PORTOS Gene Signature: A Predictor of Radiation Therapy Outcomes

Personalized Oncology through Genomic Risk Stratification

Presented by: Dr. Vikas Kothavade

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Jupiter Hospital, Pune

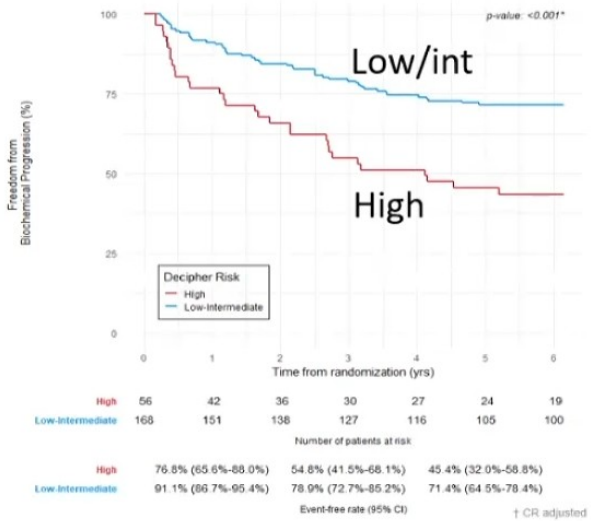
PORTOS Gene Expression Signature

- **PORTOS = Prostate Radiation Therapy Outcome Score**
- A 24-gene expression score assessing DNA damage response and radiation sensitivity(ASCO publication).
- Developed on Veracyte's Decipher® platform using these genes to calculate radiation response.

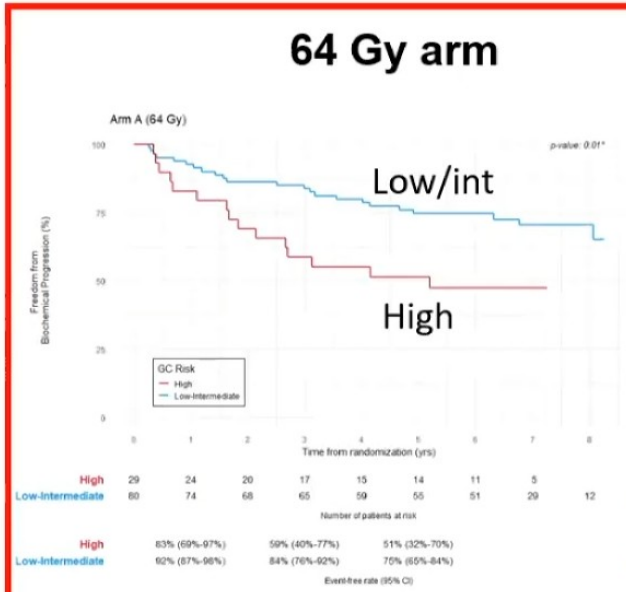
First biomarker validated in multiple randomized trials for predicting radiation dose response in any cancer, providing **level 1b evidence** to guide personalized treatment decisions

Decipher is a strong prognostic marker, but did not predict benefit from dose escalation

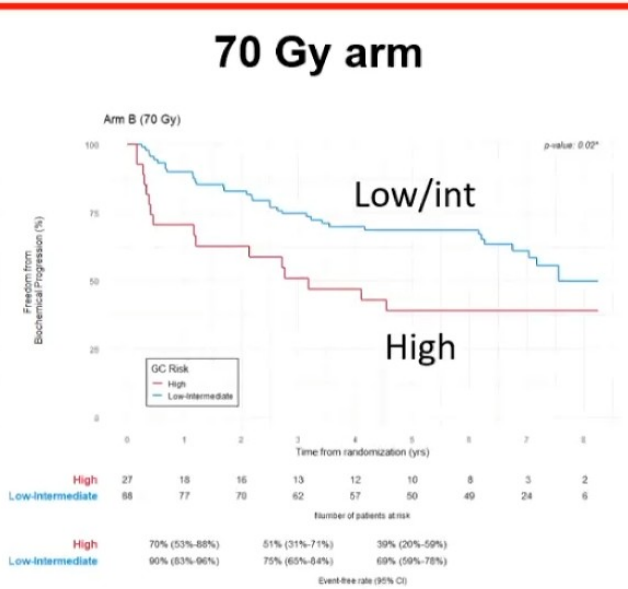
Full cohort



64 Gy arm



70 Gy arm



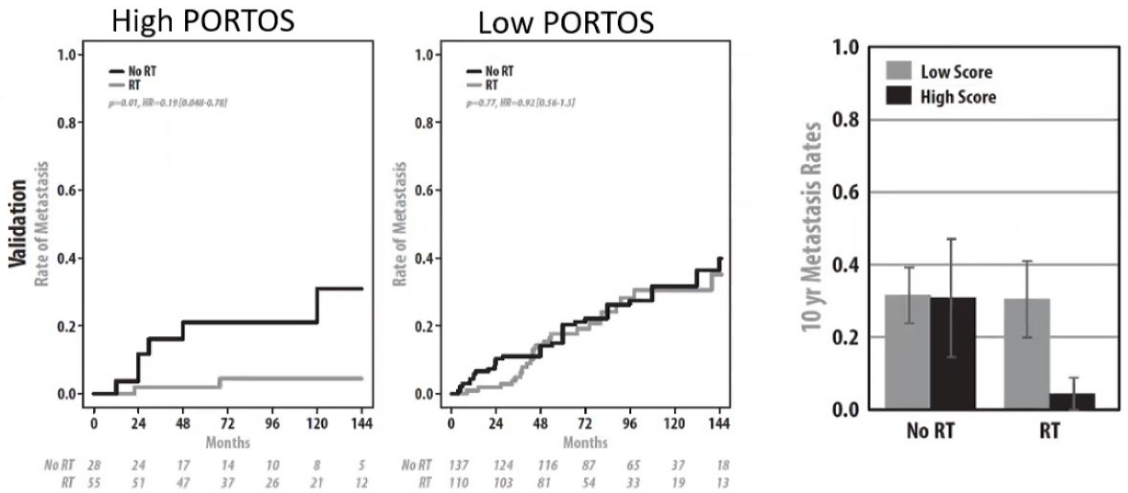
Similar estimates in the 64- vs. 70-Gy arms within GC high and within GC low–intermediate; no SS interaction between Decipher status and RT dose

Dal Pra et al., Ann Oncol 2022

Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis

Shuang G Zhao*, S Laura Chang*, Daniel E Spratt, Nicholas Erho, Menggang Yu, Hussam Al-Deen Ashab, Mohammed Alshalalfa, Corey Speers, Scott A Tomlins, Elai Davicioni, Adam P Dicker, Peter R Carroll, Matthew R Cooperberg, Stephen J Freedland, R Jeffrey Karnes, Ashley E Ross, Edward M Schaeffer, Robert B Den, Paul L Nguyen†, Felix Y Feng†

PORTOS is an expression signature of 24 DNA damage repair, and immune pathway genes



Patients with high PORTOS scores may benefit from post-op RT

Zhao et al., Lancet Oncol 2016

Key Findings:

- In patients with high PORTOS scores, postoperative radiotherapy significantly reduced the 10-year incidence of distant metastasis compared to those who did not receive radiotherapy.
- Conversely, patients with low PORTOS scores had a higher incidence of metastasis when treated with radiotherapy, suggesting potential overtreatment.

