Radical Prostatectomy vs Radiotherapy in High-Risk Prostate Cancer: Individual Patient Data from two Randomized Trials

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ASCO Genitourinary Cancers Symposium

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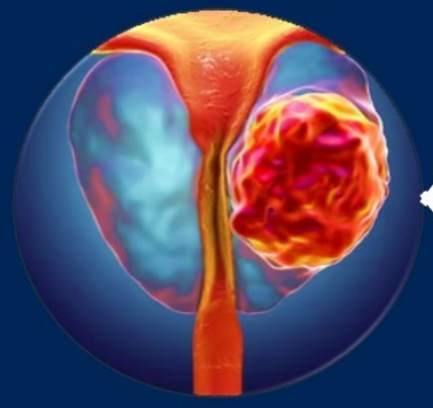
Soumyajit Roy, Yilun Sun, James Andrew Eastham, Martin Gleave, Himisha Beltran, Amar U. Kishan, Angela Y Jia, Nicholas G. Zaorsky, Jorge A. Garcia, Eric J. Small, Paul L. Nguyen, Gerhardt Attard, Rana R. McKay, Alton Oliver Sartor, Seth A. Rosenthal, Susan Halabi, Mack Roach III, Felix Y Feng, Michael J. Morris, Howard M. Sandler, Daniel E. Spratt

PRESENTED BY: Soumyajit Roy, MBBS, MSc.

Background

High Risk
Prostate Cancer



- PSA >20 ng/mL
- Gleason Score 8-10
  (Grade Group 4-5)
- Clinical ≥T3
  (Extracapsular extension or seminal vesicle invasion)

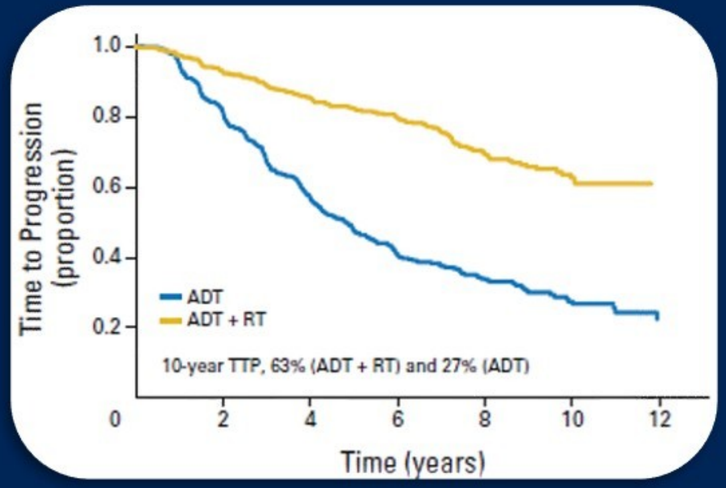
Background

NCCN

High Risk

RT + Long-term ADT

(Category 1)



RP w/ personalized post-operative therapy

(Category 2A)

SPCG-15

Primary radical prostatectomy versus primary radiotherapy for locally advanced prostate cancer: an open randomized clinical trial

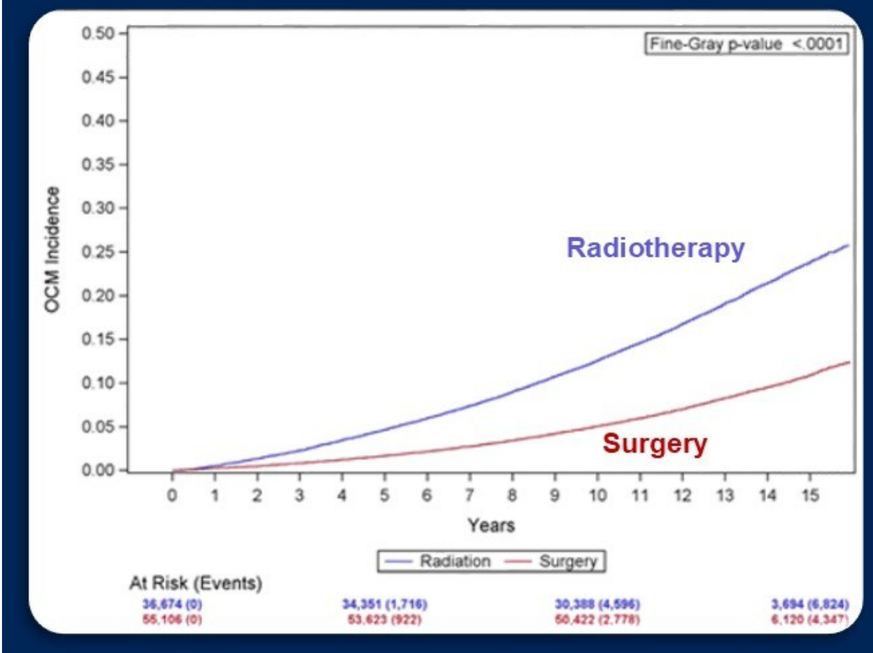
"there are no clinical trials of multi-modal treatment of locally advanced prostate cancer that includes surgical removal of the prostate."

