Associazione Italiana Radioterapia e Oncologia clinica

CODRAL Collegio Direttori Radioterapie Lombarde

aifm

RADIOTERAPIA OGGI E DOMANI, 20 ANNI DELLA U.O.C. DI RADIOTERAPIA DELL'OSPEDALE MANZONI – LECCO

Stato dell'arte, problematiche attuali e prospettive future nel trattamento di: Neoplasie della prostata

S. Arcangeli

SC Radioterapia, ASST Monza

Ospedale San Gerardo

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

DAILY MENU

Prostate Cancer

- 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[i]	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[i]	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[i]	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[i]	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

Early Stage PCa

- **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

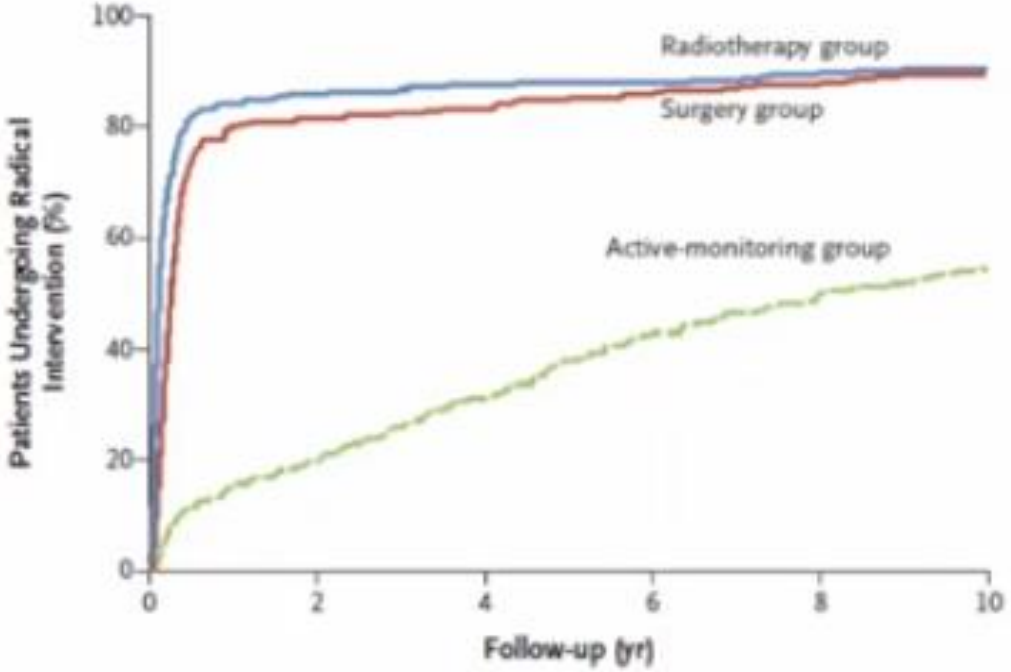
- Rationale: overtreatment may adversely affect QOL without improving OS
- **AS "preferred" by NCCN** for:
  - **Very low risk** & life expectancy >20 years
  - **Low risk** & life expectancy ≥10 years
- Consider mpMRI and/or genomic testing to rule out higher grade
- Current AS schedule
  - PSA q ≥6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

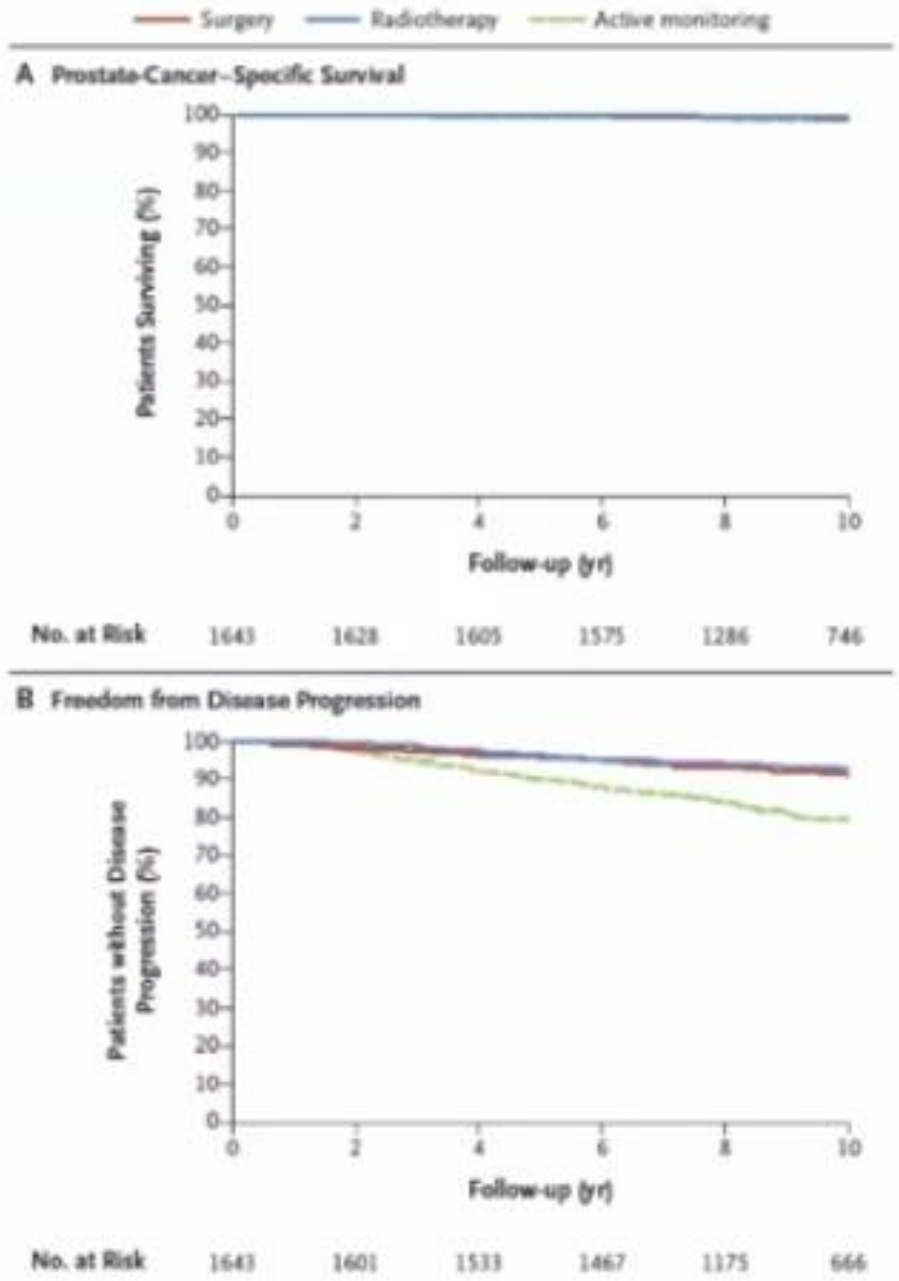
Many treatment options…but few RCTs

- **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
- **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

ProtecT

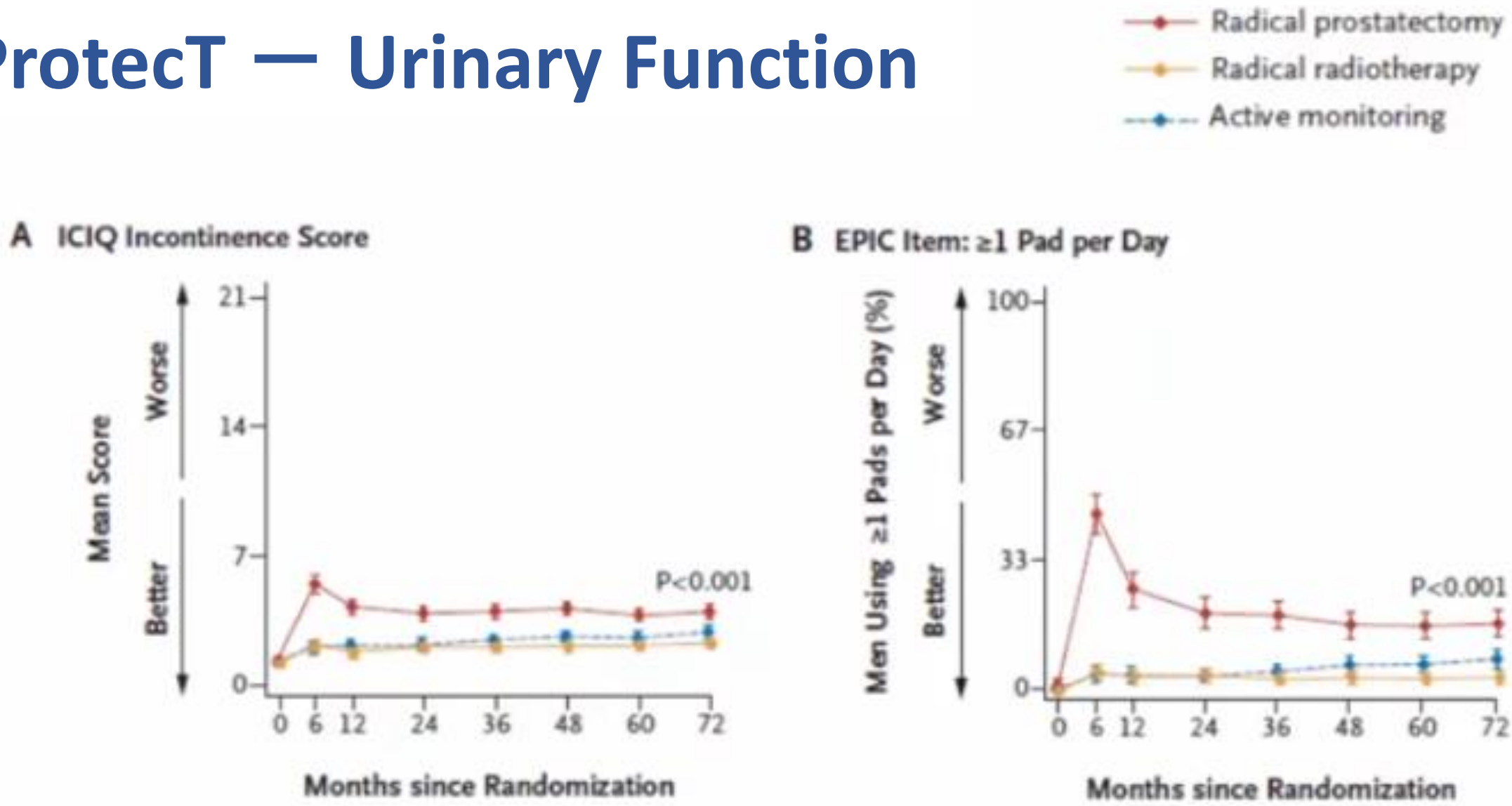
- 77% GS 6
- PCSM ~1% @ 10y
- AM: ~50% treated by 10y & 2x DM rate





Hamdy NEJM 2016

ProtecT — Urinary Function

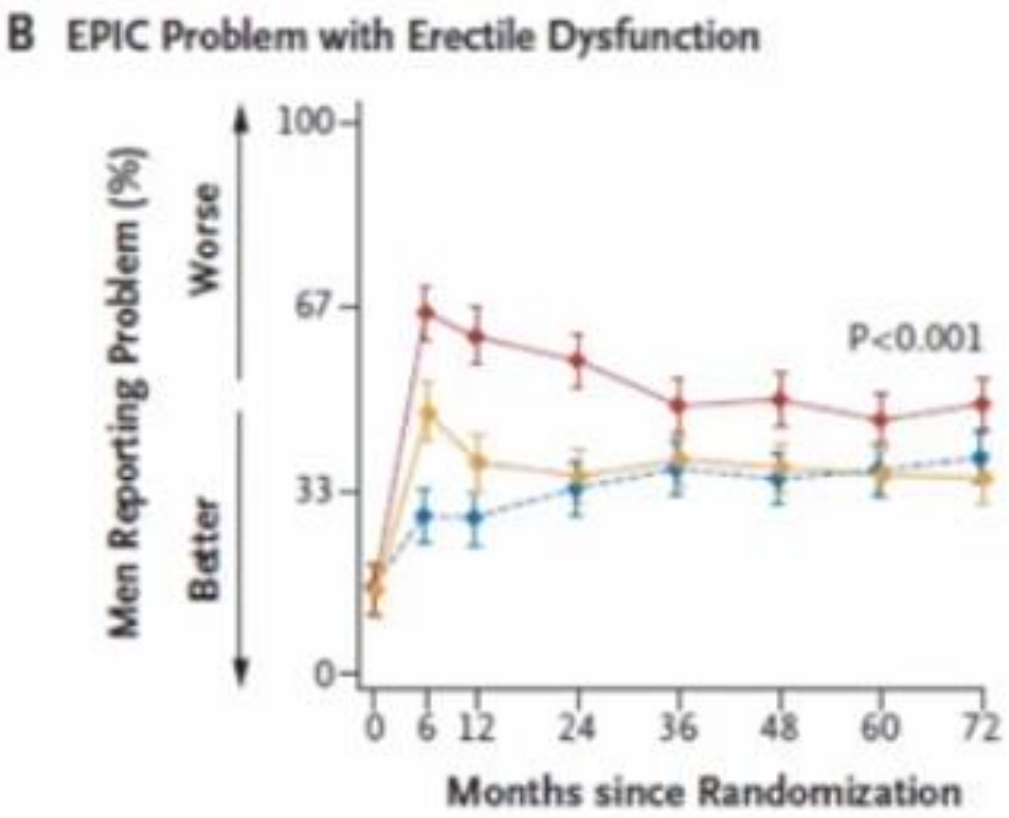


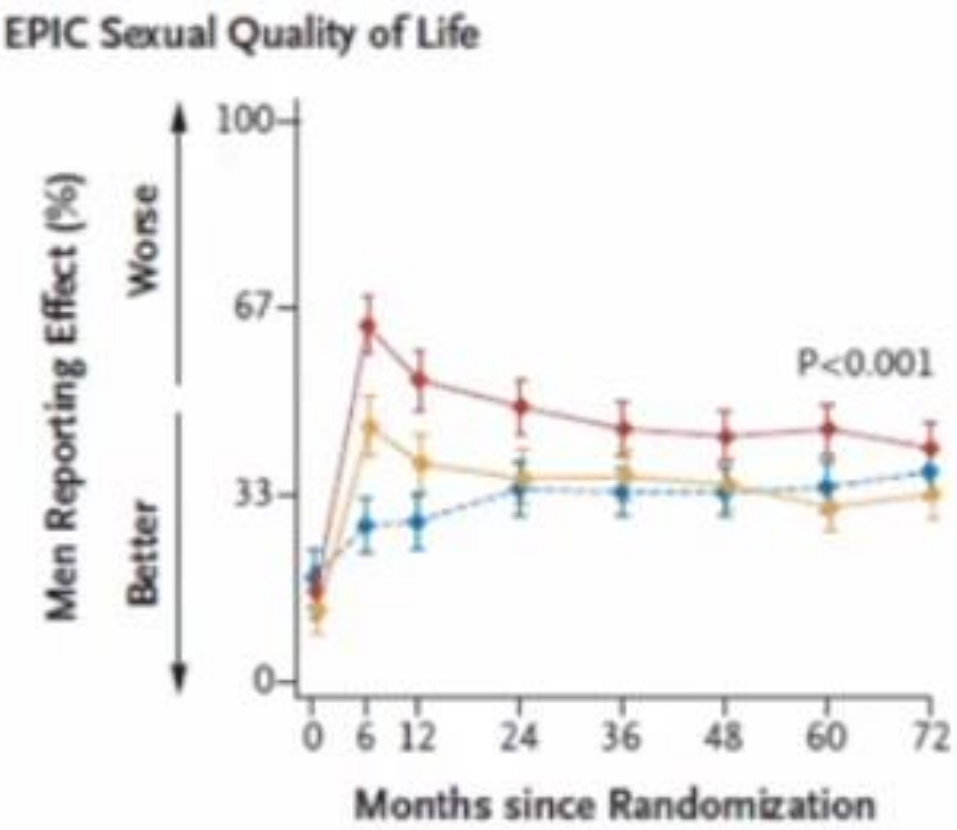
Donovan NEJM 2016

ProtecT — Sexual Function

Radical prostatectomy
Radical radiotherapy
Active monitoring

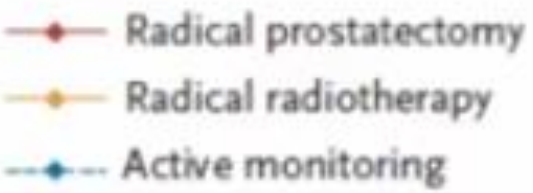
*All 3D-CRT received 3-6m ADT

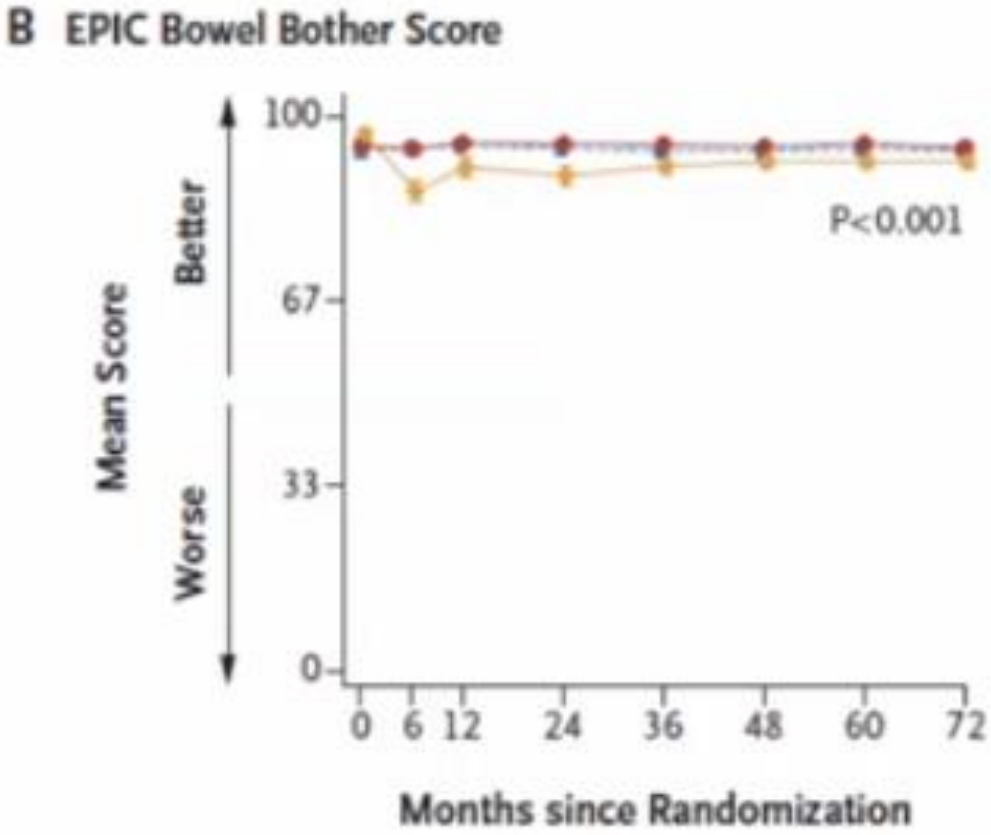


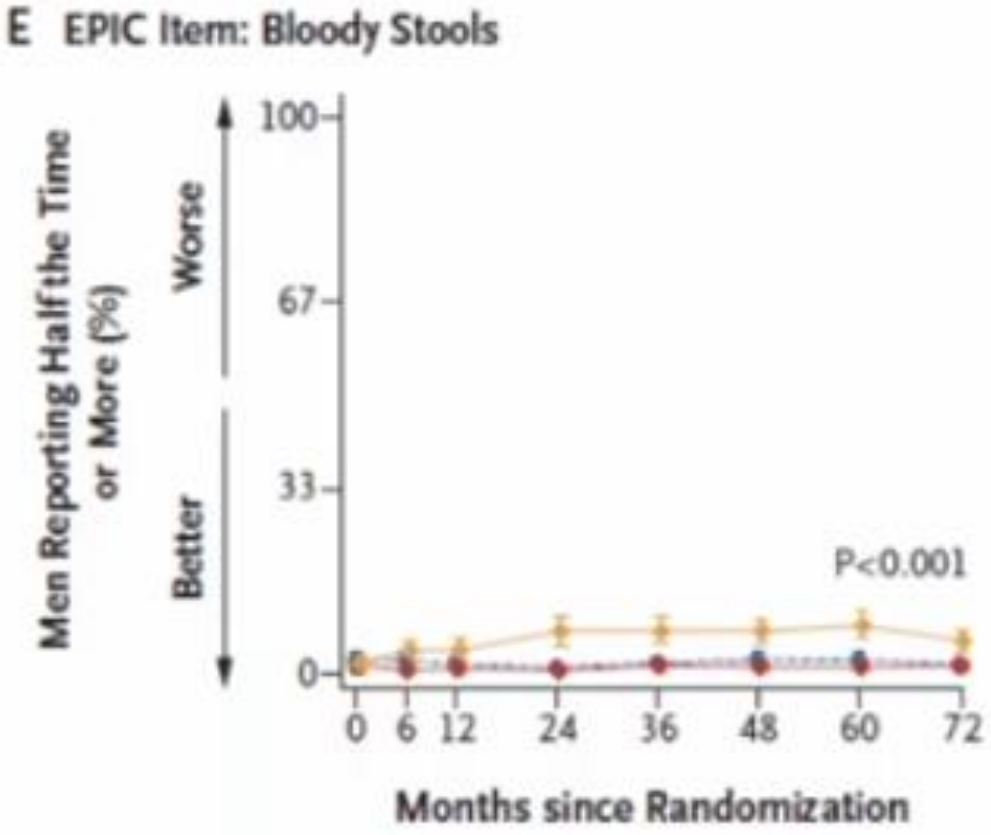


Donovan NEJM 2016

ProtecT — Bowel Function







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
- 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			✓	✓		

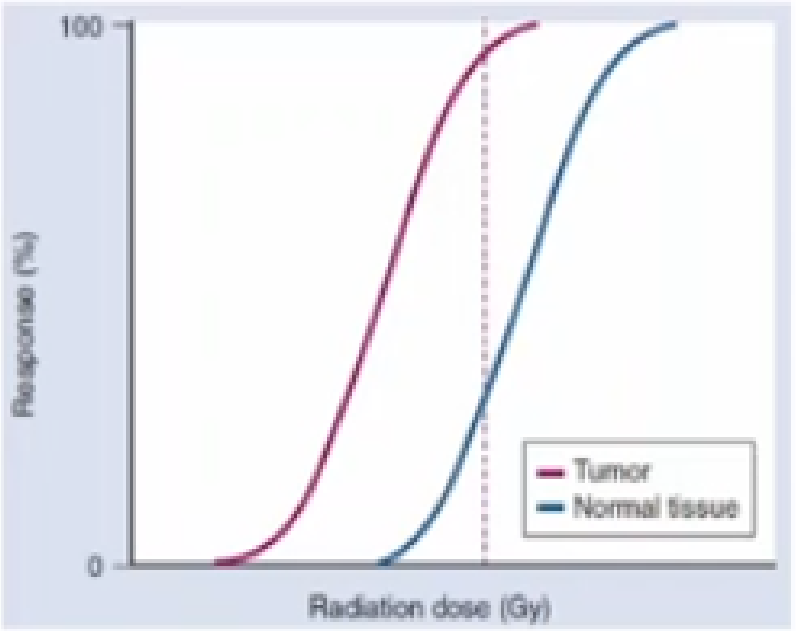
RT Dose Escalation

- Dose escalated RT improves biochemical control over "standard dose" prostate RT (5 RCTs with conventional fractionation)

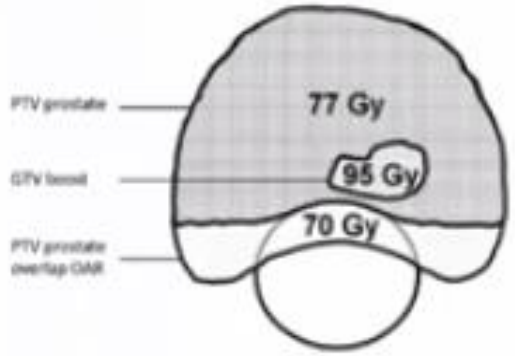
Trial	Arms	N	Technique	FFBF	Gr 3 Toxicity
MDACC Kuban 2008	78 vs. 70 Gy	301	2D + 3D boost	78% vs. 59% (8y)	7% vs. 1%
MGH Zietman 2010	79.2 vs. 70.2 Gy	392	2D + proton	83% vs 68% (8.9y)	1% vs. 1%
Dutch Al-Mamgani 2008	78 vs. 68 Gy	669	3D	56% vs. 45% (7y)	6% vs. 4%
MRC Dearnaley 2007	74 vs. 64 Gy (+ ADT)	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)

