The Role of Radiation Therapy Along the Continuum of Prostate Cancer

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Disclosures

- Research Funding-Varian

Overview

- Radiation therapy for localized prostate cancer
- Radiation Therapy in post-operative biochemically recurrent prostate cancer
- Radiation Therapy as treatment for oligometastatic prostate cancer
- Radiation Therapy’s role in de novo, metastatic prostate cancer

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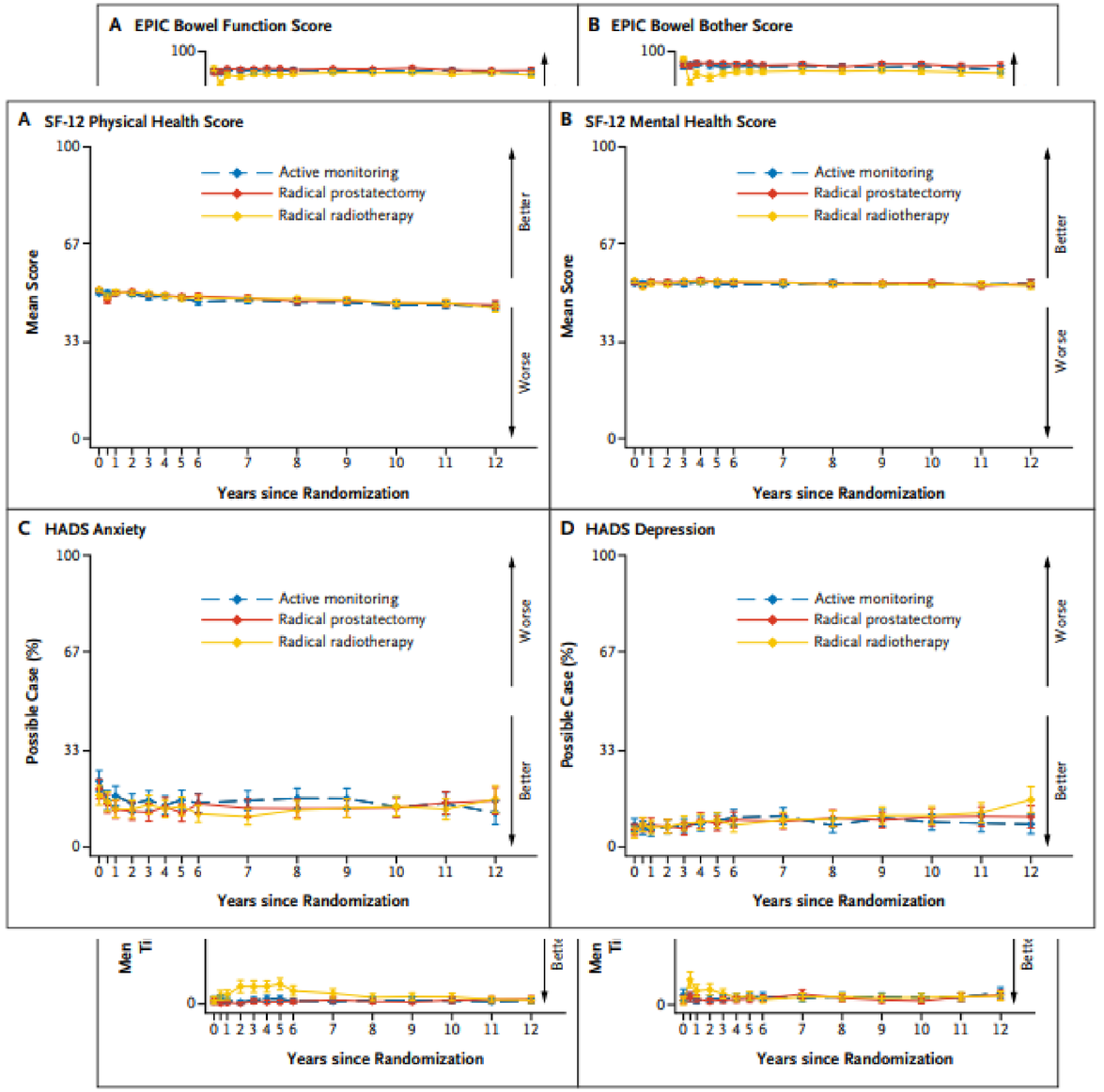
Radiation vs. Surgery for Localized Prostate Cancer

- PROTECT study randomized 1643 patients to active surveillance vs. radical prostatectomy vs. radiation therapy + androgen deprivation therapy
- Findings
  - No difference prostate cancer specific deaths between groups
  - More men developed metastases in the active surveillance group compared to RP and XRT groups
  - Definitive treatment had more upfront impact on bladder, bowel, and sexual QOL
  - Global measures regarding QOL were similar between groups
- Takeaways
  - There was NO difference in oncologic outcome between the surgery and radiation arms
  - QOL differences experienced by patient differ according to treatment modality
  - Patients with localized prostate cancer should receive counsel regarding BOTH modalities to facilitate informed decision making



Hamdy FC, et al. *NEJM* 2023; 388:1547-1558.
Donovan JL, et al. *NEJM Evid* 2023; 2 (4).

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Radiation-Technique

- In 2023, multiple techniques are available to deliver therapeutic doses of radiation therapy for localized prostate cancer
- These include:
  - Photon (or X-ray) therapy
    - Intensity Modulated Radiation Therapy (IMRT) is the current standard of care
    - Widely available and most utilized
  - Proton Beam Therapy
    - Charged particle therapy is currently available at 40 centers in US
    - Has unique physical properties compared to photon therapy
  - Brachytherapy
    - Implantation of radiation sources directly into the prostate
    - Both temporary (High Dose Rate or HDR) and permanent (Low Dose Rate or LDR) brachytherapy treatments can be used for prostate cancer
  - Heavy Ion Therapy
    - Not available in US currently, but centers are active in Europe and Asia
    - Carbon Ion Therapy is mostly common amongst this group
    - Unclear role for prostate cancer moving forward

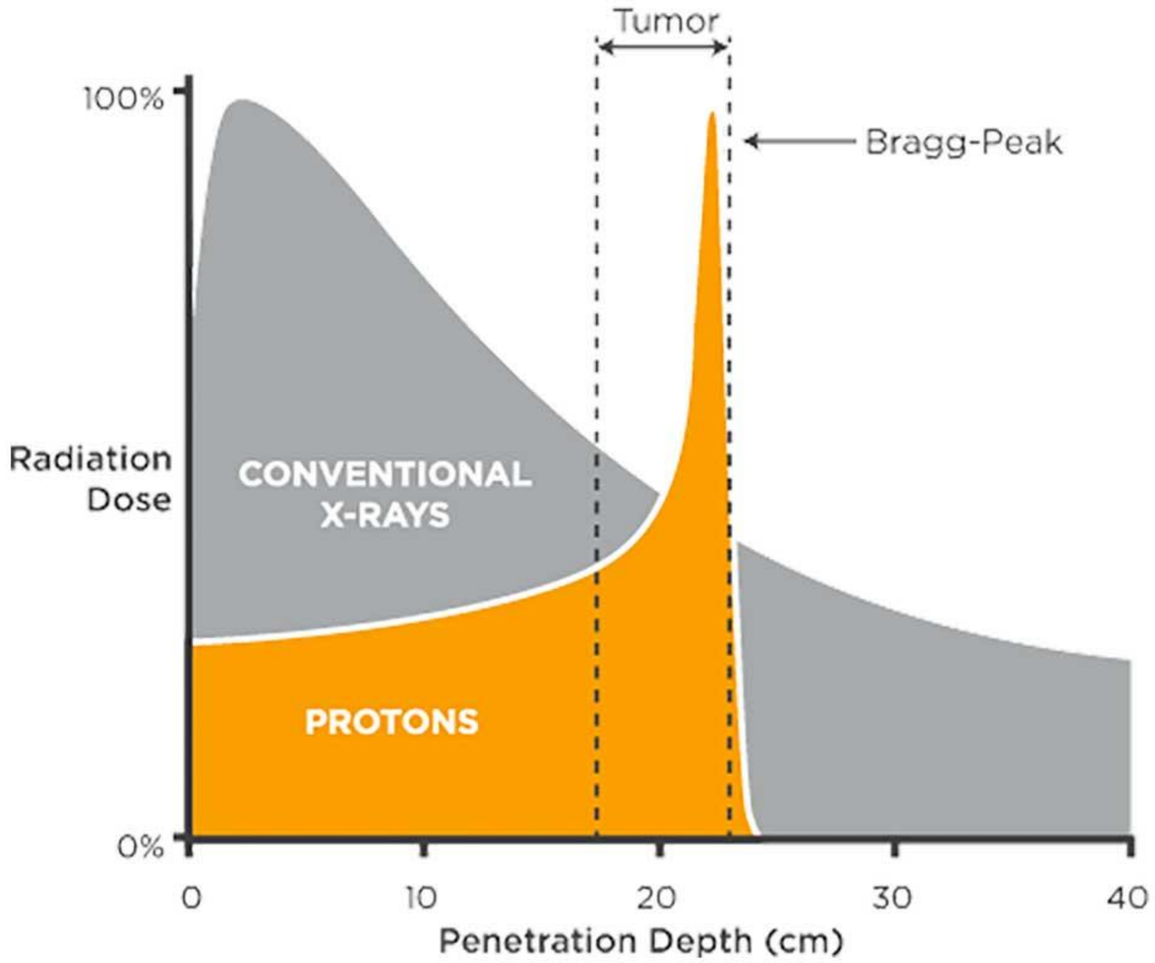
Radiation-Dose and Fractionation

- When it comes radiation dose and fractionation (dose per treatment) for patients receiving external beam treatments (i.e. photons or protons) the recent trends have supported shorter treatment courses
- SBRT (stereotactic body radiation therapy) is the fastest growing technique worldwide and use 5-7 treatments delivered over 10-20 days
- NCCN guidelines currently support multiple reasonable options across the risk spectrum

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR Iodine 125 Palladium 103 Cesium 131	145 Gy 125 Gy 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓		

National Comprehensive Cancer Network (NCCN) guidelines, www.nccn.og

Proton Beam Therapy vs Photons (IMRT)