Mason MD, et al. JCO 2015
NCCN 2024

Background

RT + Long-term ADT vs RP w/ personalized post-operative therapy

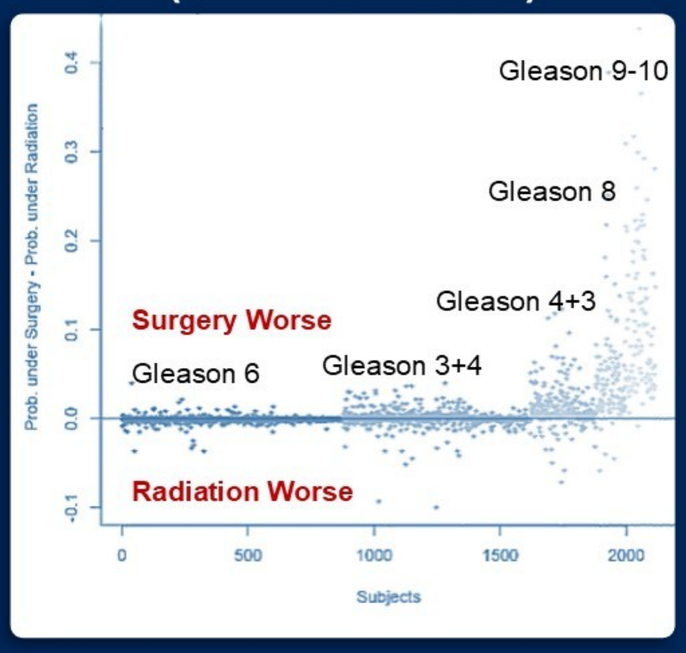
Other-Cause Mortality



- Population Registries
- Retrospective Institutional Studies

Bias and confounding
- high rates of missing data
- non-standardized treatment
- non-standardized follow-up
- incomplete information on treatment
- selection bias

Distant Metastasis (Clinical Failure)



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Finati M, et al. Clin GU Cancer. 2024
Beesley LJ, Morgan TM, et al. JAMA NO. 2019

Background

RT + Long-term ADT vs RP w/ personalized post-operative therapy

Hypothesis:

Use of national cooperative group phase III randomized trial data of patients that were contemporaneously enrolled in trials with a similar therapeutic question would reduce or obviate many sources of bias

Bias and confounding
- ~~high rates of missing data~~
- ~~non-standardized treatment~~
- ~~non-standardized follow-up~~
- ~~incomplete information on treatment~~
- selection bias

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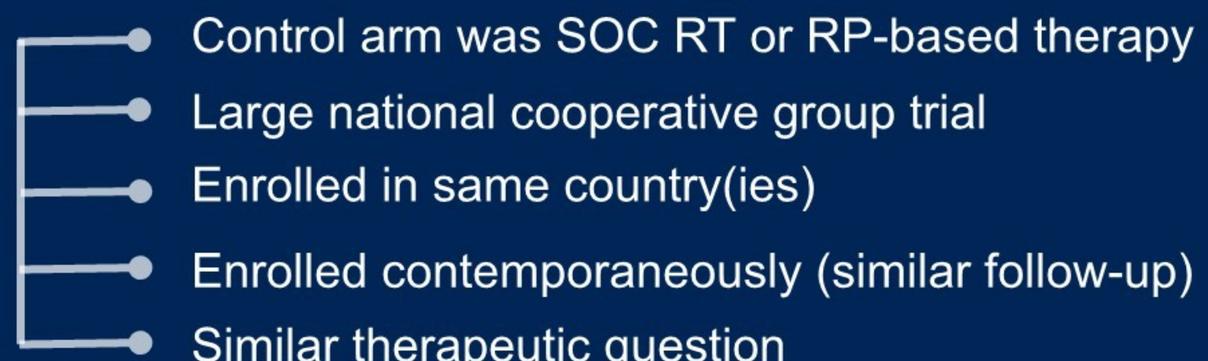
Methods

- Systematic search



CALGB 90203 (PUNCH)

High-risk Prostate Cancer

- cT1-T3a
- PSA ≤100 ng/mL
- Gleason score of 8-10
- Kattan nomogram predicted bPFS probability of <60% at 5-years

→ **RP w/ personalized post-op therapy**

23% received adjuvant RT
49% received salvage therapy.

→ **RP w/ personalized post-op therapy + 6 c of neoadjuvant docetaxel and ADT**

13% received adjuvant RT
39% received salvage therapy

Extended pelvic LN dissection used in both arms.