ASCO Genitourinary Cancers Symposium

Gene signature predictor of dose-response to prostate radiation: Validation of PORTOS in phase III trials

Shuang (George) Zhao, Hyunnam Monica Ryu, James A. Proudfoot, Elai Davicioni, Jeff M. Michalski, Daniel E. Spratt, Stefanie Hayoz, Jeffry Simko, Howard M. Sandler, Alan Pollack, Matthew Parliament, Ian S. Dayes, Rohann Jonathan M. Correa, Theodore Karrison, William A. Hall, Daniel M. Aebersold, Felix Y. Feng, Pirus Ghadjar, Phuoc T. Tran, Alan Dal Pra

PRESENTED BY: Shuang (George) Zhao MD, University of Wisconsin

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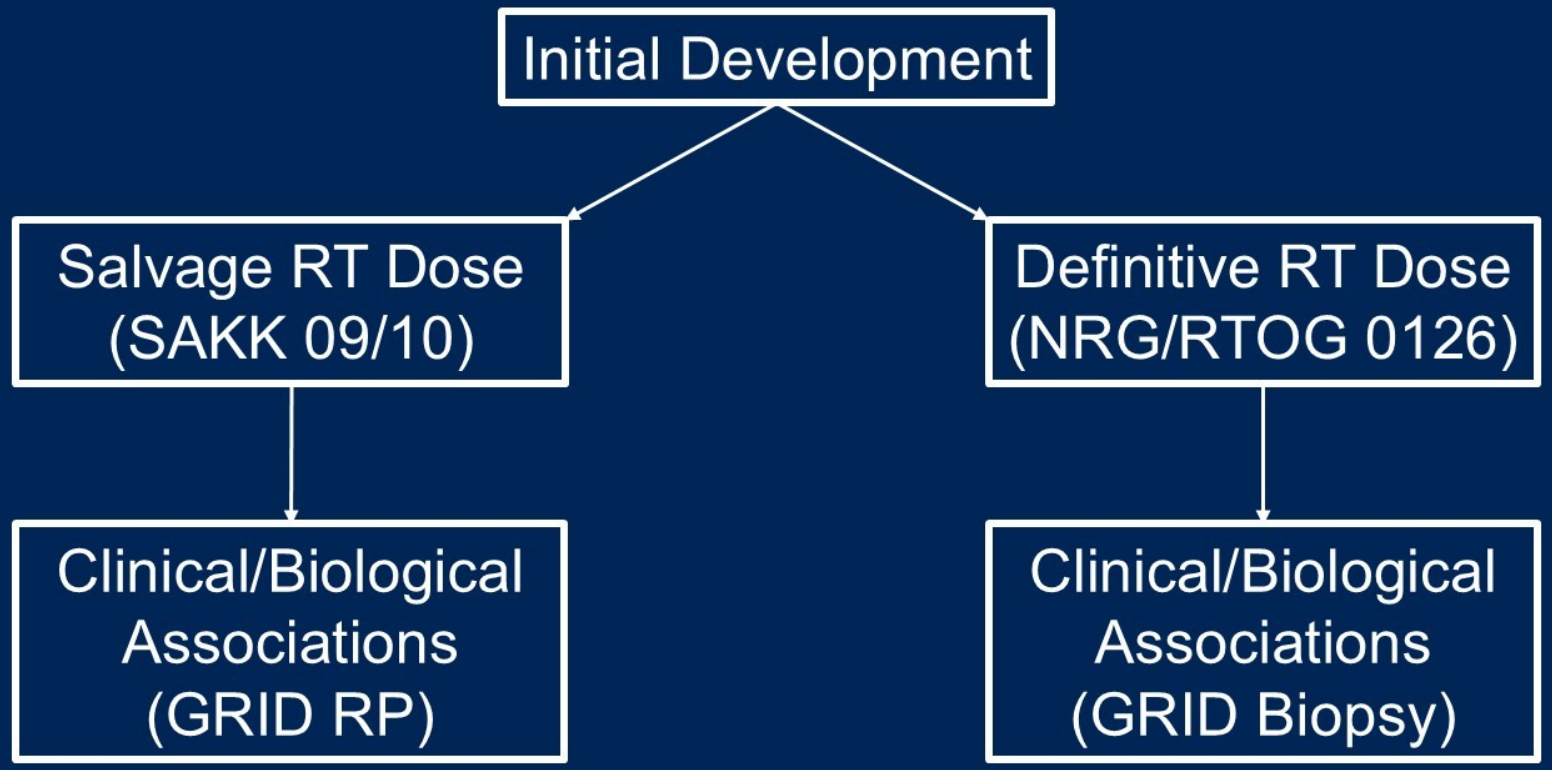
Post-Operative Radiation Therapy Outcomes Score (PORTOS)



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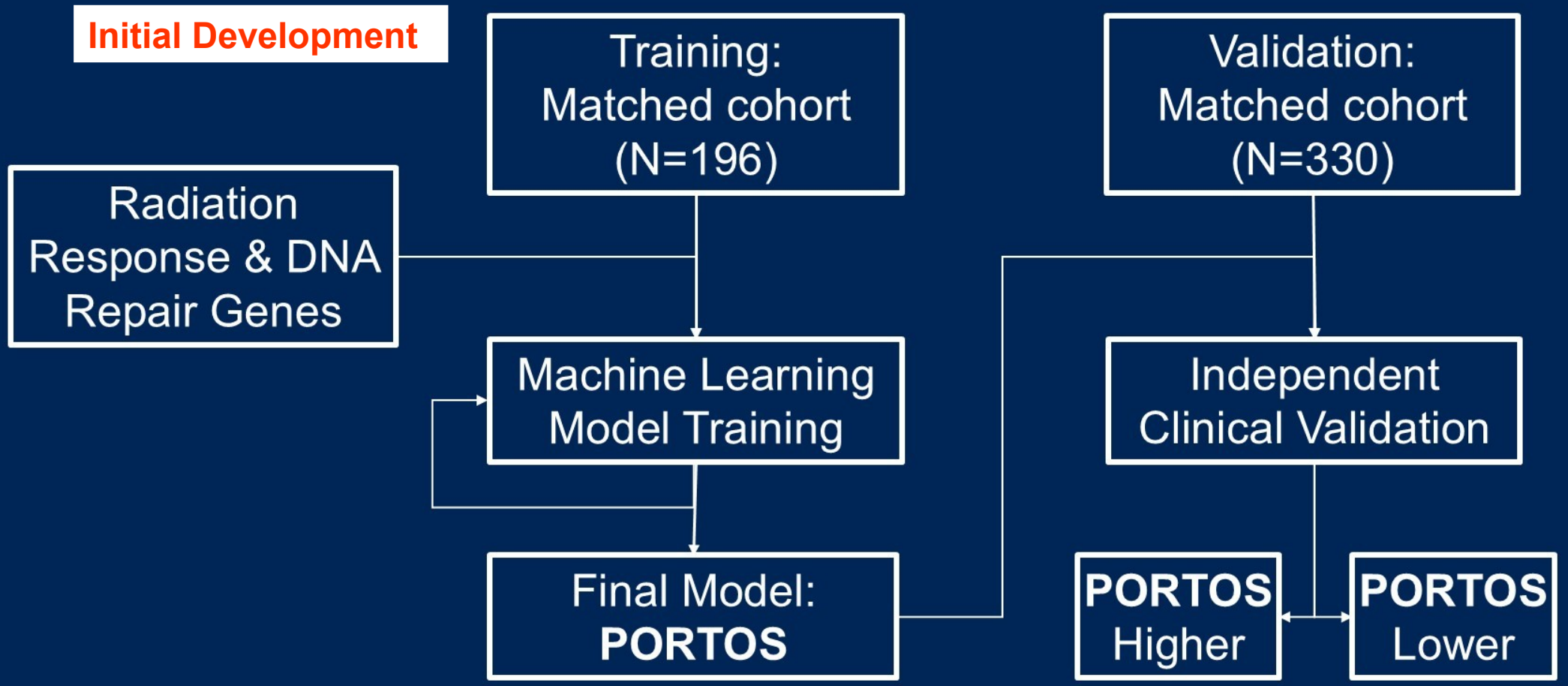
PORTOS Development: Training and Validation