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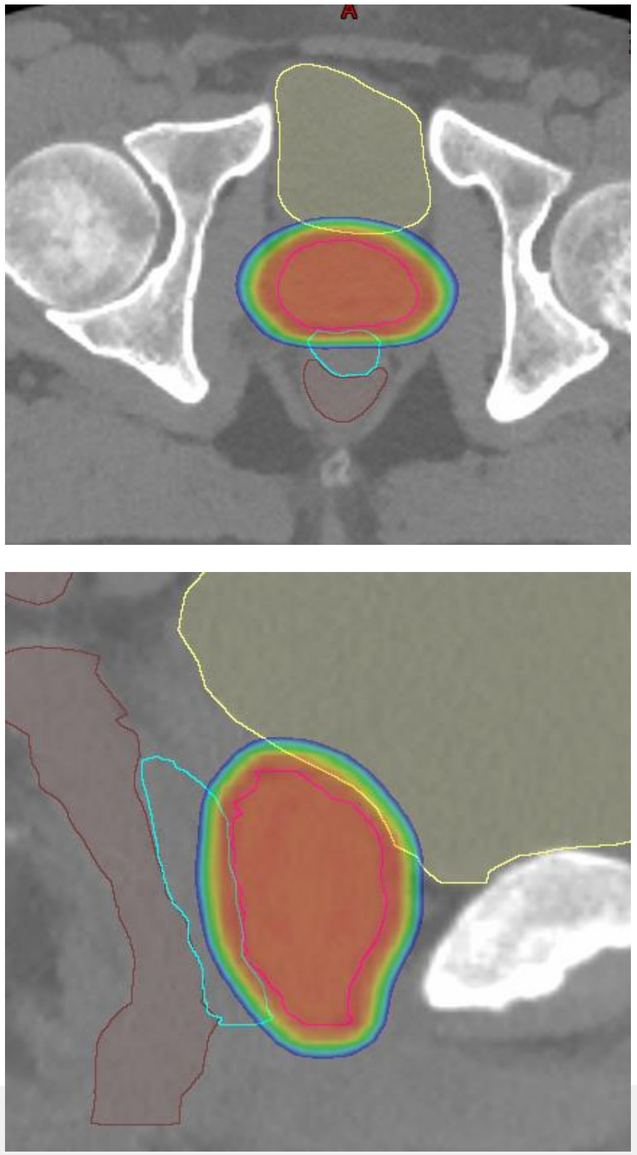
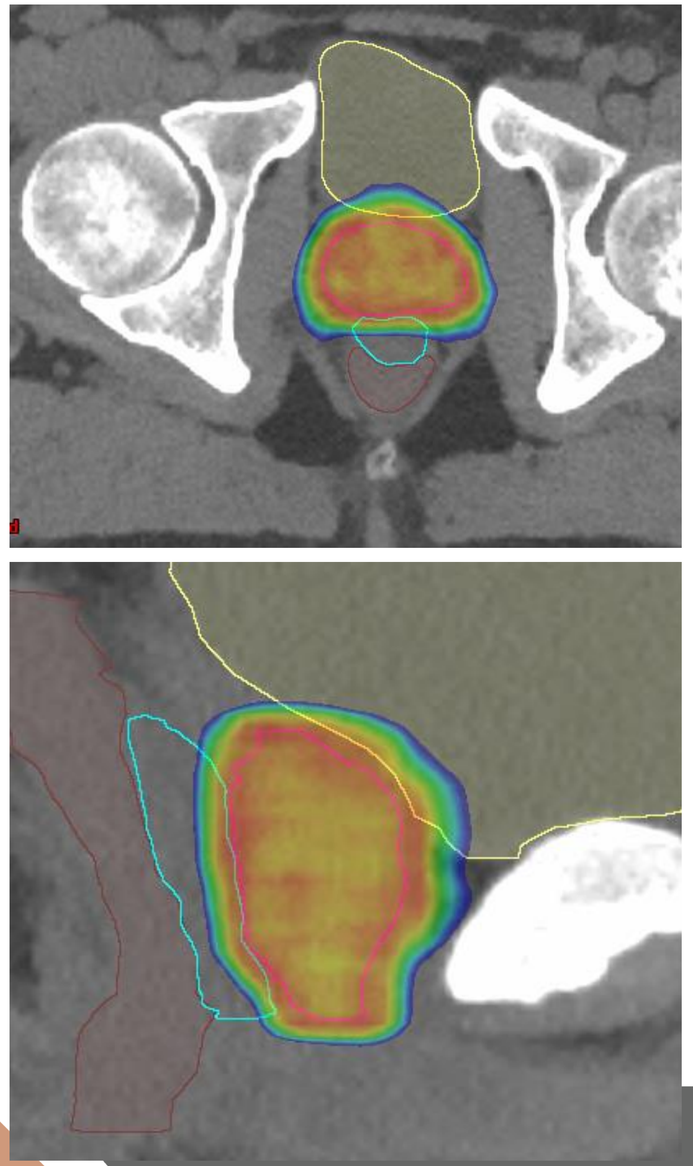
Proton Beam Therapy vs Photons (IMRT)

Protons



Photons (IMRT)



Proton vs. Photon Comparison, Brad Stish, October 2023

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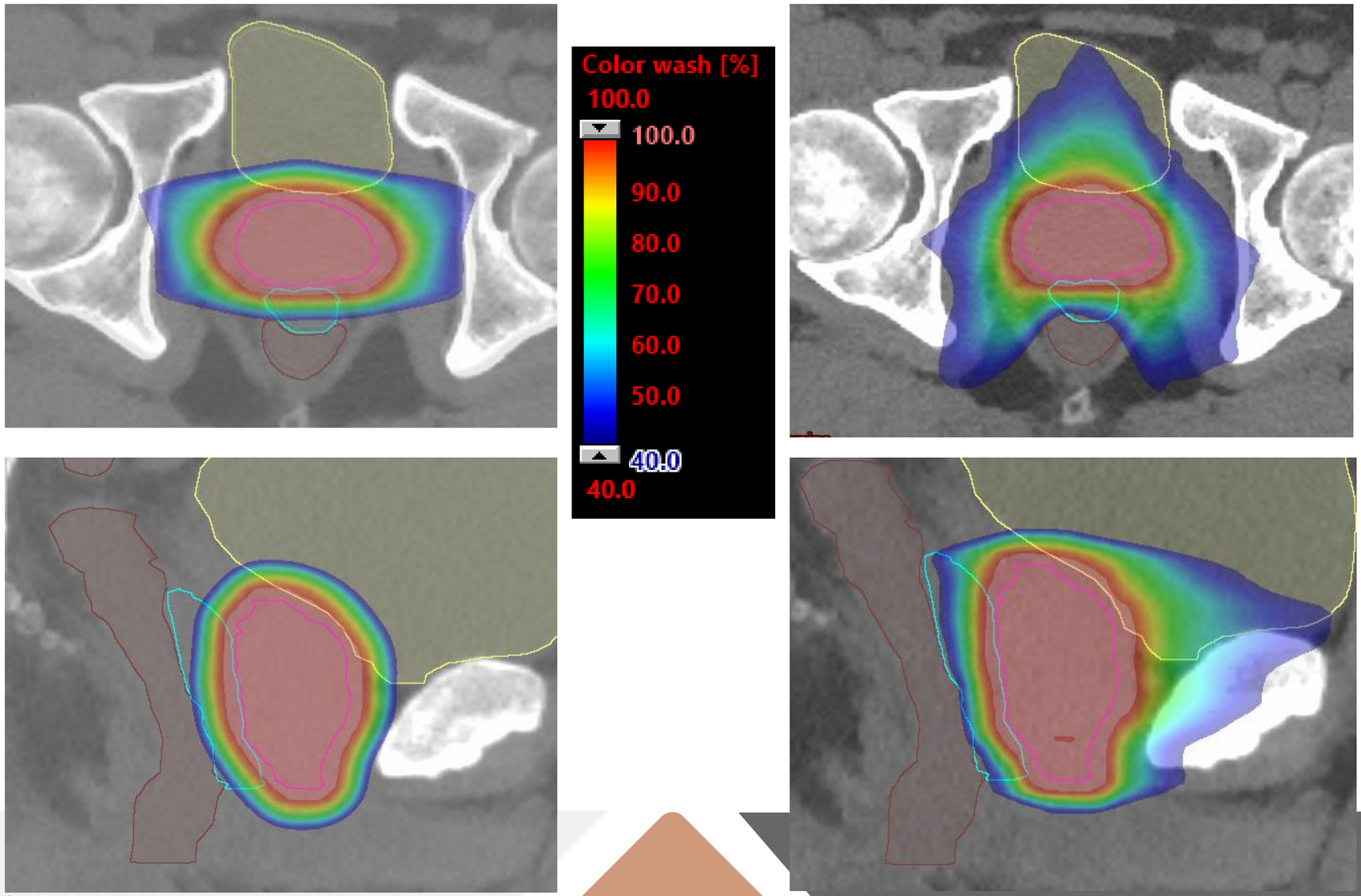
Proton Beam Therapy vs Photons (IMRT)

Protons

Photons (IMRT)



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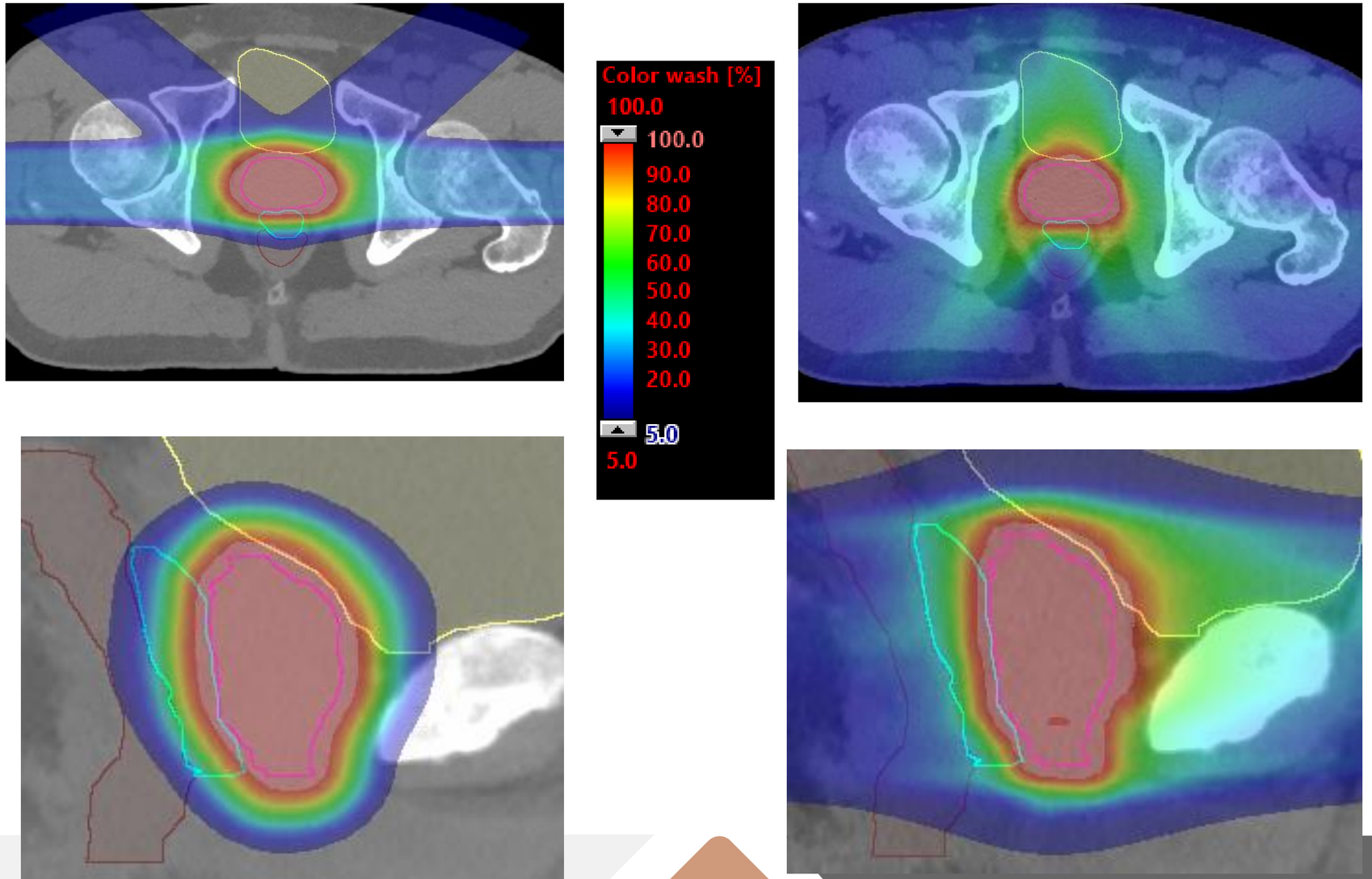
Proton Beam Therapy vs Photons (IMRT)

Protons

Photons (IMRT)



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Photons (IMRT) vs Proton Beam Therapy

- Clinical Data
  - Prospective data are lacking
    - One randomized trial and one large, non-randomized trial will report in the next 2-3 years
    - Primary endpoints focus on toxicity/QOL
- Retrospective data are mixed, but suggest no significant advantage for protons (and possible detriment)

Table 1 Current proton versus photon therapy comparative evidence for localized prostate cancer