Enhancing the Therapeutic Ratio

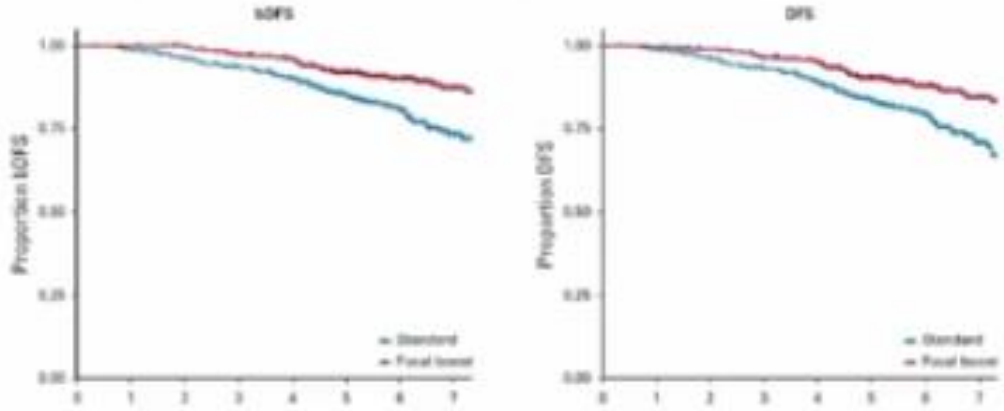
1. Focal dose escalation to dominant intraprostatic lesion
2. Rectal spacers
3. Hypofractionation
4. Ultrahypofractionation/SBRT
5. Brachytherapy
6. Adding ADT to RT



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

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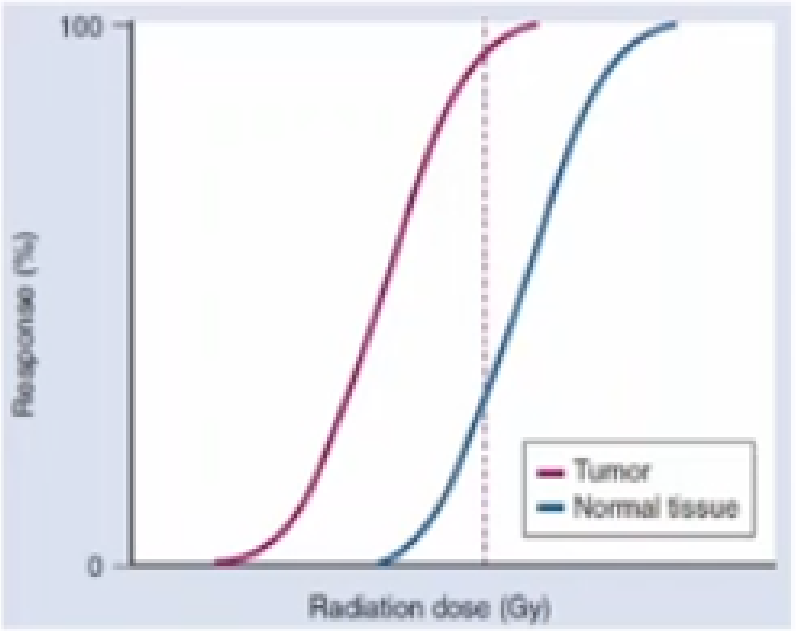
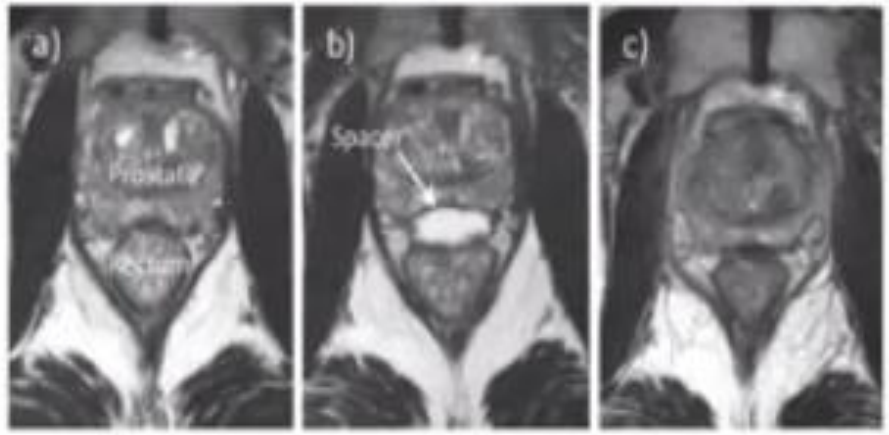
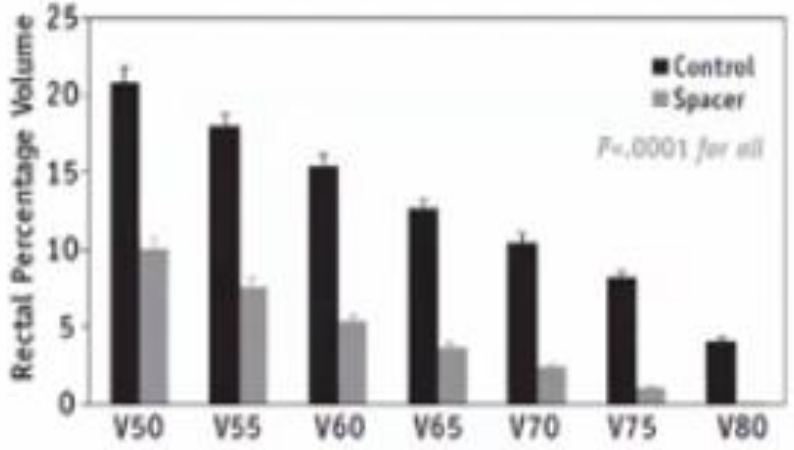


Rectal Spacers

- 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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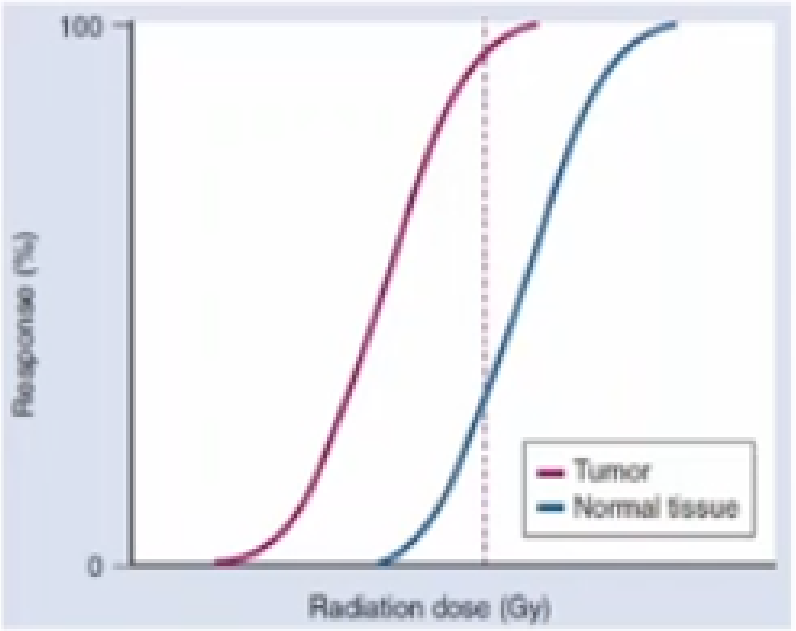


Timeline

Moderate hypofractionation

1998	2007	2015	2019
1st patient 70 Gy in 28 fx	Report >700 pts @ 70 Gy in 28 fx	CHiPP trial report	3 non-inferiority trials 4 superiority trials

Moderate Hypofractionation (4-6 wks)

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	FFBF 85% vs. 79% (hypo better). Same GI tox. 9m ADT for all.

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

- **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 SC, et al. JCO 2018

EDITORIAL

DON'T SQUEEZE HYPOFRACTIONATED SCHEDULES INTO TOO-SHORT OVERALL TIMES

JACK FOWLER, PH.D., D.SC.,* AND CHRISTOPHER R. KING, PH.D., M.D.†

*Departments of Human Oncology and Medical Physics, University of Wisconsin Medical School, Madison, WI; and †Department of Radiation Oncology, Stanford University School of Medicine, Stanford Medical Center, Stanford, CA

Acute mucosal reactions could become dose-limiting if overall times too short.

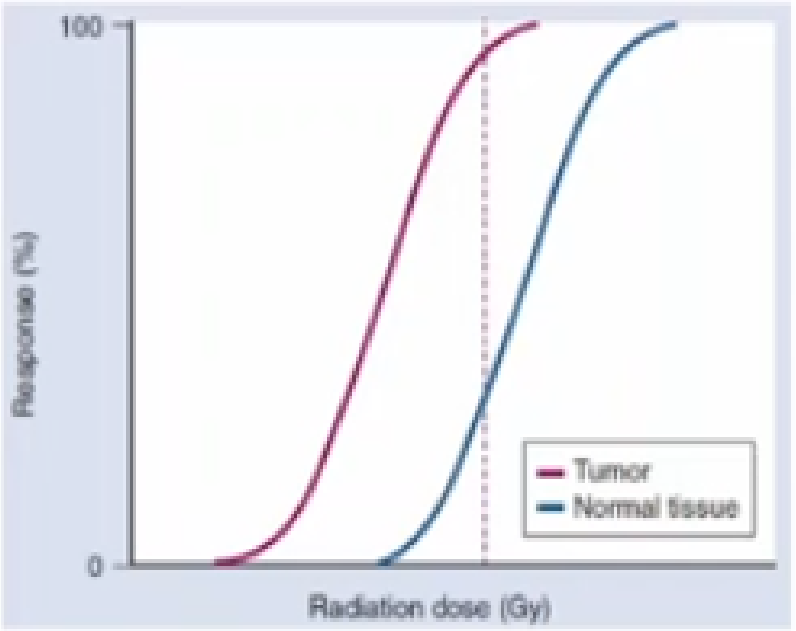
Acute Mucosal Reactions modelled by assuming $\alpha/\beta = 10$Gy, Tk = 7 days, Tp = 2.5 days
Fowler, Harari, Leborgne R&O 2003; 69: 161-8

If BED exceeds 59 – 63 Gy_{10} = 49 – 52.5 Gy NTD, Too hot in oral mucosa, now confirmed as reliable. And in rectal mucosa? Seems to work also.

Consider using alternate treatment days etc.

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



Timeline


Extreme hypofractionation
2000
1st patient
5 fractions
2009
Ph II trial
results
2013
Report
>1000 pts
2014
NCCN/ASTRO
guidelines
2016
HYPO-RT
trial
2019
Report
>6000 pts
PACE-B trial
2021
SHARP
High-Risk

SBRT/Ultrahypofractionation (1-2 wks)

- 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

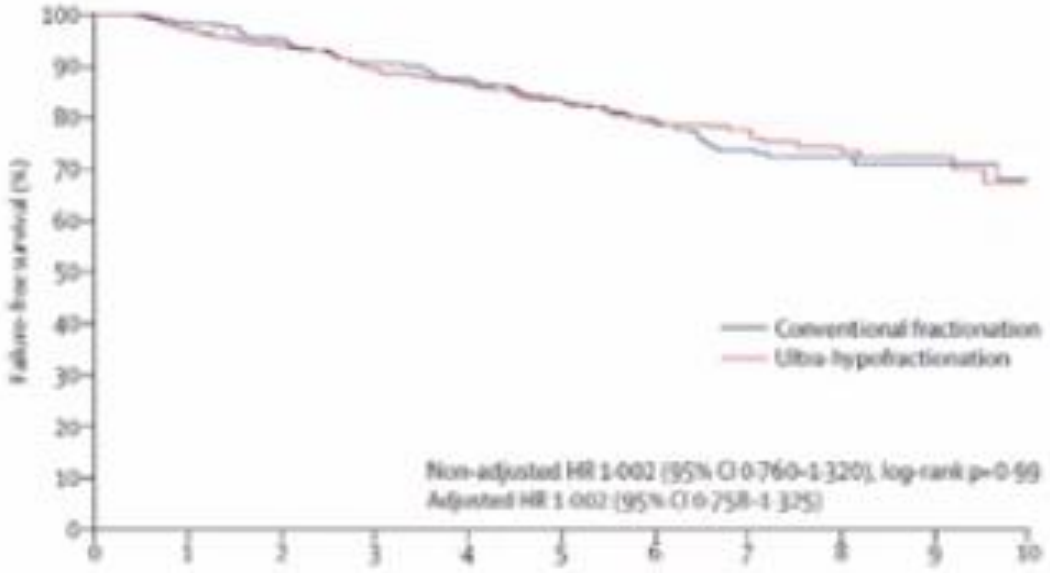
SBRT/Ultrahypofractionation (1-2 wks)

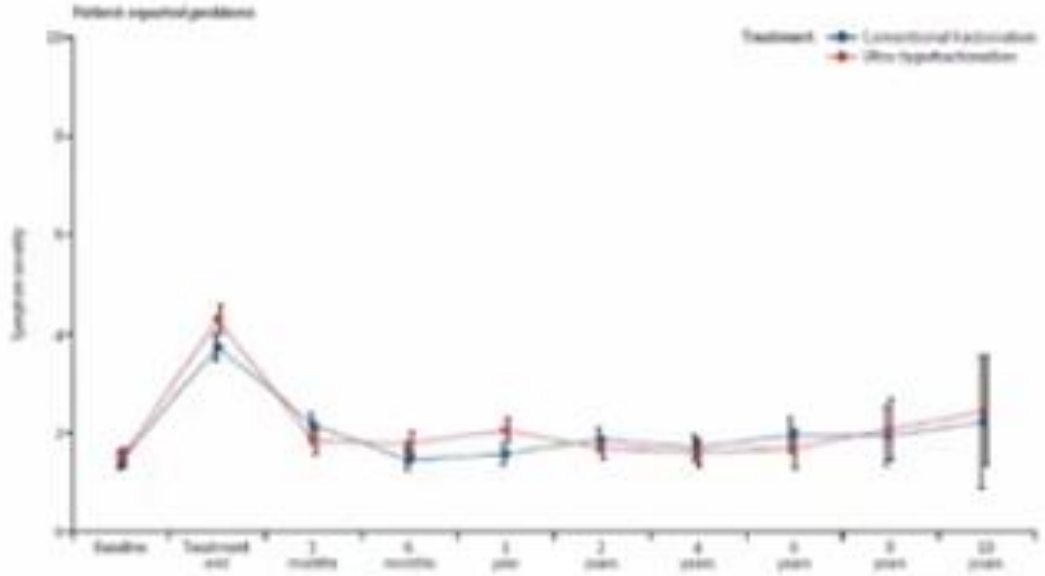
- Meta-analysis of >6,000 patients
  - 35-36.25 Gy → 5-yr bRFS 95%
  - **Grade 3+ GU and GI toxicity only 2% and 1%**, respectively
- Dose escalation 32.5 Gy → 40 Gy (MSK trial)
  - PSA failure 15% → 0% & positive biopsy 48% → 8%
- Dose escalation 45 → 50 Gy (UTSW trial)
  - Rectal injury @ 50 Gy dose 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

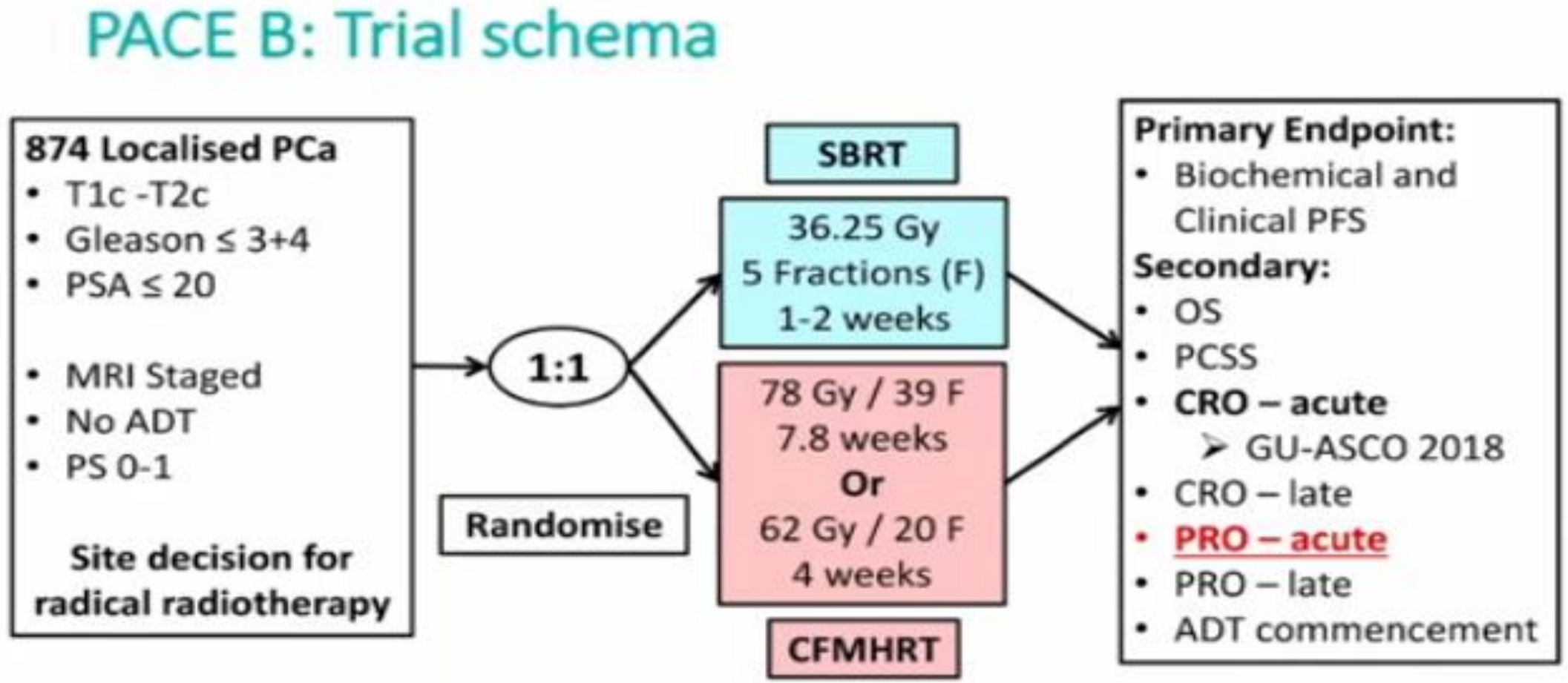
- First RCT of ultrahypofractionated RT (80% 3D-CRT)
- **42.7 Gy in 7** (QOD) was **non-inferior to 78 Gy in 39**
- **No difference in PR-QOL** at 6 years





Widmark Lancet 2019. Fransson Lancet Oncol 2021.

