ASTRO ANNUAL refresher COURSE 2021

BEST PRACTICES AND EMERGING TRENDS

March 19-21 *Live* Interactive Virtual Conference

Welcome

Genitourinary Cancers

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Disclosures

- Employed by Cleveland Clinic
- Honoraria from Varian Medical Systems for educational talks

Learning Objectives

- Upon completion of this activity, attendees should be able to do the following:
  - Treat all risk groups, including oligometastatic prostate cancer, with radiation when appropriate.
  - Utilize androgen deprivation therapy with radiation for prostate cancer when appropriate.
  - Deliver hypofractionated radiation for prostate cancer when appropriate

Outline

- Bladder cancer
- Seminoma
- Renal cell carcinoma
- Prostate cancer
  - Early stage (low & intermediate risk)
  - High risk/locally advanced
  - Salvage therapy after RP or RT
  - LN+
  - Metastatic

I will try to focus on NEW data in 2020-2021

GU Cancer Incidence 2020

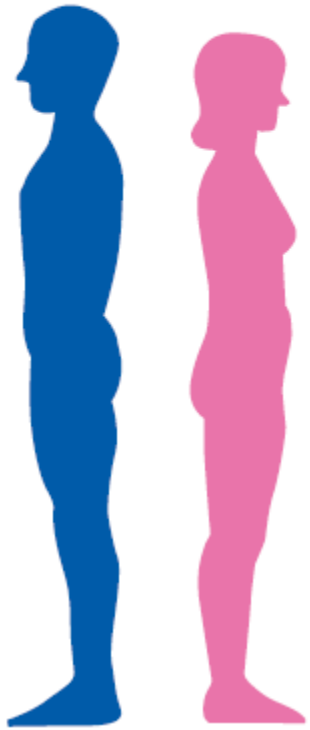
	ESTIMATED NEW CASES			ESTIMATED DEATHS		
	BOTH SEXES	MALE	FEMALE	BOTH SEXES	MALE	FEMALE
Genital system	**317,260**	**203,740**	**113,520**	**67,830**	**34,210**	**33,620**
Uterine cervix	13,800		13,800	4,290		4,290
Uterine corpus	65,620		65,620	12,590		12,590
Ovary	21,750		21,750	13,940		13,940
Vulva	6,120		6,120	1,350		1,350
Vagina & other genital, female	6,230		6,230	1,450		1,450
Prostate	191,930	191,930		33,330	33,330	
Testis	9,610	9,610		440	440	
Penis & other genital, male	2,200	2,200		440	440	
Urinary system	**159,120**	**110,230**	**48,890**	**33,820**	**23,540**	**10,280**
Urinary bladder	81,400	62,100	19,300	17,980	13,050	4,930
Kidney & renal pelvis	73,750	45,520	28,230	14,830	9,860	4,970
Ureter & other urinary organs	3,970	2,610	1,360	1,010	630	380

Siegel CA Cancer J 2020

GU Cancer Incidence 2020

Estimated New Cases

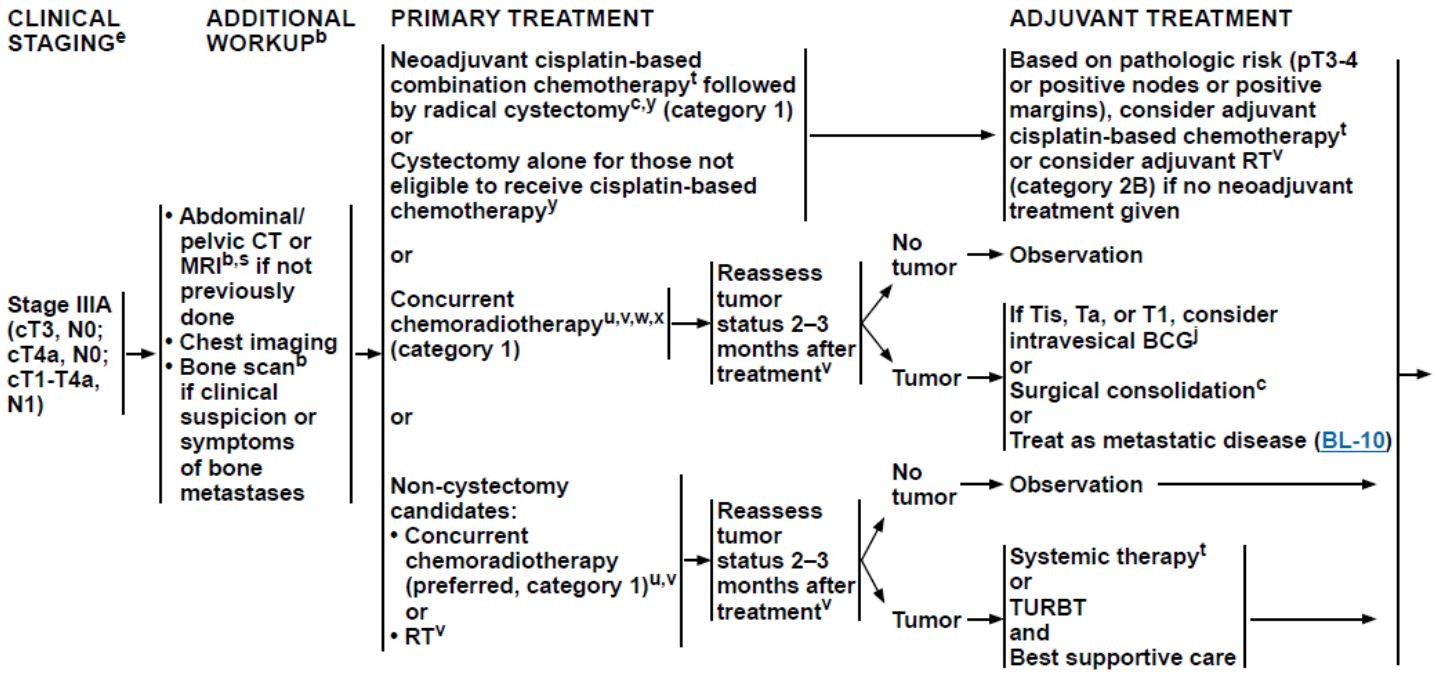
Males			Females		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All Sites	**893,660**	**100%**	**All Sites**	**912,930**	**100%**



Siegel CA Cancer J 2020

NCCN 2021: Bladder Cancer

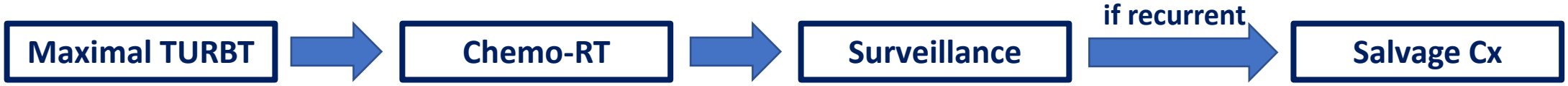
- Clinical stage II-III: **Neoadj Chemo + RCx <u>OR</u> TURBT + ChemoRT**



Chemoradiation for MIBC

Executive Summary of the American Radium Society Appropriate Use Criteria for Radiation Treatment of Node-Negative Muscle Invasive Bladder Cancer

- General paradigm



- Eligibility: cT2-T4 N0 M0, good bladder function
  - Hydronephrosis → high risk for failure (but not absolute contraindication)
- Multidisciplinary evaluation is critical

Dinh IJROBP 2021

Chemoradiation for MIBC

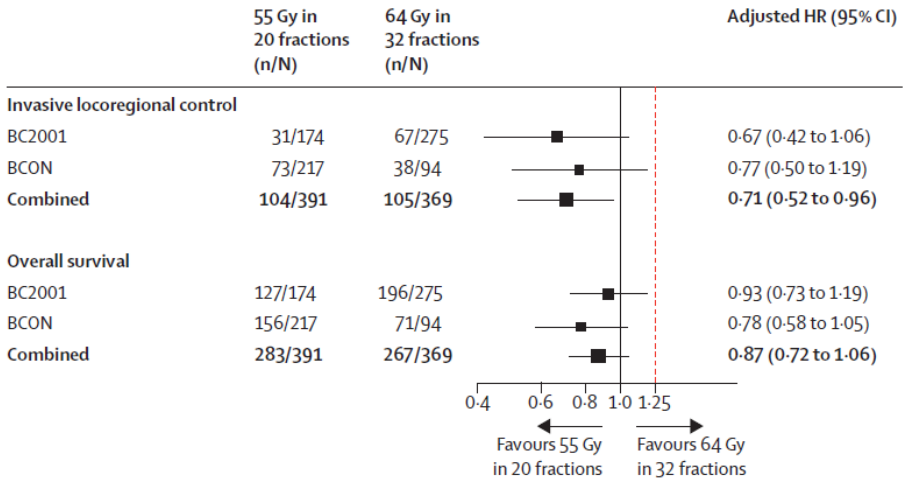
Executive Summary of the American Radium Society Appropriate Use Criteria for Radiation Treatment of Node-Negative Muscle Invasive Bladder Cancer

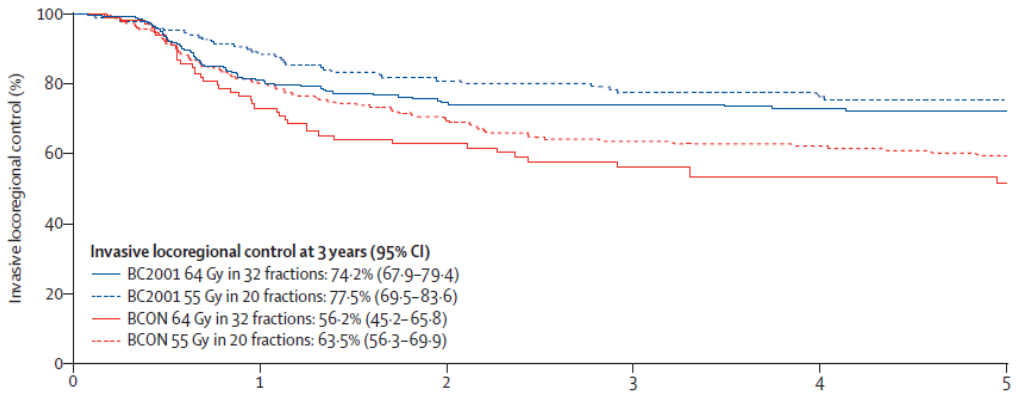
- Concurrent cisplatin-based chemo (or 5-FU/MMC or gem)
  - Consider carbogen or nicotinamide if not chemo candidate (rather than RT alone)
- RT dose 60-66 Gy @ 2 Gy/fraction
  - Either continuous course or split course with cystoscopic evaluation
  - Either IMRT or 3D appropriate
- Nodal radiation is optional
  - <10% nodal failure in BC2001 & TROG trials

Dinh IJROBP 2021

What's new? 55 Gy in 20 now preferred in U.K.

- Meta-analysis of 782 patients (BC2001 and BCON trials)
- Either 64 Gy/32 or 55 Gy/20 were allowed on trial (not randomized)
- **55 Gy/20 non-inferior** (lower iLRR and similar toxicity)

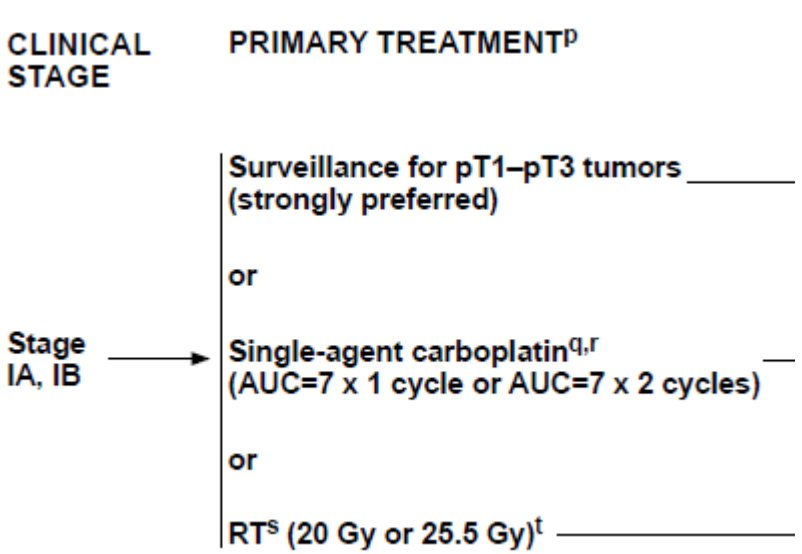




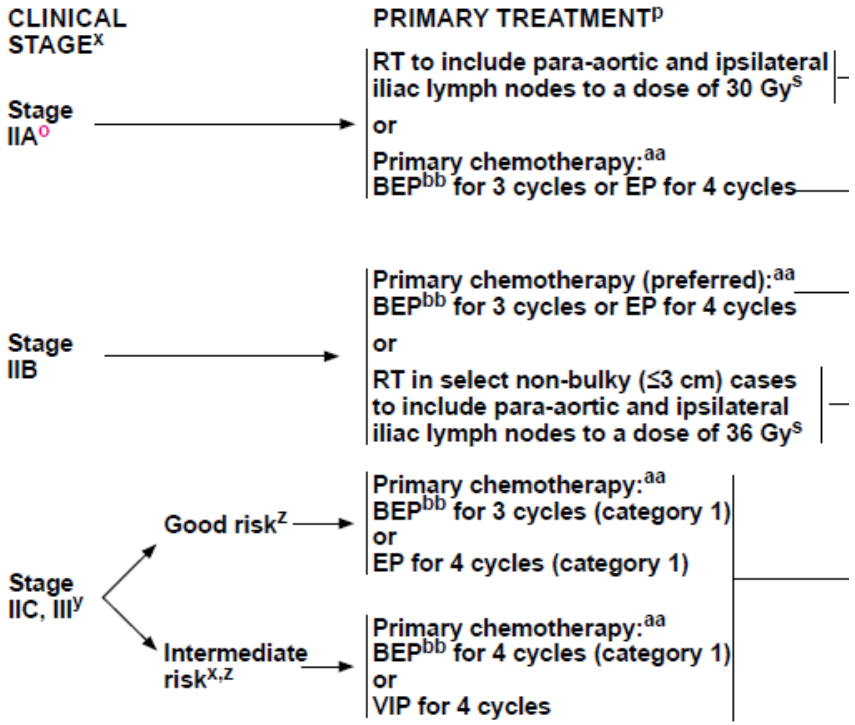
Choudhury Lancet Oncol 2021

NCCN 2021: Seminoma

Stage I: LN negative



Stage II: LN positive



Seminoma

- **Stage I → surveillance preferred**
  - If unreliable for follow up, carbo x 1 or PA strip 20 Gy/10
- If patient recurs in RPLNs (15-20% risk), treat as stage II
  - Modified dogleg 20 Gy → boost involved LN (30 Gy if IIA, 36 Gy if IIB)
  - If bulky > ~3 cm → combo chemo (BEP x 3 or EP x 4)

Critical Review

Radiotherapy Treatment Planning for Testicular Seminoma

Richard B. Wilder, M.D., M.S., M.B.A.,* Mark K. Buyyounouski, M.D., M.S.,† Jason A. Efstathiou, M.D., D.Phil.,‡ and Clair J. Beard, M.D.§

Figure 1: Stage I RT Field

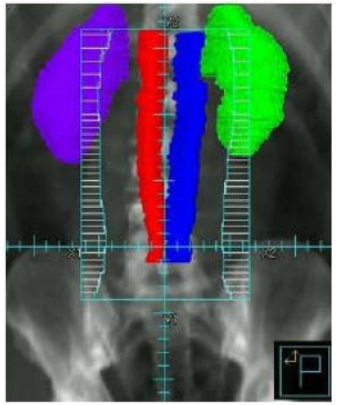
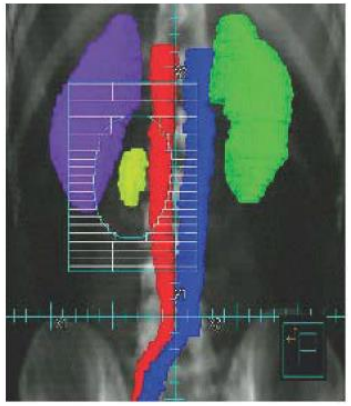


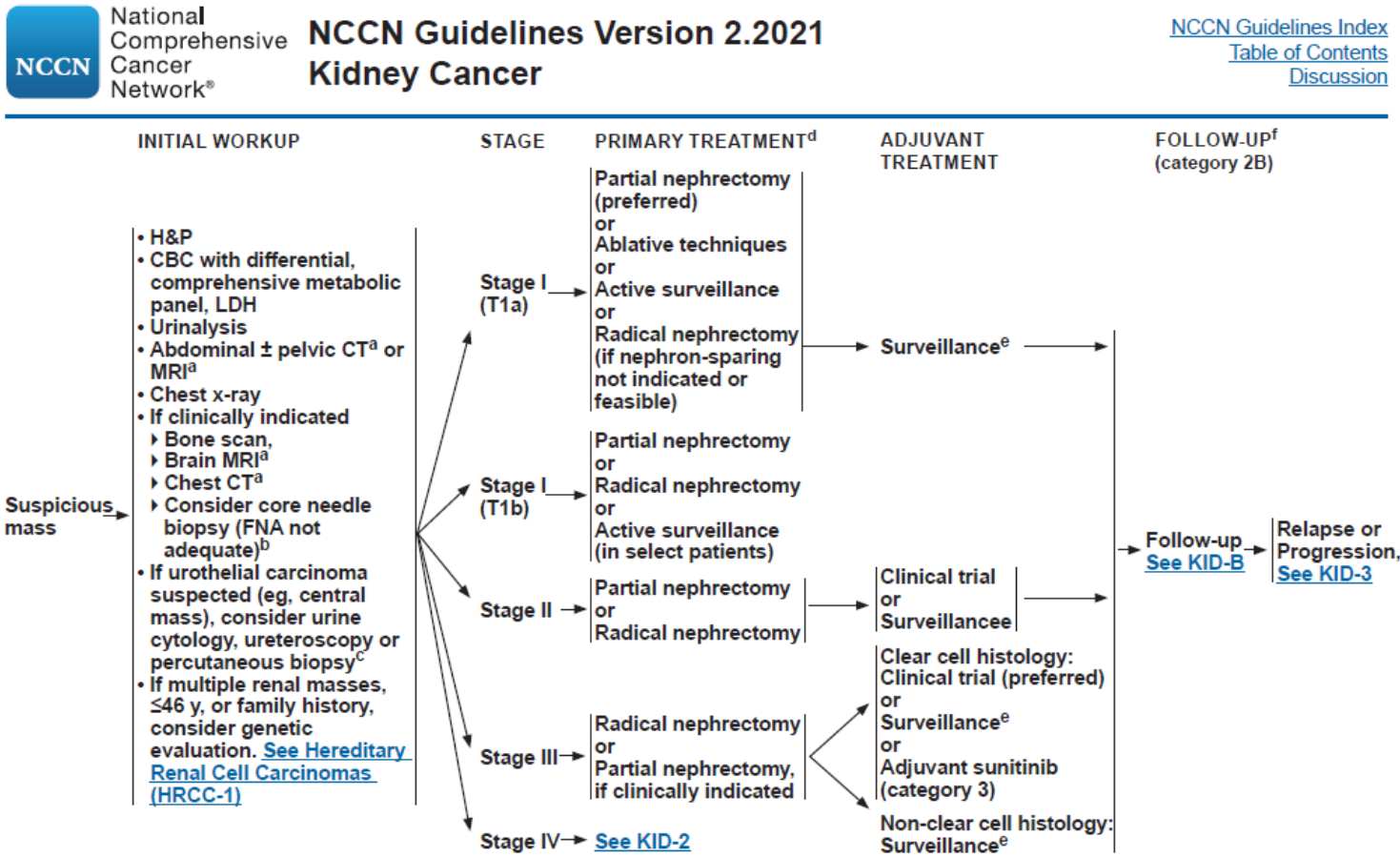
Figure 2: Stage II RT Large Field

Figure 3: Stage II Cone-down Field



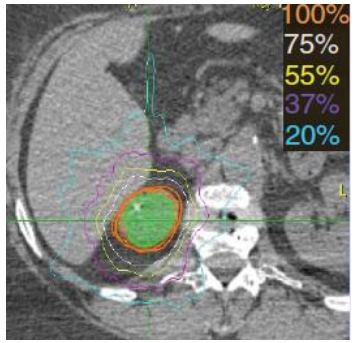
Wilder IJROBP 2012

NCCN 2021: Renal Cell Carcinoma



There is no mention of radiation in NCCN kidney guidelines except for treatment of metastases

SBRT for RCC



Consensus statement from the IROCK for primary renal cell carcinoma **CONSENSUS STATEMENT**

Table 2. Dose prescription details by individual institution.

Dosimetric parameter	Institution							
	BIDMC	*NIRS*	*UHSCC*	*ECC*	*KI*	*HMH*	*PMCC*	*UY*
Number of dose/fraction Schedules	2	> 3	1	1	> 3	> 3	2	> 3
Dose/ fractionation	36 Gy in 3 fractions 48 Gy in 3 fractions	64–80 GyE in 12 fractions	54 Gy in 3 fractions	25 Gy in 1 fraction	45 Gy in 3 fractions 50 Gy in 5 fractions 50 Gy in 10 fractions 56 Gy in 8 fractions	40–50 Gy in 5 fractions	26 Gy in 1 fraction 42 Gy in 3 fractions	40–70 Gy in 10 fractions
Objective prescription isodose	67%	100%	75%	70%	67%	80–90%	80%	80–90%
Days between fractions	Consecutive	Consecutive	1 day	NA	2 days	1 day	n/a or 1 day	1 day

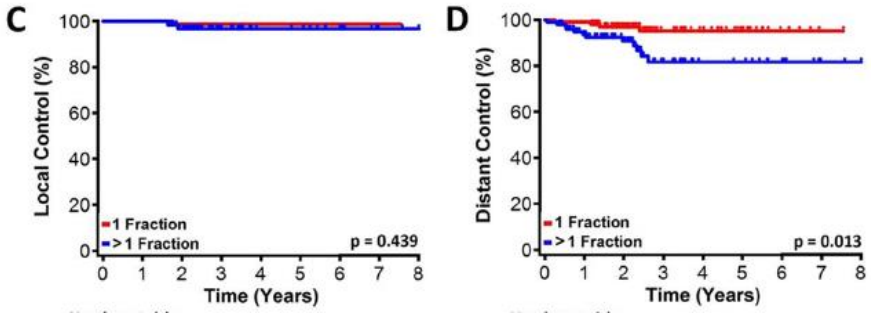
BIDMC: Beth Israel Deaconess Medical Center; ECC: European Cyberknife Center; HMH: Houston Methodist Hospital; ITV: Internal target volume; KI: Karolinska Institute; NIRS: National Institute of Radiological Sciences; OAR: Organ at risk; PMCC: Peter MacCallum Cancer Center; PTV: Planning target volume; UHSCC: University Hospitals Seidman Cancer Center; UY: University of Yamanashi.

Siva Future Oncol 2016

SBRT for RCC

Pooled Analysis of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK)

- Increasing data for **primary renal SBRT** from IROCK consortium
  - 4y **LC 97.8%**, Gr 3-4 toxicity 1.3%
  - 1 vs. >1 fraction → similar LC



- SBRT for RCC oligometastases also promising
  - Opportunity for synergy with immunotherapy?

Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies

Siva Cancer 2018. Zaorksy Eur Urol Foc 2019.

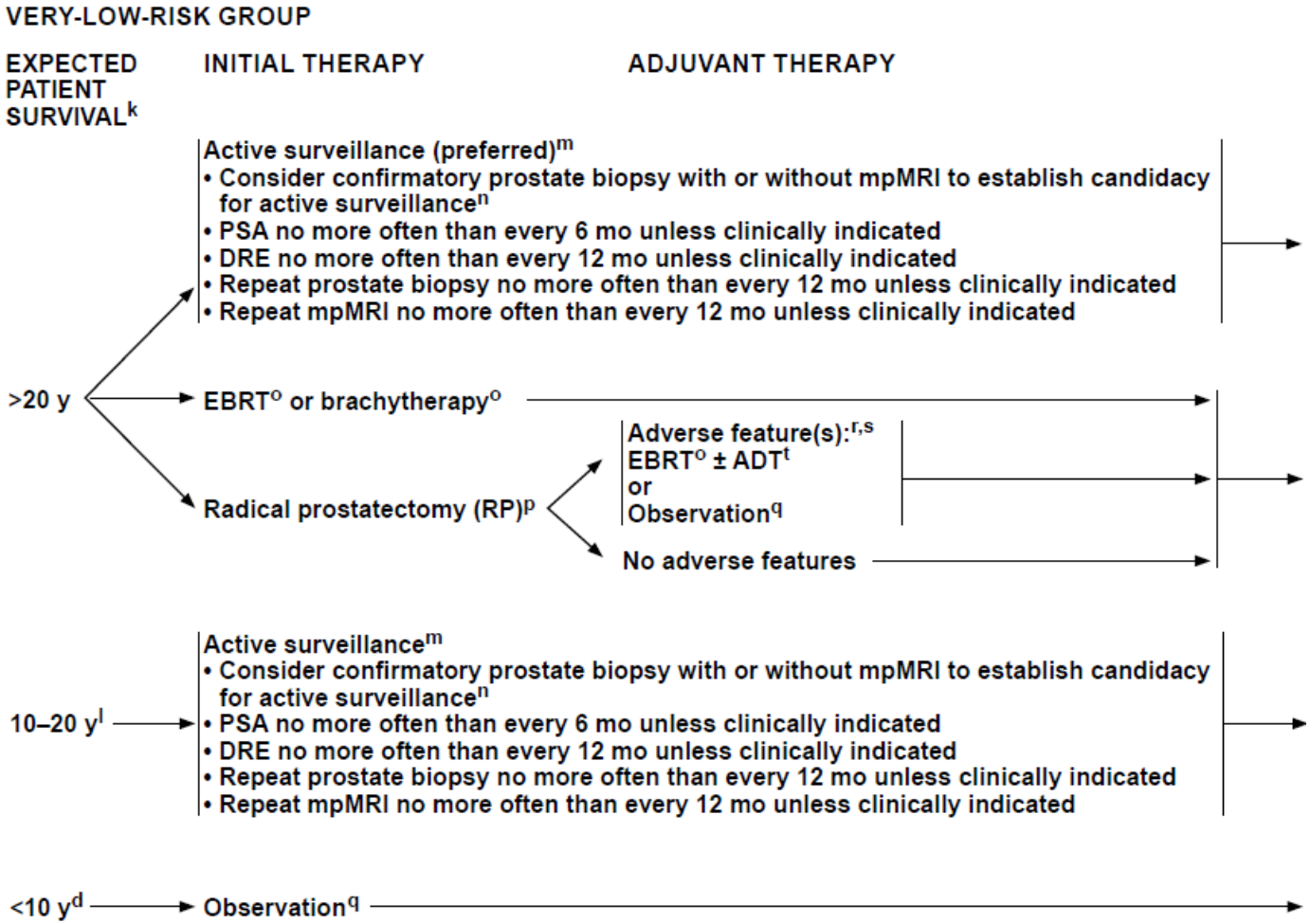
Prostate Cancer

- Buckle up…
  - Early stage (low & intermediate risk)
  - High risk/locally advanced
  - Salvage therapy after RP or RT
  - LN+
  - Metastatic

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]	Initial Therapy
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance	Recommended if family history positive See PROS-1	Not indicated	See PROS-3
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance	Recommended if family history positive See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-4
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance • Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[j]	See PROS-7
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

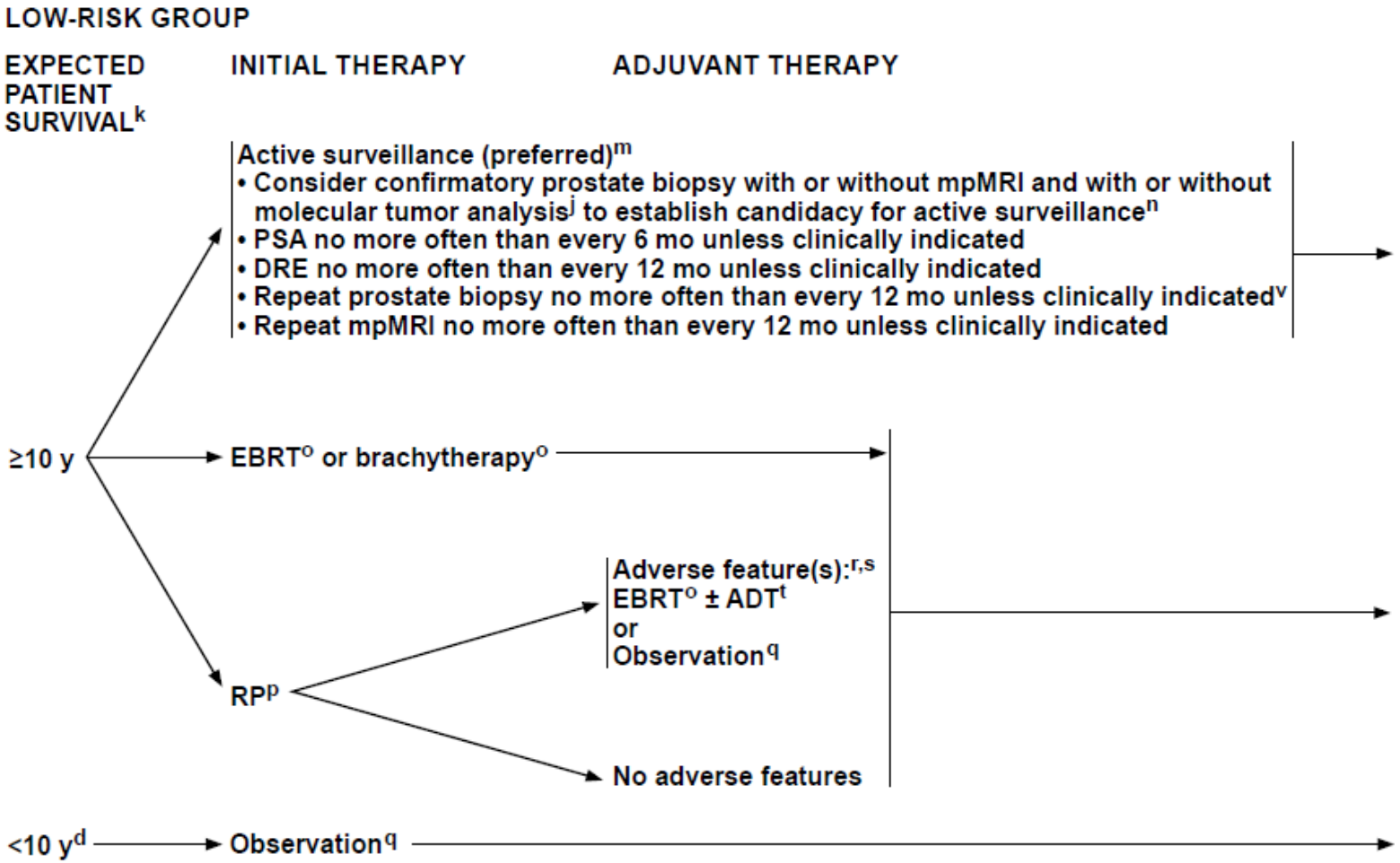
NCCN 2021: Very Low Risk

Has all of the following:
- T1c
- Grade Group 1
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e]
- PSA density <0.15 ng/mL/g



NCCN 2021: Low Risk

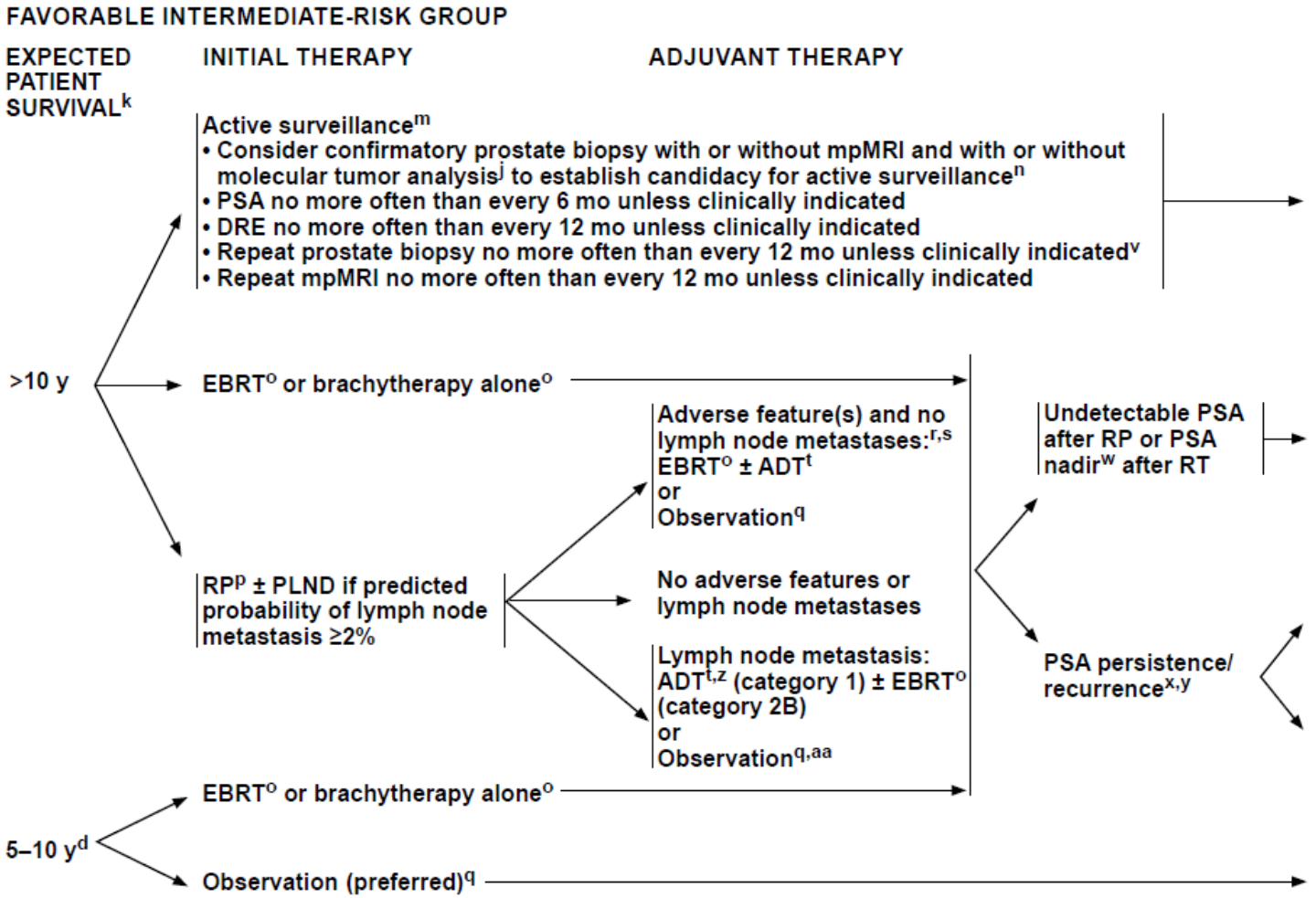
Has all of the following but does not qualify for very low risk:
- T1–T2a
- Grade Group 1
- PSA <10 ng/mL



NCCN 2021: Favorable Intermediate Risk

Has all of the following:
- 1 IRF
- Grade Group 1 or 2
- <50% biopsy cores positive[e]

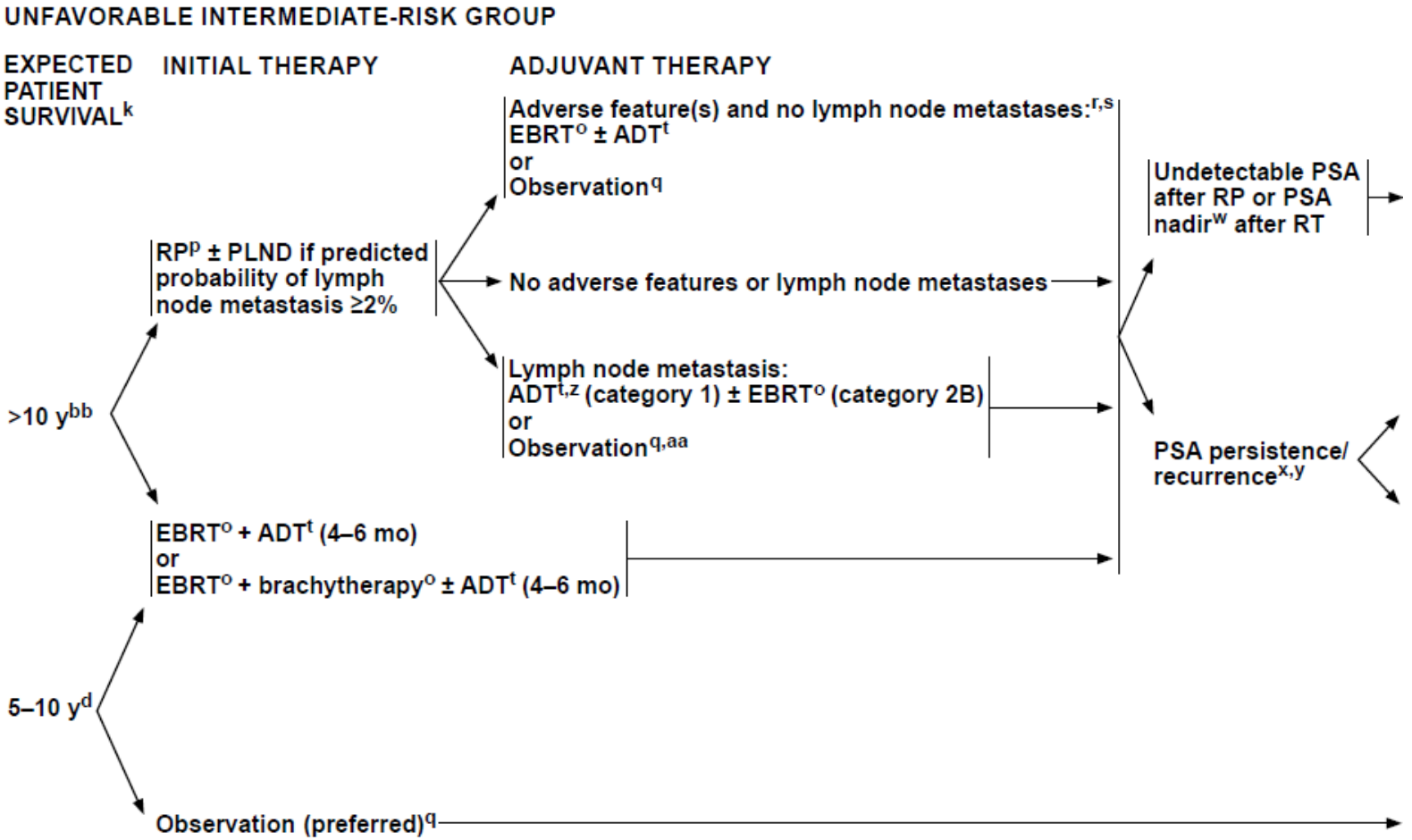
- T2b–T2c
- Grade Group 2 or 3
- PSA 10–20 ng/mL



NCCN 2021: Unfavorable Intermediate Risk

Has one or more of the following:
- 2 or 3 IRFs
- Grade Group 3
- ≥ 50% biopsy cores positive[e]

