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Introduction

Evidence Based Radiation Oncology Fact Sheets
Prostate Cancer 2022

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AZ 2022

Overview:

Epidemiology:

- Most diagnosed non-skin cancer in men: 220,800 estimated new cases (US 2015, 25% of all new cancers in men).[1]
  - Lifetime risk for diagnosis currently estimated at 15.9%.[2]
  - Lifetime risk of dying of prostate cancer is 2.8%. Note: 70% of deaths is > 75 years.
  - In organ donors, incidental prostate cancer is 1/3 of men between 60 and 69 and 46% (~1/2) of men > 70.
- 2nd estimated 2015 cause of death from cancer (#1 Lung 86,000; #2 Prostate 27,000; #3 Colon 26,000).
- Median age at diagnosis is 70.
  - Screening leads to younger patients with diagnosis.
- Age and Expected Survival (good to memorize):
  - 62 yo patients on average live another 20 years.
  - 77 yo patients on average live another 10 years.
  - 87 yo patients on average live another 5 years.
- Significant stage migration in PSA era.
  - High risk disease 36.6% in 1989-1992 to 16% in 1999-2002
  - Portion of pts with PSA > 20 from 27% in 1990 to 8.1% in 2000
  - T3-T4 from 19.2% to 4.4%
- I suspect the COVID-era will eventually show another stage migration unfortunately the other way.

Work-up

- +/- TRUS, CT, MRI.
- Magnetic resonance spectroscopy (MRS): normal prostate is high citrate, but prostate cancer is high creatinine and choline peaks.
- Bone scans. If low PSA, ↓↓ chance of bone scan being positive. Only 0.3% of patients with PSA < 20 ng/mL by Chybowski had positive bone scan at presentation. Briganti on 853 retrospective-analysis developed a classification that only GS > 7 / PSA > 10 and palpable disease should get a bone scan.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk group	Clinical/pathologic features			Imaging[h,i]	Germline testing	Molecular and biomarker analysis of tumor[l]	Initial therapy
Very low[f]	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Not indicated	See PROS-4
Low[f]	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-5
Intermediate[f]	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]	• Bone imaging[j]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-6
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]	• Bone imaging[j]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Not routinely recommended	See PROS-7
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8

- Don't forget to document: PSA velocity, AUA score, SHIM score, Prostate volume, Prior TURP, Prior RT, Hx of IBD, Co-morbid conditions (cardiac, smoking, DM, RA, etc), Recent colonscopy (primary colon ca, polyps easier to deal with before), Hip prosthesis, Medications (5AR inhibitors, anticoagulants, etc).

[1] http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf
[2] http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening

Decipher GC

Post-Biopsy Decipher (vs. NCCN Risk Categories) Validation
Two cohorts (n = 991) → training/validation clinical-genomic.
Two cohorts (n = 5,937) → reclassification analyses.
1^{O} competing risks analysis was → risk of distant metastasis.

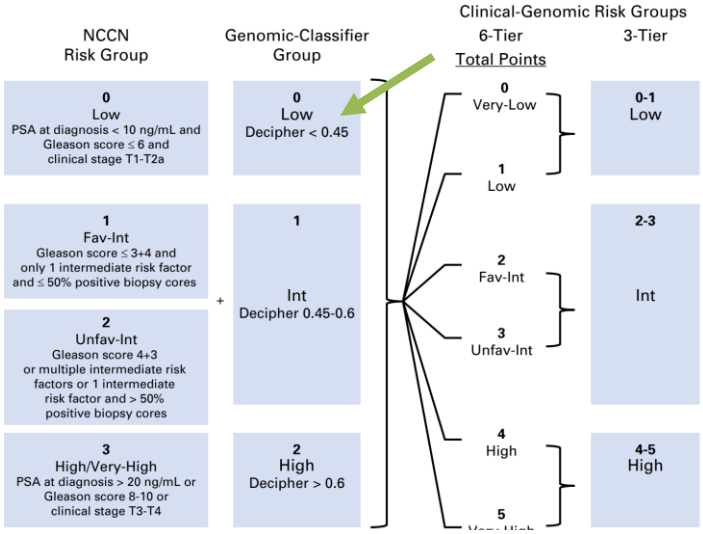
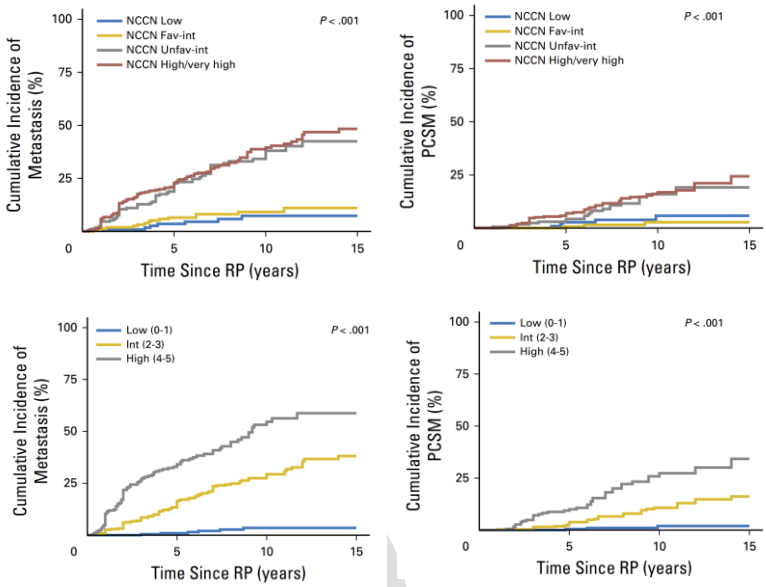


Table 2. Performance Comparison of NCCN and Clinical-Genomic Risk Grouping System

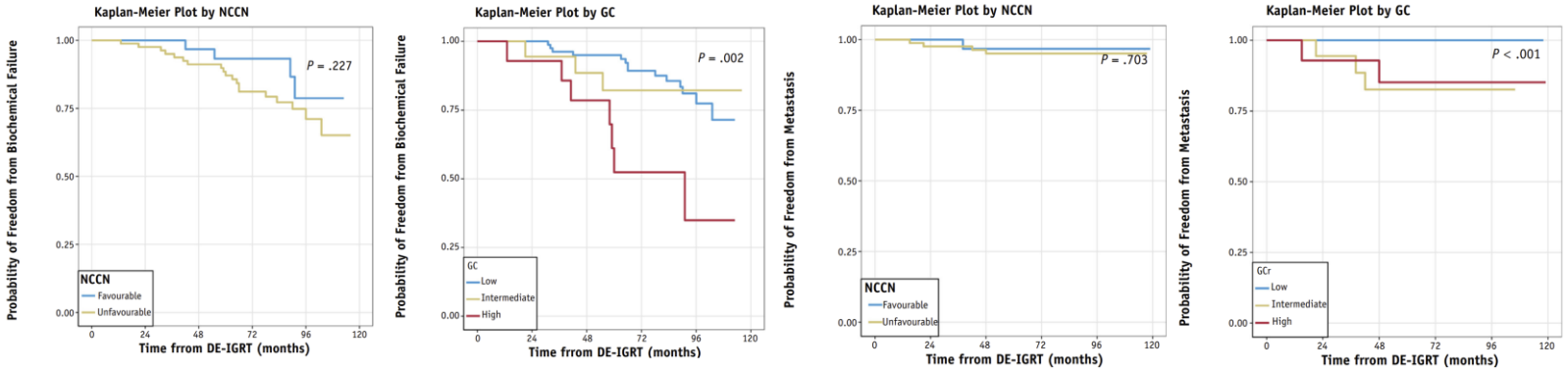
Grouping System	NCCN		Clinical-Genomic Risk Grouping System			
			Training		Validation	
10-year metastasis rate, % (95% CI)	Low	7.3 (1.9 to 12.8)	Low	3.5 (0.7 to 6.3)	Low	0.0 (0.0 to 0.0)
	Fav-int	9.2 (4.3 to 14.0)	Int	29.4 (23.8 to 35.0)	Int	25.9 (8.8 to 43.0)
	Unfav-int	38.0 (29.5 to 46.6)				
	High	39.5 (33.0 to 46.1)	High	54.6 (45.6 to 63.6)	High	55.2 (33.9 to 76.6)
C-index for 10-year metastasis (95% CI)		0.68 (0.64 to 0.73)		0.77 (0.72 to 0.81)		0.84 (0.61 to 0.93)
HR for metastasis (95% CI)	Low	Ref	Low	Ref	Low	Ref
	Fav-int	1.2 (0.5 to 3.0)	Int	9.3 (4.8 to 21.5)*	Int	21.3 (2.8 to 2,727.6)*
	Unfav-int	5.4 (2.8 to 12.0)*				
	High	6.0 (3.2 to 13.0)*	High	21.9 (11.1 to 50.4)*	High	62.5 (8.5 to 7,969.6)*



Spratt, JCO 2018. 8-years FU
NCCN Risks **10-year DM** LR 7.3%, FIR 9.2%, unFIR 38.0%, HR 39.5%.
3 Tier clinical-genomic risks **10-year DM** L 3.5%, I 29.4%, H 54.6%.
Validation cohort **10-year DM** L 0%, I 25.9%, H 55.2%.
C-indices for the clinical-genomic risk grouping system (0.84; 95% CI, 0.61 to 0.93) were improved over NCCN (0.73; 95% CI, 0.60 to 0.86) and Cancer of the Prostate Risk Assessment (0.74; 95% CI, 0.65 to 0.84), and 30% of patients using NCCN low/intermediate/high would be reclassified by the new three-tier system and 67% of patients would be reclassified from NCCN six-tier (very-low– to very-high–risk) by the new six-tier system.
Conclusion A commercially available genomic classifier in combination with standard clinicopathologic variables can generate a simple-to-use clinical-genomic risk grouping that more accurately identifies patients at low, intermediate, and high risk for metastasis and can be easily incorporated into current guidelines to better risk-stratify patients.

Post-Biopsy Decipher (Int Risk PCa).
Cohort 121 IR-Pca w/ IGRT 78 Gy in 39 fractions without ADT. All received Decipher.
NCCN subclassification → F-Int 33 (27.3%) and UnF-Int 87 (71.9%).
GC scores → high in 3 favorable IR-PCa and low in 60 unfavorable IR-PCa.
Formerly established cutoff points of **0.45 and 0.6** for GC were used for categorical analyses.

Berlin, IJROBP 2019.
↑ GC scores (but not NCCN risk subgroups) = ↑ BcF (HR 1.36; P = .007) and ↑ mets (HR 2.05; P = .004).
↑ GC predicted 5-year BcF and the combinatorial NCCN + GC model > (SS) > NCCN alone model for predicting early-onset metastasis.
Conclusions: We demonstrated the accuracy of the GC for predicting disease recurrence in IR-PCa treated with dose-escalated image guided RT alone. *Our findings highlight the need to evaluate this GC in a prospective clinical trial investigating the role of ADT-RT in clinicogenomic-defined IR-PCa subgroups*.

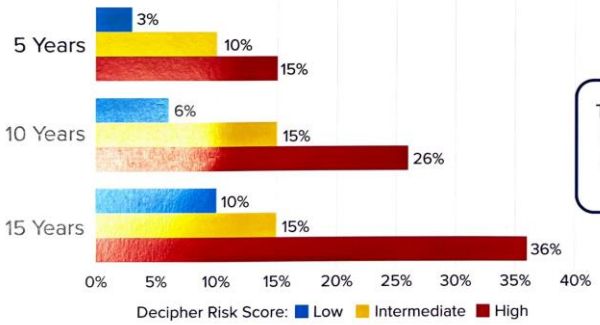


Post-Biopsy Analysis of 3 Trials using Decipher

RTOG 92-02 – LA PCa	Adj LT-ADT	Goserelin 3.6 mg SC qM + flutamide 250 mg TID for 2 months before and 2 months during XRT.		
	THEN	1. Observation (ST-ADT)	2. Two years of goserelin (LT-ADT)	
RTOG 94-13 – LA PCa	Complex ←R→	1. ADT 2 mos. NAC+C RT 50.4 Gy WP → P bst to 70.	2. NHT 2 mos. NAC+C RT to P only to 70.	
		3. RT 50.4 Gy to WP → P boost to 70. → 4 mo. AHT	4. RT P only → 4 mos. of AHT.	
RTOG 99-02 – LA PCa	Chemo Trial	1. EBRT + ADT long term GnRH agonist 2 years	2. EBRT + ADT + Chemo	

GC scores were obtained on 385 samples (n=90 on 9202, n=172 on 9413, and n=123 on 9902), of which **n=265** passed microarray quality control (69%) and had a median follow-up of 11 years (interquartile range, 9, 13).
1^{O} validate the independent prognostic ability of GC for distant metastases (DM).

Nguyen, ASTRO 2021.
MVA, the GC (per 0.1 unit) was independently associated with DM (HR 1.24, SS), PCSM (HR 1.27, SS), and OS (HR 1.12, SS).
Categorical GC, on MVA, **GC score ≥ 0.45** (InR-HR) ↑ DM (HR 2.18, SS), ↑ PCSM (HR 2.34, SS), and ↓ OS (HR 1.45, SS).
10-year DM ↑ GC 29% vs. ↓ GC 13% (SS).



Every 10% increase in Decipher score was associated with a 30% increase in risk for distant metastasis.

The Decipher Score was the strongest and most consistent predictor for DM, PCSM, and OS.

Subset with GC > 0.85 (inclusion threshold in intensification study of NRG GU009 (PREDICT-RT))
5-years DM 29% and 10-years DM 41%
GC had similar prognostic ability in patients receiving short-term or long-term androgen-deprivation therapy (ADT).

Conclusion: This is the first validation of any gene expression biomarker on pre-treatment biopsy samples from prospective randomized trials and demonstrates an independent association of GC score with DM, PCSM, and OS. High-risk prostate cancer is a heterogeneous disease state and GC can improve risk stratification to help personalize shared decision-making. NRG-GU009/PREDICT-RT (NCT04513717) will further determine the optimal therapy based on GC score.

NRG-GU009/PREDICT-RT – Open to Accrual as of 03/2022.

Post-Biopsy Michigan Real World Decipher
Prospective 855 patients had Decipher February 2015 - October 2019.

Vince, Pros Canc Pro Dis 2021.
Of the 855 men, 264 proceeded to AS (31%), and 454 (53%) received radical therapy.
MVA In men electing AS, high-risk Decipher score = ↓ TTT (HR 2.51, p < 0.001).
In men electing radical therapy, a high-risk Decipher = ↓ TTF (HR 2.98, p = 0.01).
Follow-up time was a limitation.
Conclusion: In a prospective statewide registry, high-risk Decipher Biopsy score was strongly and independently associated with conversion from AS to definitive treatment and treatment failure. These real-world data support the clinical utility of Decipher Biopsy. An ongoing phase 3 randomized trial (NCT04396808) will provide level 1 evidence of the clinical impact of Decipher biopsy testing.

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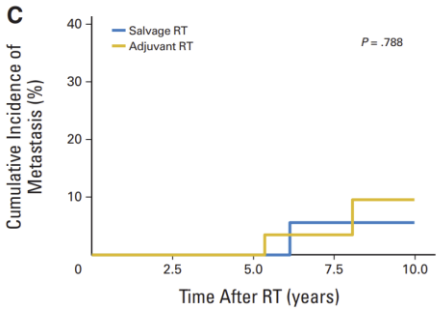
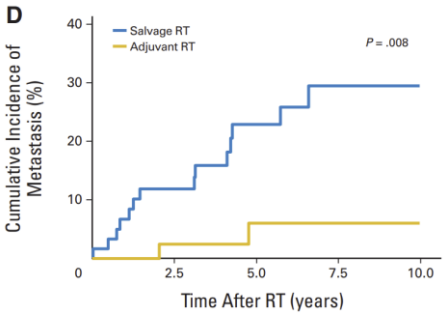
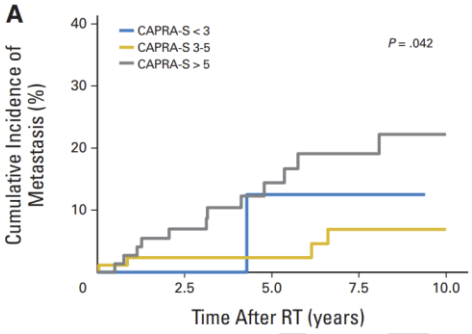
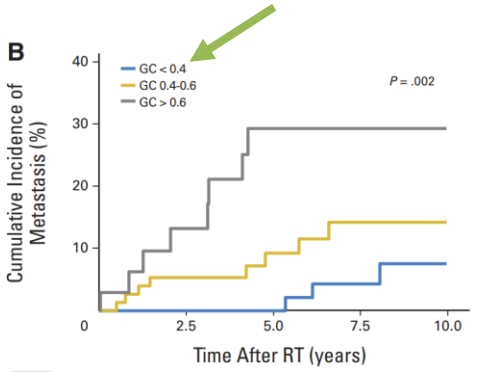
Post-RP Decipher (? ± Adj RT)
GC scores were calculated from 188 patients with pT3 or margin-positive prostate cancer.
1^{O} clinical metastasis.



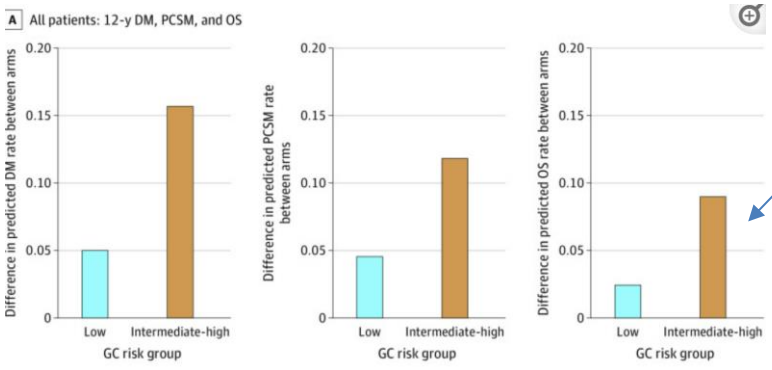
Den, JCO 2015
5-year mets (s/p RP→RT) Low GC 0%, Int GC 9%, High GC 29%. (P = .002).
MVA GC and pre-RP prostate-specific antigen were independent predictors of metastasis (both P < .01).
Low GC score (< 0.4) (Fig C ← LEFT) → NS Δ Mets if adjuvant vs. salvage RT (P = .79).
High GC scores (≥ 0.4) (**FIG D ←LEFT**) → SS Δ Mets if adj 6% vs. salv 23% (P < .01).
Conclusion In patients treated with post-RP RT, GC is prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. Although preliminary, patients with low GC scores are best treated with salvage RT, whereas those with high GC scores benefit from adjuvant therapy. These findings provide the first rational selection of timing for post-RP RT.





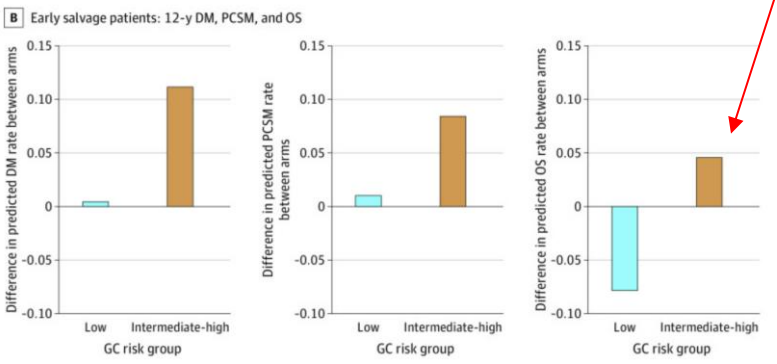


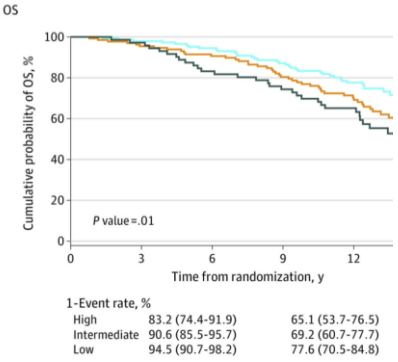
RTOG 96-01 **Post-RP** (**Salvage Radiation)** Validation for Decipher
Evaluation of Salvage radiotherapy (sRT) with or without 2 years of ADT (bicalutamide).
GC scores were generated from 486 of 760 randomized patients.
The GC risk groups were categorized based on per-protocol cut points of 0.4 and 0.6.