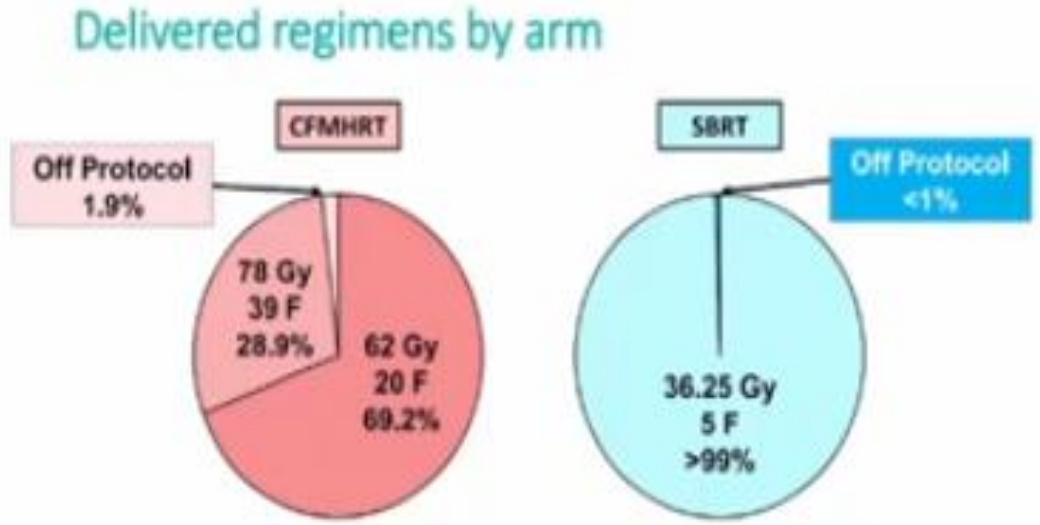
PACE B: SBRT vs IMRT

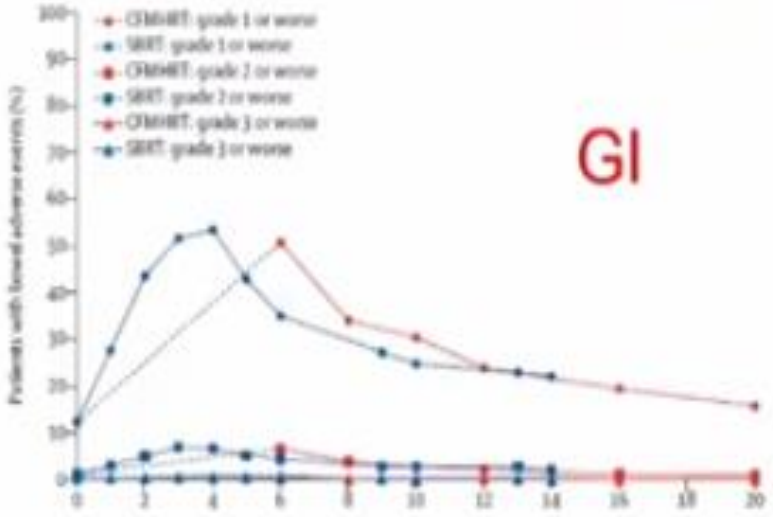


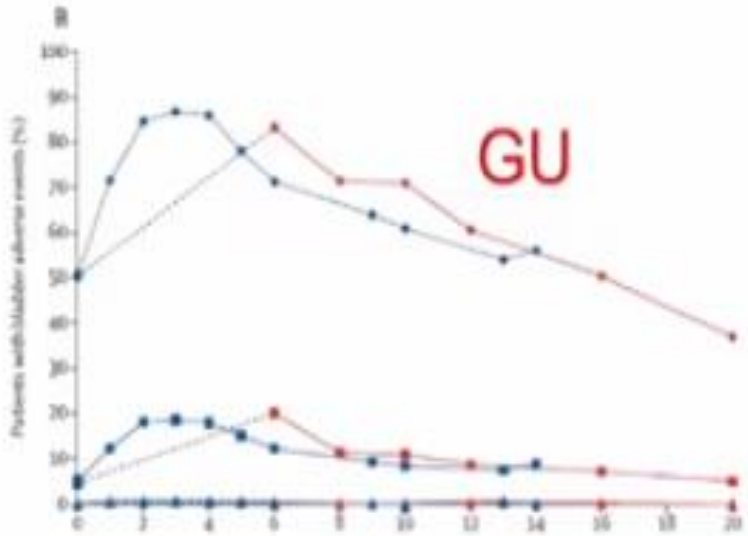
Brand Lancet Oncol 2019

PACE B: SBRT vs IMRT

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



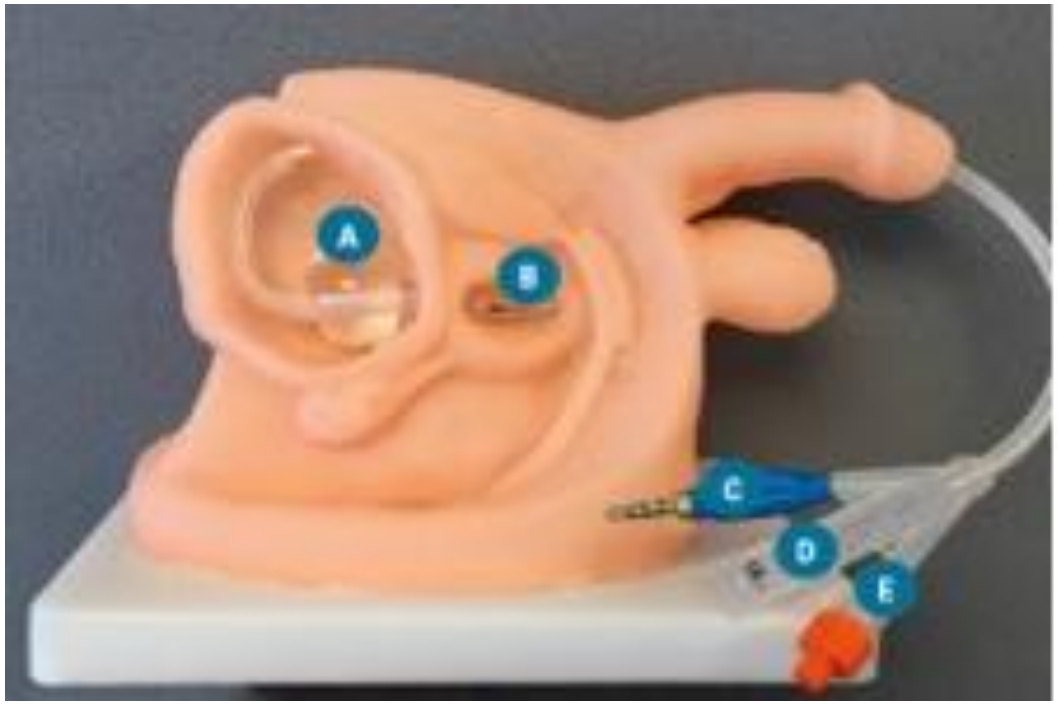


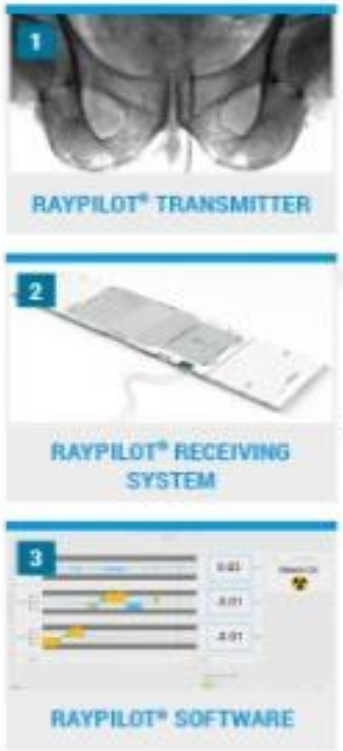


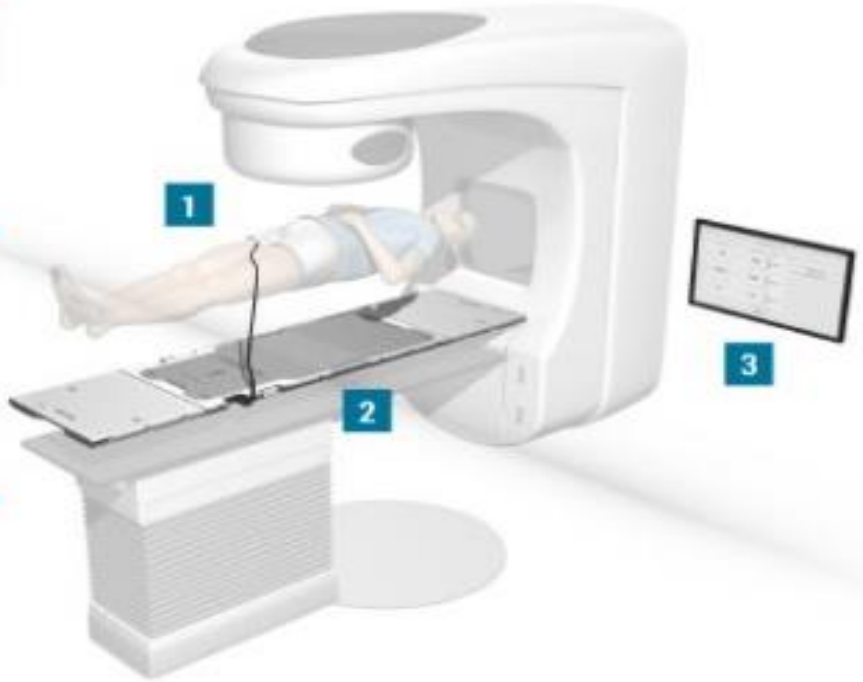
Brand Lancet Oncol 2019

How I Deliver Prostate SBRT

- RayPilot → Realtime tracking
- MRI fusion, VMAT-based delivery, heterogeneous planning
  - 40 Gy in 5 fx OR 38 Gy in 4 fx to PTV (2 mm) excluding urethra



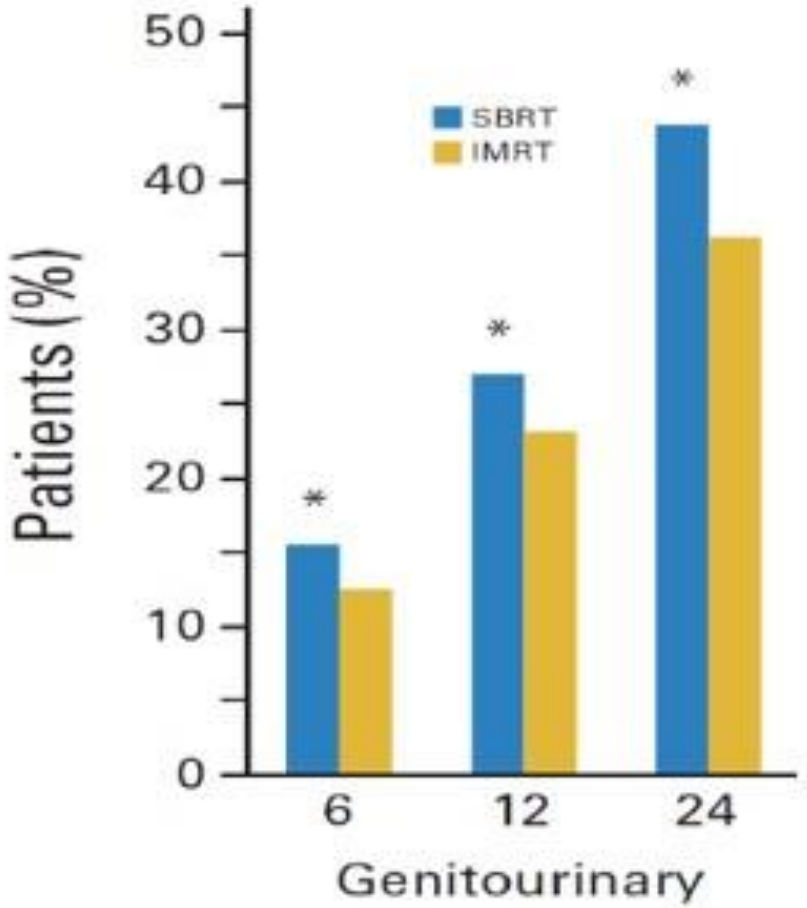




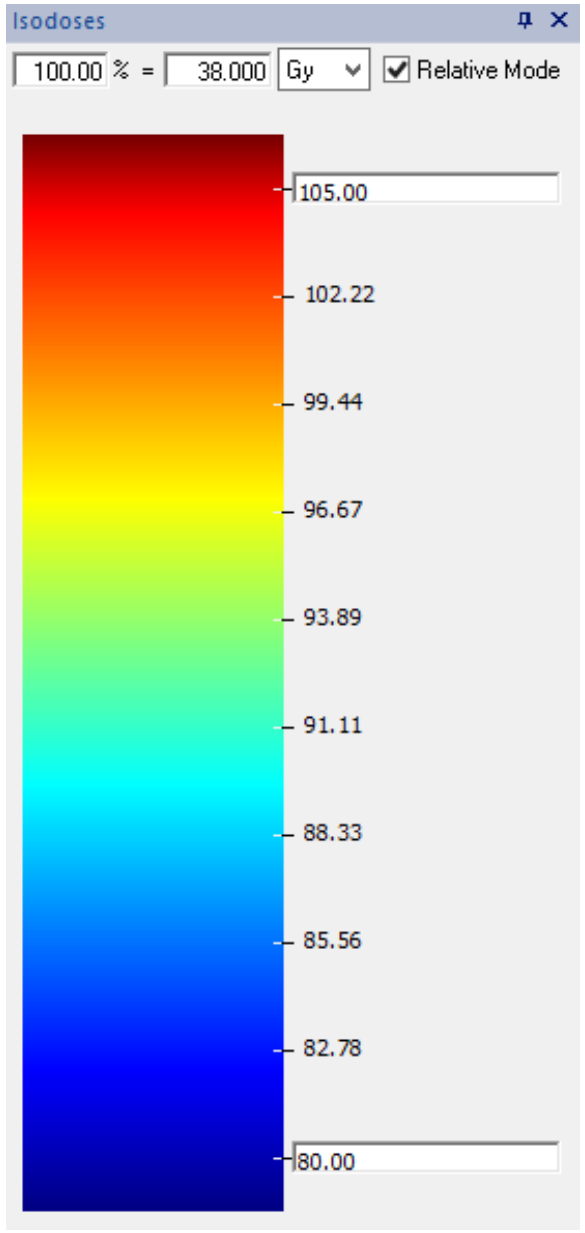
Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

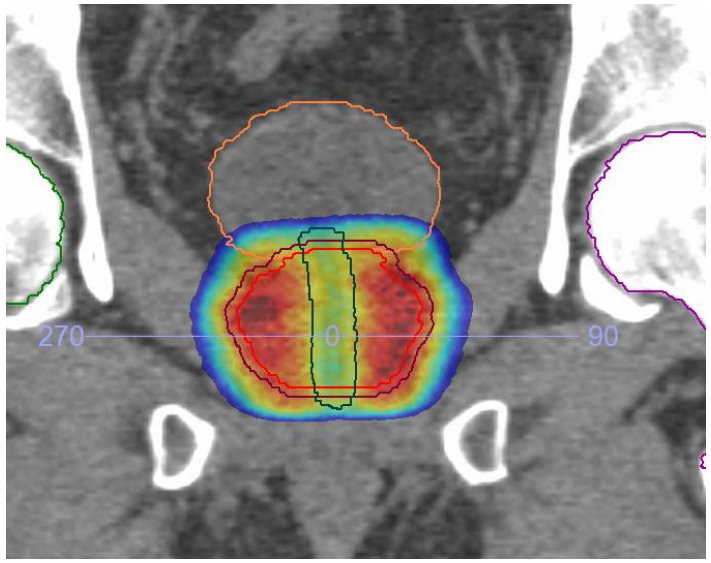
James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

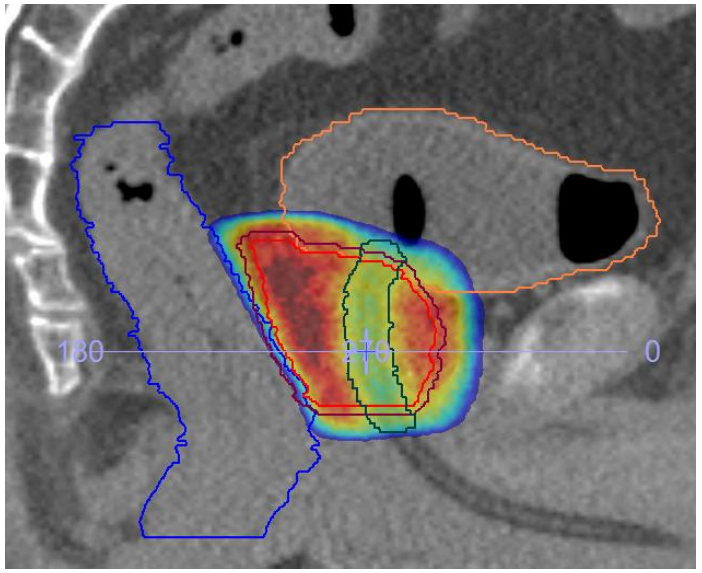
J Clin Oncol 32:1195-1201. © 2014

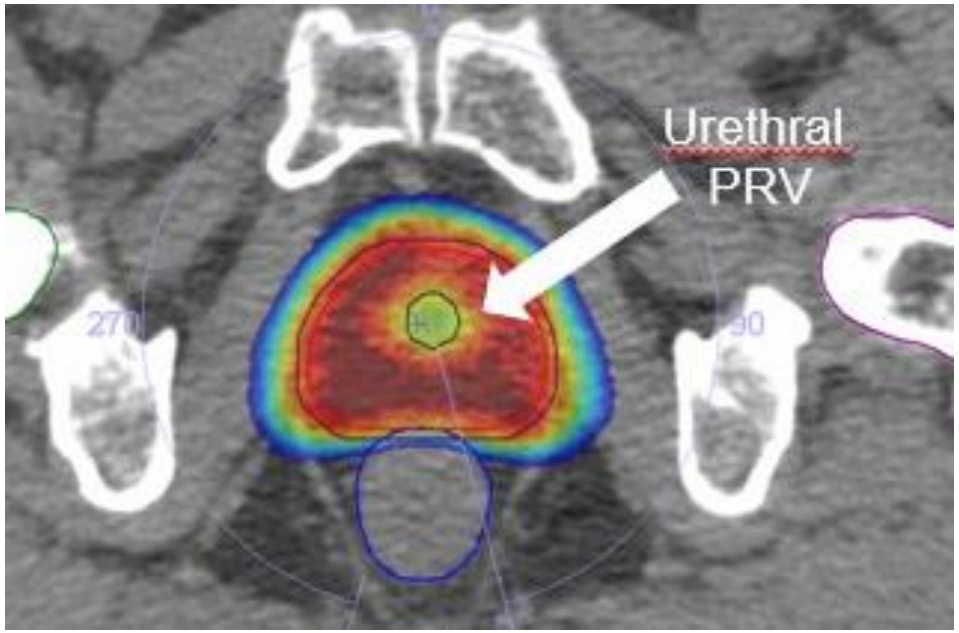


A significantly(*) increased GU toxicity (mostly urethral-related) with SBRT (696 pts) was observed compared with standard IMRT (1392 pts) in a national sample of Medicare beneficiaries









The VMAT treatment consists in two 6FFF or 10FFF arcs optimized to have the 95% isodose covering at least 95% of the PTV

OARs prioritized over target coverage

Organ motion mitigation with bowel and bladder set-up

RESEARCH Open Access

Treatment outcome and compliance to dose-intensified linac-based SBRT for unfavorable prostate tumors using a novel real-time organ-motion tracking

Treatment's characteristics		
Androgen deprivation therapy		
No	3	23,1%
Antiandrogen	4	30,8%
LHRH anologue	6	46,1%
SBRT schedule		
5 fractions of 8 Gy	4	30,8%
4 fractions of 9,5 Gy	9	69,2%
CTV (cc)		
Mean	54,76	range [32,06-96,71]
Median	47,05	range [32,06-96,71]
PTV (cc)		
Mean	66,60	range [48,89-128,53]
Median	76,24	range [48,89-128,53]
PTV(D95%)		
Mean	96%	range [95%-97%]
Median	96%	range [95%-97%]

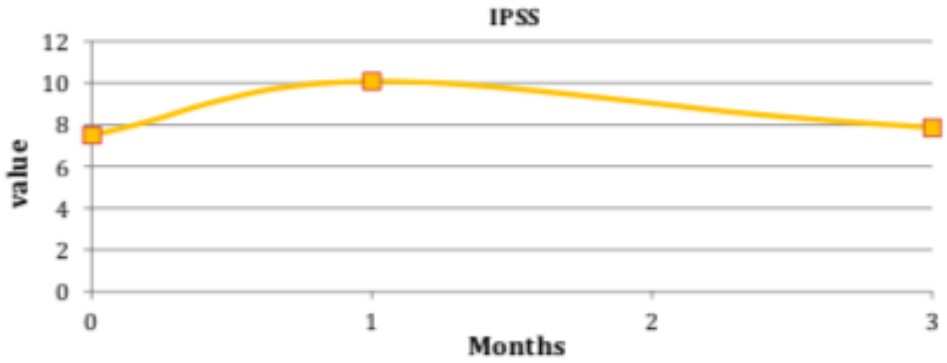
$BED_{1.5}$= 253 Gy-278 Gy

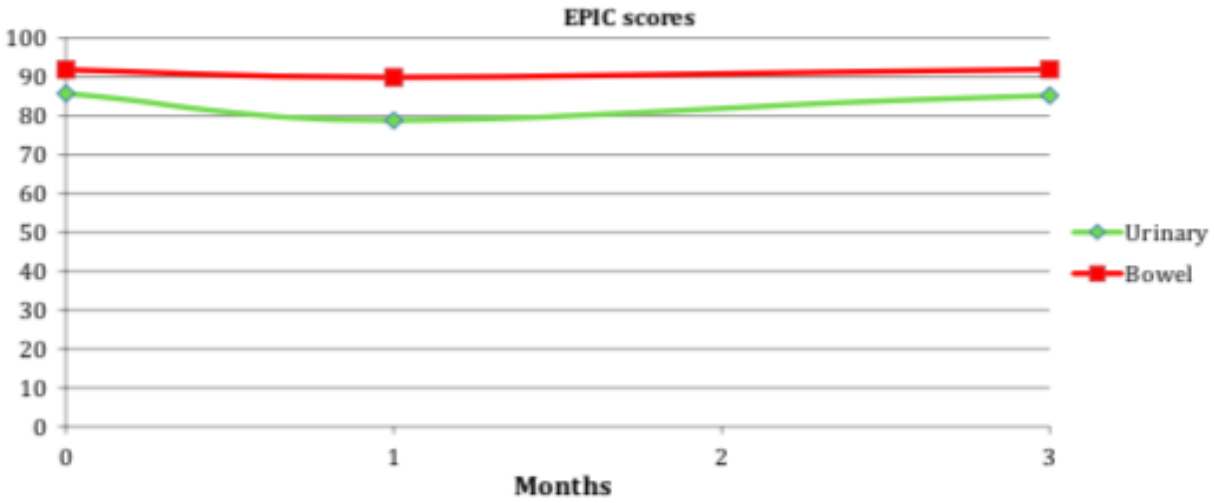
$NTD2_{1.5}$= 109 Gy-119 Gy

Lucchini et al. Rad Oncol 2021

RESEARCH Open Access

Treatment outcome and compliance to dose-intensified linac-based SBRT for unfavorable prostate tumors using a novel real-time organ-motion tracking





Genitourinary toxicity			Gastrointestinal toxicity	
	30 days	90 days	30 days	90 days
Grade				
1	5 (38.6%)	5 (38.6%)	1 (7.7%)	2 (15.4%)
2	0 (0)	0 (0)	0 (0)	0 (0)
≥ 3	0 (0)	0 (0)	0 (0)	0 (0)

Lucchini et al. Rad Oncol 2021

JAMA Oncology | Original Investigation

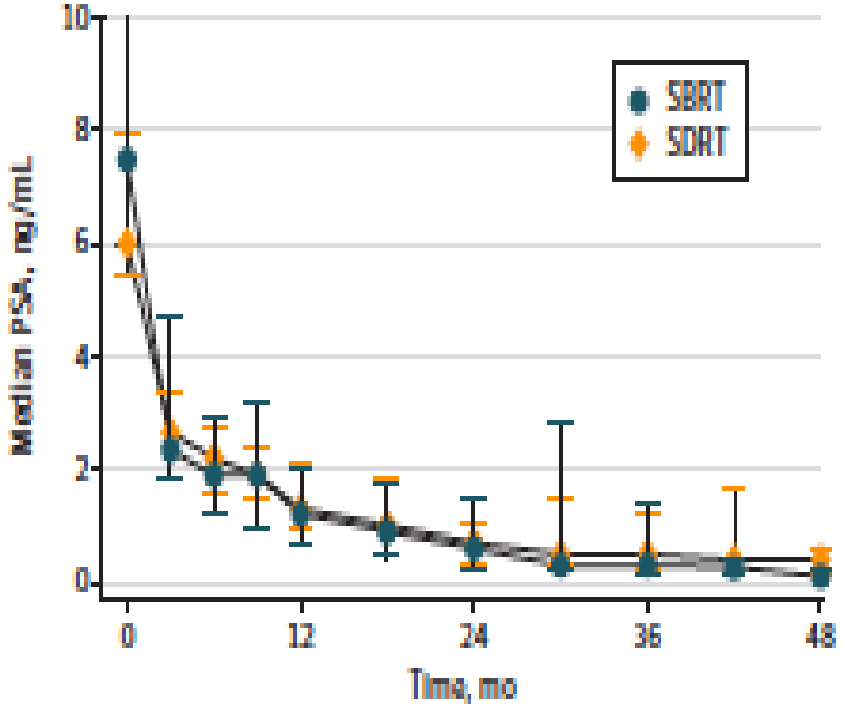
Safety and Efficacy of Virtual Prostatectomy With Single-Dose Radiotherapy in Patients With Intermediate-Risk Prostate Cancer

Results From the PROSINT Phase 2 Randomized Clinical Trial

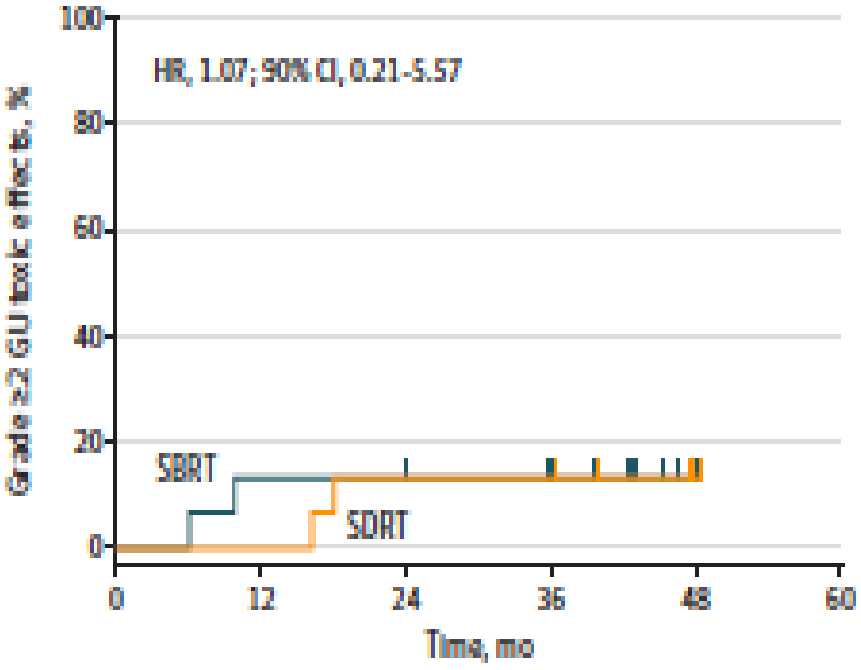
Carlo Greco, MD; Oriol Pares, MD; Nuno Pimentel, MD; Vasco Louro, MD; Inês Santiago, MD; Sandra Vieira, PhD; Joep Stroom, PhD; Dalila Mateus; Ana Soares; João Marques; Elda Freitas; Graça Coelho; Manuela Seixas; Antonio Lopez-Beltran, MD; Zvi Fuks, MD

JAMA Oncology Published online March 11, 2021

PSA decline stratified by study arm



Grade ≥2 urinary toxic effects by study arm



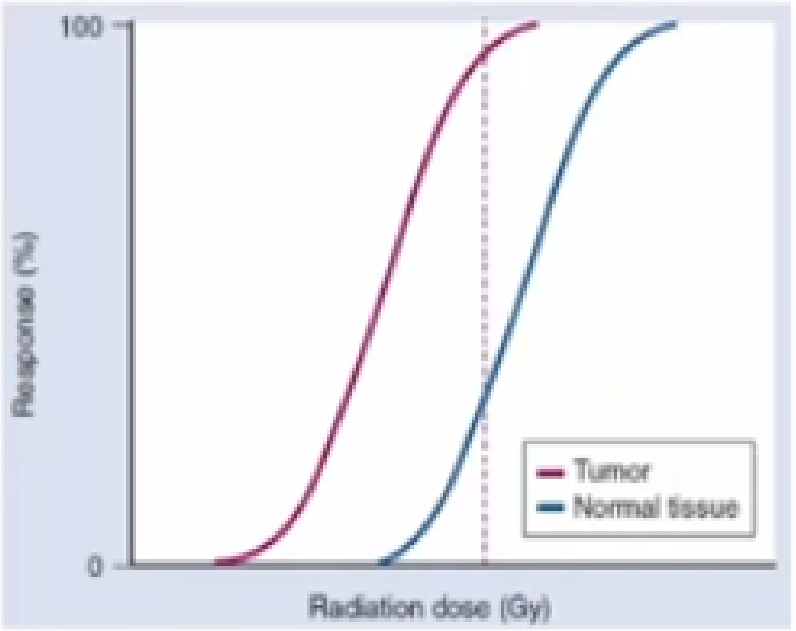
ABRUPT
ABlative Radiotherapy (for) Unfavorable Prostate Tumors

Prospective Trial of Single-Dose Image-Guided Radiotherapy (SD-IGRT) with focal boost to the MRI-defined macroscopic tumor volume for Intermediate Unfavorable and High Risk Prostate Cancer

ClinicalTrials.gov **NCT04831983**

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



Don’t forget Brachytherapy!