Zhao* & Chang* et al. Lancet Onc. 2016

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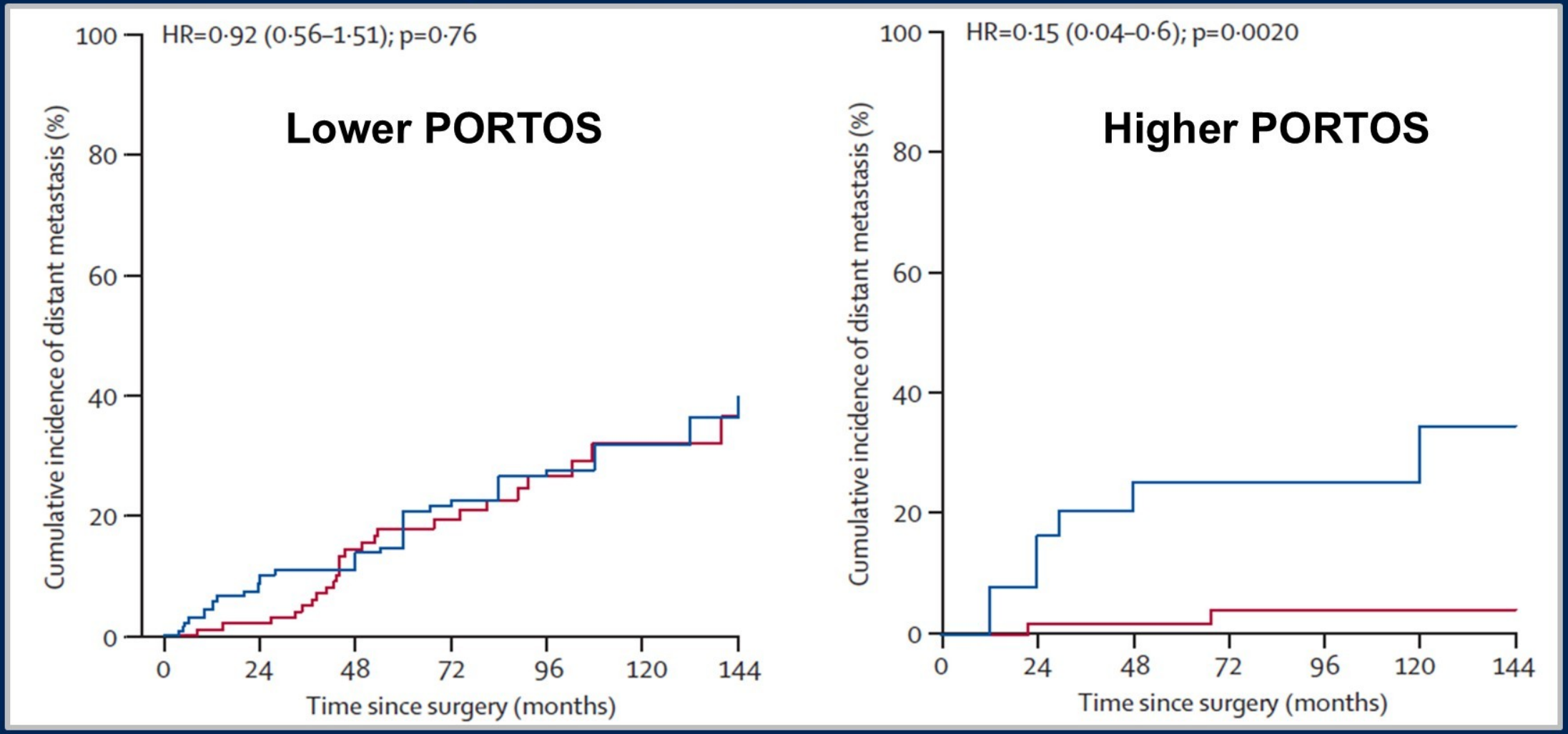
PORTOS Independent Clinical Validation



Interaction P-value <0.0001

Zhao* & Chang* et al. Lancet Onc. 2016

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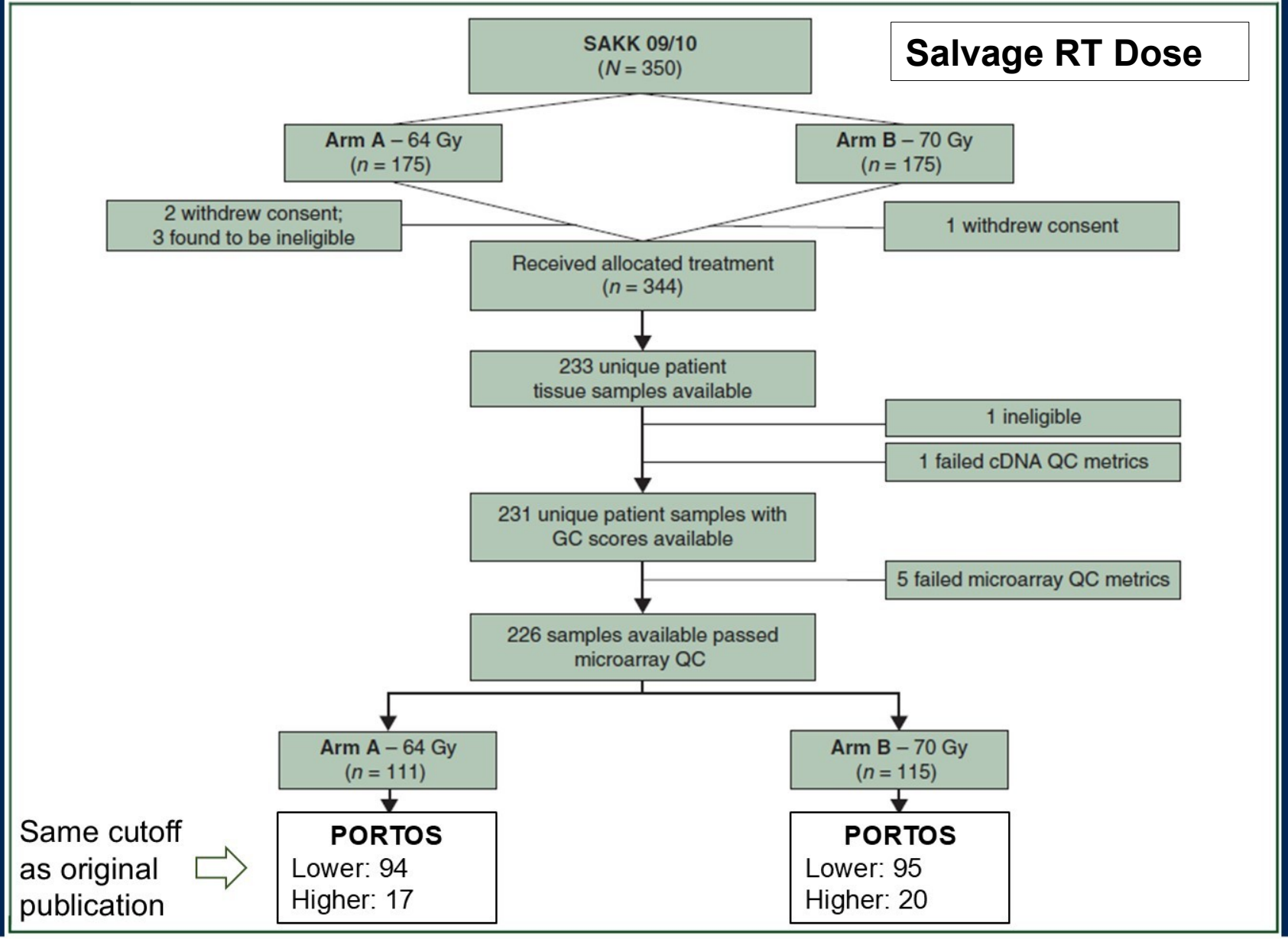
Salvage RT Dose