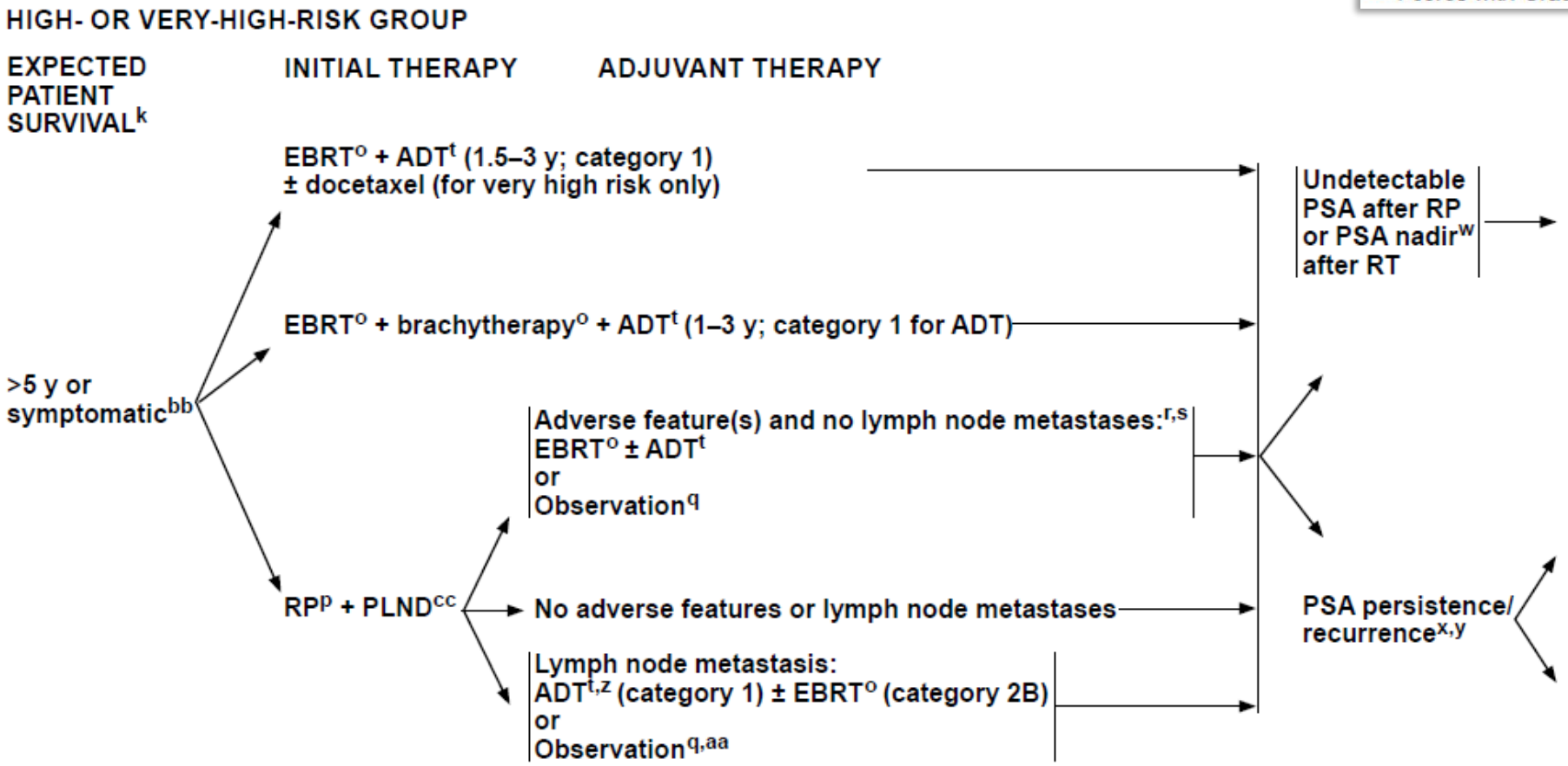
- T2b–T2c
- Grade Group 2 or 3
- PSA 10–20 ng/mL



NCCN 2021: High Risk & VHR

Has no very-high-risk features and has exactly one high-risk feature:
- T3a OR
- Grade Group 4 or Grade Group 5 OR
- PSA >20 ng/mL

Has at least one of the following:
- T3b–T4
- Primary Gleason pattern 5
- 2 or 3 high-risk features
- >4 cores with Grade Group 4 or 5



Early Stage Prostate Cancer

- **First decision: to treat or not (AS vs. curative therapy)**
  - Factors to consider:
    - Aggressiveness of the prostate cancer
    - Life expectancy
    - Patient's goals & willingness for AS
- **Second decision: which method?**
  - Factors to consider:
    - Pre-existing medical conditions & relative contraindications
    - Baseline GU/GI/sexual function
    - Quality of life after treatment
    - Cost & convenience

Active Surveillance

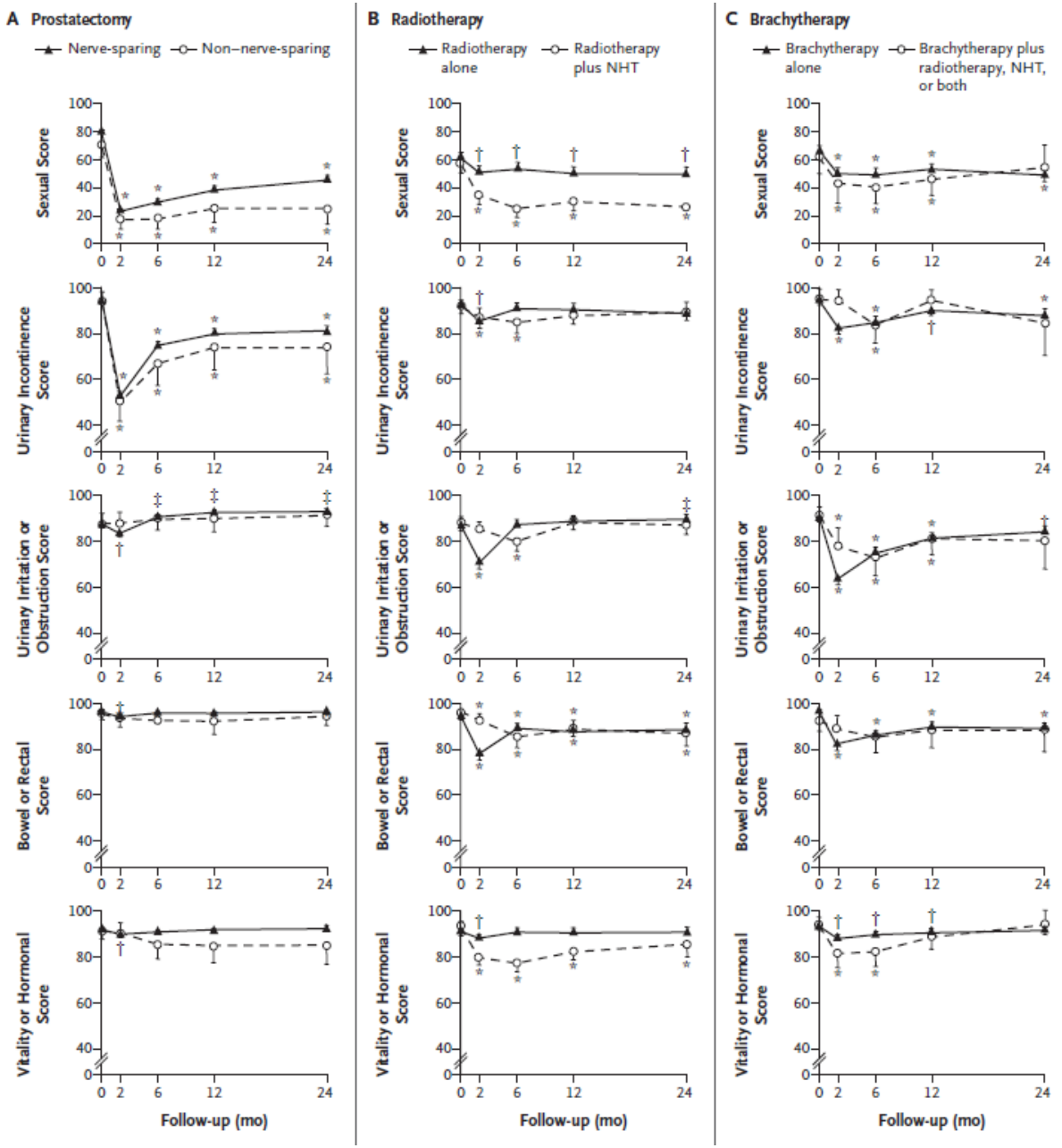
- Rationale: overtreatment may adversely affect QOL without improving OS
- **AS "preferred" by NCCN** for:
  - **Very low risk** & life expectancy >20 years
  - **Low risk** & life expectancy ≥10 years
- Consider mpMRI and/or genomic testing to rule out higher grade
- Current AS schedule
  - PSA q ≥6 months & DRE q ≥12 months
  - mpMRI q ≥12 months & repeat biopsy q ≥12 months

Many treatment options – but few RCTs

- **EBRT**
  - **Standard fractionation**: 79.2 Gy/44 fx, 78 Gy/39 fx
  - **Hypofractionation**: 70 Gy/28 fx, 60 Gy/20 fx
  - **SBRT**: 36.25-40 Gy/5 fx, 42.7 Gy/7 fx
  - **Proton beam therapy**
- **Brachytherapy**
  - **LDR**: I-125 (145 Gy), Pd-103 (125 Gy), Cs-131 (115 Gy)
  - **HDR**: Ir-192 13.5 Gy x 2 implants or 9.5 Gy BID x 2 implants
- **Prostatectomy**
- NCCN recommends cryotherapy & HIFU only for recurrence after RT

PROST-QA

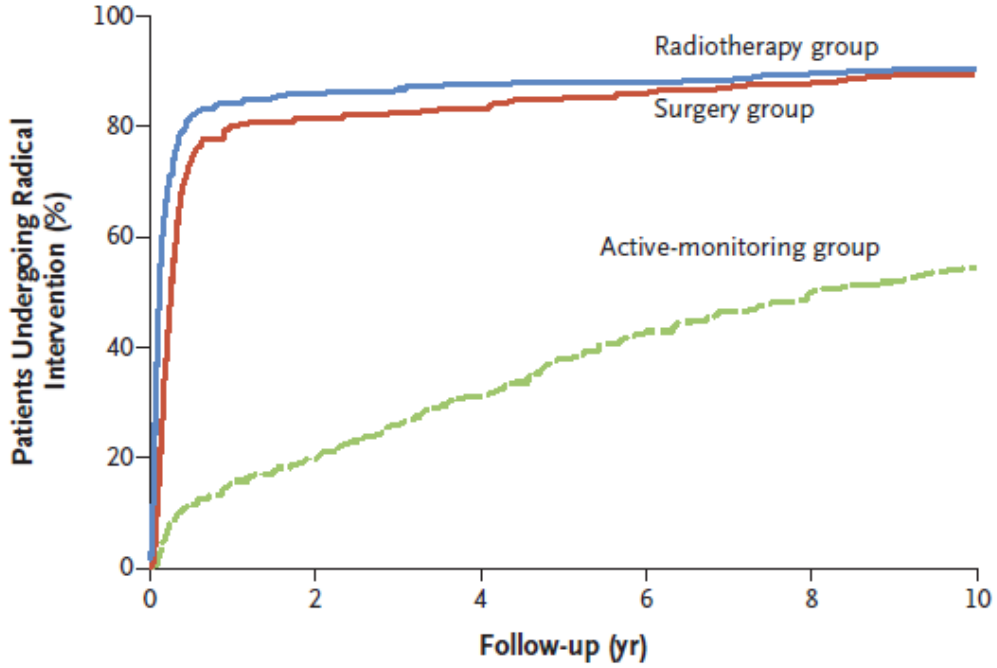
- First prospective QOL study
- Non-randomized
- Only 2 year follow up

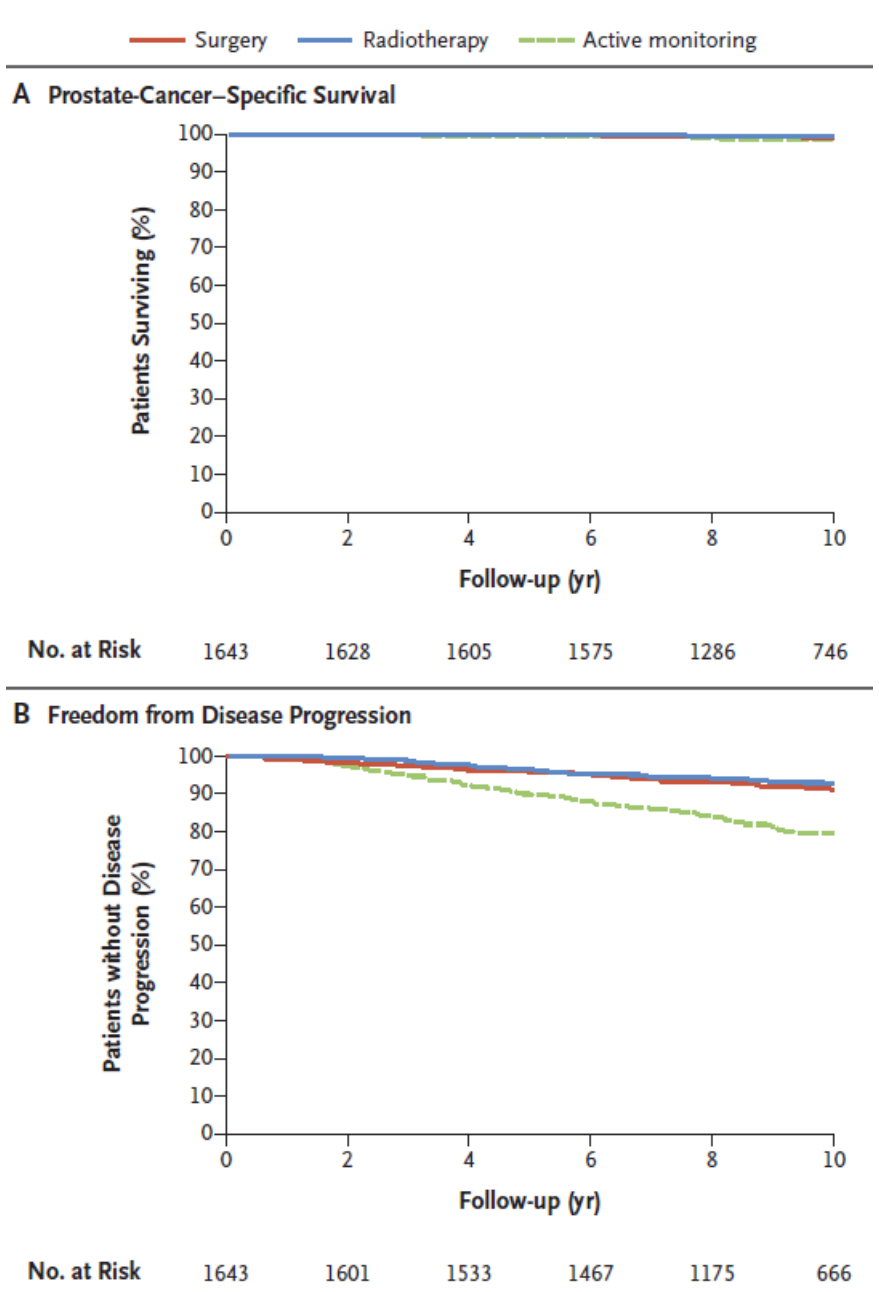


Sanda NEJM 2008

ProtecT

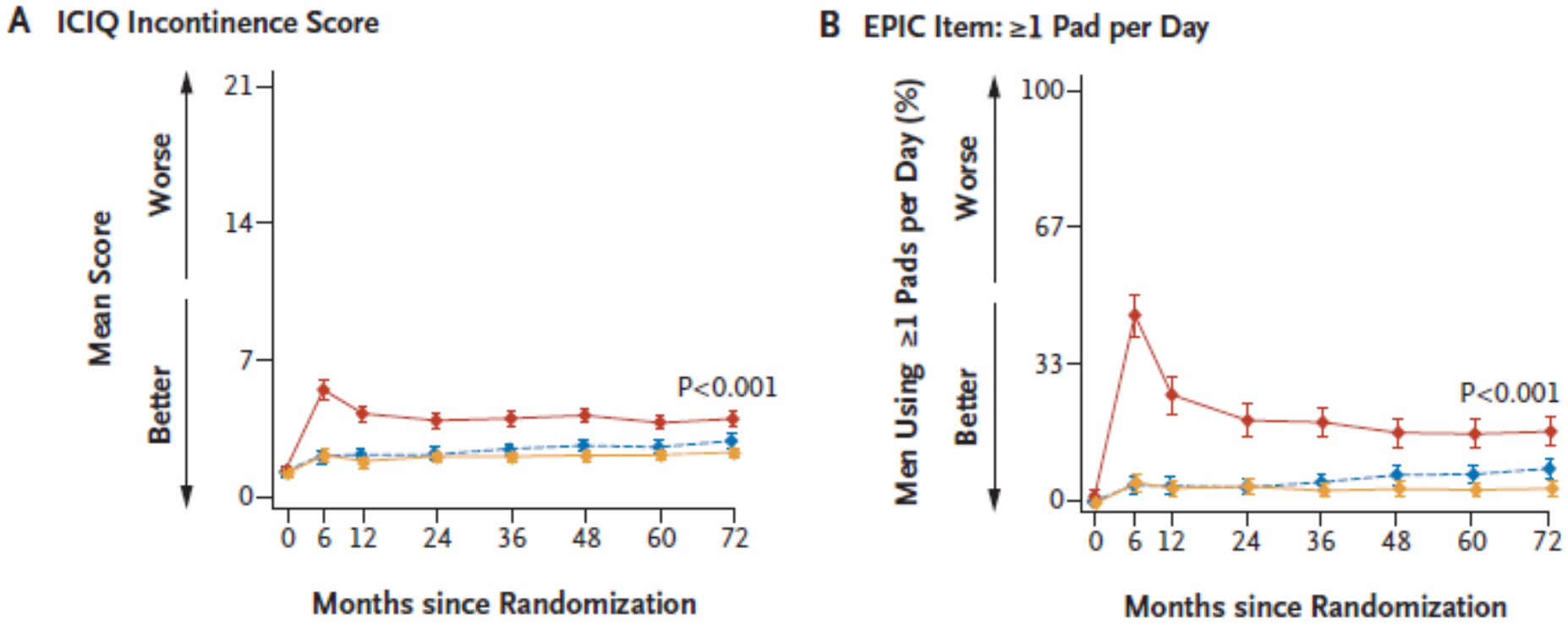
- 77% GS 6
- PCSM ~1% @ 10y
- AM: ~50% treated by 10y & 2x DM rate





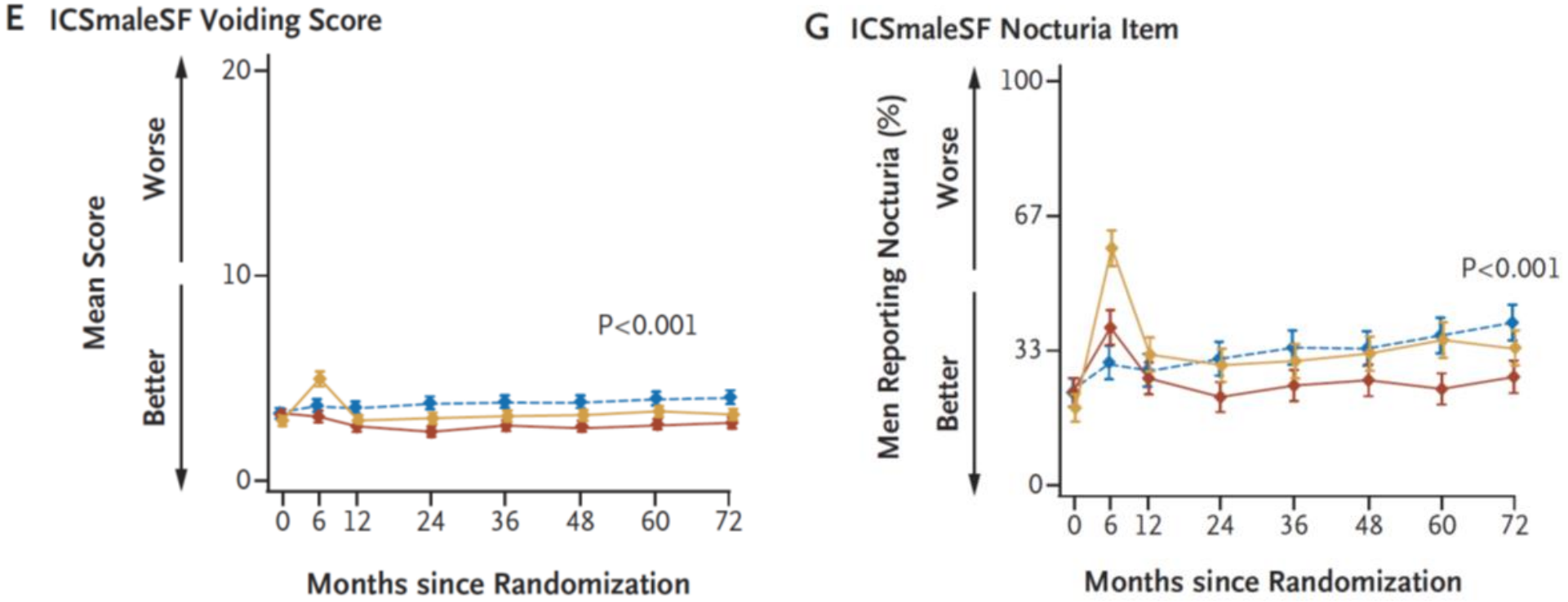
Hamdy NEJM 2016

ProtecT – Urinary Function



Donovan NEJM 2016

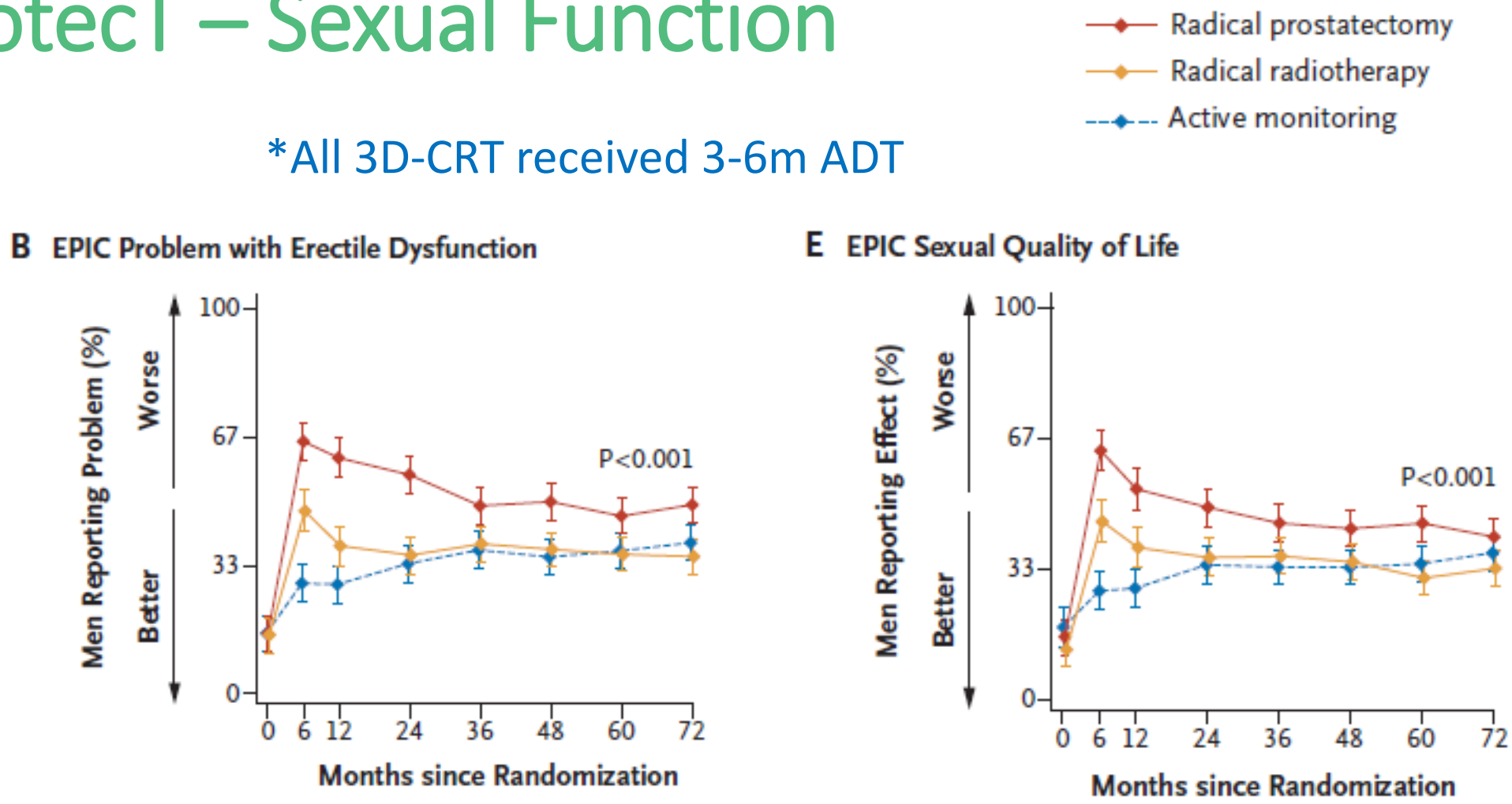
ProtecT – Urinary Function



Donovan NEJM 2016

ProtecT – Sexual Function

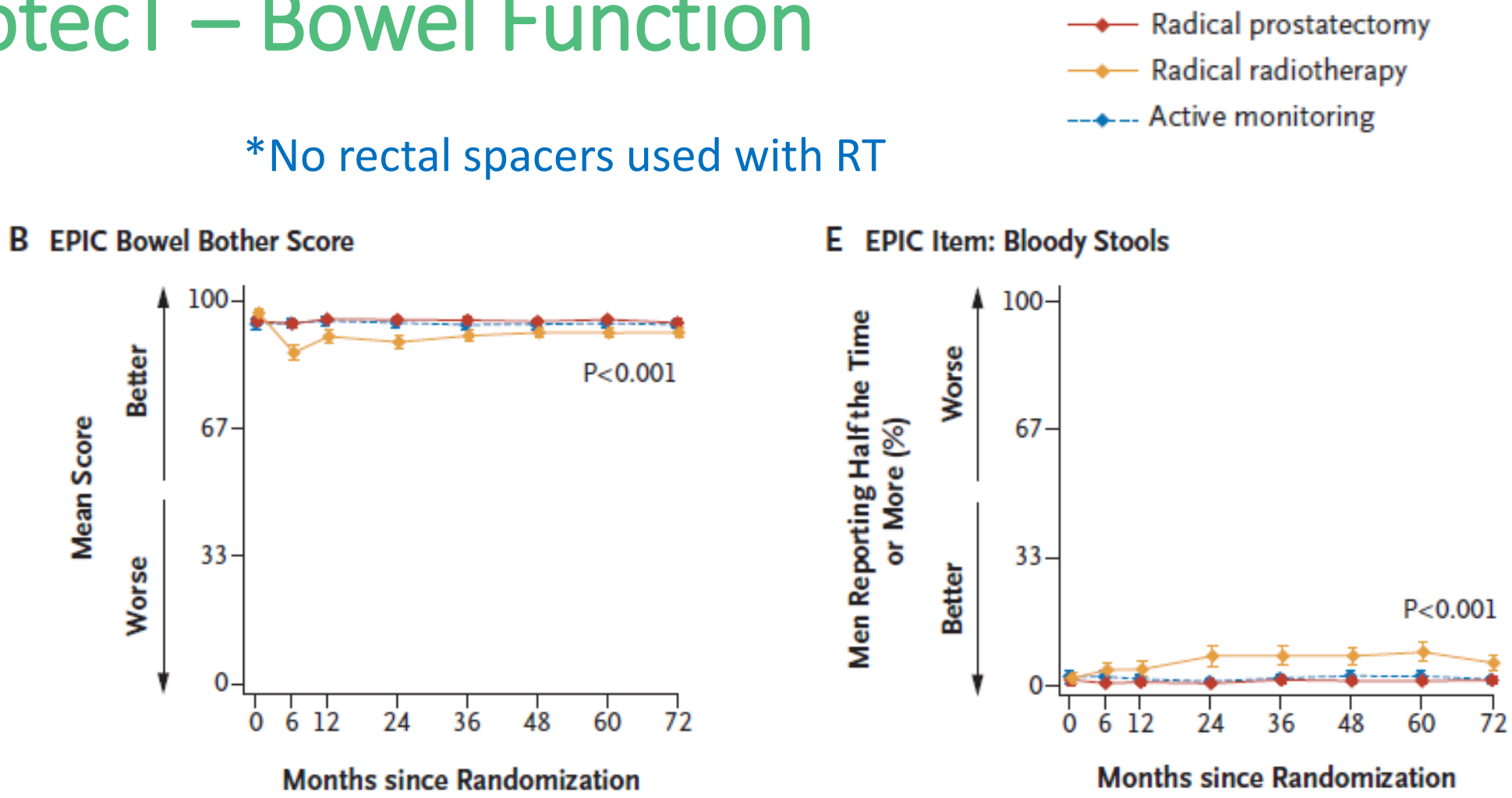
*All 3D-CRT received 3-6m ADT



Donovan NEJM 2016

ProtecT – Bowel Function

*No rectal spacers used with RT



Donovan NEJM 2016

Summary: Early Stage (LR & Favorable IR)

- **Active surveillance preferred for VLR, LR**, and can be done for some FIR
- **LR and FIR should be treated similarly (monotherapy)**
- **No one treatment is superior to another**
  - **Prostatectomy: ↑ incontinence & ED**
  - **Brachytherapy: ↑ irritative/obstructive urinary symptoms**
  - **EBRT: ↑ irritative urinary symptoms & rectal bleeding (if no spacer)**
- Cryotherapy, HIFU not endorsed by NCCN up-front

- For radiation therapy, many options exist…

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			✓	✓		

RT Dose Escalation

- Dose escalated RT improves biochemical control over "standard dose" prostate RT (5 RCTs with conventional fractionation)
  - No improvement in OS, & higher risk of toxicity

Trial	Arms	N	Technique	FFBF	Gr 3 Toxicity
MDACC Kuban 2008	78 vs. 70 Gy	301	2D + 3D boost	78% vs. 59% (8y)	7% vs. 1%
MGH Zietman 2010	79.2 vs. 70.2 Gy	392	2D + proton	83% vs 68% (8.9y)	1% vs. 1%
Dutch Al-Mamgani 2008	78 vs. 68 Gy	669	3D	56% vs. 45% (7y)	6% vs. 4%
MRC Dearnaley 2007	74 vs. 64 Gy (+ ADT)	843	3D	71% vs. 60% (5y)	10% vs. 6%
RTOG 0126 Michalski 2015	79.2 vs. 70.2 Gy	1499	3D or IMRT	70% vs. 55% (10y)	↑ GI (but not GU)

Which Endpoints Matter in Prostate Cancer?

- **Overall survival & prostate cancer-specific mortality**
- **Metastasis-free survival** → best surrogate endpoint for OS (ICECaP meta-analysis), primarily observed in trials of RT + ADT
- **Biochemical control**
- **Local control**

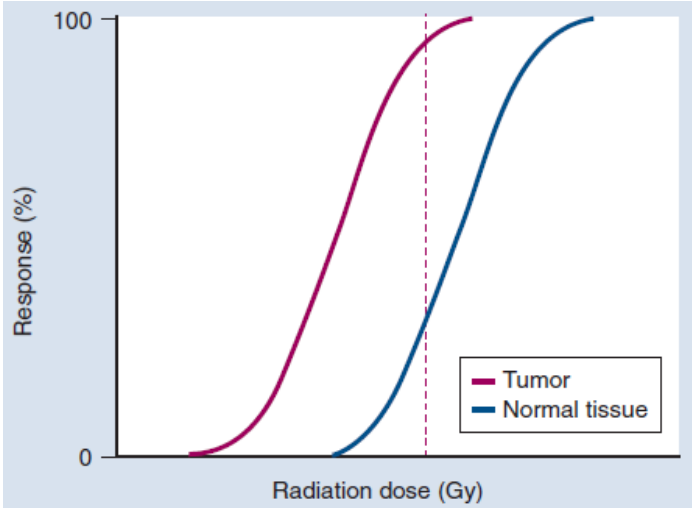
} Not surrogates for OS

- **Freedom from salvage therapy** (ADT, local therapy, metastasis-directed therapy)
- **Patient-reported QOL**
- **Physician-reported toxicity**
- **Financial toxicity**

Xie JCO 2017. Gharzai Lancet Oncol 2021.

Enhancing the Therapeutic Ratio

1. Focal dose escalation to dominant intraprostatic lesion
2. Rectal spacers
3. Hypofractionation
4. Ultrahypofractionation/SBRT
5. Brachytherapy
6. Adding ADT to RT



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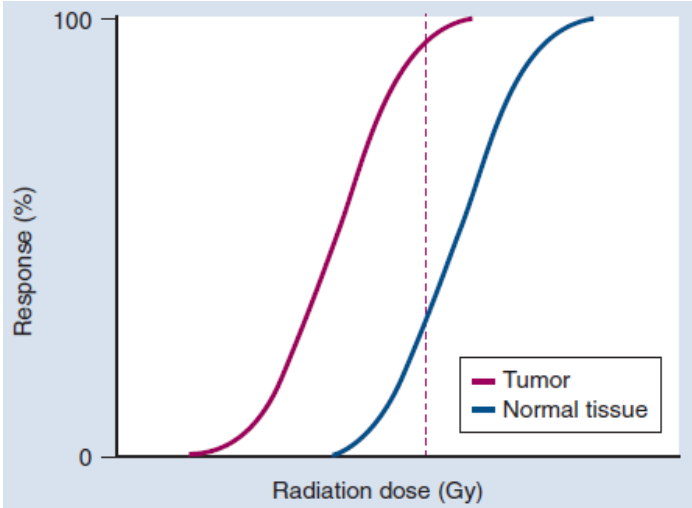
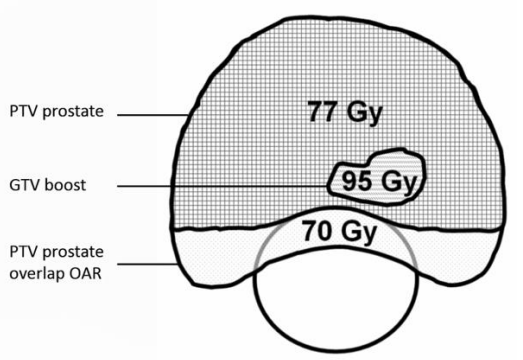
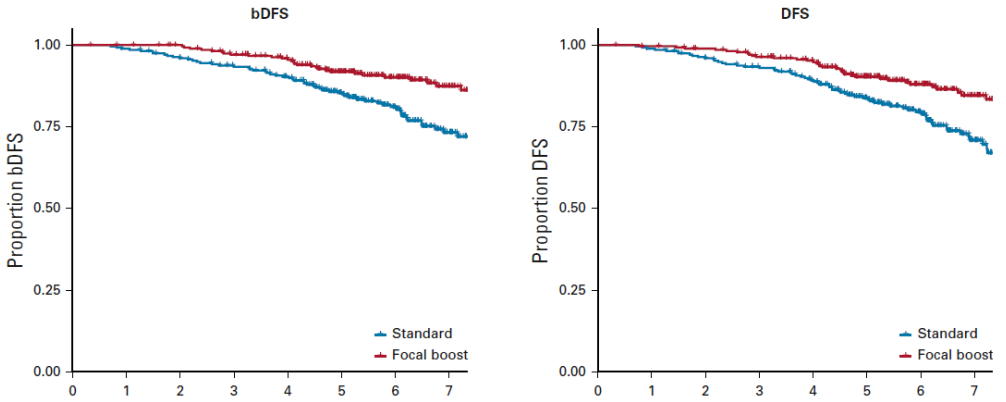


FLAME trial



- RCT of EBRT 77 Gy in 35 fractions +/- SIB boost of 95 Gy to dominant intraprostatic lesion (DIL)
- OARs prioritized over target coverage
- **FLAME improved bDFS** (1^{o} endpoint)
- No difference in toxicity or OS
- Demonstrates feasibility of **"isotoxic" focal boost**



Kerkmeijer JCO 2021

Enhancing the Therapeutic Ratio

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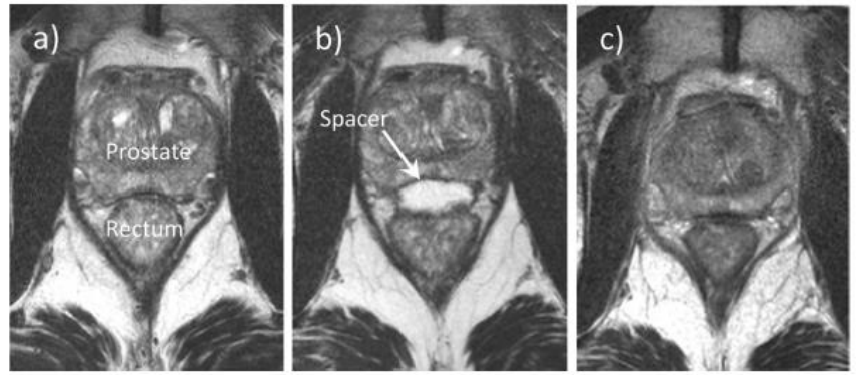
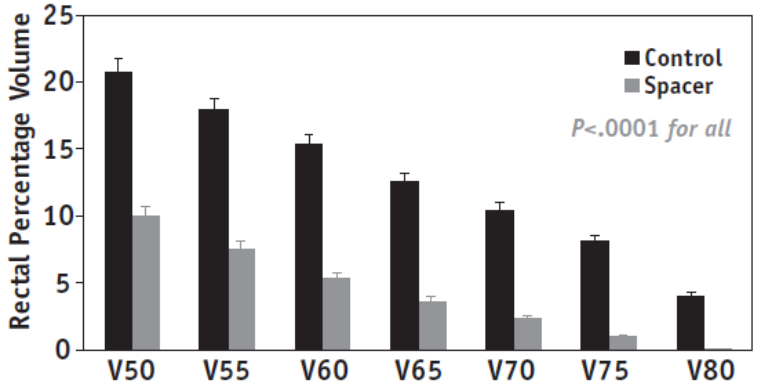
Rectal Spacers

- RCT of 222 pts randomized to fiducials + hydrogel spacer vs. no spacer
  - IMRT 79.2 Gy @ 1.8 with MRI planning
  - Exclusion: ≥80 cc, EPE, >50% PPC, ADT use
- 1° endpoint: >25% reduction in rV70
  - **3-yr Gr 2 rectal toxicity 5.7% vs. 0%** (p=0.01)
  - Spacer ↑ bowel QOL
  - No difference in Gr 2 GU toxicity
- Who "needs" it? Who doesn't? Worth cost?
  - Rare complications can occur





Mariados IJROBP 2015. Hamstra IJROBP 2017.