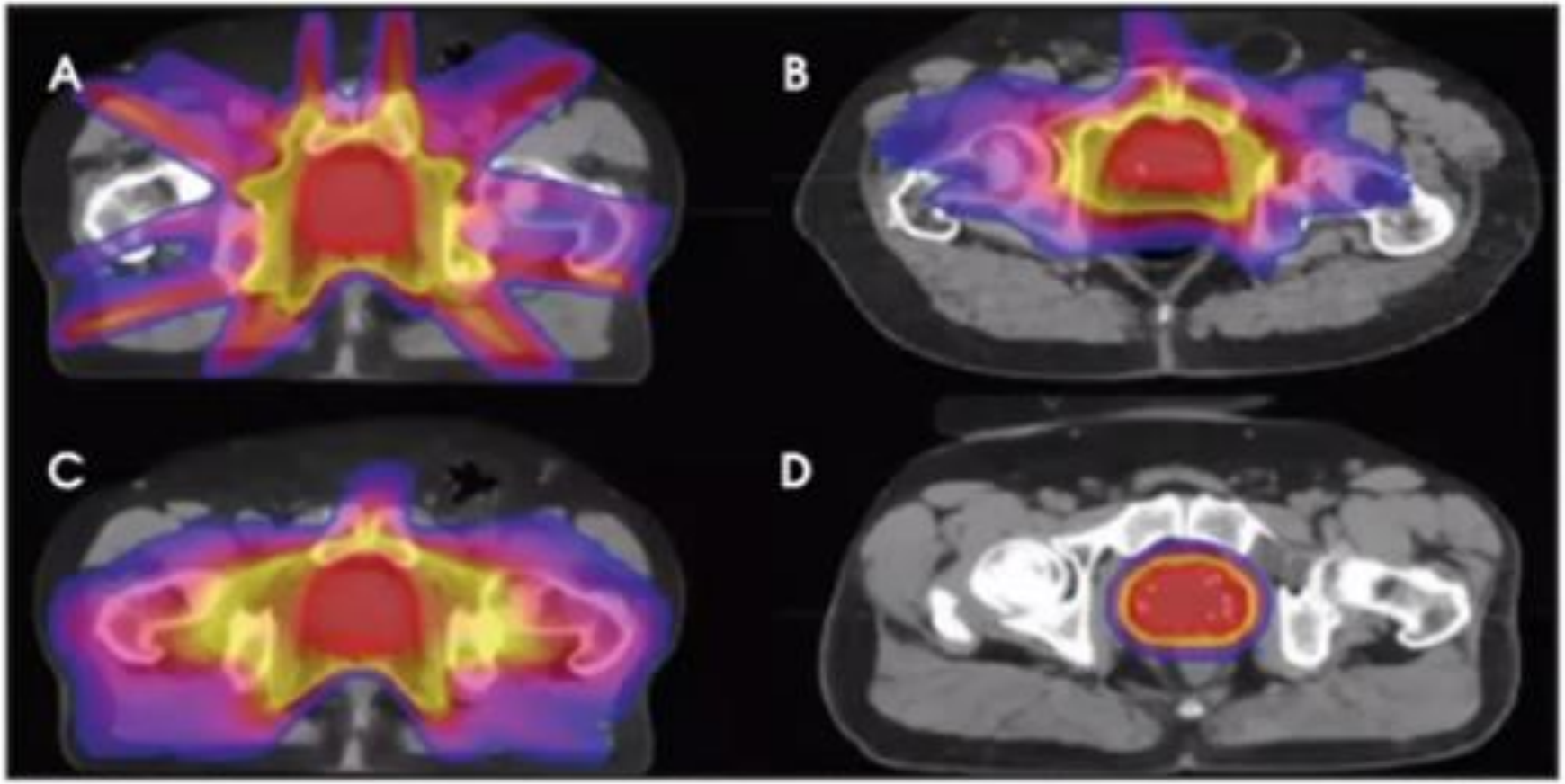
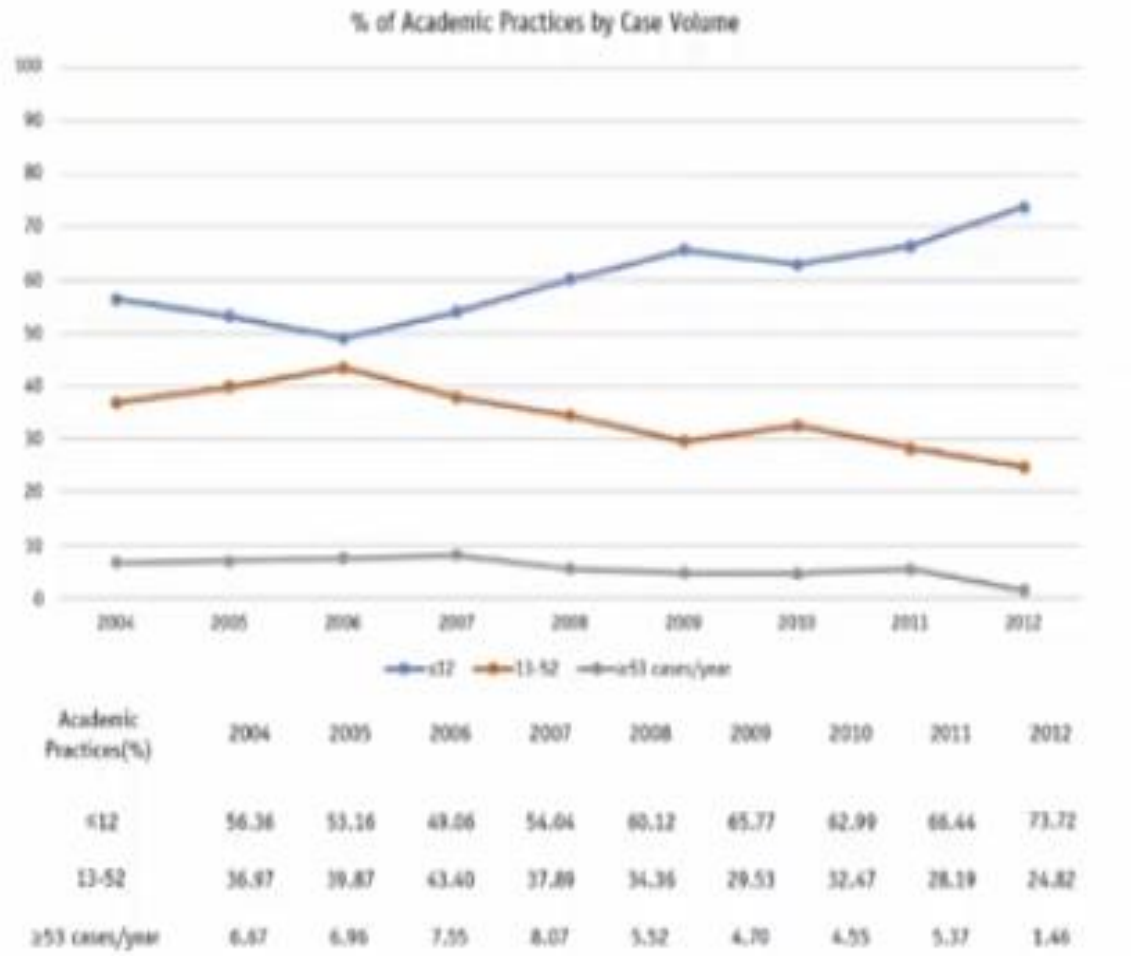


FIGURE 1. *Dosimetric comparison of (A) intensity-modulated radiation therapy (IMRT), (B) volumetric-modulated arc therapy (VMAT), (C) stereotactic body radiation therapy (SBRT), and (D) low dose rate brachytherapy (LDR-BT). Isodose lines correspond to 25% (blue), 50% (yellow), and 100% (red) of prescription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

Abu-Gheida ARO 2017

Don’t forget Brachytherapy!

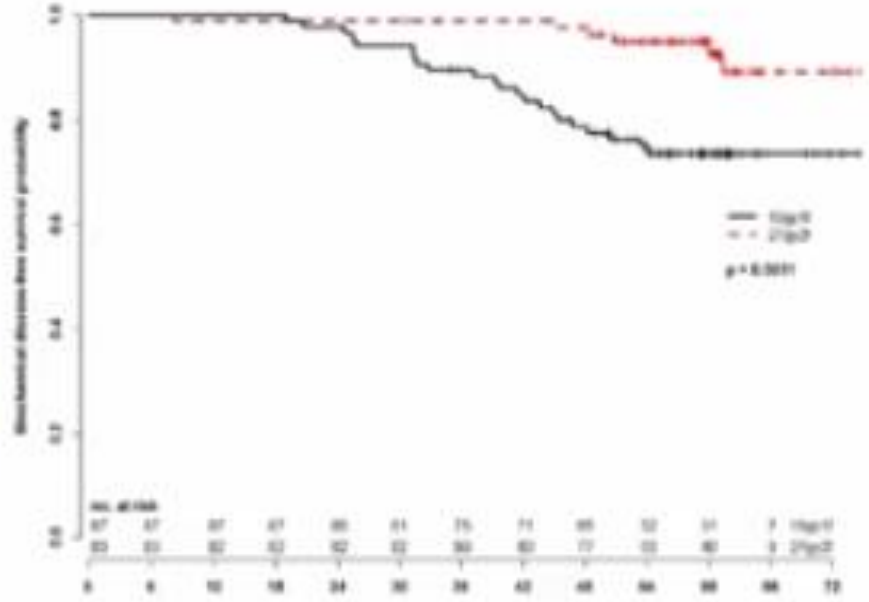


Academic Practices(%)	2004	2005	2006	2007	2008	2009	2010	2011	2012
<12	56.36	53.16	49.06	54.04	60.12	65.77	62.99	66.44	73.72
13-52	36.97	39.87	43.40	37.89	34.36	29.53	32.47	28.19	24.82
≥53 cases/year	6.67	6.96	7.55	8.07	5.52	4.70	4.55	5.37	1.46

Muralidhar Brachytherapy 2015. Orio IJROBP 2016.

Brachytherapy: Monotherapy

- **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)**

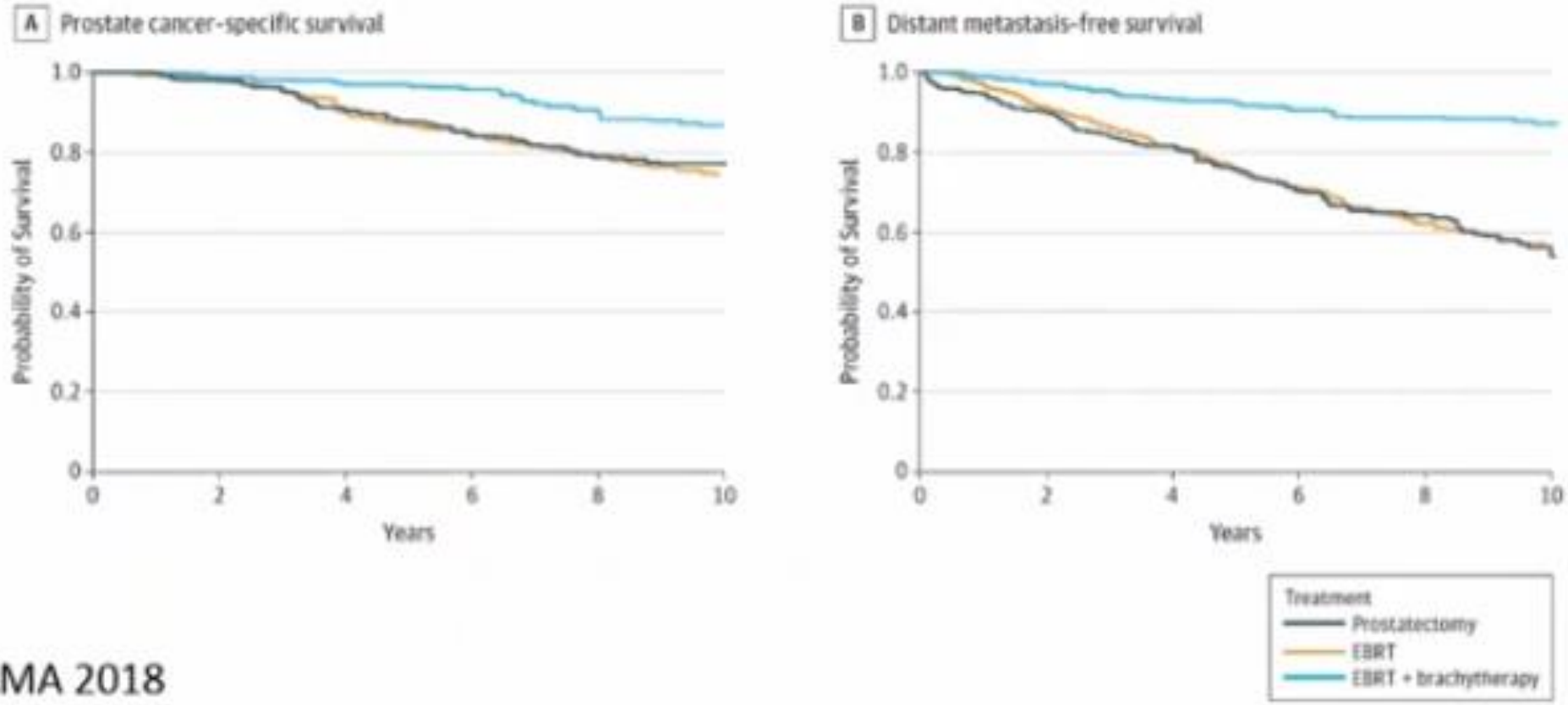
Prestidge ASTRO 2016

Brachytherapy Boost after EBRT

- **Combo EBRT + brachy boost** may be appropriate for **UIR/HR** for purpose of ENI and/or dose escalation
- **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

Brachytherapy Boost after EBRT

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

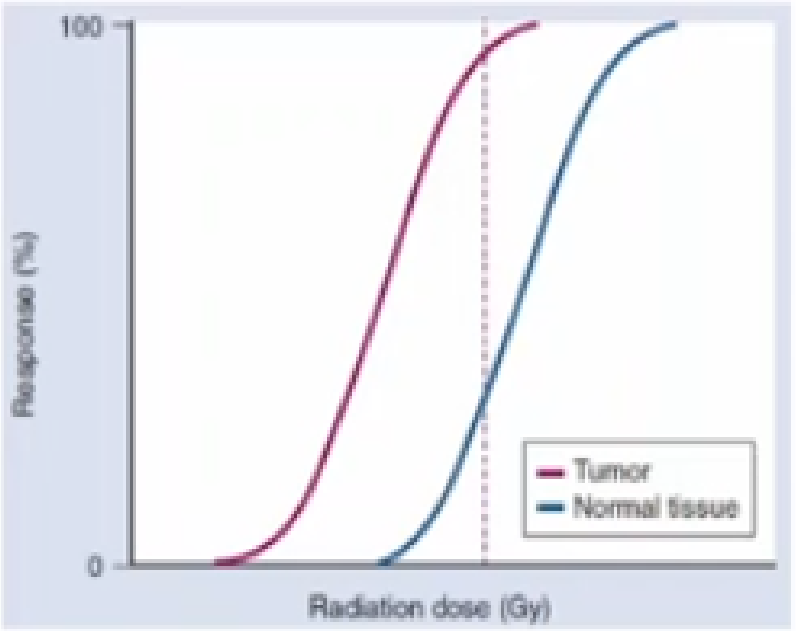


Kishan JAMA 2018

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			✓	✓		

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



NEWS RELEASE 27-OCT-2021

ASTRO: International meta-analysis quantifies impact of three prostate cancer therapy intensification strategies

Individual patient data analysis from MARCAP Consortium may be the strongest evidence to date on androgen deprivation therapy use and duration

data from 10,853 patients enrolled in 12 radiation therapy trials

- After a median follow-up of 12 years, the addition of ADT to RT improved 12-year OS by **7%**

Kishan et al. ASTRO 2021

Picking the optimal duration of ADT in combination with RT

Class Risk	ADT duration*	Referring Trial
IR (unfavorable)	RT + 4-6 m.	DFCI 95096 TROG 9601
HR (i.e: GS 8-10; PSA>20)	RT + 18-28 m.	RTOG 9202 PCS IV
Very HR (T3-4 or >2 factors)	RT + 36 m.	EORTC 22863 EORTC 22961
Any T, N+	Long lasting ± RT	RTOG 8531 SPCG-7 NCI MRC

*** If >1 cardiovascular risk factors a risk-adapted strategy should guide clinical decisions**

Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer

Contemporary Meta-Analyses

Table 1. Cardiovascular Mortality and Cardiovascular Disease Associated With ADT as a Pooled Group Compared With Non-ADT, According to Results of Meta-Analyses From 2010 to 2019

	Type	Treatment Agent (No. of Patients)	Comparator Agent (No. of Patients)	CV Mortality	Any Nonfatal CVD	Myocardial Infarction	Stroke
Nguyen et al[19]	RCT	ADT (n=2200)	Nonimmediate ADT (n=1941)	RR, 0.93 (CI, 0.79–1.10; *P*=0.41; I^2=0%; N=8)			
Bourke et al[20]	RCT	ADT (n=1065)	Nonimmediate ADT (n=814)	RR, 1.06 (CI, 0.80–1.40; *P*=0.69; I^2=0%; N=4)			
Zhao et al[18]	Obs.	ADT (n=129802)*	Non-ADT (n=165605)*	HR, 1.17† (CI, 1.04–1.32; *P*=0.01; I^2=57%; N=6)	HR, 1.10 (CI, 1.00–1.21; *P*=0.06; I^2=72%; N=6)	HR, 1.10 (CI, 0.97–1.26; *P*=0.14; I^2=68%; N=6)	
Zhao et al[18]	Obs.	ADT (n=39465)*	Watchful waiting (n=43648)*	HR, 1.30† (CI, 1.13–1.50; *P*=0.0003; I^2=0%; N=4)	HR, 1.19† (CI, 1.08–1.30; *P*=0.0004; I^2=0%; N=3)		
Carneiro et al[16]	Obs.	ADT (n=52308)	Non-ADT (n=74590)	OR, 1.92 (CI, 0.79–4.68; *P*=0.15; I^2=97%; N=3)	OR, 1.06 (CI, 0.70–1.61; *P*<0.78; I^2=100%; N=2)	OR, 2.05† (CI, 1.93–2.17; *P*<0.00001; I^2=100%; N=2)	OR, 1.07 (CI, 0.66–1.72; *P*=0.79; I^2=99%; N=2)
Carneiro et al[16]	RCT	ADT (n=8388)	Non-ADT (n=8411)	OR, 0.97 (CI, 0.81–1.18; *P*=0.79; I^2=0%; N=6)	OR, 1.55† (CI, 1.09–2.20; *P*=0.01; I^2=0%; N=3)	OR, 1.23 (CI, 0.92–1.64; *P*=0.16; I^2=0%; N=2)	OR, 1.02 (CI, 0.71–1.46; *P*=0.93; I^2=0%; N=2)
Meng et al[17]	Obs.	ADT (n=74538)	Non-ADT (n=85947)				HR, 1.12 (CI, 0.95–1.32; *P*=0.16; I^2=85%; N=6)
Meng et al[17]	Obs.	ADT (n=39029)	Watchful waiting (n=42073)				HR, 1.16† (CI, 1.03–1.31; *P*=0.01; I^2=0%; N=2)

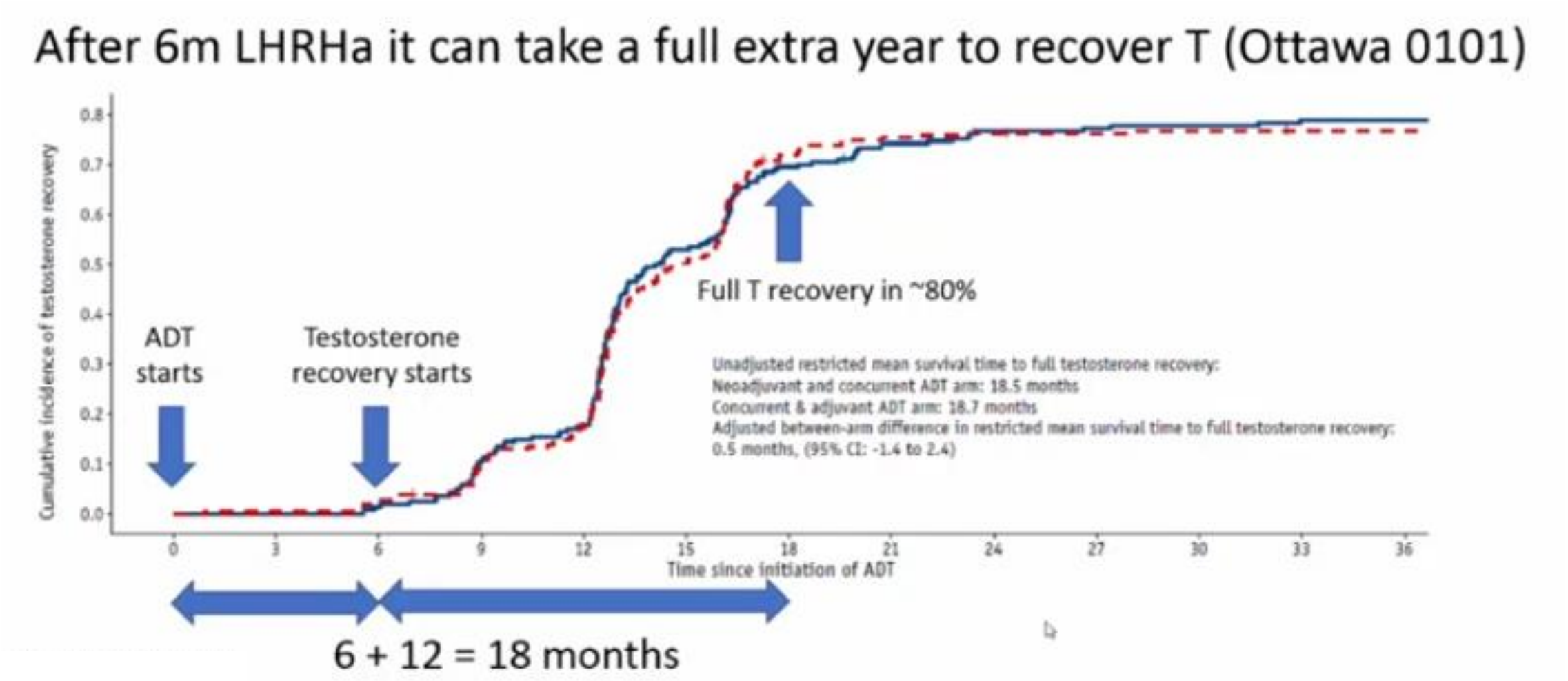
Hu, et al. Arterioscler Thromb Vasc Biol. 2020

Delayed Testosterone Recovery after LHRH-a

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, et al. EJC 2021

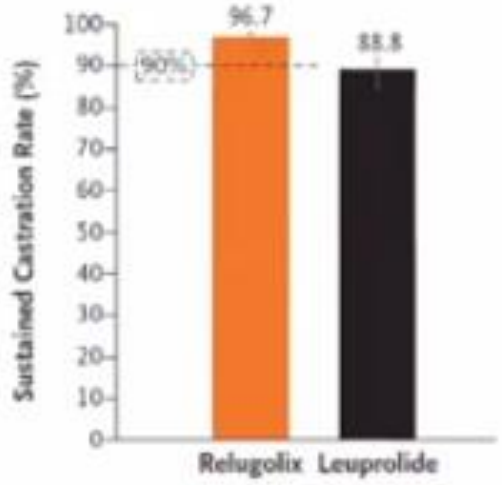
Delayed Testosterone Recovery after LHRH-a

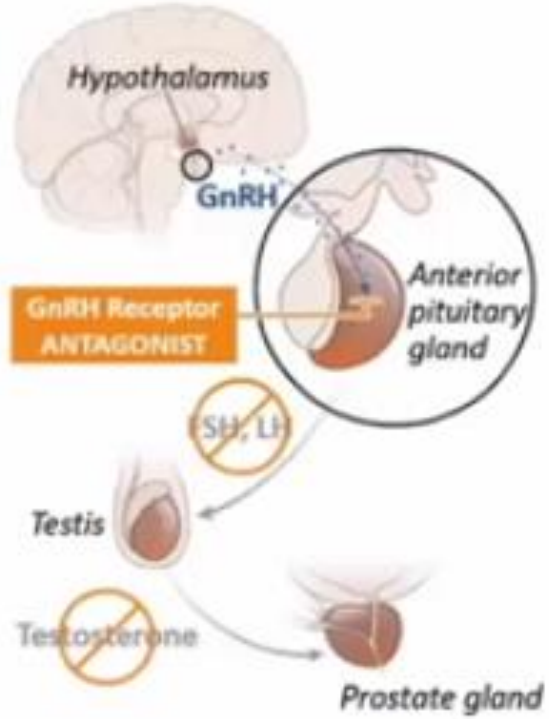


Roy, et al. IJROBP 2020

Alternatives to LHRH-a ?