Same cutoff as original publication ⇨

Dal Pra et al.
Ann Onc 2022

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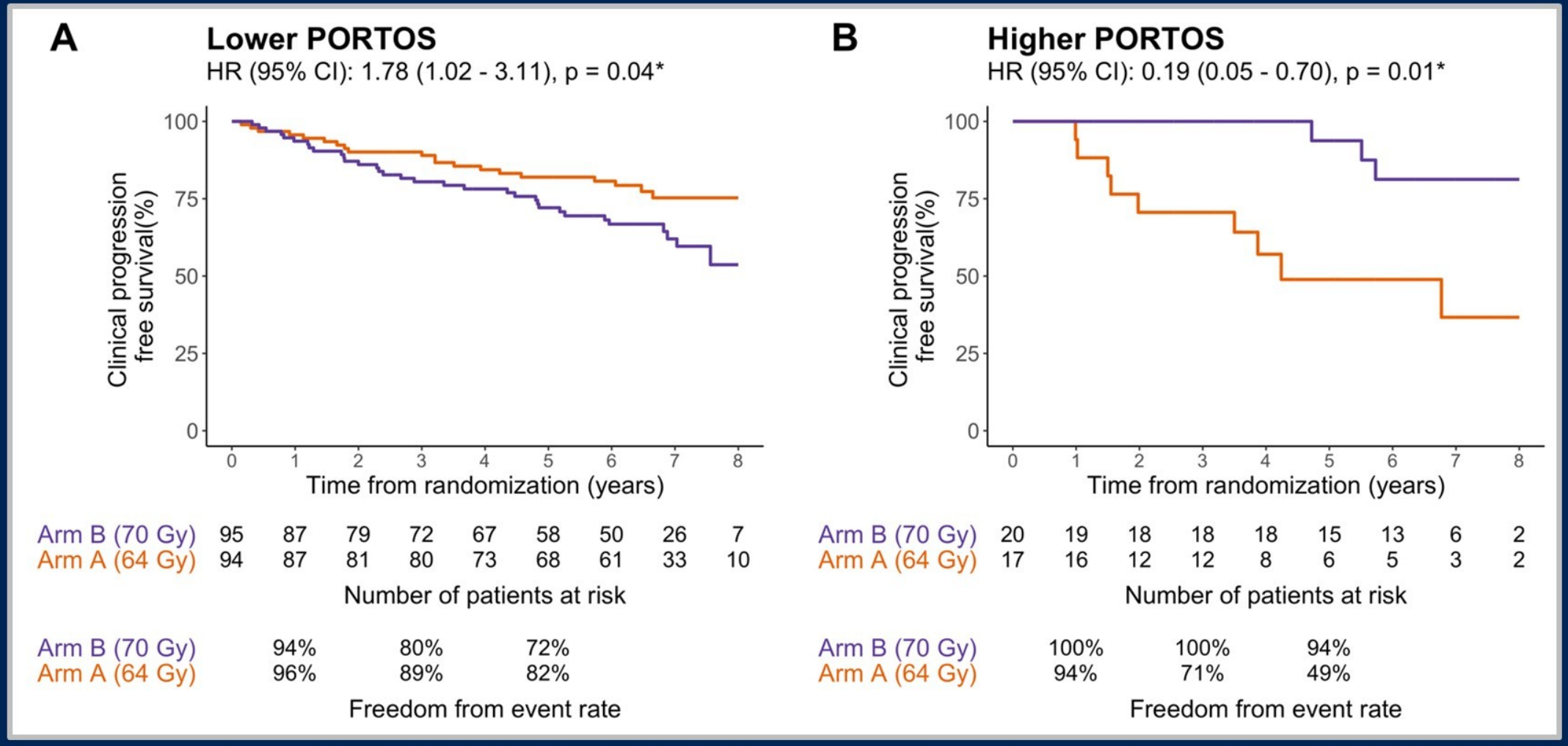
PORTOS in SAKK 09/10



Interaction P-value = 0.003

Dal Pra et al. ASTRO 2022

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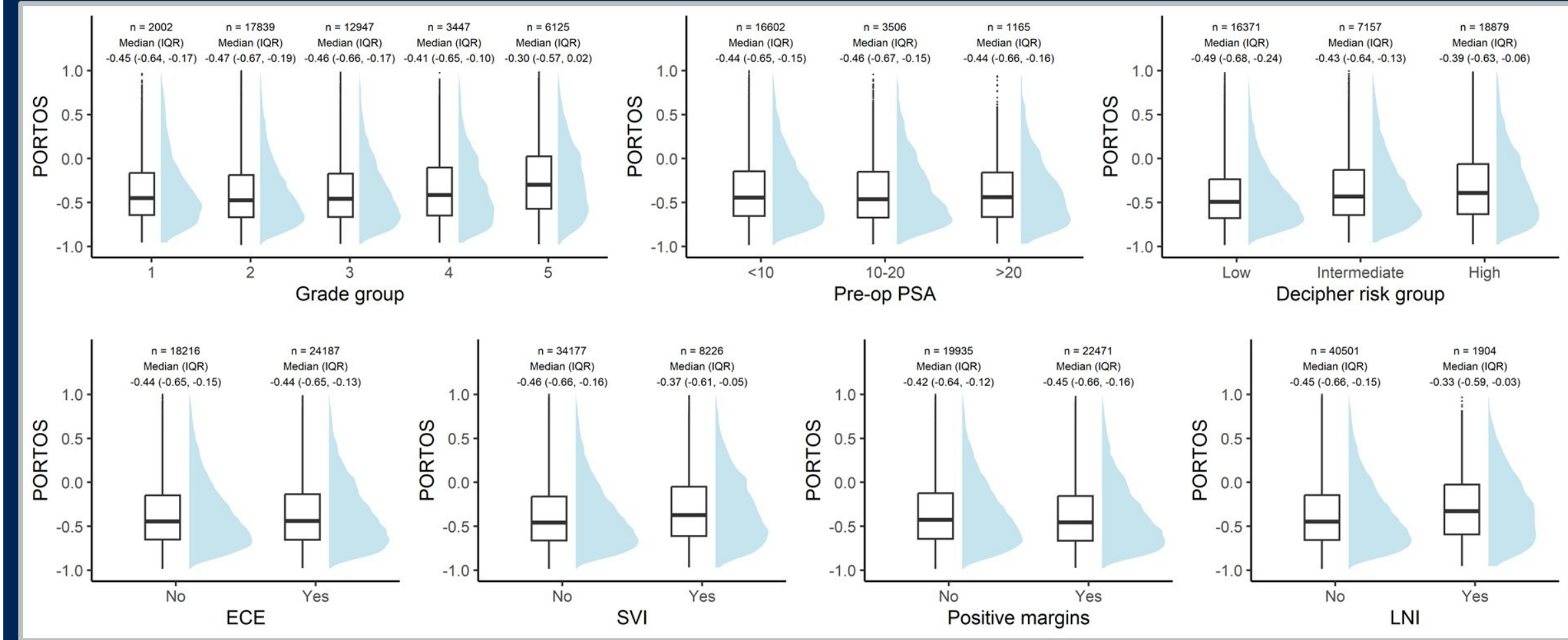
Real-world Post-RP Dataset (N=42,407)

clinical/biological association [12]