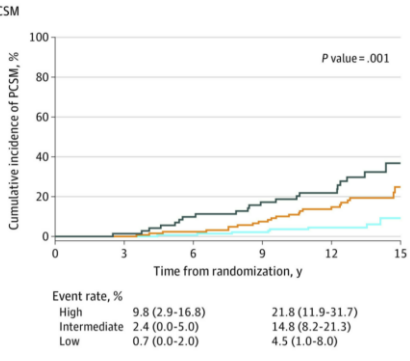


Feng, JAMA Oncol 2021. Median follow-up of 13 years.
MVA = GC (continuous v., per 0.1 unit) independently associated DM (HR 1.17; P = .006), PCSM (HR, 1.39; P < .001), OS (HR, 1.17; P = .002.

(All pts) Est. abs Δ of ADT on 12-y OS = ↓ GC +2.4% vs ↑ GC +8.9%.
(Salv RT) Est. abs Δ of ADT on 12-y OS = ↓ GC -7.8% vs. ↑ GC +4.6%.
Conclusions and relevance: This ancillary validation study of the Decipher GC in a randomized trial cohort demonstrated association of the GC with DM, PCSM, and OS independent of standard clinicopathologic variables. These results suggest that not all men with biochemically recurrent prostate cancer after surgery benefit equally from the addition of hormone therapy to sRT.







Prospective **Post-RP** Evaluation
All men underwent Decipher post-prostatectomy.
Clinical utility cohort → measured Δ in Tx decision-making from urologists across diverse practice settings (n = 3455).
Clinical benefit cohort → examined Δ in <u>outcome</u>, was from a single academic institution whose tumor board predefined "best practices" based on GC results (n = 135).

Marascio, Pros Canc Pro Dis 2020.
Clinical utility cohort, providers' recommendations pregenomic testing were primarily observation (69%).
<u>GC testing changed recommendations for 39% of patients</u> → number needed to **test of 3** to change one treatment decision.
Clinical benefit cohort **61% patients (genomic high-risk tumors)** → 2-year BcF Adj RT 3% vs. Obs only 25% (HR 0.1, p = 0.013).
39% patients (genomic Low-Int Tumors) → 93% received Obs Only. 2-year BcF NS vs. AdjRT (p = 0.93).
Conclusions: The use of GC substantially altered treatment decision-making, with a number needed to test of only 3. Implementing best practices to routinely recommend ART for genomic-high patients led to larger than expected improvements in early biochemical endpoints, without jeopardizing outcomes for genomic-low/intermediate-risk patients.

mCRPC Genetics
Retrospective classification of 634 patients → Luminal 288 (45%) vs. basal 346 (55%). 53 of 59 (90%) small cell neuroendocrine = basal (P < .001).
1^{O} OS from date of tissue biopsy/molecular profiling.
Overexpression: Primary Prostate cancer and Luminal both → AR pathway ↑↑.
Basal tumors = ↑↑ RB1 loss (23% basal vs 4% luminal; P < .001), FOXA1 Δ (36% basal vs 27% luminal; P = .03) and MYC Δ (73% basal vs 56% luminal; P < .001) were identified.

Aggarwal, JAMA Oncol 2021.
Patients with basal tumors had worse overall survival compared with those with luminal tumors only in patients treated with an ASI postbiopsy (East Coast Dream Team: hazard ratio [HR], 0.39; 95% CI, 0.20-0.74; P = .004; West Coast Dream Team: HR, 0.57; 95% CI, 0.33-0.97; P = .04). Among patients with luminal tumors, those treated with an ASI had significantly better survival (HR, 0.27; 95% CI, 0.14-0.53; P < .001), whereas patients with basal tumors did not (HR, 0.62; 95% CI, 0.36-1.04, P = .07). The interaction term between subtype and ASI treatment was statistically significant (HR, 0.42; 95% CI, 0.20-0.89; P = .02).
Conclusions and relevance: These findings represent the largest integrated clinical, transcriptomic, and genomic analysis of mCRPC samples to date, and suggest that mCRPC can be classified as luminal and basal tumors. Analogous to primary prostate cancer, these data suggest that the benefit of ASI treatment is more pronounced in luminal tumors and support the use of ASIs in this population. In the basal tumors, a chemotherapeutic approach could be considered in some patients given the similarity to SCNC and the diminished benefit of ASI therapy. Further validation in prospective clinical trials is warranted.

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Models and Equations

Roach Equations

Extracapsular extension	3/2 x PSA + ([GS-3) x 10)	Approximates actual risk.
Seminal vesicle involvement	1.0 x PSA + ([GS-6] x 10)	Cutoff is 13%. If <13%, risk 7%; if >=13%, risk 37%.
Lymph node involvement	2/3 x PSA + ([GS-6] x 10)	Cutoff is 15%. If calculated risk is <15%, actual risk 6%; if >=15%, actual risk 40%.

MSK has excellent nomograms on Prostate Risk and Treatment: https://www.mskcc.org/nomograms/prostate

PREDICT Prostate https://prostate.predict.nhs.uk/tool
←R→ 145 men median age 67, PSA 6.8 (5.1-8.8) | 1. SOC information | 2. PREDICT tool |.
1^{O} Patient feelings on decisional conflict, uncertainty, anxiety, and perception of survival.

Thurtle, Eur Urol 2021
Mean "Decisional Conflict Scale" scores were 26% lower in the Predict Prostate group (mean = 16.1) than in the SOC group (mean = 21.7; p = 0.027).
Scores on the "support", "uncertainty", and "value clarity" subscales all favoured Predict Prostate (all p < 0.05).
NS → anxiety scores or final treatment selection between the two groups.
Patient perception of 15-yr PCSM and OS from radical treatment were considerably ↓ and more accurate if PREDICT group (p < 0.001).
In total, 57% of men reported that the Predict Prostate estimates for PCSM were lower than expected, and 36% reported being less likely to select radical treatment. Over 90% of patients in the intervention group found it useful and 94% would recommend it to others.
Conclusions
Predict Prostate reduces decisional conflict and uncertainty, and shifts patient perception around prognosis to be more realistic. This randomised trial demonstrates that Predict Prostate can directly inform the complex decision-making process in prostate cancer and is felt to be useful by patients.

Testosterone

Normal testosterone levels According to recent guidelines from the American Urological Association (AUA), a testosterone level of at least 300 nanograms per deciliter (ng/dL) is normal for a man (NORMAL = ~300 to ~1000). A man with a testosterone level below 300 ng/dL should be diagnosed with low testosterone.

50 ng/mL testosterone = castrate resistance.

How does this influence PSA?

E.G. If PSA is 5 with a T of 100 (low), then the patient may really have a "real PSA" that is higher (e.g. ~10) if T is normally increased to ≥ 300.

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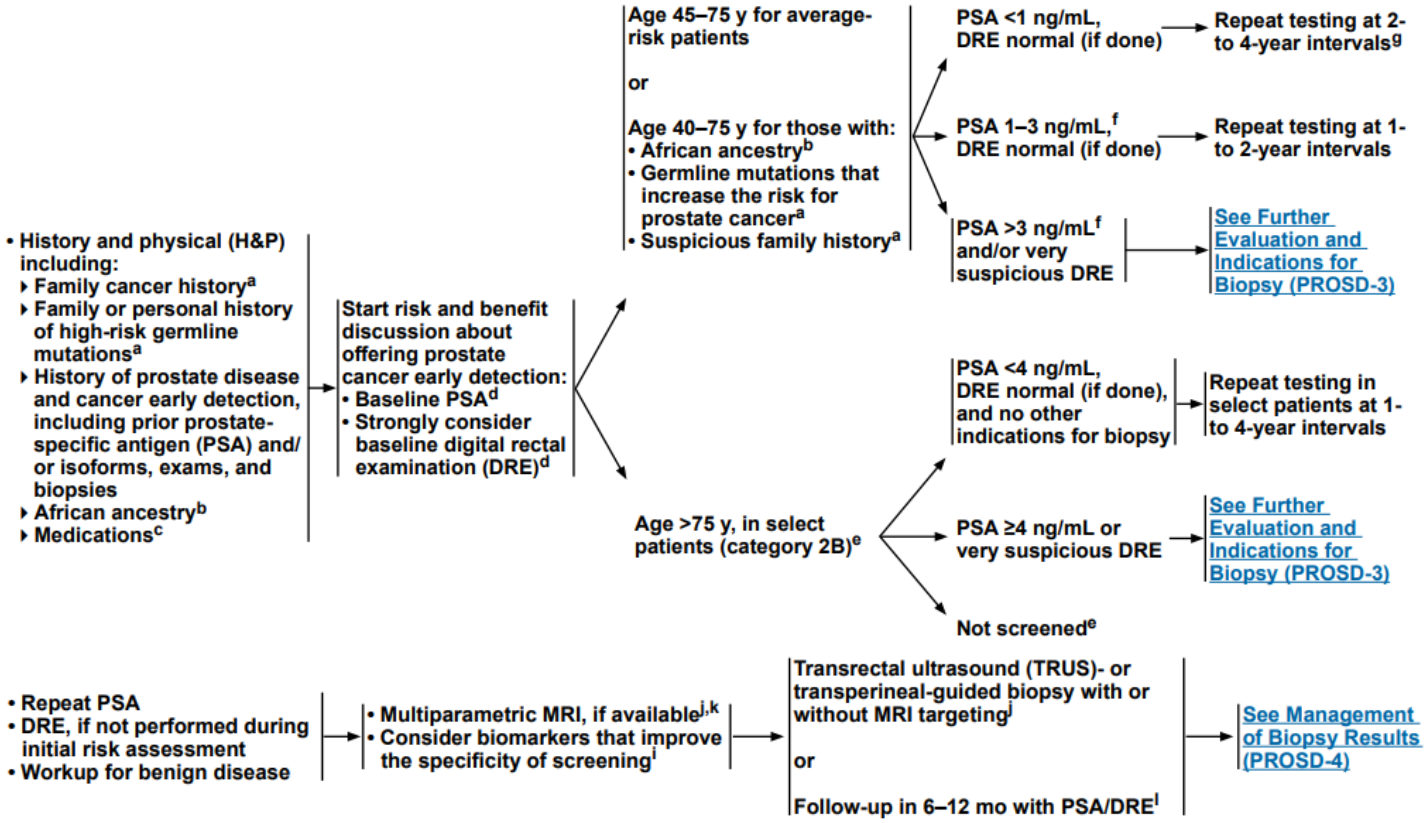
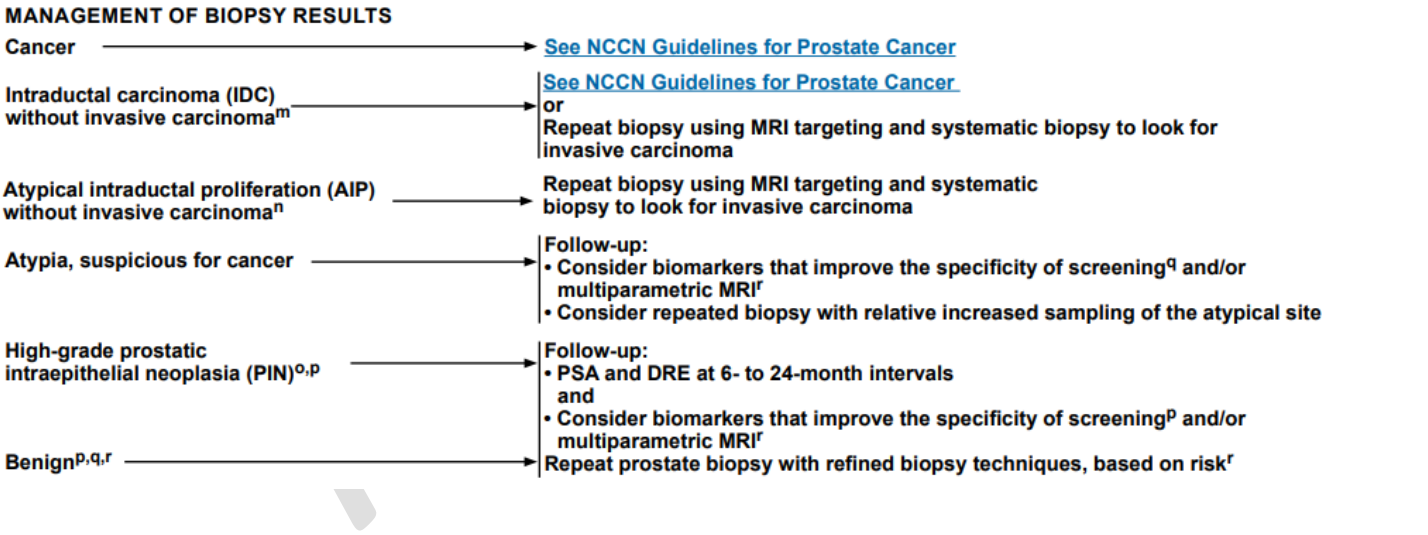
Screening/Imaging



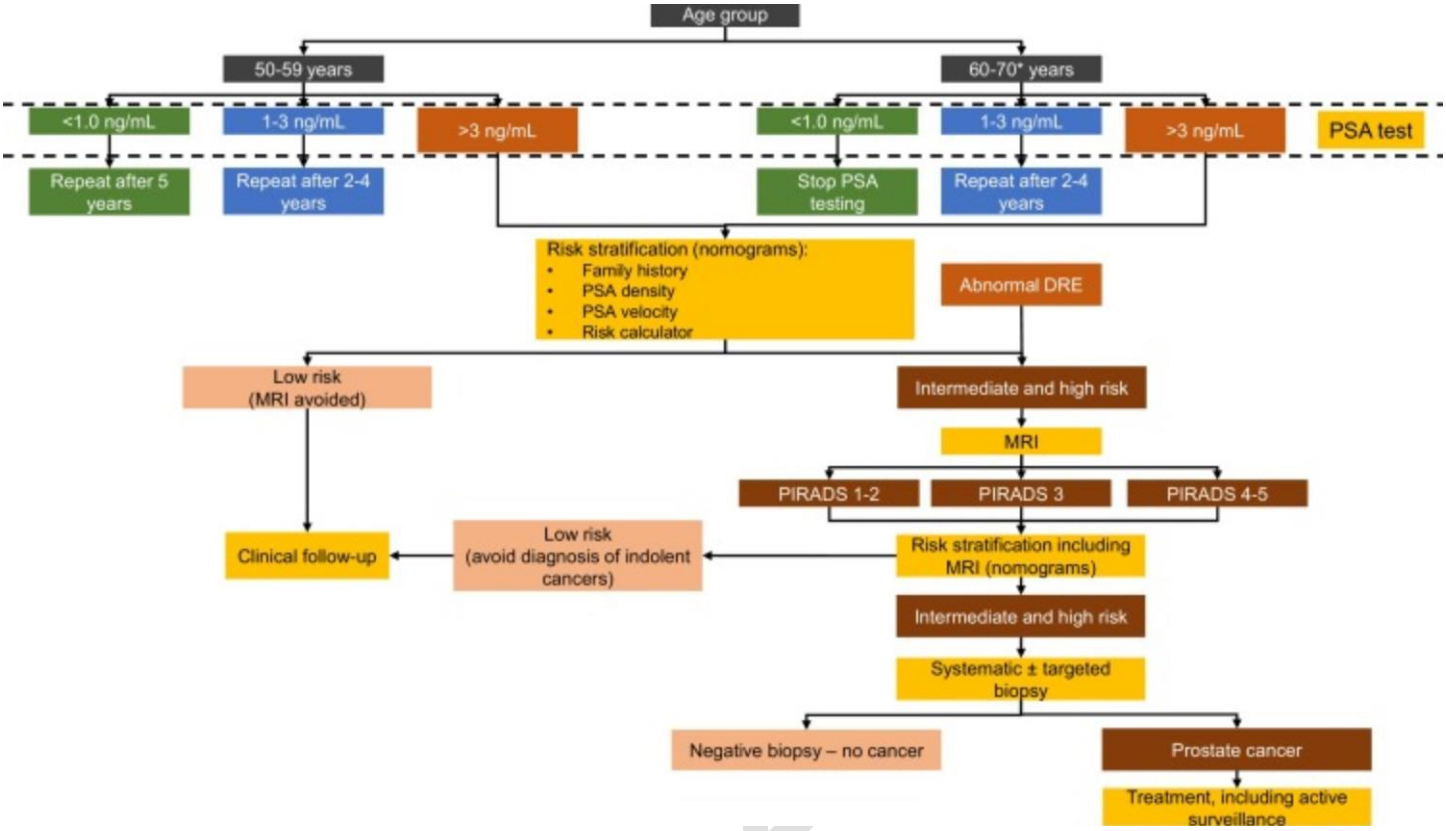


PIRADS MRI Score:

- PI-RADS 1: very low (clinically significant cancer is highly unlikely to be present)
- PI-RADS 2: low (clinically significant cancer is unlikely to be present)
- PI-RADS 3: intermediate (the presence of clinically significant cancer is equivocal)
- PI-RADS 4: high (clinically significant cancer is likely to be present)
- PI-RADS 5: very high (clinically significant cancer is highly likely to be present)
- PI-RADS X: component of exam technically inadequate or not performed

European Urology 2021 Screening Recommendations
See Figure 4 Below ↓↓↓.

Van Poppel, Eur Urol 2021
Conclusions This risk-adapted approach for the early detection of prostate cancer will reverse current unfavourable trends and ultimately save lives.



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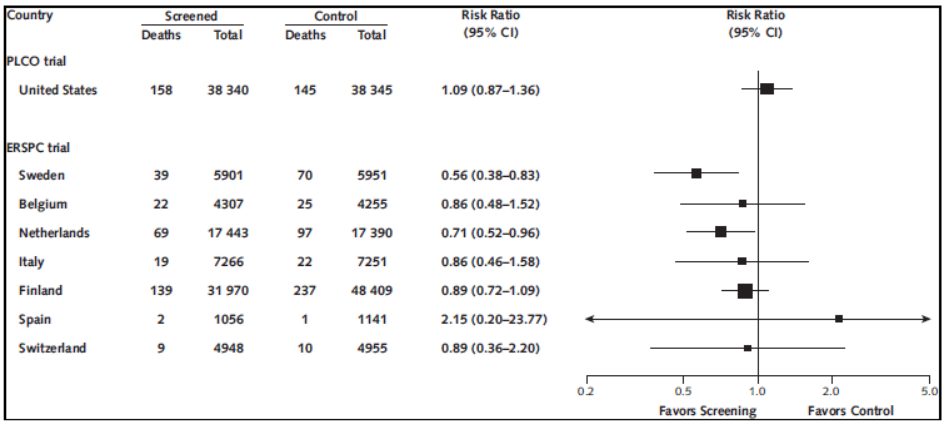
Screening Benefits

- Detect earlier disease to help with treatment.
- https://jamanetwork.com/journals/jama/fullarticle/2680553
- "For men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one and should include discussion of the potential benefits and harms of screening with their clinician. "

    - U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer).
        - PLCO → did not demonstrate any prostate cancer mortality reduction with PSA testing (cutoff PSA > 4 or + DRE).
            - HOWEVER, SUBSET ANALYSIS. Crawford, JCO 2011. IF NO COMORBIDITIES, screening DID show a benefit.
            - Otherwise, if co-morbidities, did not show.
        - ERSPC → reduction in prostate cancer deaths of approximately 1 death per 1000 men screened in a subgroup of men aged 55 to 69 years. To avoid 1 death, you need to screen (NNS) either 1055 men or (NNT) treat 37 men.
            - Critique: heavily influenced by the results of 2 countries; 5 of 7 showed NSS results. All-cause mortality in the European trial was nearly identical in the screened and nonscreened groups.
            - Decrease in prostate cancer death by 21%. NNS 781, NND (detect), 27.
        - Swedish Hugosson, Lancet 2010 → 50-64 yo men qYr. PSa > 3 ng/mL → DRE. 1^{o} PCM.
            - Prostate cancer indidence 12.7% vs. 8.2 % SS.
            - NNS 293 and NNT 12 to prevent 1 prostate cancer death.
            - Conclusion: PSA screening is worth it and ↓ risk of death by almost half.
            - Comment: this is the most "pure" trial because of the randomization and lack of informed consent with good follow-up and had the lowest NNS.