Study	Design	Source of data	Years	Toxicities: Protons compared to photons					
				Acute			Late[a]		
				GU	GI	Sexual	GU	GI	Sexual
Kim 2011[50]	Database	SEER	1992–2005	NA	↑	NA	NA	↑	NA
Sheets 2012[51b]	Database	SEER	2000–2009	NA	NA	NA	=	↑	=
Yu 2012[48c]	Database	Medicare	2008–2009	↓	=	NA	=	=	NA
Pan 2018[52d]	Database	MarketScan	2008–2015	↓	=	↓	↓	↑	↓
Gray 2013[53e]	Non-randomized comparative	MGH PROST-QA Harvard-affiliated[f]	2003–2008	↓/↑	↓/=	NA	=	=	NA
Hoppe 2014[56]	Non-randomized comparative	UF PROST-QA	2003–2010	=	=[g]	=	=	=[g]	=
Fang 2015[54]	Non-randomized comparative	University of Pennsylvania	2010–2012	=	=	NA	=	=	NA

SEER Surveillance, Epidemiology, and End Results, *MGH* Massachusetts General Hospital, *PROST-QA* Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium, *UF* University of Florida, *GI* Gastrointestinal, *GU* Genitourinary, *NA* not available

Kamran, SC, et al. *Prostate Cancer and Prostatic Diseases* 2019; 22:509-21

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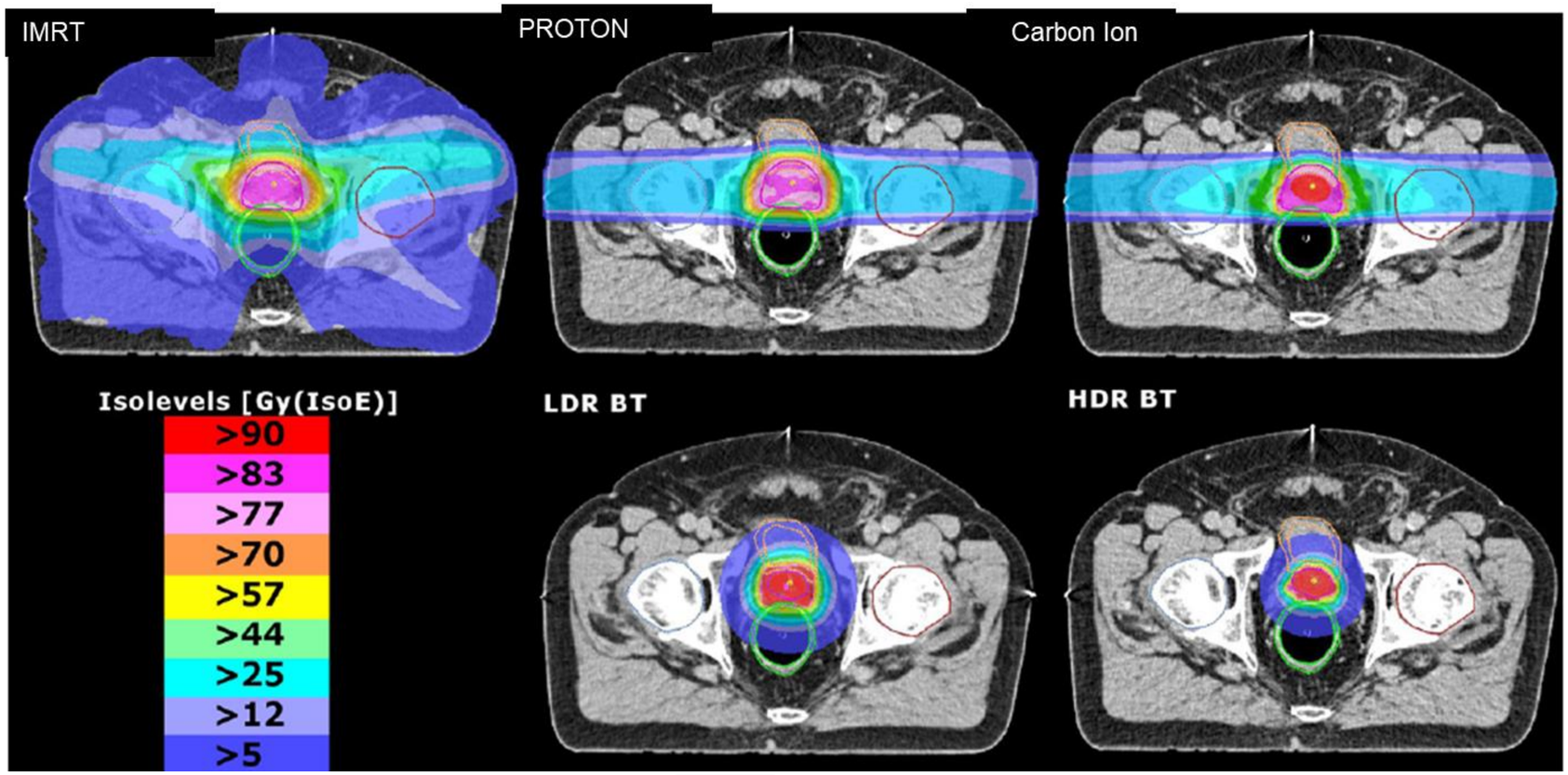
Let’s not forget about brachytherapy

- Brachytherapy allows superior dose conformality and normal tissue sparing compared to either IMRT or proton beam therapy
- Intraprostatic dose escalation from brachytherapy is superior to other techniques
- Brachytherapy is highly convenient and cost effective for patients, with treatment completed in 1-2 sessions



Georg et al. *IJROBP* 2013; 88:715-22

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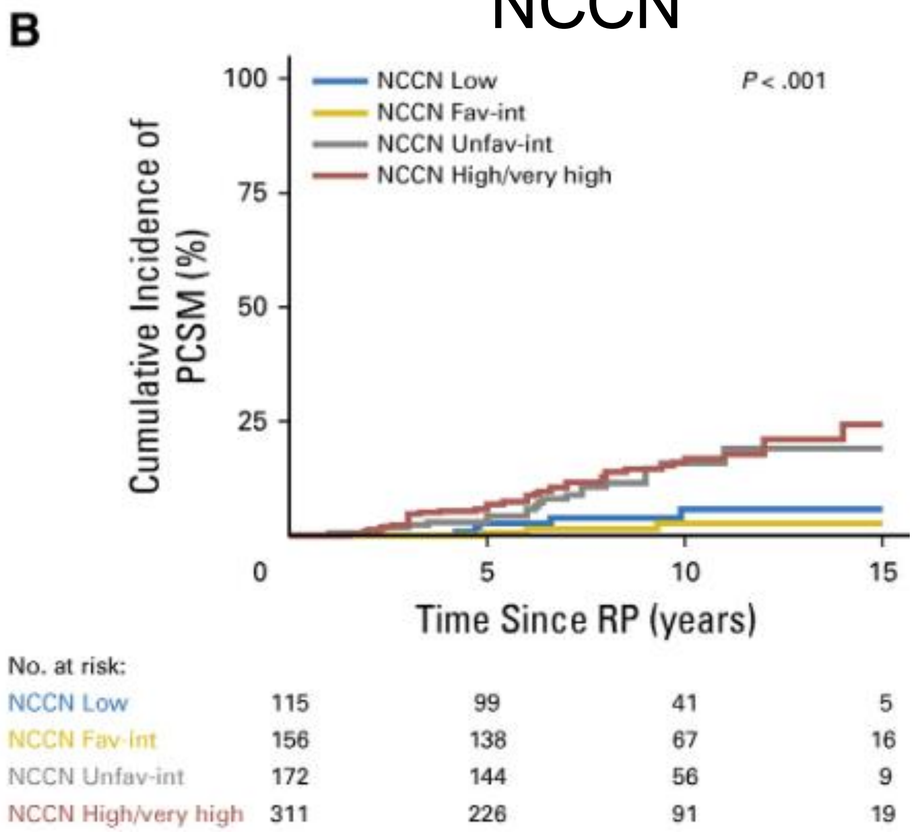
Definitive Treatment of High Risk (M0) Prostate Cancer

- Risk group categorization greatly influences prostate cancer specific mortality risk

NCCN



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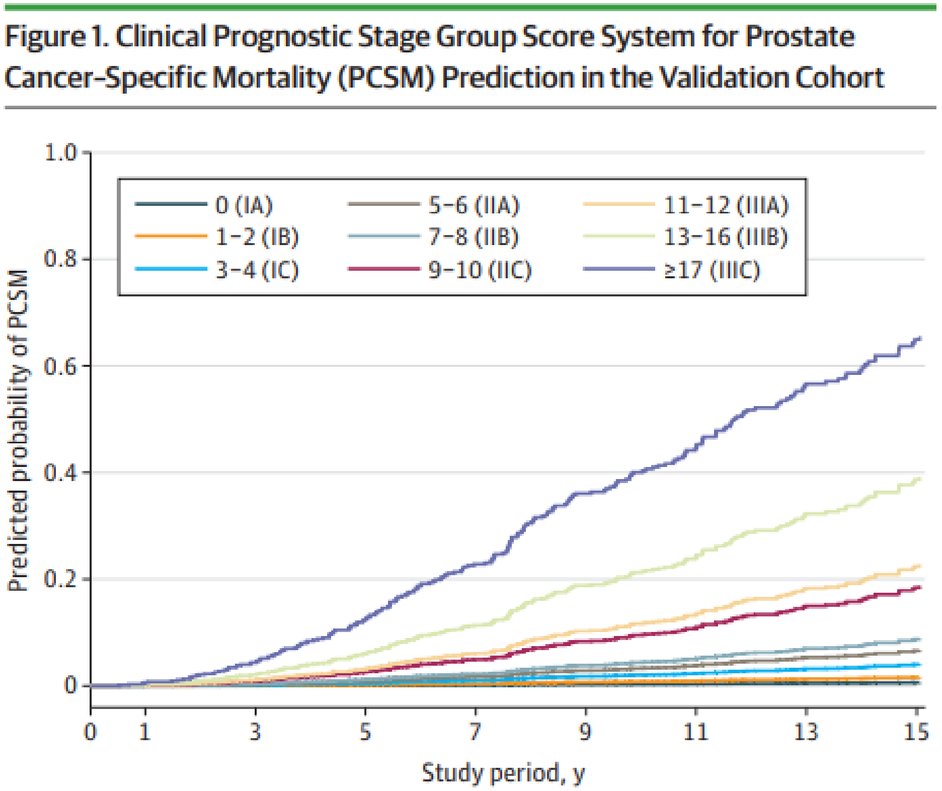

Spratt DE, et al. *JCO* 2018;36(6):581-90
Dess RT, et al. *JAMA Onc* 2020;6(12):1912-20