No strong associations with clinicopathologic variables

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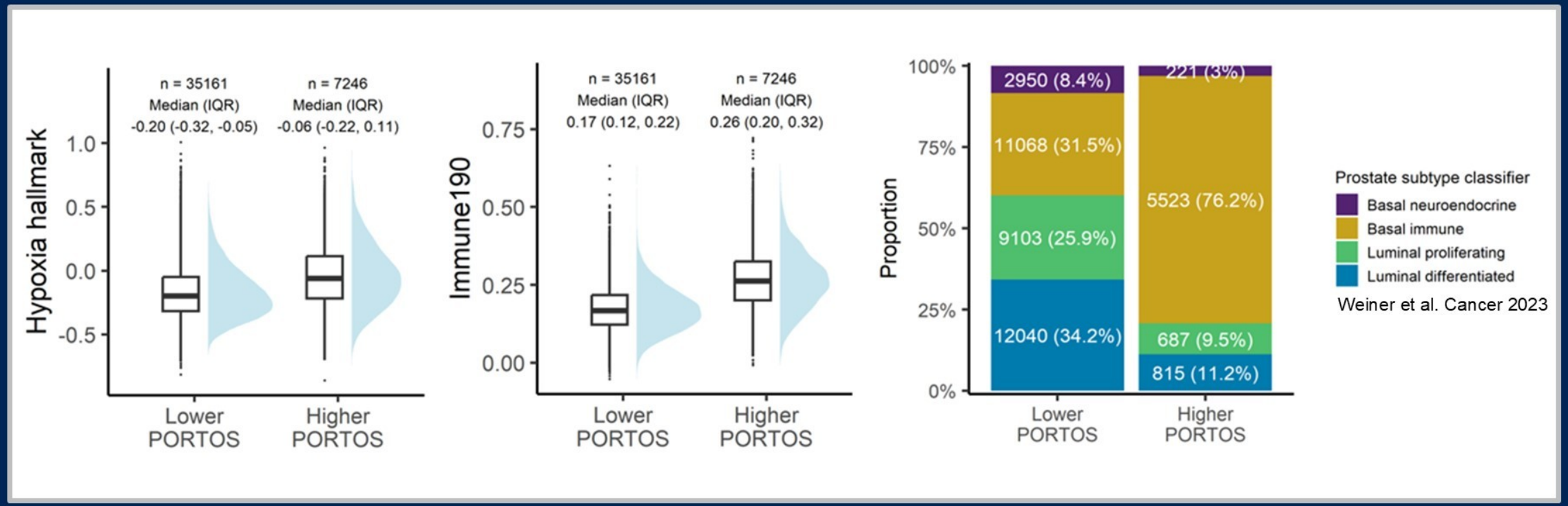
Real-world Post-RP Dataset (N=42,407)



Higher PORTOS associated with hypoxia, immune response

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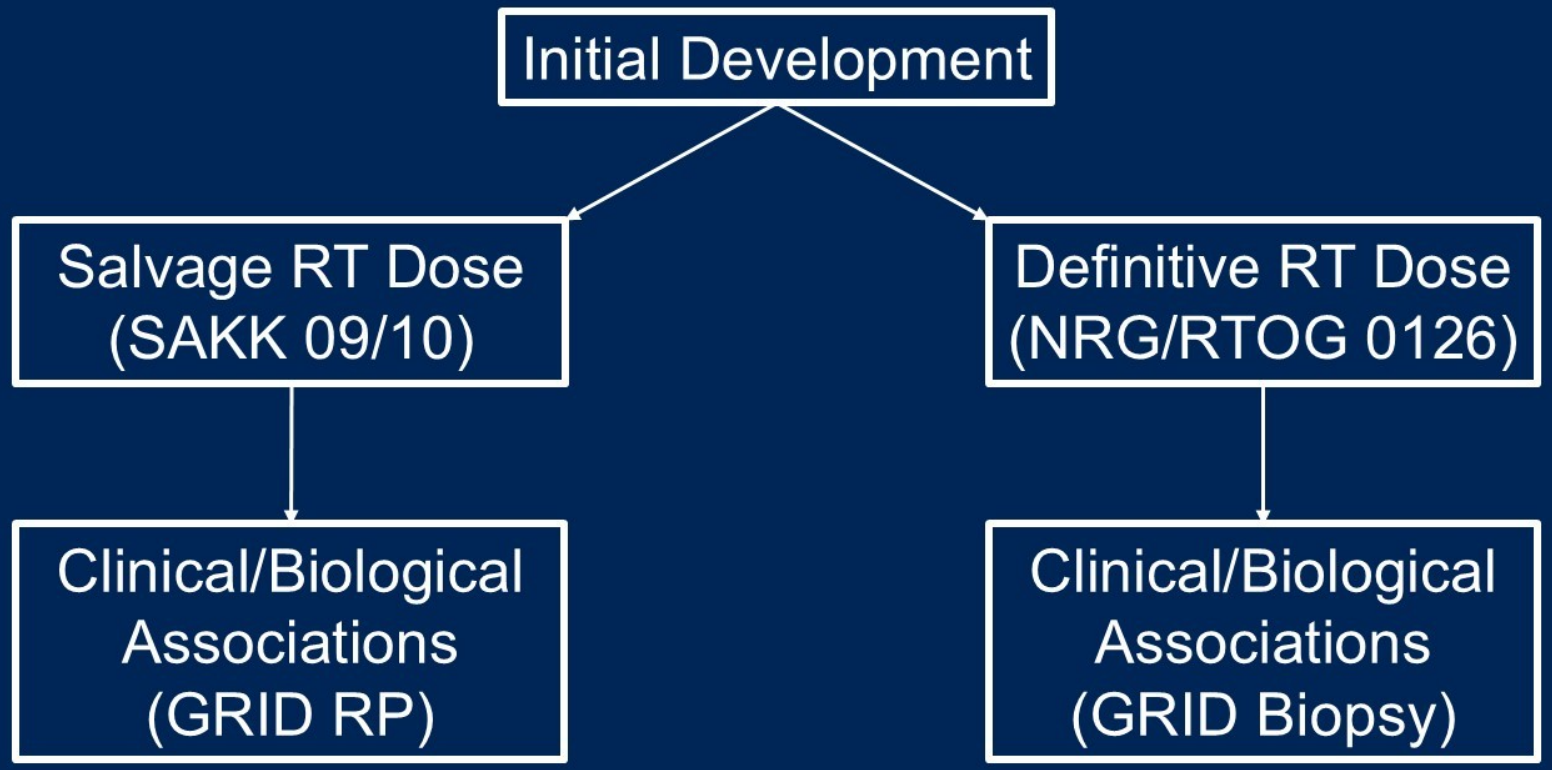
Post-Operative Radiation Therapy Outcomes Score (PORTOS)



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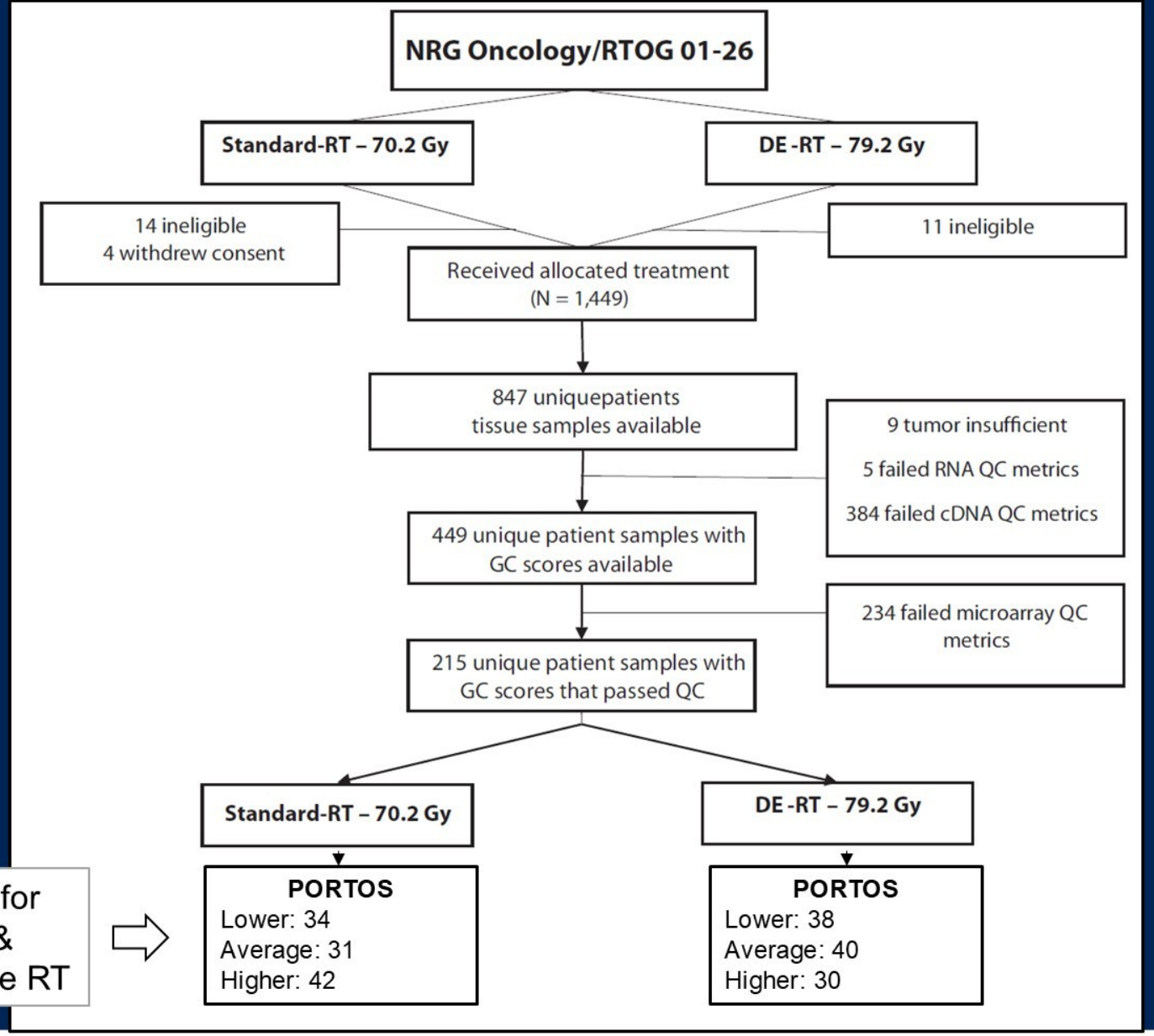

