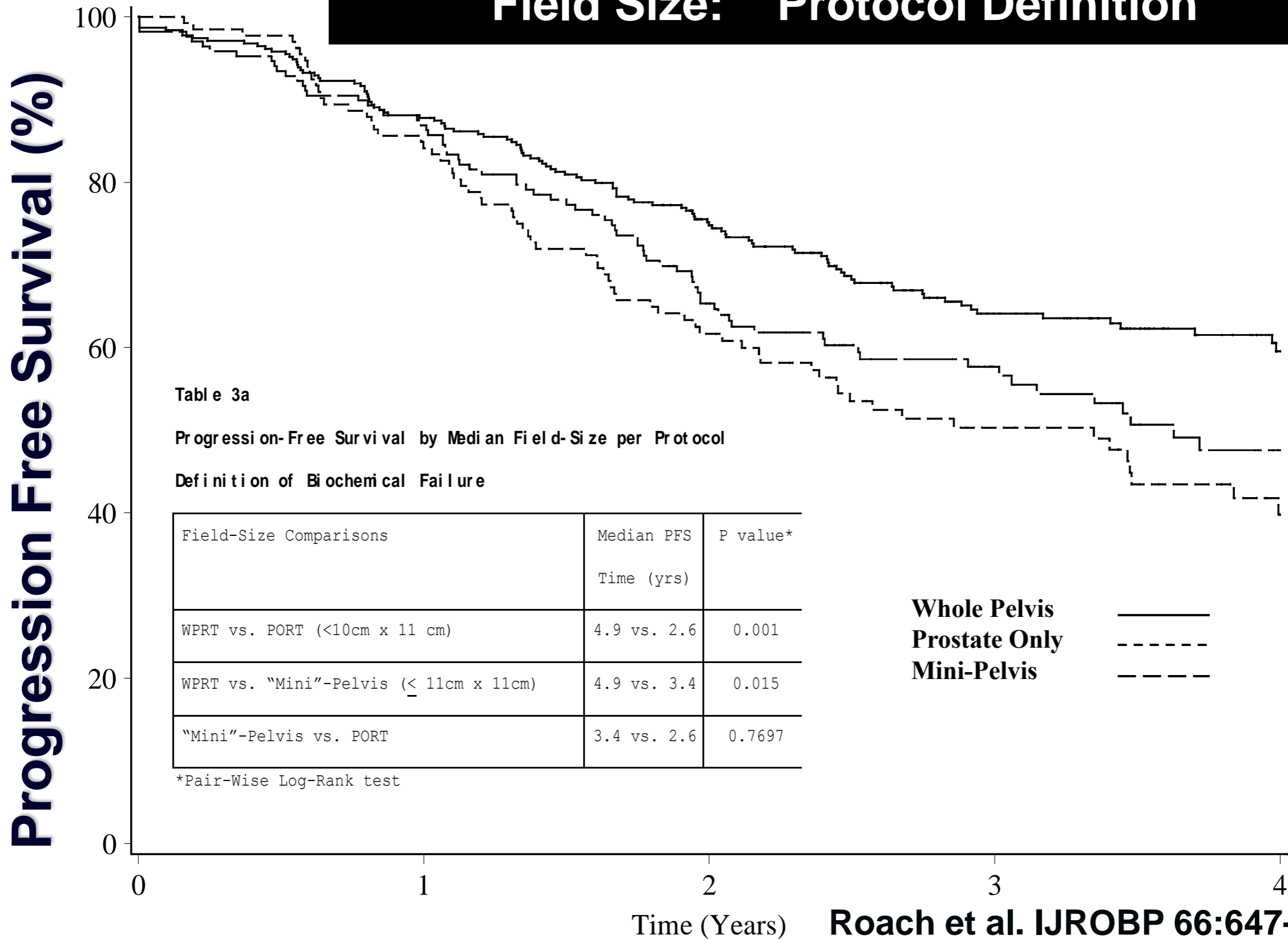
P-value from log-rank test for comparing the survival curves.

RTOG 9413* Subset middle stratification risk + nodes > 15% by Roach equation: (1) PSA <50 ng/ml & GS 7-10, T1c-T2b, or (2) GS=2-6 with Clinical Stages T2c-T4 or > 50% biopsies + & PSA <50 ng/ml, or (3) GS=2-6, PSA > 20 ng/ml and T1c-T2b

| Group | 10 yr CSS | | | | |
|--------------|-------------------|-----------------|--------|----|--------|
| PO (n=145) | 0.8497 | 0.1503 | 0.0358 | 16 | 52 |
| WPRT (n=146) | 0.9741 | 0.0259 | 0.0150 | 3 | 40 |
| | <i>Diff = 13%</i> | <i>Log-Rank</i> | 8.7735 | 1 | 0.0031 |