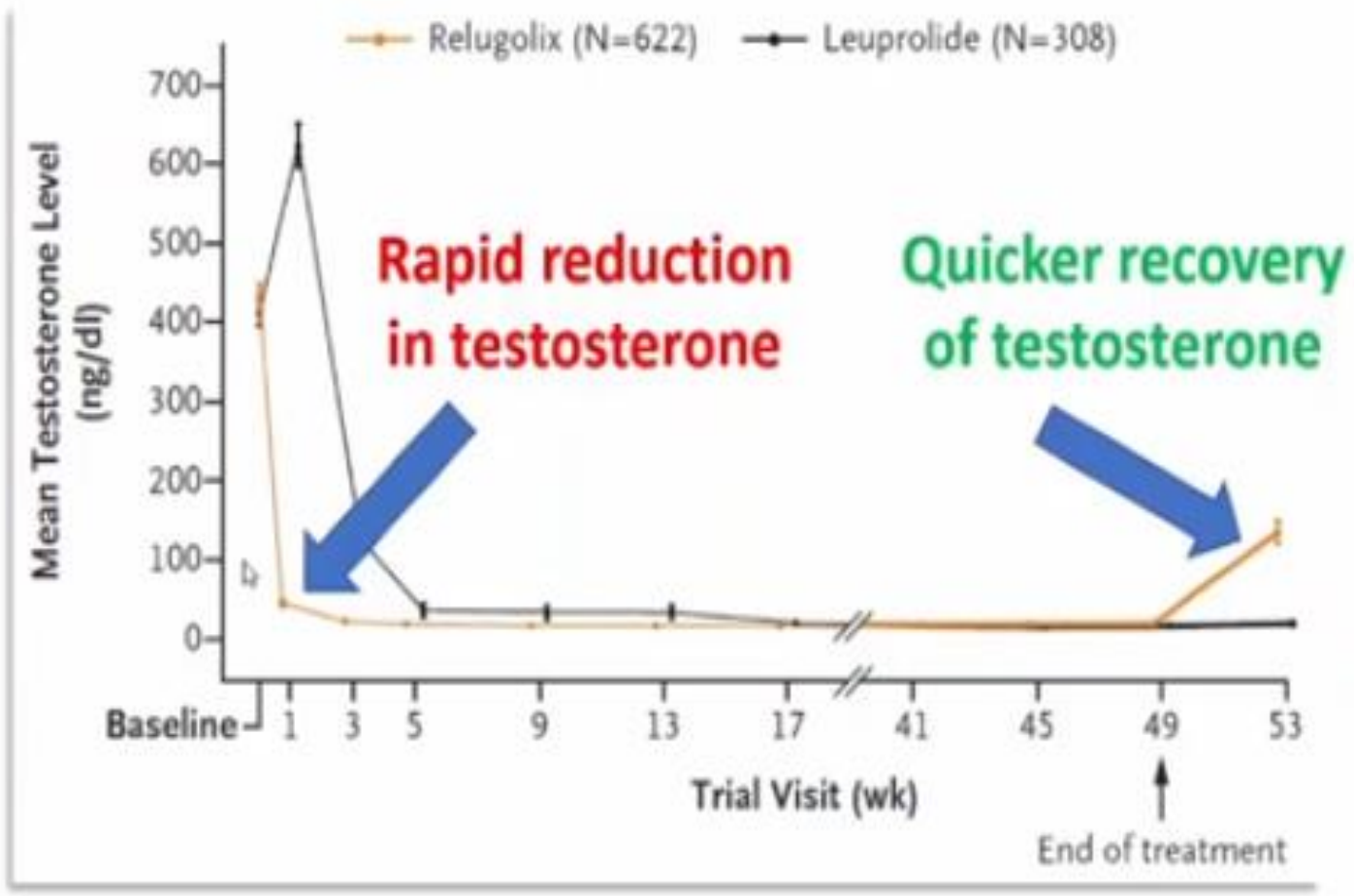
- Alternatives to LHRHa are desired
- **Relugolix is an oral GnRH <u>antagonist</u>**
- Tested on **HERO trial** vs. leuprolide (2:1)
- Met 1° endpoint: sustained castration (48 weeks)

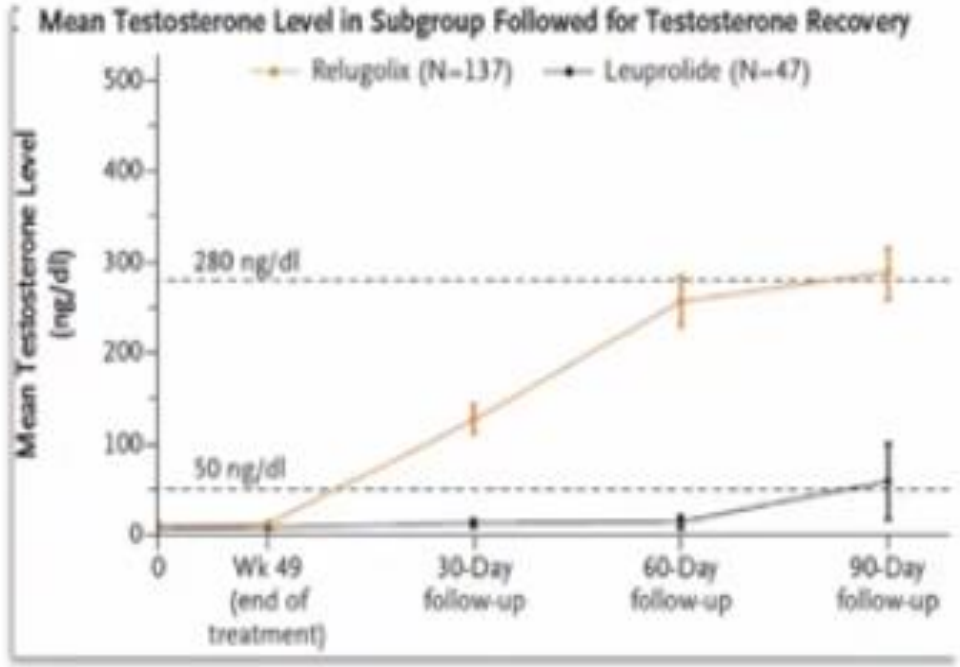




Shore, et al. NEJM 2020

Alternatives to LHRH-a → HERO trial

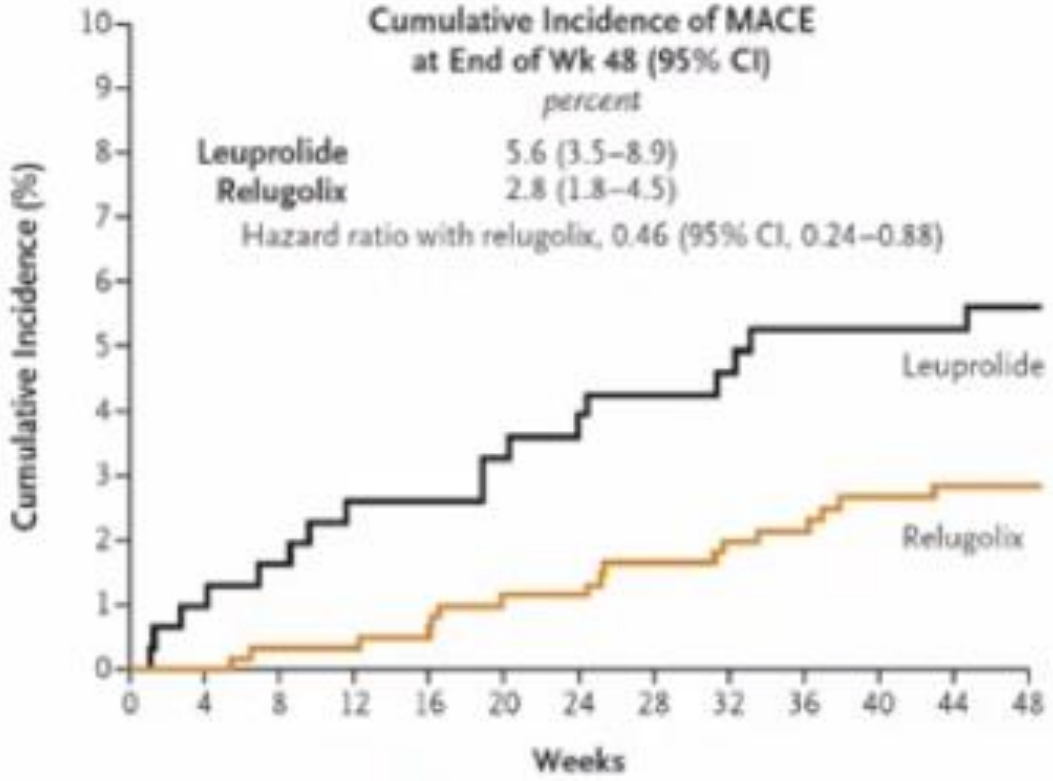




Shore, et al. NEJM 2020

Alternatives to LHRH-a → HERO trial

Relugolix ↓ major adverse cardiac events than leuprolide



MACE = non-fatal MI + stroke + ACM

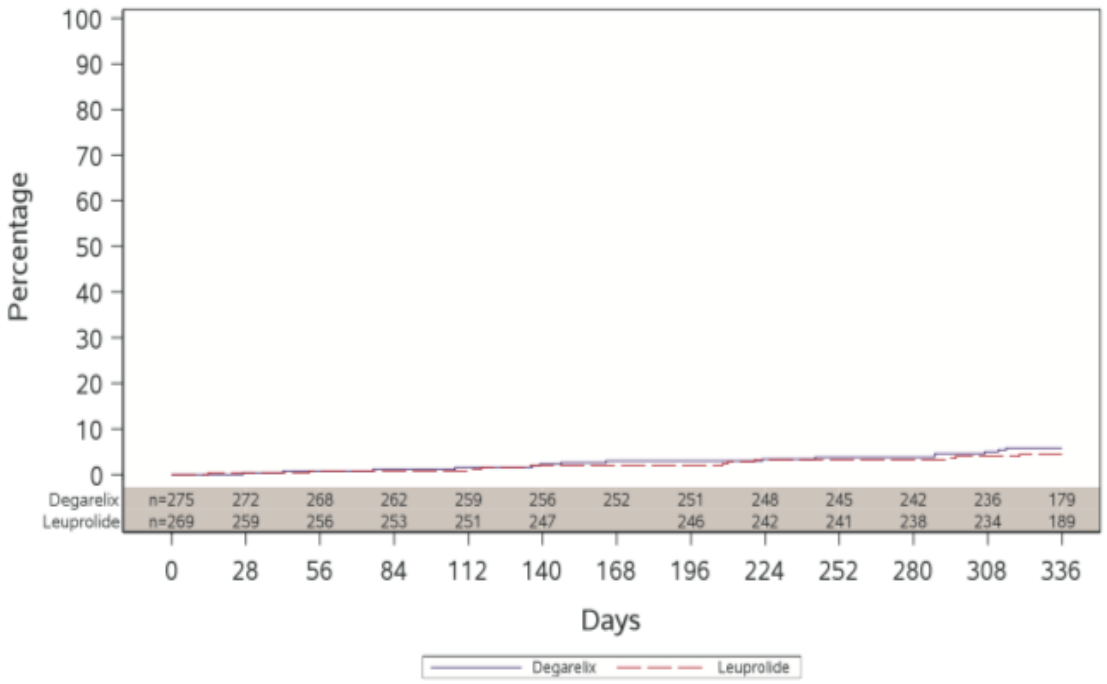
Shore, et al. NEJM 2020

Cardiovascular Safety of [illegible]lix Versus Leuprolide in Patients With Pros[illegible]ncer

The Primary Results of the PRONOUNCE Randomized Trial

First RCT with MACE as primary endpoint

Primary End Point: Inverted Kaplan-Meier Estimates of Cumulative Probability of First Adjudicated MACE - Full Analysis Set



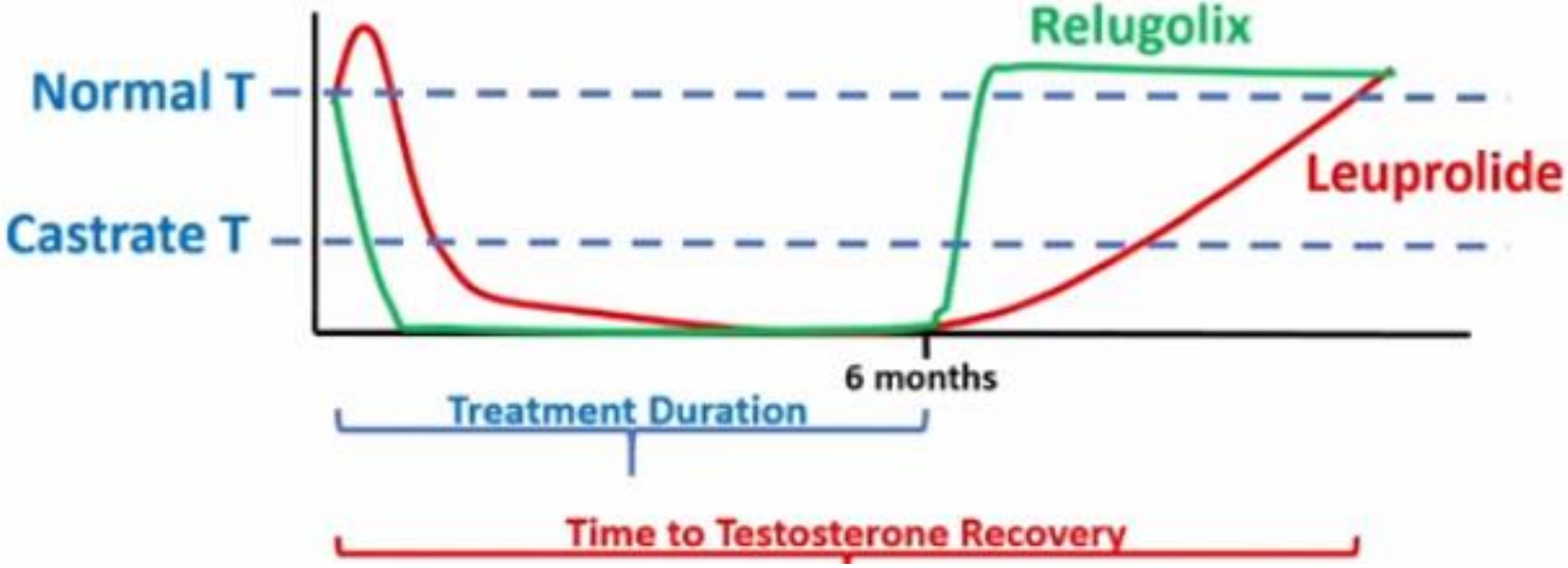
What Are the Clinical Implications?

- The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.
- Cardiovascular events might be lower in patients with prostate cancer through better awareness and attention to cardiovascular risk factor control.
- In light of improved cancer survivorship and the competing risk of cardiovascular disease, there is an ongoing need for rigorous cardio-oncology clinical trials.
- PRONOUNCE provides a model for interdisciplinary collaboration between urologists, oncologists, and cardiologists with a shared goal of evaluating the impact of cancer therapies on cardiovascular outcomes.

Lopes, et al. Circulation 2021

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



Courtesy of Dr. Tendulkar

Does Pelvic RT improve outcomes ?

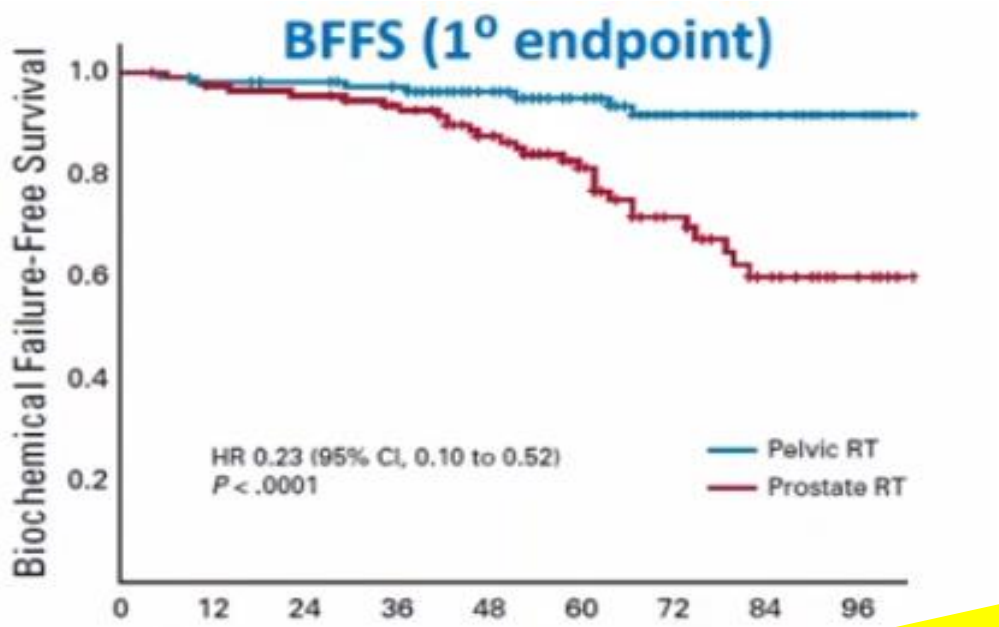
	n	Eligibility	Arms	Endpoints affected
RTOG 9413 (2003,2007)	1292	T2c-4 GS6+, or LN+ risk >15%; PSA<100	Whole Pelvis vs. Px only Neoadj HT vs. Adj HT	Trend PFS for WPRT/NHT (and PORT/AHT)
GETUG-01 (2007)	444	T1b-3	Low pelvis RT vs. Px only (ADT allowed)	None
POP-RT (2021)	224	PCa LN+ risk > 20%	WPRT vs. PORT (2 yrs ADT)	5-yr - bFFS

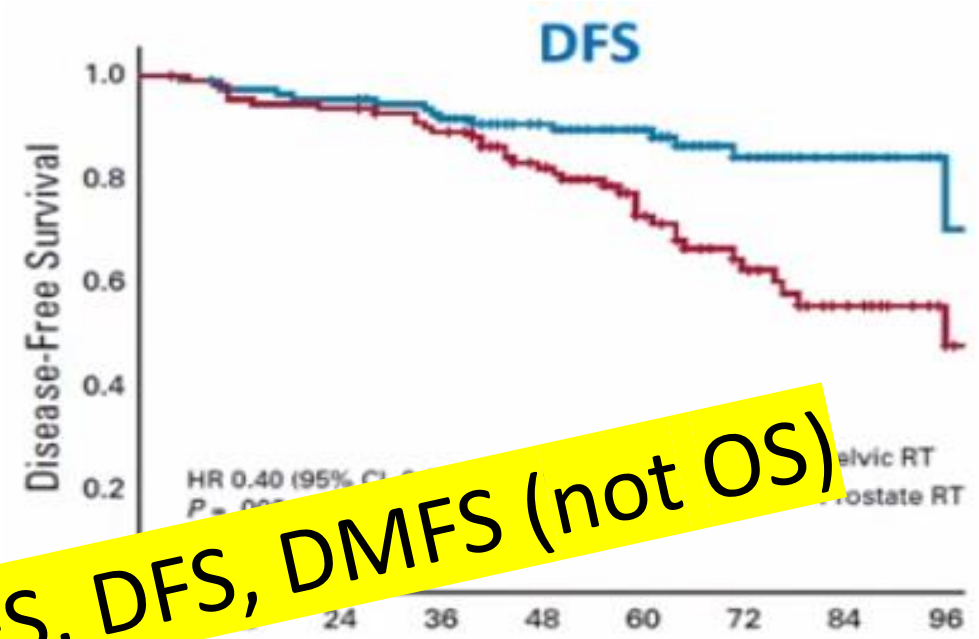
POP-RT

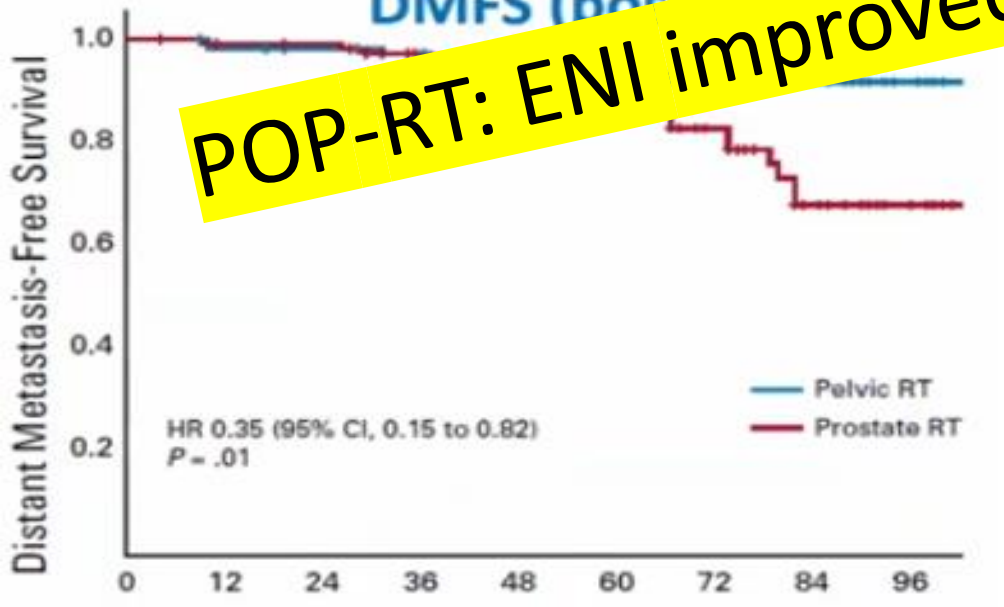
- RCT of 68 Gy/25 to prostate (~78-81 Gy EQD2) +/- 50 Gy to LNs via SIB (included common iliac LNs) with ≥2 years ADT
- Minimum estimated LN risk 20% (median 38%); 80% cT3-T4 (1% T1)
- >50% VHR; 80% had PSMA PET-CT → excluded cN1 and cM1
- **WPRT ↑ late Gr 2 GU toxicity**, but not Gr 3 GU or Gr 2-3 GI