Tertiles for biopsy & definitive RT

Spratt et al. IJROBP 2023

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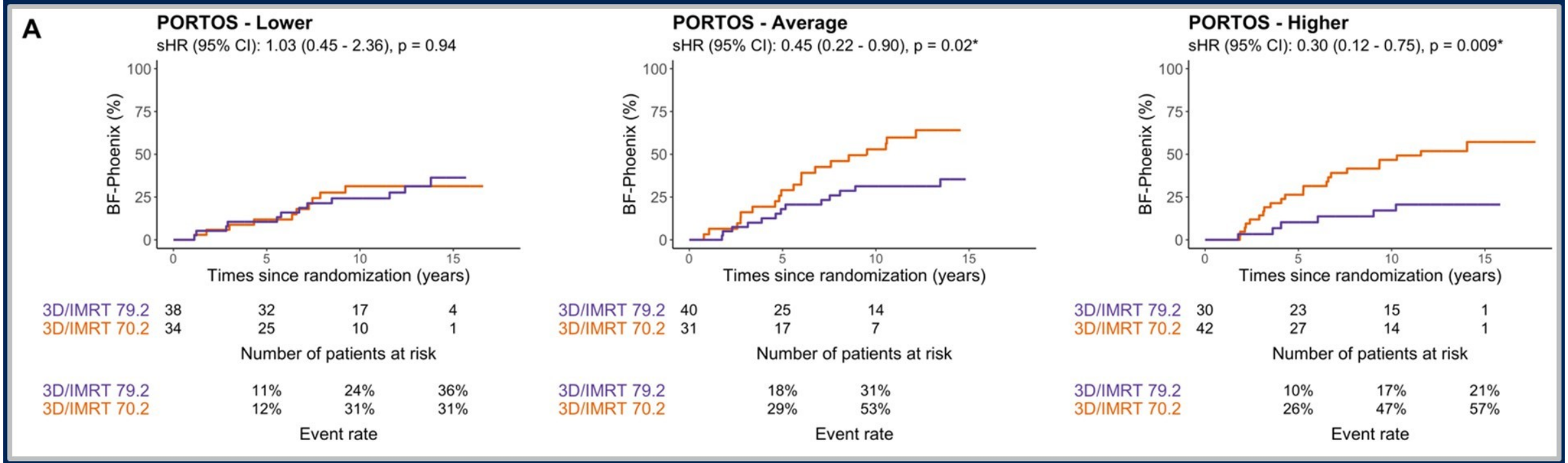
PORTOS in NRG/RTOG 0126



Lower vs. Higher: Interaction P-value = 0.003

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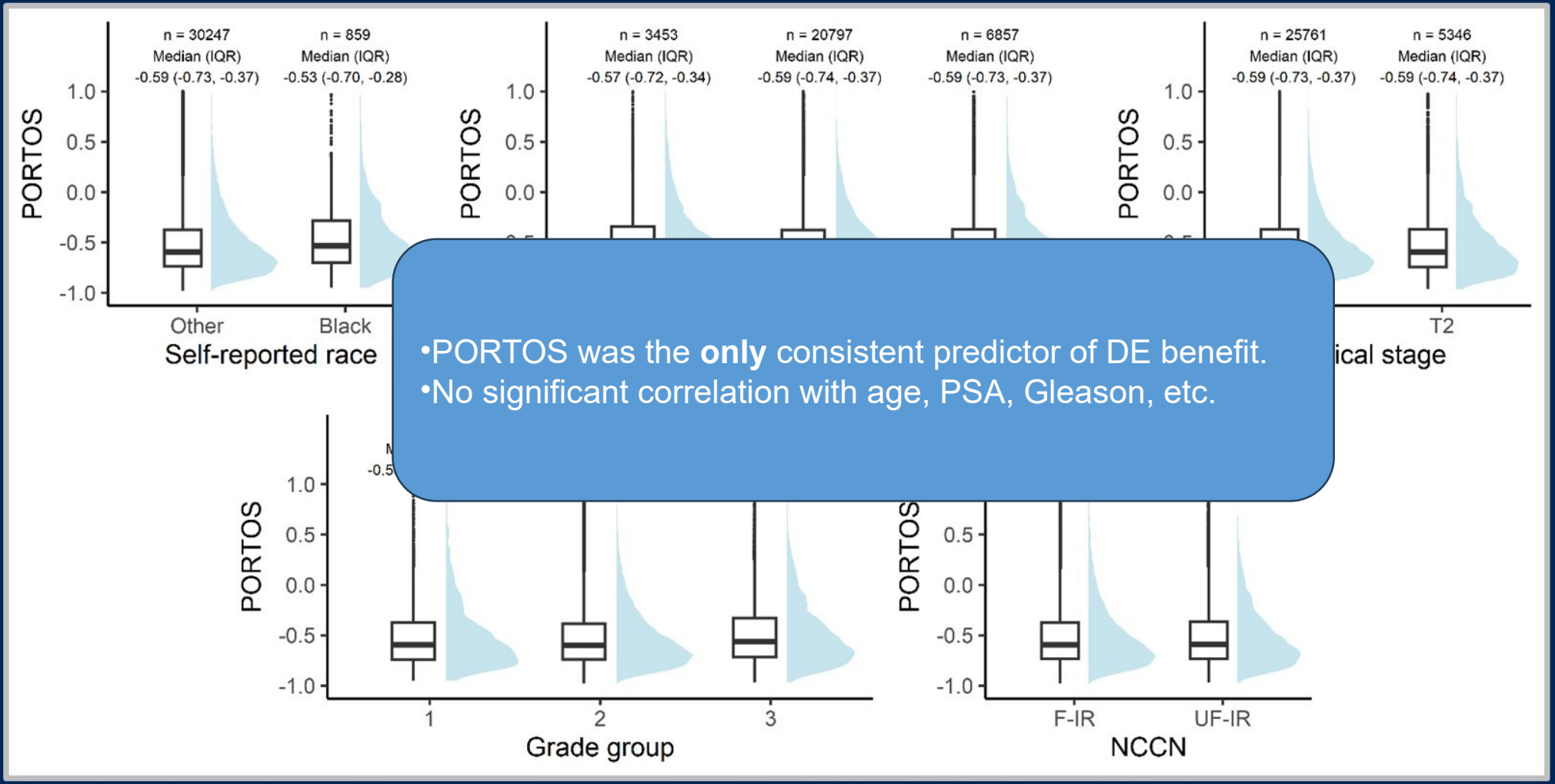
Real-world Intermediate-Risk Biopsy Dataset (N=31,107)



- PORTOS was the **only** consistent predictor of DE benefit.
- No significant correlation with age, PSA, Gleason, etc.