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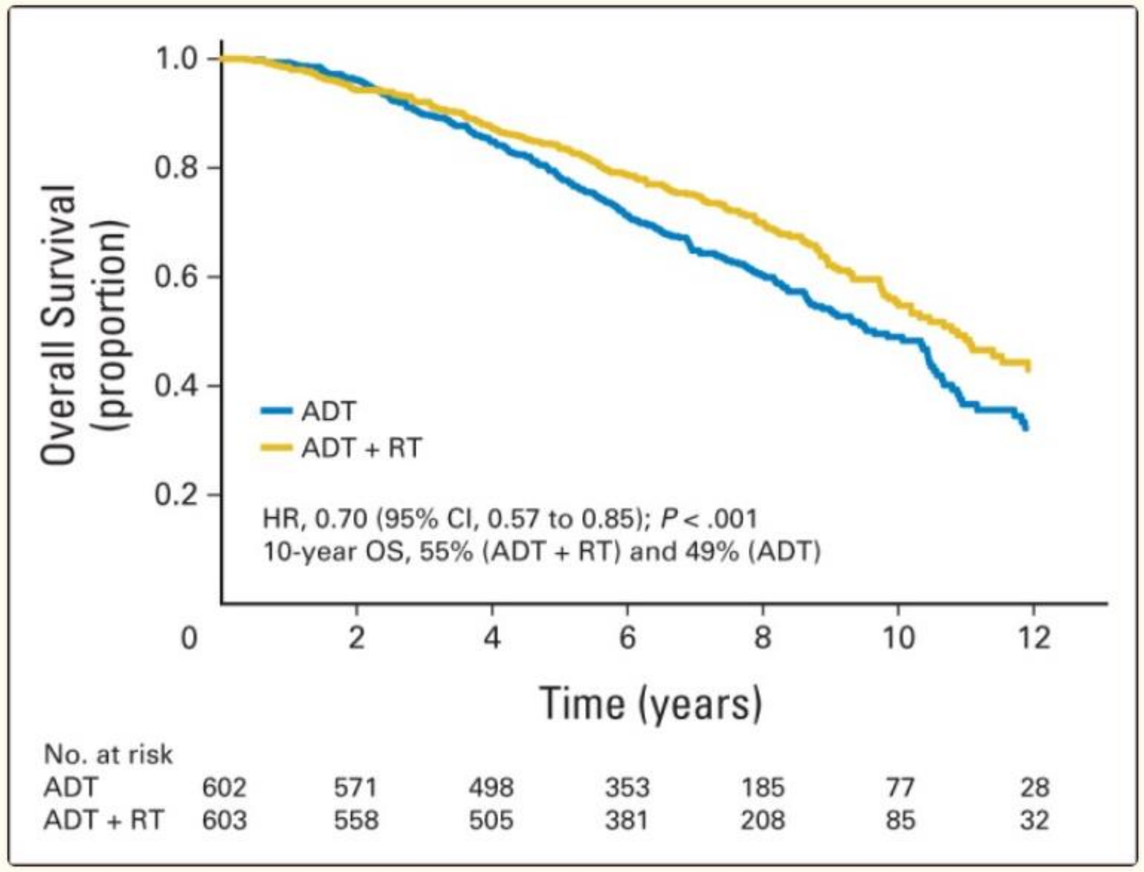
Improving Outcomes in High Risk Prostate Cancer

- What can influence PCSM in high risk, non-metastatic prostate cancer patients?
  - Randomized data have shown-
    - **Adding XRT to long-term ADT improves survival**



Mason MD, et al. JCO 2015;33(19):2143-50.

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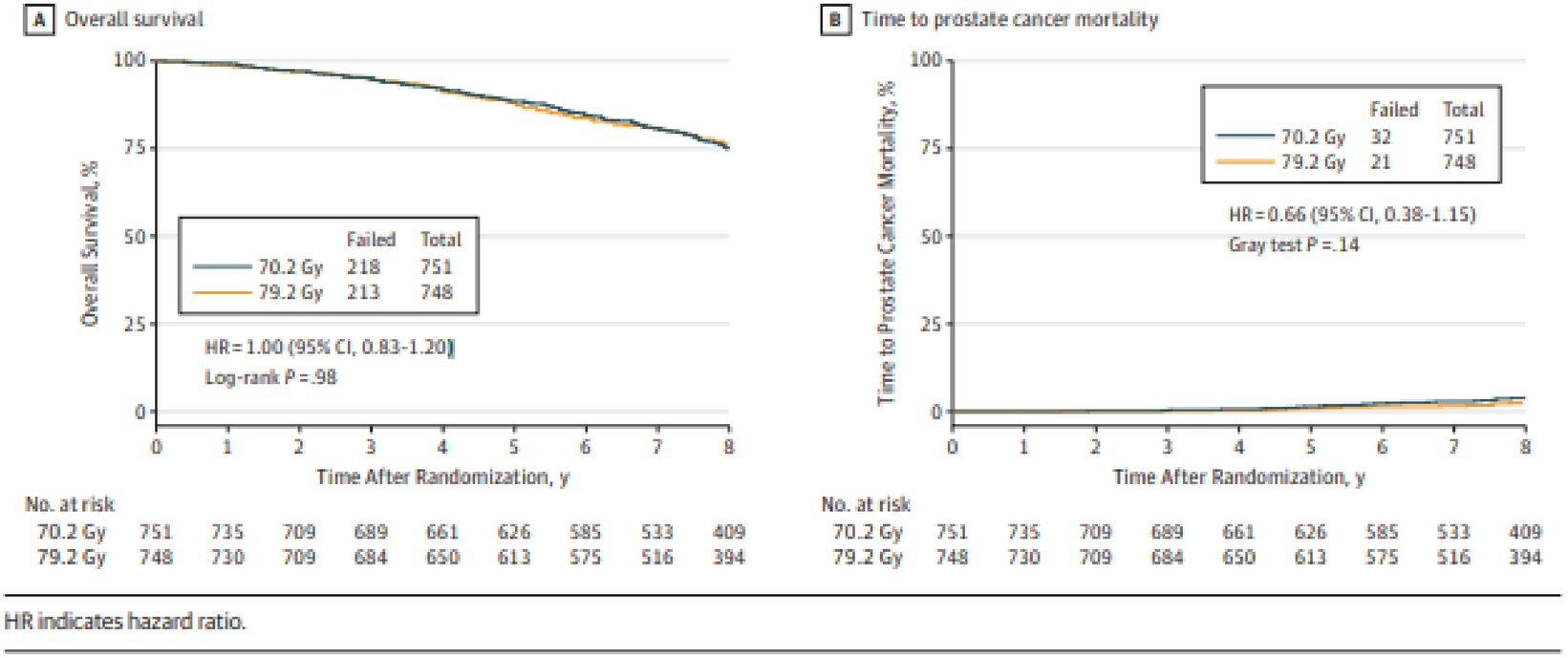
Improving Outcomes in High Risk Prostate Cancer

- What can influence PCSM in high risk, non-metastatic prostate cancer patients?
  - Randomized data have shown-
    - **Radiation dose escalation DOES NOT improve survival**



HR indicates hazard ratio.

Michalski JM, et al. *JAMA Onc* 2018;4(6)

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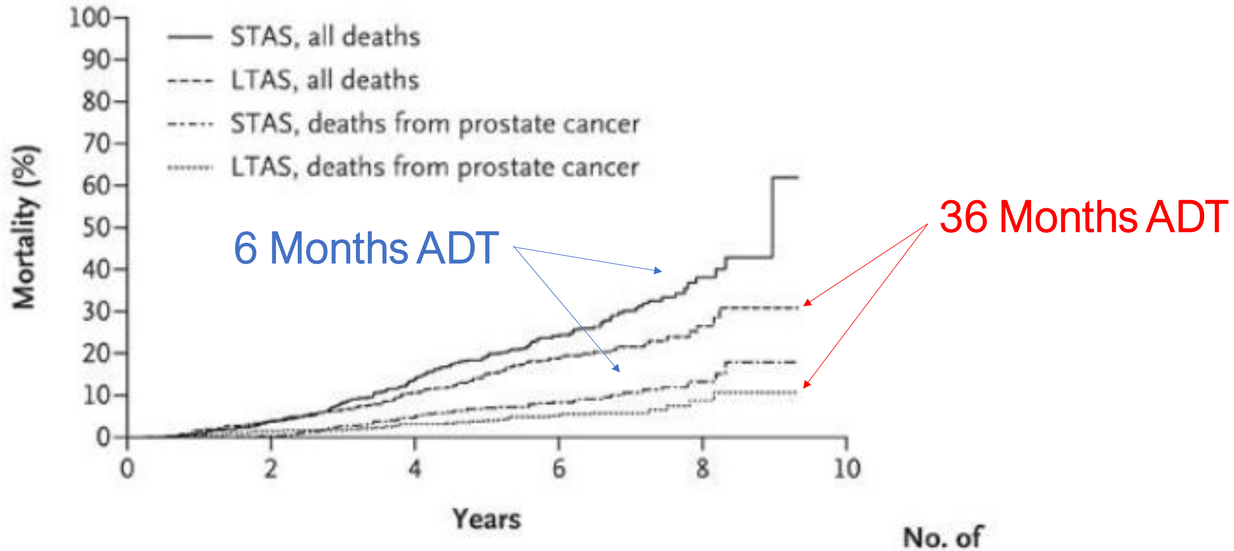
Improving Outcomes in High Risk Prostate Cancer

- What can influence PCSM in high risk, non-metastatic prostate cancer patients?
  - Randomized data have shown-
    - **Adding long-term ADT to XRT improves overall survival**



No. at Risk						No. of Events
STAS, all deaths	483	454	388	231	43	132
LTAS, all deaths	487	454	407	249	50	98
STAS, deaths from prostate cancer	483	454	388	231	43	47
LTAS, deaths from prostate cancer	487	454	407	249	50	29

Bollla M, et al. *NEJM* 2009;360:2516-27.

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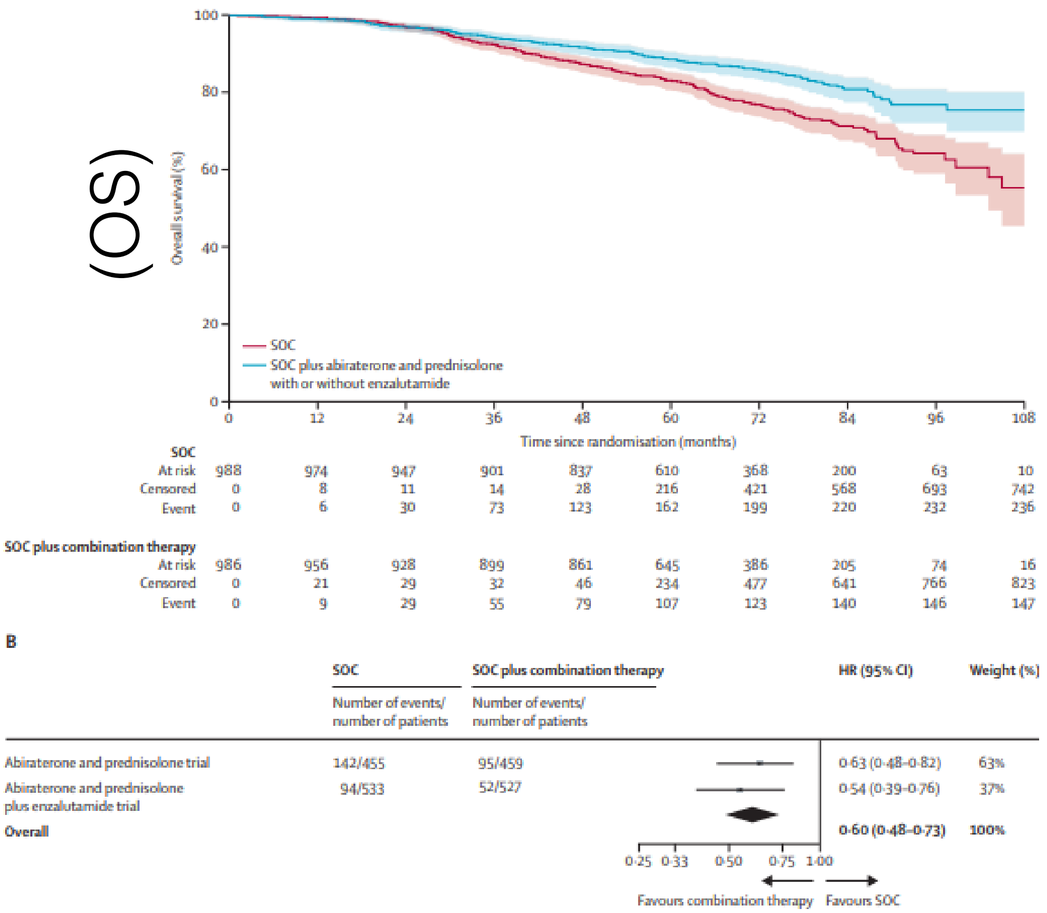
Improving Outcomes in High Risk Prostate Cancer

- **STAMPEDE Strikes Again!**
- 1974 men with non-metastatic very high risk prostate cancer randomly assigned to XRT + ADT (3 years) vs XRT + ADT + abiraterone (2 years)
- Very High Risk required at least TWO of:
  - T3/T4 tumor
  - Grade Group 4-5 (Gleason 8-10)
  - PSA ≥ 40 ng/ml



Attard G, et al. Lancet 2022;399:447-60.