NRG/RTOG 0521

High-risk Prostate Cancer

- GS 9-10
- GS 7-8 + PSA >20-150 ng/mL
- GS 8 + PSA <20 ng/mL + ≥cT2

→ **RT plus Long-term ADT**

→ **RT plus Long-term + 6 c of adjuvant docetaxel**

RT: 72-75.6 Gy with nodal coverage
ADT: 24 months of GnRH agonist

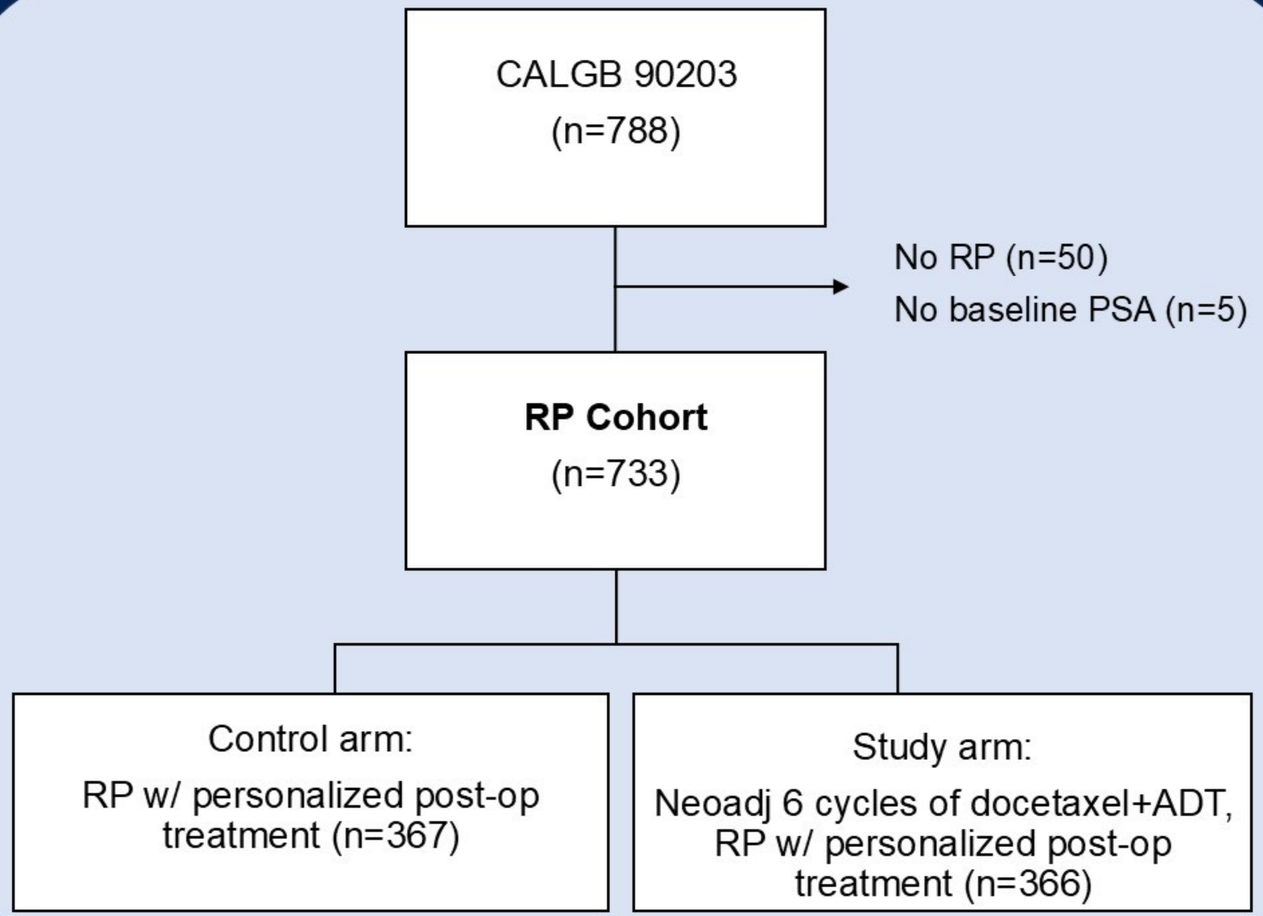
Methods: Statistical Considerations

- **Primary objective:**
  - To compare the cumulative incidence of distant metastasis (DM) between treatment groups considering deaths as competing events.
    - Inverse probability of treatment weighting (IPTW)
    - Multivariable Fine and Gray's regression
    - Multivariable Fine and Gray's regression with IPTW (doubly robust)