Screening Harms

- Overdetection: "silent cancers" and overtreatment: "tx causes no increase in survival at all."
- Lead time bias of PSA testing of around 5.9 to 7.9 years.
- False-positive results (~80% of positive PSA test results are false-positive when cutoffs between 2.5 and 4.0 µg/L are used).
- 33% w/ prostate biopsy → pain, fever, bleeding, infection, transient urinary difficulties, or other issues requiring clinician follow-up that the men consider a "moderate or major problem."[3]
    - Approximately 1% requires hospitalization.

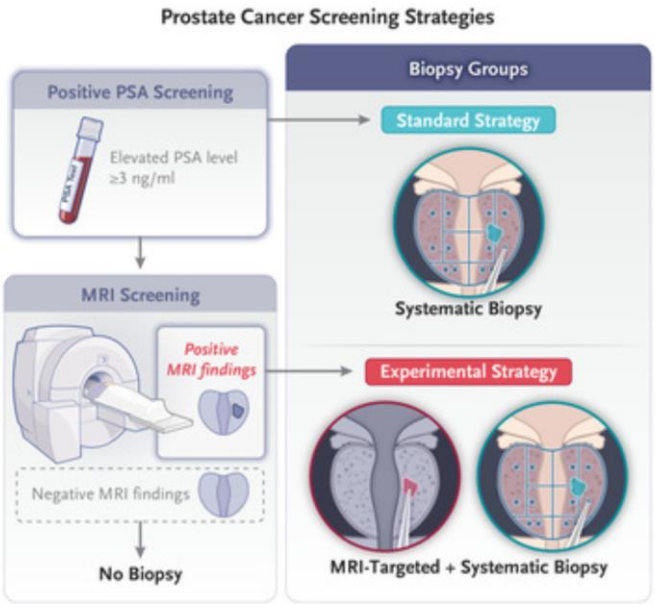


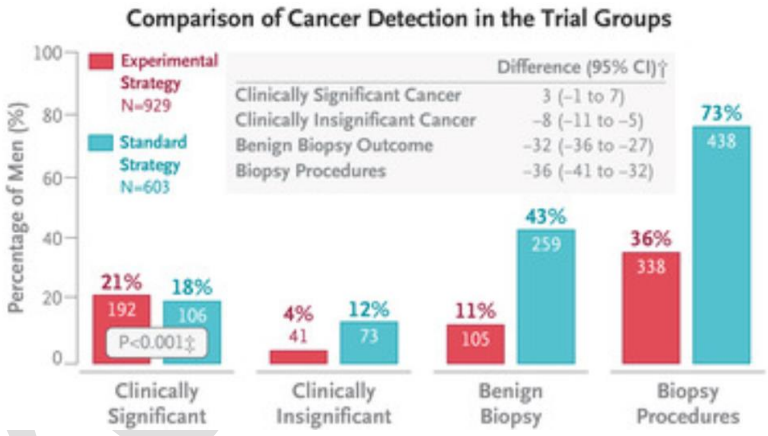
[3] Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. 2012;344:d7894.

MRI Biopsy

STHLM3 Swedish MRI Trial
←R→ 1532 50-74 yo men with PSA > 3 | 1. Standard Biopsy | 2. MRI targeted → if +, then also Standard |.
1^{O} Proportion of men with clinically diagnosed cancer (GS ≥ 7). 2^{O} detection of insignificant GS 6 cancers.

Eklund, NEJM 2021
Detection of GS ≥7 cancer 18% vs. 21% (P<0.001 for noninferiority).
CONCLUSIONS MRI with targeted and standard biopsy in men with MRI results suggestive of prostate cancer was noninferior to standard biopsy for detecting clinically significant prostate cancer in a population-based screening-by-invitation trial and resulted in less detection of clinically insignificant cancer.





Canadian MRI guided biopsy (vs standard TRUS)
←R→ 453 patient biopsy-naive men with "clinical suspicion of prostate cancer" (≥ 5% of ≥ GG2 PCa using the Prostate Cancer Prevention Trial Risk Calculator, v2). Additional criteria were PSA ≤ 20 and no contraindication to MRI | 1. MRI targeted biopsy | 2. TRUS 12-core biopsy |.

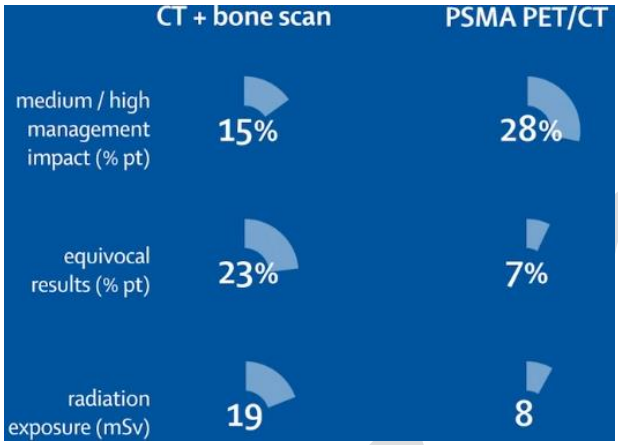
Klotz, Jama Net 2021.
A lesion with a PI-RADS ≥ 3 detected in 138 of 221 men (62.4%) who underwent MRI.
PIRADS 3 in 26 (12.1%), PIRADS 4 in 82 (38.1%), and PIRADS 5 in 30 (14.0%).
83 of 221 men who underwent MRI-TB (37%) had a negative MRI result and avoided biopsy.
Cancers ≥ GG2 identified in 79 of 227 (35%) vs. 67 of 225 men (30%).
Adverse events were less common in the MRI-TB arm.
Grade group 1 cancer detection was ↓ ≥ 50% in the MRI arm (from 22% → 10%).
Conclusions and Relevance Magnetic resonance imaging followed by selected targeted biopsy is noninferior to initial systematic biopsy in men at risk for prostate cancer in detecting GG2 or greater cancers.

Advanced PET

EMPIRE-1 Axumin
←R→ 165 phase 2/3 detectable PSA after prostatectomy and negative conventional imaging → RT directed by | 1. Std imaging alone | 2. Std + Axumin |.
Axumin = 18F-fluciclovine-PET/CT.
1^{O} 3-year EFS.

Jani, Lancet 2021.
Axumin → four patients having radiotherapy aborted.
Mean OS not reached in either arm. 3- EFS 63·0% vs. 75·5% (Δ 12·5; p=0·0028).
In adjusted analyses, study group (hazard ratio 2·04 [95% CI 1·06–3·93], p=0·0327) was significantly associated with event-free survival. Toxicity was similar NS. ↑ late urinary frequency or urgency (41-46%, NS). Acute diarrhoea (14 vs. 21%).
Interpretation Inclusion of 18F-fluciclovine-PET into postprostatectomy radiotherapy decision making and planning significantly improved survival free from biochemical recurrence or persistence. Integration of novel PET radiotracers into radiotherapy decisions and planning for prostate cancer patients warrants further study.

proPSMA Trial Gallium-68 PSMA-PET
←R→ 302 men PCa high-risk features | 1. conventional imaging with CT and bone scanning | 2. gallium-68 PSMA-11 PET-CT |.
First-line imaging was done within 21 days following randomisation. Patients crossed over unless three or more distant metastases were identified.
1^{O} accuracy of first-line imaging for identifying either pelvic nodal or DM.



Hofman, Lancet 2020.
Total 87 (30%) had pelvic nodal or distant metastatic disease.
Primary accuracy 92% vs 65% (p<0·0001).
Sensitivity 85% vs 38% (SS) Specificity 98% vs. 91% (SS).
Subgroup analyses Patients with Pelvic LN+ AoC 91% vs 59% (Δ abs 32%)
Patients with distant Met AoC 95% vs 74% (Δ abs 22%)
Management changes 41 [28%] vs. 23 [15%], p=0·008.
"Equivocal Findings" 7% vs. 23%.
Radiation exposure 8.5 mSv vs. 19·2 (p<0·001).
In patients who underwent second-line image, management change occurred in seven (5%) of 136 patients following conventional imaging, and in 39 (27%) of 146 following PSMA PET-CT.
Interpretation PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning.

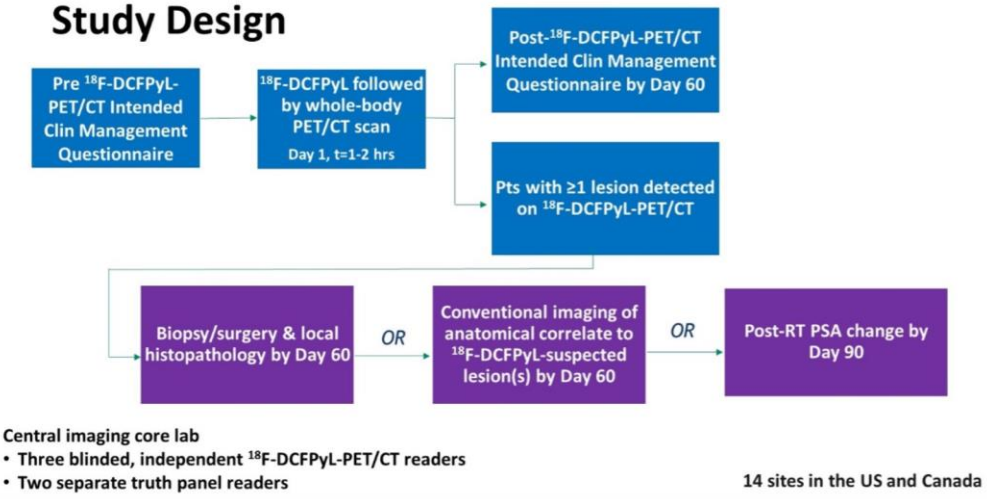
Osprey 18F-DCFPyL Pylarify
←R→ Cohort A (252 evaluable patients) → high-risk PCa undergoing RP + LND.
Cohort B (93 evaluable patients) → Median PSA 11.3 suspected recurrent/metastatic PCa on conventional imaging.
Cohort A, detection of pelvic nodal disease (with specificity and sensitivity as co-primary end points) and of extrapelvic metastases were evaluated.
Cohort B, sensitivity and positive predictive value for prostate cancer within biopsied lesions were evaluated.

Pienta, J Urol 2021.
Cohort A → 18F-DCFPyL Median specificity of 97.9% and sensitivity of 40.3% pelvic nodal involvement
Median PPV 86.7% and NPV 83.2%.
Cohort B → Median PSA 11.3 Median sensitivity 95.8% and PPV 81.9%.
Conclusions: The primary end point for specificity was met while the primary end point for sensitivity was not. The high positive predictive value observed in both cohorts indicates that 18F-DCFPyL-positive lesions are likely to represent disease, supporting the potential utility of 18F-DCFPyL-positron emission tomography/computerized tomography to stage men with high-risk prostate cancer for nodal or distant metastases, and reliably detect sites of disease in men with suspected metastatic prostate cancer.

AZ 2022

Condor 18F-DCFPyL Pylarify

208 patients with BcF PCa (PSA of ≥ 0.2 ng/mL after RP) or by ↑ PSA of at least 2 ng/mL above the nadir after other therapies.
Median serum PSA was 0.82 ng/mL. Prior treatment RP in 85% of the patients.
All enrolled patients had conventional imaging evaluation (for most patients, CT or MRI) within 60 days prior to receiving PYLARIFY PET, and this evaluation was negative or equivocal for prostate cancer. All patients received a single PYLARIFY PET/CT from mid-thigh to skull vertex with optional imaging of the lower extremities.
Three central readers independently evaluated each PYLARIFY PET scan for the presence and location of positive lesions. Location of each lesion was categorized in one of 19 subregions that were grouped into 5 regions (prostate/prostate bed, pelvic lymph nodes, other lymph nodes, soft tissue, bone).



Results: Total of 123 to 137 patients (59% to 66%) had at least one lesion that was identified as PYLARIFY PET-positive (Table 6).
Region most common to be PYLARIFY PET-positive → pelvic lymph nodes (40% to 42% of all PET-positive regions)
Least common region was soft tissue (6% to 7%).
99 to 104 patients with a PYLARIFY PET-positive region had location matched → consisted of histopathology, imaging (CT, MRI, ultrasound, fluciclovine PET, choline PET, or bone scan) or response of serum PSA level to targeted radiotherapy.
True positive = ≥ 1 matching location positive on both PYLARIFY PET and the composite reference standard.

Table 6: Patient-Level Performance of PYLARIFY PET in CONDOR (n=208)

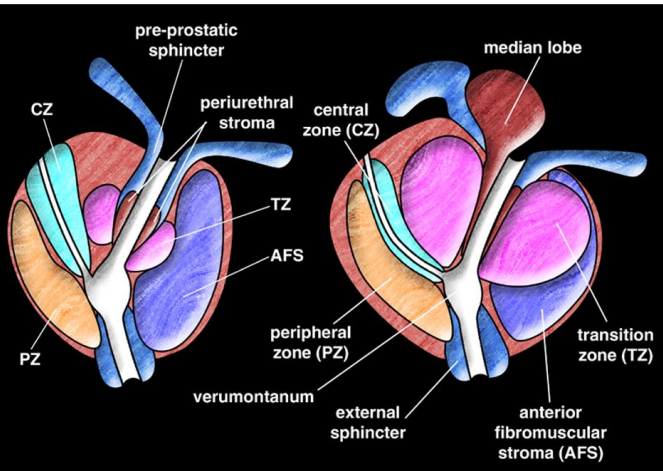
	Reader 1	Reader 2	Reader 3
True Positive (TP)	89	87	84
False Positive (FP)	15	13	15
PET-Positive Without Reference Standard	33	24	24
PET-Negative	71	84	85
CLR % (95% CI)	86 (79, 92)	87 (80, 94)	85 (78, 92)
Imputed CLR % (95% CI)	78 (71, 85)	81 (74, 88)	79 (72, 86)

Retrospective Ga68-PSMA Recurrence Sites
RR 144 patient M0 (69% HR PCa) s/p EBRT+ADT → rising PSA → Ga68-PSMA.
Extra-prostatic recurrences ≤5 were considered oligometastases.
Local and oligometastatic recurrences were deemed suitable for focal salvage therapy.
Probabilities of identifying recurrent lesion and potentially salvageable recurrences in Ga68-PSMA PETCT in relation to PSA were calculated.
RT hypofractionated in 57% (moderate 40%, extreme 17%), with median prostate EQD2 78.5 Gy.
Time from RT → PSMA = 4.3 years.
PSA 4.7 median.

Maitre, Radiotherapy Oncol 2022.
Uptake suggesting recurrence was observed in 91.2% patients
PSA threshold and positivity ≤2 (75%), ≤5 (87%), ≤ 10 (89%), and > 10 (100%).
Probability of detecting recurrence in Ga68-PSMA PETCT increased with higher PSA at scan (AUC = 0.82).
Uptake was local in 20 (17.5%), oligometastatic in 39 (34.2%), and polymetastatic in 45 (39.5%) patients.
Potentially salvageable recurrence if PSA ≤2 = 59/104 (56.7%), and if PSA > 10 = 38%.
Probability of recurrence being potentially salvageable declined with increasing PSA at scan (AUC = 0.68).
Conclusion Early Ga68-PSMA PETCT for rising PSA after definitive prostate radiotherapy detected majority of recurrent lesions and identified

Anatomy

Denoviller's Fascia → when it is not atrophied in young men, compared to old, this is why there is a bigger gap between prostate and rectum in young men.
Think: Green Montana: Veru-Montanam



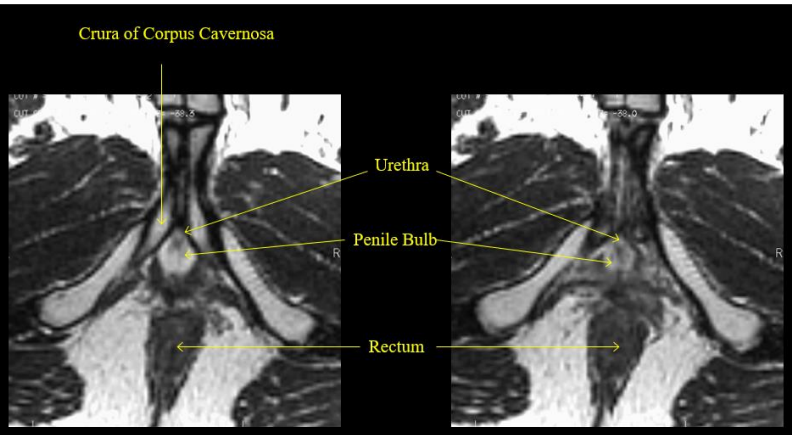


Image 1 Image 2

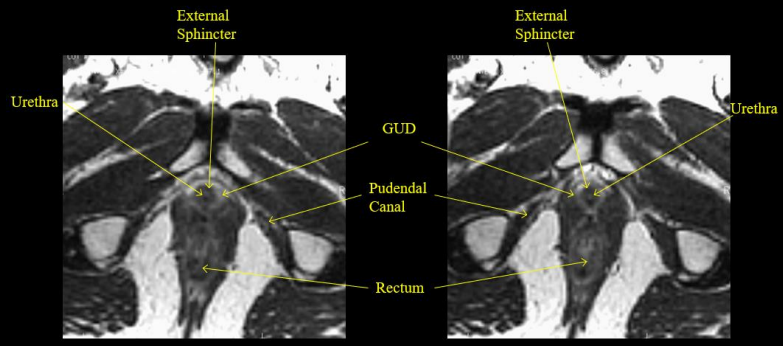


Image 5 Image 6

Note the thickness of the External Sphincter muscle. The circular shape of the GUD suggests prostate but this is still 1 cm below the prostate. Also note the Pudendal Canal is clear near the GUD level.

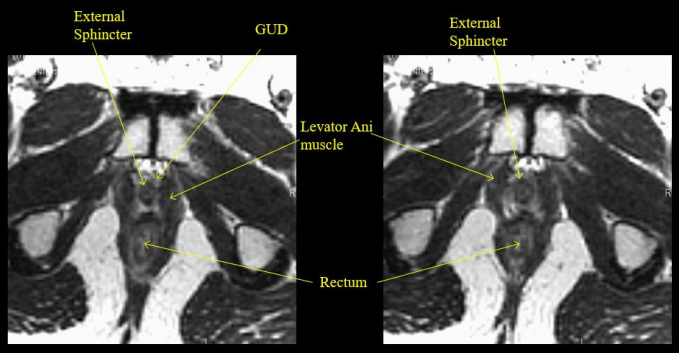


Image 7 Image 8

Note the convex shape of the Levator Ani at the upper GUD (Image 7). On image 8 the concave shape of the Levator Ani marks the transition to the prostate apex.