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Improving Outcomes in High Risk Prostate Cancer

- **Do STAMPEDE data translate to standard NCCN high risk patients?**
- **Do ALL high risk patients need treatment escalation or can some have similar outcomes with less intense ADT?**
- **Prospective studies are underway to determine if systemic therapy can be personalized**

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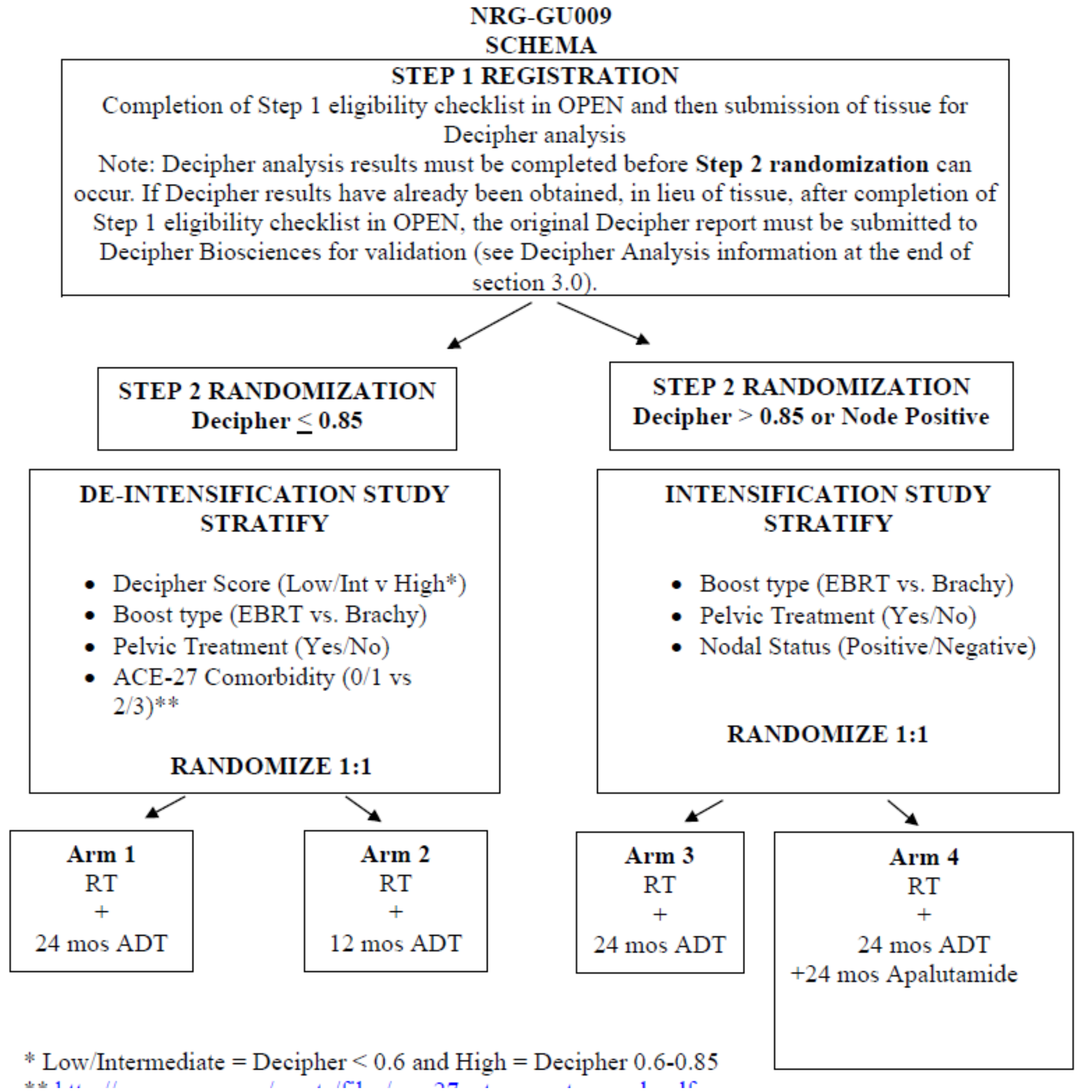
NRG-GU009: PARALLEL PHASE III RANDOMIZED TRIALS FOR HIGH RISK PROSTATE CANCER EVALUATING DE-INTENSIFICATION FOR LOWER GENOMIC RISK AND INTENSIFICATION OF CONCURRENT THERAPY FOR HIGHER GENOMIC RISK WITH RADIATION (PREDICT-RT*)

**Prostate RNA Expression/Decipher To Individualize Concurrent Therapy with Radiation*

ClinicalTrials.gov Identifier NCT# 04513717
NCI Version Date: (September 24, 2021)

Principal Investigator:
Paul Nguyen, MD
Dana-Farber/Brigham and Women's
Radiation Oncology
75 Francis St
Boston, MA



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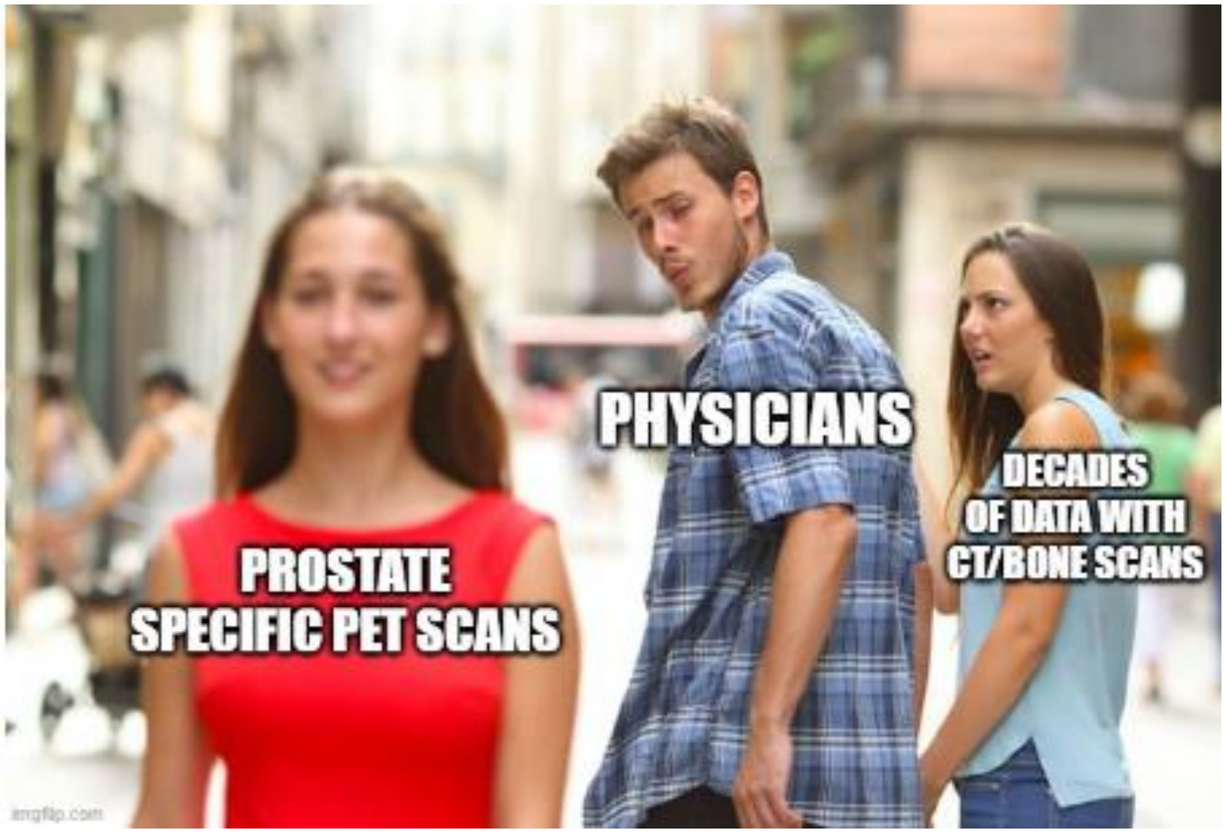
Recurrent Prostate Cancer After Definitive Treatment

- **Management of biochemically recurrent/progressive prostate is a rapidly evolving field**
- **The development of novel PET imaging has allowed earlier anatomical localization of disease sites**
- **Enthusiasm for metastasis-directed therapy has grown simultaneously, but what is its real role in clinical care?**



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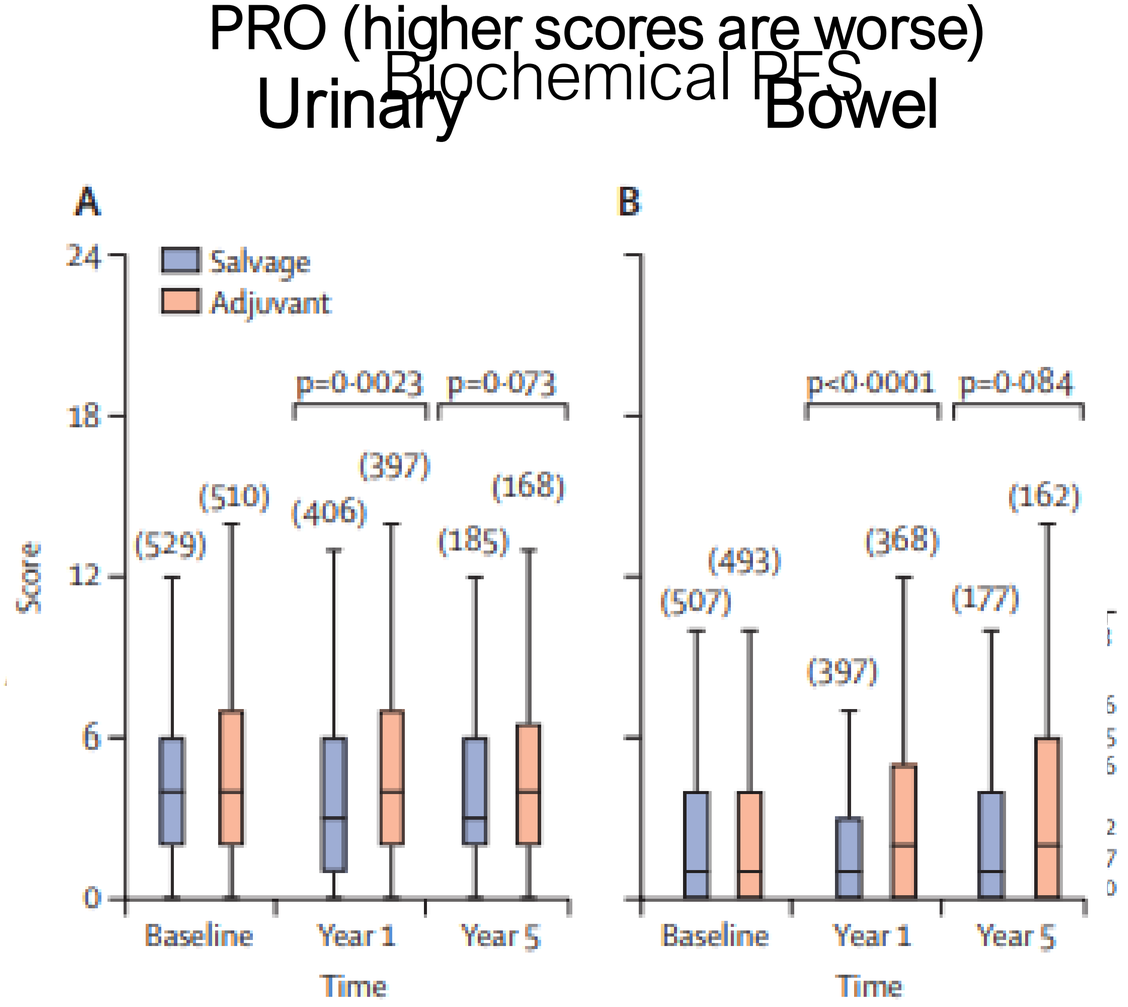
Adjuvant vs. Salvage Radiation

- Data supporting meaningful improvements in patient outcomes following radiation therapy to the prostate fossa +/- pelvic lymph nodes are plentiful
- Recent randomized trials have shown that **adjuvant** radiation therapy for those with high-risk features (pT3/pT4, + margins) provides **no oncologic advantage** over **early salvage** radiation therapy but does **increase toxicity**



Parker, CJ et al. *Lancet* 2020. 396:1413-21.