Enhancing the Therapeutic Ratio

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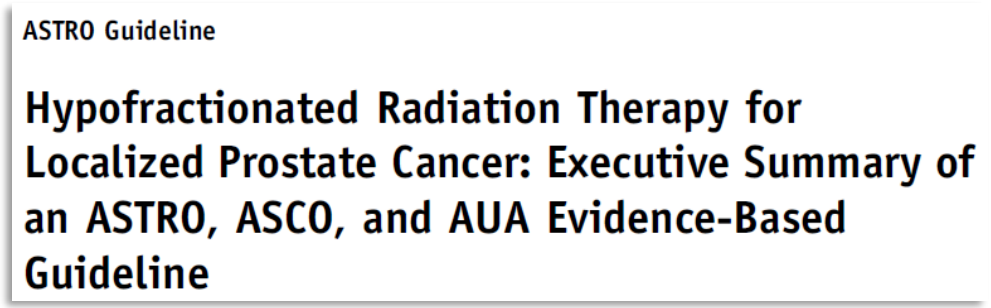
Moderate Hypofractionation (4-6 weeks)

Trial	N	Risk Group	Dose/Fractions	Key Findings
RTOG 0415*	1115	LR	73.8/41 vs 70/28	Same FFBF. More gr 2 GI tox w/ hypo but similar PR-QOL.
PROFIT*	608	IR	78/39 vs 60/20	Same FFBF. More acute GI tox but less late GI in hypo. GU same.
CHHiP*	3216	15% LR, 73% IR, 12% HR	74/37 vs 57/19 vs 60/20	60 Gy not inferior to 74 Gy (uncertain for 57 Gy). 3-6m ADT for all.
MDACC	206	28% LR, 71% IR	75.6/42 vs 72/30	FFBF 89% vs. 76% favoring hypofrac (p=0.03). No diff in tox.
HYPRO	820	26% IR, 74% HR	78/39 vs 64.6/19	Same FFBF. More gr 3 GU tox w/ hypo.
Fox Chase	303	66% IR, 33% HR	76/38 vs. 70.2/26	Same FFBF. Worse GU tox w/ hypo for IPSS >12.
Italian	168	HR	80/40 vs 62/20	4y FFBF 85% vs. 79% (hypo better). Same GI tox. 9m ADT for all.



practical radiation oncology
pro
www.practicalradonc.org

- **Cancer control similar between HF and CF**
- **HF works across all risk groups**
- HF acute side effects occur earlier, & slightly higher acute GI toxicity
- **Late effects similar** (except RTOG 0415 & HYPRO → higher GU toxicity likely related to higher BED in HF arms)
- Most trials did not treat LNs

Morgan PRO 2018

Enhancing the Therapeutic Ratio

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SBRT/Ultrahypofractionation (1-2 weeks)

- Prostate SBRT utilization doubled from 2010 to 2015
- Many advantages to prostate SBRT
  - Low α/β → improved therapeutic ratio
  - Minimally-invasive, convenient, safe
  - Real-time tracking w/ fiducials or MR linac → tight margins
- Barriers to SBRT
  - Limited randomized trial data
  - Limited experience/technology

Mahase JAMA Network Open 2020

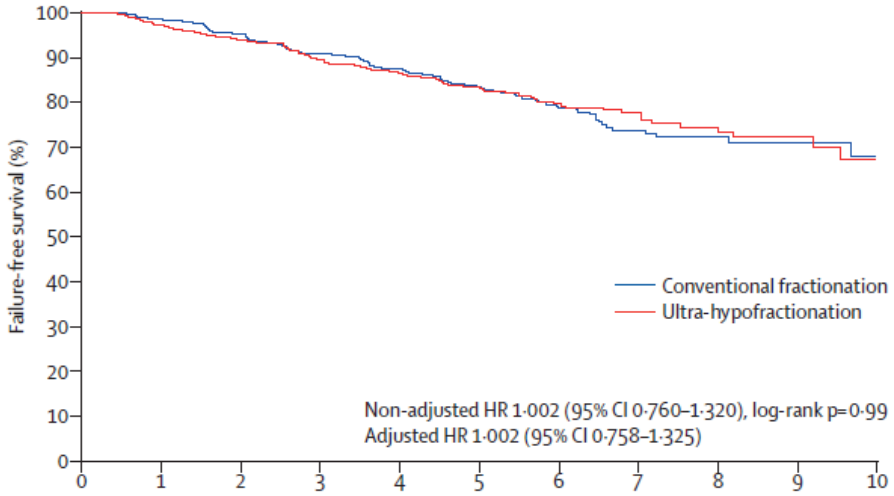
SBRT/Ultrahypofractionation (1-2 weeks)

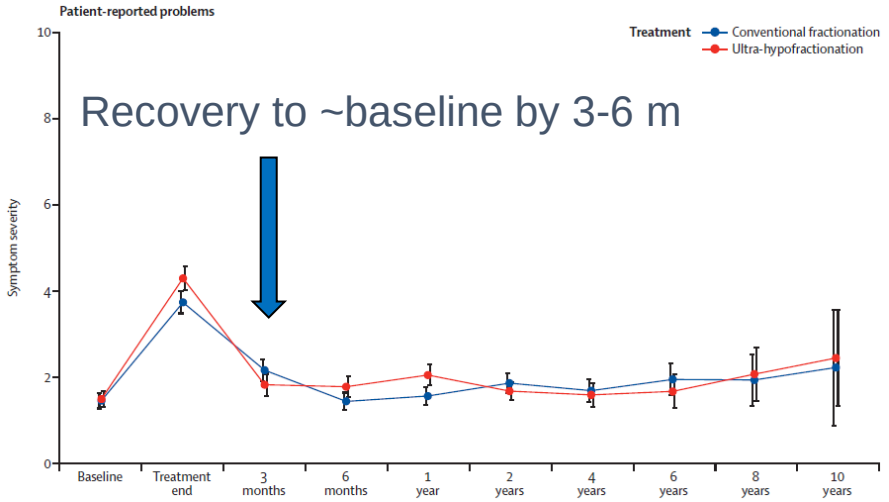
- Meta-analysis of >6,000 patients
  - 35-36.25 Gy → 5-yr bRFS 95%
  - **Grade 3+ GU and GI toxicity only 2% and 1%**, respectively
- Dose escalation 32.5 Gy → 40 Gy (MSK trial)
  - PSA failure 15% → 0% & positive biopsy 48% → 8%
- Dose escalation 45 → 50 Gy (UTSW trial)
  - Rectal injury @ 50 Gy dose level (no rectal spacers used)
- The "right dose" may be ~**40 Gy** (36.25-45 Gy) in **5 fractions**

Jackson IJROBP 2019. Zelefsky IJROBP 2019. Kim IJROBP 2014.

HYPO-RT-PC

- First RCT of ultrahypofractionated RT (80% 3D-CRT)
- **42.7 Gy in 7** (QOD) was **non-inferior to 78 Gy in 39**
- **No difference in PR-QOL** at 6 years

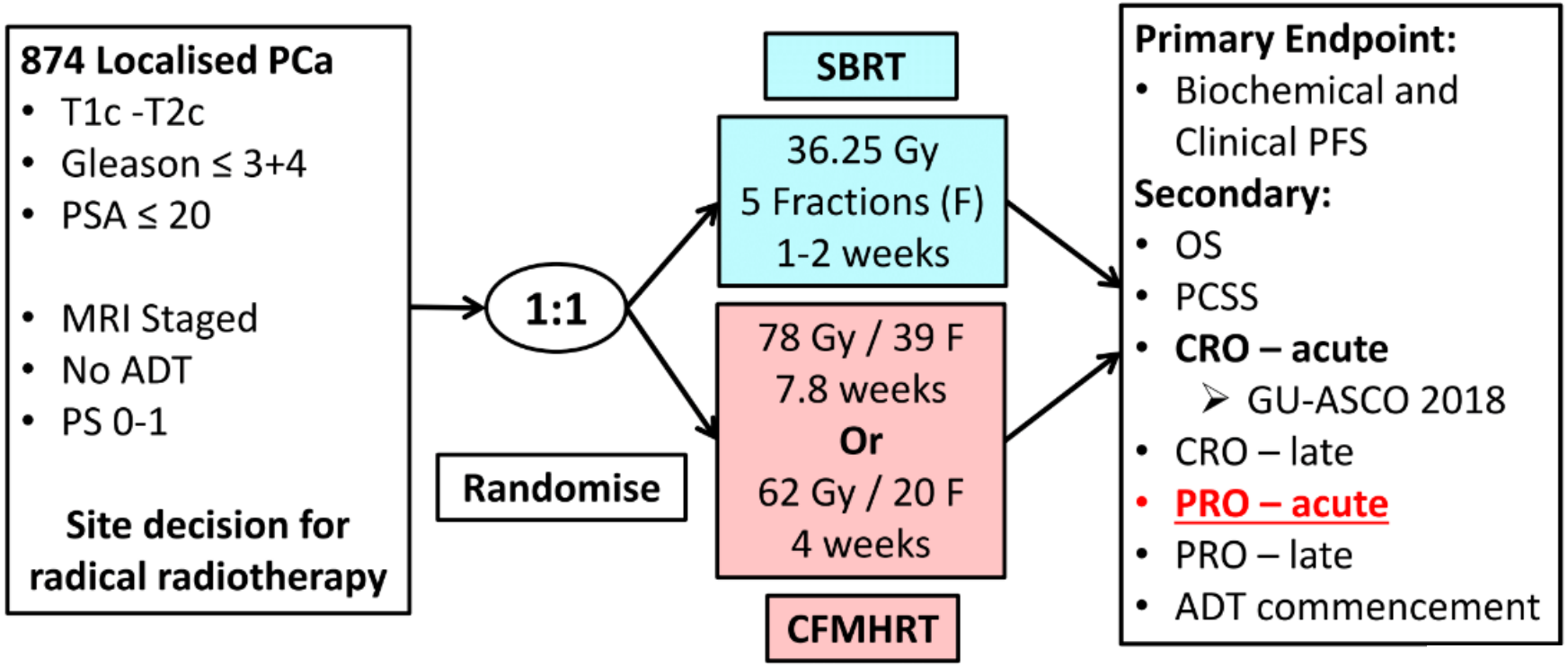




Widmark Lancet 2019. Fransson Lancet Oncol 2021.

PACE-B: SBRT vs. IMRT

PACE B: Trial schema

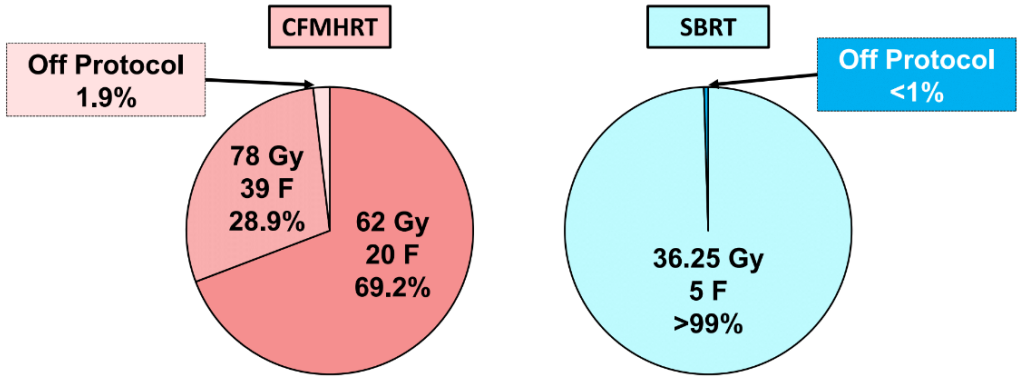


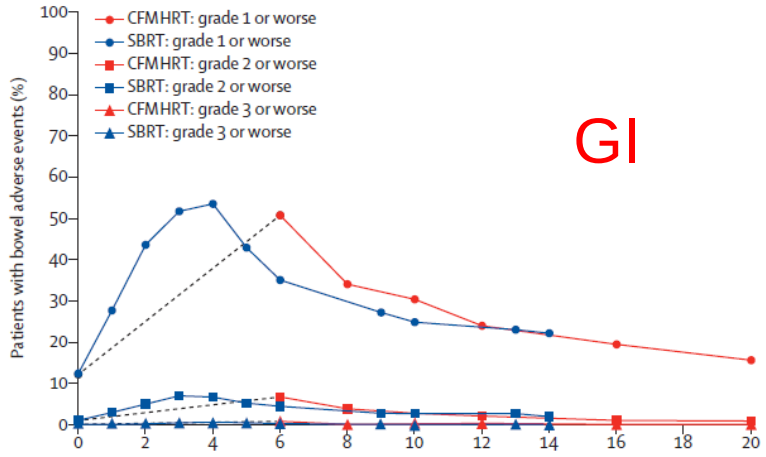
Brand Lancet Oncol 2019

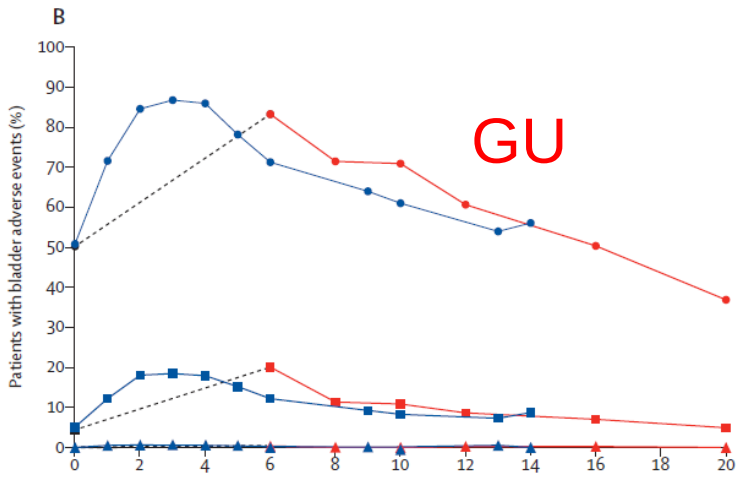
PACE-B: SBRT vs. IMRT

- **No difference in acute toxicities** (SBRT occurs earlier)

Delivered regimens by arm



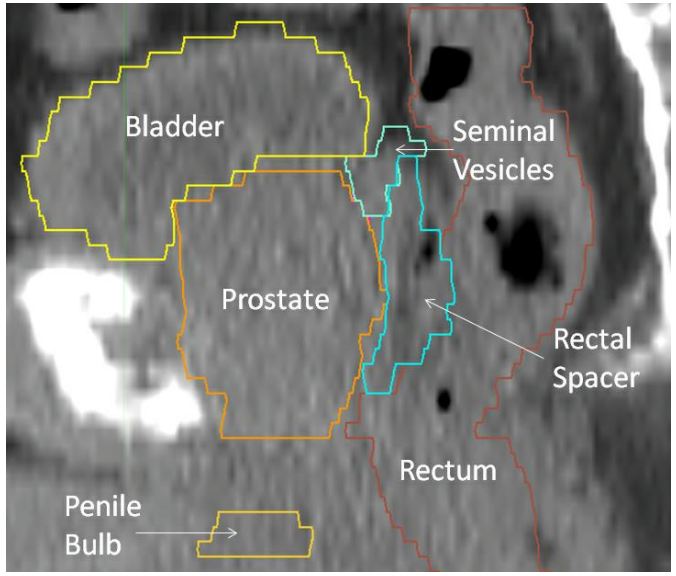


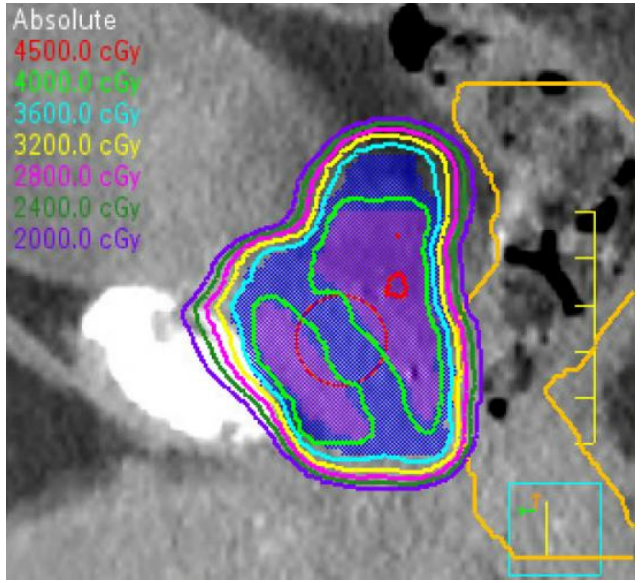


Brand Lancet Oncol 2019

How I Deliver Prostate SBRT in 2021

- Rectal spacer + fiducial markers → real-time tracking
- MRI-fusion, heterogeneous planning, VMAT-based delivery
  - 36.25 Gy to PTV (3 mm), 40 Gy to prostate (excl. urethra), 45 Gy to DIL





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Don’t Forget Brachytherapy!

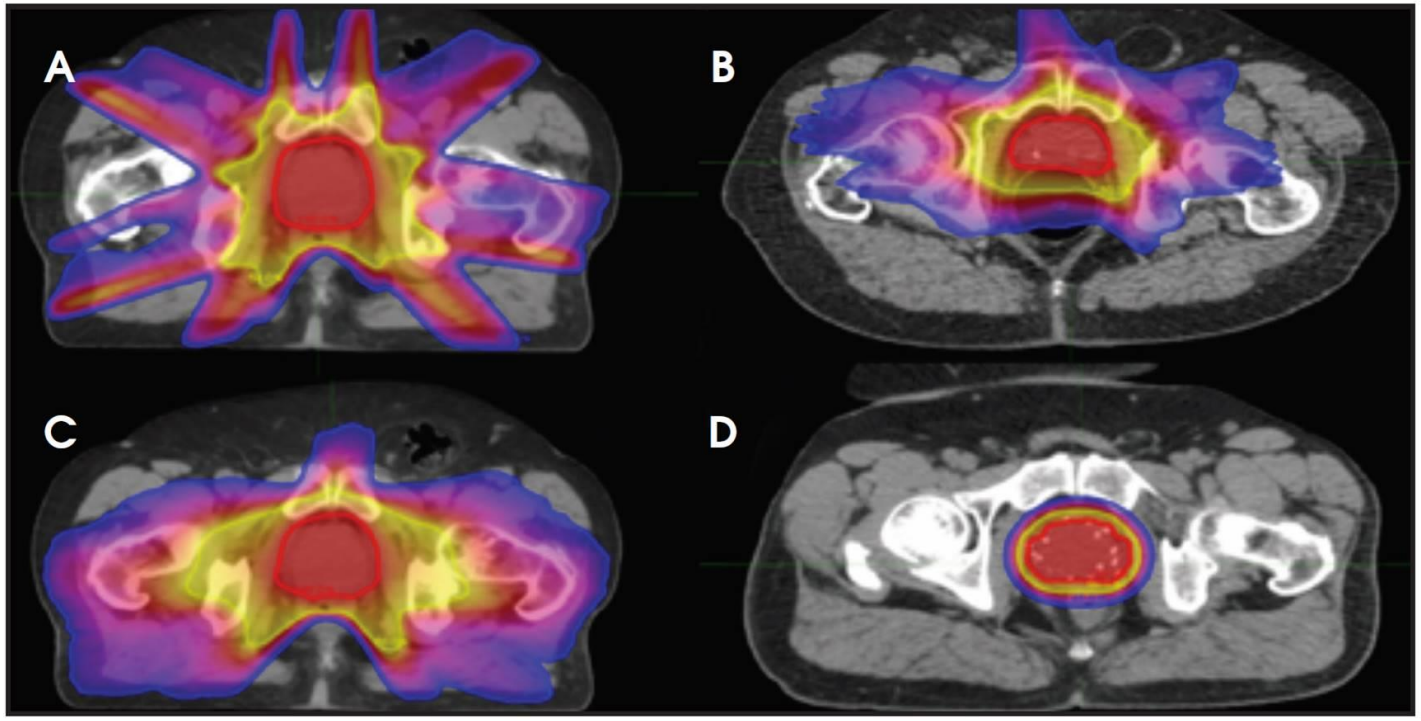
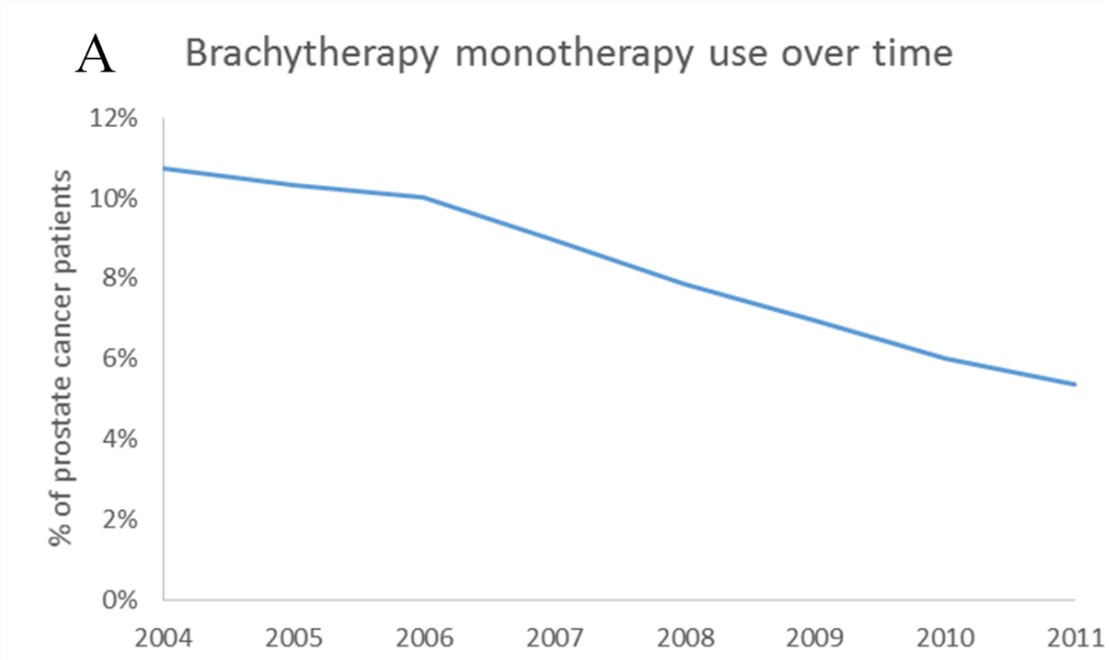
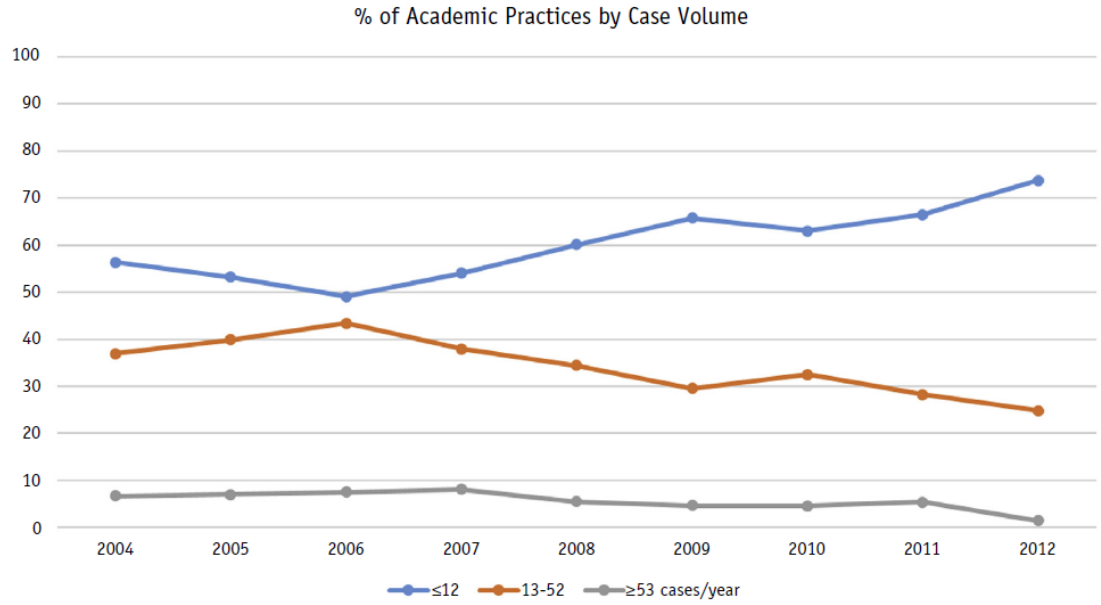


FIGURE 1. *Dosimetric comparison of (A) intensity-modulated radiation therapy (IMRT), (B) volumetric-modulated arc therapy (VMAT), (C) stereotactic body radiation therapy (SBRT), and (D) low dose rate brachytherapy (LDR-BT). Isodose lines correspond to 25% (blue), 50% (yellow), and 100% (red) of prescription dose.*

Abu-Gheida ARO 2017

Don’t Forget Brachytherapy!



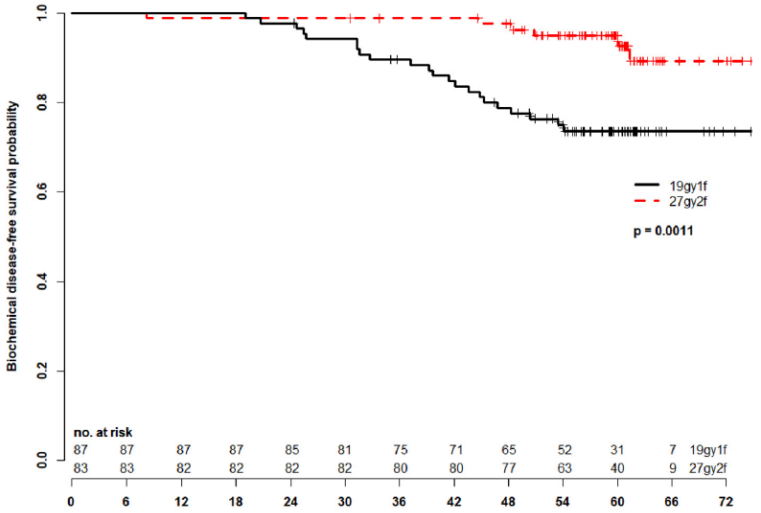


Academic Practices(%)	2004	2005	2006	2007	2008	2009	2010	2011	2012
≤12	56.36	53.16	49.06	54.04	60.12	65.77	62.99	66.44	73.72
13-52	36.97	39.87	43.40	37.89	34.36	29.53	32.47	28.19	24.82
≥53 cases/year	6.67	6.96	7.55	8.07	5.52	4.70	4.55	5.37	1.46

Muralidhar Brachytherapy 2015. Orio IJROBP 2016.

Brachytherapy: Monotherapy Dosing (NCCN)

- **LDR**
  - I-125: 145 Gy
  - Pd-103: 125 Gy
  - Cs-131: 115 Gy
- **HDR**
  - Ir-192: 13.5 Gy x 2 implants
  - Ir-192: 9.5 Gy BID x 2 implants
  - Single fraction HDR is inferior



Morton Radiother Oncol 2020

Brachytherapy for IR: Monotherapy vs. Boost?

- **RTOG 0232**: RCT of LDR brachytherapy alone vs. EBRT + brachytherapy boost for intermediate risk
  - GS 7 or PSA 10-20, not both
  - **>80% favorable IR**
- **No difference in BF, DM, or OS**
- **Higher late gr 2 & gr 3 toxicity with EBRT + LDR-B**

- Conclusion: **Brachytherapy alone for FIR (no need for combo)**

Prestidge ASTRO 2016

Brachytherapy Boost after EBRT

- **Combo EBRT + brachy boost** may be appropriate for **UIR/HR** for purpose of ENI and/or dose escalation (more on this later…)
- **LDR boost**
  - I-125: 110-115 Gy
  - Pd-103: 90-100 Gy
  - Cs-131: 85 Gy
- **HDR boost**
  - Ir-192: 15 Gy x 1
  - Ir-192: 10.75 Gy x 2

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			✓	✓		

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Integrating ADT with EBRT

0 months	4-6 months	18 months	24-36 months
Low Risk	Unfavorable Intermediate Risk	High Risk	Very High Risk
Favorable Intermediate Risk			LN+

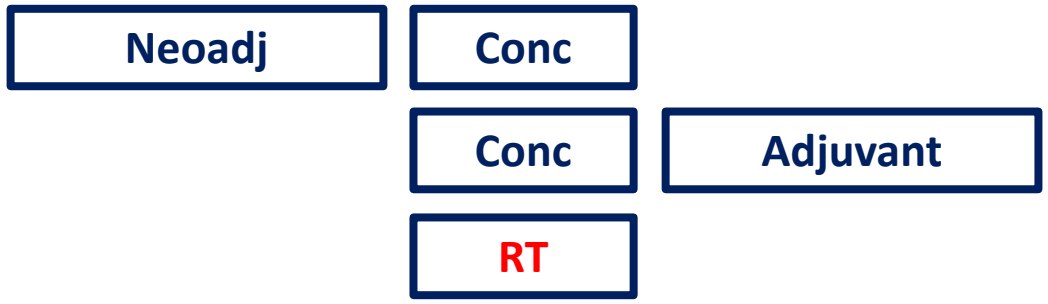
ADT for Intermediate Risk: Duration

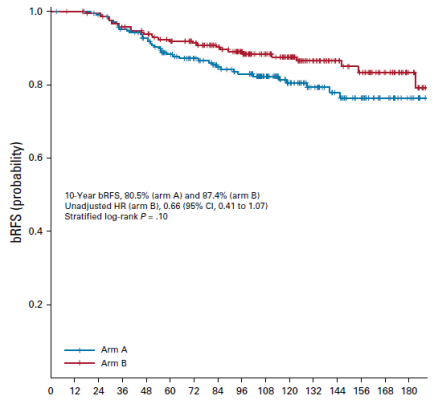
- **Standard duration for IR = 4-6 months**

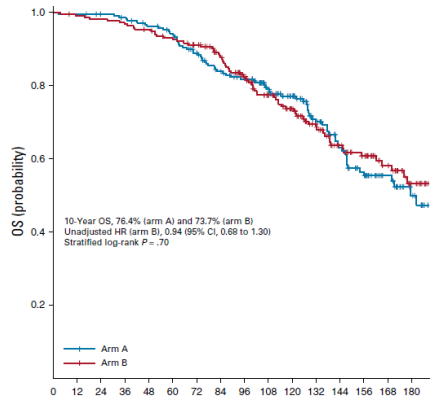
	ADT (months)	RT Dose	% IR	Reference
RTOG 9408	4 > 0	66.6 Gy	54%	Jones NEJM 2011
GETUG 14	4 > 0	80 Gy	100%	Dubray ASCO 2016
EORTC 22991	6 > 0	70, 74, 78 Gy	75%	Bolla JCO 2016
PCS III	6 > 0	70, 76 Gy	100%	Nabid EJC 2021
RTOG 9910	4 = 9	70.2	100%	Pisansky JCO 2015
DART 01/05	4 = 28	76-82 Gy	100% (subset)	Zapatero Lancet Oncol 2015

ADT for Intermediate Risk: Timing

- Ottawa 0101 tested sequence of ST-ADT (**6 months**) with 76 Gy
- All **GS ≤7**, only 1% T3 (**95% were IR**)
- **Neoadjuvant/concurrent** (4m before RT) **vs. Concurrent/adjuvant**
  - **<u>No significant differences in bRFS, OS, or grade 3+ toxicity</u>**







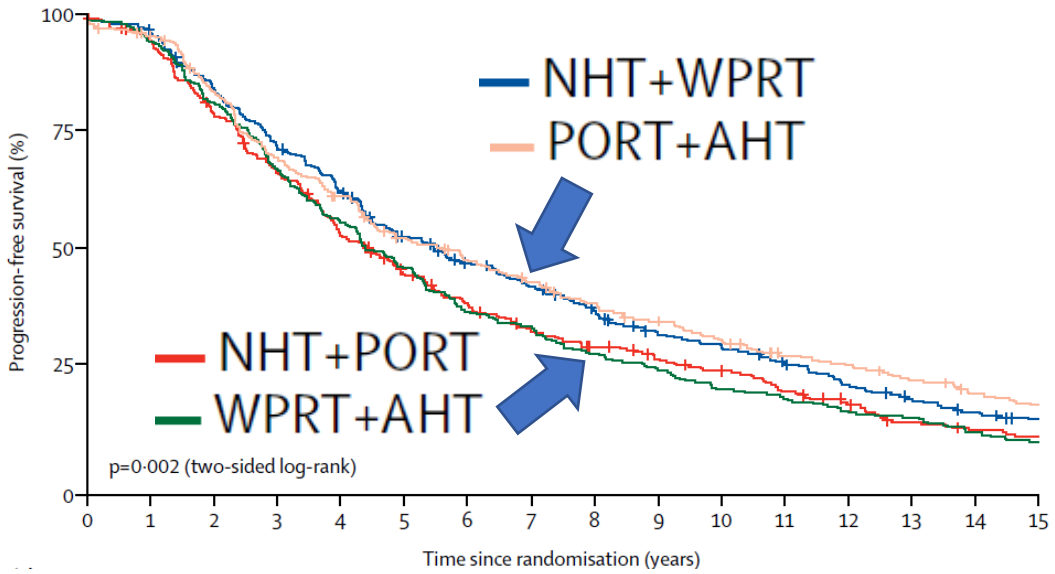
Malone JCO 2019

ADT for Intermediate Risk: Timing

- Ottawa 0101 applies only to ST-ADT with prostate-only RT in IR
- Optimal sequencing uncertain for LT-ADT, HR, or with WPRT

RTOG 9413 (2x2)

- Mostly HR: GS 7-10 in 74%, T2c-T4 in 66%
- 4m ADT: 2m neo + 2m conc vs. 4m adjuvant (started after RT)



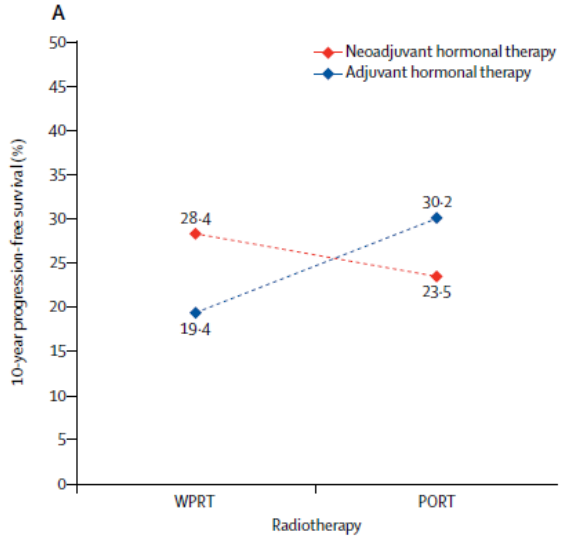


Figure 2: **Interaction of radiotherapy and hormone therapy on progression-free survival**
(A) By radiotherapy treatment group. (B) By hormone therapy treatment group. Progression-free survival was defined according to the Phoenix definition of biochemical failure. PORT=prostate only radiotherapy. WPRT=whole pelvic radiotherapy.

Roach Lancet Oncol 2018

ADT for Intermediate Risk: Selection

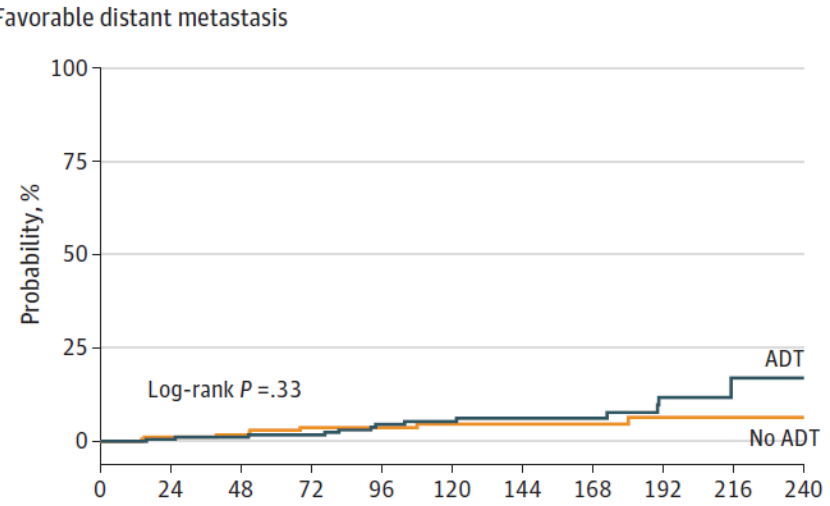
- **Unfavorable IR subgroup** originally defined by Zumsteg
  - **Grade group 3 (GS 4+3), or**
  - **≥50% cores positive, or**
  - **Multiple IR factors**
- Validated by Berlin and others

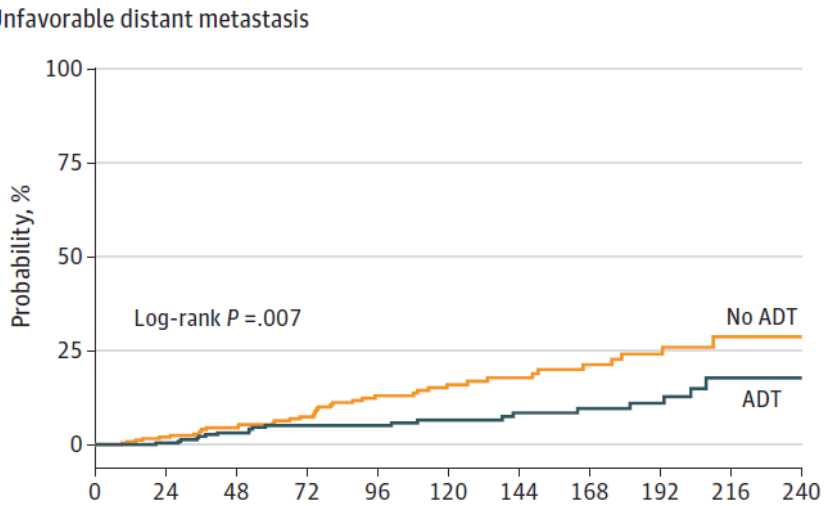
> **Conclusions:** This multicenter international effort independently validates the prognostic value of the intermediate risk prostate cancer subclassification in androgen deprivation treatment naïve cases across all radical treatment modalities. It is unlikely that treatment intensification would meaningfully improve oncologic outcomes in men at favorable intermediate risk.

Zumsteg Eur Urol 2013. Berlin J Urol 2018.