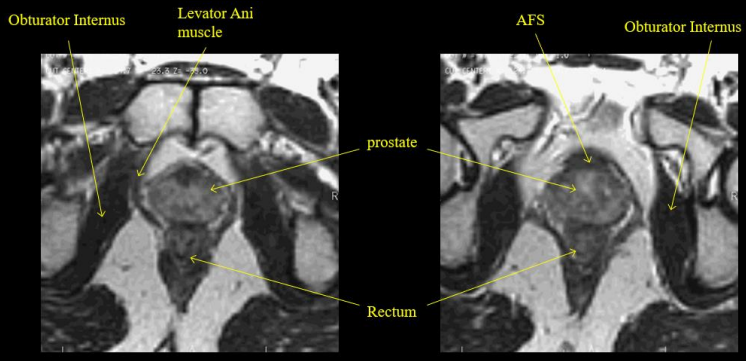
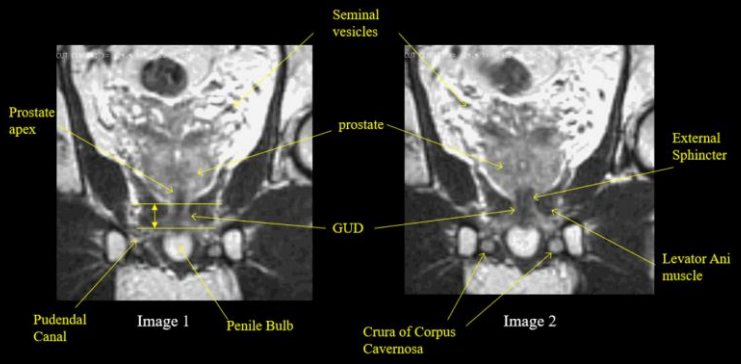
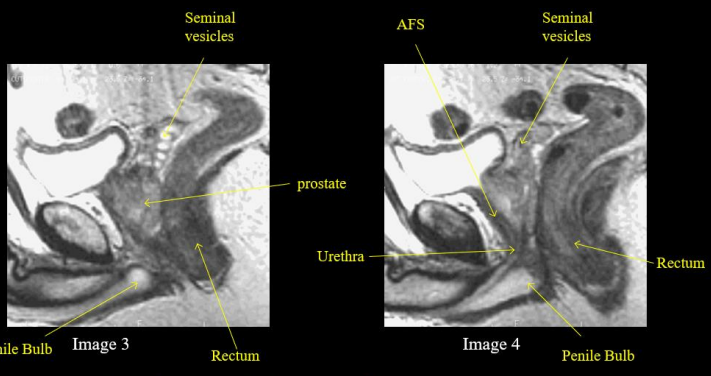


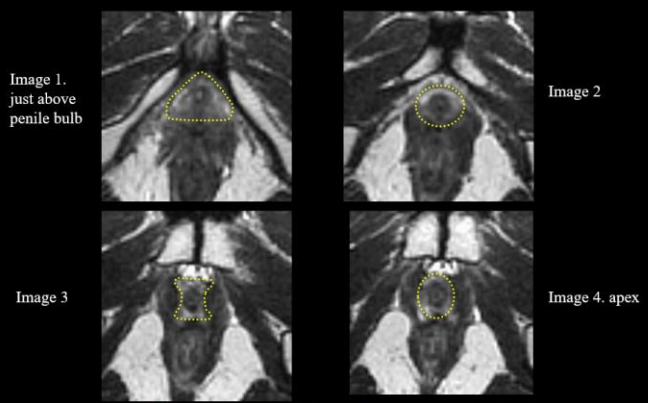
Image 11 Image 12



The distance ↕ between the prostate apex and the penile bulb is visible on the coronal images. Also note, the external sphincter extends through the GUD and into the prostate.

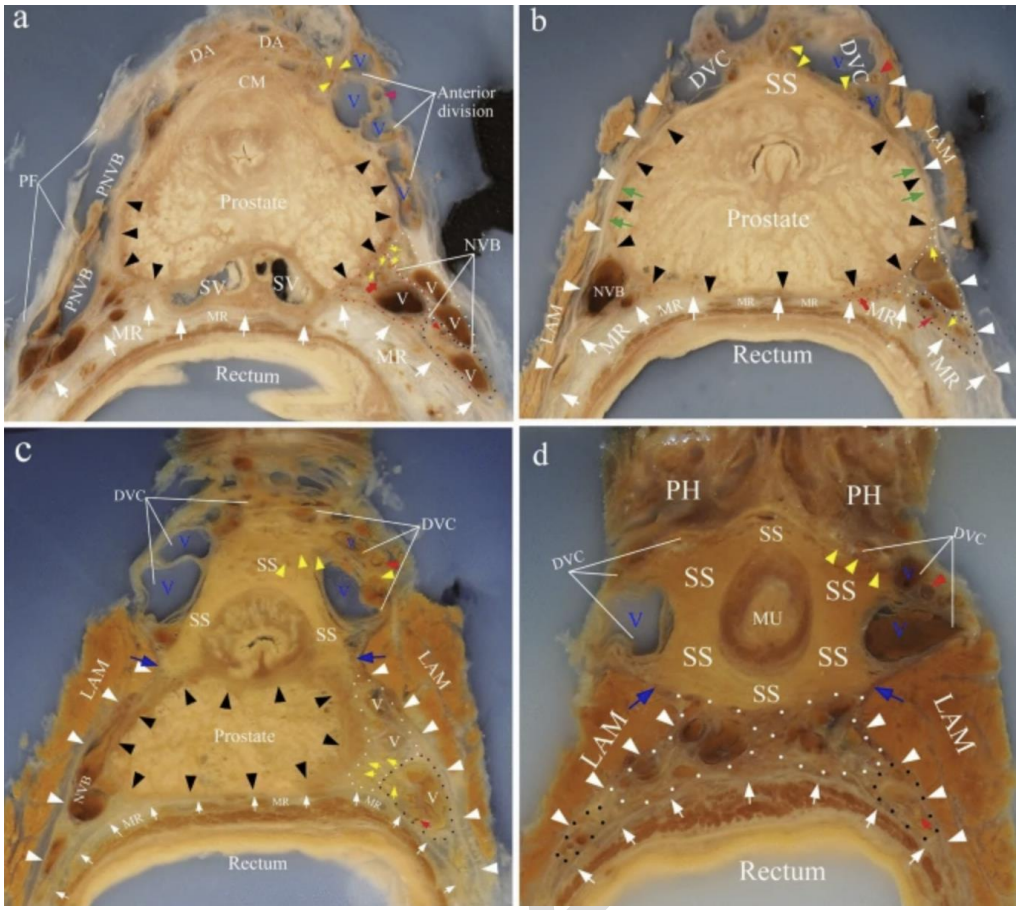


Note the urethra is visible through the center of the prostate in image 4. Also, the definition of the apex is less distinct on sagittal than on coronal. Sagittal views often clarify the prostate base/ seminal vesicle region.



Note the change in shape of the GUD: just above the penile bulb it is triangular in shape, near the mid-diaphragm it is circular, then hourglass shaped. These

Gross Specimen



Li, BMC Urology 2021.

Axial celloidin sections. a The axial section through the bladder prostatic groove. b The section through the upper and middle prostate. Note that the capsule and the levator fascia adhered together at lateral aspect of prostate (green arrow). c The section through the prostatic apex. d The section through the membranous urethra.

Blue arrow indicated the position where DVC (dorsal vascular complex) and CS (cavernous supply, circled by white dots) were separated by posterolateral portion of SS (striated sphincter). This portion of SS was attached to the outlet of LAM (Levator ani muscle).

Black (capsule), white (levator fascia), red (anterolateral branch prostatic artery in DVC) and yellow (nerves in DVC).

White arrows showed fascia proper of rectum; yellow arrows indicated nerves in NVB; broad red arrow indicated posterior-lateral branch of prostatic artery in NVB; red arrow indicated middle rectal artery; the prostatic supply was circled by red dots; the rectal supply was circled by black dots. PNVB, pelvic neurovascular bundle; PF, pelvic fascia; SV, seminal vesicles; MR, mesorectum; CM, circular muscle of detrusor; DA, detrusor apron; PH, penile hilum; V (blue), veins in DVC; V (white), veins in NVB.

Staging: AJCC 8th Edition

Clinical staging		Pathologic staging	
cTX	Primary tumor cannot be assessed.	NOTE:	R1 = positive margins / residual disease.
cT0	Primary tumor not found.		
cT1	No primary tumor found.	pT1	Does not exist.
a	Incidental histologic < 5% of resected tissue.		
b	Incidental histologic > 5% of resected tissue		
c	Identify by needle biopsy because PSA ↑.		
cT2	Tumor PALPABLE + confined within prostate. *, **	pT2	Organ confined.
a	Tumor ≤ ½ of 1 lobe.	~~a~~	~~Unilateral ≤ ½ lobe.~~
b	Tumor > ½ of 1 lobe but not 2 lobes.	~~b~~	~~Unilateral ≥ ½ lobe.~~
c	Tumor in both lobes.	~~c~~	~~Bilateral.~~
cT3	Tumor extends through prostate capsule.	pT3	Extraprostatic extension.
a	Extracapsular extension.	a	Extraprostatic extension or invasion into the bladder neck.
b	Seminal vesicle invasion.	b	Seminal vesicle invasion.
cT4	Tumor is fixed or invades adjacent structures.	pT4	Invades adjacent structures.

* EXCEPTION: If extends into prostate apex or capsule, it is automatic T3.
** MRI or biopsy (for example showing bilateral disease) does not upstage a non-palpable prostate CA to T2.

Clinical staging		Pathologic staging	
cNx	Regional LN not assessed	pNx	Same.
cN0	Negative	pN0	Same.
cN1	Metastasis in regional LN	pN1	Same.

- M0 – none ***Common met sites: Lung, liver, bone brain. "LLBB."
- M1 – Distant mets M1a: Nonregional LN. M1b: Bone. M1c: Other sites.
  BATSON VENUS PLEXUS (Valve-less).

FINAL STAGING:

AJCC PROGNOSTIC STAGE GROUPS*

Group	T	N	M	PSA (ng/mL)	Grade Group
I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
IIB	T1-2	N0	M0	PSA <20	2
IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
IIIA	T1-2	N0	M0	PSA ≥20	1-4
IIIB	T3-4	N0	M0	Any PSA	1-4
IIIC	Any T	N0	M0	Any PSA	5
IVA	Any T	N1	M0	Any PSA	Any
IVB	Any T	Any N	M1	Any PSA	Any

*Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Histopathologic Type
This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell (urothelial) carcinoma of the prostate. Adjectives used to describe histologic variants of adenocarcinomas of the prostate include mucinous, signet ring cell, ductal, and neuroendocrine, including small cell carcinoma. There should be histologic confirmation of the disease.

Definition of Histologic Grade Group (G)
Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

VERY IMPORTANT NOTE !!!!!!!
N+ = Stage IV cancers Prostate, Sarcoma, uveal melanoma, HCC
Cancers w/o a T4 / Stg 4 Testicular M+ = IIIC (no Stage IV) Vulvar No T4

STRATIFICATION

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

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			Not indicated	Recommended if family history positive or intraductal/cribriform histology 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			Not indicated	Recommended if family history positive or intraductal/cribriform histology 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]	• 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 at least 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 nomogram predicts >10% probability of pelvic lymph node involvement • 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 nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

AZ

Treatment Paradigm

Hormone Categories

- Bilateral orchiectomy
- Estrogens
  - Diethyl stilbestrol (DES)
  - Estramustine - derivative of estradiol with nitrogen mustard, an alkylating agent with estrogen-induced specificity
- Progestins
  - Medroxyprogesterone acetate (Provera)
  - Megestrol acetate (Megace) - synthetic progestin, able to lower testosterone and LH/FSH, and block binding of testosterone and dihydrotestosterone to androgen receptor

Types of Hormones:

1) GnRH agonists — leuprolide/leupron, LA Lupron/Eligard, Groserlin/Zoladex.
50 ng/mL testosterone = castrate resistance.
300 is "normal"
Leupron: 7.5 mg IM monthly, 22.5 mg IM every 3 months, 30 mg IM every 4 months, or 45 mg IM every 6 months.

2) 5α reductase inhibitor — (steroid antiandrogens "name –(fin/dut)aster-ide") finasteride/proscar, dutasteride.

3) Testosterone R antagonist — (non-steroidal antiandrogens): flutamide/eulexin, bicalutamide/casodex, enzalutamide/xtandi.

4) 17-α-hydroxylase inhibitor — abiraterone/Zytiga.
Must give it with steroids: Give 5 mg prednisone to counteract effects.

5) GnRH antagonist — degarelix/firmagon, **relugolix**

GnRH agonists:

- Initially bind and cause transient increase in LH, FSH and testosterone
- GnRH receptors downregulated after approx 1 week
- Testosterone reduced to castration levels after approx 3-4 weeks
- Generally given with concurrent anti-androgen starting 1 week before and 2 weeks after

HERO Relugolix Trial
←R→ 930 advanced prostate cancer, in a 2:1 ratio, | 1. relugolix (120 mg orally once daily) | 2. leuprolide (injections every 3 months) | for 48 weeks.
1^{O} sustained testosterone suppression to castrate levels (<50 ng per deciliter) through 48 weeks.
2^{O} noninferiority with respect to the primary end point, castrate levels of testosterone on day 4, and profound castrate levels (<20 ng per deciliter) on day 15. Testosterone recovery was evaluated in a subgroup of patients.

Shore, NEJM 2020.
2-year maintenance of castration 96.7% vs. 88.8%. Δ of 7.9% showed noninferiority and superiority of relugolix (P<0.001 for superiority).
All other key secondary end points showed superiority of relugolix over leuprolide (P<0.001).
Castrate levels of testosterone on day 4 was 56.0% vs. 0%.
Subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group.
Major adverse CV events was 2.9% vs. 6.2% (HR 0.46, SS; 95% CI, 0.24 to 0.88).
CONCLUSIONS: In this trial involving men with advanced prostate cancer, relugolix achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide, with a 54% lower risk of major adverse cardiovascular events.

AY 2021

Radiation

Dosing

PRINCIPLES OF RADIATION THERAPY

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

√ indicates an appropriate regimen option if radiation therapy is given. See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-9, PROS-13, and PROS-G for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

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[c]	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	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	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x1 fx 10.75 Gy x 2 fx			✓	✓		

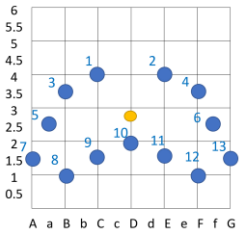
[a] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

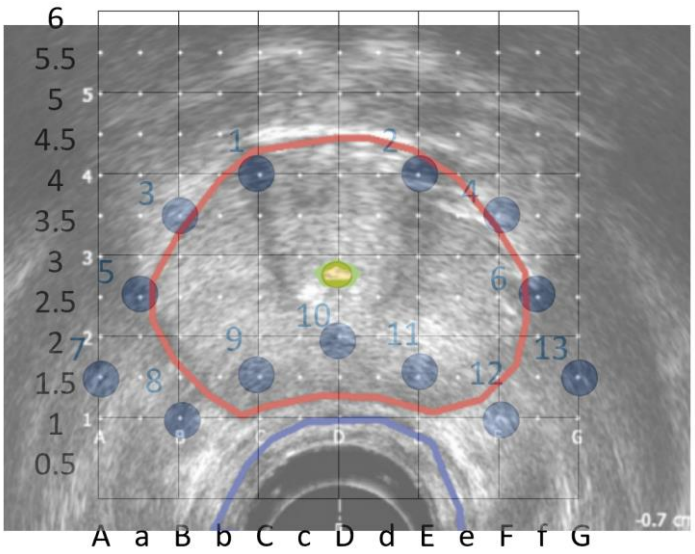
Acceptable Range of Radiation Dose Options Note how much variability there can be!

Regimen	Sequencing	WPRT	LN+	Primary	Notes
Standard	Sequential	4500 (25 in 1.8) 5040 (28 in 1.8)	5940 (33 in 1.8) 6480 (36 in 1.8)	7920 (44 in 1.8) 8100 (45 in 1.8)	
Hypofractionated	SIB	4680 (26 in 1.8) 5040 (**28** in 1.8)	5720 (26 in 2.2) 5936 (**28** in 2.12)	7020 (26 in 2.7) 7000 (**28** in 2.5)	
Salvage	Sequential	5040 (28 in 1.8)	6480 (36 in 1.8)	7200 (40 in 1.8)	
Combined EBRT + BT	HDR → EBRT Sequential	5040 (28 in 1.8)	5940 (33 in 1.8) 6480 (36 in 1.8)	5940 (33 in 1.8)	EQD_2 (P+SV) 7940 cGy

Please See: **2021 NRG Prostate WPRT** - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7736505/pdf/nihms-1637222.pdf

Brachytherapy





General Rules of Thumb
Resource: ABS Brachy Guidelines Yamada, 2012
Ir192, 380 KeV, 73.8 Days half-life.
HDR dose: ≥ 12 Gy/h

Example of needle Placement (varies by cancer centers):
13 needles (**blue**) placed equidistantly at periphery of prostate (**red**)
to avoid hot spots and urethra (**yellow**).
Needles 7-13 require advancement of stepper for insertion into the SVs.
Needles 1-2 require cystoscopy to verify tenting of bladder.

After removal of HDR catheter, irrigate bladder to remove blood clots.
Perineal Pressure after HDR removal to prevent hematoma.
Consider antibiotics after implant.

For Combination BT+EBRT, HDR probably should be done first.
Notes:
1. Ease of implanting SpaceOAR and Fiducials immediately after last BT.
2. If SpaceOAR is done before BT, the U.S. visualization and/or anatomy can be compromised when attempting HDR.
3. Patient preference as trials (e.g. THEPCA) show no difference in sequencing.
4. There are many published and acceptable fractionations for BT boost (see section below).

Example (below) of an Excel HDR Template that is helpful for documentation.
A similar worksheet is highly recommended for any brachytherapy center.
Here, prostate Final (BT + EBRT) EQD_2 Dose is 79.4 Gy.
HDR Dose Constraints assume entire Bladder and Rectum Receive Full EBRT dose of 59.4 Gy (unlikely with SpaceOAR).
Absolute Limit Allowed = D2cc Rectum (75) and Bladder (80) ≈ as Gyn.
Secondary constraint to consider V75 < 1cc for bladder and rectum.
Urethra stricter guidelines of DMax 120% Gy (many centers consider V125 < 1cc, V150 < 0cc).

PHYSICAL - BIOLOGICAL DOCUMENTATION OF PROSTATE HDR BT

PATIENT , ID-number							**Special**	
IDENTIFICATION								
EXTERNAL BEAM THERAPY	**RT**		**Prostate**	**Bladder**	**Rectum**		**Risk**	
Dose per Fx (Gy)	1.8		D_{iso} [α/β=3Gy]	D_{iso} [α/β=3Gy]	D_{iso} [α/β=3Gy]		**PSA**	
Pelvis	28		50.4	50.4	50.4			
Boost	5		9.0	9.0	9.0		**Prostate Size**	cm^3
Total Dose (Gy)	**59.4**		**57.0**	**57.0**	**57.0**		**Systemic**	
BRACHYTHERAPY	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**		
date								
physicist								
MR / CT	CT	CT	CT	CT				
applicator(s): type	Template	Template	Template	Template				
applicator(s): dimensions	13 Needles	13 Needles	13 Needles	13 Needles				
eval plan, remarks								
							TOTAL Dose BT	**TOTAL Dose BT + EBT**
PROSTATE [cm^3]								
HDR Fraction Dose	4.0	4.0	4.0	4.0				
EQD2 [α/β=3Gy]	5.6	5.6	5.6	5.6			22.4	**79.4**
BLADDER [cm^3]								
Max Dose as % (< 110%)	100.0	101.0	102.0	103.0			101.5	
V75 as cc (< 1cc)	0.5	1.0	2.0	3.0			1.6	
2cm^3 - dose (< 85 Gy)	4.0	4.0	5.0	4.0				
2cm^3 - D_{iso} [α/β=3Gy]	5.6	5.6	8.0	5.6			24.8	**81.8**
RECTUM [cm^3]								
Max Dose as % (< 100%)	0.0	0.0	0.0	0.0			0.0	
V75 as cc (< 1cc)	0.0	0.0	0.0	0.0			0.0	
2cm^3 - dose (< 75Gy)	3.0	3.0	3.0	3.0				
2cm^3 - D_{iso} [α/β=3Gy]	3.6	3.6	3.6	3.6			14.4	**71.4**
URETHRA [cm^3]								
Max Dose as % (< 120%)	0.0	0.0	0.0	0.0			0.0	
V120 as cc (< 1cc)	0.0	0.0	0.0	0.0			0.0	

2022

Definitive

Note: per RTOG 08-15 prostate starts 5 mm above GUD (which is the top of the urethrogram beak).

Table 1
Overview of the recommendations for the delineation of the rectum and clinical target volume of the prostate and seminal vesicles.