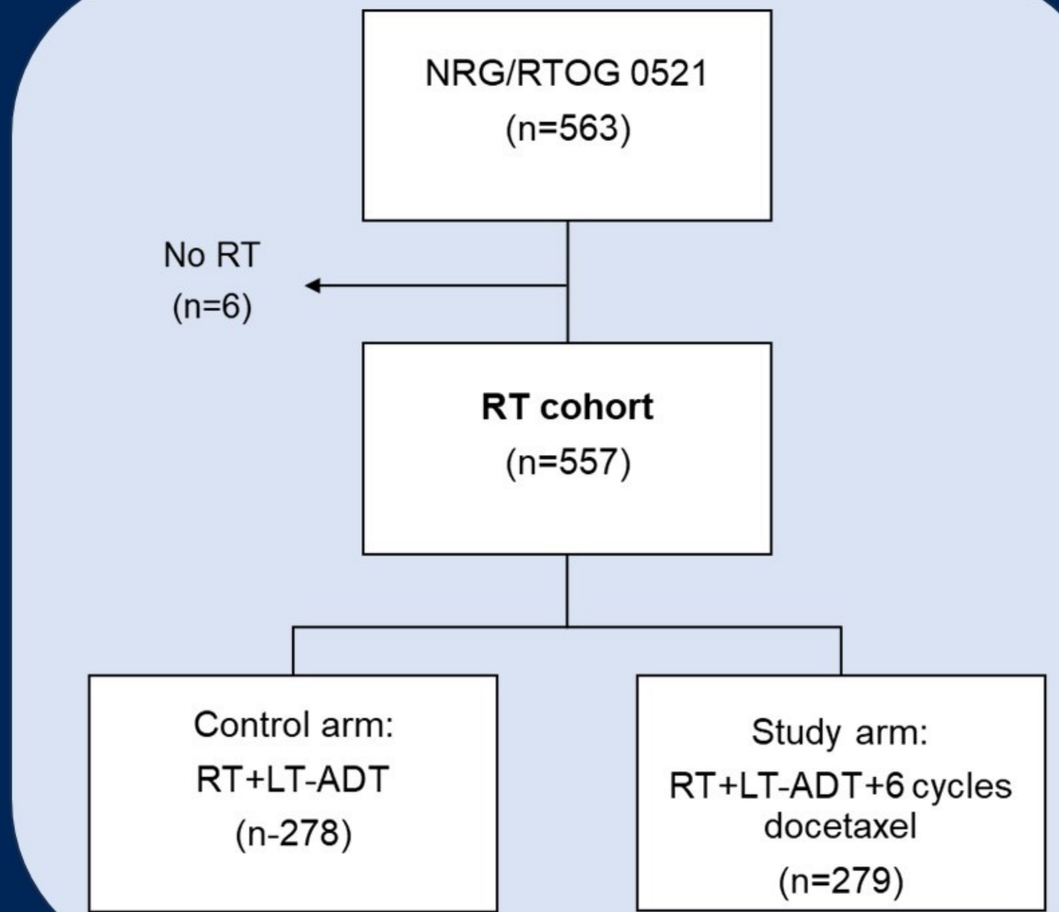
Methods: Statistical Considerations

- **Secondary endpoints have variable limitations, but are reported:**
  - Cumulative incidence of BCR: *BCR definition different post-RT or post-RP*
    - Considering PSA progression (as defined each trial), or onset of salvage therapy prior to reaching BCR as events of interest.
  - Prostate cancer specific mortality: *Attribution bias*
    - Definition 1: Death after DM
    - Definition 2: Death after progression
  - Other cause mortality: *Selection bias and attribution bias*
    - Definition 1: Death without DM
    - Definition 2: Death without progression

Radical Prostatectomy Cohort



Radiotherapy Cohort



Results: Baseline Characteristics

	Surgery-based treatment (n=733)	RT-based treatment (n=557)	P-value
Age			
Median (IQR)	63 (57 to 67)	66 (60 to 72)	<0.001
>70	69 (9%)	173 (31%)	
Biopsy Gleason score			
6-7	93 (13%)	89 (16%)	0.03
8	279 (38%)	176 (32%)	
9-10	361 (49%)	292 (52%)	
Clinical tumor stage			
T3-T4	127 (17%)	152 (27%)	<0.001
Baseline PSA			
Median (IQR)	10 (6.0 to 20)	15 (7.0 to 34)	<0.001
>20 ng/mL	187 (25%)	236 (43%)	
Risk Groups			
High (NCCN)	578 (79%)	379 (66%)	<0.001
Very High (STAMPEDE)	155 (21%)	178 (34%)	