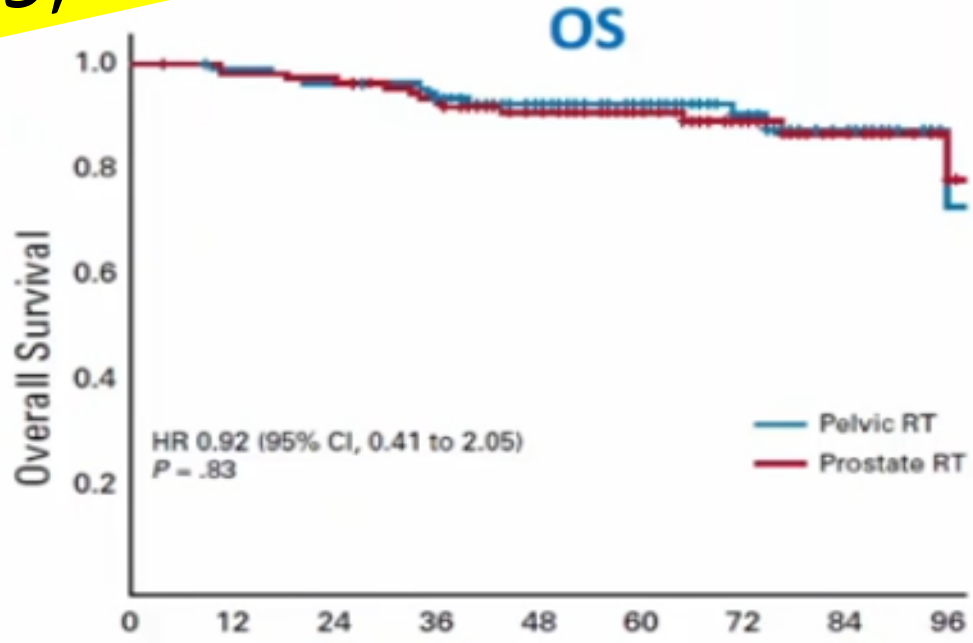
Late Toxicity	Gr 2 GU	Gr 3 GU	Gr 2 GI	Gr 3 GI
WPRT	**18.2%**	1.8%	6.4%	1.8%
PORT	**7.1%**	1.8%	4.5%	0%
P value	0.02		0.28	

Murthy JCO 2021









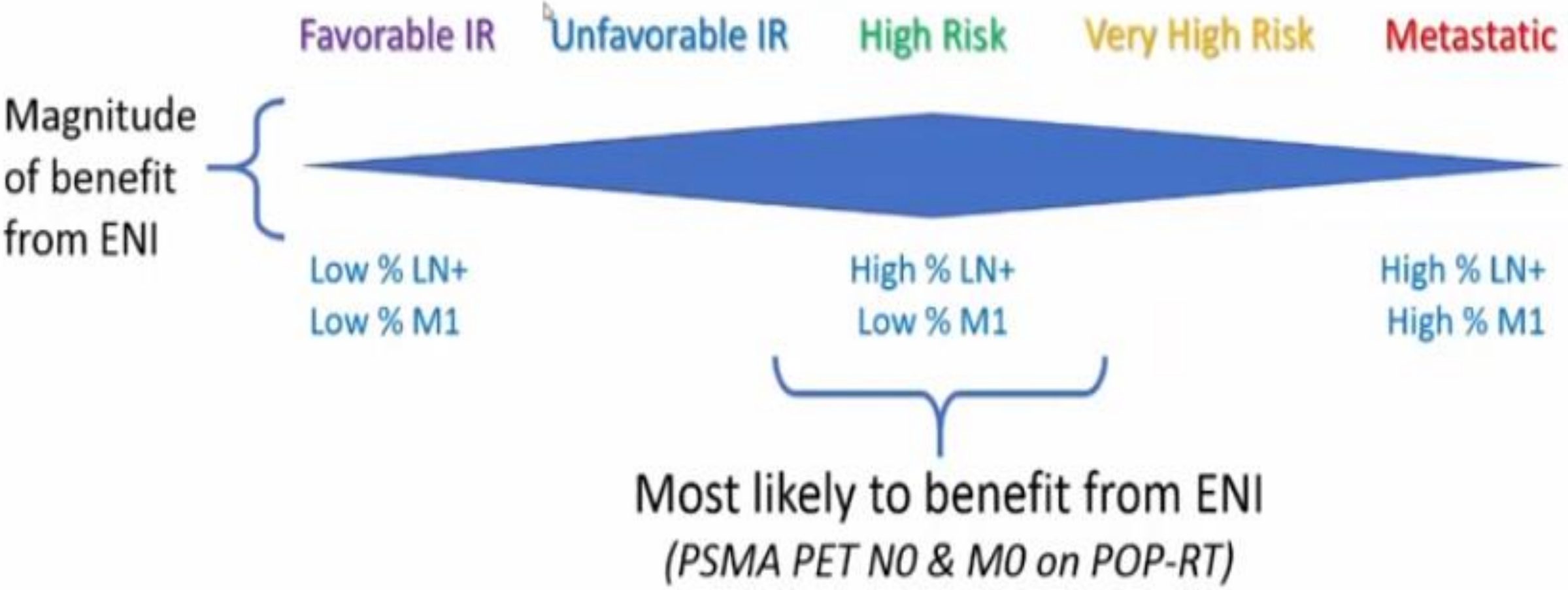
POP-RT: ENI improved BFFS, DFS, DMFS (not OS)

Murthy JCO 2021

Which Patients Need PNRT?

- 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 E.U population (not screen detected; 80% PET staged)
  - Outcomes better than historical controls → Will Rogers or real effect?
- RTOG 0924 results still a decade away

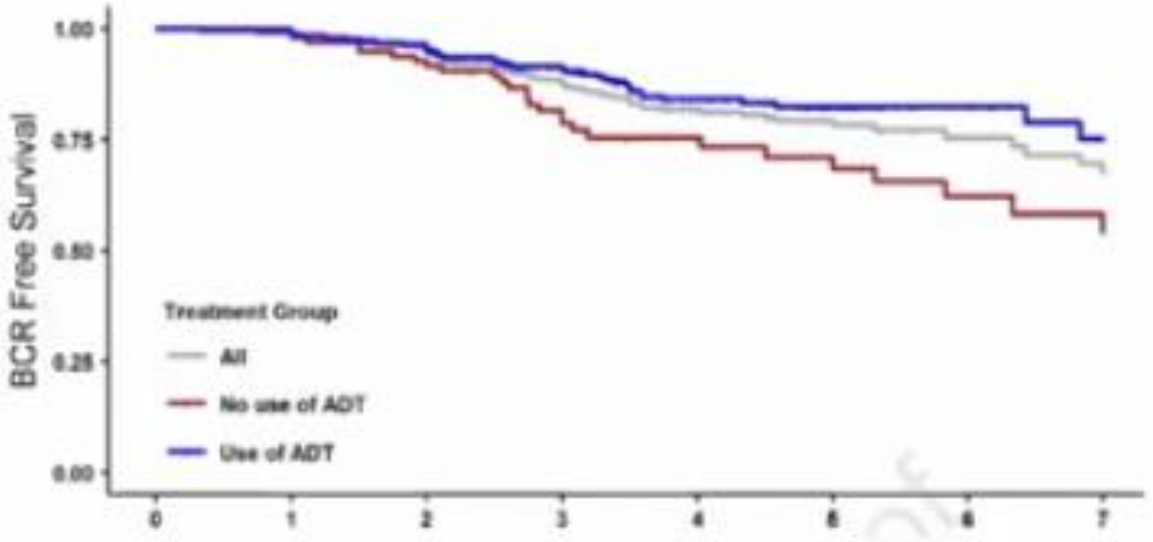
Which Patients Need PNRT?



Courtesy of Dr. Tendulkar

SBRT for High Risk

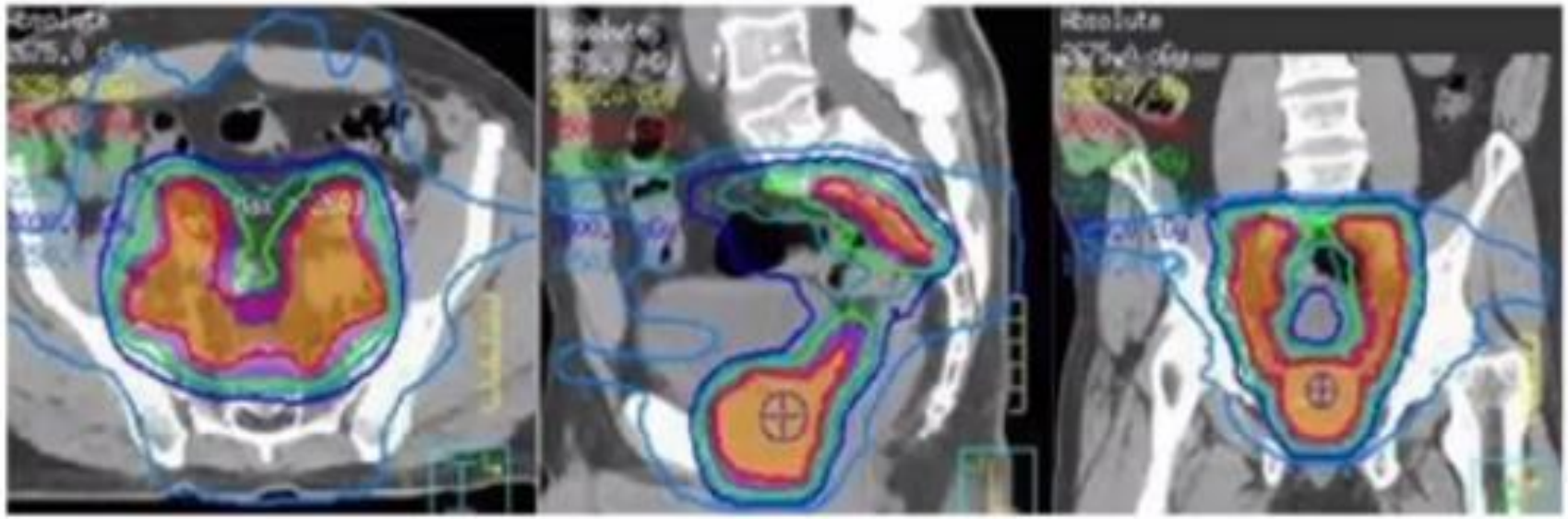
- Emerging data on SBRT in HR
- HYPO-RT-PC: included 126 patients with HR (no ADT used)
- SHARP consortium: 344 patients treated at 7 institutions
  - 72% ADT; 19% received nodal SBRT on protocol
  - 4y bRFS 82%, DMFS 89%
  - Late Gr 3 GU toxicity 2.3%, GI 0.9%



Van Dams IJROBP 2021

High Risk: SBRT + ENI?

- 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



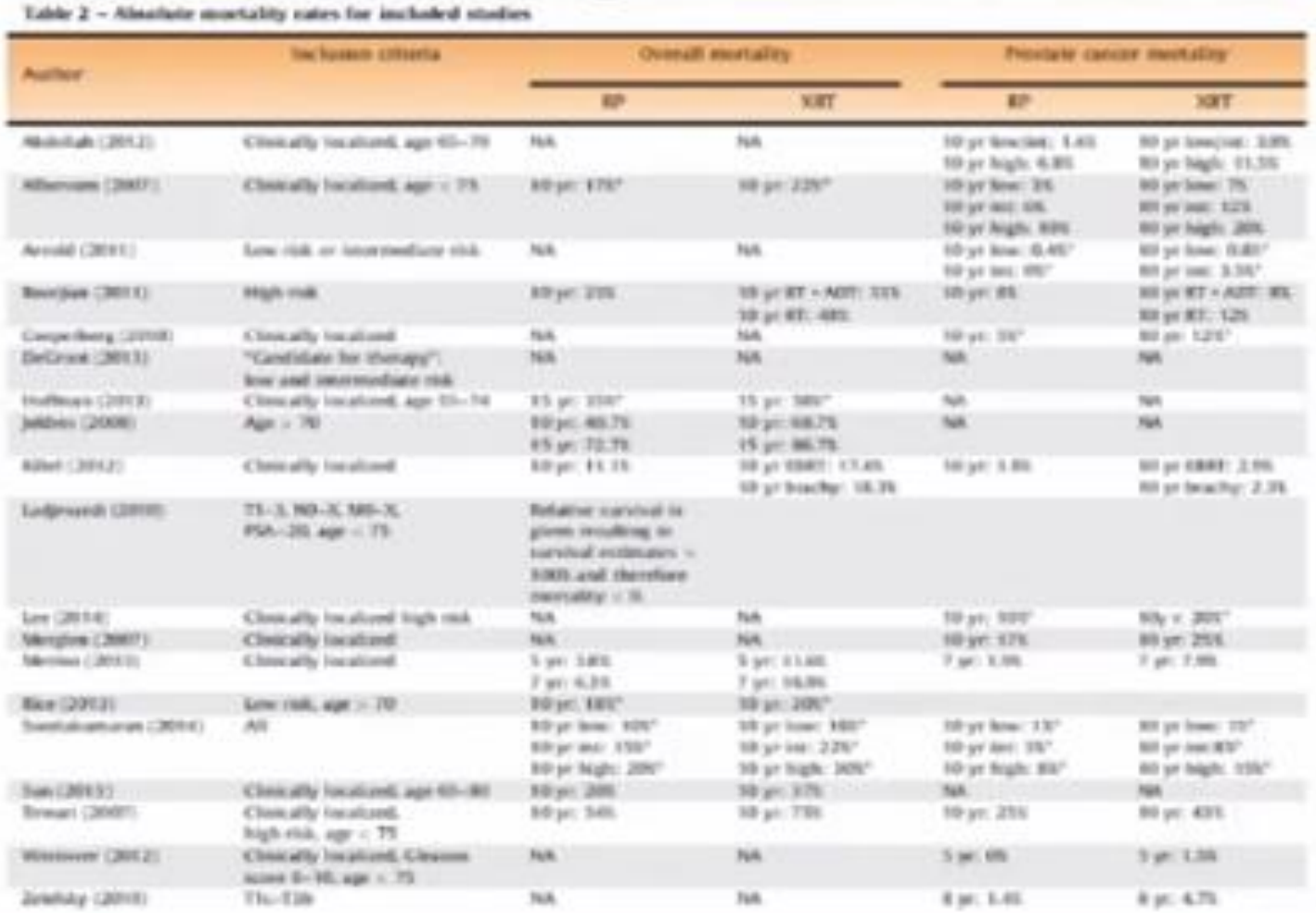
Musunuru IJROBP 2018. Bauman IJROBP 2015. Kothari TCRT 2018.

High Risk: Prostatectomy or Radiation ?

- Retrospective studies are subject to huge selection bias

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

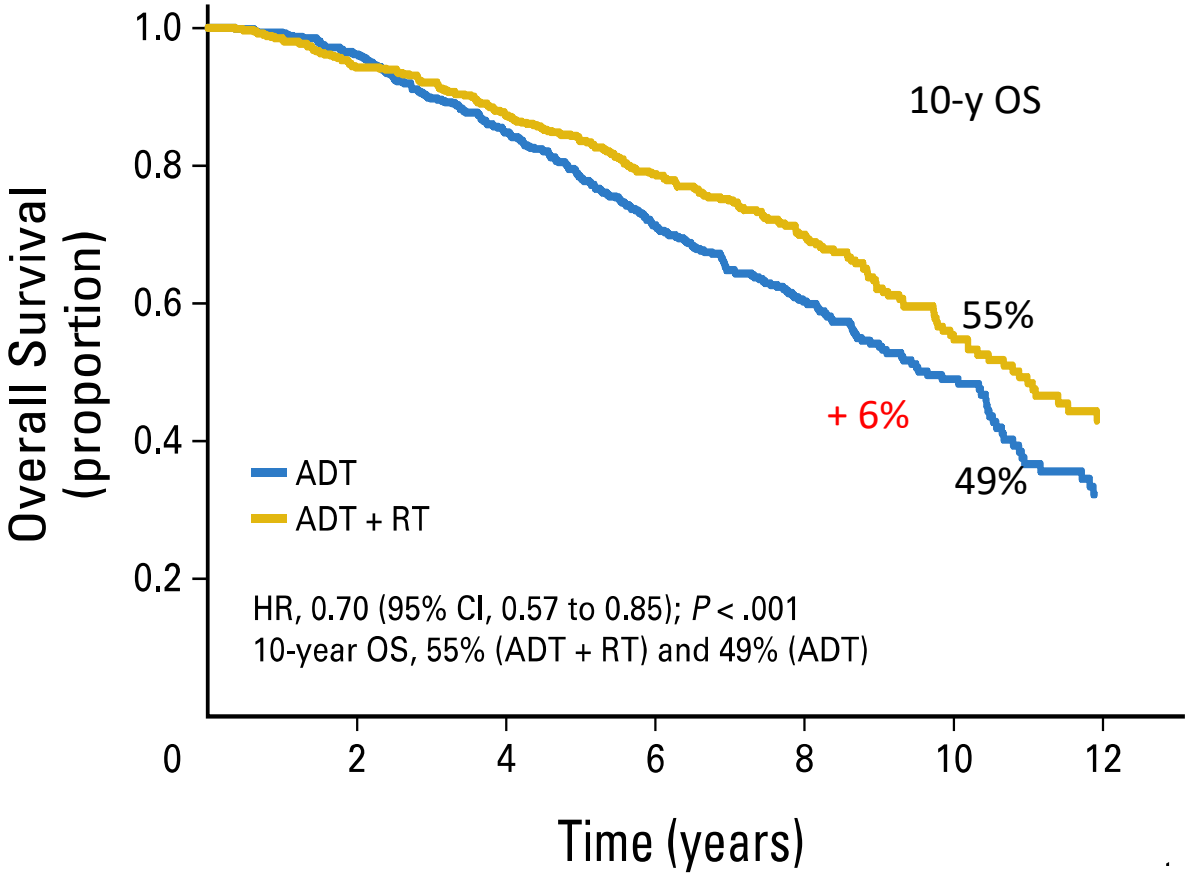
Results awaited



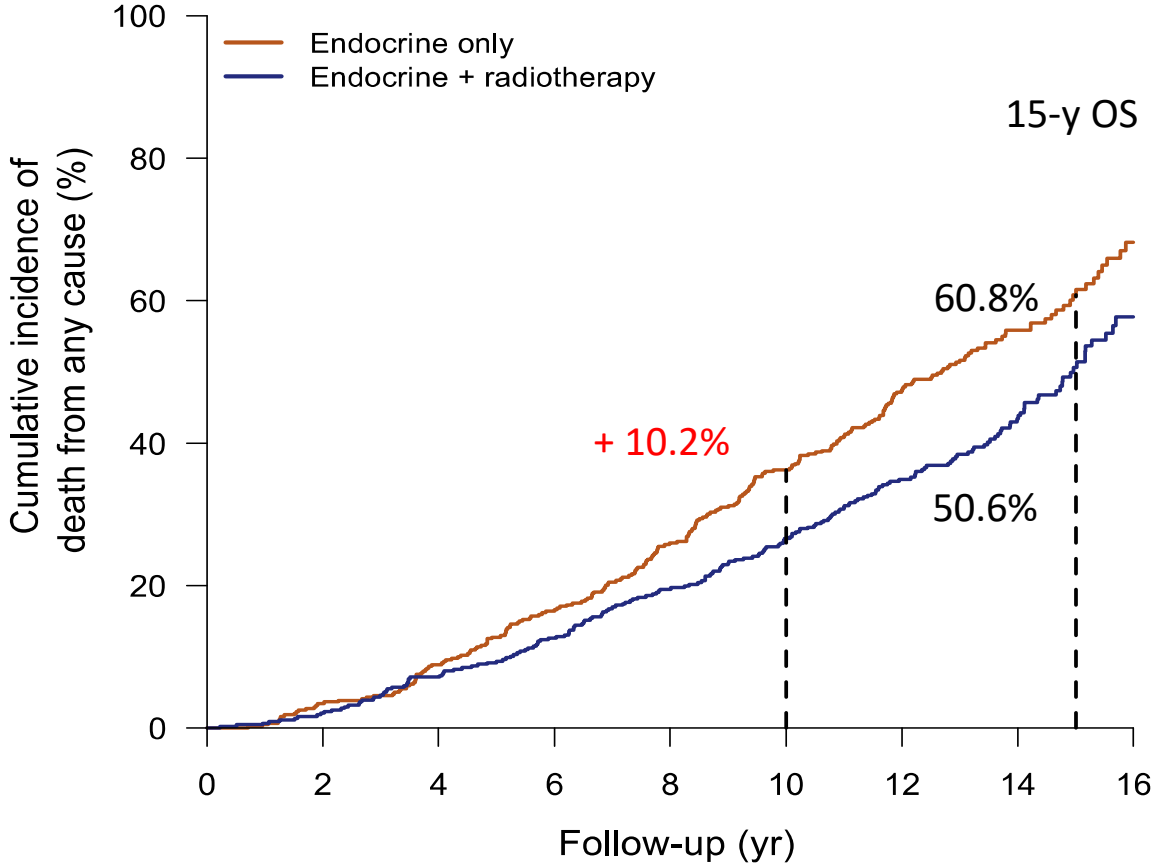
Author	Inclusion criteria	Overall mortality		Prostate cancer mortality	
		RP	XRT	RP	XRT
Abdollah (2012)	Clinically localized, age 65–79	NA	NA	10 yr low/int: 1.4%	10 yr low/int: 3.8%
				10 yr high: 6.8%	10 yr high: 11.5%
Albertsen (2007)	Clinically localized, age < 75	10 yr: 17%*	10 yr: 23%*	10 yr low: 3%	10 yr low: 7%
				10 yr int: 6%	10 yr int: 12%
				10 yr high: 19%	10 yr high: 28%
Arnold (2011)	Low risk or intermediate risk	NA	NA	10 yr low: 0.4%*	10 yr low: 0.8%*
				10 yr int: 6%*	10 yr int: 3.5%*
Boorjian (2011)	High risk	10 yr: 23%	10 yr RT + ADT: 33%	10 yr: 8%	10 yr RT + ADT: 8%
			10 yr RT: 48%		10 yr RT: 12%
Casperberg (2010)	Clinically localized	NA	NA	10 yr: 5%*	10 yr: 12%*
DeGroot (2013)	"Candidate for therapy", low and intermediate risk	NA	NA	NA	NA
Hoffman (2013)	Clinically localized, age 55–74	15 yr: 35%*	15 yr: 38%*	NA	NA
Jaldbin (2008)	Age > 70	10 yr: 40.7%	10 yr: 68.7%	NA	NA
		15 yr: 72.7%	15 yr: 86.7%		
Kibel (2012)	Clinically localized	10 yr: 11.1%	10 yr EBRT: 17.4%	10 yr: 1.8%	10 yr EBRT: 2.9%
			10 yr brachy: 16.3%		10 yr brachy: 2.3%
Lu-Yao (2009)	T1–3, N0–X, M0–X, PSA < 20, age < 75	Relative survival in given resulting in survival estimates – 10(X) and therefore mortality = X			
Lee (2014)	Clinically localized high risk	NA	NA	10 yr: 10%*	10y = 20%*
Mangione (2007)	Clinically localized	NA	NA	10 yr: 17%	10 yr: 25%
Merrick (2013)	Clinically localized	5 yr: 3.8%	5 yr: 11.6%	7 yr: 1.9%	7 yr: 7.9%
		7 yr: 6.3%	7 yr: 16.9%		
Rice (2012)	Low risk, age > 70	10 yr: 18%*	10 yr: 20%*		
Sooriakumaran (2014)	All	10 yr low: 10%*	10 yr low: 18%*	10 yr low: 1%*	10 yr low: 7%*
		10 yr int: 15%*	10 yr int: 22%*	10 yr int: 5%*	10 yr int: 8%*
		10 yr high: 20%*	10 yr high: 30%*	10 yr high: 8%*	10 yr high: 15%*
Sun (2013)	Clinically localized, age 65–80	10 yr: 20%	10 yr: 37%	NA	NA
Stewart (2007)	Clinically localized, high risk, age < 75	10 yr: 54%	10 yr: 73%	10 yr: 25%	10 yr: 43%
Wiesbauer (2012)	Clinically localized, Gleason score 8–10, age < 75	NA	NA	5 yr: 6%	5 yr: 1.5%
Zelefsky (2010)	T1c–T2b	NA	NA	8 yr: 1.4%	8 yr: 4.7%

Wallis Eur Urol 2016

OS improved when ADT is combined with RT in locally advanced PCa



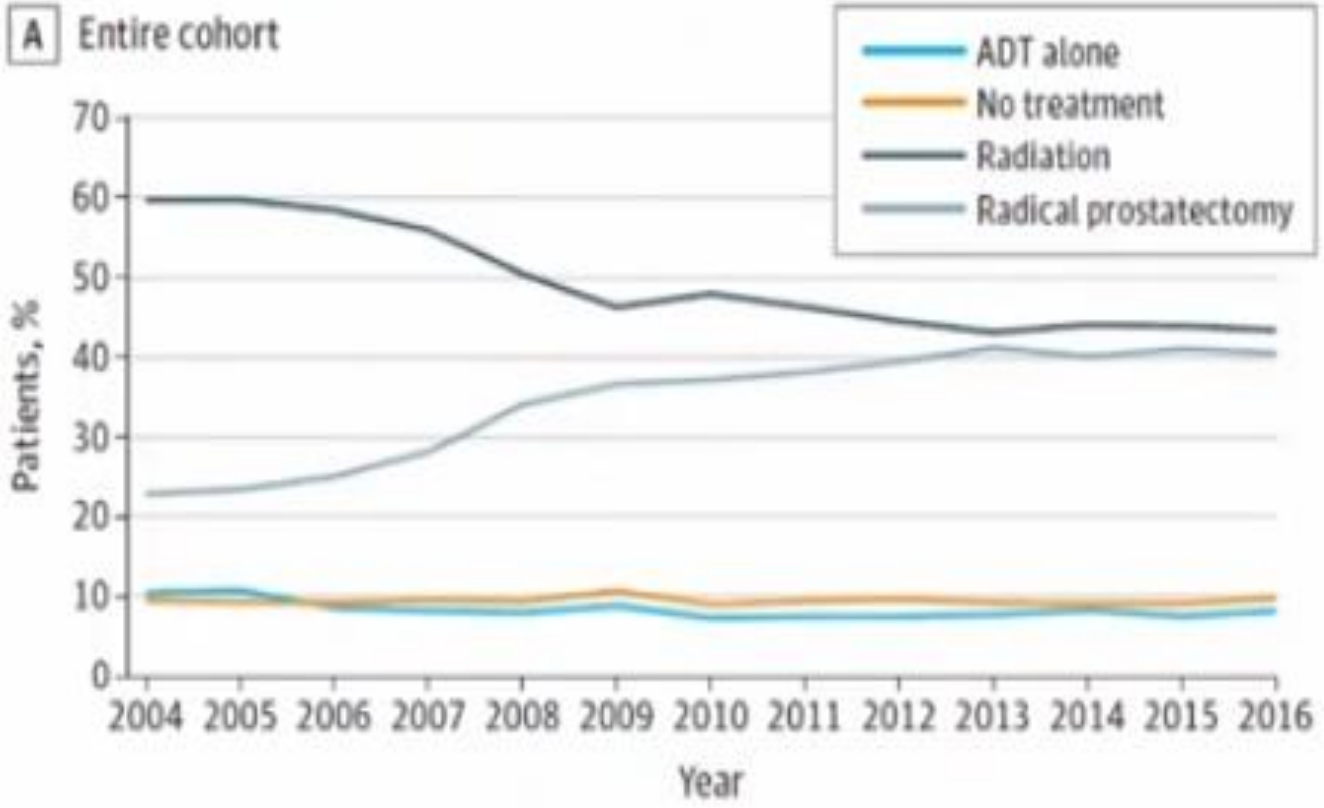
NCI-MRC, JCO 2015



SPC-G7, 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?