		MRI based	CT-scan based		
Rectum		The delineation of the rectum starts at the recto-sigmoid junction, i.e. where the sigmoid colon becomes the rectum, and which usually takes the form of an acute angle The rectum contouring ends approximately 2 cm below the lowest prostate-apex contour Correct delineation of the rectum can be performed by visualization of the rectum in the sagittal plane. Delineation of the target volume is performed in the axial plane and reviewed in the sagittal and coronal planes. If there are inconsistencies or protrusions, adapt in order to obtain the typical inverted triangular shape of the prostate			
Apex		Butterfly-shaped structure, excluding the urethra and starting above the penile bulb and genito-urinary diaphragm	Starts approximately 1 cm above the upper border of the penile bulb (13)		
Mid prostate	Lateral border	Bounded by the musculus levator ani; at the level of the external urethral sphincter the levator ani muscle is thicker than at the level of the mid-prostate	After correct delineation of the rectum, the thickness of the musculus levator ani can be defined; the same thickness of the levator ani muscle defined at the level of the rectum can be extrapolated over the full length of the prostate. This forms the lateral border of the prostate		
	Anterior border	Exclude the retropubic space unless signs of invasion	Include the anterior fascia and exclude the fat area in front of the anterior fascia unless protrusion of the prostate is visible on CT		
	Posterior border	Anterior border of the rectum	Anterior border of the rectum		
Base		In continuity with the bladder, to be controlled in the sagittal and coronal view	In continuity with the bladder, easier to define when contrast is used, to be controlled in the sagittal an coronal view		
			Low risk	Intermediate risk	High risk
Seminal vesicles		Include the part of the seminal vesicles that is at risk for invasion and exclude the ductus deferens	No inclusion or inclusion of proximal 1.4 cm of the SV (in the axial plane) according to institutional policy	Inclusion of at least proximal 1.4 cm of the SV (in the axial plane)	Inclusion of at least proximal 2.2 cm of the SV (in the axial plane)
ECE		Include the area of suspicion of ECE; in the absence of ECE on MRI: no additional expansion	No expansion	Expansion of the prostate contour with 3 mm in the inferior, lateral, anterior and posterior direction with exclusion of the rectum contour in absence of suspicion of rectal wall invasion on digital rectal examination	

Abbreviations: MRI: magnetic resonance imaging; CT: computed tomography; ECE: extra capsular extension; SV: seminal vesicles.
Risk stratification:
1. *low risk* (PSA ≤ 10 ng/ml; biopsy Gleason score ≤6 (Grade group 1) and clinical stage ≤T2a and <50% of the biopsies involved.
2. *intermediate risk* (PSA > 10 and ≤20 ng/ml or Gleason score of 7 (Grade group 2 and 3) or clinical stage T2b).
3. *high risk* (PSA > 20 ng/ml or Gleason score ≥8 (Grade group 4 and 5) or clinical stage ≥T2c).

SBRT GU005
https://www.astro.org/ASTRO/media/ASTRO/AffiliatePages/arro/PDFs/ARROCase_ProstateSBRT.pdf

History of "Proximal SV CTV."

- RTOG 94-06 Phase II DE-RT study had a CD after 55.8 Gy to P+SV to final volume and dose.
- RTOG 01-26 Phase III DE-RT study started with 3D-CRT plans, but decided to allow IMRT.
    - Should IMRT plans also include a similar CD, that would mean two IMRT plans and two QAs, which would be too much work in the early days.
- Kestin's article (https://pubmed.ncbi.nlm.nih.gov/12377319/) was influential.
    - 85% patients would not have pathological SV involvement.
    - 1% of low-risk patients vs. 27% of high-risk patients had SV involvement.
        - 1 HR feature = 15% risk of SV involvement
        - 3 HR features = 58% risk of SV involvement.
    - If they did, half of them would be within the first 1cm.
    - In the entire population, 7% had SV involvement beyond 1.0 cm.
    - Approximate 1% risk of SV involvement beyond 2.0 cm or 60% of the SV.
        - In addition, this risk was less than 4% for all subgroups, including high-risk patients.
- Proximal SV CTV thus should be used in low-intermediate risk patients and should NOT be used for high-risk prostate cancer patients.

Post-op

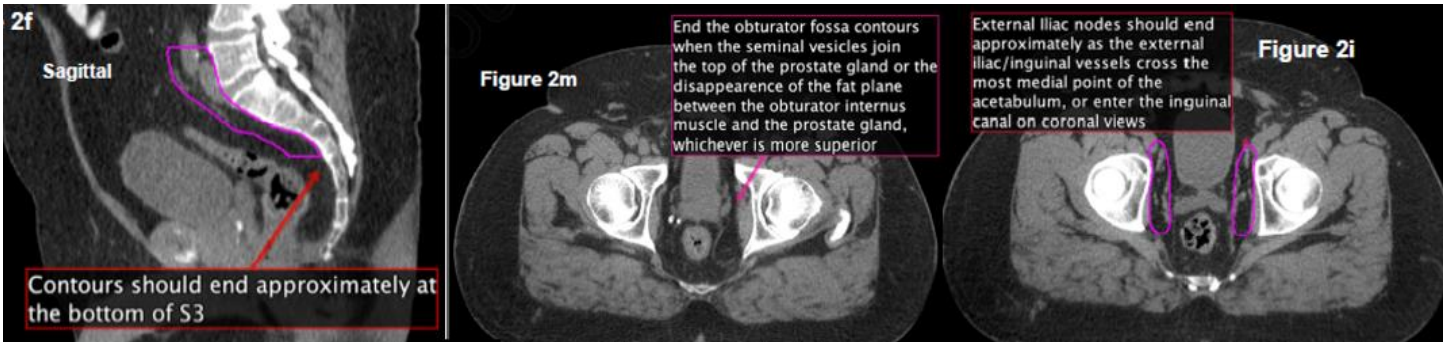
NOTES:
Borders: RTOG Consensus https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847420/

Below the superior edge of the symphysis pubis		
Anterior	Posterior edge of pubic bone	
Posterior	Anterior rectal wall	May need to be concave around lateral aspects
Inferior	8-12 mm below VUA	May include more if concern for apical margin. Can extend to slice above penile bulb if VUA not well visualized
Lateral	Levator ani muscles, obturator internus	
Above the superior edge of the symphysis pubis		
Anterior	Posterior 1-2cm of bladder wall	
Posterior	Mesorectal Fascia	
Superior	Level of cut end of vas deferens or 3 cm above top of symphysis	Vas may retract postoperatively, Include seminal vesicle remnants if pathologically involved
Lateral	Sacrorectogenitopubic fascia	If concern about extraprostatic disease at base may extend to obturator internus

Resource: Francophone Group of Urological Radiation Therapy https://www.redjournal.org/article/S0360-3016(20)34498-9/fulltext

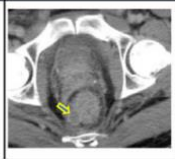
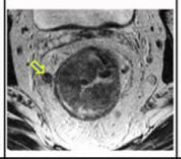
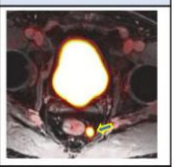
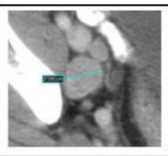
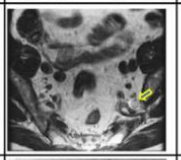
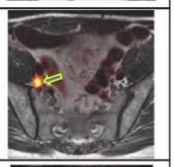
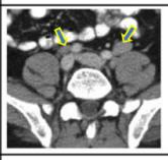
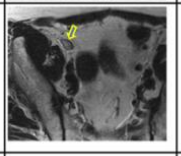
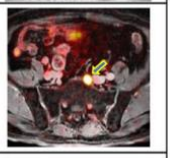
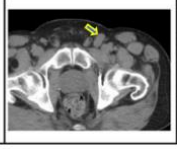
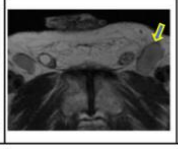
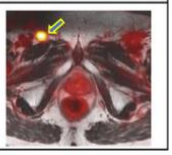
AZ 2022

Pelvic RT



2021 NRG Prostate WPRT - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7736505/pdf/nihms-1637222.pdf

Notes: Superior = Bifurcation of Common Iliacs (Generally L4/L5)
Inferior = Prevertebral, presacral, and posterior mesorectal nodes to the bottom of S3 (Fig. 3f).
Dose: Prophylactic nodes: 45 to 50.4 Gy using conventional fractionation (same intact vs. post-op).
Gross nodes: "Should be treated as high as clinically feasible." AKA to tissue (bowel generally) tolerances.

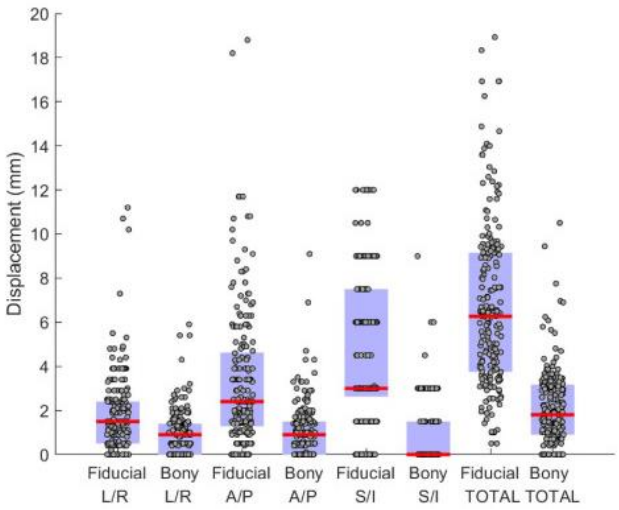
Anatomic Location	CT/MRI-based Size	CT/MRI-based Morphology	PSMA PET-based Criteria	Fluciclovine PET-based Criteria	Example of positive node on CT	Example of positive node on MR	Example of positive node on PET
Mesorectal, Presacral	Short axis > 4 mm	Irregular Border and/or heterogenous morphology (only 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			

Older Recommendations RTOG contouring AND Nancy Lee: Superior L5/S1
RECALL Cervical = Start at L4/L5 (bifurcation of common iliac) and end at S2-S3.

Pelvic LN Contouring Resource:
https://www.redjournal.org/article/S0360-3016(20)34124-9/fulltext

Wu, Adv Rad Onc 2022.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7736505/pdf/nihms-1637222.pdf
If SIB LN boost, IGRT alignment to the fiducials (vs. bony pelvis) may ↓ LN treatment accuracy!
75 CBCTs evaluated from 15 patients with cLN+.
Either SBRT 20% or VMAT 80% IMRT.
41 LN targets evaluated.

	Fiducial	Bony	Paired differences (Bony minus Fiducial)	p-value
Left/right	1.5 (0.5 - 2.4)	0.9 (0.0 - 1.4)	-0.5 (-1.5 - 0.0)	<0.0001
Ant/post	2.4 (1.3 - 4.6)	0.9 (0.0 - 1.5)	-1.5 (-3.4 - -0.5)	<0.0001
Sup/inf	3.0 (2.6 - 7.5)	0.0 (0.0 - 1.5)	-3.0 (-6.0 - -1.5)	<0.0001
TOTAL	6.3 (3.7 - 9.2)	1.8 (0.9 - 3.2)	-4.0 (-7.3 - -2.0)	<0.0001



Meta-Analysis SpaceOAR
←M→ 7 Studies = 1011 men (486 hydrogel spacer and 525 controls).
Cochrane Central Register of Controlled Trials, MEDLINE, and Embase for articles published through September 2019.
1^{O} Rectal V70, early (≤3 months) and late (>3 months) rectal toxic effects, and early and late changes in bowel-related quality of life on the Expanded Prostate Cancer Index Composite (minimal clinically important difference, 4 points).

Miller, JAMA Net 2020. FU 26 months.
Success rate of hydrogel spacer placement was 97.0%. Weighted Mean Sep 11.2 mm.
Procedural complications were mild and transient, occurring in 0% to 10% of patients.
V70 rectal irritation 3.5% vs 10.4% (mean difference, −6.5%; P = .001).
Early ≥ G2 Rectal AE 4.5% vs. 4.1% (RR 0.82; NS)
Late ≥ G2 Rectal AE 1.5% vs 5.7% (RR 0.23; P = .05).
Early FU Δ in bowel-related QoL (mean difference, 0.2; P = .92 [2 studies]) NS.
Late FU Δ in bowel-related QoL (mean difference, 5.4; P < .001 [2 studies]) benefiting SpaceOAR.
Conclusions and Relevance For men receiving prostate radiotherapy, injection of a hydrogel spacer was safe, provided prostate-rectum separation sufficient to reduce v70 rectal irradiation, and was associated with fewer rectal toxic effects and higher bowel-related quality of life in late follow-up.

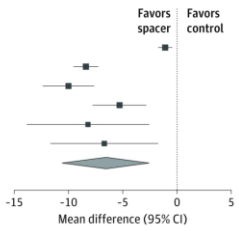
Table 1. Characteristics of Primary Studies of Radiotherapy With vs Without Hydrogel Spacer for Prostate Cancer

Primary study[a]	Secondary studies	Design	No. of sites	Country	No. of patients who received HGS/No. of controls	Radiotherapy protocol	Follow-up for patients who received HGS/controls, mo
Chao et al,[18] 2019	Chao et al,[23] 2019	RCS	1	Australia	32/65	BT: 18 Gy (3 fx) or 16 Gy (2 fx); IMRT: 50.4 Gy (28 fx)	42/65
Mariados et al,[4] 2015	Pieczonka et al,[24] 2016; Hamstra et al,[25] 2017; Hamstra et al,[26] 2018	RT	20	United States	149/73	IMRT: 79.2 Gy (44 fx)	37/37[b]
Pinkawa et al,[14] 2017	Pinkawa et al,[15] 2017; Pinkawa et al,[16] 2012; Pinkawa et al,[17] 2013	RCS	1	Germany	101/66	IMRT: 76-80 Gy (38-40 fx)	63/63[c]
Taggar et al,[19] 2018	None	RCS	1	United States	79/136	BT with or without EBRT	<12[d]
te Velde et al,[20] 2019	te Velde et al,[27] 2017	RCS	3	Australia	65/56	IMRT: 81 Gy (45 fx)	<36[d]
Whalley et al,[21] 2016	None	PCS[e]	1	Australia	30/110	IMRT: 80 Gy (40 fx)	28/26
Wolf et al,[22] 2015	None	PCS	1	Austria	30/19	IMRT: 75.85 Gy (41 fx)	3[d]

Rectal V70

Source	Mean (SE) difference	Mean difference (95% CI)
Chao et al,[18] 2019	-1.1 (0.33)	-1.10 (-1.75 to -0.45)
Mariados et al,[4] 2015	-8.4 (0.58)	-8.40 (-9.54 to -7.26)
Pinkawa et al,[14] 2017	-10.0 (1.21)	-10.00 (-12.37 to -7.63)
te Velde et al,[20] 2019	-5.3 (1.26)	-5.30 (-7.77 to -2.83)
Whalley et al,[21] 2016	-8.2 (2.87)	-8.20 (-13.83 to -2.57)
Wolf et al,[22] 2015	-6.7 (2.53)	-6.70 (-11.66 to -1.74)
Total		-6.51 (-10.51 to -2.51)

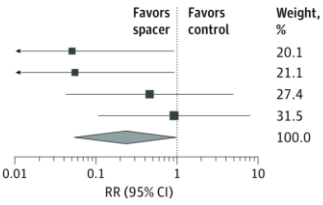
Heterogeneity: $\tau^2 = 22.37$; $\chi^2_5 = 159.40$; $P < .001$; $I^2 = 97\%$
Overall effect: $z = 3.19$; $P = .001$



Late ≥ G2 Rectal AE

Source	Log RR (SE)	RR (95% CI)
Mariados et al,[4] 2015	-2.982 (1.479)	0.05 (0.00-0.92)
Pinkawa et al,[14] 2017	-2.898 (1.435)	0.06 (0.00-0.92)
te Velde et al,[20] 2019	-0.78 (1.21)	0.46 (0.04-4.91)
Whalley et al,[21] 2016	-0.087 (1.099)	0.92 (0.11-7.90)
Total		0.23 (0.06-0.99)

Heterogeneity: $\tau^2 = 0.51$; $\chi^2_3 = 3.92$; $P = .27$; $I^2 = 24\%$
Overall effect: $z = 1.97$; $P = .05$



Phase II SBRT + SpaceOAR

Background: High-dose SABR for prostate cancer offers the radiobiologic potency of the most intensified radiation therapy regimens but was associated with >90% rates of ulceration of the anterior rectal wall on endoscopic assessment; this infrequently progressed to severe rectal toxicity in prior prospective series. A multi-institutional phase 2 prospective trial was conducted to assess whether placement of a perirectal hydrogel spacer would reduce acute periprostatic rectal ulcer events after high-dose (>40 Gy) SABR.

Prospective 44 men stage ≤T2c, GG 1-3 PSA level ≤15 ng/mL, AUA ≤18, Prostate ≤80 cc.
All underwent perirectal hydrogel spacer placement → SABR of 45 Gy in 5 fractions QoD to the **prostate only** (PTV 3mm isotropic margin).
Androgen deprivation was not allowed except for cytoreduction.
The rectal wall was directly assessed by serial anoscopy during follow-up to determine whether the spacer would reduce acute periprostatic rectal ulcer events from >90% to <70% within 9 months of treatment.

Folkert, IJROBP 2021.
Acute periprostatic ulcers were observed in 6 of 42 patients (14.3%; P < .001) at a median of 2.9 months posttreatment (range, 1.7-5.6 months).
All ulcers (grade 1, 5 ulcers; grade 2, 1 ulcer) resolved on repeat anoscopy within 8 months of incidence.
There were no grade ≥3 late gastrointestinal toxicities.
Late grade-2 gastrointestinal toxicities was 14.3%, with a prevalence at 3 years of 0%.
No toxicities greater than grade 3 occurred in any domain.
4-year BcF 93.8%.
Conclusions Temporary hydrogel spacer placement before high-dose SABR treatment for localized prostate cancer and use of strict dose constraints are associated with a significant reduction in the incidence of rectal ulcer events compared with prior phase 1/2 trial results.

SpaceOAR Distribution and Rectal Dosimetry
RR 160 patients classified into 3 groups
| 1. No spacer (group 1; n = 30) |
| 2. spacer placed using conventional technique (group 2; n = 100) | → needle tip at midgland.
| 3. spacer placed using new technique (group 3; n = 30) | → needle top at a level corresponding to a cranial:caudal ratio of 6:4 and as close to the prostate gland as possible (group 3). The separation effect was examined and compared among the groups.

Fukumitsu, PRO 2022.
Separation in group 2 > group 1 from base to the apex level of the prostate (4 mm)
Separation in group 3 > group 2 from middle to the apex level of the prostate (4 mm).
Conclusions
The separation, spacer thickness, and rectal exclusion from the middle to the apex of the prostate and the laterality of the hydrogel spacer affected the reduction in the rectal dose. The rectal dose can be further reduced by implanting a spacer on the caudal and prostate side.
Takeaway: Injections should be slightly caudal to the midgland prostate for maximum separation.

Iodinated SpaceOAR
RR 100 patients with prostate cancer receiving non-iodinated SpaceOARs (nI-SP, n=50) vs. Iodinated SpaceOARs (I-SP, n = 50).
Contoured and evaluated throughout treatment.

Kamran, PRO 2021.
HU were easily different 138 vs 12, (P < .001), allowing delineation on CT alone.
Delineated volume volume 8.9 vs 10.6 mL, P < .001 Surface area (SA); 28 vs 35 cm2, (P < .001).
Yet relative spacer position and prostate-rectal separation were similar (P = .79).
No significant change in HU, volume, SA, or relative position of the I-SPs hydrogel occurred over courses of treatment (all P > .1).
Dosimetric analysis concluded there were no significant changes in plan quality or robustness for I-SPs compared to nonI-SPs.
The I-SP relative linear stopping power was 1.018, necessitating HU override for proton planning.
Conclusions I-SPs provide a manifest CT contrast, allowing for delineation on planning CT alone with no magnetic resonance imaging necessary. I-SPs radiopacity, size, and relative position remained stable over courses of treatment from 28 to 44 fractions. No changes in plan quality or robustness were seen comparing I-SPs and nonI-SPs.