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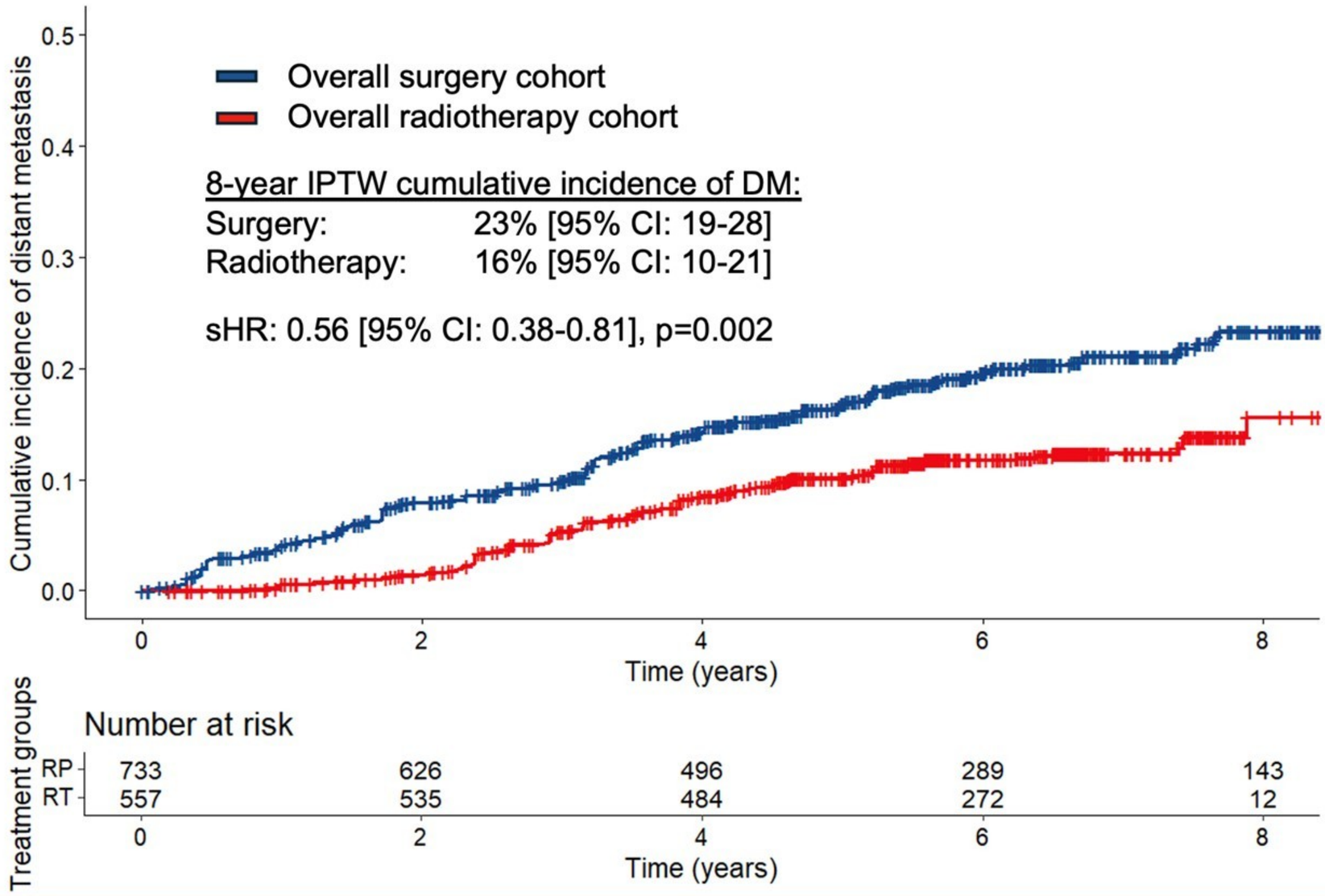