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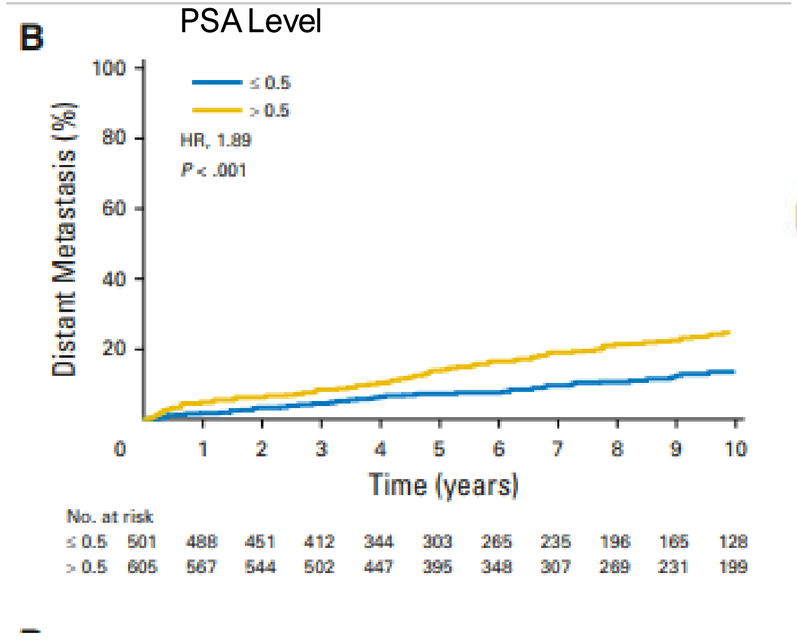
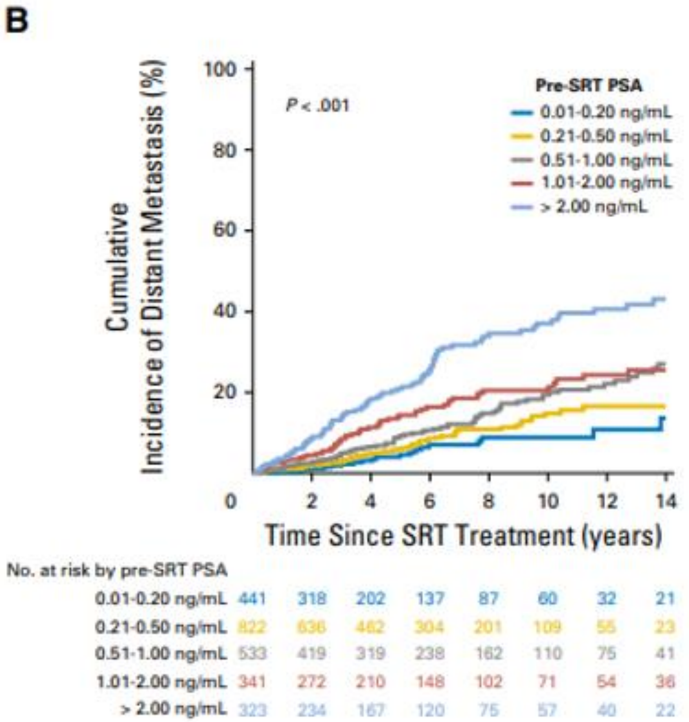
Salvage Radiation Remains an Important Tool for Treating Recurrent Prostate Cancer

- Data supporting meaningful improvements in patient outcomes following radiation therapy to the prostate fossa +/- pelvic lymph nodes are plentiful
- Early salvage radiation (pre-radiotherapy PSA <0.5 ng/ml) significantly improves outcomes compared to “Late” salvage radiation





Stish BJ, et al *JCO*. 2016: 34(32).
Tendulkar RD, et al. *JCO.* 2016: 34(30).

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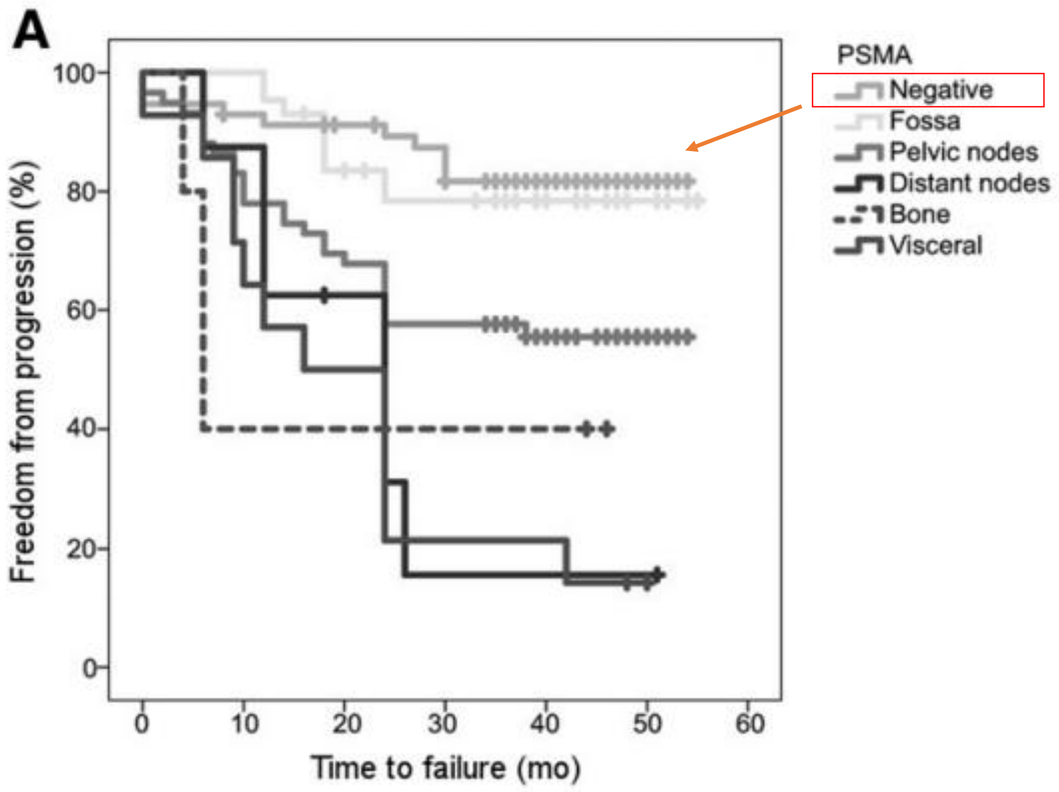
PSMA PET Imaging Prior to Salvage

- PSMA PET is a useful tool for initial biochemical recurrence
  - Waiting to invoke salvage RT until local recurrence is **NOT** yet standard of care and may jeopardize outcomes
    - Recall PET resolution is limited to around 4 mm
    - Salvage XRT works **BEST** in **PET negative** patients!

TABLE 3
PSMA PET Result Stratified by Increasing PSA Level

PSA (ng/mL)	PSMA PET-negative	PSMA PET-positive	Overall
<0.2	41 (49.4%)	42 (50.6%)	83
0.2–0.5	36 (34.9%)	67 (65.1%)	103
0.51–0.99	9 (27.3%)	24 (72.7%)	33
1.0–5.0	4 (9.8%))	37 (90.2%)	41
Total	90 (34.6%)	170 (65.4%)	260

Outcomes following salvage radiation, based on pre-salvage RT PET findings



Emmett L, et al. *The Journal of Nuclear Medicine* 2020: 61(6).

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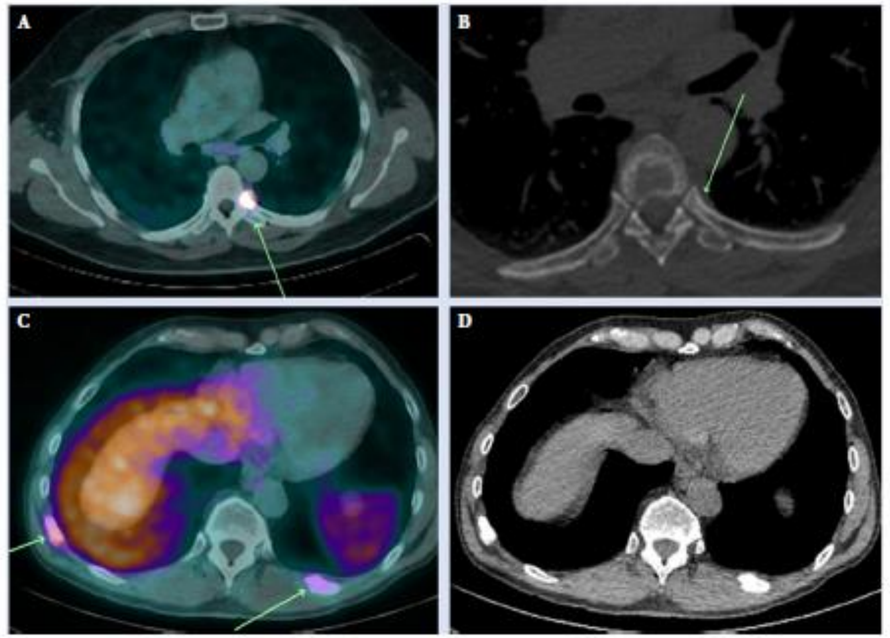
PSMA PET Imaging-Interpret With Care

- PSMA is a useful tool for initial biochemical recurrence
  - Be VERY CAREFUL to carefully evaluate small rib lesions on PSMA PET as false positives are common
  - True determination of rib lesions (biopsy confirmation or positivity on another imaging modality) can be challenging.
  - Consider pre-test probability and sometimes empiric treatment is reasonable
  - Other sites frequently cited for false positives:
    - Excreted urine near bladder
    - Ureters
    - Nerve ganglia in paraspinal/presacral regions



Benign PSMA-avid solitary rib lesions

In all, 61 men (98.4%) with solitary rib lesions on pre-treatment ^{68}Ga-PSMA PET/CT scans satisfied the criteria for benign lesions (Table 2). Follow-up ^{68}Ga-PSMA PET/CT scans were not routinely performed and only three patients had follow-up ^{68}Ga-PSMA PET/CT scans due to clinical suspicion.

Chen, MY et al. *BJU Int* 2020. 126: 396-401.