2022

Surgery

Pelvic Lymph Node Dissection:

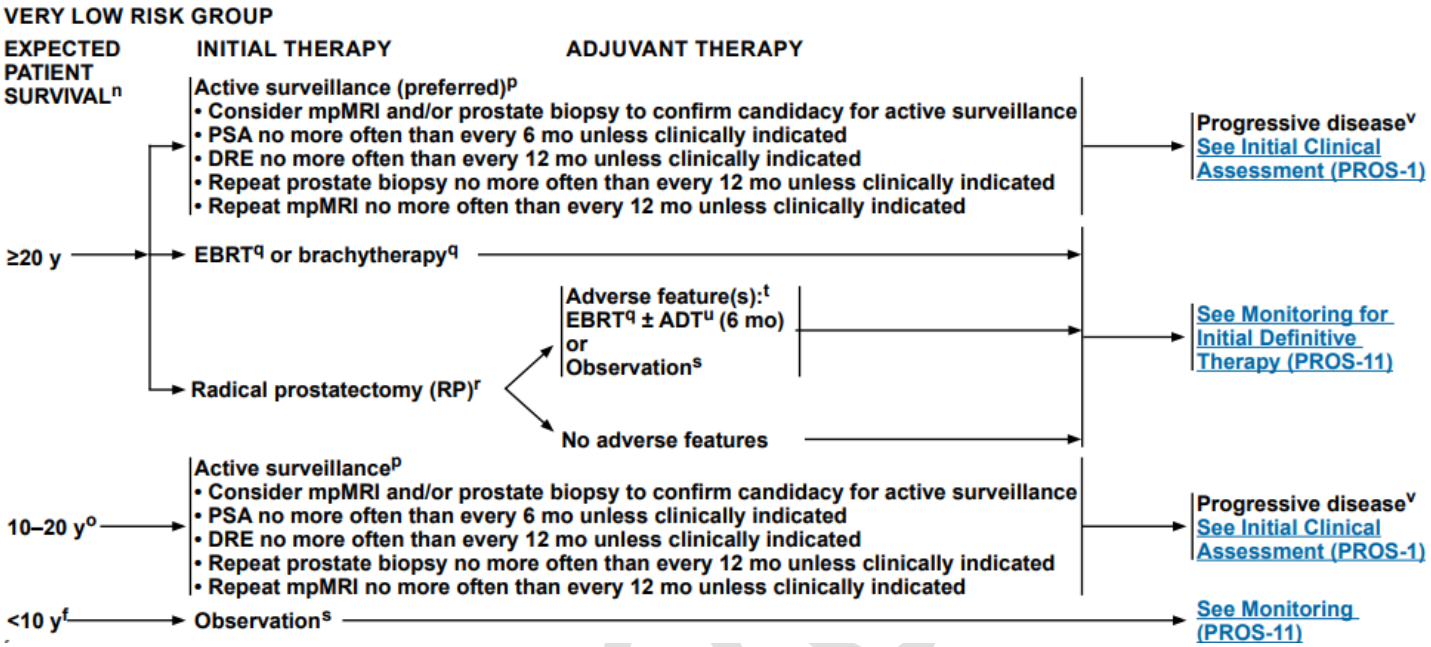
- Performed through open, laproscopic, or robotic technique.
- An extended PLND (exPLND) will discover metastases approximately 2x as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases. ∴ extended PLND is preferred.
  - exPLND includes removal of all node bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.
  - Can be excluded patients with < 2% predicated probability of nodal metastases by nomograms.

Radical Prostatectomy:

- Appropriate for clinically localized prostate cancer that can be completely excised + life expectancy of ≥ 10 years.
- High volume surgeons in high volume centers = better outcome.
- In experienced hands, lap or RP = similar results to open surgery.
- Blood loss can be substantial with RP, but can be reduced by careful control of the dorsal vein complex and periprostatic vessels.
- Urinary incontinence ↓ by preservation of urethral length beyond the apex at the prostate and avoiding damage to the distal sphincter mechanism. Bladder neck preservation may decrease the risk of incontinence. Anastomotic strictures ↑ risk of long term incontinence.
- Recovery of erectile function proportional to age at RP, preoperative erectile function, and preservation of cavernous nerves.
  - Replacement of resected nerves with nerve grafts has not been shown to be beneficial.
  - Early restoration of erections may improve late recovery.
- Salvage RP is an option for highly selected patients with local recurrence after EBRT, brachy, or cryotherapy.
  - Morbidity (ie. incontinence. loss of erection, anastomotic stricture) is high.

AZ 2022

Very Low Risk Disease: Low risk + (T1c + PSA < 0.15 ng/dL/g, < 50% cores +, < 3 cores)



Active Surveillance

- Consists of DRE (q12 months) and PSA (q6 months) with routine repeat biopsy (q1 year) to rule out GS progression.
  - Discontinue biopsy after age 75 years or when life expectancy < 10 years.
- EPSTEIN CRITERIA of when you go for A.S.: PSA density < 0.15 ng/mL/g, GS ≤ 6, < 3 cores involved, ≤ 50% involvement in any core.
- This is the very low risk stratification of NCCN.
  - PSA doubling time is only useful in adjuvant setting. NOT RELIABLE IN ACTIVE SURVEILLANCE.
- Advantages: avoids side effect from Tx.
- Disadvantages: chance of missed opportunity for cure, risk of progression and or mets, next tx may have increased risk of side effects, increased anxiety, uncertain long-term natural history of prostate cancer.
- Life expectancy can be estimated from www.ssa.gov. Adjust if best quartile of health + 50%, worst quartile – 50%, middle no Δ.
- 33% fail active surveillance and require TX.
- PSA < 4: Velocity > 0.35 ng/mL/year suggestive of prostate cancer
- PSA 4-10: Velocity > 0.75 ng/mL/ year.
- Free PSA: < 25% suggestive. If malignancy, more % of patient's PSA bound and thus less free PSA.

- Note: Previously, there was a treatment option called watchful waiting or expectant management. This was the idea that noncurative treatment would be offered at the time of progression and would consist of primarily of hormonal therapy to induce tumor regression and alleviate symptoms.
  - The goal of WW (NEVER standard of care anymore) is to avoid treatment.
  - The goal of AS is to individualize patient care and only treat men who will benefit.

SPCG-4 Swedish (Scandinavian) trial. ←R→ 695 patients with T1b-T2, PSA < 50, life exp > 10 yr. 6.6% were LN+. AGE < 75 yo.
T1c 12%, T2 76% = this is NOT the current population in post-PSA era.
| WW | RP + PLND | Progression for WW group defined as palpable ECE or symptoms of obstruction w/ voiding requiring intervention.
Med fu = 10.8 yr. Hormone Tx - discretion of the MD. LN mets, which precluded surgery, were found in frozen sections → 23 men in the RP arm.

Bill-Axelson, NEJM 2014

	18-year DSM	18-year DM	10-year OM (100% - OS%)	Daily urinary leak	ED	Urinary obstruction
WW	28.7%	38.3%	68.9%	11%	80%	40%
RP + PLND	17.7%	26.1%	56.1%	41%	84%	29%
P	0.001	< 0.001	< 0.001	SS	?	SS

CONCLUSIONS
Extended follow-up confirmed a substantial reduction in mortality after radical prostatectomy; the number needed to treat to prevent one death continued to decrease when the treatment was modified according to age at diagnosis and tumor risk. A large proportion of long-term survivors in the watchful-waiting group have not required any palliative treatment. (Funded by the Swedish Cancer Society and others.)

Sweden National Prostate Registry
6849 age ≤ 70 prostate cancer cT1-2, ≤ G7, PSA ≤ 20 from 1997-2002 → TX with A.S. OR Curative (RP, RT).
2686 had low risk prostate cancer.

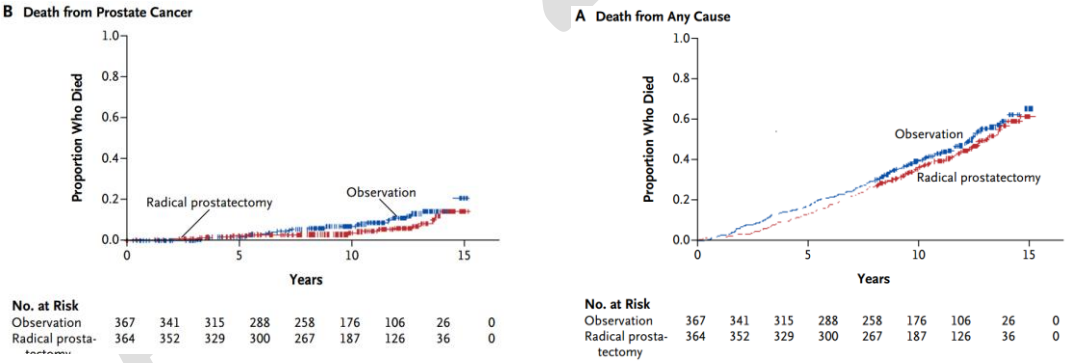
Stattin, J Natl Cancer Inst, 2010

All Comers	10-year PaCSM 3.6% in the surveillance group and 2.7% in the curative intent group.
Low-risk disease	10-year PaCSM 2.4% in the surveillance group and 0.7% in the curative intent group.
	10-year risk of dying competing causes 19.2% vs. 10.2%.

Conclusion: A 10-year prostate cancer-specific mortality of 2.4% among patients with low-risk prostate cancer in the surveillance group indicates that surveillance may be a suitable treatment option for many patients with low-risk disease.

Prostate Cancer Intervention Versus Observation Trial (PIVOT) 1994-2002. 730 men T1-T2NxM0. 40% low risk, 34% int risk, 21% high risk. AGE < 75
←R→ RP | WW. In the AS group, definitive TX offered for patients with PSA doubling time < 3 years, GS ↑ to ≥ 4+3 or ↑ clinical progression.

Wilt, NEJM 2017. FU 12.7 years.
All-cause mortality: 61.3% | 66.8% (p=0.06). SUBSET: RP ↓ ACM for int risk patients, but NOT low risk patients.



REDEEM TRIAL
BACKGROUND: Safety and efficacy of dutasteride, a 5α-reductase inhibitor, pCa with low-risk disease on active surveillance.
←R→ Double Blind Placebo. 289 patients 48-82 yo GS 5-6 prostate cancer | 1. once-daily dutasteride 0·5 mg | 2. Placebo |.
Participants were followed up for 3 years, with 12-core prostate biopsy samples obtained after 18 months and 3 years. 1^{O} time to progression, defined as the number of days between the start of study treatment and the earlier of either pathological progression (in patients with ≥1 biopsy assessment after baseline) or therapeutic progression (start of medical therapy). This trial is registered with ClinicalTrials.gov, number NCT00363311.

Fleshner, Lancet, 2012.
Results: 3-year pathologic or therapeutic progression 38% vs. 48% (p=0·009).
Tox: Incidence of adverse events same 24% vs. 15% NS (sexual adverse events or breast enlargement or tenderness). Eight (5%) men in the dutasteride group and seven (5%) controls had cardiovascular adverse events, but there were no prostate cancer-related deaths or instances of metastatic disease.
INTERPRETATION: Dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer.
As of 2018, Finasteride is not FDA approved for prevention of prostate Ca.

UK PROTECT

←R→ 1643 patients localized prostate cancer | 1. Active Monitoring (PSA monitoring only) | 2. RP | 3. RT + ADT. AGE 50-69 yo

Median age 62. Median PSA 4.6. 77% GS 6 76% T1c. RT 3DCRT 74 Gy. ADT 3-6 months concurrent and adjuvant.

EITHER ARM → 1st year q3mo PSA→ q6-12 months thereafter.

AM ARM → If PSA ↑ 50%, triggers review to continue AM or go to Tx. 1O PCSS.

Hamdy, NEJM 2016.

In the AM arm, 54% received a radical treatment at 10 years.

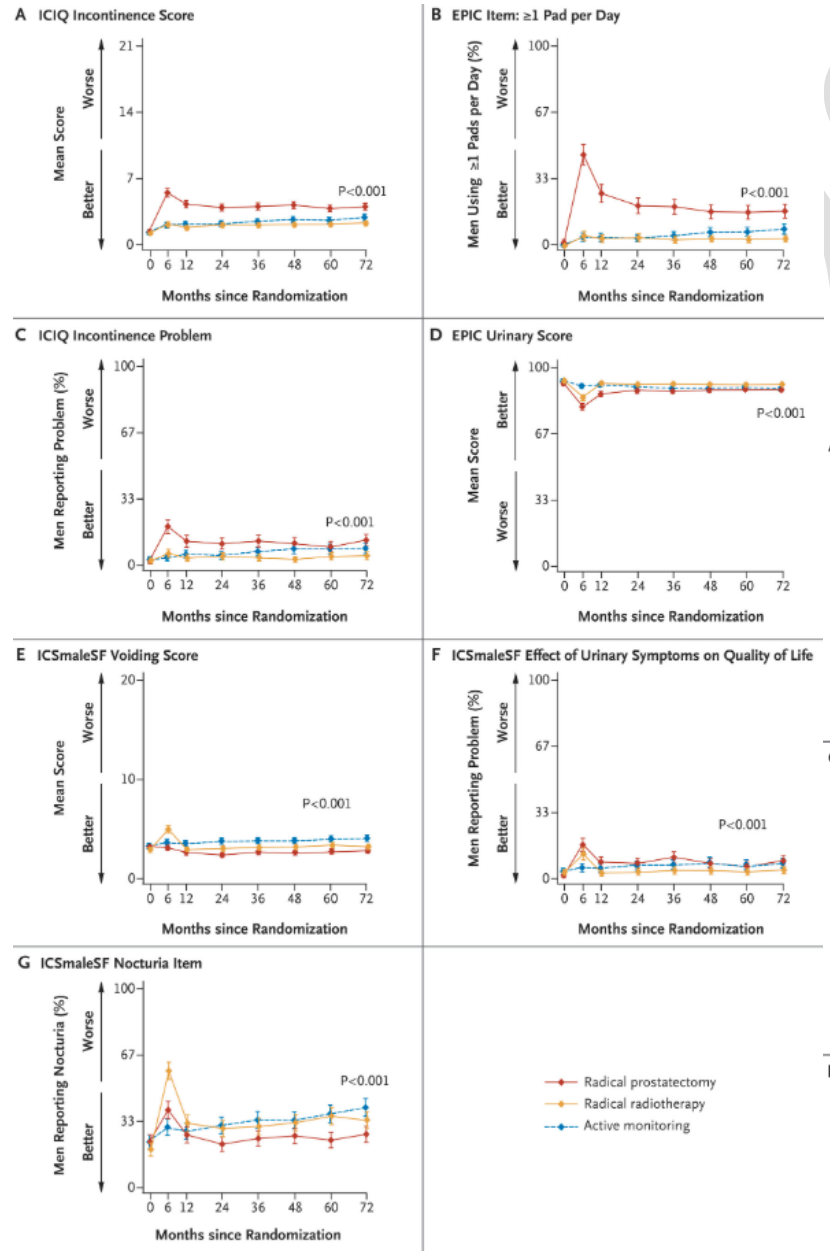
RP NNT = 27 and RT NNT = 33 to avoid 1 metastatic disease. RP NNT = RT NNT = 9 to avoid 1 clinical progression.

	5-year PCSS	10-year PCSS	Clinical Progression per 1000 Person years	Met disease per 1000 Person years	All Cause Death per 1000 Person years
AM	99.4%	98.8%	22.9	6.3	10.9
RP	100%	99%	8.9	2.4	10.1
RT + ADT	100%	99.6%	9	3	10.3
P	NS	NS	< 0.001	0.004	NS

CONCLUSIONS

At a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring.

NOTE: ACM and PCSM were much lower in the this PROTECT trial than SPCG-4 or PIVOT.



Donovan, NEJM 2016. Patient reported QOL of STUDY

1643 men in the Prostate Testing for Cancer and Treatment (ProtecT) trial who completed questionnaires before diagnosis, at 6 and 12 months after randomization, and annually thereafter. Patients completed validated measures that assessed urinary, bowel, and sexual function and specific effects on quality of life, anxiety and depression, and general health. Cancer-related quality of life was assessed at 5 years. Complete 6-year data were analyzed according to the intention-to-treat principle.

Conclusion:

Urinary Void = RT worst at 6 months, then normalize at 12.

Urinary Incontinence = RP worse at all time points.

Bowel = RT worst at 6 month, but at 12 mo. only proctitis (not diarrhea).

Sexual = RP worst across all time points.

NOTE: ALL RT patients got 4-6 months ADT. Could be due to ADT, which would account for the rapid improvement in AD immediately after 6 months.

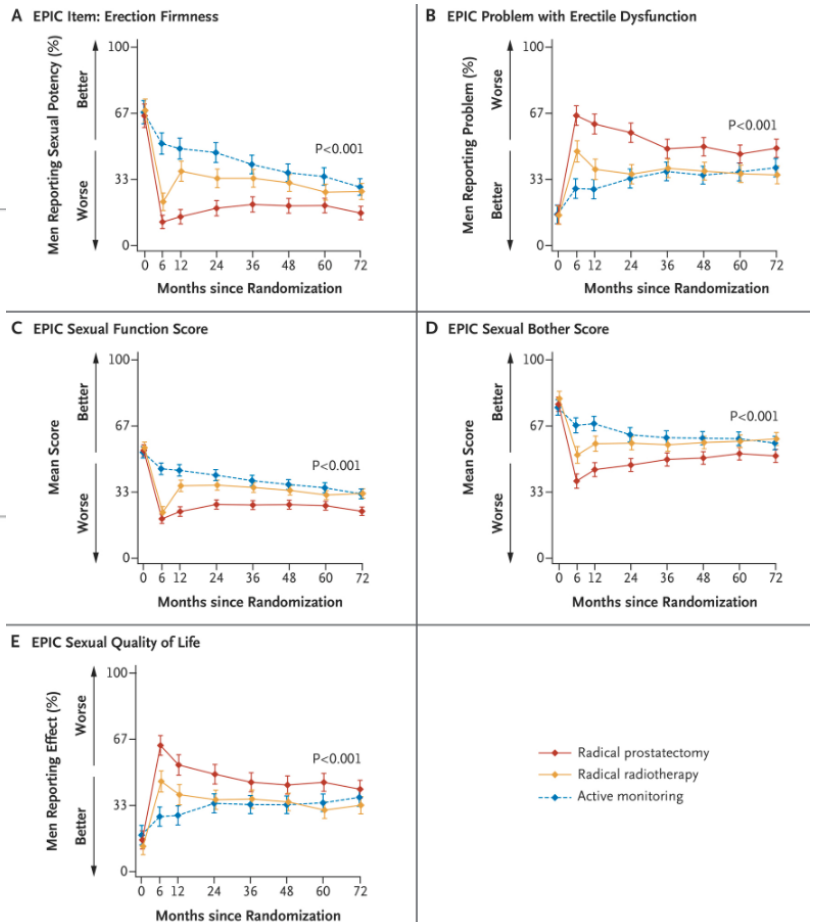


Table 2. Comparisons of Key ProtecT Trial Outcomes with Those Found in Other Trials and Cohorts.*

Variable	Treatment			
	Watchful Waiting	Active Monitoring or Active Surveillance	Radical Prostatectomy	Radical Radiotherapy
	percentage of participants			
Erection not firm enough for intercourse				
At 12-mo follow-up				
ProtecT	—	51	85	62
SPCG-4[9]	45	—	80	—
Sanda et al.[6]	—	—	75	64
At 24-mo follow-up				
ProtecT	—	53	81	66
PIVOT[11]	44	—	81	—
Resnick et al.[29]	—	—	79	61
At 36-mo follow-up				
ProtecT	—	59	79	66
Smith et al.[7]	—	54	68 and 87†	68
At 60-mo follow-up: Resnick et al.[29]	—	—	76	72
At 72-mo follow-up: ProtecT	—	70	83	73
At 144-mo follow-up: SPCG-4[30]	80	—	84	—
Incontinence: any use of absorbent pads				
At 12-mo follow-up				
ProtecT	—	4	26	4
SPCG-4[9]	16	—	71	—
Sanda et al.[6]	—	—	24	3
At 24-mo follow-up				
ProtecT	—	4	21	4
PIVOT[11]‡	6	—	17	—
Resnick et al.[29]	—	—	27	2
At 36-mo follow-up				
ProtecT	—	5	20	3
Smith et al.[7]	—	3	9 and 15§	3
At 60-mo follow-up: Resnick et al.[29]	—	—	28	4
At 72-mo follow-up: ProtecT	—	8	17	4
At 144-mo follow-up: SPCG-4[30]	25	—	54	—

Natural History: Johansson, NEJM 2004.
Swedish subset analysis of 223 patients T0-2 started on WW.
Most cancer had indolent course for first 15 years, but from 15-20 years there was substantial decrease in PFS, DMFS, CCS.
Conclusion: Most early stage PC have indolent course, but aggressive metastatic disease may develop over long period of time.
Take home point: very low risk distinction btw LE > 20 years, vs. 10-20 years in terms of preference for management.
So if you live 10-20 years, go A.S.
But if live > 20 years, go DEFINTIIVE TREATMENT.