ADT for Intermediate Risk: Selection

- Subset analysis of RTOG 9408 supports **ADT for UIR but not FIR**



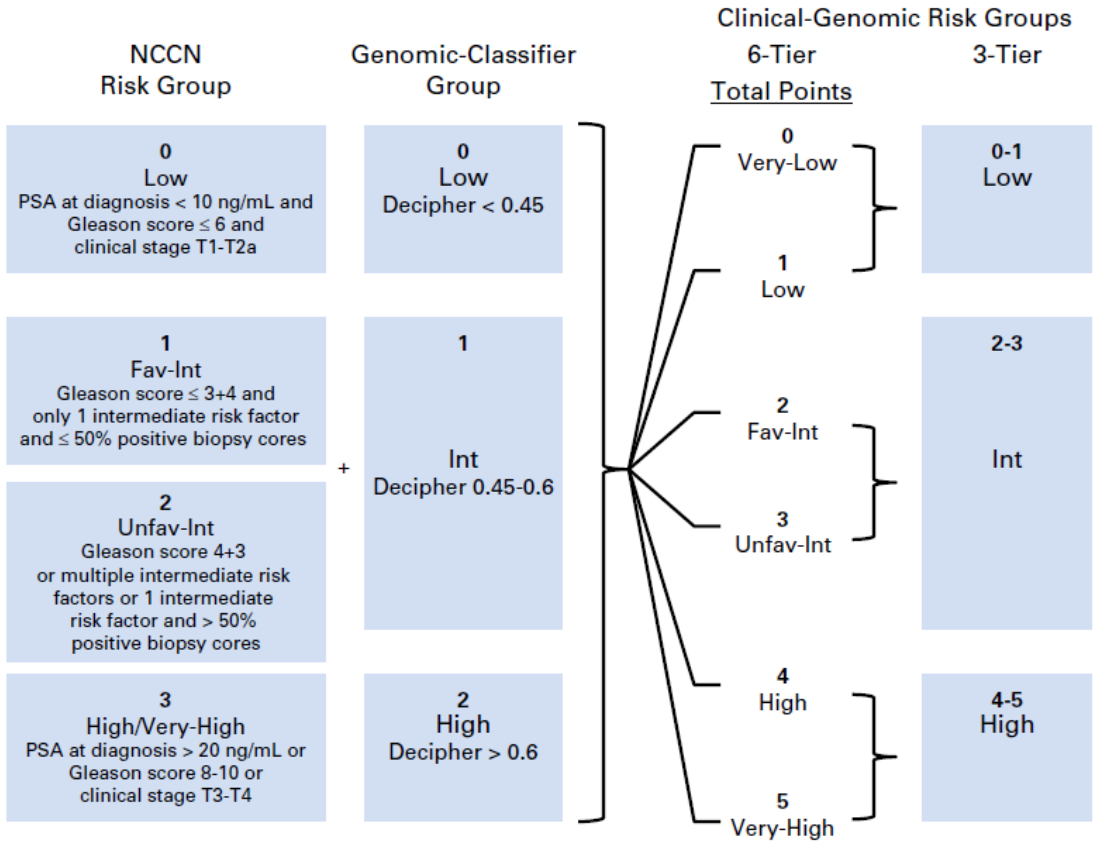


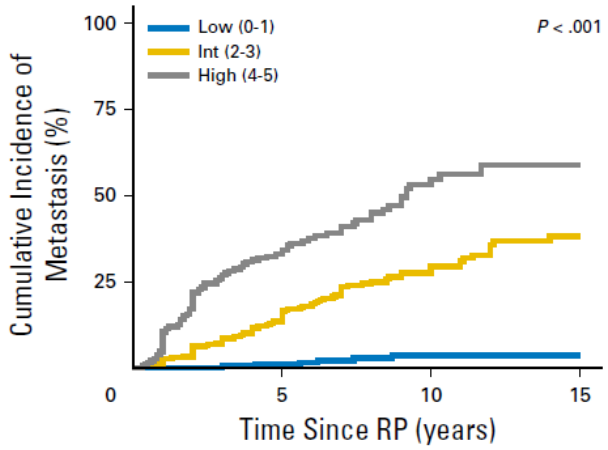
- Await RTOG 0815 results (dose-escalated RT +/- ST-ADT)

Zumsteg JAMA Open 2020

Intermediate Risk: Stratification

- Integrated Clinical-Genomic risk group classification proposed

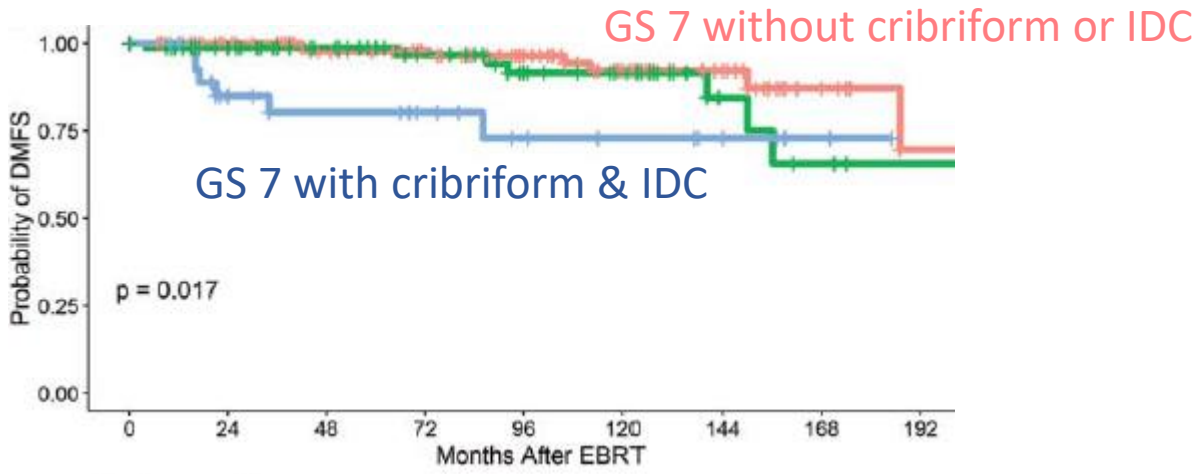




Spratt JCO 2017

Intermediate Risk: Stratification

- Presence of cribriform pattern 4 & intraductal carcinoma associated with poorer outcomes
  - However not included in AJCC staging or NCCN risk grouping
- Should we treat these as high risk?



Tom J Urol 2019

ADT for Intermediate Risk: Summary

- Indications for ADT: **Unfavorable IR** (with EBRT)
  - ADT not needed for most favorable IR (unless maybe GC score ≥0.45)
  - Await confirmation in RTOG 0815
- Duration: **4-6 months**
- Sequence: **start ADT and RT concurrently**
  - No benefit from or need for neoadjuvant ADT

ADT for High Risk/Locally Advanced

- **LT-ADT improves OS** over RT alone in HR/LA

Trial	N	Inclusion	Arms	Findings
EORTC 22863 Bolla 2010	415	T1-2 Grade 3 or T3-4	70 Gy +/- LHRHa 36 months	ADT improved all endpoints including OS
RTOG 8531 Pilepich 2005	977	T3N0-1	65-70 Gy +/- lifelong LHRHa or orchiectomy	ADT improved all endpoints including OS
RTOG 8610 Roach 2008	456	T2-4N0-1	65-70 Gy +/- 4 months LHRHa + AA	ADT improved all endpoints except OS (4 months may be insufficient?)
DFCI 95-096 D'Amico 2015	206	PSA 10-40, GS 7-10, or T3	70 Gy +/- 6 months LHRHa + AA	ADT improved OS in pts without comorbidities

ADT for High Risk/Locally Advanced

- **ST-ADT < LT-ADT** = intermediate term ADT??

Trial	N	Inclusion	Arms	Findings
RTOG 92-02 Horwitz 2008	1554	T2c-T4	65-70 Gy + ADT **4 vs. 28 months**	LT-ADT improved OS for GS 8-10
DART 01/05 Zapatero 2015	355	T1c-T3a (IR or HR)	76-82 Gy + ADT **4 vs. 28 months**	LT-ADT improved OS for HR (but not IR)
EORTC 22961 Bolla 2009	970	T2c-T4 or N1	70 Gy + ADT **6 vs. 36 months**	LT-ADT improved OS
PCS IV Nabid 2018	630	T3-T4, Gl 8-10, PSA >20	70 Gy + ADT **18 vs. 36 months**	LT-ADT not better than IT-ADT
RADAR Denham 2018	1071	T2b-T4 or T2a & GS ≥7 & PSA ≥10	66-74 Gy (or HDR-B) + ADT **6 vs. 18 months**	IT-ADT improved PCSM (~2/3 HR, ~1/3 IR)

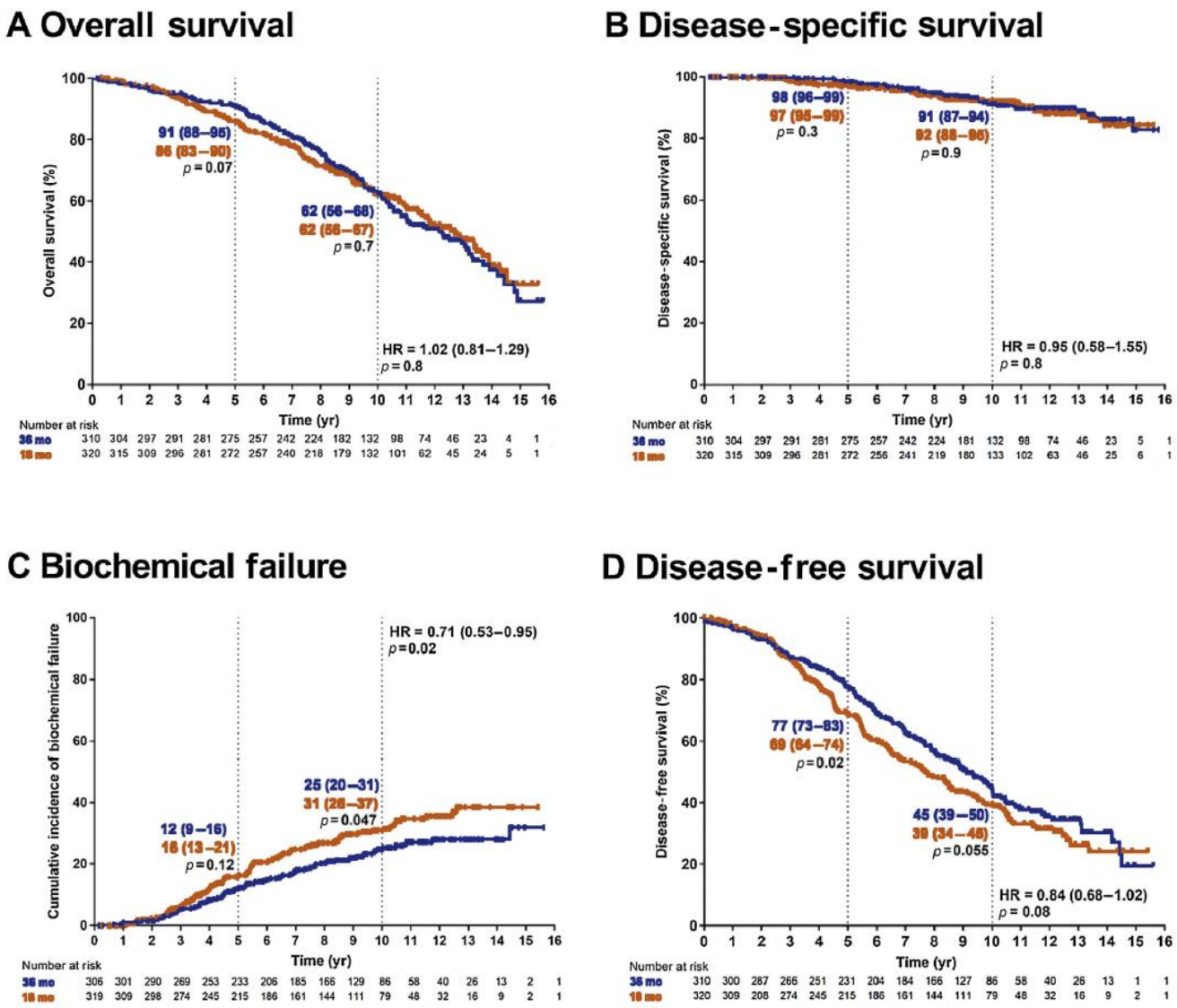
Is 18 months ADT enough for High Risk?

PCS IV: 18 vs. 36 months ADT (LHRHa)

- 1^{o} endpoint was OS, powered for superiority (expected to improve 5y OS from 70% to 79%) → actual 5-yr OS 91% vs. 86%, p=0.07
- Only 53% of 36m ADT arm received full duration (vs. 88% of 18m)
  - Bias towards null hypothesis?
- No difference in OS, DFS, or CSS
- 18m: ↑ testosterone recovery & QOL (hot flashes & enjoyable sex)
- Criticized for statistical design of testing superiority instead of non-inferiority; also, event rate lower than anticipated

Nabid Eur Urol 2018

PCS IV



Nabid Eur Urol 2018

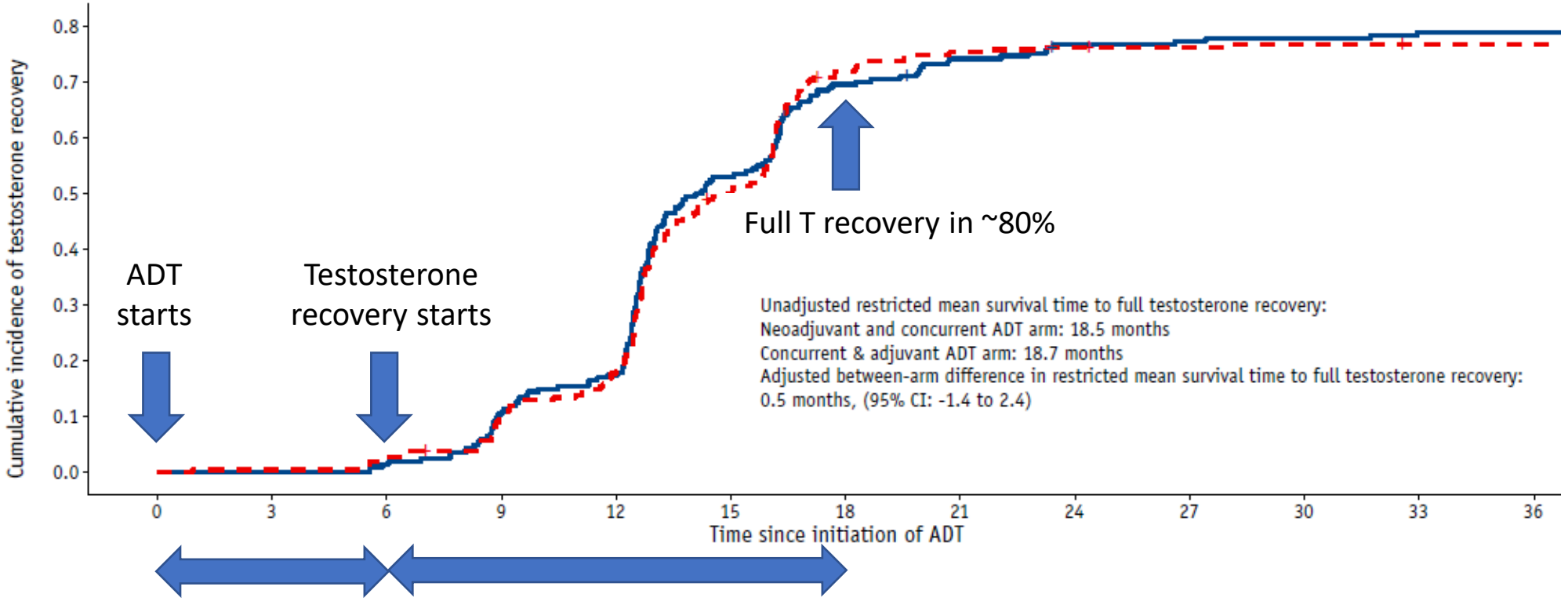
Delayed Testosterone Recovery after LHRHa

Trial	LHRHa Duration	Median T Recovery	% T Normalized
PCS III	0 months	NA	~80%
PCS III	6 months	20 months	~70%
PCS IV	18 months	3.6 years	~60%
PCS IV	36 months	6.6 years	~50%

Nabid Eur Urol 2018. Nabid EJC 2021.

Delayed Testosterone Recovery after LHRHa

After 6m LHRHa it can take a full extra year to recover T (Ottawa 0101)

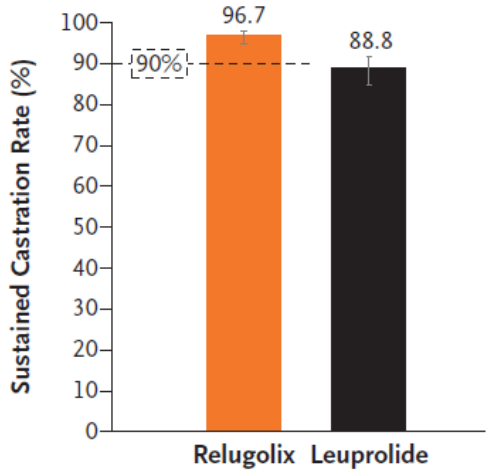


6 + 12 = 18 months

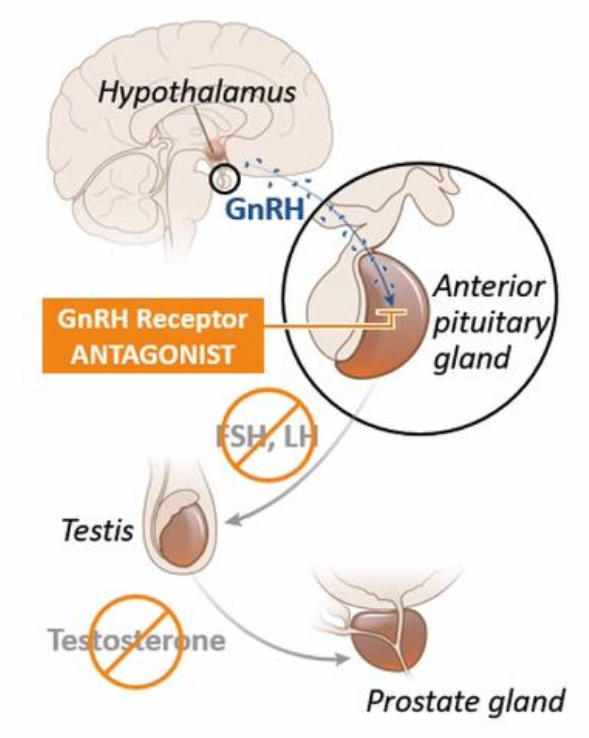
Roy IJROBP 2020

Alternatives to LHRH Agonists

- Alternatives to LHRHa are desired
- **Relugolix is an oral GnRH <u>antagonist</u>**
- Tested on **HERO trial** vs. leuprolide (2:1)
- Met 1° endpoint: sustained castration (48 weeks)

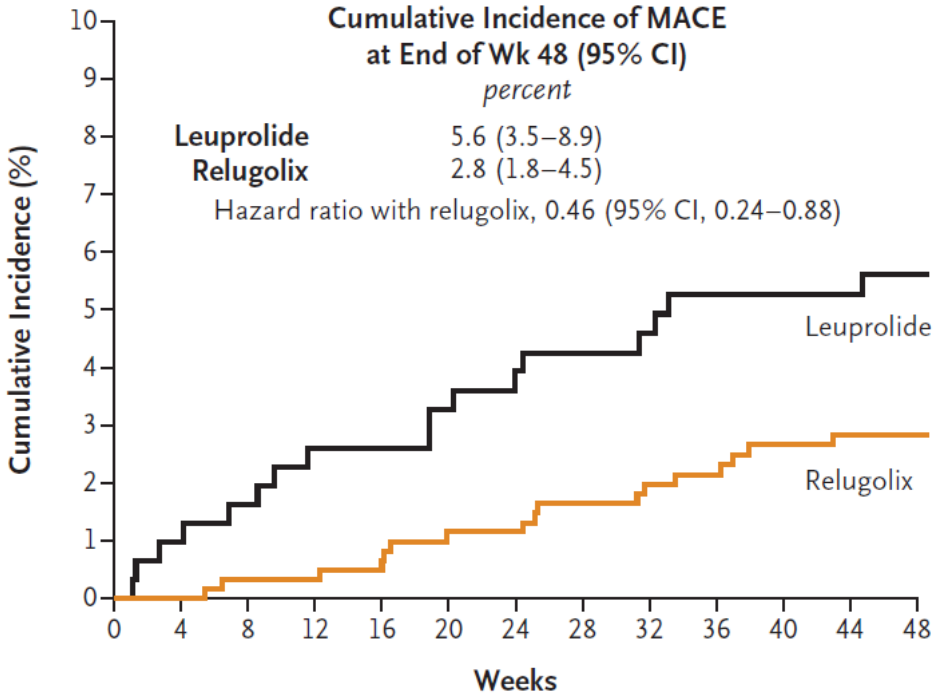


Shore NEJM 2020



HERO

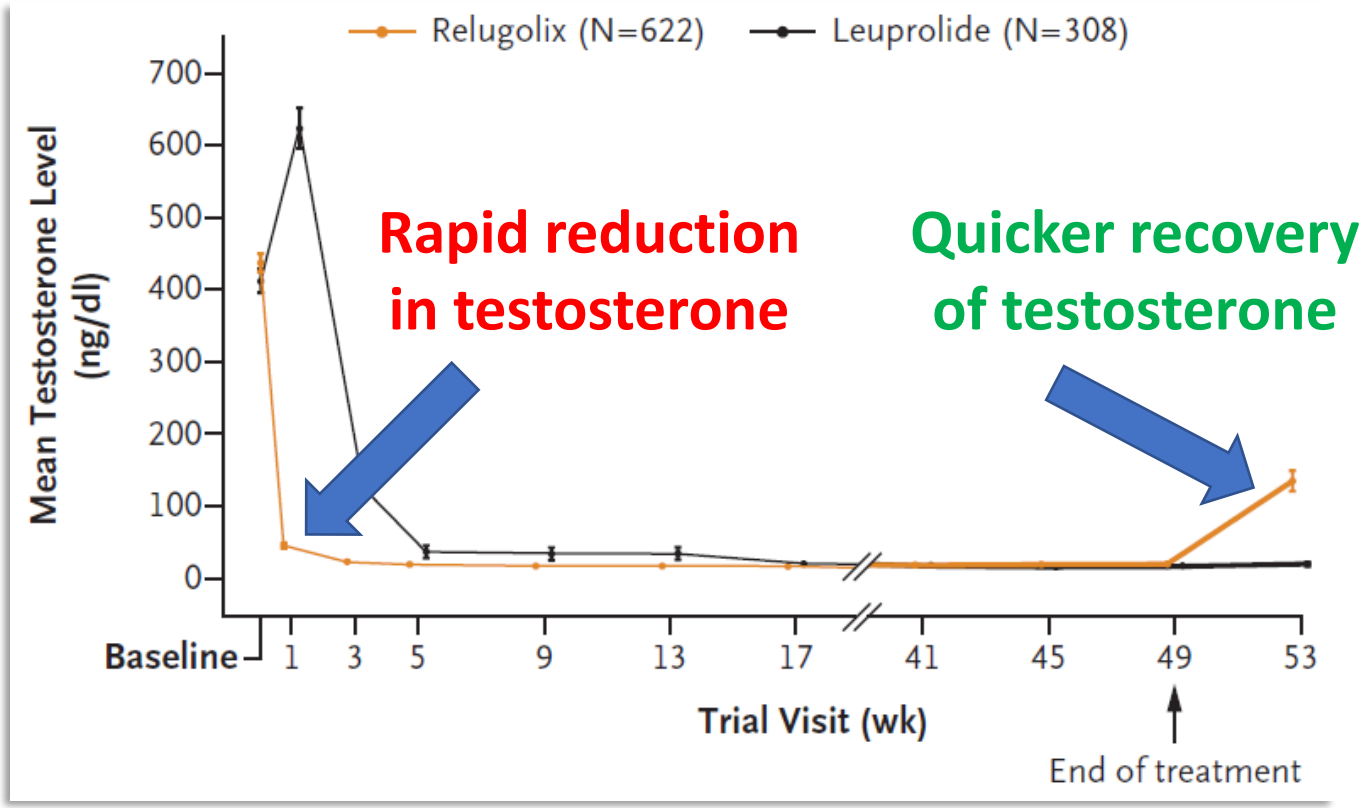
Relugolix ↓ major adverse cardiac events than leuprolide

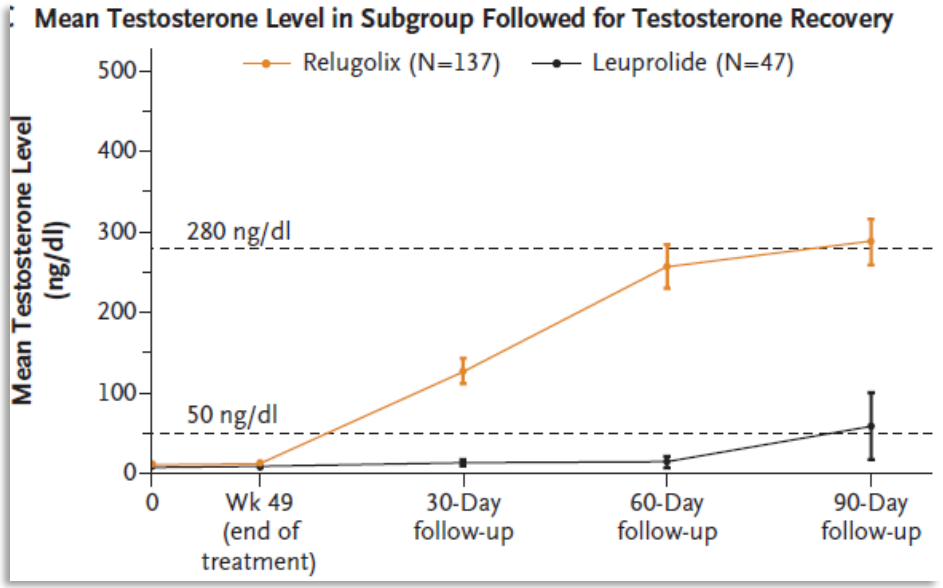


MACE = non-fatal MI + stroke + ACM

Shore NEJM 2020

HERO

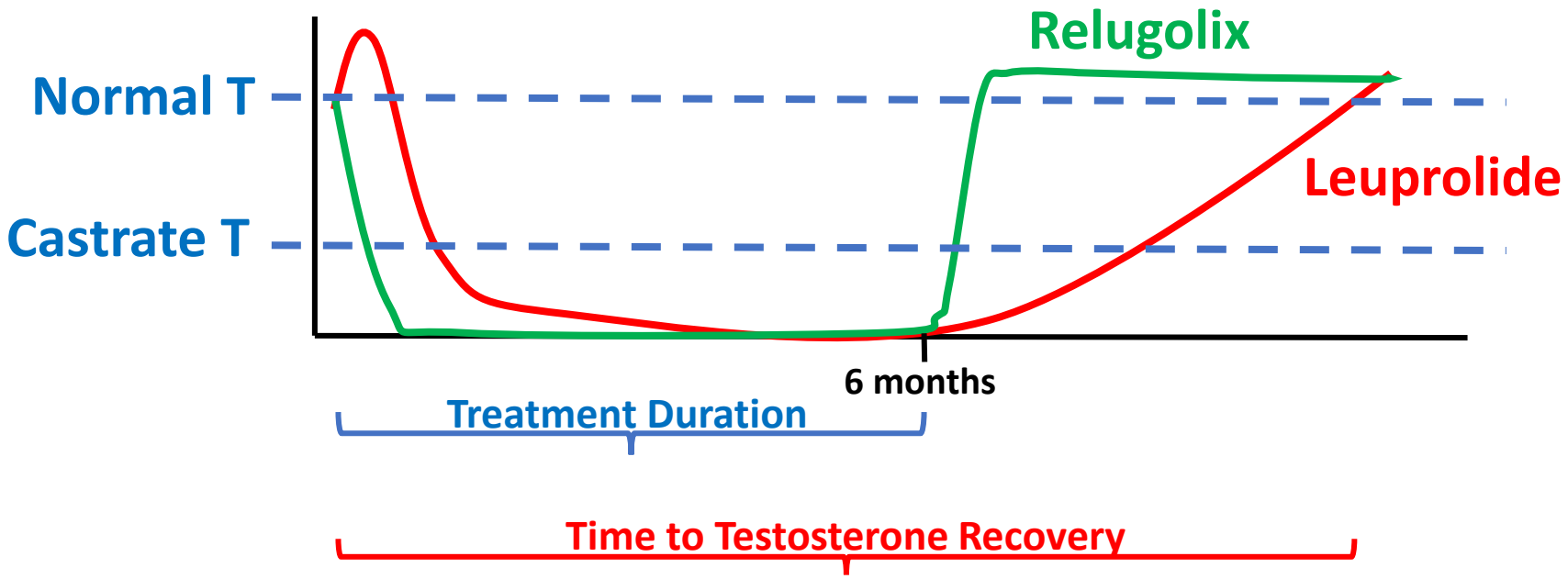




Shore NEJM 2020

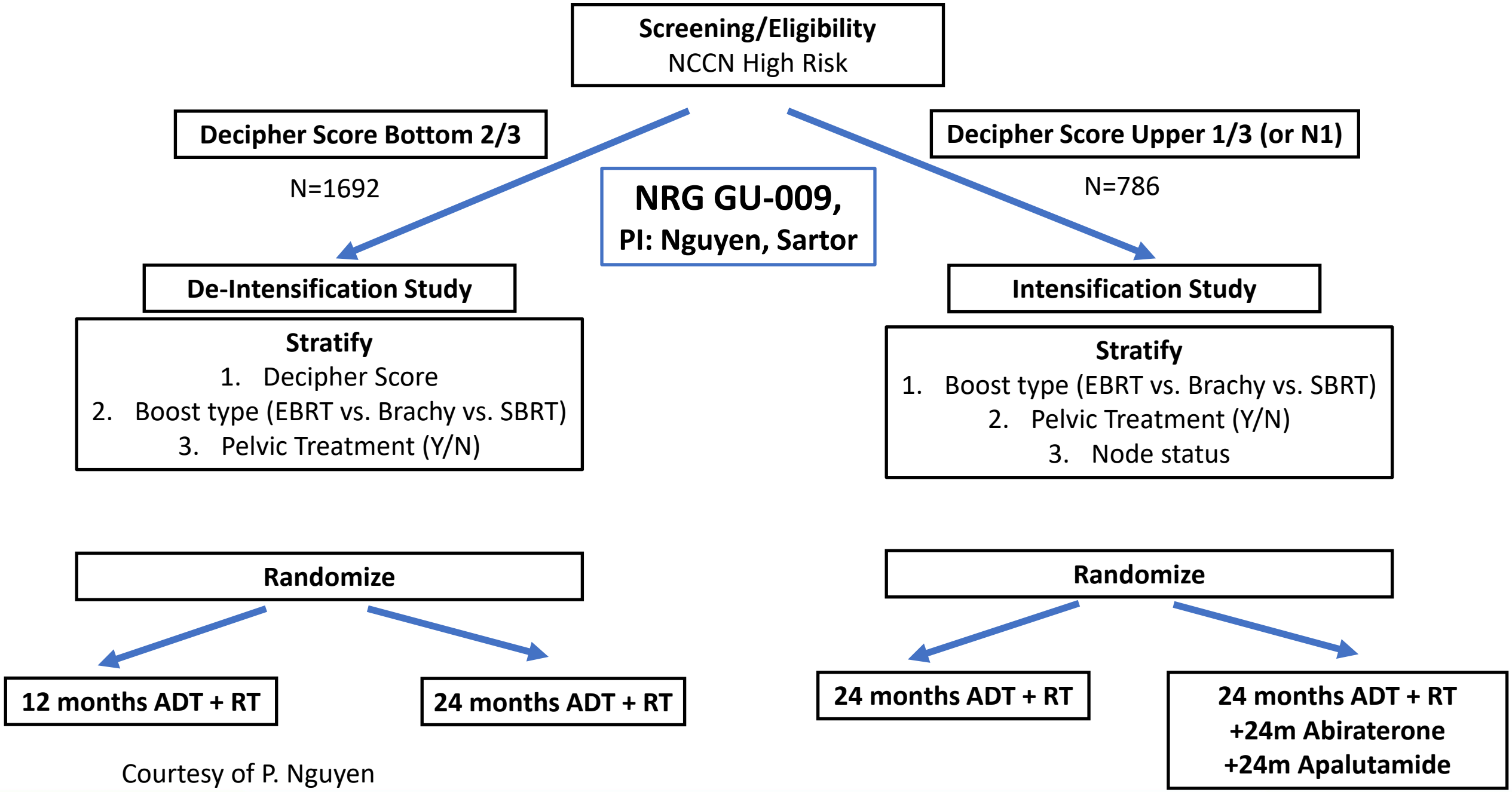
A Better Way to Report ADT Duration?

- Instead of "**treatment duration**" should we report **"# months of castration"**?
- With quicker acting drugs, **time to testosterone recovery** should be monitored & reported in all future ADT trials



High Risk: Still Many Decisions to Make

- **With EBRT, 18-36 months ADT is current standard for HR**
- Which drugs?
  - GnRH agonist vs. antagonist?
  - Chemo (docetaxel) or novel AA (enzalutamide, apalutamide, abiraterone)?
- How to incorporate genomic profiling?
- Pelvic nodal radiation?
- Dose/technique?
  - Standard vs. hypofractionation?
  - SBRT?
  - Rectal spacer if no EPE?
  - Brachytherapy boost?
- Surgery vs. radiation?



Courtesy of P. Nguyen

Docetaxel

TABLE 2. Prospective Studies of Adjuvant Docetaxel Chemotherapy

Study	Intervention and Primary Outcome	Select Patient Characteristics	Primary Therapy	Results on Primary Outcome	Comments
GETUG-12[15] (n = 413)	ADT plus docetaxel and estramustine for four cycles *v* ADT alone for 36 months RFS (BCR, death, distant metastasis, use of salvage therapy)	T3-4, GS ≥ 8, PSA > 20 ng/mL, or pN+	Prospectively determined RT or RP; most patients had RT	At 12 years: 49.4% *v* 36.3% favoring intervention Median RFS, 11.6 *v* 8.1 years 12-year prostate cancer OS rate was 88.2% *v* 83.9% (adjusted HR, 0.70; 95% CI, 0.40 to 1.22)	Most patients GS < 8 Patients with GS < 8 derived the greatest benefit from chemotherapy
SPCG-12[16] (n = 459)	Six cycles of docetaxel or surveillance after RP PSA > 0.5 ng/mL	High-risk pT2 margin positive or pT3a GS ≥ 4 + 3; pT3b or pN1+	RP	45% in docetaxel arm *v* 38% in surveillance arm	No ADT in either arm
VA CSP #553[17] (n = 297; study stopped early)	Six cycles of docetaxel and prednisone or SOC (surveillance) PFS	High-risk pathologic features on RP	RP	Median PFS, 55.5 months in chemotherapy and 45.6 months in SOC	Subgroup analyses showed benefit in PFS for patients with tumor stage pT3b (HR, 0.58; 95% CI, 0.34 to 0.98) and for African Americans (HR, 0.54; 95% CI 0.29 to 1.01)
SPCG-13[18] (n = 376)	Six cycles of docetaxel without prednisone or surveillance after RT PSA ≥ 2 ng/mL above nadir	Intermediate- or high-risk patients	RT	31% on docetaxel and 30.3% in surveillance met end point	GS was significant predictor of PSA progression

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; GS, Gleason score; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RFS, recurrence-free survival; RP, radical prostatectomy; RT, radiation therapy; SOC, standard of care.