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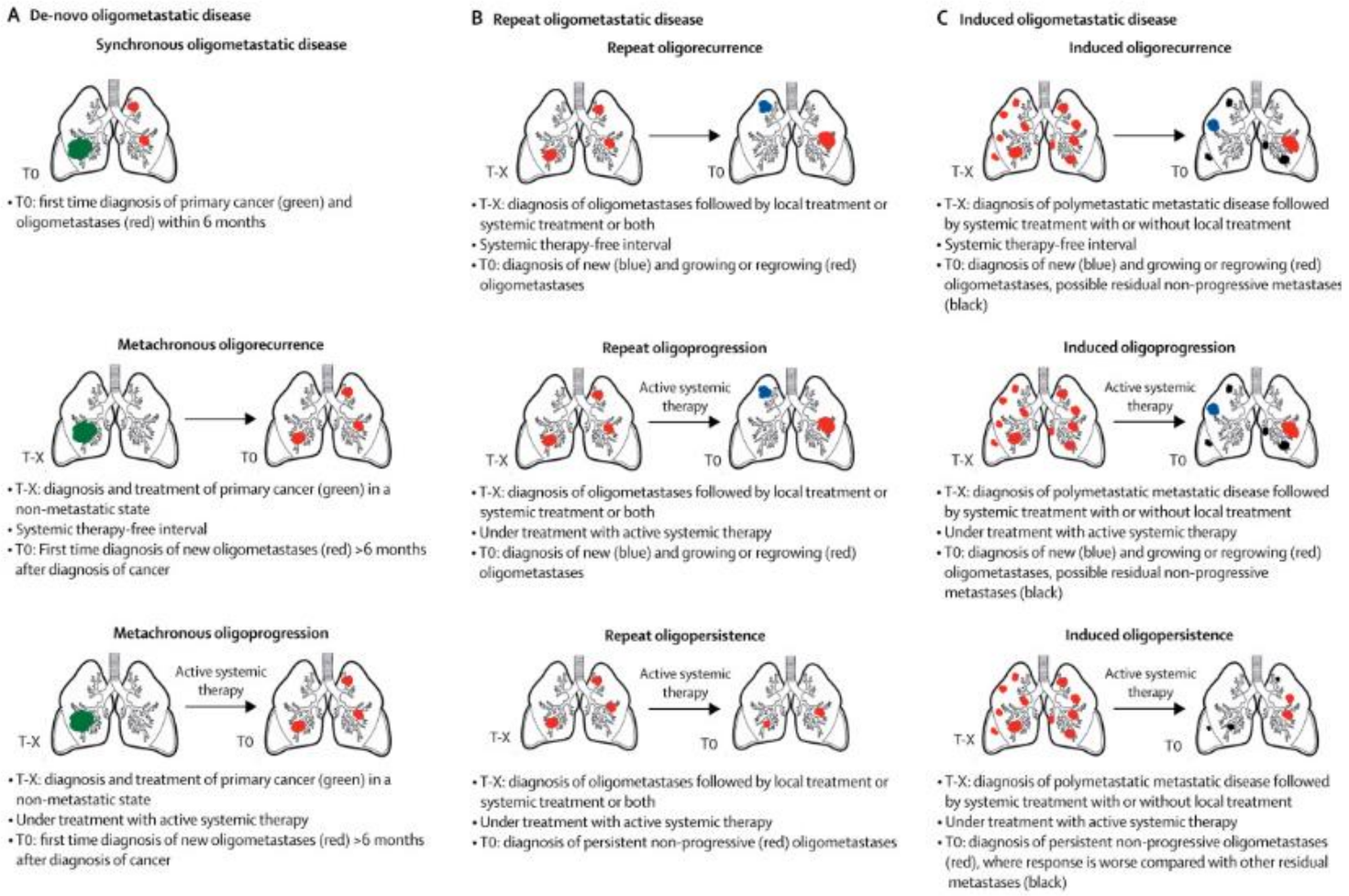
Oligometastatic Prostate Cancer

- Definitions are important
  - And evolving!



Guckenberger M et al. *Lancet Oncol* 2020. 21(1): e18-e28.

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Metastasis-Directed Therapy to Delay ADT

- STOMP and ORIOLE were two prostate-specific studies of metastasis-directed therapy (MDT) in patients with oligometastatic prostate cancer
- Both showed that MDT could delay progression and initiation of ADT
- However, the benefit of MDT with regards to more definitive oncologic outcomes remains to be proven

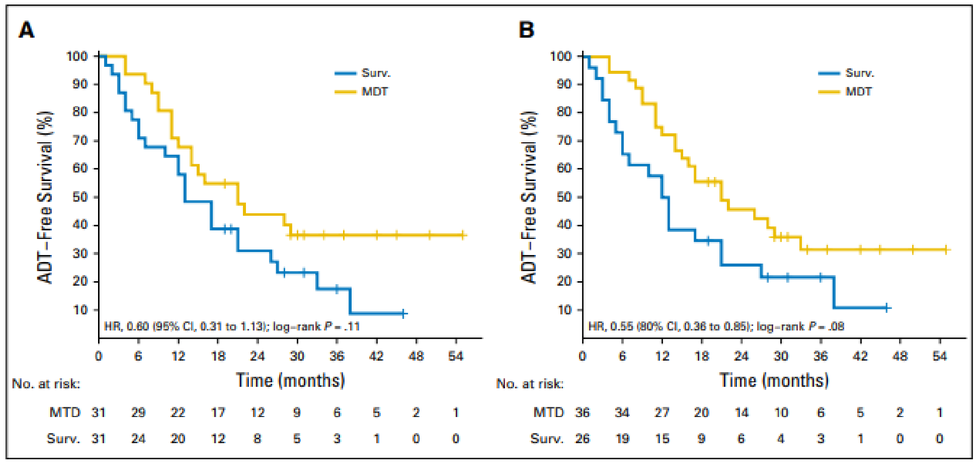
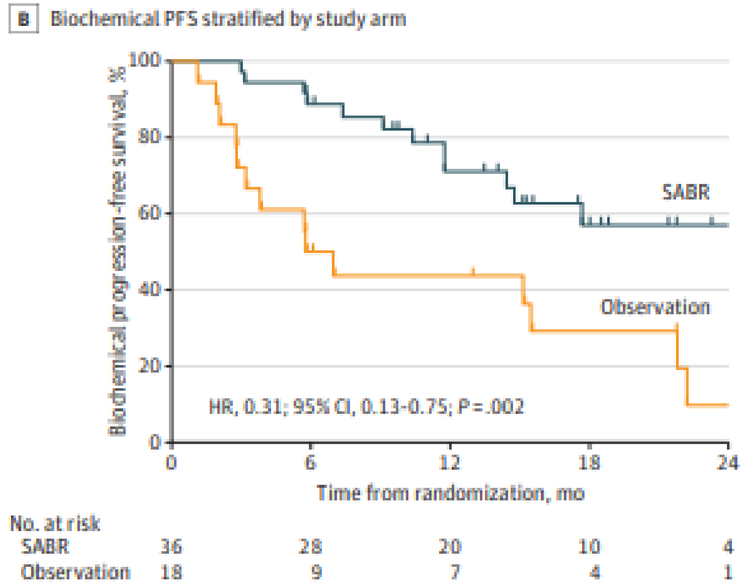


Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)–free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.



Ost P, et al. *JCO* 2018. 36(5):446-53.
Philips RM, et al. *JAMA Oncol* 2020. 6(5): 650-9.

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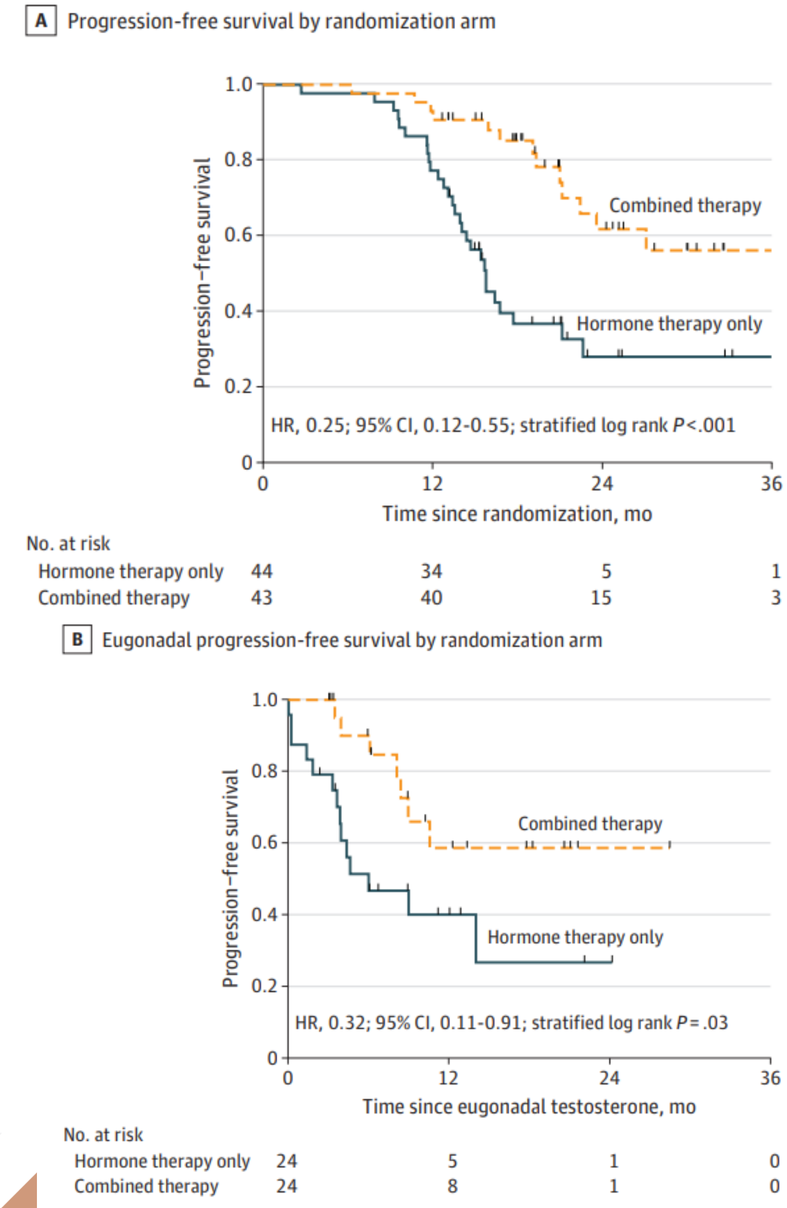
Metastasis-Directed Therapy to Supplement ADT

- EXTEND Study
  - Randomized Comparison in Oligometastatic Prostate Cancer
  - Intermittent ADT vs Intermittent ADT + MDT
  - Progression Free Survival and Eugonadal PFS both significantly improved with addition of MDT
  - MDT also improved serum markers of immune activation



Tang C, et al. *JAMA Oncol* 2023. 9(6):825-34.

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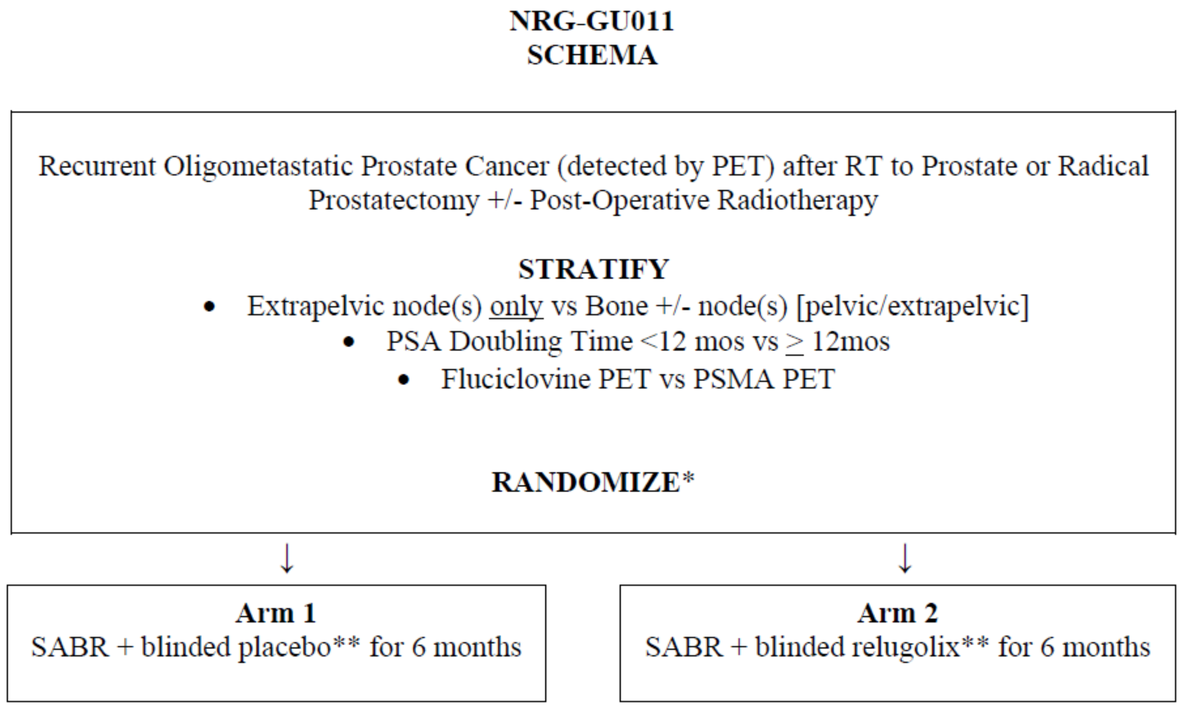
Metastasis-Directed Therapy-More Data Coming