Dall'Era, Cancer 2008. UCSF Retrospective. 321 patients with low risk PCA, initially undergoing active surveillance. Initial mean PSA 6.5.
AS Criteria: PSA <10 ng/ml, bx GS <=6, <33% bx cores, cT1-T2a. Surveillance: PSA and DRE q3-6 months, trans-rectal U/S q6-12 months, repeat prostate bx at 12-24 months. Disease progression: increase in re-bx GS, PSA velocity change >0.75 ng/ml
Median F/U 3.6 years (1-17). Outcome: 120 pts (37%) had progression; 63 (38% of those undergoing bx) had higher grade on re-bx, 78 (26%) had high PSA velocity. 78 pts (24%) received treatment; 52 (16%) received treatment due to progression, 26 (8%) due to personal preference, without having progression. Treatment was at a median of 3 yrs after diagnosis. Freedom from treatment 85% at 2 yrs and 67% at 5 yrs. DSS 100%.
Note: 2/3 of those with progression did not receive treatment. Also, 13% of those without progression were treated.
Conclusion: Select individuals may be candidates for active surveillance

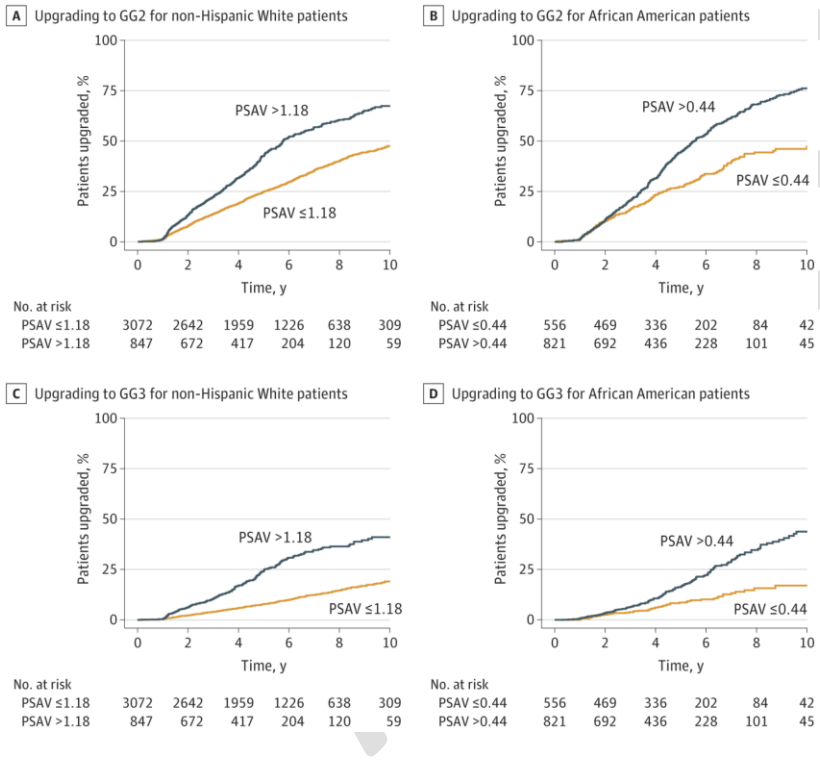
V.A. Study African American vs. White Men
Retrospective 8726 Low-risk prostate cancer 2280 AA vs. (median age, 63.2 years) and 6446 non-Hispanic White men (median age, 65.5 years),
All Managed with A.S.

Deka, JAMA Oncol 2020. **7.6 year**

10-year CI of disease progression	59.9% vs 48.3% (SS P < .001)
10-year receipt of definitive treatment	54.8% vs 41.4% (SS P < .001)
10-year rate of metastasis	1.5% vs 1.4% (NS).
10-year PCaSM	1.1% vs 1.0% (NS)
10-year all-cause mortality	22.4% vs 23.5% (NS TREND, P = 0.09).

Conclusions and Relevance In this retrospective cohort study of men with low-risk prostate cancer followed up for a median of 7.6 years, African American men, compared with non-Hispanic White men, had a statistically significant increased 10-year cumulative incidence of disease progression and definitive treatment, but not metastasis or prostate cancer–specific mortality. Longer-term follow-up is needed to better assess the mortality risk.

African American Retrospective PSAV (prostate specific antigen velocity)
5296 men 3919 non-Hispanic White men (74.0%; mean [SD] age, 65.7 [5.8] years) and 1377 AA men (26.0%; mean [SD] age, 62.8 [6.6] years).
All Low-Risk Prostate Cancer.
All underwent A.S.
White patients Older (mean [SD] age, 65.7 [5.8] years vs 62.8 [6.6] years; P < .001),
↑ cT stage (stage T2, 608 [15.5%] vs 111 [8.1%]; P < .001)
↑ Charlson Comorbidity Index score (1 and ≥2, 912 [23.3%] vs 273 [19.8%]; P = .002),
↑ Median income ($60 000 to ≥$100 000, 1223 [31.2%] vs 282 [20.5%]; P < .001),
↑ median level of education (20% to ≥30% with college degree, 1192 [30.4%] vs 333 [24.2%]; P < .001).



Nelson, JAMA Netw Open 2021
Gleason progression to ≥ GG2 occurred in 2062 patients (38.9%).
Gleason progression to ≥ GG3 occurred in 728 patients (13.7%).
Fifty-four patients (1.0%) developed metastases.

MVA → PSAV was SS associated with progression to GG2 (HR 1.32), GG3 (HR 1.51), and mets (HR 1.38).

Optimal PSAV thresholds that were associated with progression were significantly lower for African American patients (0.44 ng/mL/y) compared with non-Hispanic White patients (1.18 ng/mL/y).

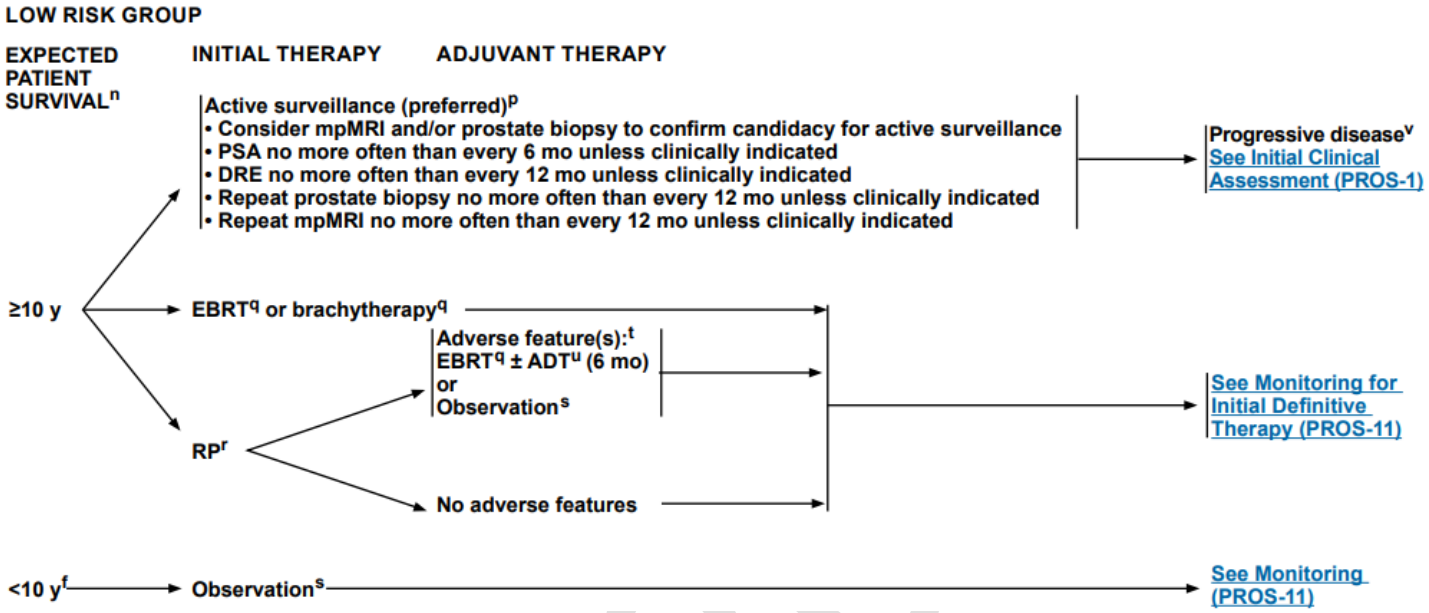
Conclusions and Relevance This study suggests that PSAV is significantly associated with grade progression among patients with low-risk prostate cancer managed with active surveillance, but at lower values for African American patients compared with non-Hispanic White patients. These data suggest that serial PSA measures may potentially substitute for multiple prostate biopsies and that African American patients may merit increased frequency of PSA testing.

MRI in Lieu of Biopsy for A.S Study → Ans: No.
←M→ 15 studies with 2240 patients. Six used PRECISE criteria and nine institution-specific definitions of MRI progression.

Rajwa, Euro Urol 2021.
Pooled PCa progression rate, which included histological progression to Gleason grade ≥2, was 27%.
Pooled sensitivity and specificity were 0.59 (95% confidence interval [CI] 0.44–0.73) and 0.75 (95% CI 0.66–0.84) respectively.
SS heterogeneity between included studies.
Depend on PCa prog. prevalence, the pooled NPV for serial prostate MRI ranged from 0.81 (95% CI 0.73–0.88) to 0.88 (95% CI 0.83–0.93)
pooled PPV ranged from 0.37 (95% CI 0.24–0.54) to 0.50 (95% CI 0.36–0.66).
NS differences in the pooled sensitivity (p = 0.37) and specificity (p = 0.74) of PRECISE and institution-specific schemes.
Conclusions Serial MRI still **should not** be considered a sole factor for excluding PCa progression during AS, and changes on MRI are not accurate enough to indicate PCa progression. There was a nonsignificant trend toward improved diagnostic estimates of PRECISE recommendations. These findings highlight the need to further define the optimal triggers and timing of biopsy during AS, as well as the need for optimizing the quality, interpretation, and reporting of serial prostate MRI.

Low Risk Disease: T1-T2a, Grade Group 1, PSA < 10.

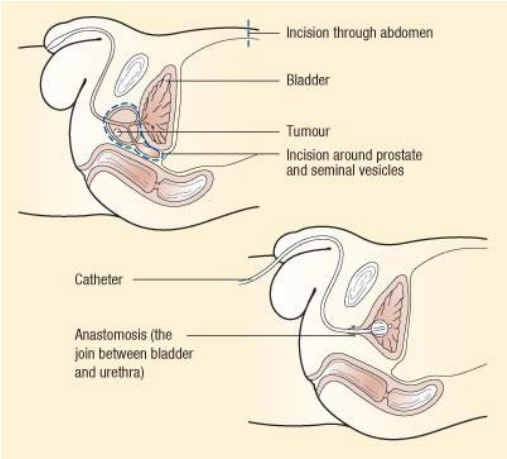
Survival by TX



SEER Survival and Tx Selection Bias (TBS)
50,804 low-risk prostate cancer (cT1-T2a, PSA < 10, and GS 6) s/p RP, brachy (BT), or EBRT from 2005 to 2015.
The TSB effect was defined as the unadjusted 10-year OS difference between modalities that was not due to differences in PCSS.
Propensity score matching was used to estimate the TSB effect on OS due to measured confounders (variables present in the database and associated with OS) and unmeasured confounders.
FU 7.4 years

Miccio, Prostate Cancer +PDis 2020
10-year PCSS for the entire cohort was 99%.
10-year OS RP 92.9% BT 83.6% EBRT 76.9% ($p < 0.001$).
OS differences persisted after propensity score matching of RP vs. EBRT (7.4%), RP vs. BT (4.6%), and BT vs. EBRT (3.7%) (all $p < 0.001$).
Estimated 10-year OS due to TSB effect 15.0% for RP vs. EBRT (8.6% measured, 6.4% unmeasured)
8.5% for RP vs. BT (4.8% measured, 3.7% unmeasured)
6.5% for BT vs. EBRT (3.1% measured, 3.4% unmeasured).
Conclusions Patients with low-risk prostate cancer selected for RP exhibited large OS differences despite similar PCSS compared to radiotherapy, suggesting OS differences are almost entirely driven by TSB. The quantities of these effects are important to consider when interpreting prostate cancer CER using national registries.

RP



- Retropubic (> 90%) or Transperineal. Laparoscopic, Robotic techniques have similar outcome and ↑ recovery and ↓ hospital stay.
- Pelvic Lymph Node Dissection performed only if ↑ risk of LN metastasis (Partin tables). Abort for +LN disease on frozen histology.
- Biochemical failure less ambiguous, potential for salvage XRT

- The entire prostate and seminal vesicles are removed through an incision in the abdomen. Sometimes nearby lymph glands are also removed. The urethra is joined to the bladder and a catheter is inserted to drain urine.
  - Adv are pathological evaluation, especially of LN.
  - Disadv are impotence, incontinence. bioc

Extent of Pelvic LN Dissection Study
←R→ 700 single-center randomized Prostatectomy + | 1. Limited PLND (ext iliac) | 2. Extended PLND (ext Iliac, obturator, hypogastric) |.
Median LN retrieved 12 vs. 14.
1^{O} BcR

Touijer, Eur Urol Oncol 2021 Median FU 3.1 years.
Corresponding rate of positive nodes was 12% vs. 14% (NS).
Rate of biochemical recurrence (HR 1.04, NS)
Rates for grade 2 and 3 complications were similar at 7.3% vs. 6.4%.
There were no grade 4 or 5 complications.
Conclusions Extended PLND did not improve freedom from biochemical recurrence over limited PLND for men with clinically localized prostate cancer. However, there were smaller than expected differences in nodal count and the rate of positive nodes between the two templates. A randomized trial comparing PLND to no node dissection is warranted.

Beta-Blocker Study
11,117 men s/p RT for Prostate CA (ie, no prior hormonal therapy, radiotherapy, or chemotherapy).
Minimum progression-free follow-up of 6 months.
Study with non-selective β-Blockers (ns-BBs)

Sivanesan, JAMA Net Open 2022.
1622 (14.6%) later received treatment for cancer recurrence during a median follow-up of 4.3 years.
Use of nsBBs at time of surgery among 209 patients = SS ↓ risk of treatment for cancer recurrence (HR 0.64, P = .03).
No such association was observed for use of sBBs (HR 0.96; P = .62).
Subanalyses with (1) relaxed inclusion criteria allowing for inclusion also of patients with early progression (within 6 months) and (2) only the healthiest patients (Eastern Cooperative Oncology Group performance status of 0) supported the main findings.
Conclusions and Relevance In this cohort study, use of nsBB but not sBBs at the time of radical prostatectomy was associated with less treatment initiation for cancer recurrence. This finding, together with accumulated preclinical and clinical evidence, provides a foundation for

AE 2022

Dose Escalation Origins

RTOG 75-06 originally established 70 Gy as the maximum tolerable dose, beyond which significant GI toxicity (diarrhea) developed. Treatment fields were generally 6x6 cm up to 11x11 cm "four-field box" determined by bony landmarks, and if necessary rectal contrast and foley catheter ←R→. 523 patients with clinical Stage A2-B N+ or Stage C. 1.8-2.0 Gy/fx x5 days per week to 45-50 Gy either to whole pelvis or prostate only.
| 1. Pelvic RT 40-45 Gy + prostate boost 20-25 Gy (minimum 65 Gy) | 2. Pelvic + PA RT 40-45 Gy + prostate boost (minimum 65 Gy) |

Pilepich, IJROBP 1986. Median F/U 4.2 years. Outcome: No difference between arms for DFS, DM, OS.
Toxicity: Periaortic RT does not increase bowel injury. Prostate doses > 70 Gy result in increased bowel injury (20% vs 10% rectal bleed) but not bladder injury. Conclusion: No benefit to elective peri-aortic irradiation.

Cooperberger, Cancer 2010. Solo therapy trial of RT | surgery | ADT. Retrospective 7538 men (clinical stage ≤T3aN0) with local disease analyzed → underwent R, received EBRT, or received primary ADT. At least 6 mo. f/u recorded.
HR for CSM relative to RP was 2.21 for RT and 3.22 for ADT. Absolute Δ b/t RP and RT were ↓ at low risk but ↑↑↑ for int. and high risk.

MAJOR STUDIES

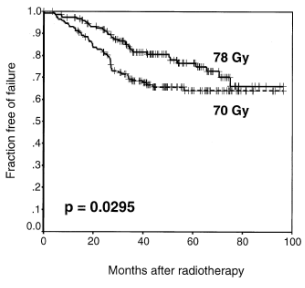
Institution	Stage	Dose (Gy)	5-year Outcome	Grade 3 Toxicity
UK MRC ADT-RT 01 Dealaney	T1b-T3a	64 vs 74	NED 60% vs 71% (SS)	GI 6% vs 10% GU 2% vs 4%
Dutch CKVO96-10 Peeters	T1b-T4	68 vs 78	NED 54% vs 64% (SS)	GI 4% vs 5% (NS) GU 12% vs 13% (NS)
PROG 95-09 (1996-1999)	T1b-T2b	70.2 vs 79.2	NED 79% vs 91% (SS)	GI 1% vs 1% (NS) GU 1% vs 2% (NS)
MD Anderson Pollack	T1-T3	70 vs 78	FFF 59% vs 78% (SS)	GI 1% vs 7% (SS) GU 5% vs 4% (NS)
Ontario LDR Boost (1992-1997)	T2-T3	66 vs 75	FFP 39% vs 71% (SS)	GI 2% vs 4% (NS) GU 4% vs. 14% (NS)
Harvard Proton Boost Zietman	T3-T4 N0-2	67.2 vs 75.6	LC 92% vs 80% (NS)	GI bleeding 15% vs 32% (NS) GU stricture 8% vs 19% (NS)

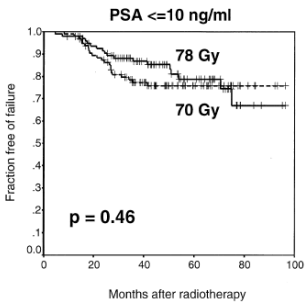
MD Anderson. ←R→ 301 patients. Stage T1b - T3 (20%) EBRT. Low (20%), int (45%), high (35%). GS ≥ 8 (18%). | 78 Gy | 70 Gy |.
NOTE: this was prescribed to isocenter. We do it now to volume. ∴ prostate didn't get all 78 Gy, really it was like 76 or 75 Gy.
Both were 4 field technique to 46 Gy. THEN 70 Gy arm used smaller 4 field box. The 78 Gy arm used 6 fields conformal boost.