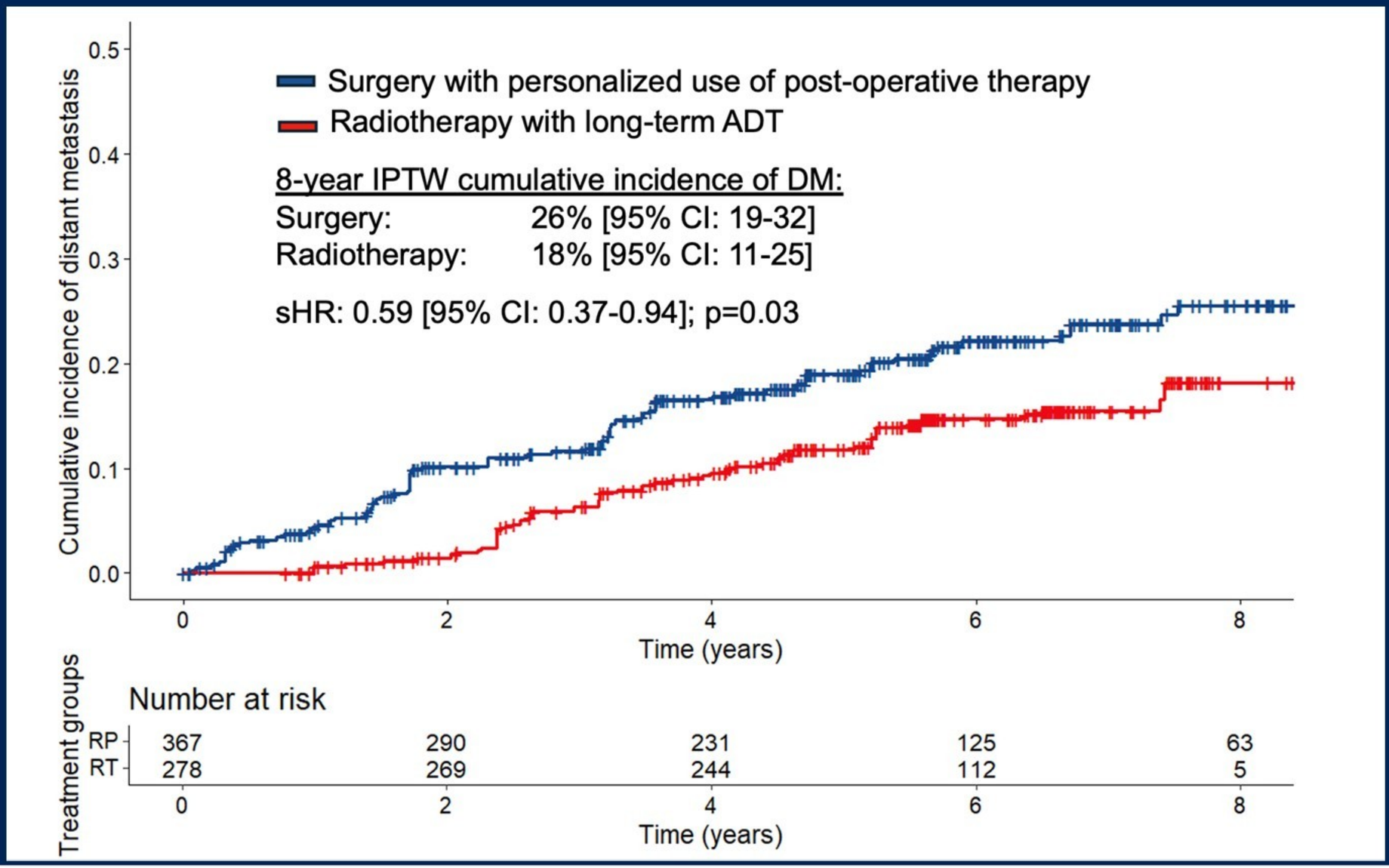
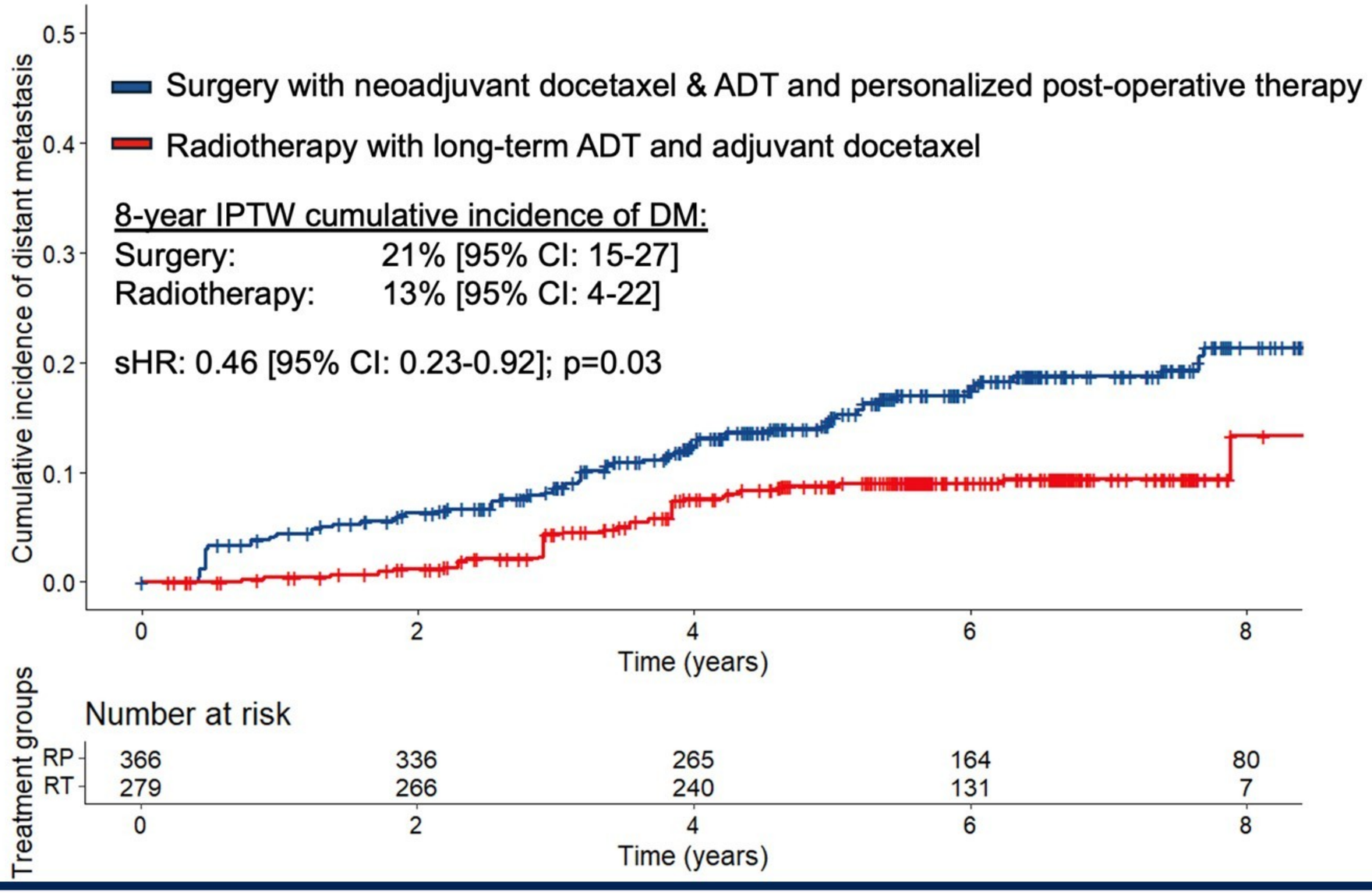
Primary Objective: Overall Cohort