No strong associations with clinicopathologic variables

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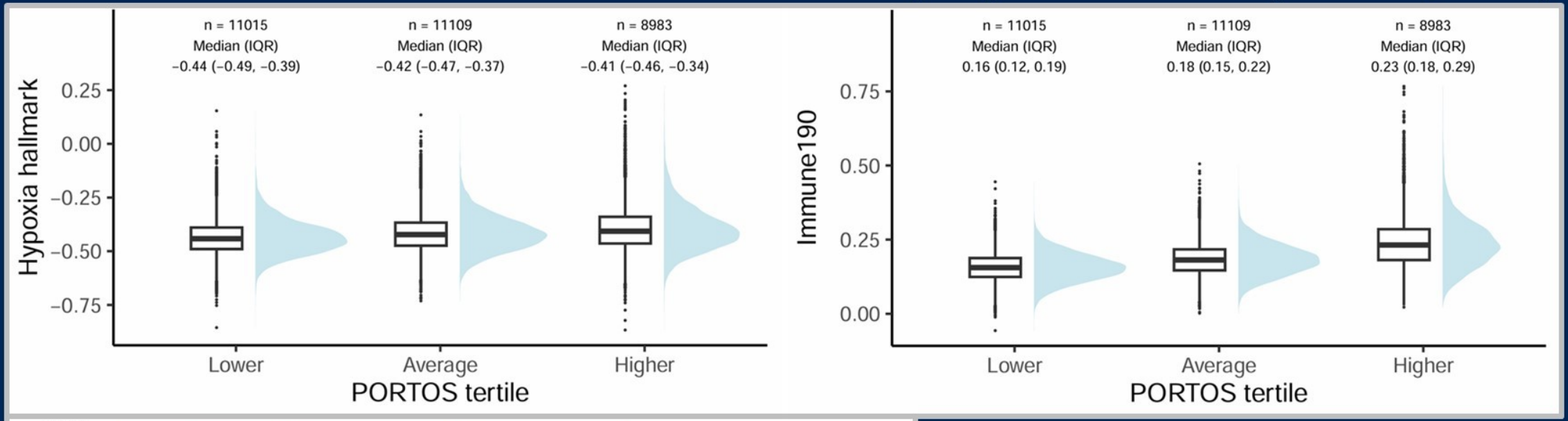
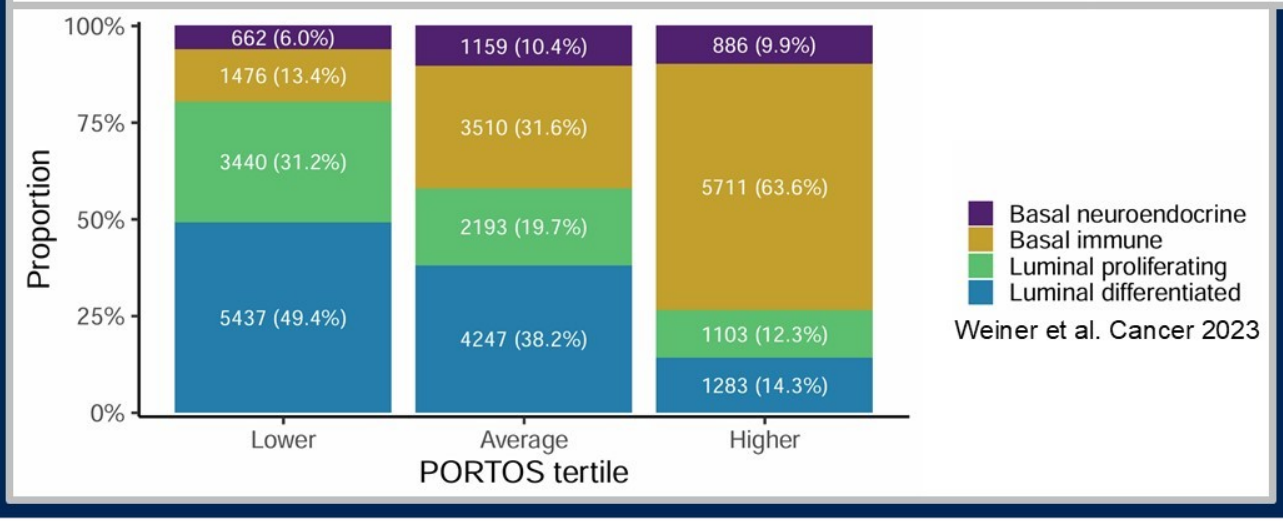
Real-world Intermediate-Risk Biopsy Dataset (N=31,107)





Higher PORTOS associated with hypoxia, immune response

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Conclusions

- PORTOS predicts salvage dose response in SAKK 09/10
- PORTOS predicts definitive dose response in NRG/RTOG 0126
- PORTOS is associated with hypoxia and immune response
- Could be used to help guide radiation dose escalation/de-escalation
  - Limitations: no ADT, ENI, PSMA PET
- Rename to the PrOstate cancer Radiation Therapy Outcomes Score
- Studies investigating PORTOS and ENI, toxicity, ADT, etc. ongoing
  - Toxicity in NRG/RTOG 0126 (Karen Hoffman): Abstract 375, Poster Bd K5

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Abstract #375: PORTOS Gene Signature Predicts Risk of Adverse Events after Dose-Escalated vs. Lower-Dose Prostate Radiation Therapy in NRG/RTOG 0126

Karen E Hoffman, Sophia C Kamran, Hyunnam Monica Ryu, James A Proudfoot, Elai Davicioni, Paul L Nguyen, Stephanie L Pugh, Daniel E Spratt, Jeff M Michalski, Matthew B Parliament, Ian S Dayes, Rohann J M Correa, John M Robertson, Elizabeth M Gore, Desiree E Doncals, Eric Vigneault, Luis Souhami, Felix Y Feng, Phuoc T Tran, S George Zhao

Background

- Dose-escalated radiation therapy improves prostate cancer control but also increases the risk of treatment adverse effects[1].
- We hypothesized RNA-based tumor gene expression recapitulates normal tissue gene expression and therefore could identify patients at increased risk of adverse events after dose-escalated radiation. We specifically evaluated the 24-gene PORTOS score which characterizes response to DNA damage and radiation[2].

Methods

- PORTOS scores were calculated from biopsy samples obtained from 215 patients[3] treated on the NRG/RTOG 0126 clinical trial that randomized patients with intermediate-risk prostate cancer between 70.2 Gy and 79.2 Gy delivered in 1.8 Gy fractions. In this trial, adverse events were categorized using RTOG criteria.
- Fine-Gray multivariable analysis of continuous and categorical PORTOS (tertiles) were used to calculate subdistribution hazard ratios (sHR), treating death without events as a competing risk, adjusting for age.