Parikh JCO 2019

Pelvic Nodal Radiation: 3 RCTs

Parameter	RTOG 9413	GETUG-01	POP-RT
T Stage	T2c-T4: 67%	T3: 25.5%	T3b-T4: 46.4%
Estimated pelvic nodal risk	> 35% risk in 24.5%	> 35% risk in 9.8%	Median 38% > 35% risk in 55% > 50% risk in 29%
GS	GS 7-10: 72%	GS 7-10: 50.7% GS 8-10: 10.9%	GS 7-10: 90.2% GS 8-10: 49.1%
Baseline median PSA	22.6 ng/mL	12 ng/mL	28.2 ng/mL
Staging imaging	Chest x-ray, CT pelvis or lymphangiogram, bone scan	CT thorax abdomen and pelvis, bone scan	MRI pelvis, PETCT (F-18 or Ga-68 PSMA) 80% had PSMA PETCT
Pelvic field upper limit	L5-S1	S1-S2	L4-L5 including common iliac nodes
Pelvic dose	50.4 Gy	46 Gy	50 Gy
Prostate dose (biologically effective dose)	70.2 Gy, 1.8 Gy per fraction (112.32 Gy)	66.25-72 Gy, 1.8-2 Gy per fraction (110-122 Gy)	68 Gy, 2.72 Gy per fraction (129.6 Gy)
Radiotherapy technique	Conventional 2-dimensional box fields	Conventional 2-dimensional box fields and 3-dimensional conformal radiotherapy	Image-guided IMRT
ADT	4 months	4-8 months	≥ 24 months

POP-RT

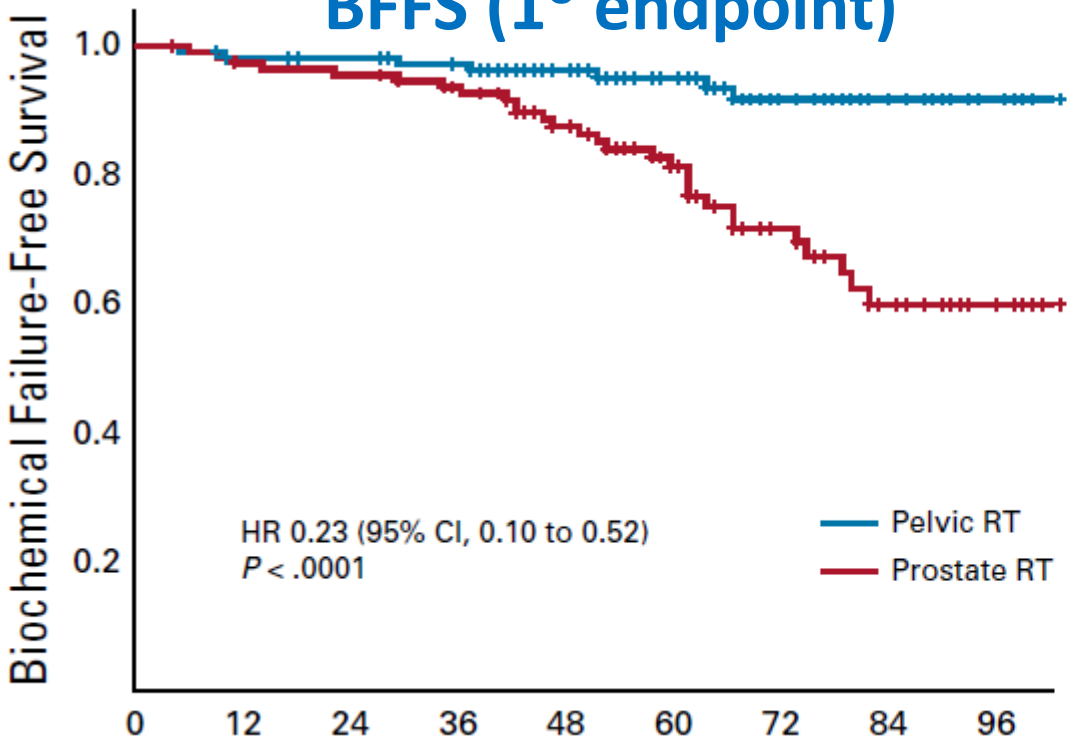
- RCT of 68 Gy/25 to prostate (~78-81 Gy EQD2) +/- 50 Gy to LNs via SIB (included common iliac LNs) with ≥2 years ADT
- Minimum estimated LN risk 20% (median 38%); 80% cT3-T4 (1% T1)
- >50% VHR; 80% had PSMA PET-CT → excluded cN1 and cM1
- **WPRT ↑ late Gr 2 GU toxicity**, but not Gr 3 GU or Gr 2-3 GI

Late Toxicity	Gr 2 GU	Gr 3 GU	Gr 2 GI	Gr 3 GI
WPRT	**18.2%**	1.8%	6.4%	1.8%
PORT	**7.1%**	1.8%	4.5%	0%
P value	0.02		0.28	

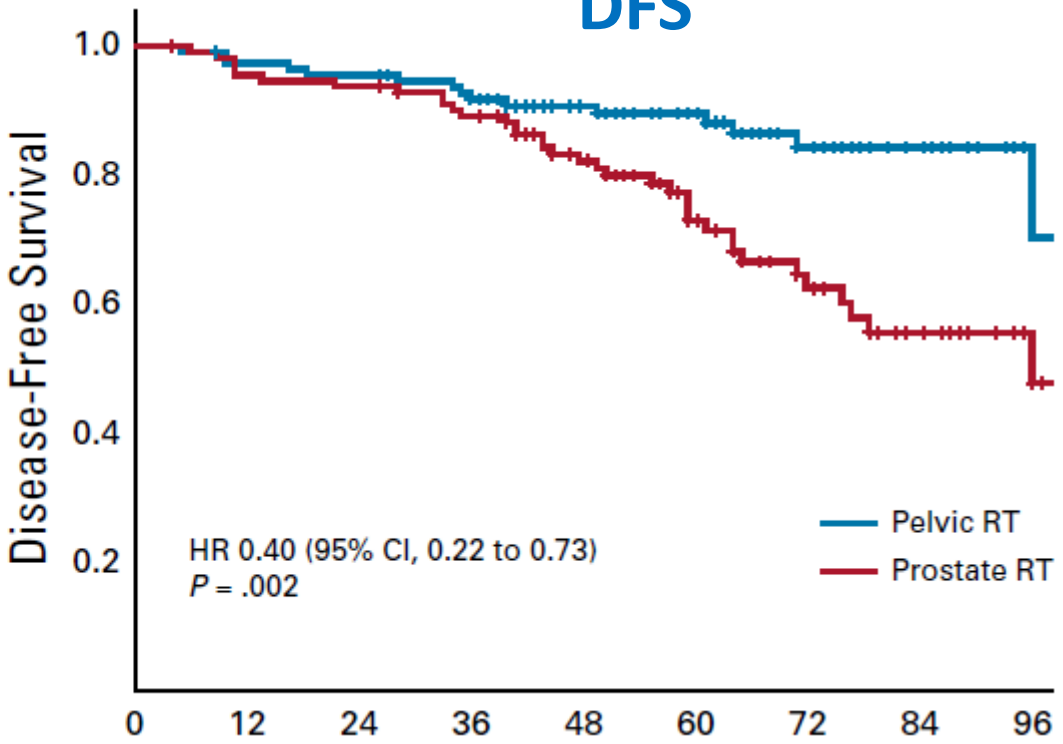
Murthy JCO 2021

POP-RT: ENI improved BFFS, DFS, DMFS (not OS)

BFFS (1^{o} endpoint)



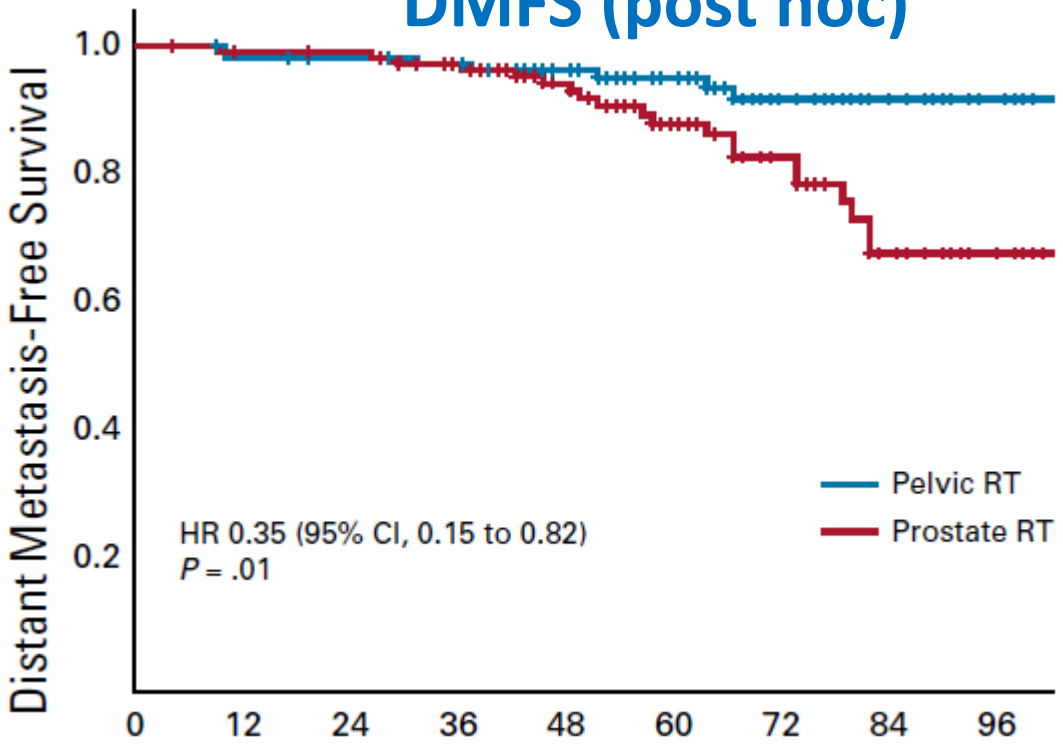
DFS



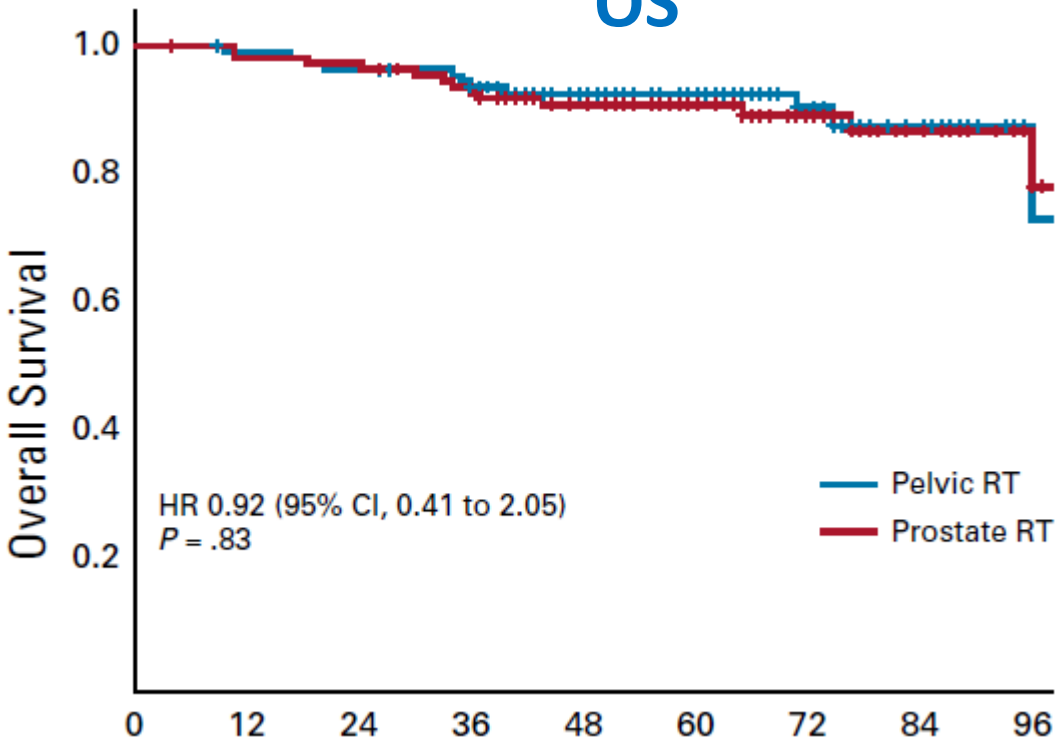
Murthy JCO 2021

POP-RT: ENI improved BFFS, DFS, DMFS (not OS)

DMFS (post hoc)

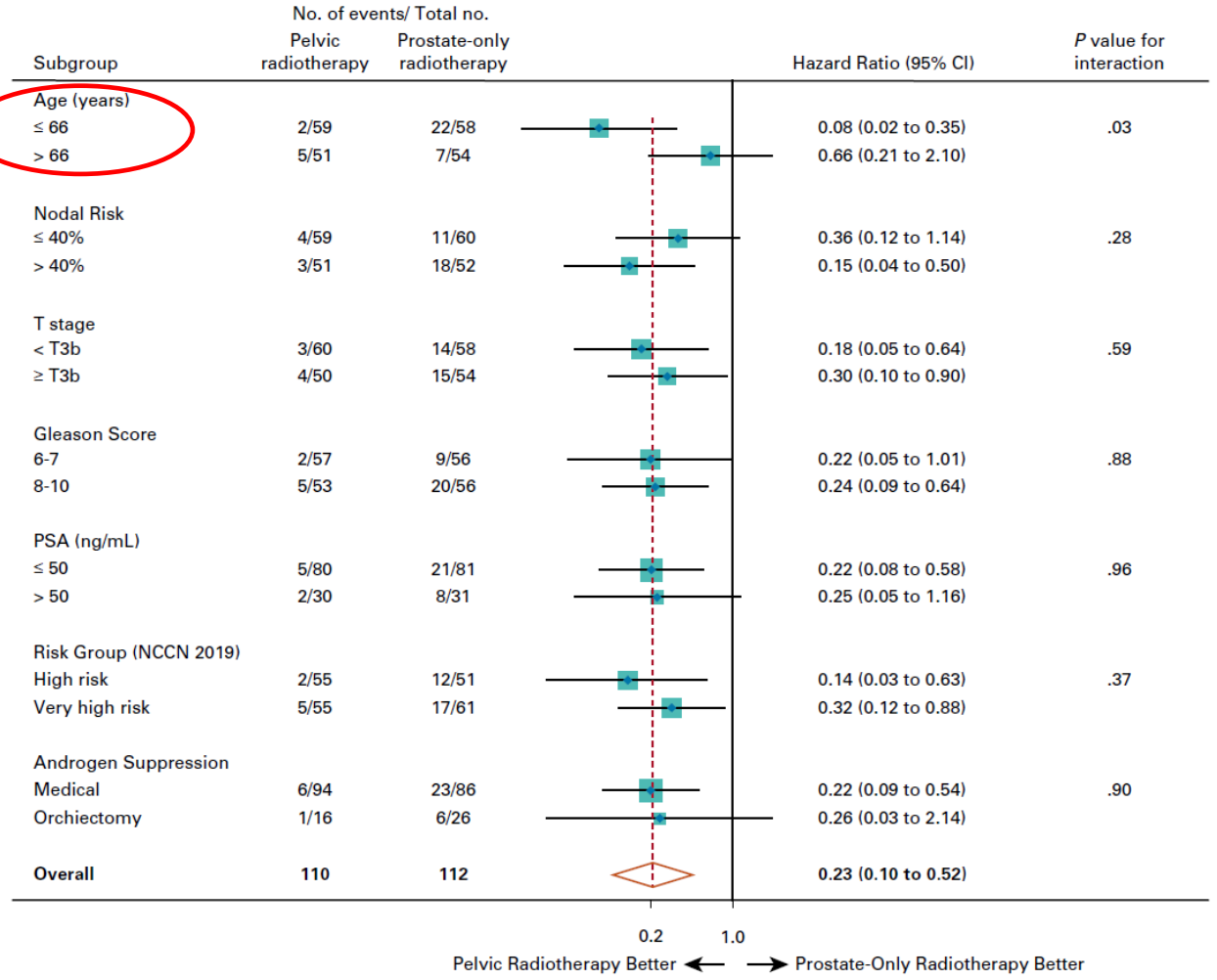


OS



Murthy JCO 2021

POP-RT: Subgroup Analysis for BFFS

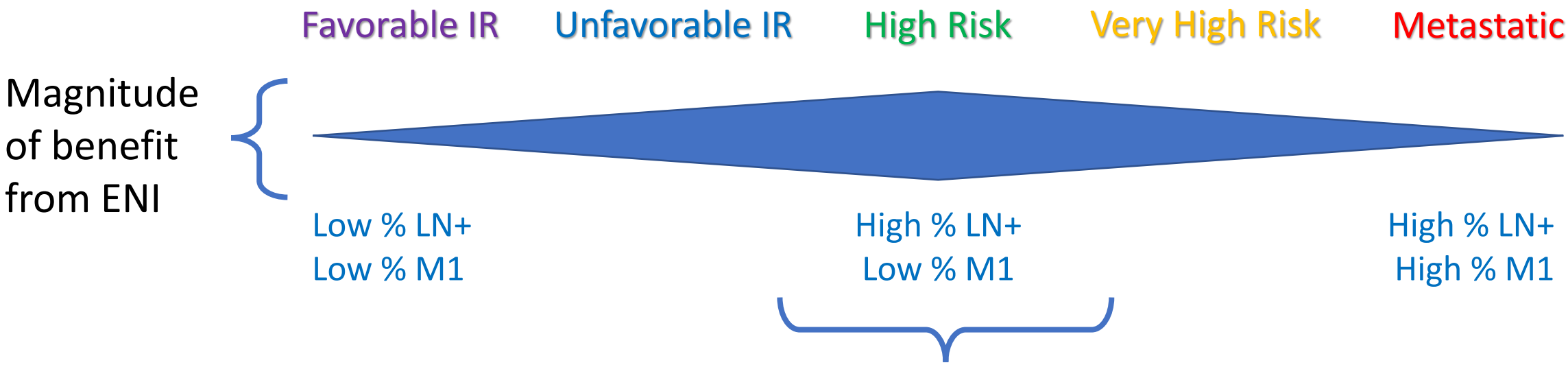


Murthy JCO 2021

Which Patients Need Nodal Radiation?

- Limitations of RTOG 9413
  - Older era: low dose RT (70 Gy) & short term ADT (4 months) → suboptimal control of primary tumor → obscures impact of ENI?
  - 2x2 design make results confusing to interpret
- Limitations of POP-RT
  - Single institution, small size
  - Not representative of U.S. population (not screen detected; 80% PET staged)
  - Outcomes better than historical controls → Will Rogers or real effect?
- RTOG 0924 results still a decade away

Which Patients Need Nodal Radiation?



Selecting Patients for Elective Nodal Irradiation

Estimate LN involvement
- Roach formula
  2/3 PSA + 10(GS-6)
- Nomograms
- Genomic profiling

Higher risk of LN+ → ENI
Target = prostate, SV, LNs
- EBRT sequential (CF) or SIB (HF)
- EBRT + brachy boost

Lower risk of LN+ → No ENI
Target = prostate, proximal SV
- EBRT
- SBRT
- EBRT + brachy boost
- Brachytherapy alone?

NRG Pelvic LN Atlas – 2021 update

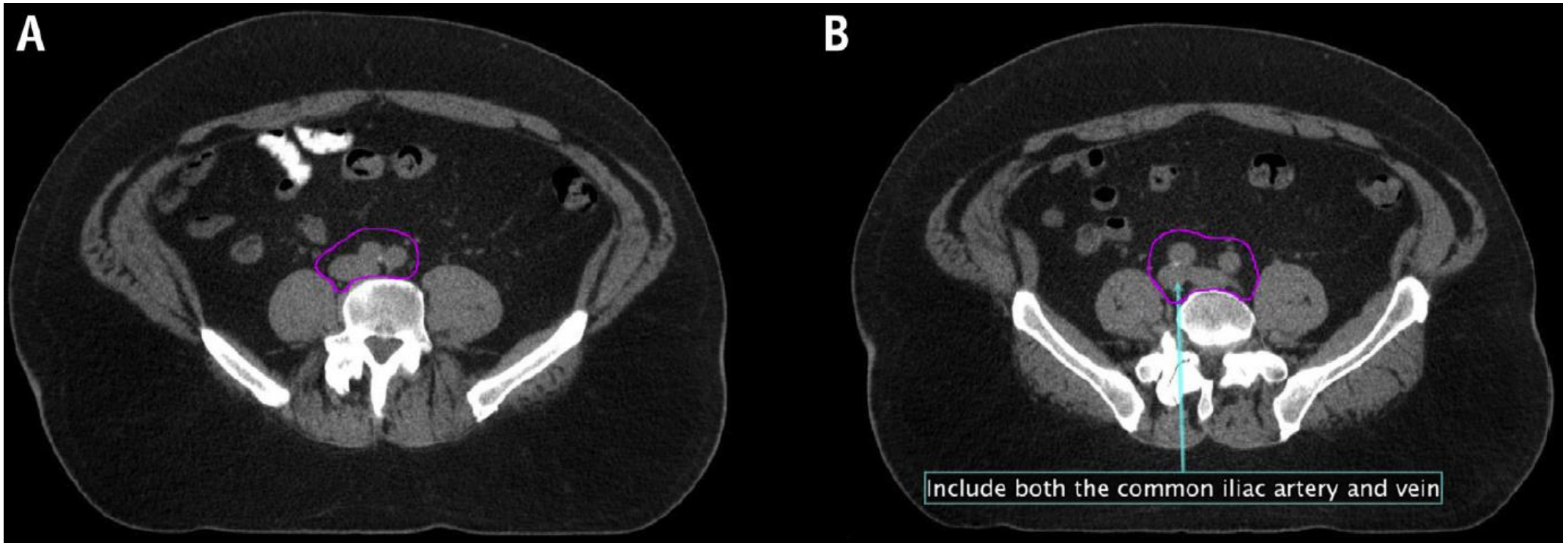
NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer

- Update of previous consensus in 2009 (Lawton et al)
- Not designed to establish *indications* for ENI
- General principles:
  - CTV should exclude bone, bladder, muscle, bowel (unless indicated)
  - Normal tissues should be prioritized when treating ENI
  - Be aware of altered nodal drainage patterns, esp. postop (e.g. perirectal LNs)

Hall IJROBP 2021

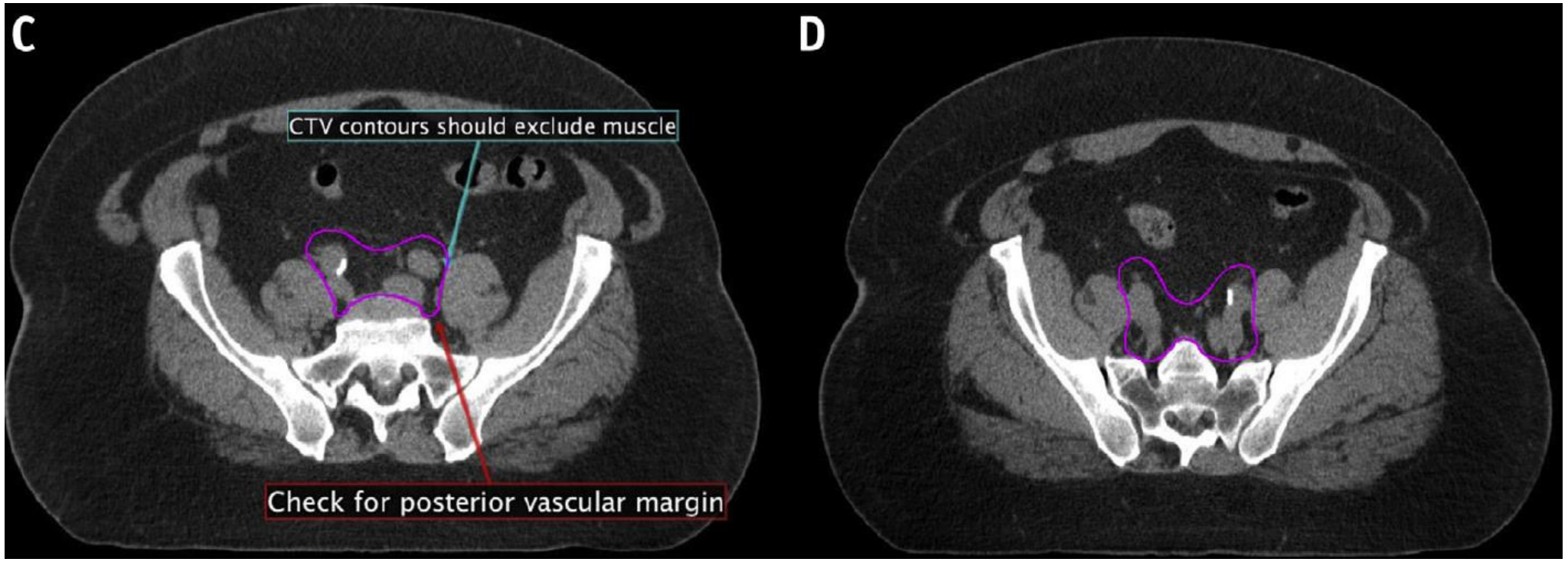
Common Iliac LNs

- Commence contours at bifurcation of aorta into common iliac a. or proximal IVC to common iliac v. (whichever is more superior) ~L4-L5



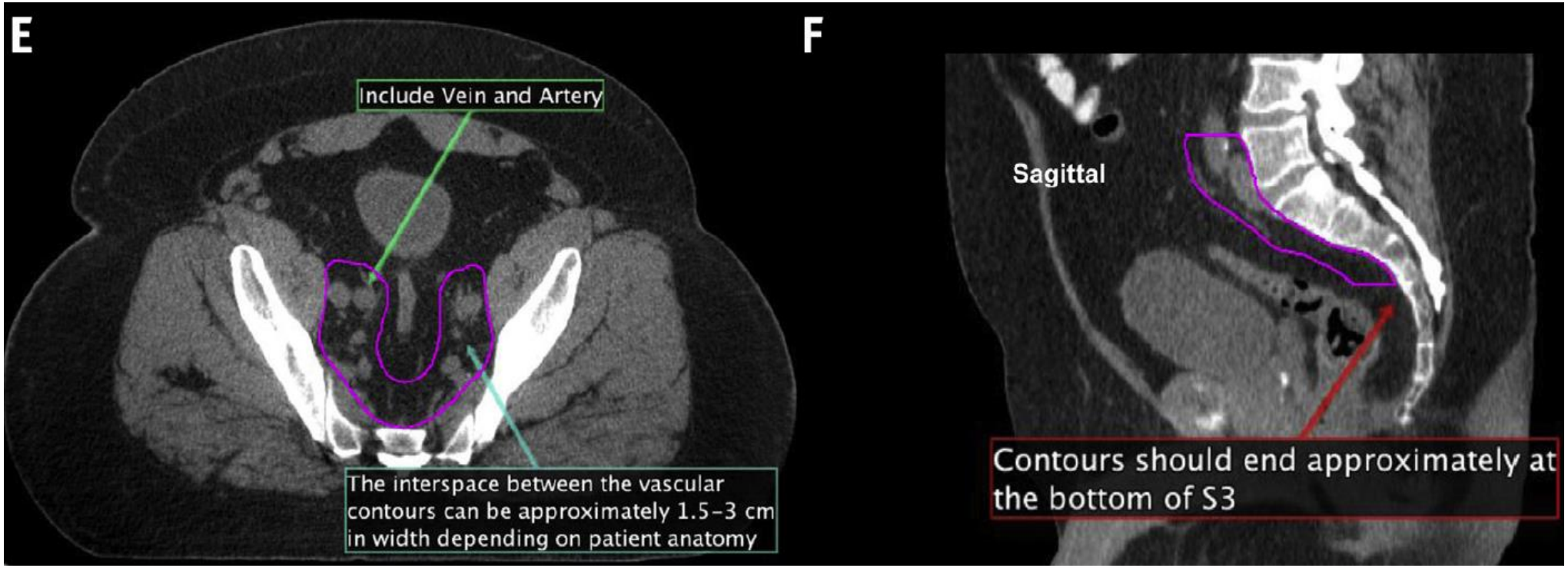
Common Iliac LNs

- Contour 5-7 mm around each iliac vessel, & be more generous anterior to vessels (10 mm) when clinically indicated
- Cover posteriorly in between psoas and vertebral body



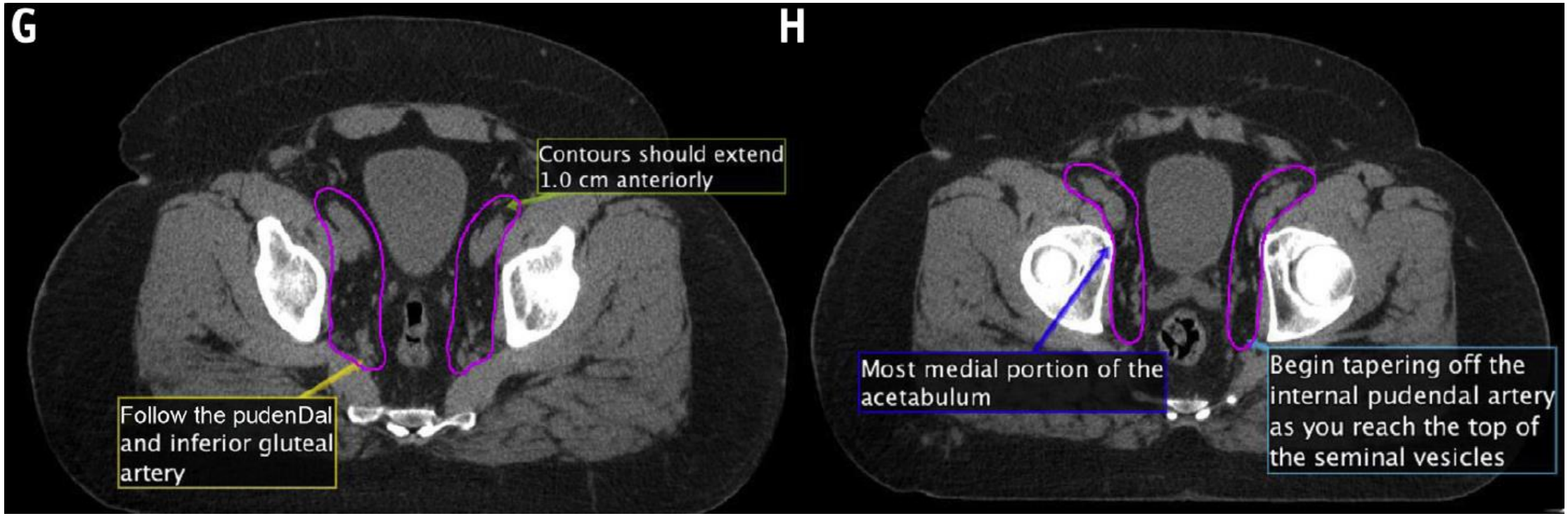
Pre-sacral, External/Internal Iliac LNs

- Width of interspace between external and internal iliac contours ~1.5 to 3 cm, depending on patient anatomy
- Contour posterior mesenteric, prevertebral & presacrals to bottom of S3



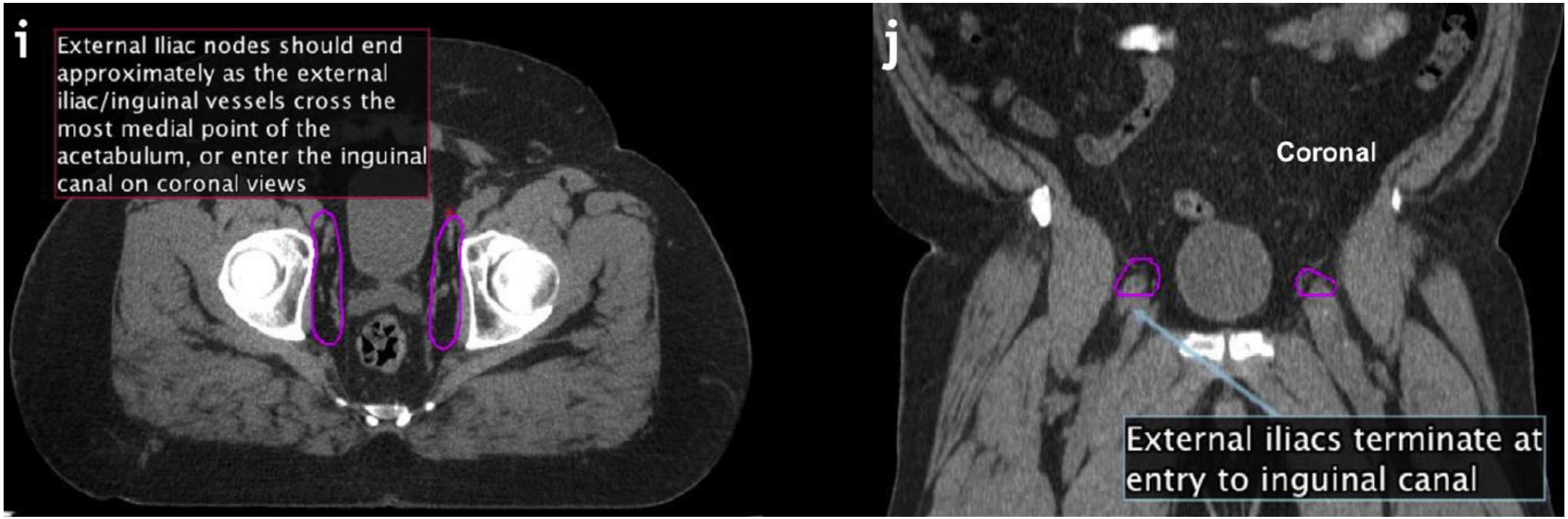
External/Internal Iliac LNs

- Posterior border of internal iliac vessels extends to anterior edge of piriformis m. following course of the pudendal a. and inferior gluteal a.



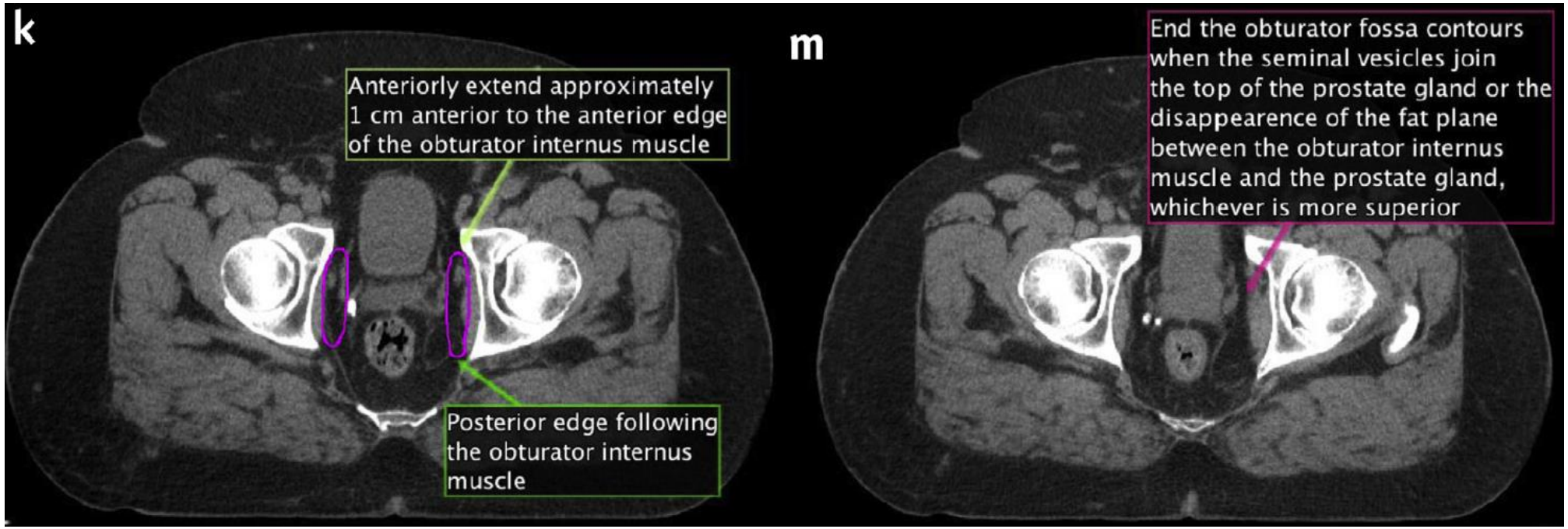
Transition of External Iliac to Inguinal LNs

- External iliacs end when they cross inguinal ligament into inguinal canal (vessels are completely lateral to medial acetabulum) – best seen on coronal



Obturator LNs

- ~1-2 cm wide; extend to posterior edge of obturator internus m. and 1 cm anterior to edge of obturator internus m.
- Taper obturator LNs at the top of the SVs (or top of post-op bed); end inferiorly where SVs join prostate or ~mid-portion of contoured post-op CTV



NRG 2021 Consensus Dose Constraints

Conventional Fractionation 75.6-79.2 Gy

Sequential boost 45-50.4 Gy to LNs

75.6-79.2 Gy in 42-44 fractions, treating nodes to 45-50.4 Gy with a sequential boost	
Rectum (24)	V (≥4500 cGy) ≤50%
	V (≥7000 cGy) ≤15%
	V (>7200 cGy) <10 cm^3
Bladder	V (≥4500 cGy) ≤50%
	V (≥7000 cGy) ≤15%
Femur_L	V (≥5000 cGy) ≤2%
	Dmax ≤5250 cGy
Femur_R	V (≥5000 cGy) ≤2%
	Dmax ≤5250 cGy
Colon	V (≥6000 cGy) ≤2%
	Dmax ≤6250 cGy
Small bowel (bowel loops)	V (≥5000 cGy) ≤10%
	Dmax ≤5200 cGy
Pubic bone	V (≥7000 cGy) ≤25%
Penile bulb (should not sacrifice PTV coverage)	V (≥5000 cGy) ≤50%

Hall IJROBP 2021

NRG 2021 Consensus Dose Constraints

Hypofractionation
70 Gy/28 fx

SIB
45-50.4 Gy to LNs

70 Gy in 28 fractions, treating nodes to 45-50.4 Gy with a simultaneous integrated boost	
Rectum (24)	V ($\geq$4500 cGy) $\leq$45% V ($\geq$5500 cGy) $\leq$25% V ($\geq$ 6500 cGy) $\leq$15% V (>6500 cGy) <10 cm^3
Bladder	V ($\geq$4500 cGy) $\leq$45% V ($\geq$5500 cGy) $\leq$25% V ($\geq$6500 cGy) $\leq$15%
Femur_L	V ($\geq$5000 cGy) $\leq$1% Dmax $\leq$5250 cGy
Femur_R	V ($\geq$5000 cGy) $\leq$1% Dmax $\leq$5250 cGy
Colon	Dmax $\leq$5500 cGy
Small bowel (bowel loops)	V ($\geq$4650 cGy) $\leq$2 cm^3 Dmax $\leq$5200 cGy
Pubic bone	V ($\geq$6000 cGy) $\leq$30%
Penile bulb (should not sacrifice PTV coverage)	Make dose as low as reasonably achievable

Hall IJROBP 2021

NRG 2021 Consensus Dose Constraints

Hypofractionation
60 Gy/20 fx

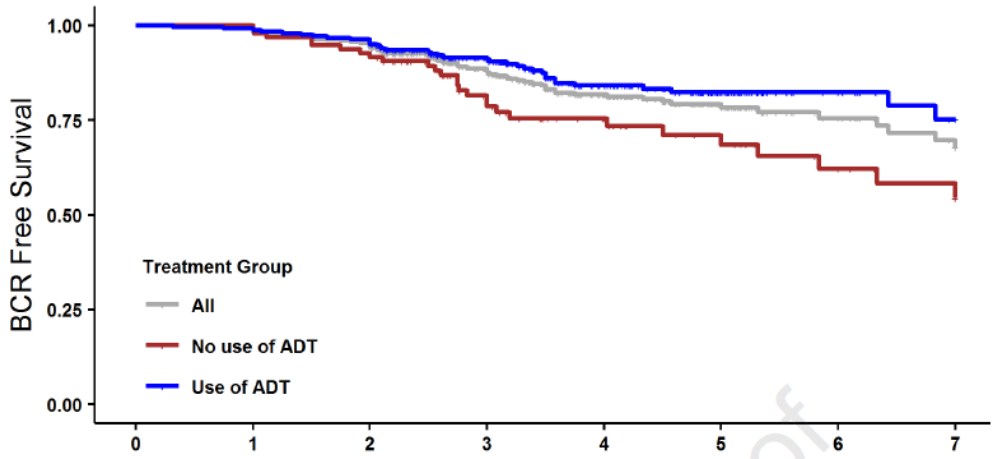
SIB
44-47 Gy to LNs

60 Gy in 20 fractions (treating nodes to 44-47 Gy over 20 fractions*) (8)	
Rectum (22)	V (≥2000 cGy) ≤85% (no circumferential dose)
	V (≥3000 cGy) ≤57%
	V (≥4000 cGy) ≤38%
	V (≥5000 cGy) ≤22%
	V (≥6000 cGy) ≤1%†
Bladder‡	V (≥4000 cGy) ≤50%
	V (≥4800 cGy) ≤25%
	V (≥5680 cGy) ≤5%
	V (≥6000 cGy) ≤3 %
Femur_L	V (≥3500 cGy) ≤5%
	Dmax ≤3700 cGy
Femur_R	V (≥3500 cGy) ≤5%
	Dmax ≤3700 cGy
Colon	Dmax ≤5000 cGy
Small bowel (bowel loops)	Dmax ≤4000 cGy
	V (≥3700 cGy) ≤90 cm^3
	V (≥3300 cGy) ≤130 cm^3
Pubic bone	V (≥5700 cGy) ≤20%
Penile bulb (25)	V (≥2200 cGy) ≤50%

Hall IJROBP 2021

High Risk: Is SBRT safe/effective?

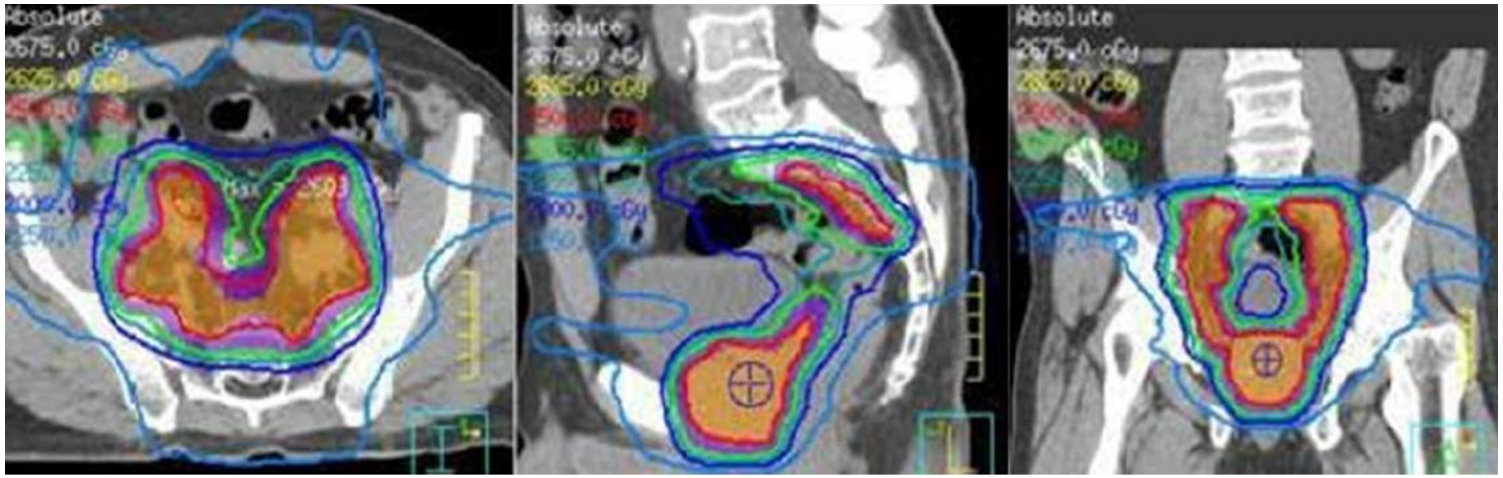
- Emerging data on SBRT in HR
- HYPO-RT-PC: included 126 patients with HR (no ADT used)
- SHARP consortium: 344 patients treated at 7 institutions
  - 72% ADT; 19% received nodal SBRT on protocol
  - 4y bRFS 82%, DMFS 89%
  - Late Gr 3 GU toxicity 2.3%, GI 0.9%



Van Dams IJROBP 2021

High Risk: Can you give ENI with SBRT?

- Emerging data on SBRT with ENI in HR: SATURN & FASTR trials
- 25 Gy in 5 weekly fractions to pelvic LNs → SIB 40 Gy to prostate/SVs
  - Toxicity results mixed → needs further study



Musunuru IJROBP 2018. Bauman IJROBP 2015. Kothari TCRT 2018.