Adjuvant RT Trials

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

SWOG 8794 | EORTC 22911 | ARO 96-02

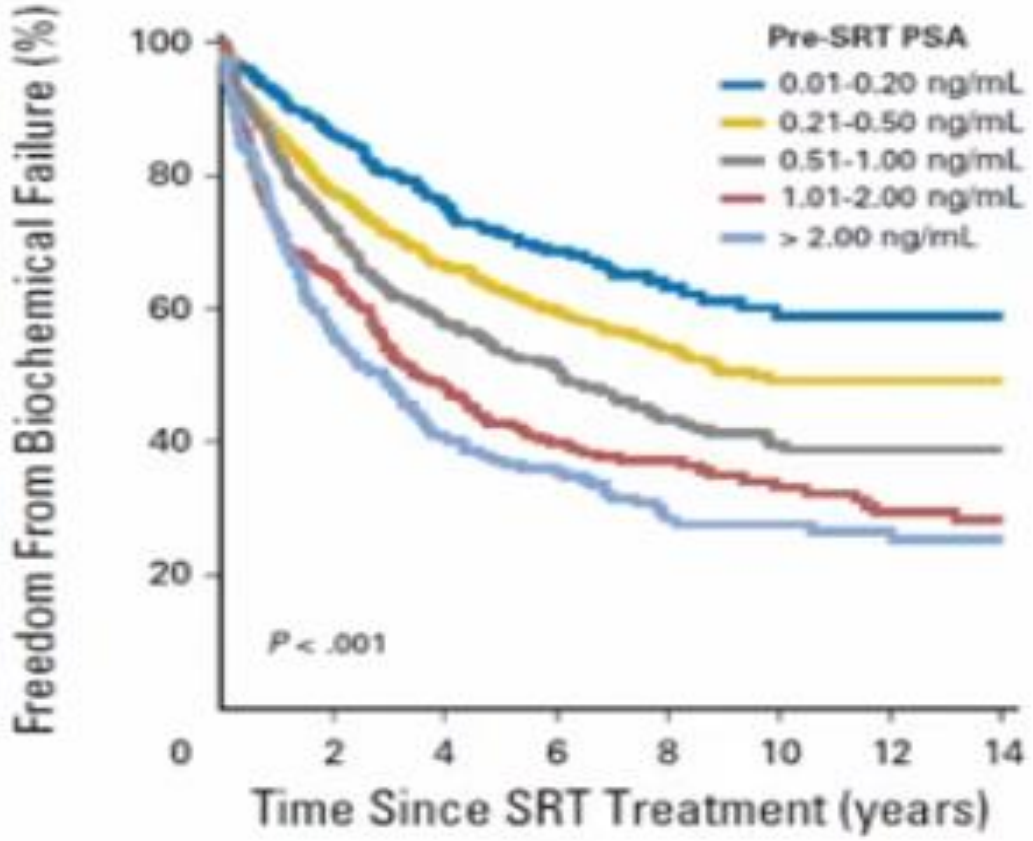
~1/3 had PSA >0.2

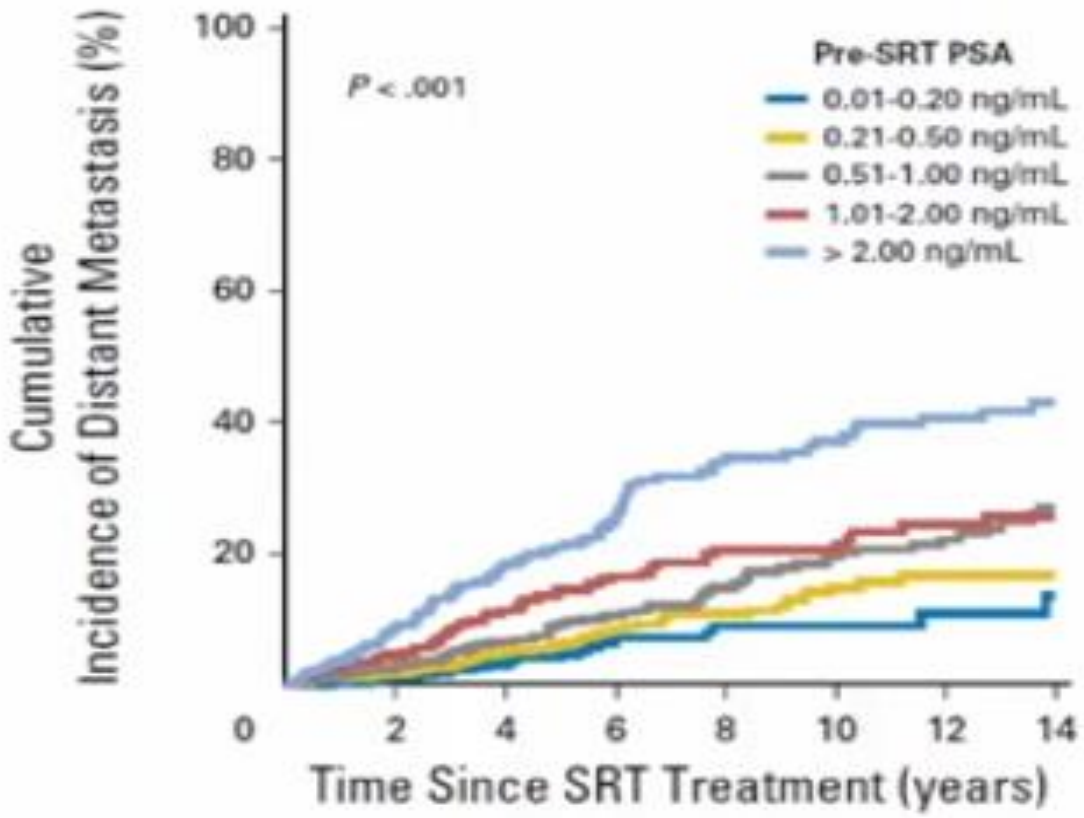
All had PSA <0.1

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

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

Salvage RT is Effective at Lower PSA Levels





Tendulkar JCO 2016

Adjuvant vs (early) Salvage RT RCTs

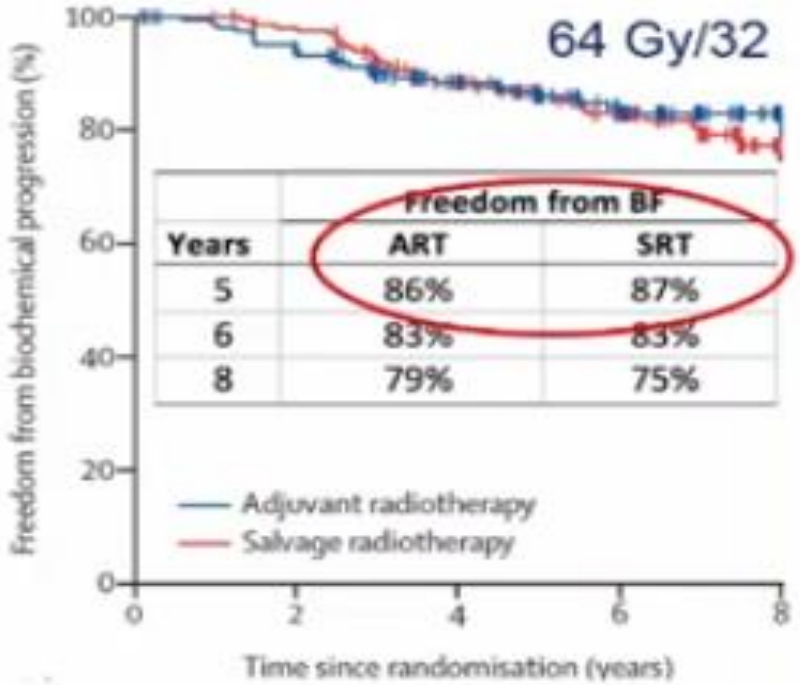
- >2000 patients randomized

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

Kneebone Lancet Oncol 2020. Parker Lancet 2020.

RAVES

64 Gy/32



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

ESRT: PSA ≥0.2

RADICALS

66 Gy/33 or 52.5 Gy/20

5-yr PFS 85% vs. 88% (p=0.56)

ESRT: PSA ≥0.1 or 3 consecutive rising PSAs

ART: Worse GU toxicity

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

Kneebone Lancet Oncol 2020. Parker Lancet 2020.

ARTISTIC Metanalysis

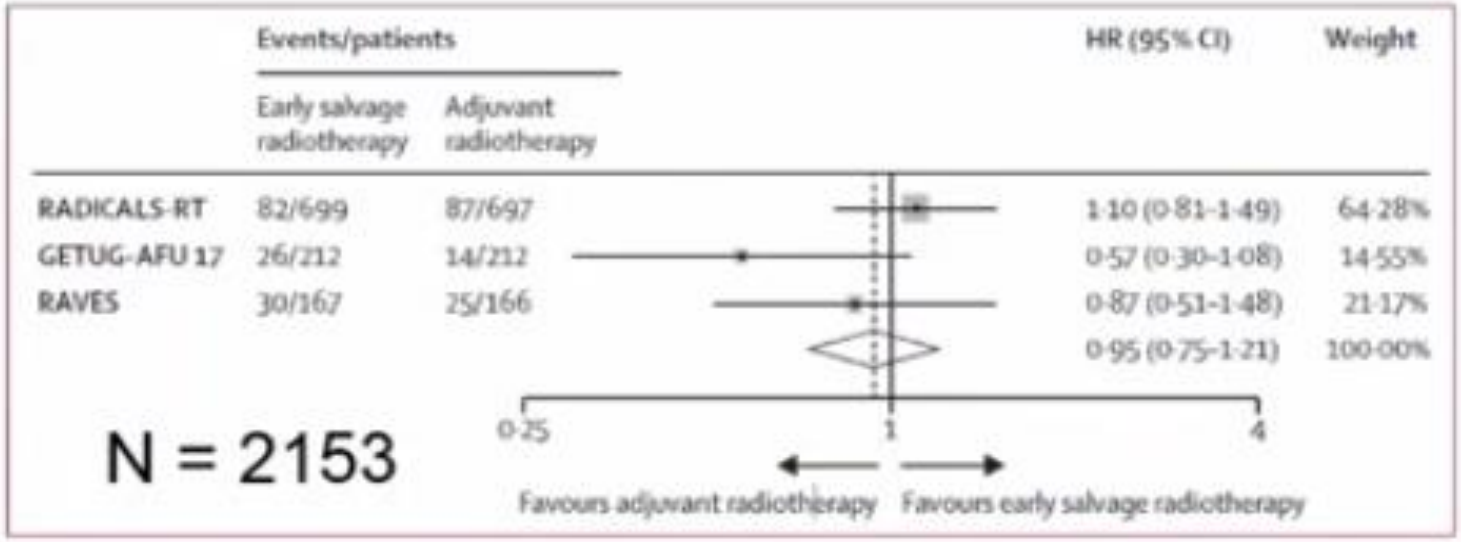


Figure 2: Effect of radiotherapy timing on event-free survival

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

Vale Lancet 2020

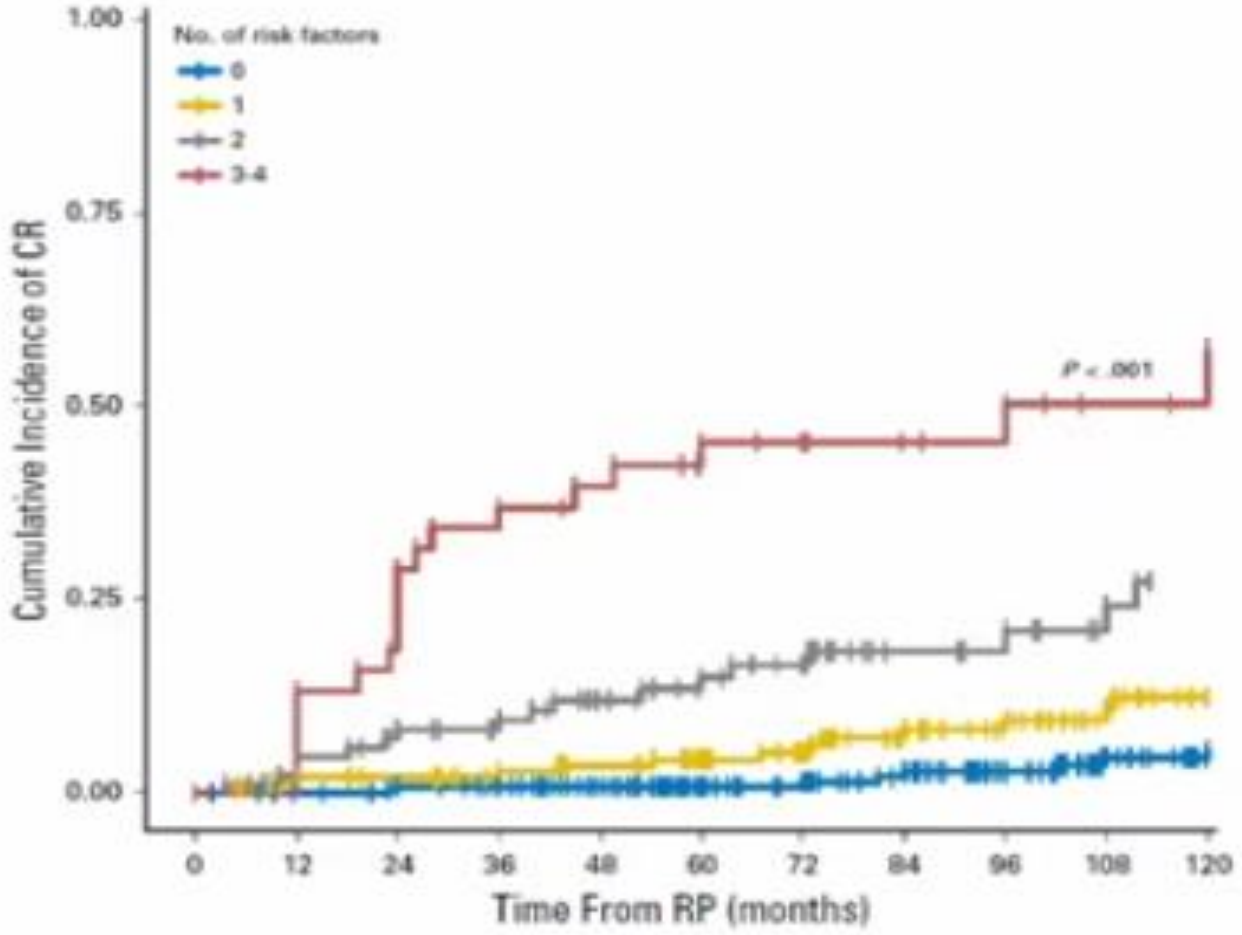
Who Benefits from Adjuvant RT ?

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

4 Risk Factors:

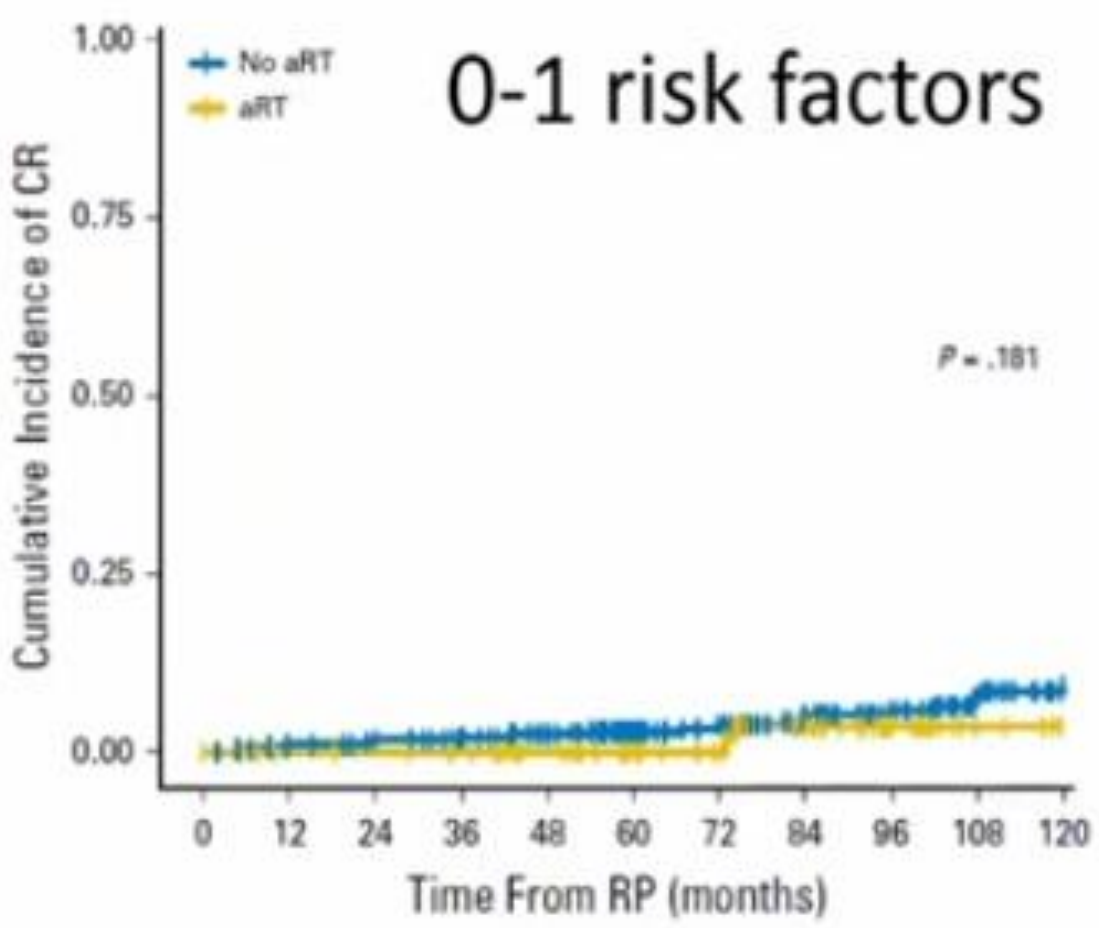
- pT3b/T4
- pGS 8-10
- LN+
- high GC score (>0.6)

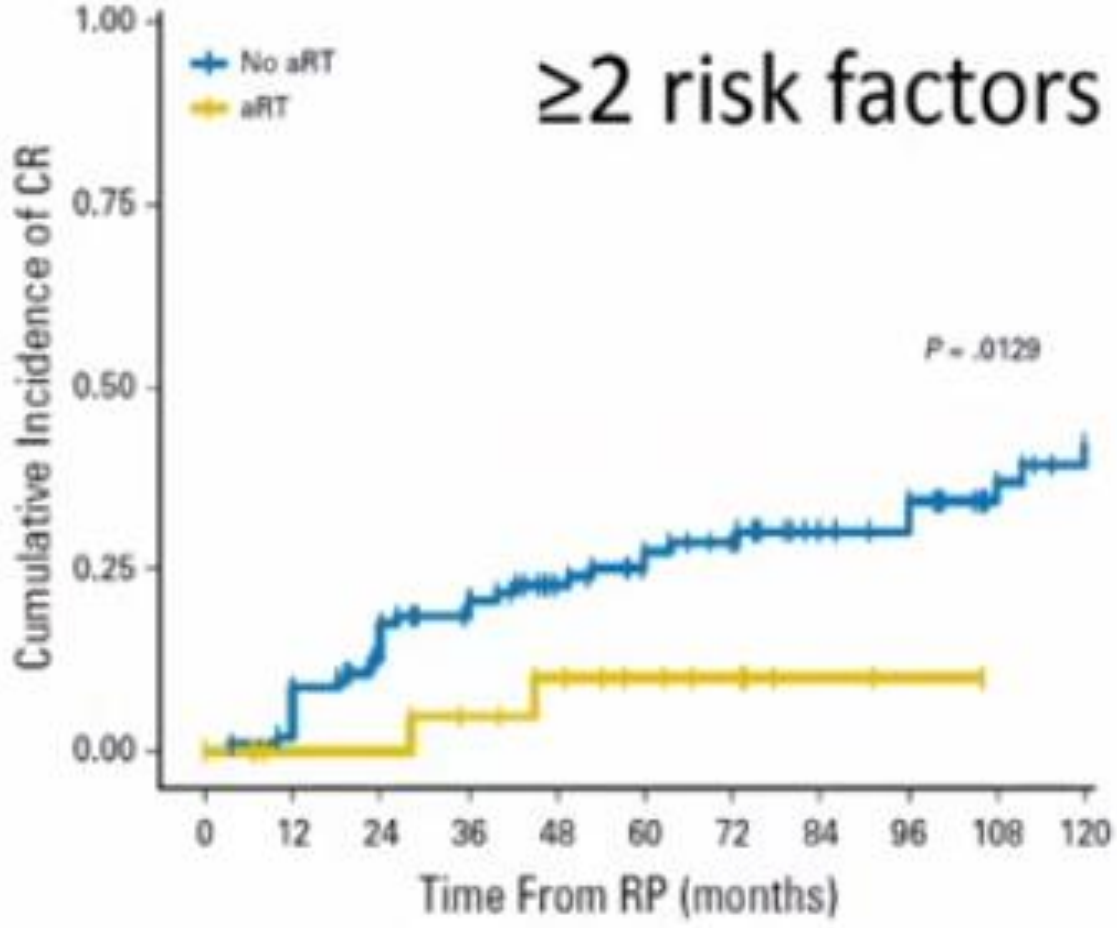
Not prospectively validated



Dalela JCO 2017

Who Benefits from Adjuvant RT ?