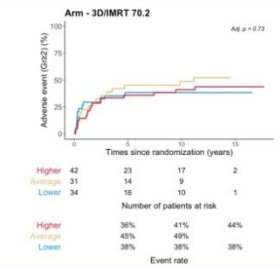
Patient Characteristics

	70.2 Gy (n=107)	79.2 Gy (n=108)	P-value
Age [median (Q1, Q3)]	70 (64, 74)	70 (65, 74)	0.66
Number Int-Risk Features, No. (%)			
0	1 (0.9)	1 (0.5)	
1	76 (71.0)	157 (73.0)	0.52
2	28 (26.2)	51 (23.7)	
3	2 (1.9)	6 (2.8)	
RT Modality			
3D-CRT	69 (64.5)	68 (63.0)	0.88
IMRT	38 (35.5)	40 (37.0)	
PORTUS			
Median (Q1, Q3)	0.54 (0.72, 0.29)	0.59 (0.74, 0.36)	0.32

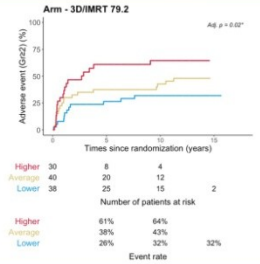
- **Higher PORTOS scores were associated with an increased risk of adverse events after administration of dose-escalated radiation compared to lower dose radiation.**
- **PORTOS is the first radiation sensitivity biomarker to be validated for toxicity with data from a phase III randomized trial and could be used to help personalize radiation therapy dose for patients to limit risk of treatment toxicity.**

Results

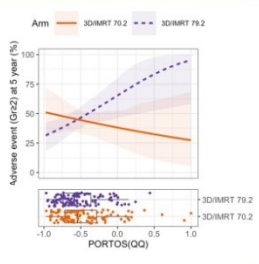
70.2 Gy Arm
PORTOS NOT associated w/ grade 2 or higher AE



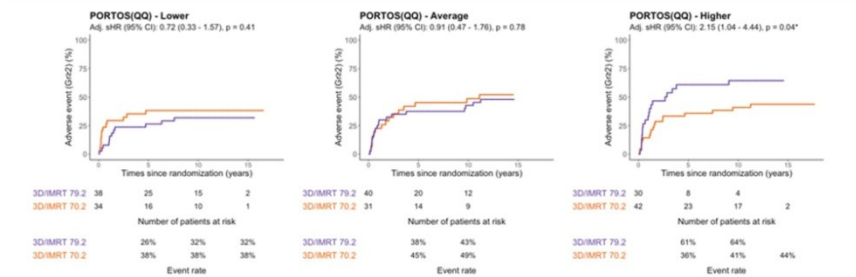
79.2 Gy Arm
PORTOS ASSOCIATED w/ grade 2 or higher AE



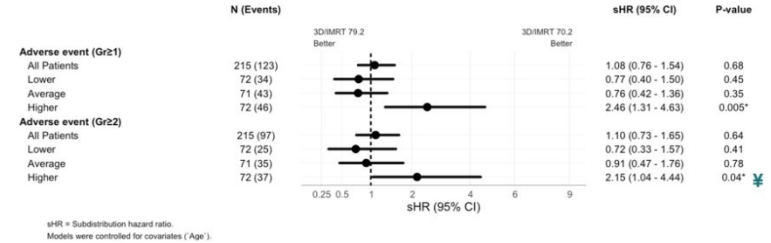
Interaction significant
Continuous PORTOS and treatment arm



Cumulative Incidence Plots of Adverse Events (grade ≥2) for each PORTOS subgroup



Arm effects [79.2 Gy vs. 70.2] by PORTOS



sHR = Subdistribution hazard ratio.
Models were controlled for covariates ('Age').

¥This was driven by increased risk of grade 2 or higher genitourinary events (sHR = 5.80 [1.36 - 24.7], p = 0.02; 5% vs. 34%).

References and Funding

References

1. Michalski JM, Moughan J, Purdy J et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol 2018; 4 (6): e180039.
2. Zhao SG, Chang SL, Spratt DE et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol 2016.
3. Spratt DE, Liu VYT, Michalski J et al. Genomic Classifier Performance in Intermediate-Risk Prostate Cancer: Results From NRG Oncology/RTOG 0126 Randomized Phase 3 Trial. Int J Radiat Oncol Biol Phys 2023; 117 (2): 370-377.

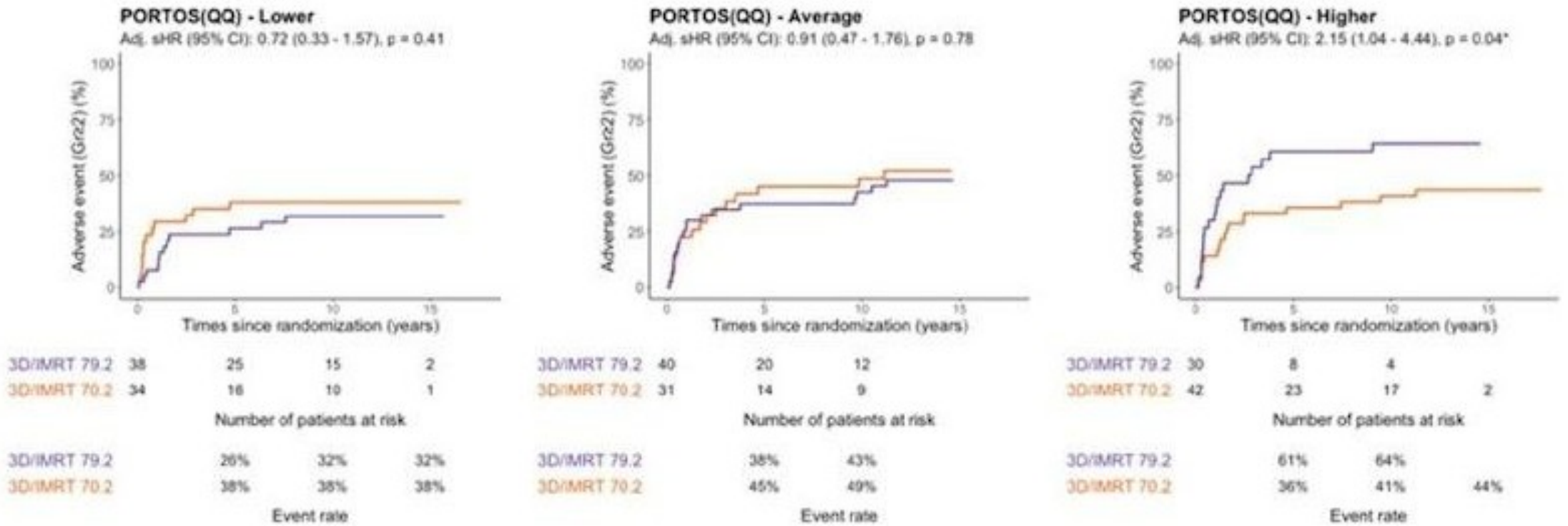
Funding

NIHU10CA180868: NRG Oncology Operations, U10CA180822: NRG Oncology SDMC, UG1CA189867: NCORP, U24CA196067: NRG Specimen Bank

NRG/RTOG 0126 Trial Overview

- Phase III randomized trial with 215 intermediate-risk prostate cancer patients.
- **Treatment Arms:** Standard-dose RT: 70.2 Gy vs. Dose-escalated RT: 79.2 Gy (1.8 Gy fractions).
- **Objective:** Evaluate PORTOS as a predictor of grade ≥2 adverse events post-RT.

Cumulative Incidence Plots of Adverse Events (grade ≥2) for each PORTOS subgroup



- **Overall Adverse Events:** 45% experienced grade ≥2 toxicity.

PORTOS Stratification and Toxicity Risk

- **High PORTOS Tertile:**
  Dose-escalated RT led to higher toxicity
  (5-year incidence: 61% vs 36% sHR = 2.15; p=0.04).

- **Low/Mid PORTOS Tertiles:** No significant difference in toxicity between RT doses.

- **Standard-Dose RT:** No significant association with toxicity.

What's Next for PORTOS?

- **Further Validation:** Ongoing studies in other trials like SAKK 09/10
- **Integration into Clinical Practice:** Potential to incorporate PORTOS into treatment planning for better outcomes
- **Exploration of Biological Associations:** Investigating links between PORTOS, hypoxia, and immune response
- PORTOS may complement tools like **PSA density, Gleason score, and MRI findings** for comprehensive treatment planning.

Summary

- PORTOS fits into a growing movement toward **genomically guided cancer therapy.**
- Identifies RT responders and avoids toxicity in non-responders.
- PORTOS helps **personalize radiation therapy** : giving more when it's helpful and avoiding harm when it's not.
- Incorporating PORTOS can optimize therapeutic outcomes.

THANK YOU