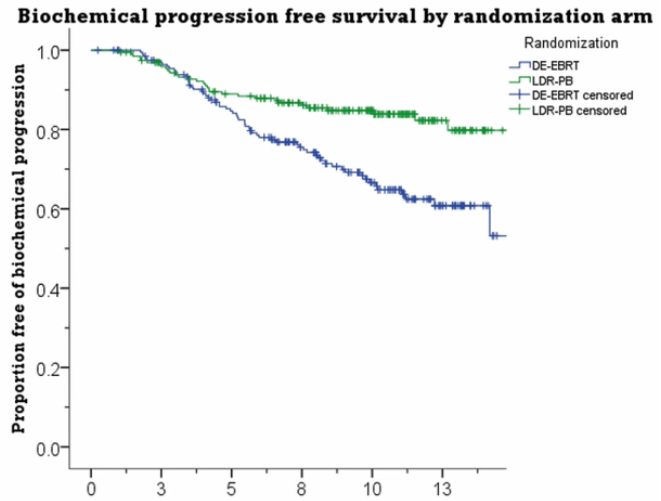
High Risk: Is Brachy Boost Superior?

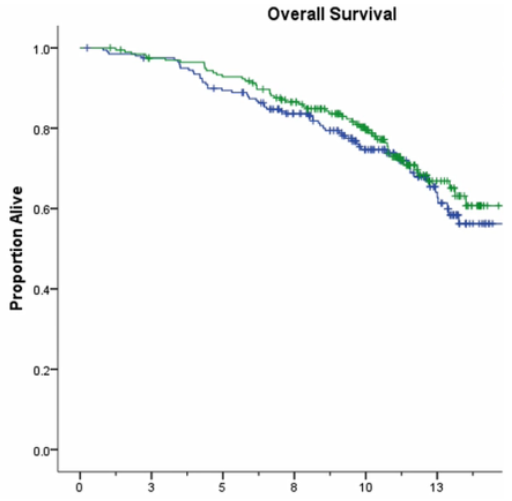
- **ASCENDE-RT**: 398 pts (276 HR, 122 IR) treated with 12 months ADT (8 months neoadjuvant) & WPRT 46 Gy/23 fx
  - Randomized to boost by EBRT 32 Gy (total 78 Gy) or I-125 LDR-B 115 Gy (*1st randomized brachy boost trial)
  - Exclusion: PSA >40, stage cT3b-T4, prior TURP, prostate >75 cc, inability to tolerate anesthesia
- 5-yr Gr 3 **GU toxicity higher with LDR-B**: 18% vs. 5%
  - In LDR-B, baseline IPSS ≥16 associated with Gr 2 GU toxicity
- 5-yr Gr 3 GI toxicity 8% vs. 3%
- Erectile function similar: 45% and 37% preserved EF

Morris IJROBP 2017; Rodda IJROBP 2017

High Risk: Is Brachy Boost Superior?

- **LDR-B improved bPFS** over EBRT alone (10y: 85% vs. 67%) for IR & HR





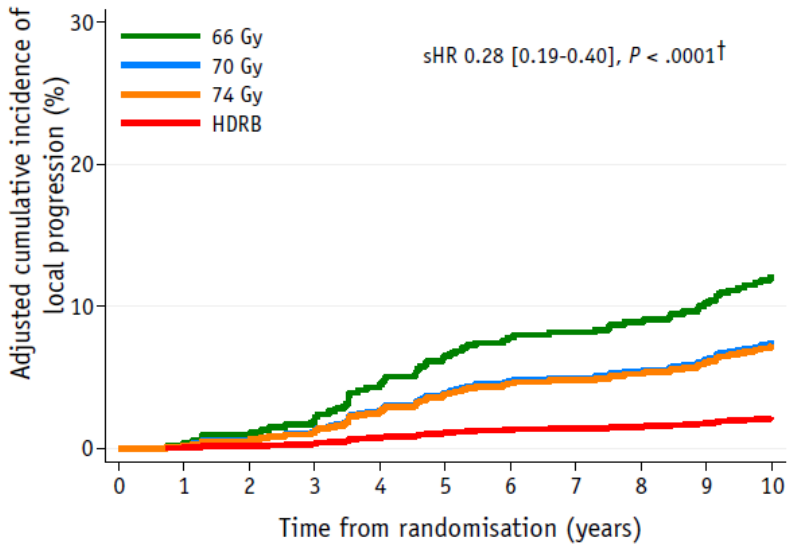
Less need for ADT in LDR-B arm

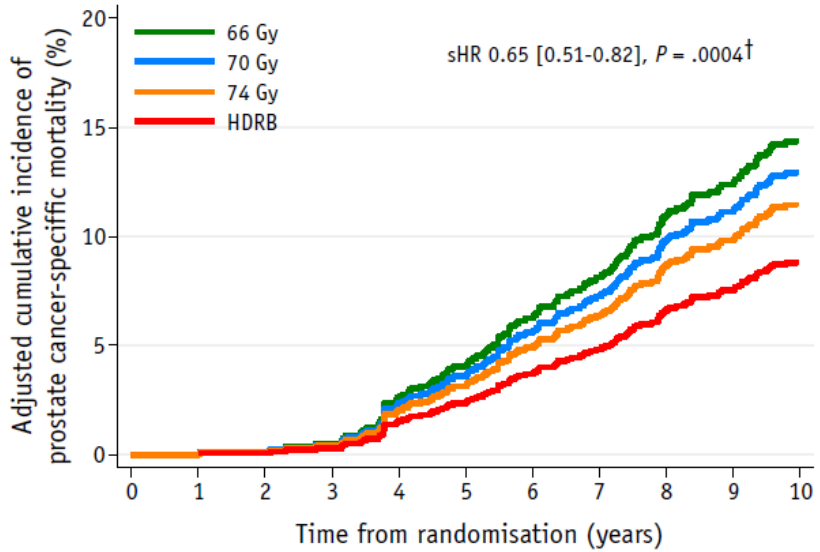
- On MVA: LDR-B, % pos cores, PSA, & T-stage associated with RFS
- **No DM or OS difference** (ASTRO 2020 update)

Morris IJROBP 2017. Rodda IJROBP 2017. Oh ASTRO 2020.

High Risk: Is Brachy Boost Superior?

- On TROG 03.04 RADAR trial, HDR-B was optional
- Non-randomized subset → favorable outcomes with HDR-B + 18m ADT

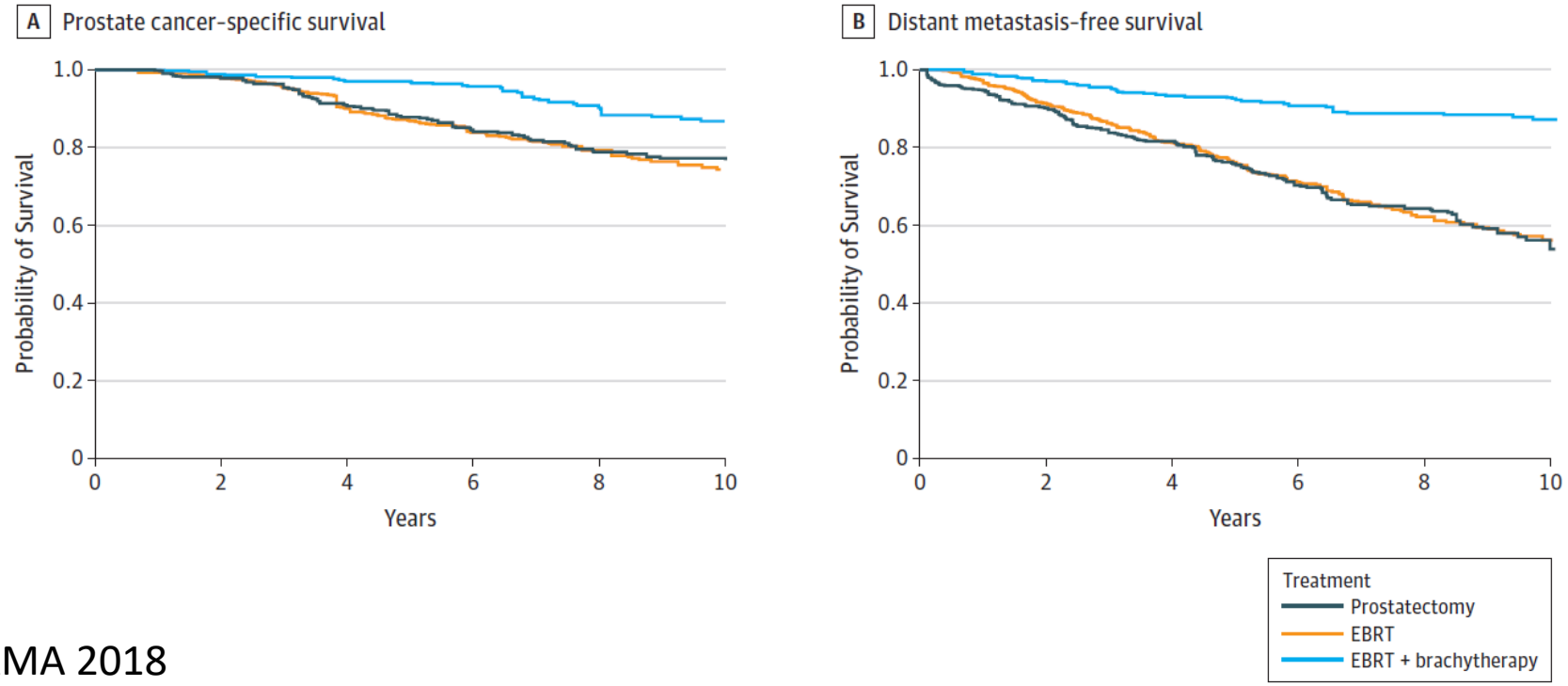




Joseph IJROBP 2020

High Risk: Is Brachy Boost Superior?

- GS 9-10: EBRT+BT+ADT had better PCSM & DM than EBRT+ADT or RP (retrospective multi-institutional)



Kishan JAMA 2018

High Risk: Prostatectomy or Radiation?

- Retrospective studies are subject to huge selection bias

SPCG-15 randomized trial: RP vs. RT + ADT for T3-T4 LAPC

Results awaited

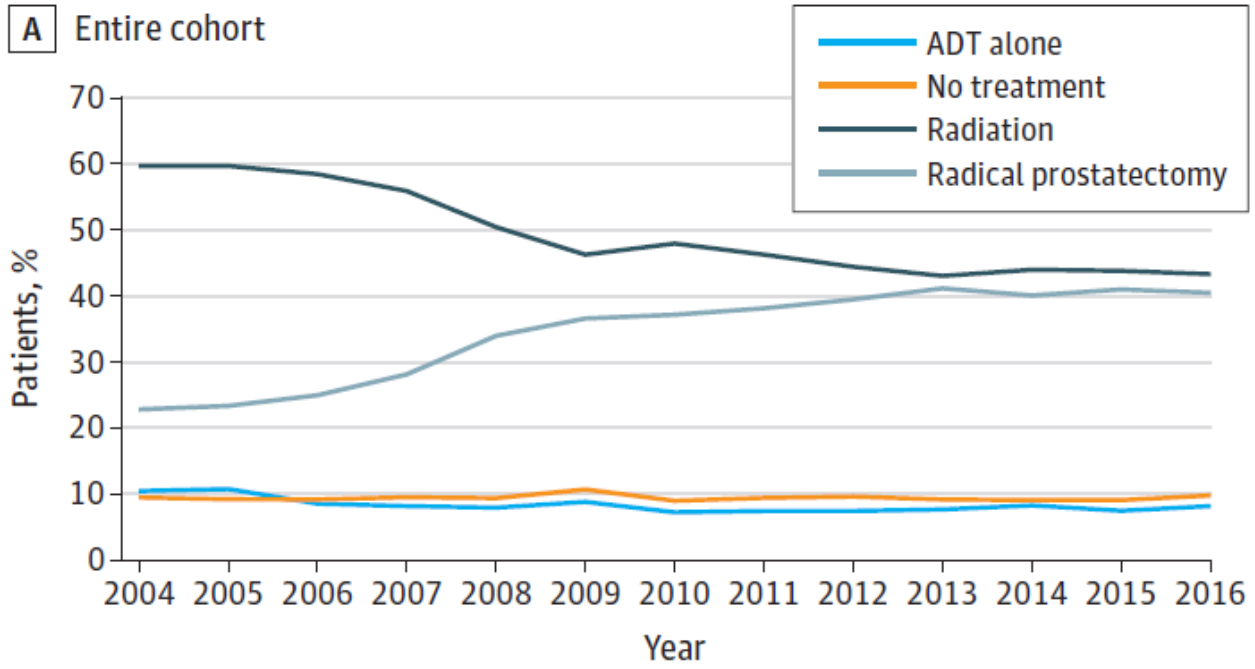
Table 2 – Absolute mortality rates for included studies

Author	Inclusion criteria	Overall mortality		Prostate cancer mortality	
		RP	XRT	RP	XRT
Abdollah (2012)	Clinically localized, age 65–79	NA	NA	10 yr low/int: 1.4% 10 yr high: 6.8%	10 yr low/int: 3.9% 10 yr high: 11.5%
Albersten (2007)	Clinically localized, age < 75	10 yr: 17%[a]	10 yr: 22%[a]	10 yr low: 3% 10 yr int: 6% 10 yr high: 10%	10 yr low: 7% 10 yr int: 12% 10 yr high: 20%
Arvold (2011)	Low risk or intermediate risk	NA	NA	10 yr low: 0.4%[a] 10 yr int: 0%[a]	10 yr low: 0.8%[a] 10 yr int: 3.5%[a]
Boorjian (2011)	High risk	10 yr: 23%	10 yr RT + ADT: 33% 10 yr RT: 48%	10 yr: 8%	10 yr RT + ADT: 8% 10 yr RT: 12%
Cooperberg (2010)	Clinically localized	NA	NA	10 yr: 5%[a]	10 yr: 12%[a]
DeGroot (2013)	"Candidate for therapy": low and intermediate risk	NA	NA	NA	NA
Hoffman (2013)	Clinically localized, age 55–74	15 yr: 35%[a]	15 yr: 58%[a]	NA	NA
Jeldres (2008)	Age > 70	10 yr: 40.7% 15 yr: 72.7%	10 yr: 69.7% 15 yr: 86.7%	NA	NA
Kibel (2012)	Clinically localized	10 yr: 11.1%	10 yr EBRT: 17.4% 10 yr brachy: 18.3%	10 yr: 1.8%	10 yr EBRT: 2.9% 10 yr brachy: 2.3%
Ladjevardi (2010)	T1–3, N0–X, M0–X, PSA<20, age < 75	Relative survival is given resulting in survival estimates > 100% and therefore mortality < 0.			
Lee (2014)	Clinically localized high risk	NA	NA	10 yr: 10%[a]	10y r: 20%[a]
Merglen (2007)	Clinically localized	NA	NA	10 yr: 17%	10 yr: 25%
Merino (2013)	Clinically localized	5 yr: 3.8% 7 yr: 6.3%	5 yr: 11.6% 7 yr: 16.9%	7 yr: 1.9%	7 yr: 7.9%
Rice (2013)	Low risk, age > 70	10 yr: 18%[a]	10 yr: 30%[a]		
Sooriakumaran (2014)	All	10 yr low: 10%[a] 10 yr int: 15%[a] 10 yr high: 20%[a]	10 yr low: 16%[a] 10 yr int: 22%[a] 10 yr high: 30%[a]	10 yr low: 1%[a] 10 yr int: 3%[a] 10 yr high: 8%[a]	10 yr low: 1%[a] 10 yr int:8%[a] 10 yr high: 15%[a]
Sun (2013)	Clinically localized, age 65–80	10 yr: 20%	10 yr: 37%	NA	NA
Tewari (2007)	Clinically localized, high risk, age < 75	10 yr: 54%	10 yr: 75%	10 yr: 25%	10 yr: 43%
Westover (2012)	Clinically localized, Gleason score 8–10, age < 75	NA	NA	5 yr: 0%	5 yr: 1.5%
Zelefsky (2010)	T1c–T3b	NA	NA	8 yr: 1.4%	8 yr: 4.7%

Wallis Eur Urol 2016

High Risk: Prostatectomy or Radiation?

Figure. Trends in Prostate Cancer Treatment From 2004-2016



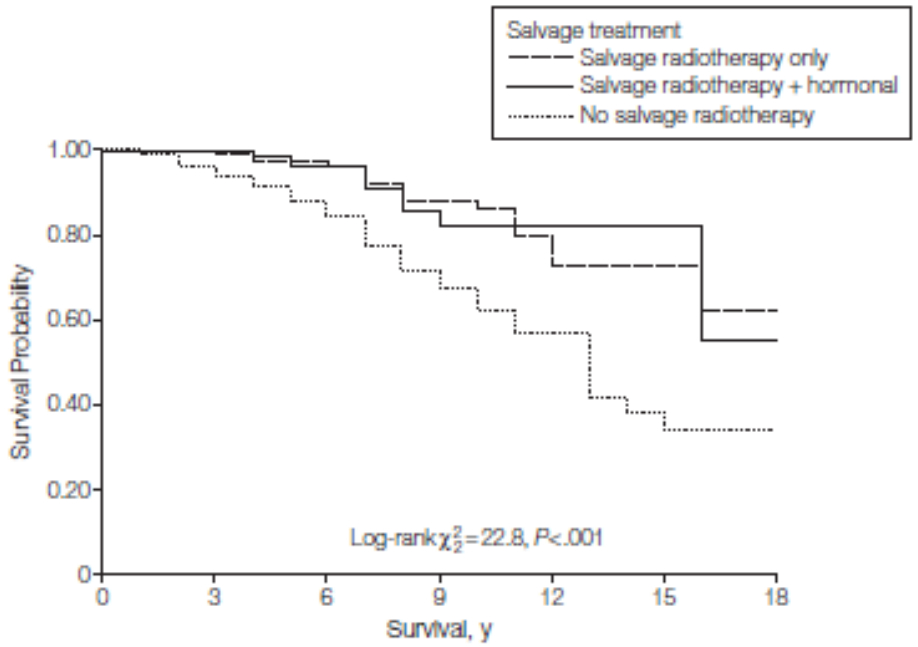
↑ RP for high risk
↑ Adverse pathology

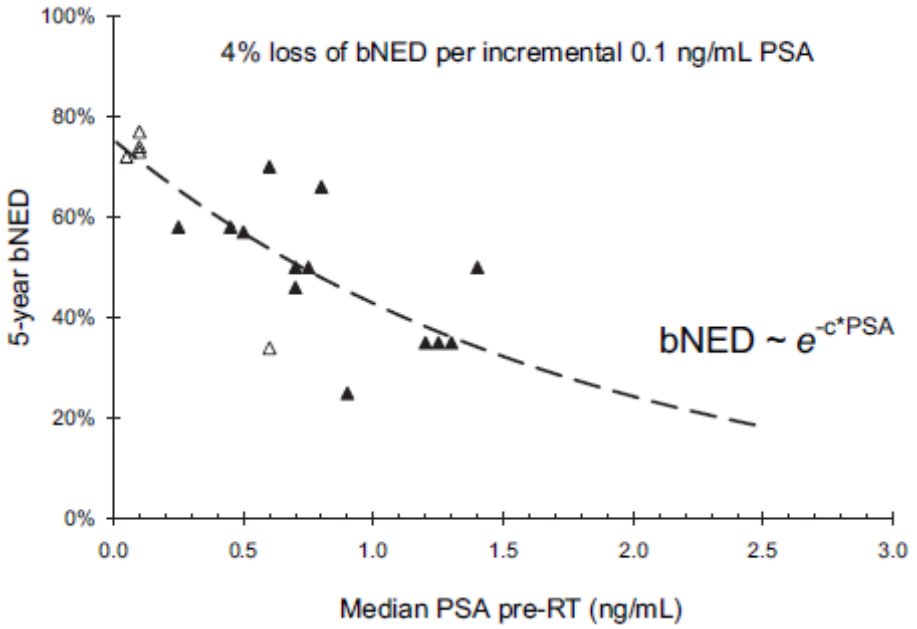
Agrawal JAMA Network Open 2020

Radical Prostatectomy

- After radical prostatectomy, 20-35% positive margin rates
- 25-35% will have a biochemical recurrence
  - >50% if pT3 and/or + margins
- Which patients need postop therapy?
  - Local vs. systemic?
  - Adjuvant vs. salvage?

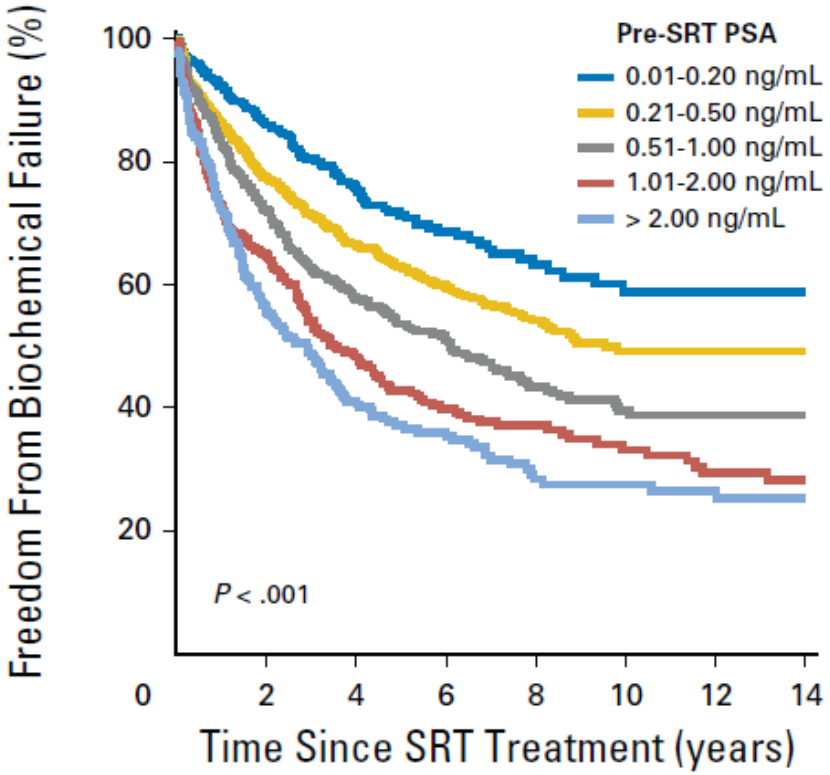
Salvage RT is Effective, Especially at Lower PSA

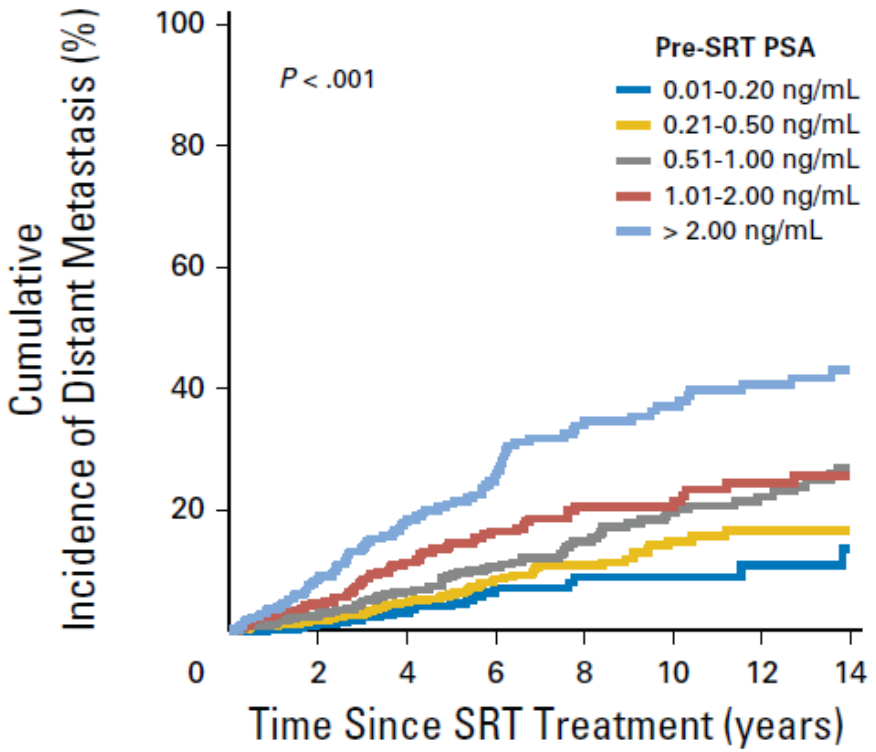




Trock JAMA 2008. King IJROBP 2011.

Salvage RT is Effective, Especially at Lower PSA





Tendulkar JCO 2016

“Adjuvant” RT Trials

- 3 randomized trials of “Immediate” RT vs. Observation for pT3 or M+
  * No pre-specified parameters for salvage therapy*

- FFBF ~50% with observation vs. ~75% with immediate RT

Bolla Lancet 2012. Thompson J Urol 2009. Wiegel Eur Urol 2014.

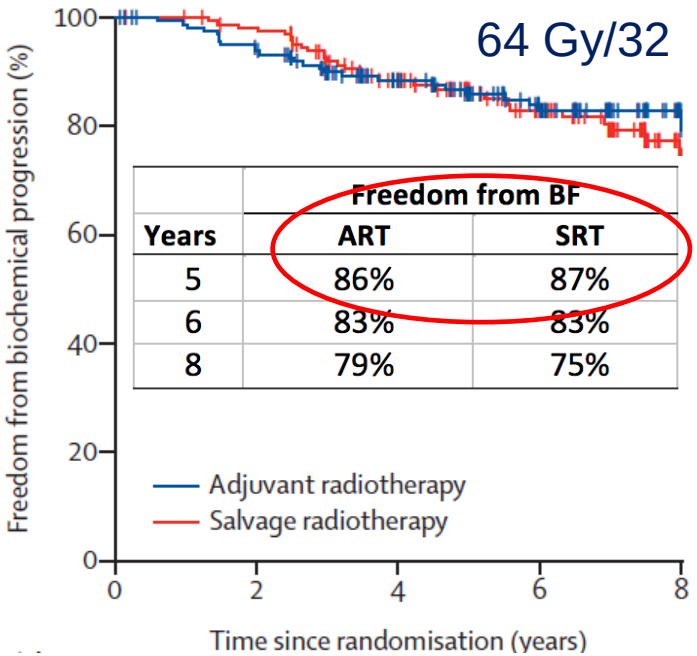
Adjuvant vs. Early Salvage RT Trials

- >2000 patients randomized

RAVES	RADICALS	GETUG 17
64 Gy, no ADT N=333 (not 470) 1^{o} endpoint = BF	N=1396 to RT randomization N=2840 to randomization of 0 vs. 6 vs. 24 m ADT 1^{o} endpoint = PCSS	6 m ADT both arms N~718 1^{o} endpoint = EFS

Kneebone Lancet Oncol 2020. Parker Lancet 2020.

RAVES

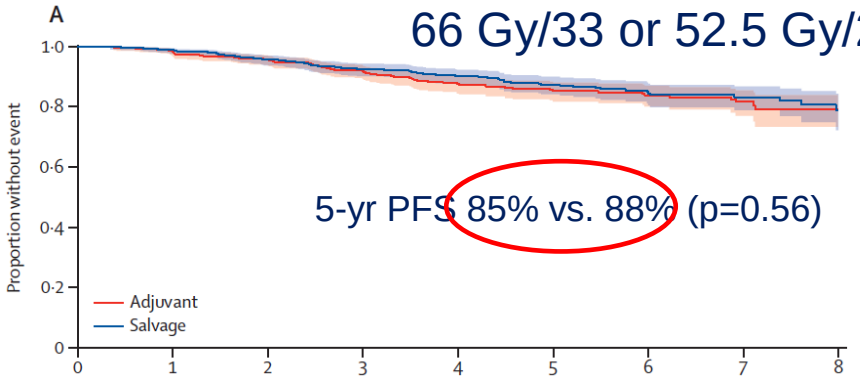


Years	Freedom from BF ART	SRT
5	86%	87%
6	83%	83%
8	79%	75%

ESRT: PSA ≥0.2

ART: Worse GU toxicity

RADICALS



ESRT: PSA ≥0.1 or 3 consecutive rising PSAs

5y FFBF with ART
SWOG 77%
EORTC 74%
German ARO 72%

Kneebone Lancet Oncol 2020. Parker Lancet 2020.

ARTISTIC Meta-analysis

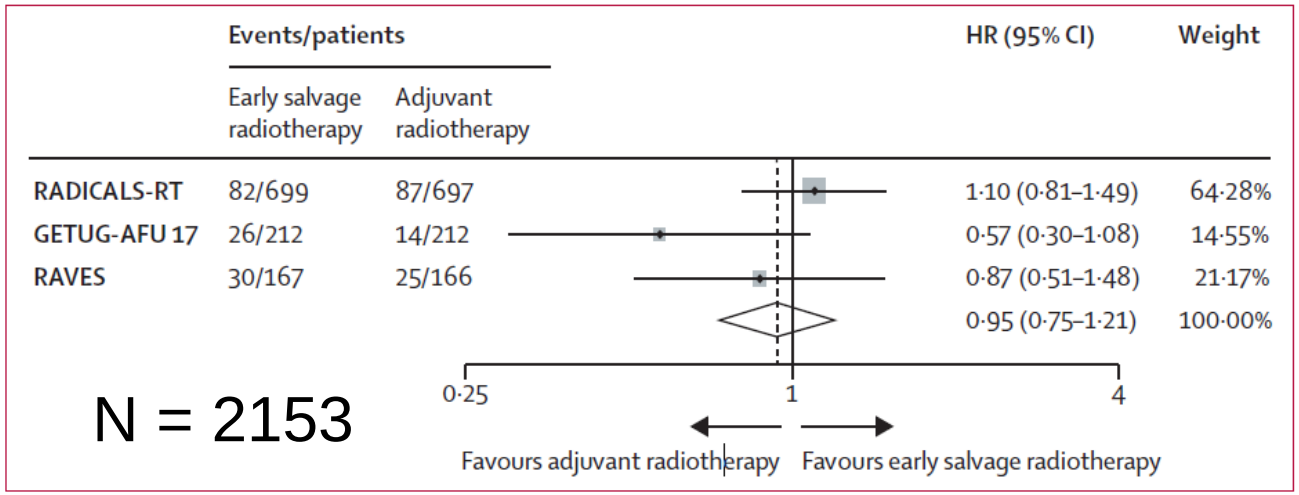


Figure 2: Effect of radiotherapy timing on event-free survival

- Observation/ESRT should be standard of care for <u>most</u> with PSA <0.1
  - Favorable population: 78% Gleason 7, 71% positive margin
  - Only 15% Gleason 8-10, 19% SVI

Vale Lancet 2020

Is the Door Closed on Adjuvant RT? Not yet.

Adjuvant Versus Early Salvage Radiation Therapy After Radical Prostatectomy for Men With Adverse Pathologic Features—The Debate Continues

By Ronald C. Chen, MD, MPH, FASCO, FASTRO,* and Ananya Choudhury, MA, PhD, MRCP, FRCR†

- Biases <u>against ART</u> can make observation/ESRT appear better
  - Due to timing of ADT on RADICALS/GETUG-17 trials
  - Due to defining BF after completion of RT
- Few high grade/stage patients enrolled → results not generalizable
- Longer term follow up needed

Chen IJROBP 2021

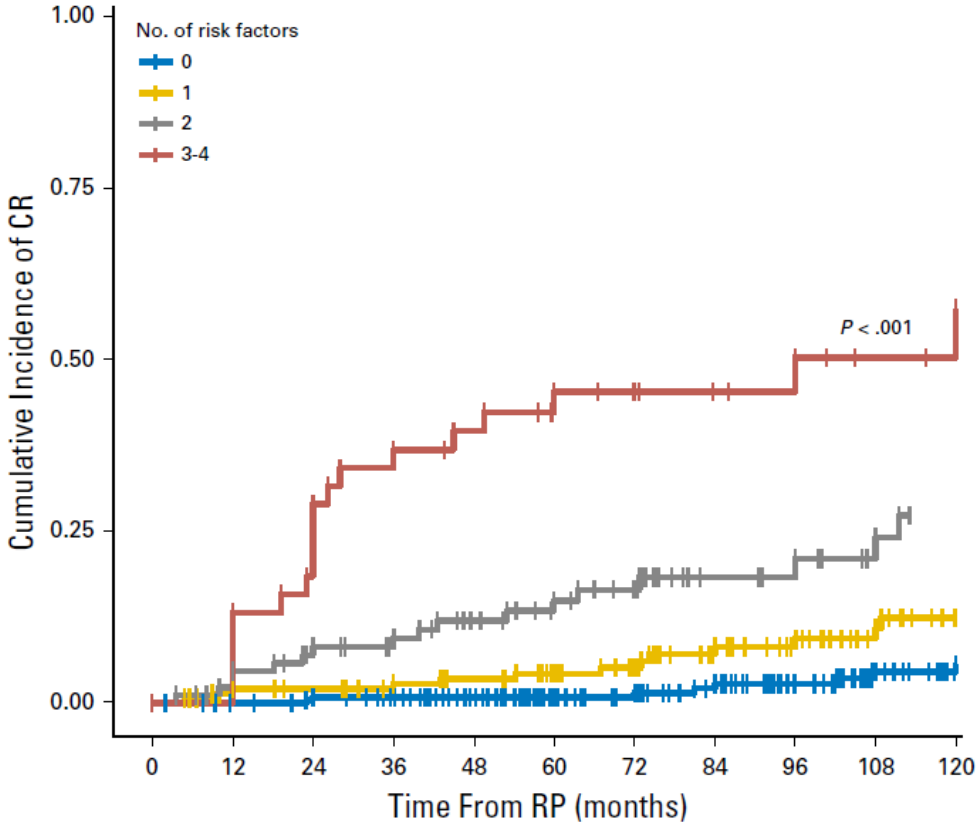
Who Might Benefit from Adjuvant RT?

Genomic classifier (Decipher™) score a/w clinical recurrence

4 Risk Factors:

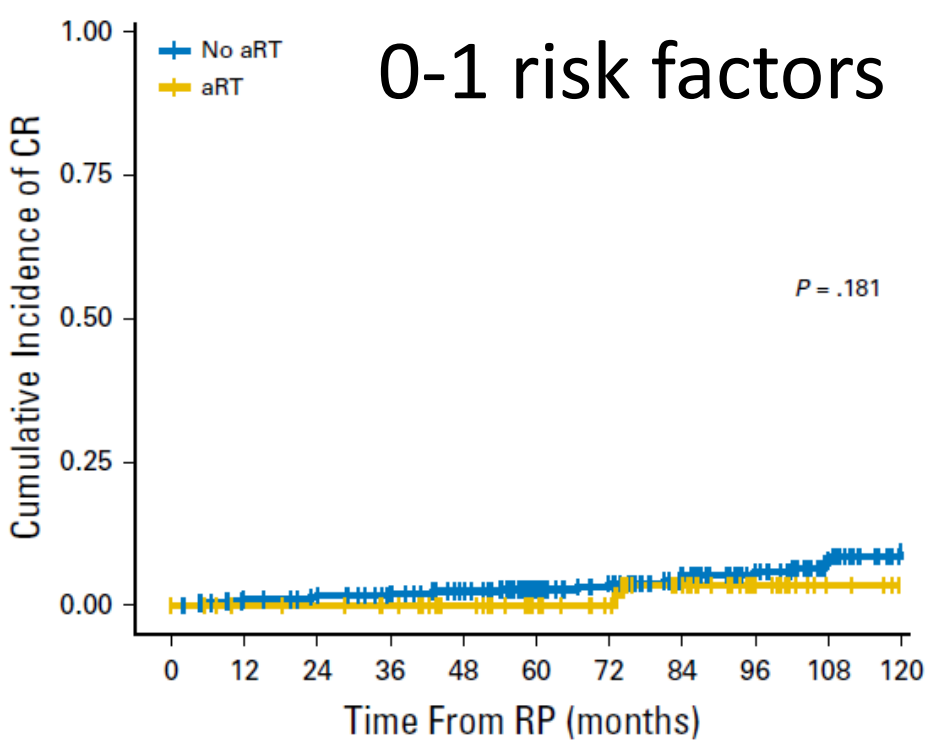
- pT3b/T4
- pGS 8-10
- LN+
- high GC score (>0.6)

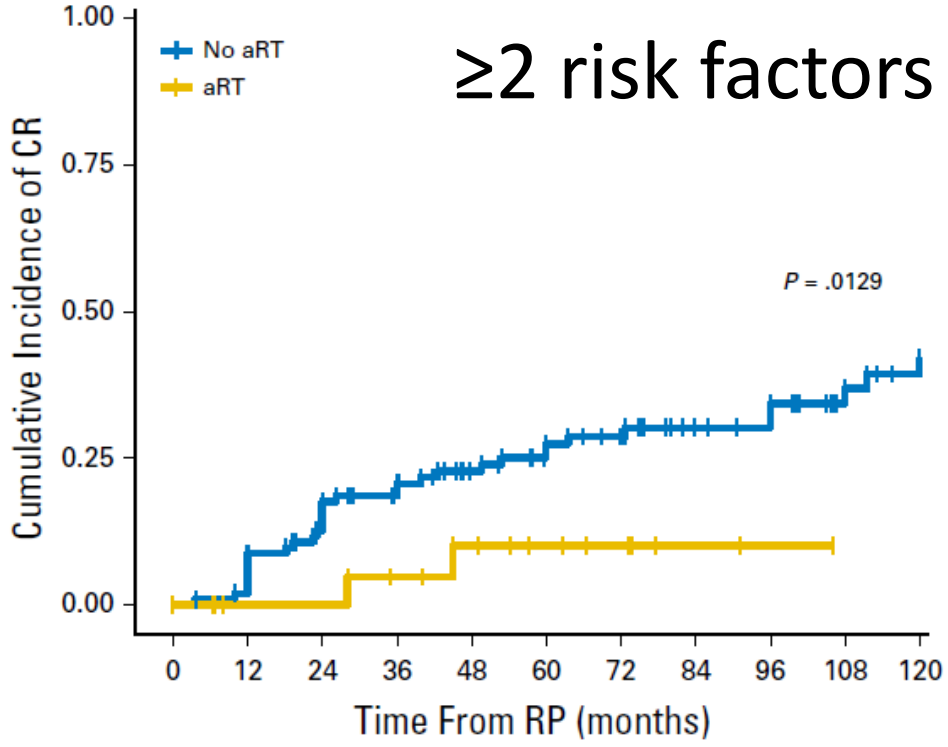
Not prospectively validated



Dalela JCO 2017

Who Might Benefit from Adjuvant RT?