Standard of Care Comparison: RT+LT-ADT vs RP+Personalized Post-op Rx

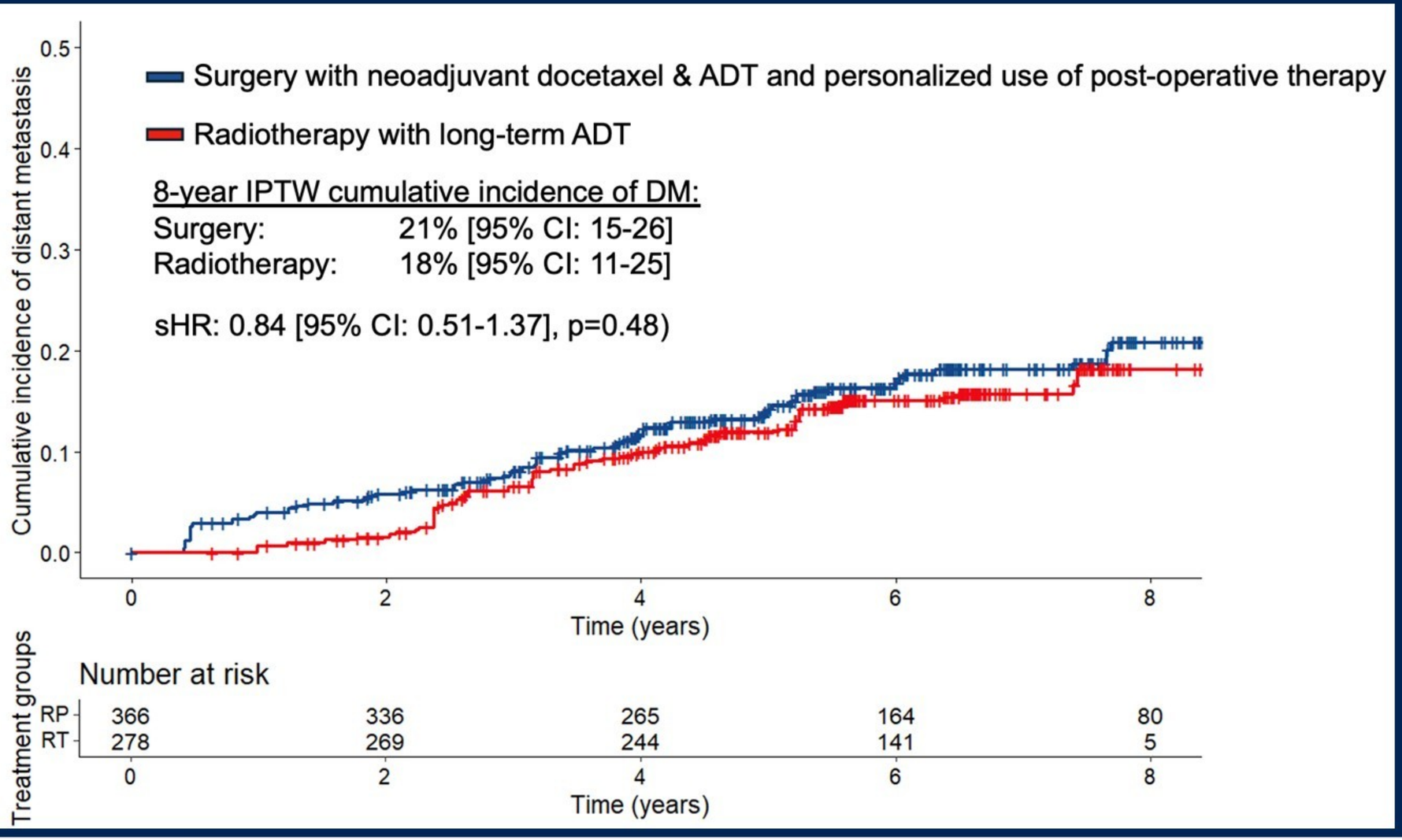


Experimental (docetaxel) Arm Comparison



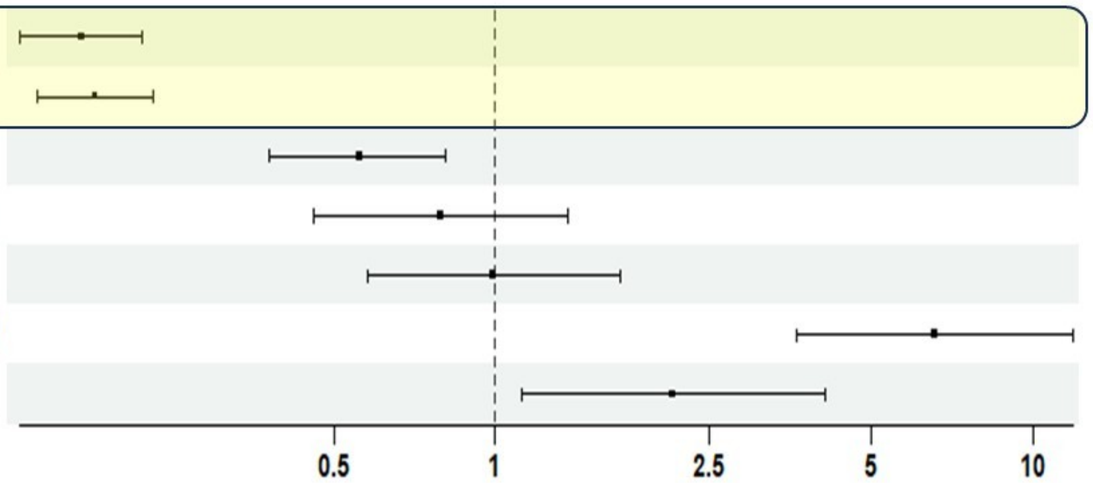
RT+LT-ADT vs Chemotherapy+ADT+RP+Personalized Post-op Rx

(Doublet) (Triplet/Quadruplet)