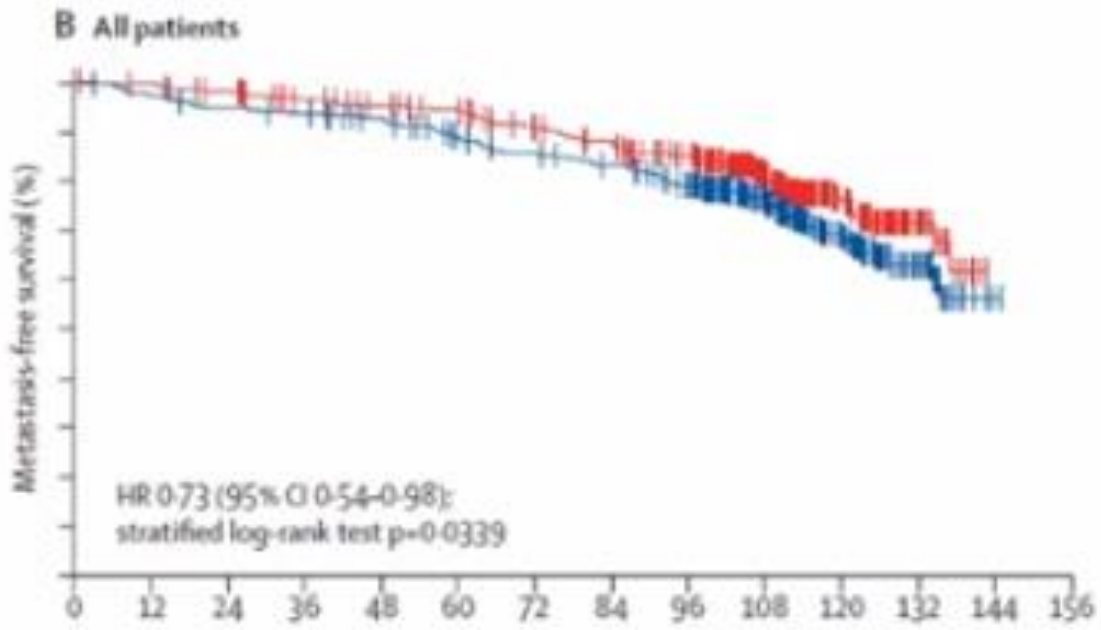


Dalela JCO 2017

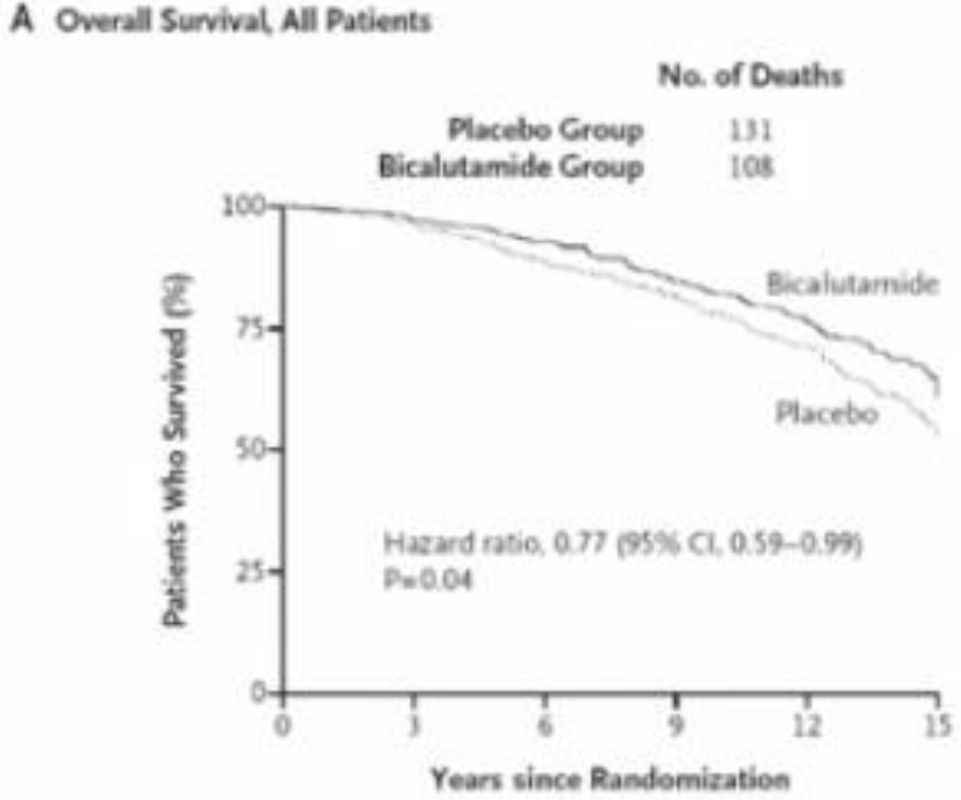
Adding ADT to Salvage RT

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

GETUG AFU-16: ↑ MFS



RTOG 9601: ↑ OS



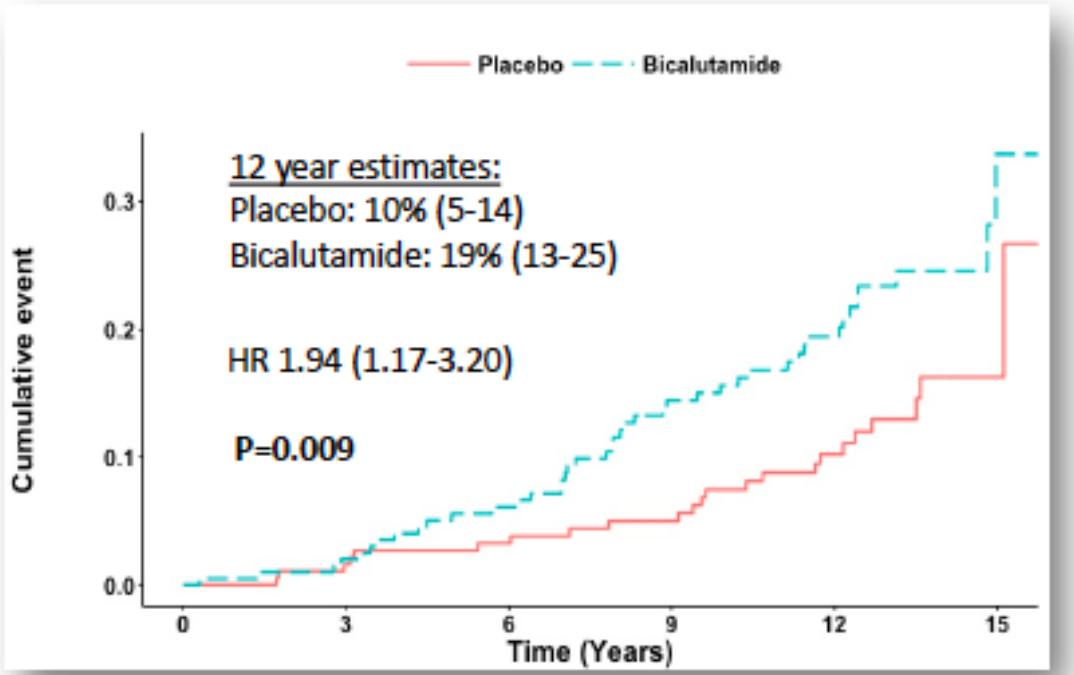
Carrie Lancet Oncol 2019. Shipley NEJM 2017.

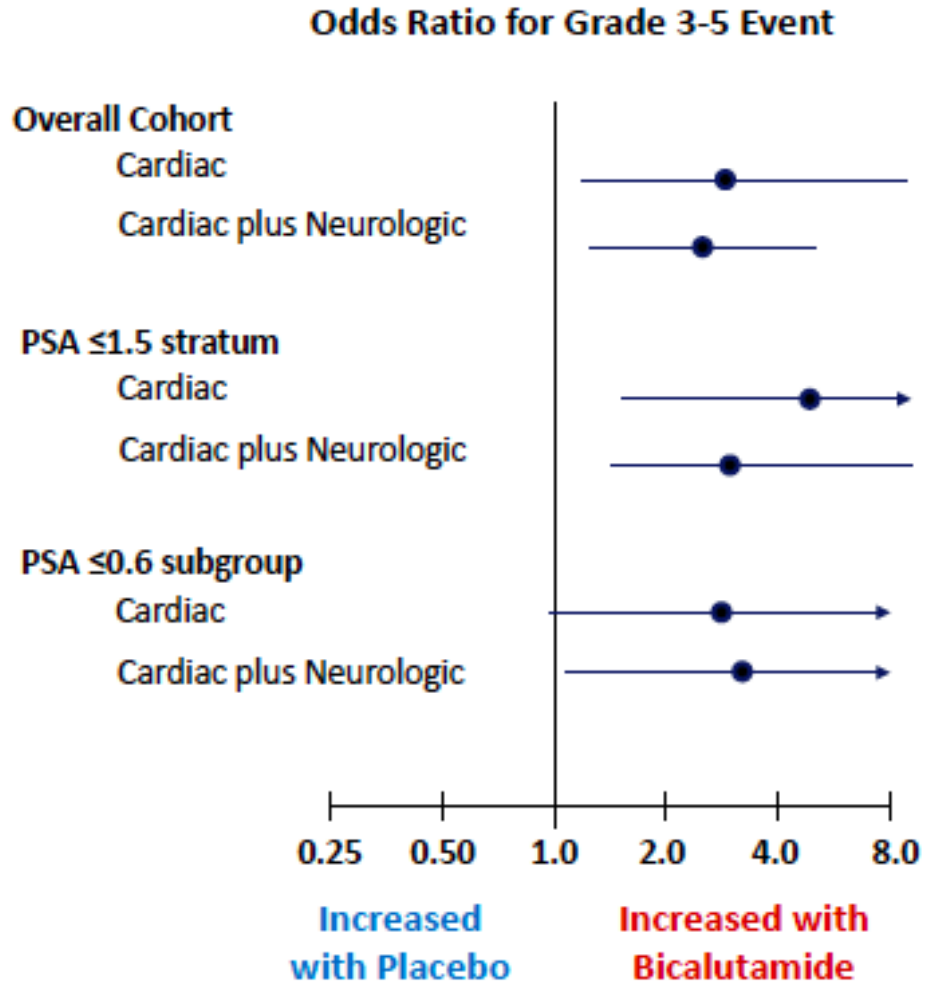
Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy:

A Secondary Analysis of the NRG Oncology/ RTOG 9601 Randomized Phase III Trial

Other-Cause Mortality

PSA 0.2-0.6 ng/mL

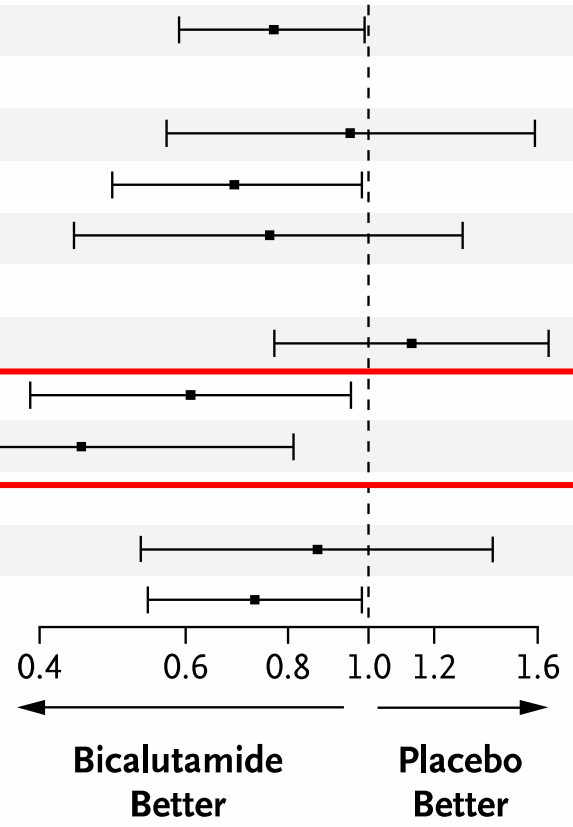




ASTRO 2019

PSA is Predictive of Treatment Effect

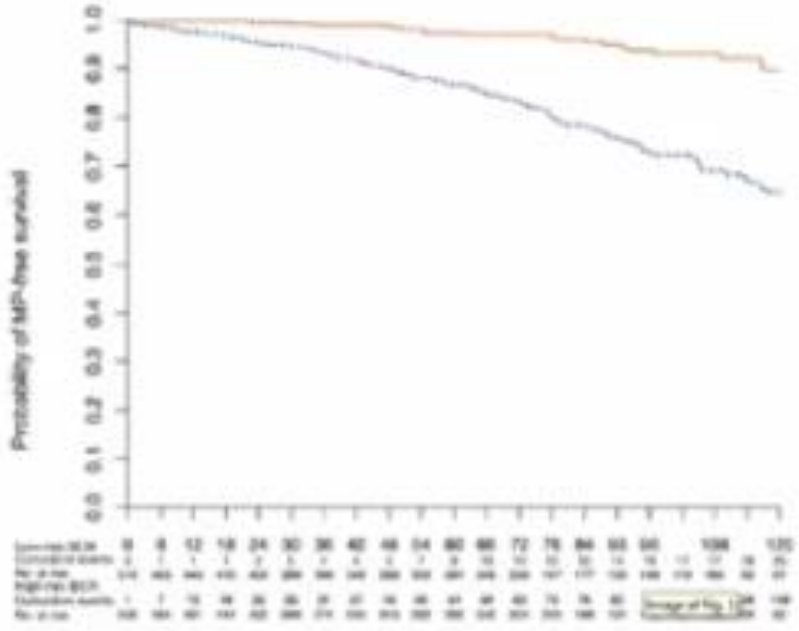
Subgroup	No. of Patients (%)	Bicalutamide Group	Placebo Group	Hazard Ratio (95% CI)	P Value
		12-yr overall survival rate (%)			
Overall	760 (100.0)	76.3	71.3	0.77 (0.59–0.99)	0.04
Gleason score					
2–6	214 (28.2)	79.5	79.2	0.95 (0.57–1.59)	0.84
7	413 (54.5)	78.5	70.9	0.69 (0.49–0.98)	0.04
8–10	131 (17.3)	63.9	58.4	0.76 (0.44–1.30)	0.32
PSA level at trial entry					
<0.7 ng/ml	405 (53.3)	76.8	80.7	1.13 (0.77–1.65)	0.53
0.7–1.5 ng/ml	237 (31.2)	77.0	67.5	0.61 (0.39–0.95)	0.03
>1.5 ngl/ml	118 (15.5)	73.5	48.9	0.45 (0.25–0.81)	0.007
Positive surgical margin					
No	191 (25.1)	73.5	72.9	0.87 (0.53–1.41)	0.56
Yes	569 (74.9)	77.3	70.7	0.73 (0.54–0.98)	0.04



Shipley et al, NEJM 2017

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

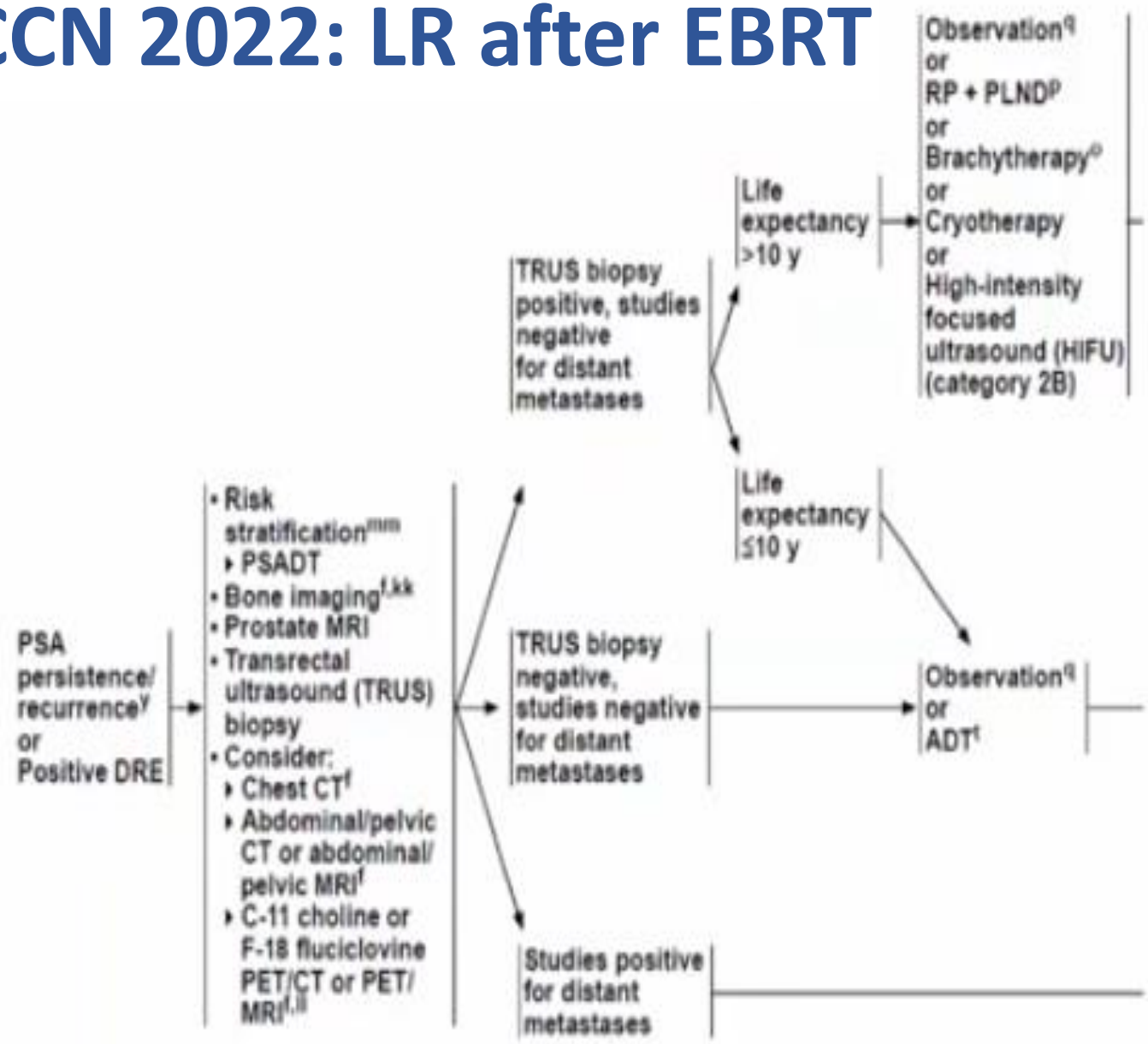


Van den Broeck Eur Urol 2018. Tikki Eur Urol 2019.

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?

NCCN 2022: 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° 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.

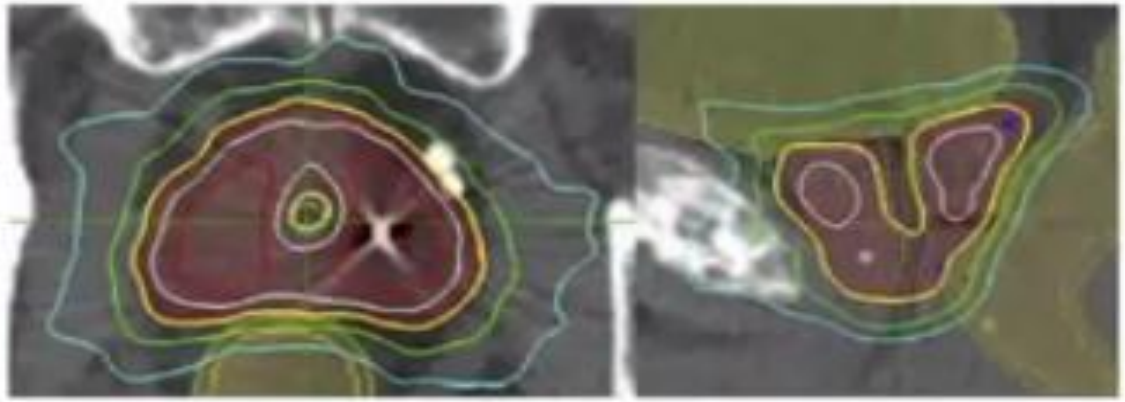
Salvage Therapy for LR after EBRT: SBRT

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 Chauvelnc, 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

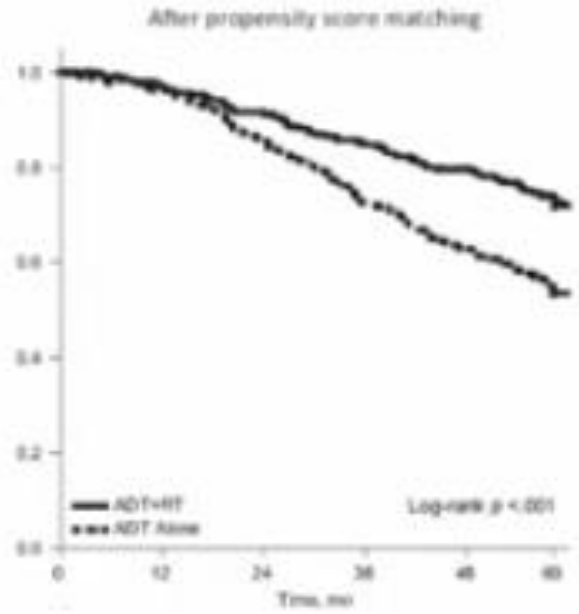
Modality	5y RFS	GU toxicity	GI toxicity
RP	53%	21%	1.5%
Cryo	57%	15%	0.9%
HIFU	46%	23%	0.8%
SBRT	56%	**5.6%**	0.0%
HDR	58%	**9.6%**	**0.0%**
LDR	53%	**9.1%**	2.1%

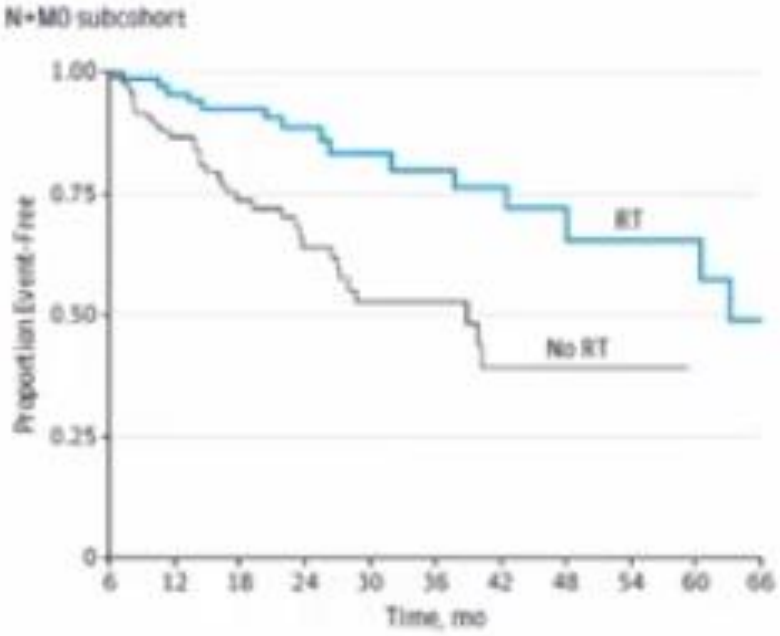
Covariate-adjusted meta-regression % rates shown; $p<0.05$ in **bold**

Valle Eur Urol 2020

Management of Pelvic LN+

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

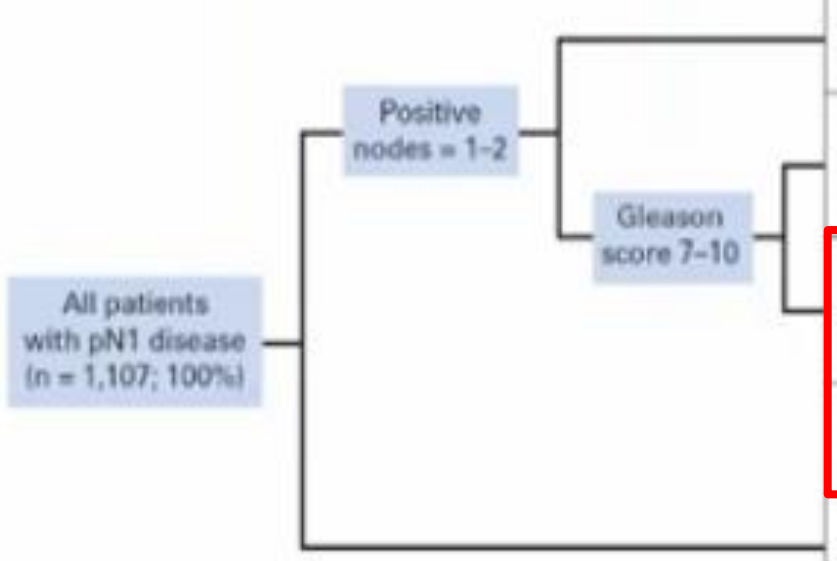




Lawton JCO 2005. Lin JNCI 2015. James JAMA Oncol 2015.

Management of Pelvic LN+

- **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

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.


Thank you