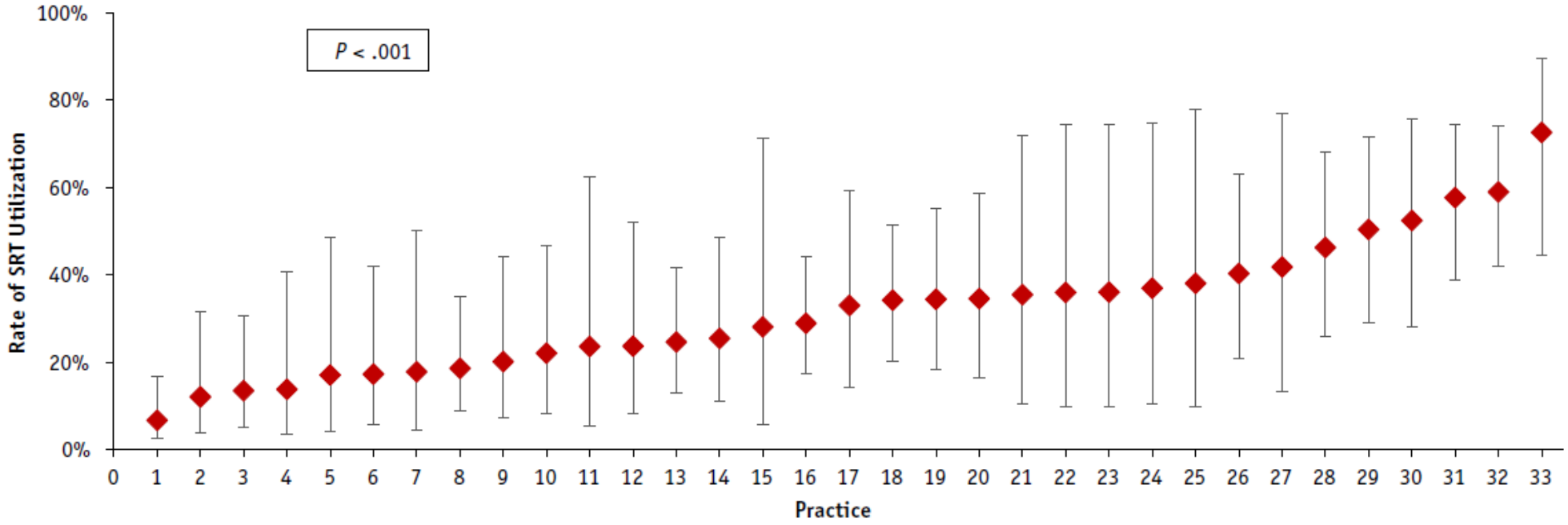




Dalela JCO 2017

Early Salvage RT Remains Underutilized

- MUSIC: Only 26% received ESRT after PSA >0.2 ng/ml



Hawken IJROBP 2019

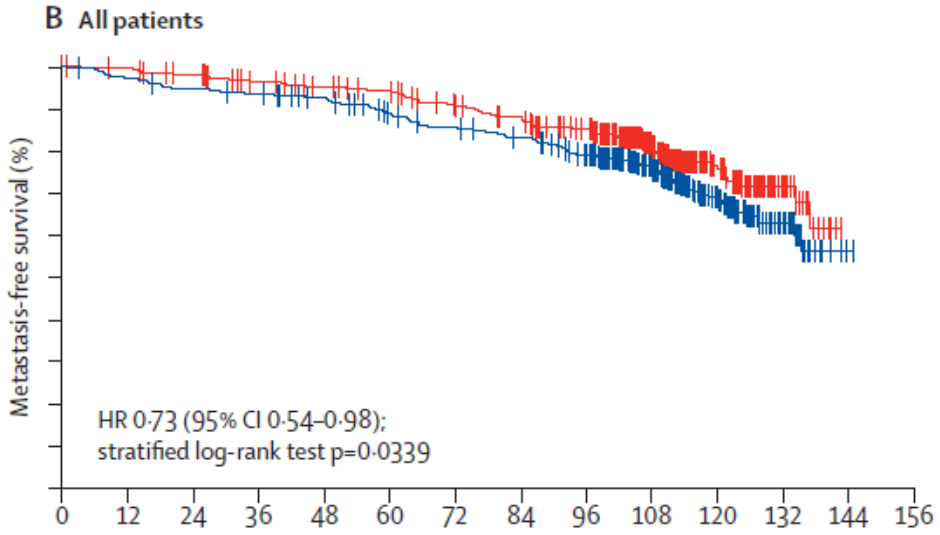
Treatment (De-)Intensification Strategies?

"Lower" Risk	"Intermed" Risk	"Higher" Risk
GG 1-2 Lower PSA Long PSADT Low GC score T2/+ margins	GG 3 Rising PSA Intermed PSADT Intermed GC score SVI	GG 4-5 Higher PSA Short PSADT High GC score LN+
Observe & early SRT (or none)	SRT +/- ST-ADT? Novel AA?	ART? Pelvic RT? LT vs. ST ADT? Novel AA?

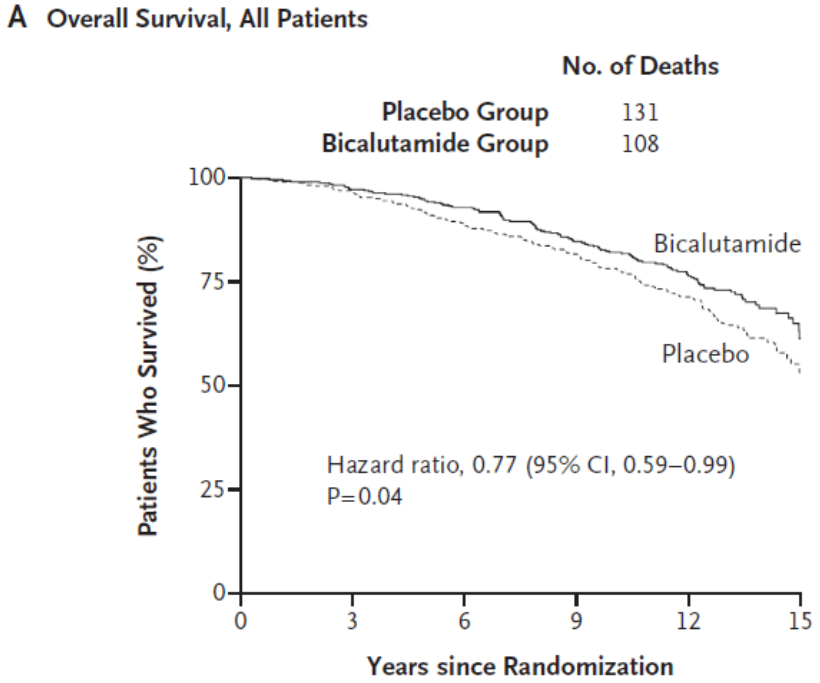
Adding ADT to Salvage RT

- 3 randomized trials of RT +/- ADT reported (2 published)

GETUG AFU-16: ↑ MFS



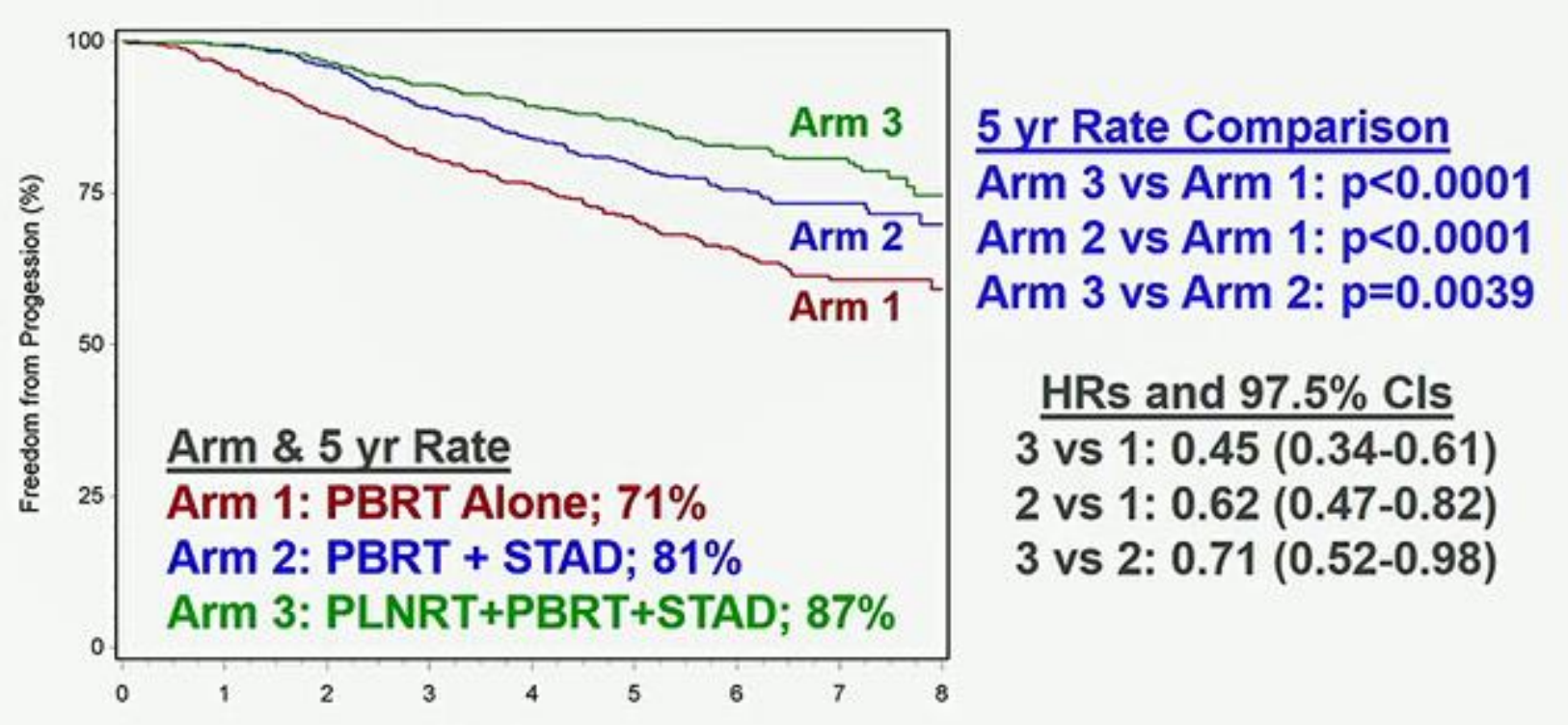
RTOG 9601: ↑ OS



Carrie Lancet Oncol 2019. Shipley NEJM 2017.

Adding Pelvic Nodal RT

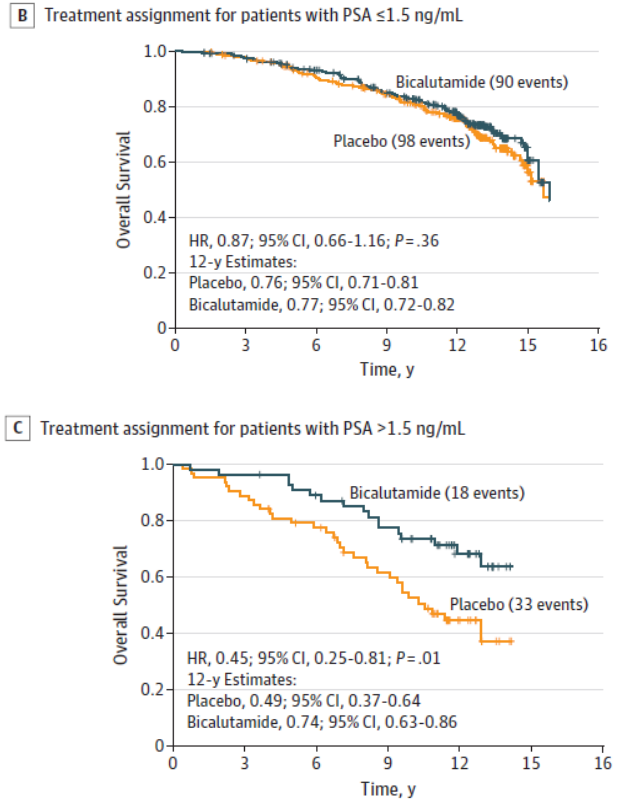
- RTOG 0534 (interim analysis)



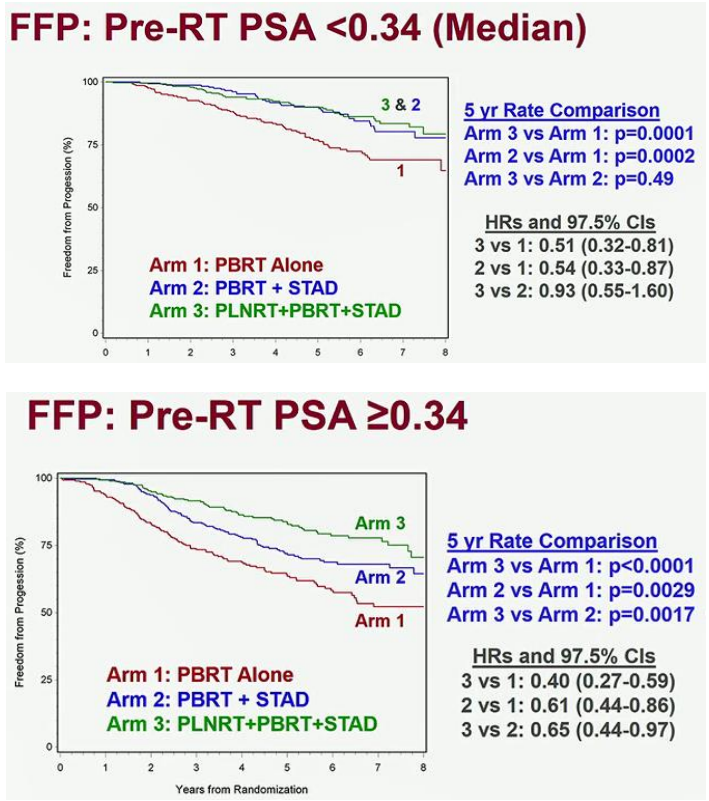
Pollack ASTRO 2018

PSA is Predictive of Treatment Effect

RTOG 9601



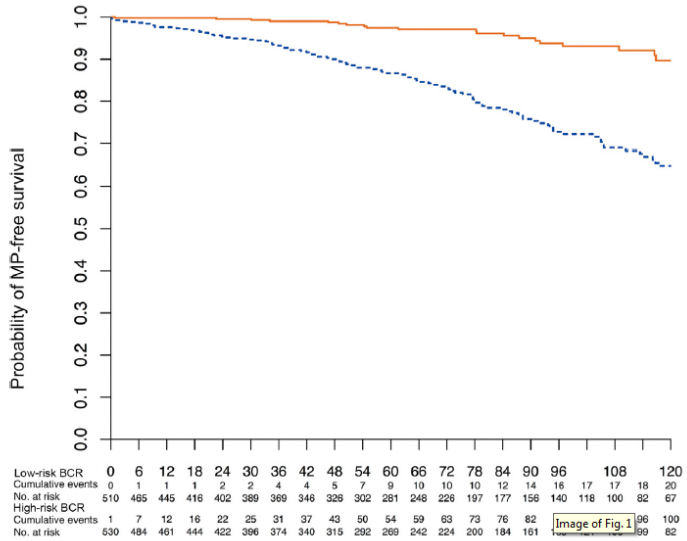
RTOG 0534



Dess JAMA Oncol 2020. Pollack ASTRO 2018.

PSA Doubling Time is Prognostic

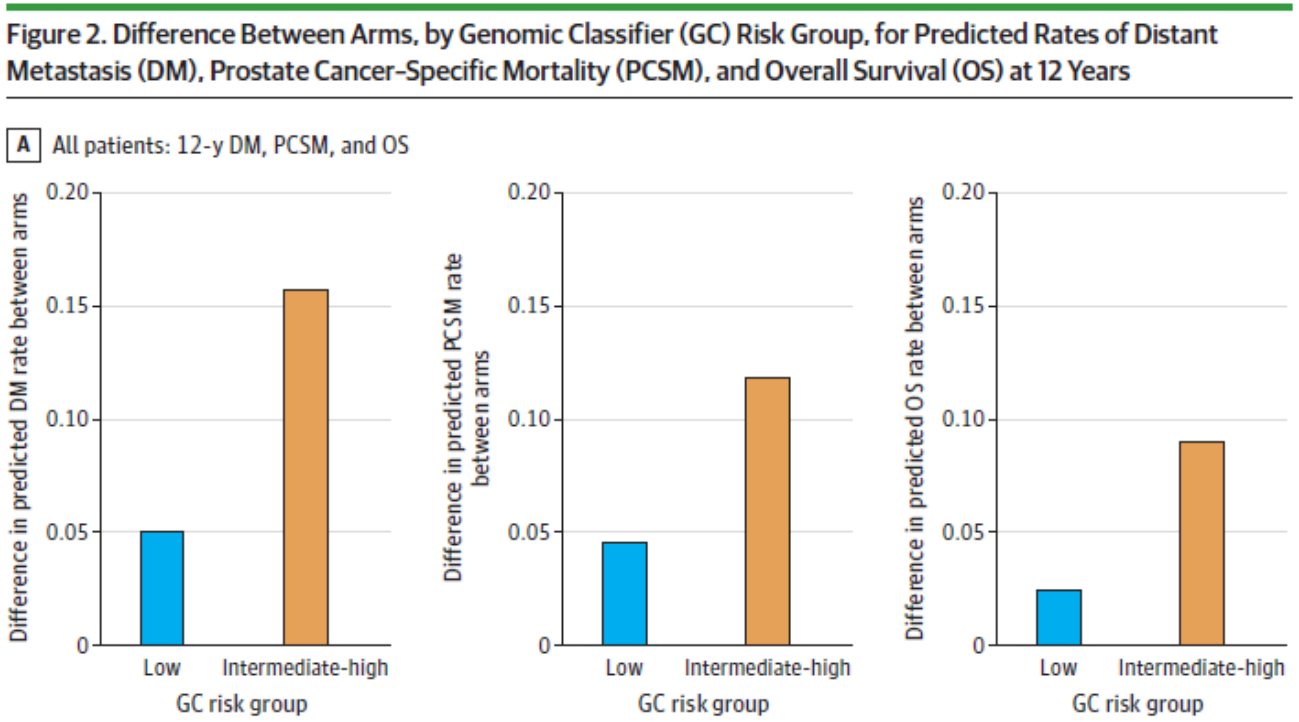
- European Association of Urology (EAU) proposed risk stratification:
  - Low risk: PSA-DT >1 year and pGS <8
  - High risk: PSA-DT ≤1 year or pGS 8–10



Van den Broeck Eur Urol 2018. Tikki Eur Urol 2019.

Incorporating Genomic Classifiers

Subset of RTOG 9601



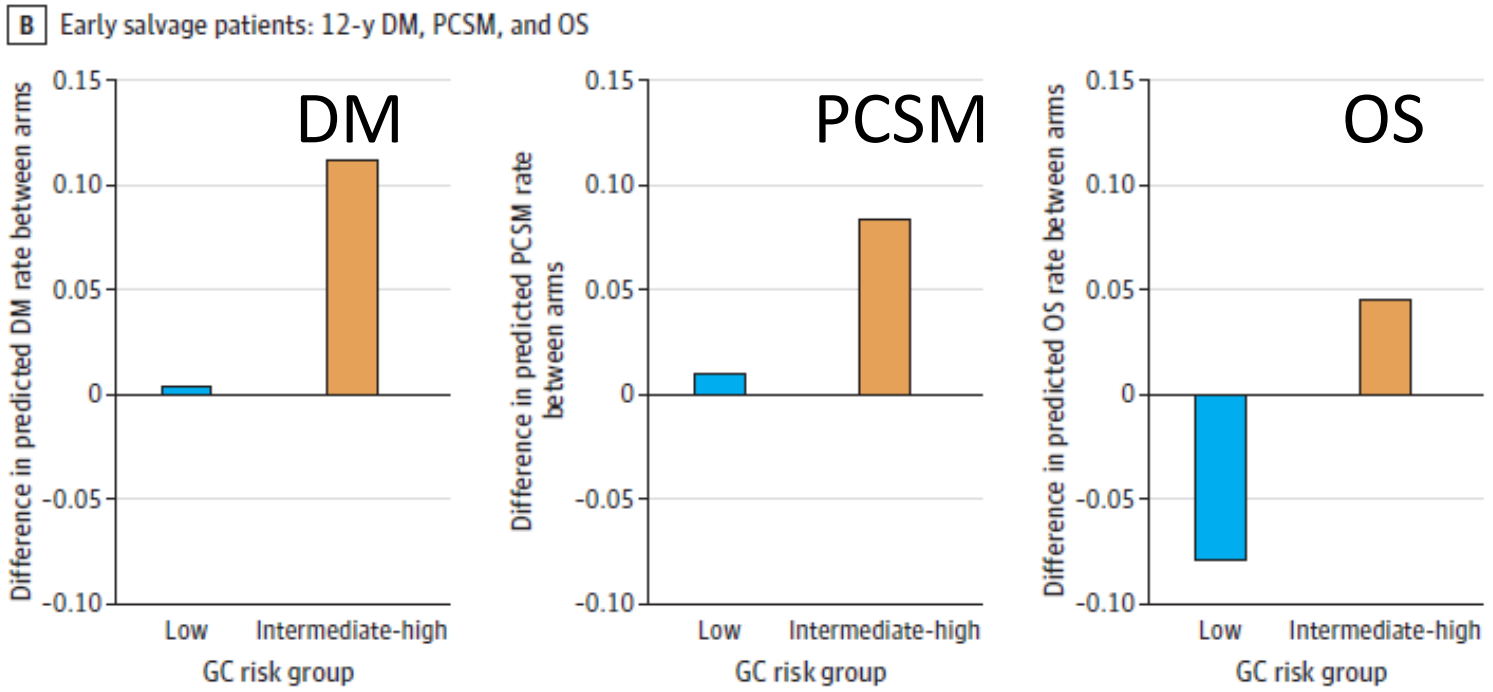
Patients with Intermediate-High GC score had greater benefit from ADT

Feng JAMA Oncol 2021

Incorporating Genomic Classifiers

Subset of RTOG 9601

"Early"
PSA <0.7
subset



Patients with Intermediate-High GC score had greater benefit from ADT

Feng JAMA Oncol 2021

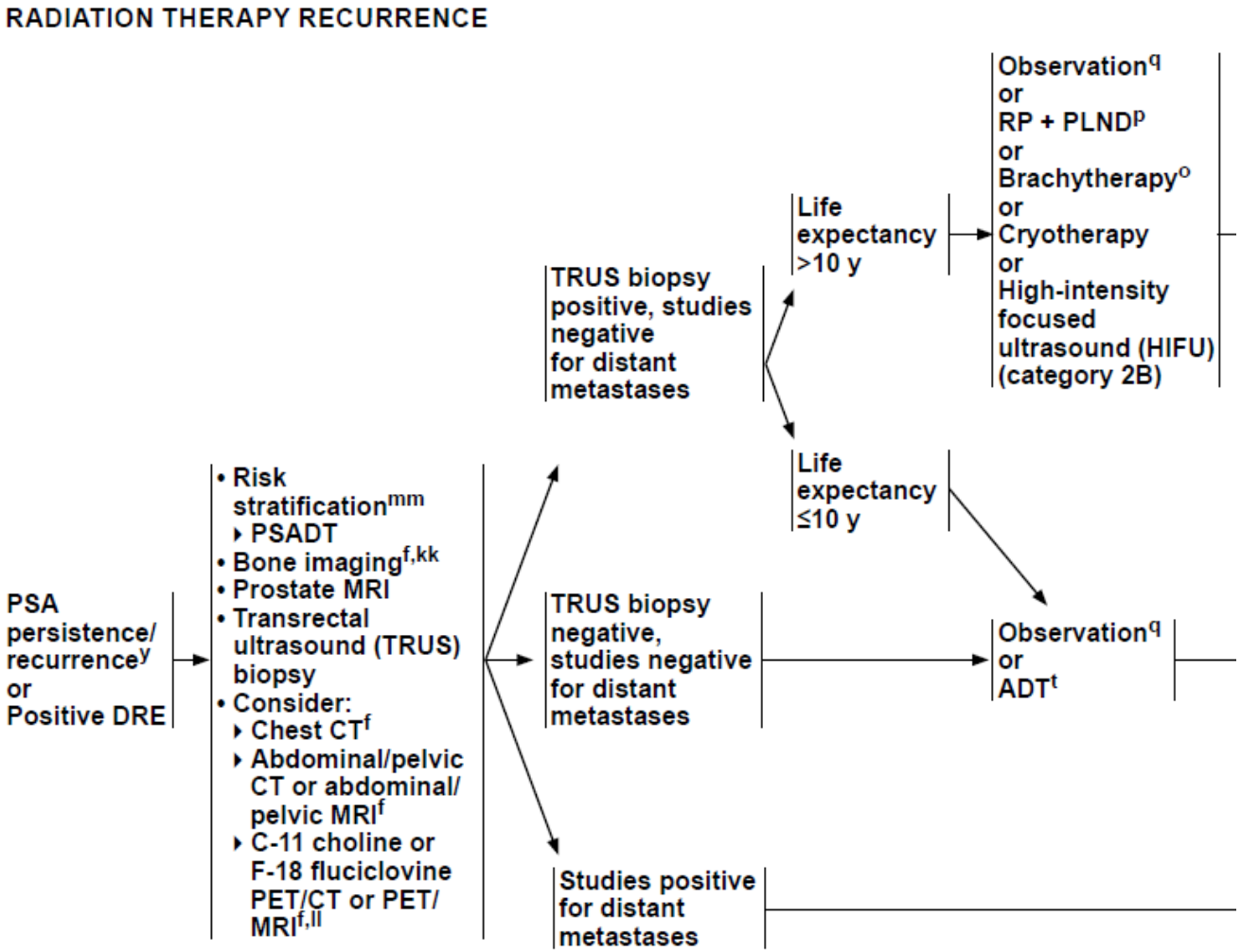
Treatment Intensification of Post-op RT

1. Earlier RT (at lower PSA)?
   - Observation/early salvage appropriate for most
   - Consider adjuvant RT if multiple adverse risk features
2. ADT?
   - Higher post-op PSA (what cut-off?)
   - Adverse biology (high grade/GC score, maybe short PSA-DT?)
3. Pelvic nodal RT?
   - Higher post-op PSA (≥0.34 in RTOG 0534 prelim analysis)
   - Other indications? TBD

How I Treat Post-Prostatectomy in 2021

PSA	General Management
<0.2	GS 6-7 → observe (& ESRT if PSA rises)
	GS 8-10 → *consider* ART only if (multiple) T3b, high GC score >0.6, LN+ (Dalela)
~0.2-0.5	GS 6-7 → ESRT
	GS 8-10 → SRT +/- ADT (based on GC?)
~0.5-2.0	PET- → ADT + pelvic RT (as per RTOG 0534)
	PET+ in pelvis only → same + boost PET-avid
	PET+ outside pelvis → ADT + SBRT to oligomets?

NCCN 2021: LR after EBRT



- For rising PSA, stage with bone scan & CT A/P or PET-CT
- If no mets, then prostate MRI & biopsy
- If biopsy proven LR, consider salvage local therapy if PSA <10 and life expectancy >10 years
- Otherwise consider ADT if short PSA-DT

Salvage Therapy for LR after EBRT: Brachy

- **RTOG 0526**: Ph II trial of salvage LDR, I-125 (n=85) or Pd-103 (n=7)
  - All originally LR/IR, biopsy proven >30 m after EBRT, PSA <10, N0, M0
  - 1^{o} endpoint: GU/GI toxicity
  - Secondary endpoints: OS, DFS, patterns of recurrence, time to BF
- Late Gr 3 GU/GI toxicity 14%
- FFBF 68% at 5 yrs, 54% at 10 yrs
- 10-yr LR 5%, DM 19%
- Conclusion: **local salvage LDR brachytherapy is feasible** and effective

Crook IJROBP 2018. Crook ASTRO 2020.

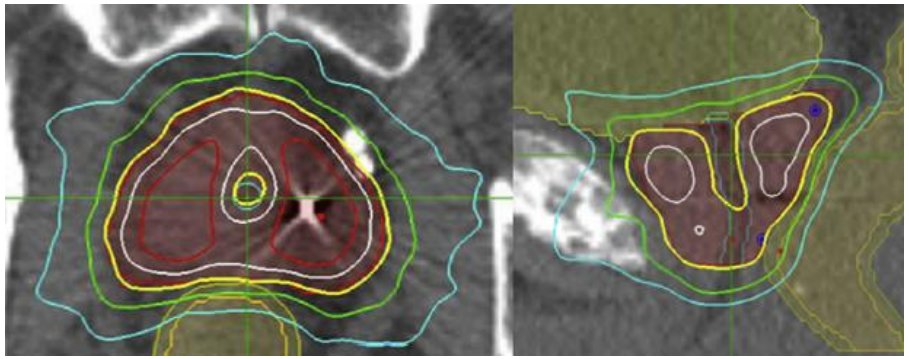
Salvage Therapy for LR after EBRT: SBRT

Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT

Donald Fuller, MD,* James Wurzer, MD,† Reza Shirazi, MD,* Stephen Bridge, MD,‡ Jonathan Law, DABR,† Tami Crabtree, PhD,§ and George Mardirossian, PhD*

Salvage Stereotactic Body Radiation Therapy for Local Prostate Cancer Recurrence After Radiation Therapy: A Retrospective Multicenter Study of the GETUG

David Pasquier, MD, PhD,*,† Geoffrey Martinage, MD,* Guillaume Janoray, MD,‡,§ Damaris Patricia Rojas, MD,‖ Dario Zerini, MD,‖ Flora Goupy, MD,¶ Renaud De Crevoisier, MD, PhD,¶,#,** Emilie Bogart, MSc,†† Gilles Calais, MD, PhD,‡,§ Alain Toledano, MD,‡‡ Laurent Chauveinc, MD, PhD,‡‡ Nathaniel Scher, MD,‡‡ Pierre Yves Bondiau, MD, PhD,§§ Jean Michel Hannoun-Levi, MD, PhD,§§ Marlon Silva, MD,‖‖ Emmanuel Meyer, MD,‖‖ Philippe Nickers, MD, PhD,* Thomas Lacornerie, MSc,¶¶ Barbara Alicja Jereczek-Fossa, MD, PhD,‖ and Eric Lartigau, MD, PhD*,†



Fuller IJROBP 2019. Pasquier IJROBP 2019.

Salvage Therapy for LR after EBRT

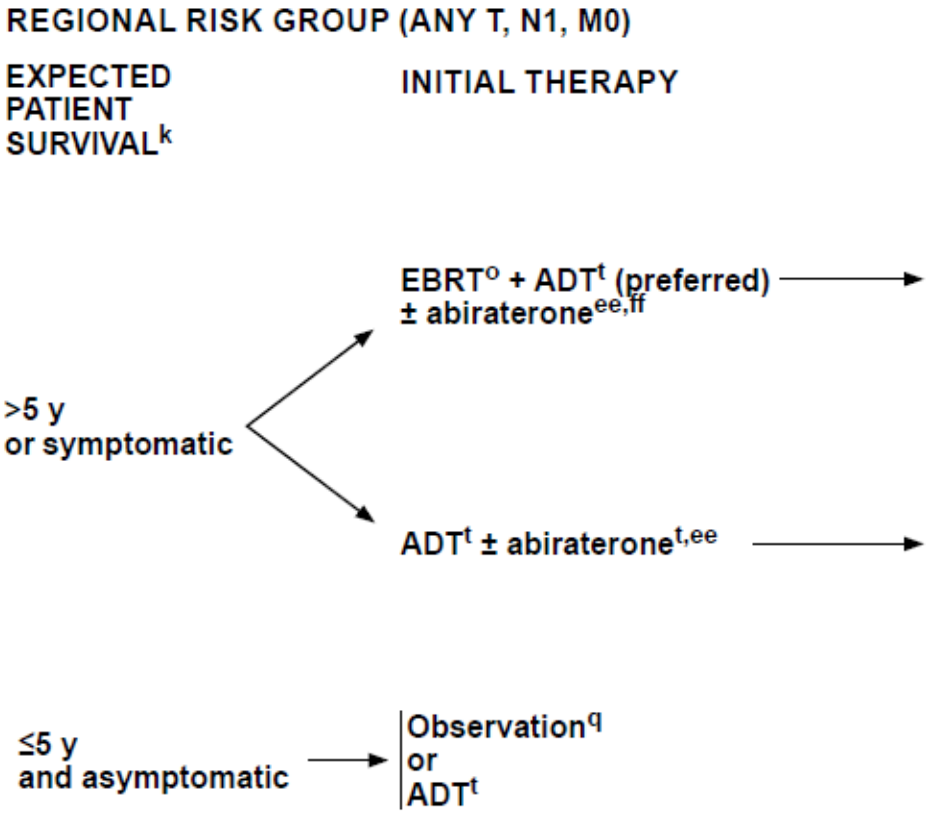
- **MASTER** meta-analysis: very similar efficacy between modalities
  - Less GU tox from SBRT/HDR/LDR than RP; less GI tox from HDR than RP

Modality	5y RFS	GU toxicity	GI toxicity
RP	53%	21%	1.5%
Cryo	57%	15%	0.9%
HIFU	46%	23%	0.8%
SBRT	56%	**5.6%**	0.0%
HDR	58%	**9.6%**	**0.0%**
LDR	53%	**9.1%**	2.1%

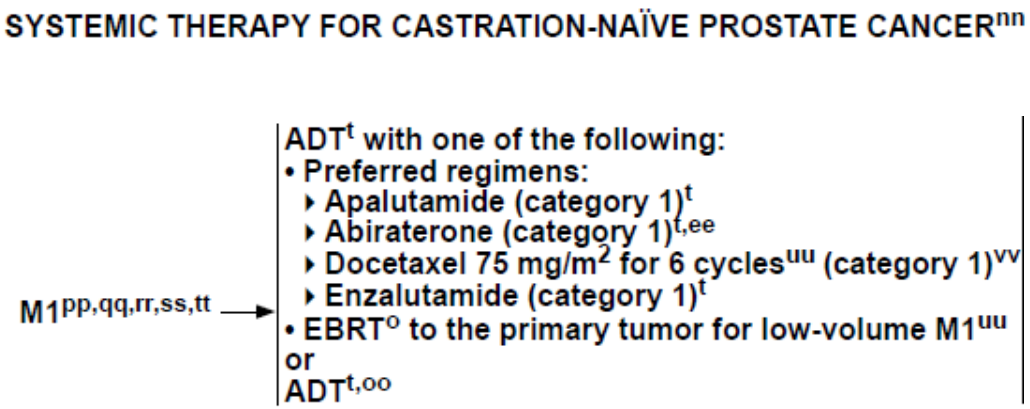
Covariate-adjusted meta-regression % rates shown; p<0.05 in **bold**

Valle Eur Urol 2020

NCCN 2021: N1

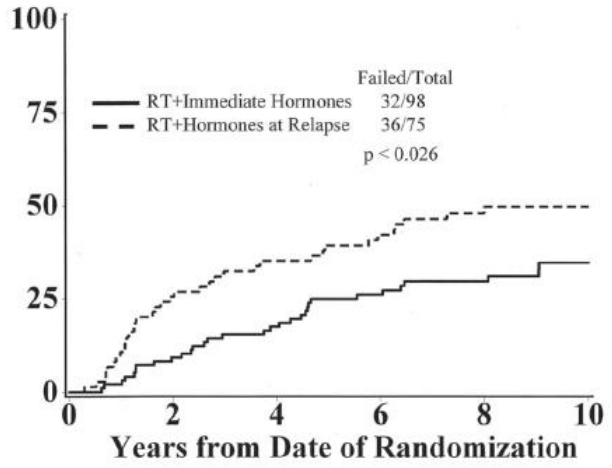


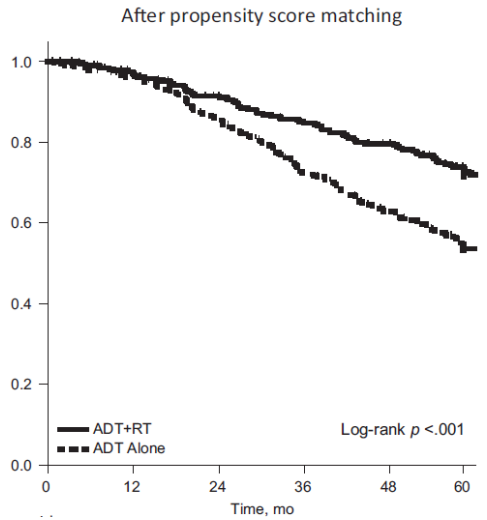
NCCN 2021: M1

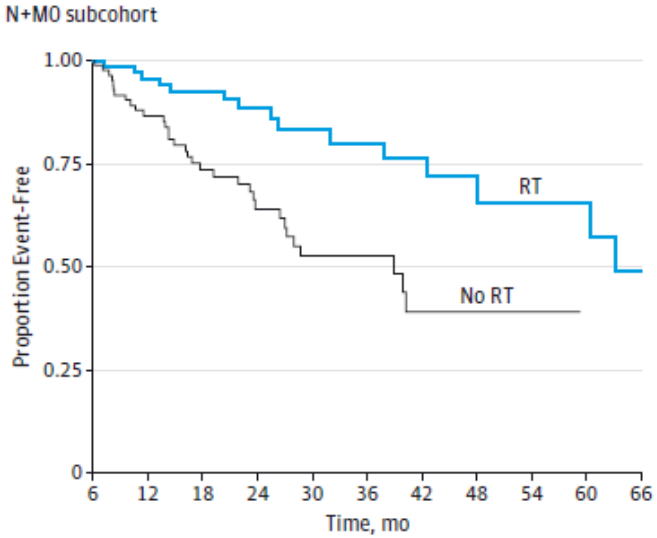


Management of Pelvic LN+

- **cN1 and M0 at diagnosis** → treat with curative intent
  - EBRT + ADT +/- abiraterone







Lawton JCO 2005. Lin JNCI 2015. James JAMA Oncol 2015.

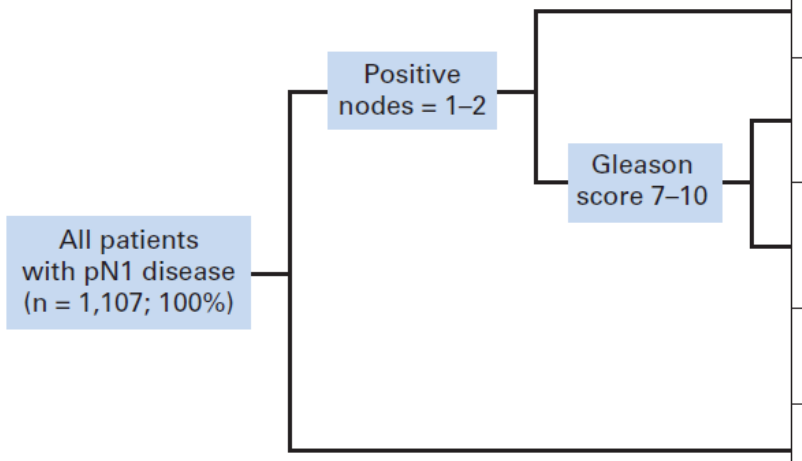
Management of Pelvic LN+

- **Regional nodal oligorecurrence** after prior local therapy (RP or RT)
  - Treatment options
    - Salvage PLND +/- EBRT +/- ADT
    - EBRT + ADT
    - SBRT +/- ADT
    - ADT alone
  - De Bleser: Pelvic nodal RT → ↓ LN recurrence but ↑ toxicity than SBRT
  - Bravi: Salvage node dissection alone insufficient → 10y FFBF only 11%
    - 10y PCSM 34%; improved with adjuvant ADT
    - Implications for MDT with SBRT alone?

De Bleser Eur Urol 2019. Bravi Eur Urol 2020.