- We must be aware that there really is no standard of care defined for biochemically recurrent, oligometastatic prostate cancer detected by PET imaging
- Thus, equipoise exists to evaluate the role of MDT in lieu of ADT in these patients
- Current NCCN guideline endorse MDT as an option for patient with oligometastatic prostate cancer



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NRG-GU011: A PHASE II DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL OF **PRO**STATE OLIGO**MET**ASTATIC RADIOT**HER**APY WITH OR WITHOUT **AN**DROGEN DEPRIVATION THERAPY IN OLIGOMETASTATIC PROSTATE CANCER (NRG PROMETHEAN)

ClinicalTrials.gov Identifier NCT# 05053152
NCI Version Date: (March 15, 2022)

Principal Investigator:
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Farmington Hills, MI
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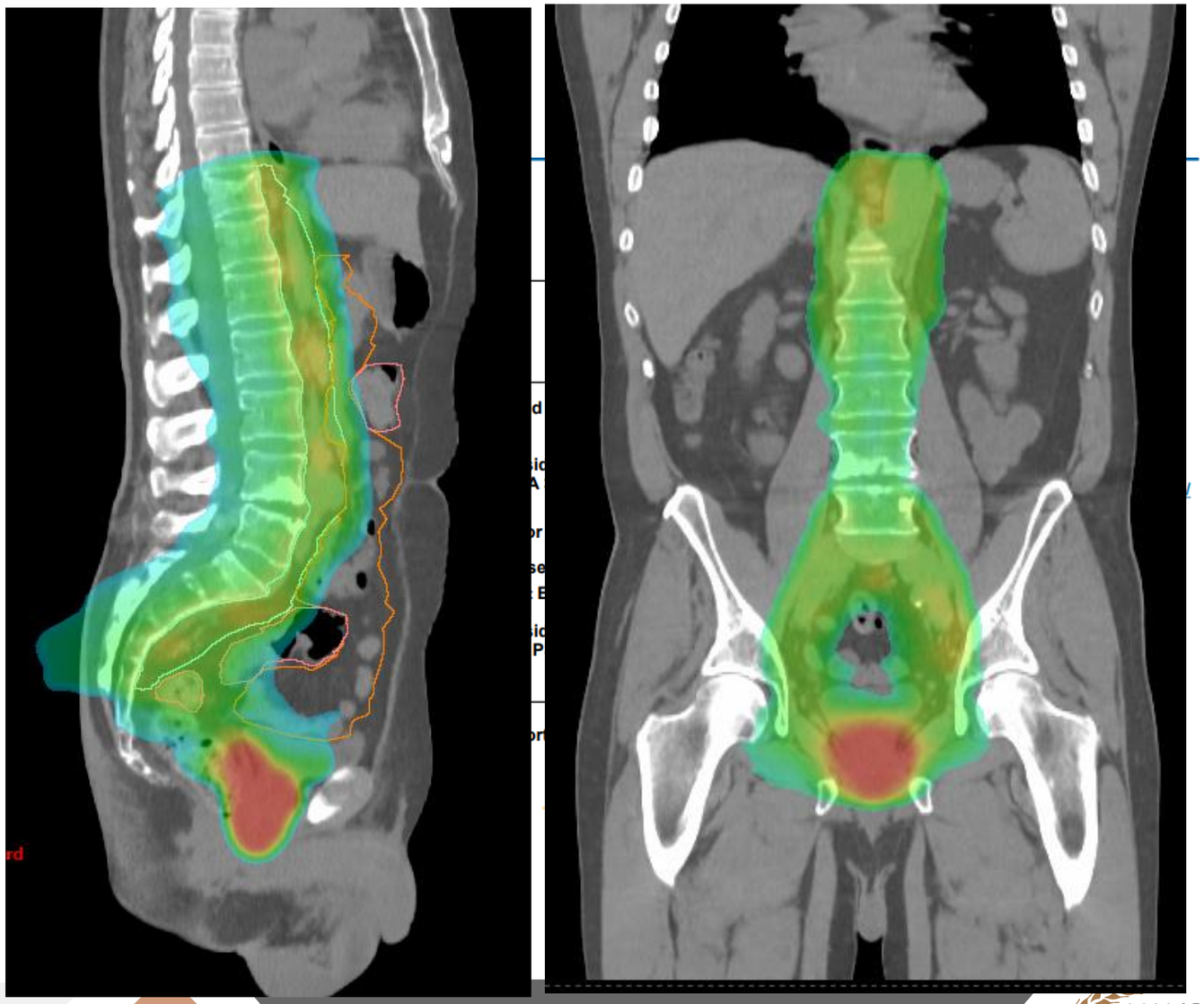
Radiation Therapy In Lymph Node Positive Prostate Cancer

- In patients with clinical N1 (and some with M1a) prostate cancer, radiation is an important component of treatment that should not be overlooked
- Treatment of extended lymph node volumes is generally well tolerated in the modern era
- Data also strongly support the addition of an ASIR
- ADT duration of 2 years to indefinite is reasonable



James ND, et al. *JAMA Oncol* 2016. 2(3):348-57.
NCCN Guidelines, www.nccn.org

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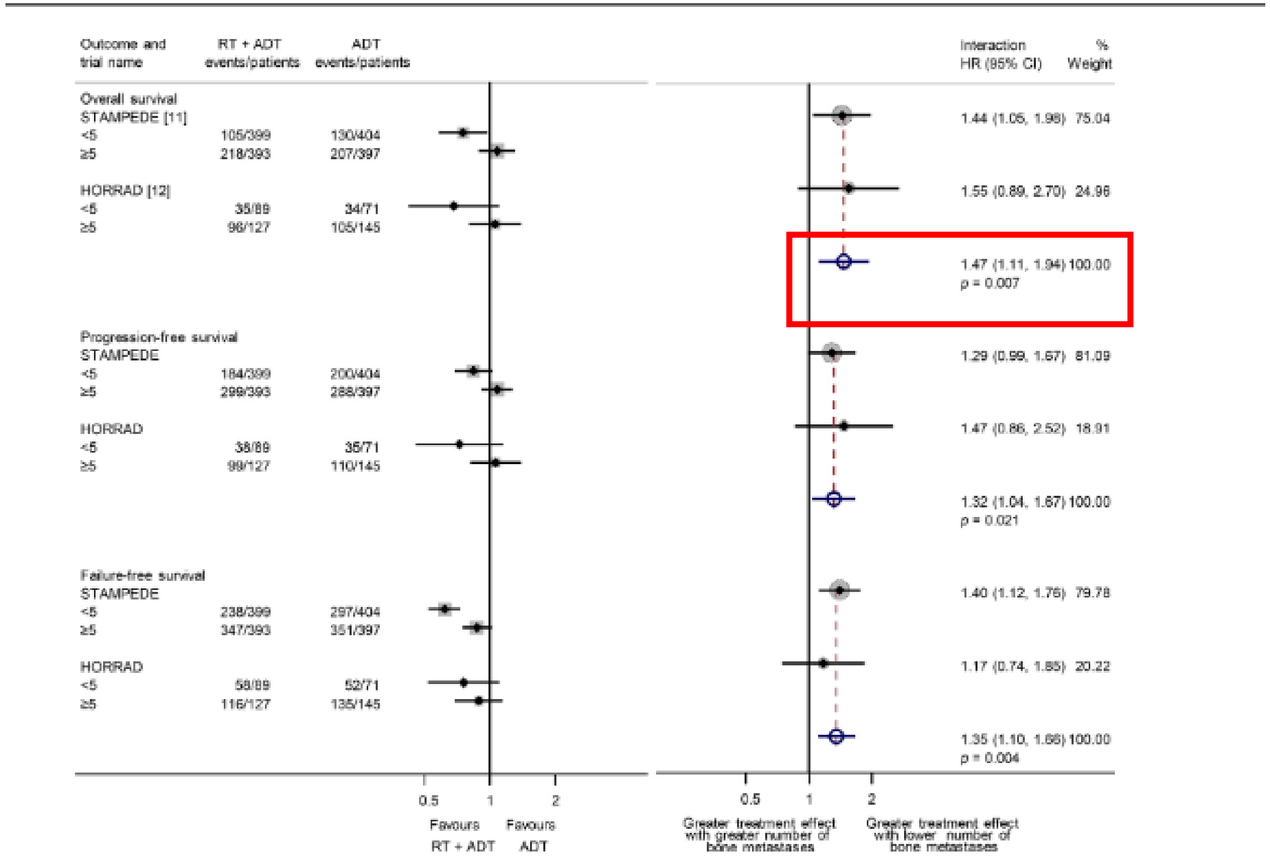
Radiation Therapy In Newly Diagnosed Metastatic Prostate Cancer

- HORRAD and STAMPEDE Arm H results pooled
  - These both included newly diagnosed M1 Pca
  - Arms were ADT vs ADT + RT to prostate
- Overall survival in **entire cohort** no different between ADT and ADT+RT
- Interaction of RT was assessed by disease volume.
  - < 5 metastases vs ≥ 5 metastases
  - **Overall survival** significantly improved with RT
  - 3 year OS=77% vs 70%



Burdett S, et al. *Eur Urol 2019*. 76(1):115-24.

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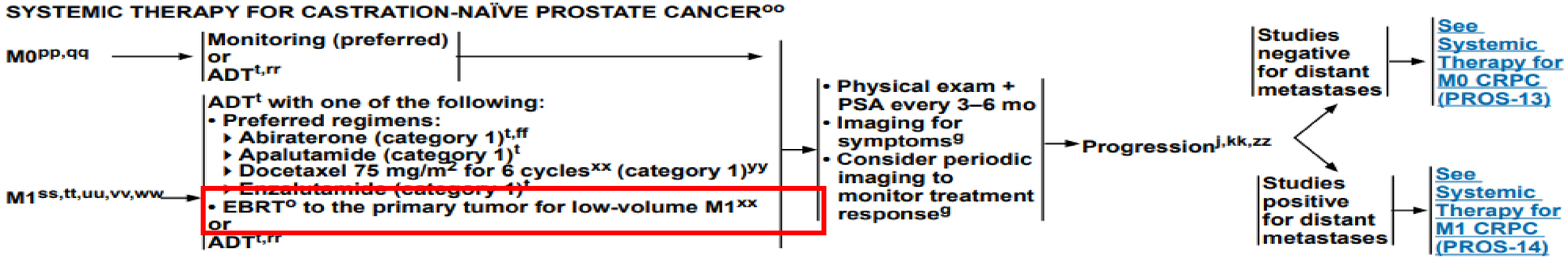
- Thus, XRT to the primary is listed in NCCN guidelines as a recommendation for low volume M1 patients



- However, many questions remain:
  - Does this benefit remain when more intensive systemic therapy regimens are employed?
  - These studies utilized CT/Bone scan staging, what do we do in the PSMA PET era?
  - Should we consider metastasis-directed therapy in conjunction with prostate only radiation?

Conclusions

- Radiation therapy is an excellent option for most men with localized prostate cancer
  - Current data support multiple techniques with similar long-term outcomes
- There appears to be a role for escalated systemic therapy in some men with high-risk prostate cancer receiving XRT
  - Personalization may be possible, although studies are pending
- Radiation plays an important, and potentially curative, role in initial biochemical recurrence after radical prostatectomy
  - Evolving technology may prove to guide patient selection, but this remains outside the current standard of care
- Current data support prostate radiation therapy in patients with newly diagnosed low volume M+ prostate cancer
  - Future studies will help further define the place of radiotherapy in this rapidly evolving landscape