Max PSA < 100 ng/ml

RTOG 9413 Progression-Free Survival & Field Size: Protocol Definition

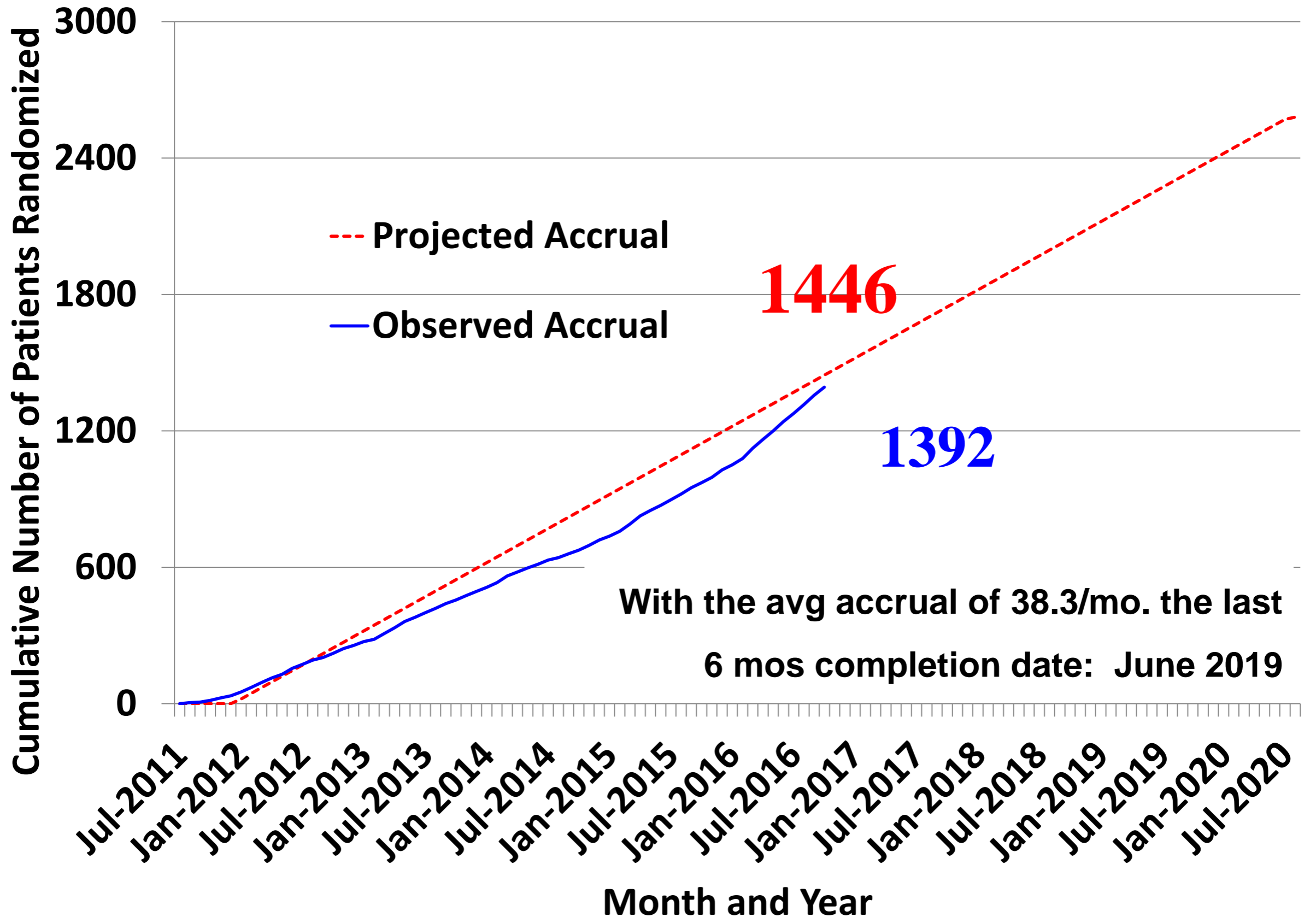


RTOG 0924

Treatment Schema

| | | | | |
|--|--|--|--|---|
| S T R A T E G Y | <p>1. Risk Group:</p> <p>“Favorable” High or “Unfavorable” Intermediate Risk:</p> <p>1.GS=7-10 and T1c-T2b and PSA < 50 ng/ml or</p> <p>2.GS=6, T2c-T4 or > 50% biopsies + & PSA <50 or</p> <p>3.GS=6, PSA > 20 ng/ml and T1c-T2b</p> | R E G I S T E R | R A N D O M I Z E | vs |
| | <p>2. Type of RT Boost:</p> <p>IMRT vs Brachytherapy (HDR + PPI)</p> | | | |
| | <p>3. Duration of Androgen Deprivation Therapy</p> <p>Short Term vs Long Term ADT</p> | | | |
| | | | | <p>Arm 1: NADT + Prostate & SV</p> <p>Arm 2: NADT + Whole-Pelvic RT</p> |

Cumulative Accrual for RTOG 0924 - Data as of 10/31/2016



Major Take Home Message: RT+/-ADT

- 1. More high level evidence supporting RT+ADT for unfavorable prostate ca. (e.g. > 65 yrs) than for RP**
- 2. Better PSA control rates with higher doses (particularly with brachytherapy e.g. ACENDE RT)**
- 3. Progression Free Survival higher with NHT & WPRT than NHT and PORT (RTOG 9413)**
- 4. RTOG (NRG) 0924 (n=2580) should allow the impact of prophlactic WPRT to be determined**