Management of Pelvic LN+

- **pN1 after prostatectomy**
- Indications for postop pelvic RT + ADT:
  - 1-2 LN+, GS 7-10, pT3b/pT4, or M+
  - 3-4 LN+



Eight-Year CSM-Free Survival (95% CI)

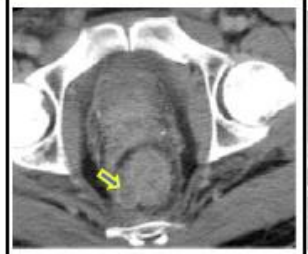
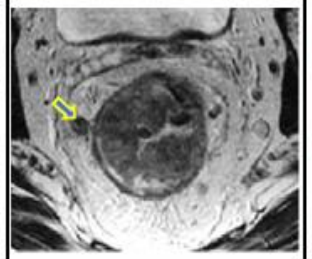
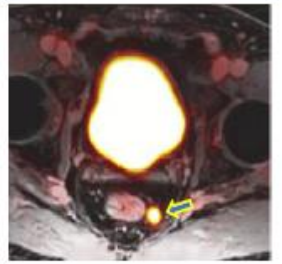
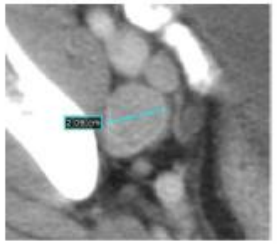
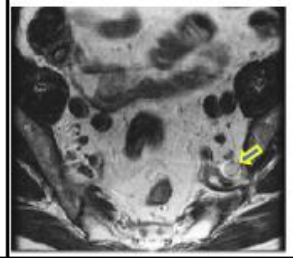
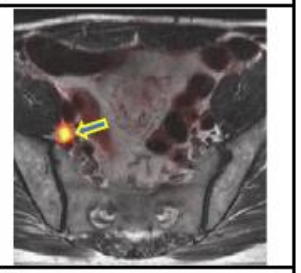
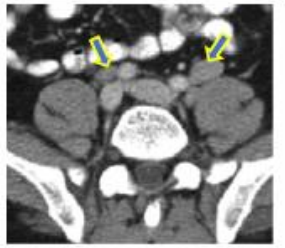
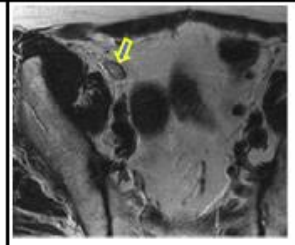
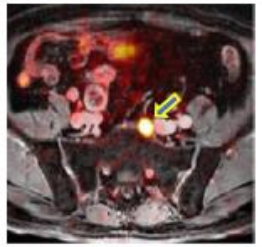
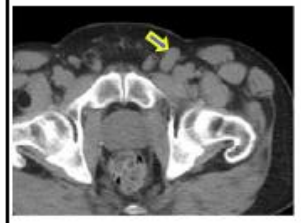
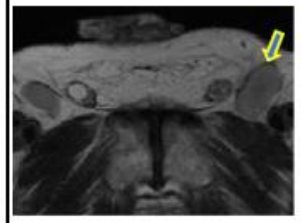
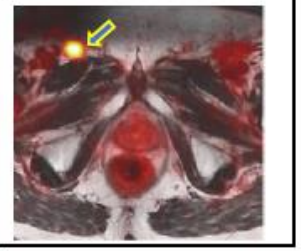
	Entire Cohort	aHT Alone	aRT + aHT	*P*
Gleason score 2–6 (n = 133; 12%)	98.6 (95.8 to 100)	98.4 (95.4 to 100)	100 (100 to 100)	.7
pT2/pT3a and negative SM (n = 131; 11.8%)	96.6 (93.4 to 99.9)	96.8 (93.2 to 100)	96.3 (89.4 to 100)	.4
pT3b/pT4 or positive SM (n = 552; 49.9%)	86.7 (83.0 to 90.6)	84.2 (79.7 to 89.0)	93.1 (87.5 to 99.1)	.03
Positive nodes = 3–4 (n = 160; 14.5%)	85.3 (78.9 to 92.1)	78.8 (69.7 to 89.0)	96.5 (91.8 to 100)	.02
Positive nodes > 4 (n = 131; 11.8%)	72.2 (62.7 to 83.1)	72.0 (60.9 to 85.2)	74.7 (59.2 to 94.3)	.9

Abdollah JCO 2014

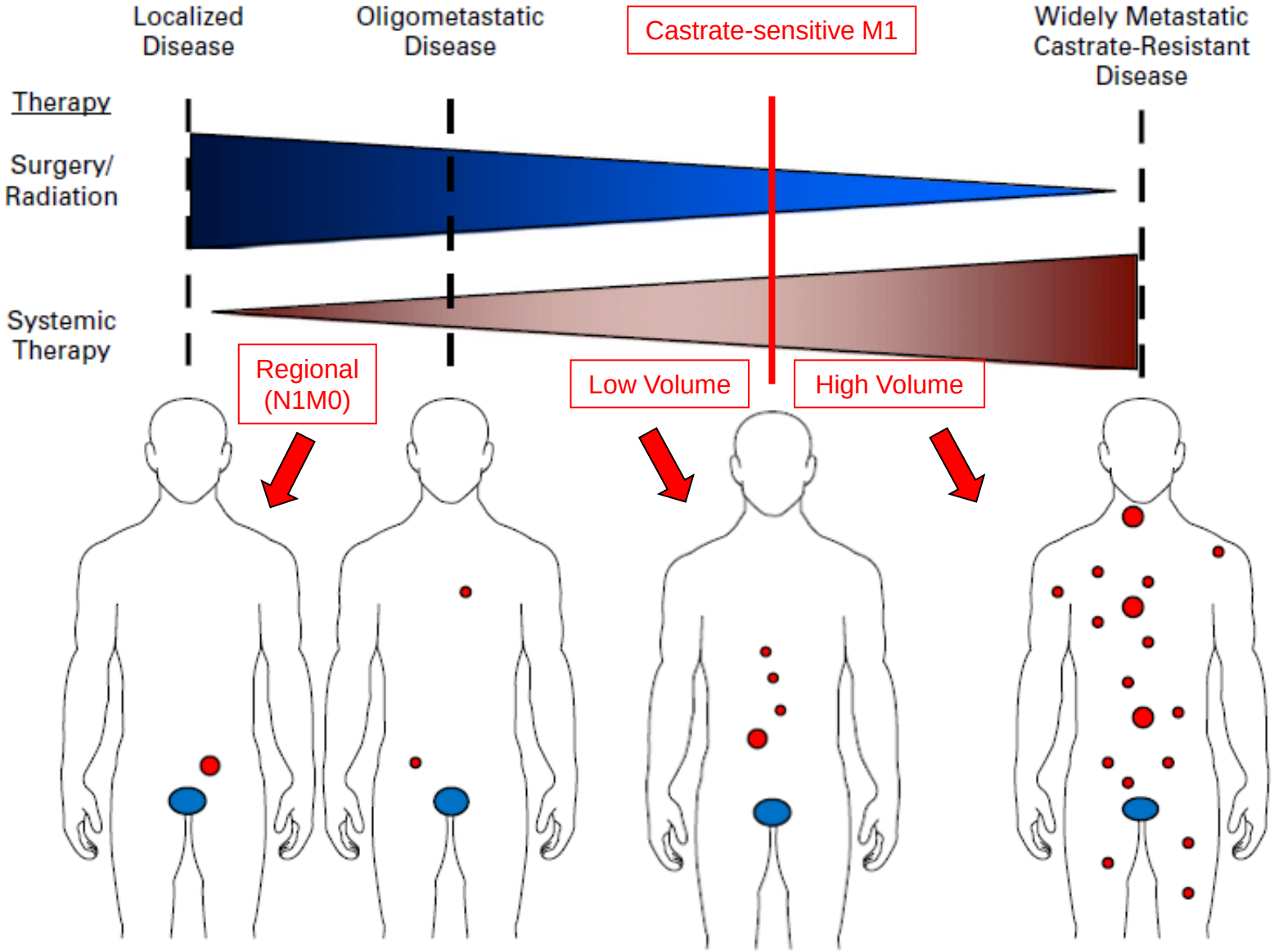
General Guidelines for cN+

- See 2021 NRG Atlas, Table 1 (next slide)
- Prophylactic nodal volumes should extend ~5-7 mm around clinically suspicious LNs → dose 45-50.4 Gy
- Boost residual nodes post-ADT to dose for primary disease (if possible, respecting normal tissues)
- My practice for LN+: SIB 70 Gy/28 to prostate, prox SV & +LN (if far from bowel), with 50.4 Gy ENI + 2-3 years ADT +/- abiraterone
  - If +LN is close to bowel, aim for 60+ Gy

Hall IJROBP 2021

Anatomic Location	CT/MRI-based Size	CT/MRI-based Morphology	PSMA PET-based Criteria	Fluciclovine PET-based Criteria	Example of positive node on CT	Example of positive node on MR	Example of positive node on PET
Mesorectal, Presacral	Short axis > 4 mm	Irregular Border and/or heterogenous morphology (only for LN > 3mm on MRI)	Uptake greater than blood pool	> 1 cm: Uptake greater than BM < 1 cm: Uptake greater than blood pool			
Internal Iliac, Obturator	Short axis > 7mm	Irregular Border and/or heterogenous morphology	Uptake greater than blood pool	> 1 cm: Uptake greater than BM < 1 cm: Uptake greater than blood pool			
Common Iliac and External Iliac	Short axis > 8 mm	Irregular Border and/or heterogenous morphology	Uptake greater than blood pool	> 1 cm: Uptake greater than BM < 1 cm: Uptake greater than blood pool			
Inguinal	Short axis > 8 mm	Irregular Border and/or heterogenous morphology	Asymmetric uptake that is greater than liver	Asymmetric uptake greater than BM			

Metastatic Prostate Cancer



Tran JOP 2017

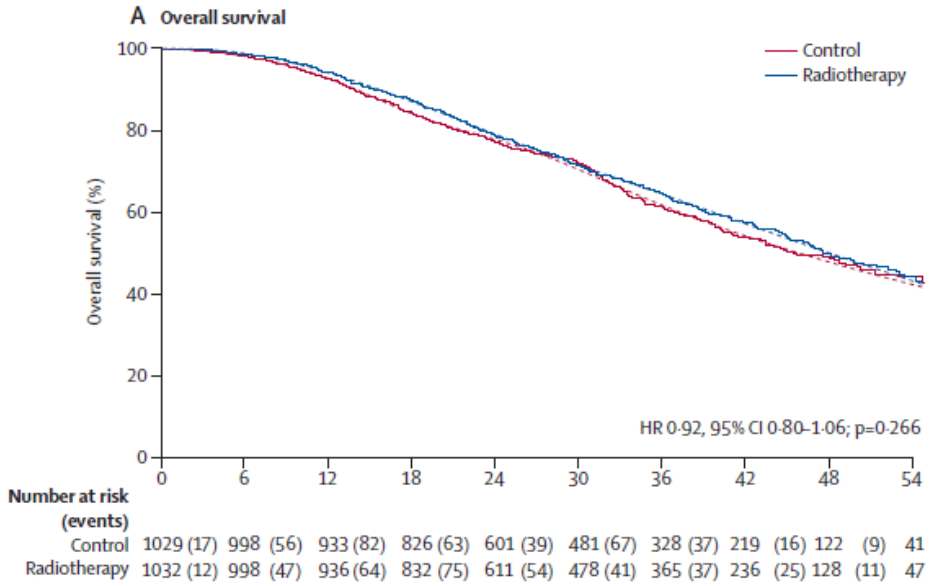
Treatment of mCSPC

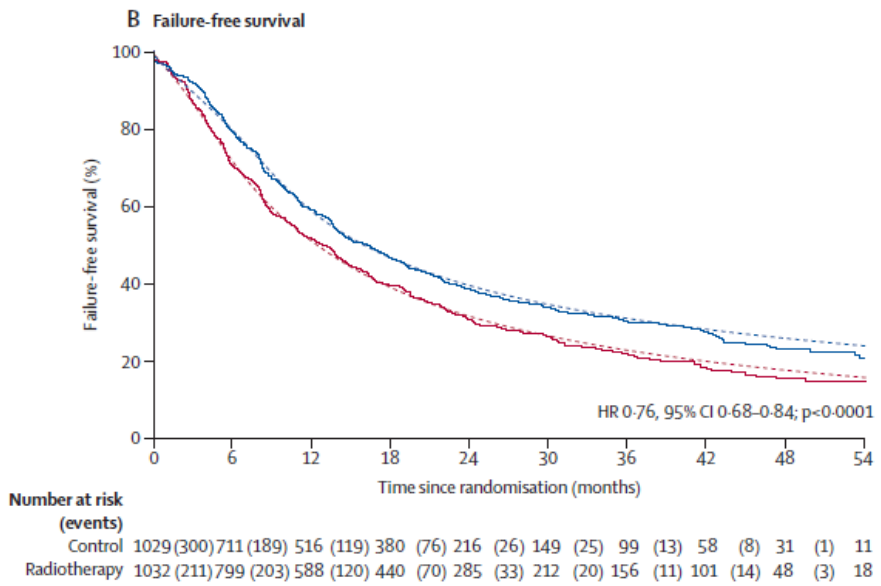
- ADT alone = SOC for decades
- Now, many options for *de novo* mCSPC

ADT + ??	Trial	Outcome
Docetaxel	CHAARTED, STAMPEDE	↑ OS
Abiraterone	LATITUDE, STAMPEDE	↑ OS
Enzalutamide	ENZAMET, ARCHES	↑ OS
Apalutamide	TITAN	↑ OS
Prostate RT	STAMPEDE, HORRAD	↑ OS (low vol)

STAMPEDE: RT for mCSPC

- Overall cohort: no OS benefit to prostate RT, but FFS benefit
- Toxicity <u>same</u> between prostate RT vs. none (both arms: 4% late tox)

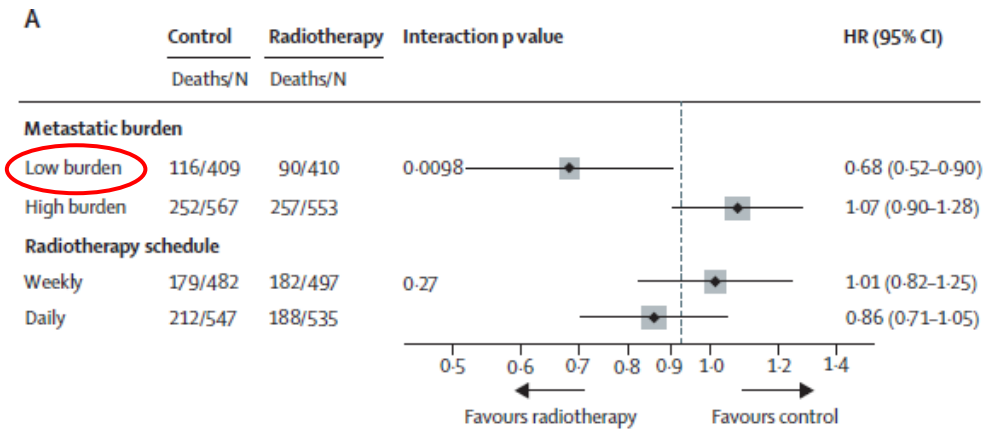




Parker Lancet 2018

STAMPEDE: RT for mCSPC

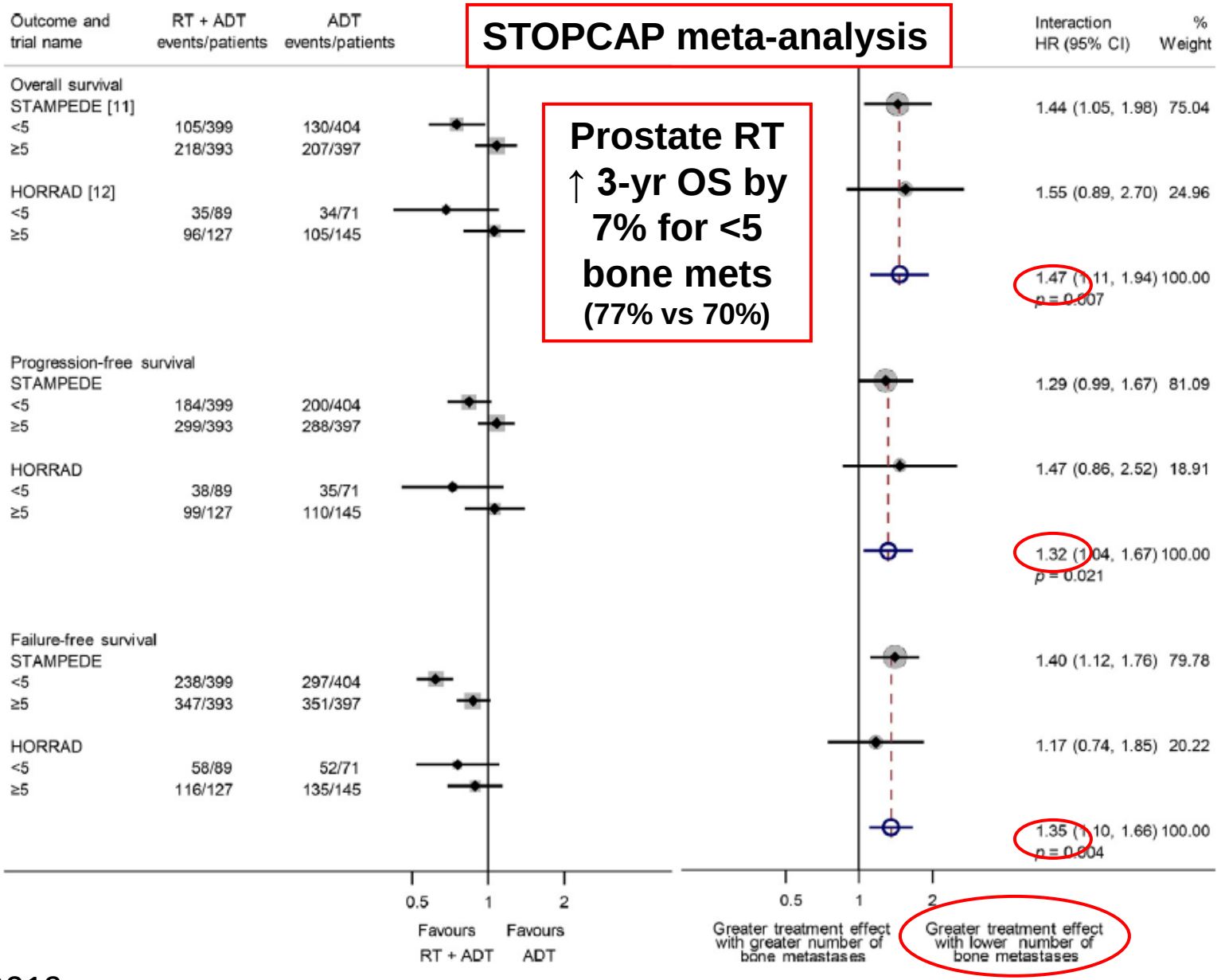
- Pre-specified subgroup of **LMB had ↑ OS from prostate RT** (HR 0.68) over ADT alone



	Adjusted hazard ratio (95% CI)	Survival at 3 years*	
		Control	Radiotherapy
Overall survival			
All patients	0·92 (0·80–1·06)	62%	65%
Low metastatic burden	0·68 (0·52–0·90)	73%	81%
High metastatic burden	1·07 (0·90–1·28)	54%	53%
Failure-free survival			
All patients	0·76 (0·68–0·84)	23%	32%
Low metastatic burden	0·59 (0·49–0·72)	33%	50%
High metastatic burden	0·88 (0·77–1·01)	17%	18%
Progression-free survival			
All patients	0·96 (0·85–1·08)	44%	44%
Low metastatic burden	0·78 (0·63–0·98)	58%	63%
High metastatic burden	1·09 (0·94–1·26)	35%	30%

(HMB = ≥4 bone mets with ≥1 outside vertebral bodies or pelvis, or visceral mets, or both – based on conventional imaging BS/CT/MRI)

Parker Lancet 2018

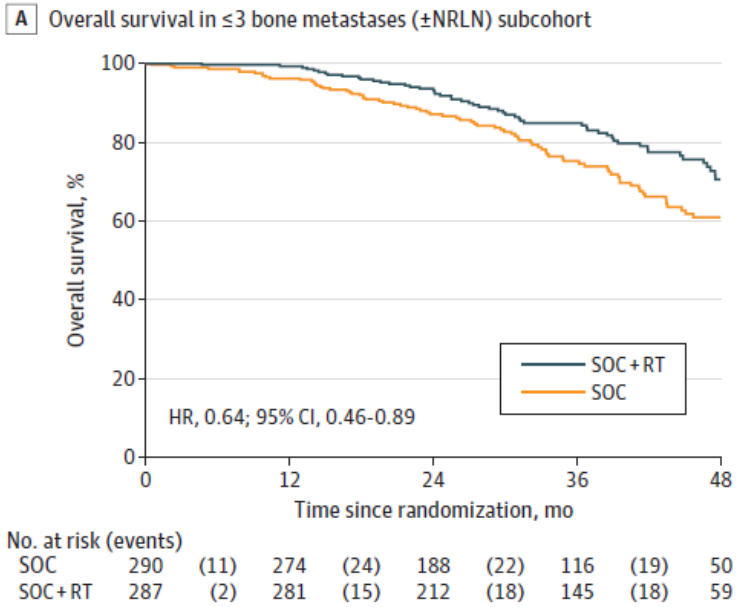


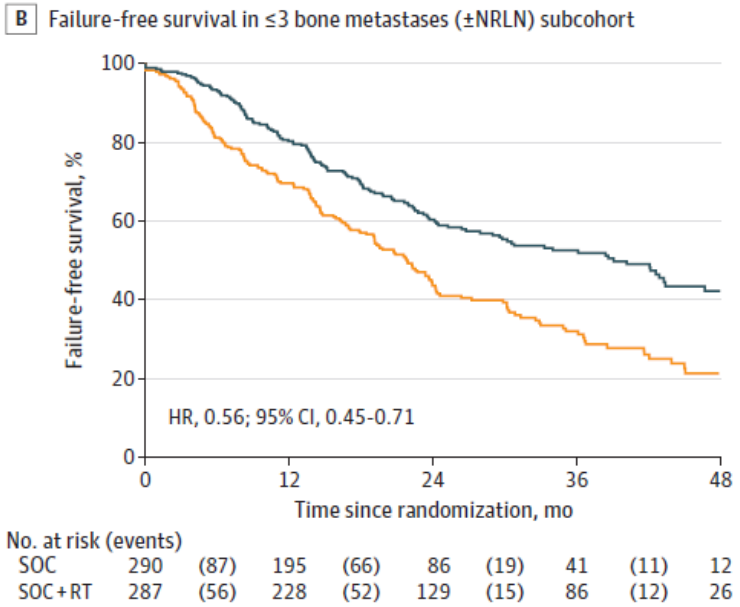
Burdett Eur Urol 2019

STAMPEDE: RT for mCSPC (secondary analysis)

- OS & FFS benefit to prostate RT for **1-3 bone mets**

Figure 3. Kaplan-Meier Curves for Overall and Failure-Free Survival by Treatment in 1587 Patients With Bone Metastases



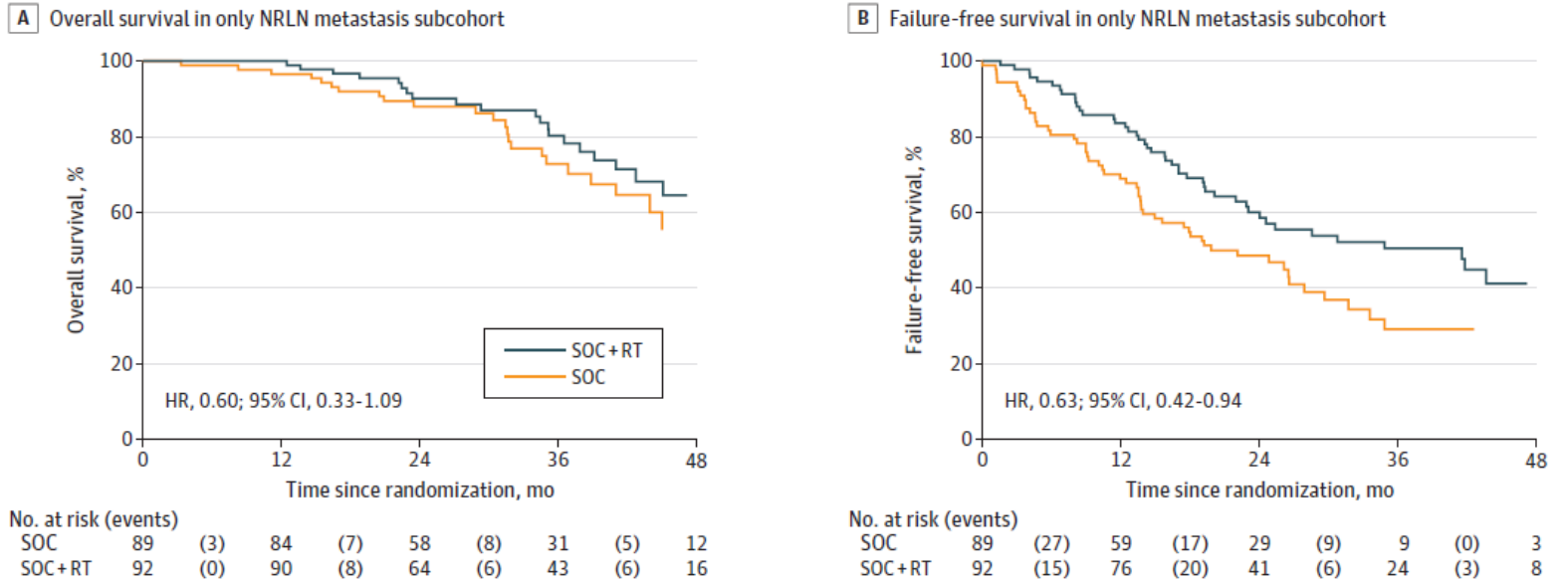


Ali JAMA Oncol 2021

STAMPEDE: RT for mCSPC (secondary analysis)

- FFS benefit to prostate RT for **NRLN mets** without visceral mets

Figure 4. Kaplan-Meier Curves for Overall Survival (OS) and Failure-Free Survival (FFS) by Treatment in Patients With Only Nonregional Lymph Node (NRLN) Metastasis (M1a) and Any Visceral or Other Metastasis



Ali JAMA Oncol 2021

Role of Prostate RT with ADT + Abi?

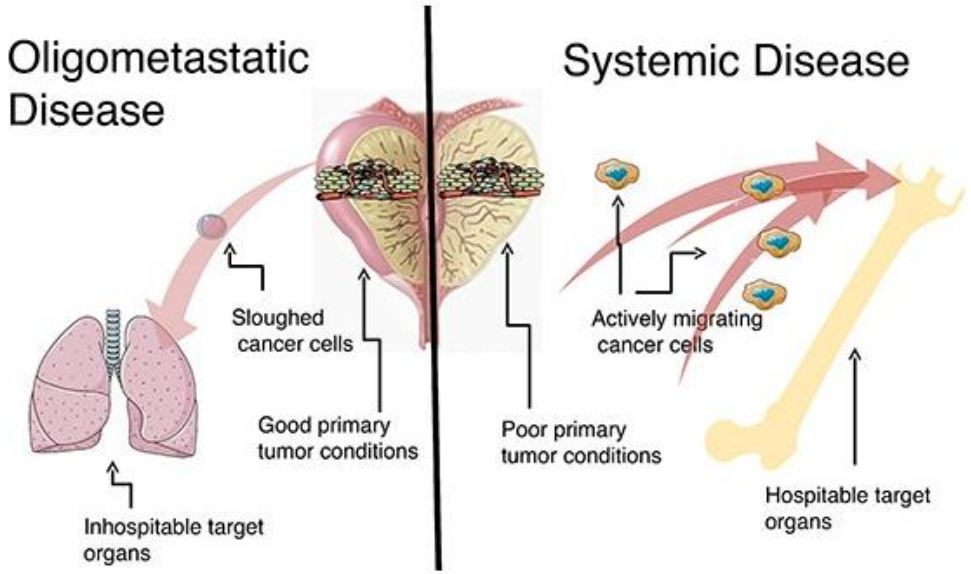
PEACE-1 trial (closed): 4 arms (N=1173)

- Arm A: ADT + Docetaxel
- Arm B: arm A + Abiraterone
- Arm C: arm A + Prostate RT
- Arm D: arm A + Prostate RT + Abiraterone

- RT: 74 Gy/37 fractions to prostate

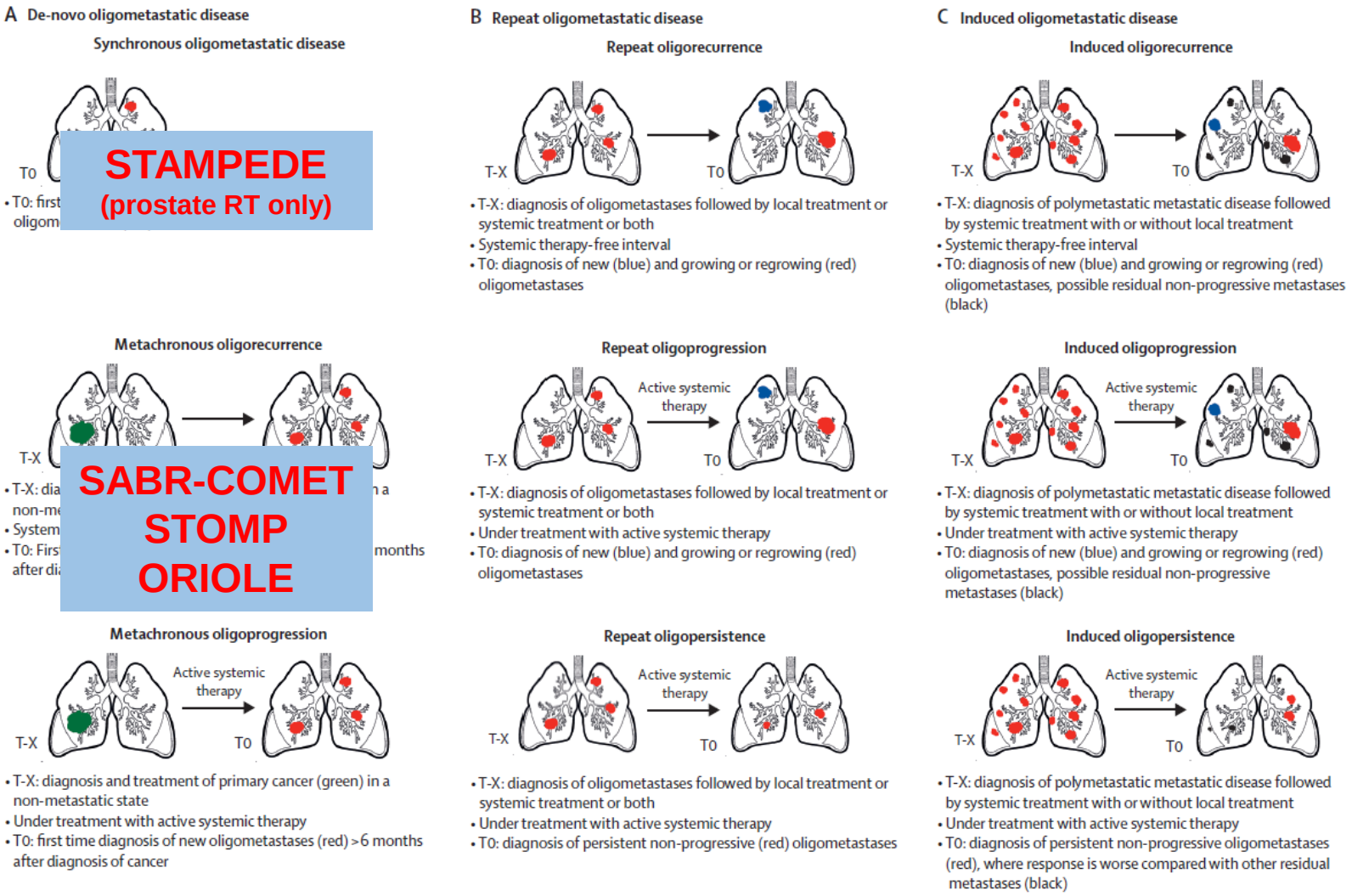
How about metastasis-directed therapy (MDT)?

- STAMPEDE → RT to primary site ↑ OS for low volume mCSPC
- No trials of SBRT to synchronous oligomets <u>yet</u>



Reyes Oncotarget 2015

ESTRO 2020: Dynamic Oligometastatic State Model

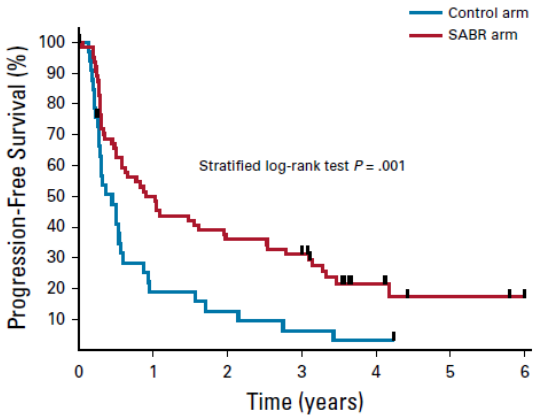


Guckenberger Lancet Oncol 2020

MDT for Oligorecurrence

- Metachronous oligorecurrence = after primary therapy
  - SABR-COMET (n=16 prostate): SABR ↑ PFS
  - STOMP (n=62): MDT ↑ ADT-free survival
  - ORIOLE (n=54): SABR ↑ PFS & ↓ DM

→ No concurrent ADT



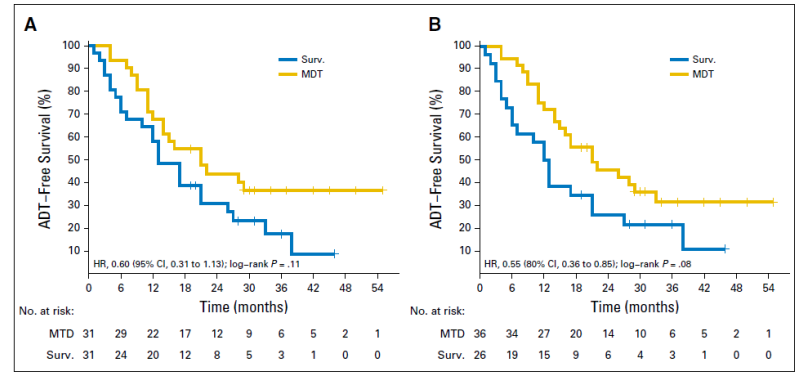
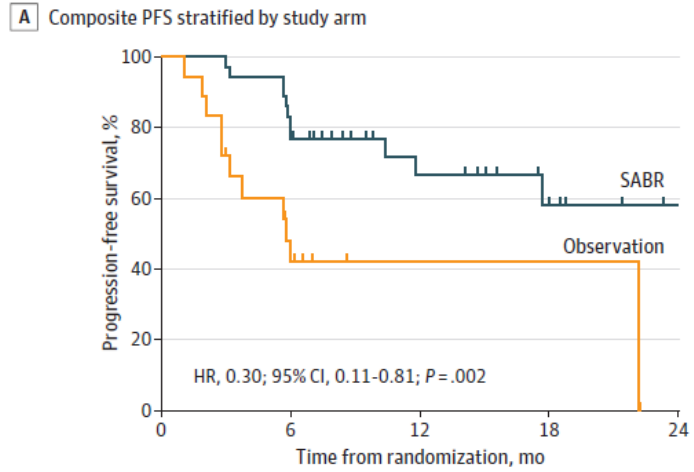


Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)–free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.

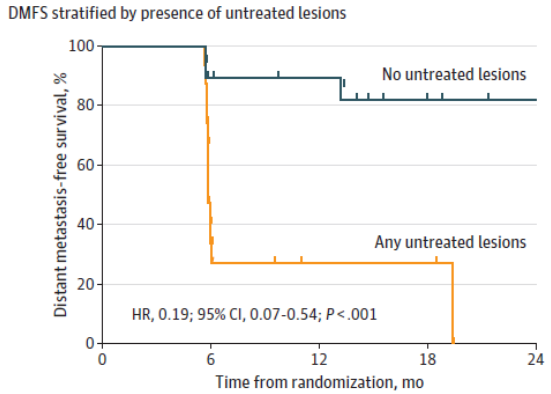


Palma JCO 2020. Ost JCO 2018. Phillips JAMA Oncol 2020.

ORIOLE trial

- **Total consolidation of all PET-avid lesions ↑ PFS and ↓ DM**, with no grade 3+ toxicities

	New metastases at 6 months	95% CI	P-value
Total consolidation (n = 19)	16%	4.9 - 38.6%	0.006
Subtotal consolidation (n = 16)	63%	38.5 – 81.5%	



- **SBRT may alter the natural history of oligorecurrent prostate cancer**

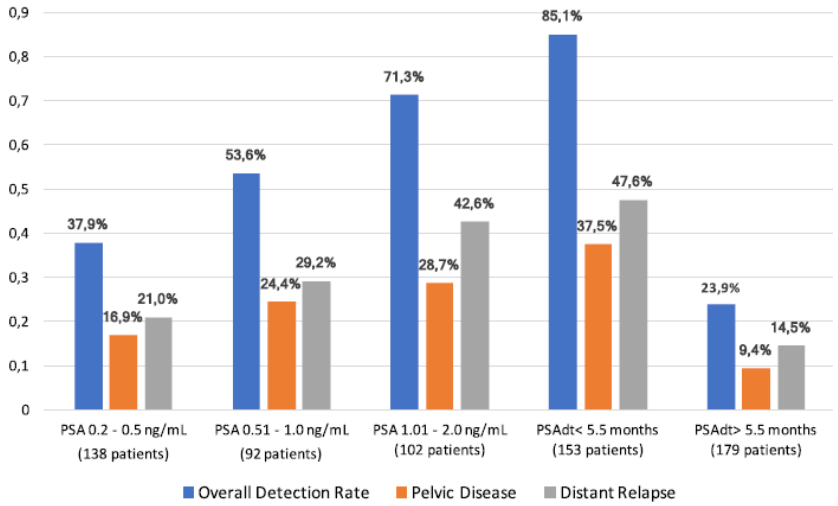
  ?? benefit with concurrent systemic therapy

  … or, can we delay/avoid/limit ADT ??

Phillips JAMA Oncol 2020

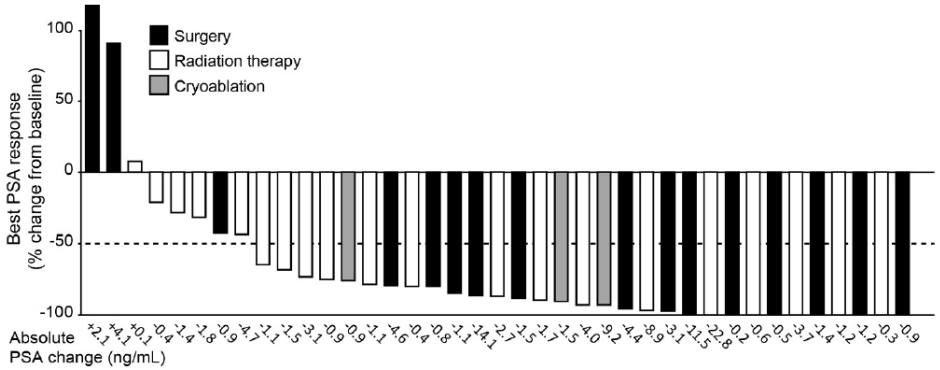
PSMA-PET will change everything

- Oligomets (1-3) in 46%
  - Local only in 25%
  - Widespread 29%



- After MDT, PSA ↓ in 92% (undetectable in 26%)

Best PSA response of individual patients (n=39) is shown as percent change from baseline (bars) and given as absolute change in ng/mL. Patients were stratified by treatment.



Ceci EJNMMI 2019. Fendler JAMA Oncol 2019.

NCCN 2021: Genetic Testing

- Germline genetic testing is recommended for patients with prostate cancer and any of the following:
  - High-risk, very-high-risk, regional, or metastatic prostate cancer
  - Ashkenazi Jewish ancestry
  - Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation)
  - A positive family history of cancer:
    - A strong family history of prostate cancer consists of: brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at <60 years of age or who died from prostate cancer
      OR
    - ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer
- Limited data suggest that prostate cancers with cribriform (ductal or intraductal) histology have increased genomic instability.
- Family history for known germline variants and genetic testing for germline variants should include *MLH1, MSH2, MSH6*, and *PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1, BRCA2, ATM, PALB2*, and *CHEK2*.

Congratulations – We Made It!

- Bladder cancer
- Seminoma
- Renal cell carcinoma
- Prostate cancer
  - Early stage (low & intermediate risk)
  - High risk/locally advanced
  - Salvage therapy after RP or RT
  - LN+
  - Metastatic