Results: Secondary Endpoints

Endpoints	8-yr Incidence (RP)	8-yr Incidence (RT)	IPTW HR [95% CI]
Biochemical recurrence	0.72 (0.67-0.76]	0.30 [0.24-0.35]	0.17 [0.13-0.22]
Progression	0.77 [0.72-0.80]	0.33 [0.27-0.38]	0.18 [0.14-0.23]
Distant Metastasis (DM)	0.23 [0.19-0.28]	0.16 [0.10-0.21]	0.56 [0.38-0.81]
PCSM1 (Death after Progression)	0.15 (0.10-0.19)	0.11 (0.07-0.15)	0.79 (0.46-1.36)
PCSM2 (Death after DM)	0.10 [0.06-0.13]	0.08 [0.05-0.12]	0.99 [0.58-1.71]
OCM1 (Death without Progression)	0.01 [0.004-0.02]	0.11 [0.07-0.15]	6.57 [3.64-11.85]
OCM2 (Death without DM)	0.07 [0.03-0.10]	0.14 [0.09-0.18]	2.14 [1.12-4.10]



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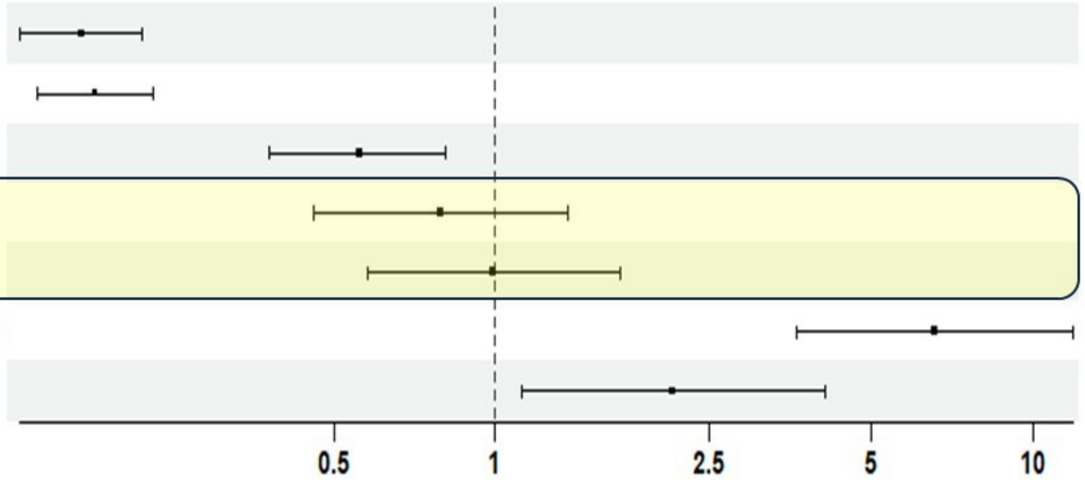

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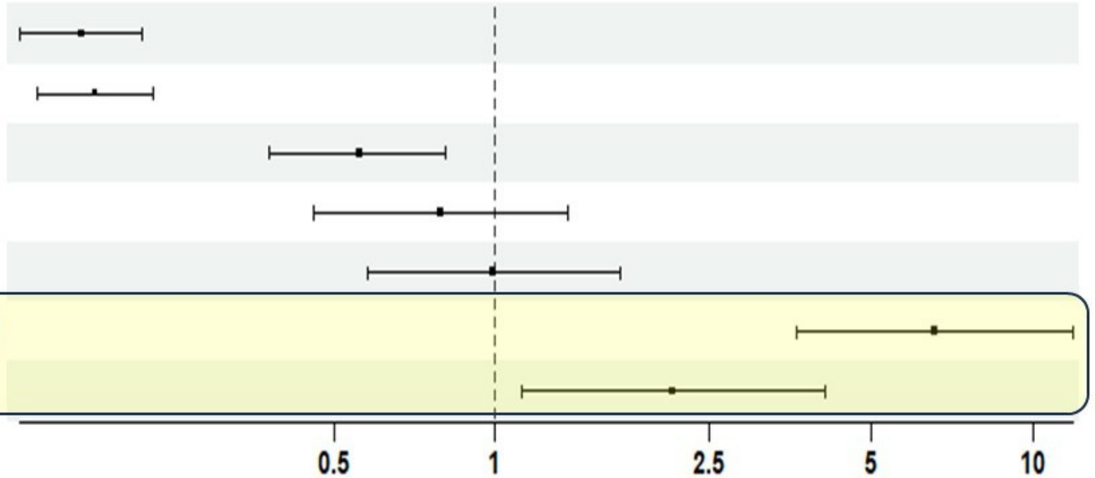

Limitations

- Residual unmeasured confounding and selection bias.
  - Seen by early and large differences in OCM as anticipated.

- Intermediate follow-up (6.4 years) with limited PCSM events.

- Contemporary practice implications:
  - PSMA PET imaging
  - Abiraterone acetate/prednisone now SOC w/ RT for very high-risk

Key Takeaway Points/Conclusions

- Of the current NCCN guideline recommended treatment regimens, a radiotherapy-based treatment regimen appears to result in a lower incidence of distant metastasis than a surgery-based regimen for patients enrolled on phase III RCTs.
  - Approximately 80% of men with high-risk prostate cancer treated with surgery will receive further treatment or experience recurrence.
    - Adjuvant/Early Salvage RT remains critical for this population
  - Use of triplet/quadruplet therapy of neoadjuvant chemoADT, RP, and personalized post-op RT/ADT may mitigate these differences when compared to a doublet of RT+LT-ADT. Toxicity and cost implications require further study.
- SPCG-15 is an actively enrolling Phase III trial aimed to directly address this question.
  - Notably, it is in a more favorable risk population than the present study.

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Thank You