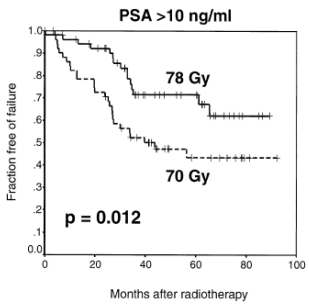
Pollack, JCO 2010. Kuban, IJROBP 2008
The median follow-up 8.7 years. Results: 8 yr freedom from biochem or clinic failure (FFF), all patients 78% | 59% | SS.
First stratification: If PSA > 10, 78% | 39% | SS.
Second stratification: Low risk 88 vs 63… intermediate risk 86 vs 76 (probably not enough time).....High risk 63% vs 26%. FFF all over 8 years.
Clinical failure rate ↓ in the 78-Gy arm as well | 7% | 15% | SS. 2x patients either died of CA or currently alive with CA in the 70-Gy arm.
Toxicity: GI toxicity ≥ 2 = twice as often in the high dose patients 26% | 13% (SS), although genitourinary toxicity ≥ 2 was less 8% | 13% (NS).
Significantly higher late rectal toxicities (≥ grade 2) related to rectal volume (> 25% vs < 25%).
Conclusion: Dose escalation improved PSA and clinical control, particularly if PSA >10 ng/ml.

	8-year FFF	8-yr FFF PSA >10	8-year FFF PSA < 10	FFF Low R	FFF Int R	FFF High R	8-year clinical LC	8-yr FF Distant met	8-year FFDM HighR	8-year OS
78 Gy	78%	78%	78%	88%	86%	63%	93%	99%	96%	78%
70 Gy	59%	39%	66%	63%	76%	26%	85%	95%	83%	79%
	SS	SS	-	SS	-	SS	SS	-	SS	-

Pasalic, IJROBP 2019. LONG TERM 14.3 yr.
15-year BcF 12% vs. 18.9% (P = 0.042).
15-year DM 1.1% vs. 3.4% (P = 0.018).
15-year PCaSM 3.2% vs. 6.2% (P = .045).
15-year OS NS.
15-year rate salvage 21.9% vs. 38.7% (P = 0.002).
15-year rate 2^{O} malignancy = 2.3% (NS).
1 bladder, 6 rectal within the RT field.
Conclusions: Sustained ↑ BcF and ↓ Salvage.
NS OS. Long Term Data = low 2^{O} cancers.







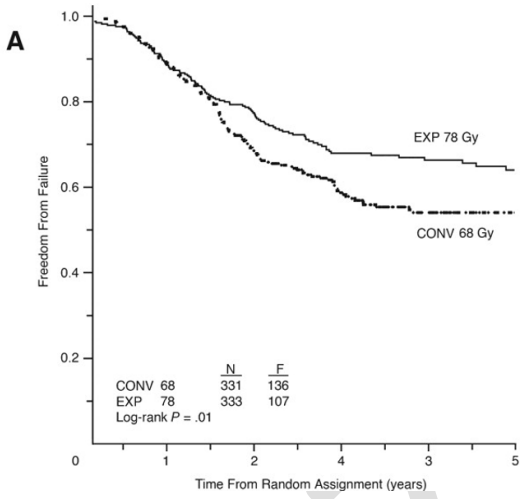
NOTE: Sub-group analysis = NS CI of BcF or clinical F in patients with low risk (P=0.064), intermediate risk (P=0.344) and high risk (P=0.223).

Harvard Proton (PROG 95-09). ←R→ 400 patients. Stage T1b-T2b, PSA <15 ng/mL (median PSA 6.3); 75% GS <7. Low risk 58%, intermediate 37%.
| 1. Proton boost 19.8/11 GyE → photons 50.4/28 (total = 70.2) | 2. Proton boost 28.8/16 → photons 50.4/28. (total = 79.2) |
Proton CTV = prostate + 5 mm margin. PTV = CTV + 7-10 mm. Loma Linda used opposed lateral beams, 250 MeV protons; Harvard used perineal boost, 160 MeV protons. Rectal Lucite probe, inflated 25-50 mL saline. Photons = 4F plan, photon CTV = prostate + 10 mm margin. No hormones.

Zietman, JCO 2010.
Outcome: 10-year ASTRO (backdating)
bPFS ↓ 68% vs. ↑ 83% (SS). For low-risk disease 72% vs 93% (SS); for intermediate-risk 58% vs. 70% (p=0.06).
No difference in OS (78% vs 83%).
Started salvage hormones 6% vs 11% (SS).
Toxicity: Late Grade 2+ low-dose 29% vs. high-dose 39% (SS); Grade 3+ 2% in both arms (NS)
Conclusion: Long-term advantage for high dose in low/intermediate risk PCA patients, with comparable Grade 3 toxicity.

Talcott, JAMA 2010. Patient survey. 280 patients (83% of surviving cohort). Median F/U 9.4 years.
Outcome: No difference in urinaty obstruction/irritation, urinary incontinence, bowel problems, sexual dysfunction, and most other outcomes. Patients receiving standard dose had less confidence that their dose was under control (76% vs 86%, SS). Many patients reported their function as normal, despite substantial symptoms.
Conclusion: Higher dose not associated with increase in patient-reported symptoms

Nguyen, IJROBP 2010. Rectal dose volume and GI QoL.
Trend toward an association between ↑ long-term GI dysfunction and higher V60, V65, V70, and V75.
There was no difference in long-term GI dysfunction between men on the conventional vs. high-dose arms (p = 0.49).

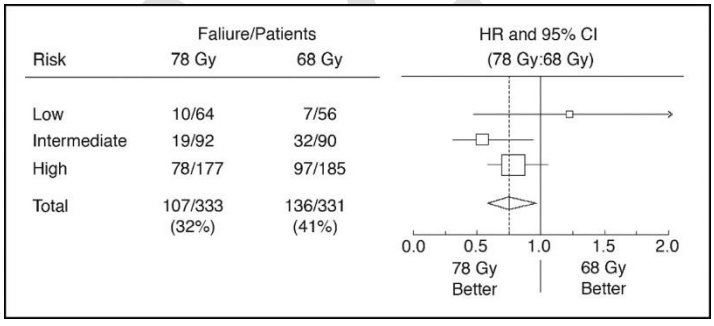


Peeters, JCO 2006 (Dutch CKVO 96-10). ←R→ 664 patients T1b-T4, with PSA < 60 (excluded many low risk: T1a, T1b-c with GS < 5 and PSA ≤4; ALSO pN+). | 1. 68/34 Gy | 2. 78/39 Gy |.
Both 3D-CRT. CTV = prostate ± SV (depending on risk group); PTV = 1.0 cm margin to 68 Gy, then 0.5 mm and 0 mm posteriorly. Prescription dose was to the isocenter. Stratified by risk group.

Hormonal therapy in 22% patients. Note: HT was allowed but not recommended until ongoing studies had defined groups that benefit from HT. Its prescription was left at the discretion of the treating physician.

Gleason Score	Differentiation	Treatment Group					
		T1b, T1c, T2a				T2b, T3a	T3b, T4
		iPSA 0-4 µg/L	4-10	10-20	20-60	0-60	0-60
2-4	Good	I	I	I	II	III	IV
5-7	Moderate	I	II	II	III	III	IV
8-10	Poor	II	III	III	III	III	IV

Outcome: 5 yr FFS ↑ 64% vs ↓ 54% (SS). Clinical fail both groups 76% (NS), OS 82% vs. 83% (NS).
Toxicity: GI Grade 2+ high-dose 32% vs. low-dose 27% (NS), GI Grade 3+ 5% vs. 4% (NS).
GU Grade 2+ 39% vs. 41% (NS), GU Grade 3+ 13% vs. 12% (NS).
Conclusion: Significantly improved FFF, with comparable toxicity.
Intermediate risk responded best (See chart ←).



Your acute GU toxicities are predicted by baseline AUA.
Your late GU toixicity predicted by bladder neck in trigone > 80

Michalski, IJROBP 2012. (RTOG 94-02). ←R→ 1055 men. 3D Conformal.
3 initial patient groups, then opened to 5.
| 1. T1-T2, (low risk of SV) → TX prostate only |
| 2. T1-T2, (>15% of SV involvement) → TX prostate + SV → prostate boost |
| 3. T3 → TX prostate + SV. |
Doses: 68.4 Gy (1.8 Gy/fx; level I), 73.8 Gy (1.8 Gy/fx; level II), 79.2 Gy (1.8 Gy/fx; level III), 74 Gy (2 Gy/fx;level IV), 78 Gy (2 Gy/fx; level V).
PTV margins 5-10 mm. No Group 3 in Levels III-V.

Biochemical disease-free survival, all patients →.

Dose level	Risk Group	n	5-year	10-year
68.4 Gy	Low	55	57	26
	Intermediate	37	46	25
	High	16	50	21
73.8 Gy	Low	91	59	37
	Intermediate	75	52	34
	High	134	34	23
79.2 Gy	Low	85	52	48
	Intermediate	54	54	42
	High	28	46	16
74 Gy	Low	92	64	45
	Intermediate	109	56	31
	High	55	34	13
78 Gy	Low	80	75	61
	Intermediate	109	63	45
	High	31	61	50

UK MRC _ADT _ RT01 (The ONLY one here to use ADT). There will be others see below.
←R→ T1b-T3a, N0, M0 with PSA < 50 ng/mL.
| 1. 64 Gy in 32 fractions | 2. 74 Gy in 37 fractions (dose escalation) |. All patients received neoadjuvant ADT 3-6 months before EBRT → end EBRT.
The coprimary outcome measures were biochemical progression-free survival and overall survival. All analyses were done on an intention-to-treat basis.

Dearnaley, Lancet 2014.
10-year OS 71% both (NS). 10-year bPFS 43% vs. 55% (SS).
INTERPRETATION: At a median follow-up of 10 years, escalated-dose conformal radiotherapy with neoadjuvant androgen deprivation therapy showed an advantage in biochemical progression-free survival, but this advantage did not translate into an improvement in overall survival. These efficacy data for escalated-dose treatment must be weighed against the increase in acute and late toxicities associated with the escalated dose and emphasise the importance of use of appropriate modern radiotherapy methods to reduce side-effects.

Kupelian, IJROBP 2004. 2991 T1-2 patients at CCF or MSK. Neoadjuvant ADT ≤ 6 mo. given in 622 cases (21%). No adjuvant therapy was given after local therapy. RP for 1034 (35%), EBRT < 72 for 484 (16%), EBRT ≥ 72 for 301 (10%), PI (permanent seed implantation) for 950 (32%), and COMB (combined seed/EBRT) for 222 (7%).

The median RT doses in EBRT <72 and EBRT ≥ 72 was 68.4 and 78.0 Gy, respectively. The median f/u 56 mo (range 12-145).
Biochemical relapse was defined as PSA levels >0.2 for RP cases and 3 consecutive ↑ PSA for all other cases.
A multivariate analysis for factors affecting the bRFS rates was performed using the following variables: clinical T stage, iPSA, bGS, androgen deprivation, year of treatment, and treatment modality. The multivariate analysis was repeated excluding the EBRT <72 cases.

	RP	EBRT < 72	EBRT ≥ 72	Seeds	Combo
5-year bRFS	81	51	81	83	77
7-year bRFS	76	48	81	75	77

Results: Multivariate analysis showed iPSA (p <0.001), bGS (p <0.001), year of therapy (p <0.001), and treatment modality (p <0.001) to be independent predictors of relapse. Because EBRT <72 cases had distinctly worse outcomes, the analysis was repeated after excluding these cases to discern any differences among the other modalities. The multivariate analysis excluding the EBRT <72 cases revealed iPSA (p <0.001), bGS (p <0.001), and year of therapy (p = 0.001) to be the only independent predictors of relapse. Treatment modality (p = 0.95), clinical T stage (p = 0.09), and androgen deprivation (p = 0.56) were not independent predictors for failure.

Conclusions: The biochemical failure rates were similar among PI, high-dose EBRT, COMB, and RP for localized prostate cancer. The outcomes were significantly worse for low-dose (<72 Gy) EBRT.

Zelefsky, Urology 2008. Dose Escalation Biopsy results.
RR 339 patients 10 years after the completion of RT and 6.25 years after posttreatment biopsy.
RESULTS:
Overall biopsy positive 32%, severe treatment effect 21% and negative 47%. A higher radiation dose in the intermediate and high risk subgroups was associated with a lower incidence of positive biopsy. Of patients at intermediate risk who received a dose of 75.6 or greater 24% had a positive biopsy compared to 42% who received 70.2 Gy or less (p = 0.03).

Positive Biopsies: ≤ 70.2 Gy 51%, 75.6 Gy 33%, and ≥ 81 Gy 15%. (p = 0.05).
Short course neoadjuvant ADT ↓ + biopsy from 16% to 42% (p <0.0001).
MVA biochemical failure posttreatment biopsy status (positive vs severe treatment effect or negative p <0.001), pretreatment prostate specific antigen (p = 0.05) and clinical T stage (p = 0.09). Similarly multivariate analysis revealed that a positive posttreatment biopsy was one of the strongest predictors of distant metastasis and prostate cancer death in this cohort of patients.
CONCLUSIONS:
As assessed by posttreatment prostate biopsies, local control is improved with higher radiation doses. Long-term biochemical outcomes in patients with posttreatment biopsies demonstrating severe treatment effect changes were not different than those in patients with negative biopsies. We also noted that local tumor control was associated with a decrease in distant metastases and prostate cancer mortality, further highlighting the importance of achieving optimal tumor control in patients with clinically localized disease.

PA 2024

Dose Escalation Contemporary

Dose Ceiling Metaanalysis

←M→ 14 randomized trials including 13,384 patients yielded a best estimate of α/β = 1.6 Gy with highly SS heterogeneity (I2 = 70%, P = .0005). Further analysis indicated an association between increasing dose per fraction in the experimental arm and increasing α/β ratio (slope, 0.6 Gy increase in α/β per Gy increase in fraction size; P = .017). This deviation from the linear quadratic model could, however, also be explained by biochemical control maxing out at doses above approximately 80 Gy.

Conclusions

Biochemical control data from randomized controlled trials of dose-per-fraction escalation in prostate cancer radiation therapy are inconsistent with the presence of a constant fractionation sensitivity in the linear-quadratic model and/or a monotonic dose response for biochemical control beyond 80 Gy equivalent dose. These observations have a potential effect on the optimal doses in future trials and the interpretation of ongoing trials of ultrahypofractionation.

MSK 81 Gy Long Term Data

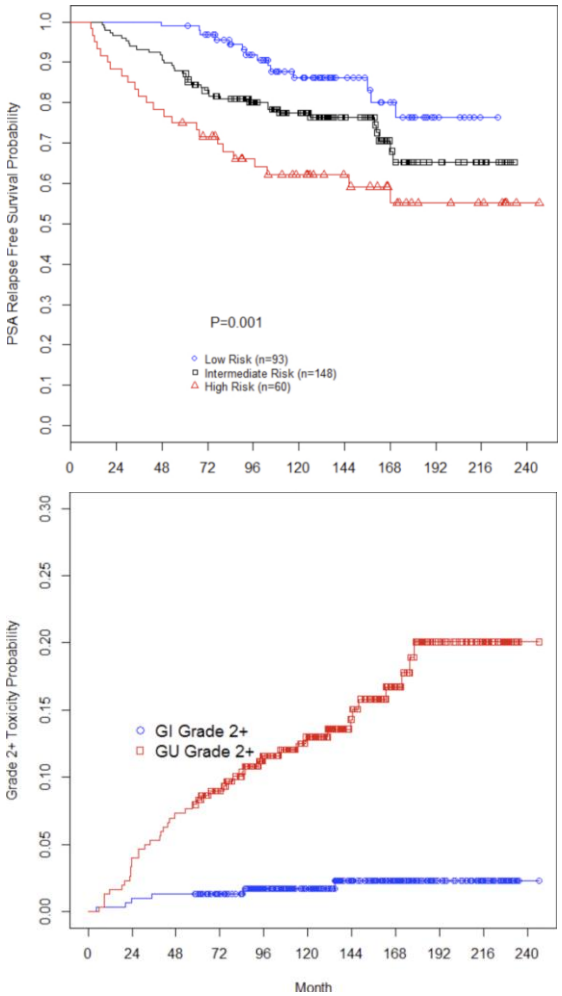
561 Single Institution with prostate contained disease (1. low, 2. fav-int, 3. unfav-int) treated with 81 Gy to PTV.

Zelefsky, J Urol 2006.

By ASTRO (old 3 consecutive rise) 8-year PSA RFS 1. 85% vs. 2. 76% vs. 3. 72% (SS),
By Houston (Nadir+2) 8-year PSA RFS 1. 89% vs. 2. 78% vs. 3. 67% (SS),
8-year G2 rectal bleeding was 1.6%. 8-year G3 0.1% (n=3) → requiring either transfusions or laser cauterization procedure. No G4.
8-year G2 urethral stricture 9% 8-year G3 3%.
Among patients who were potent before intensity modulated radiation therapy, erectile dysfunction developed in 49%.
8-year CSS 100%, 96% and 84%, respectively.
Conclusions: These long-term results confirm our previous observations regarding the safety of high dose intensity modulated radiation therapy for clinically localized prostate cancer. Despite the application of high radiation doses, the incidence of rectal bleeding at 8 years was less than 2%. Despite the increased conformality of the dose distribution associated with intensity modulated radiation therapy, excellent long-term tumor control outcomes were achieved.

Alicikus, Cancer 2011

10-year PSA RFS 81%, 78%, 62%.
10-year MetFS 100%, 94%, 90%. 10-year CSS 100%, 97%, and 86%, respectively.
10-year G2-3 late GU 11% and 5%, respectively 10-year G2-3 late GI 2% and 1%, respectively. No grade 4 toxicities were observed.
Conclusions: To the authors' knowledge, this report represents the longest followed cohort of patients who received high-dose radiation levels of 81 Gy using IMRT for localized prostate cancer. The findings indicated that high-dose IMRT is well tolerated and is associated with excellent long-term tumor-control outcomes in patients with localized prostate cancer.



Weg, Adv. Rad Oncol 2019. **15-year Side Effects**

301 patients → 81 Gy (n = 269, 89%) or 86.4 Gy (n = 32, 11%).
29% low risk (LR), 49% intermediate risk (IR), and 22% high risk (HR).

Late G3 GI → 3 patients (1.0%). No grade 4 GI toxicity events occurred.
Median time from RT → late G3 GI toxicity = 2.9 years.
One event occurred after 10 years.

Late G3 GU → 6 patients (2%). G4 GU toxicity 1 (0.3%).
Median time from RT → late ≥ G3 GU = 5.5 years.
Two events occurred after 10 years.

In addition, 38 (12.6%) developed second primary malignancies (SPMs), 8 of which were in-field malignancies.
Median time from RT → all SPM and in-field SPM was 10 years.

15-year RFS	76% LR vs. 65% IR vs. 55% HR.
15-year DMFS	88% LR vs. 75% IR vs. 63% HR.
15-year PCaSM	1.9% LR vs. 7.1% IR vs 12.2% HR.

Conclusions This report represents the longest follow-up data set to our knowledge of patients treated with high-dose IMRT for PC. Our findings indicate that it is well tolerated with 1.0% and 2.3% incidence of long-term grade 3+ GI and GU toxicity, respectively. The cohort had excellent PC-specific survival.

NOTE: Dose constraints included that no more than 30% of the rectal wall volume should receive >75.6 Gy (V75.6 Gy <30) and that no more than 53% of the rectal and bladder walls should receive >47 Gy (V47 <53). In the overlap region between the PTV and these critical organs, the constraint was set at 88% of the prescription dose for the rectum and at 98% for the bladder.

RTOG 01-26.
←R→ 1532 men 3DCRT/IMRT study. cT1b-T2bN0M0, GS ≤ 6 + PSA 10-20 OR GS 7 + PSA < 15 | 1. 7920 cGy = 180 x 44 | 2. 7020 cGy = 180 x 39 |.
Median age was 69, 70% had PSA < 10 ng/ml, 84% with GS 7, 57% had T1 disease, and 66% used 3D-CRT.

Michalski, JAMA Oncol 2018 7-year FU
8-year OS were 76% vs. 75% (NS). 8-year DM 4% vs. 6% (NS).
8-year BcF 31% vs. 47% (SS, ASTRO DEF) 8-year BcF 20% vs. 35% (SS, PHOENIX DEF).
The high-dose arm had a lower rate of salvage therapy use.
5-year ≥ G2 GI 21% vs. 15% (SS). 5-year ≥ G2 GU 12% vs. 7% (SS).
Conclusions and Relevance Despite improvements in biochemical failure and distant metastases, dose escalation did not improve OS. High doses caused more late toxic effects but lower rates of salvage therapy.

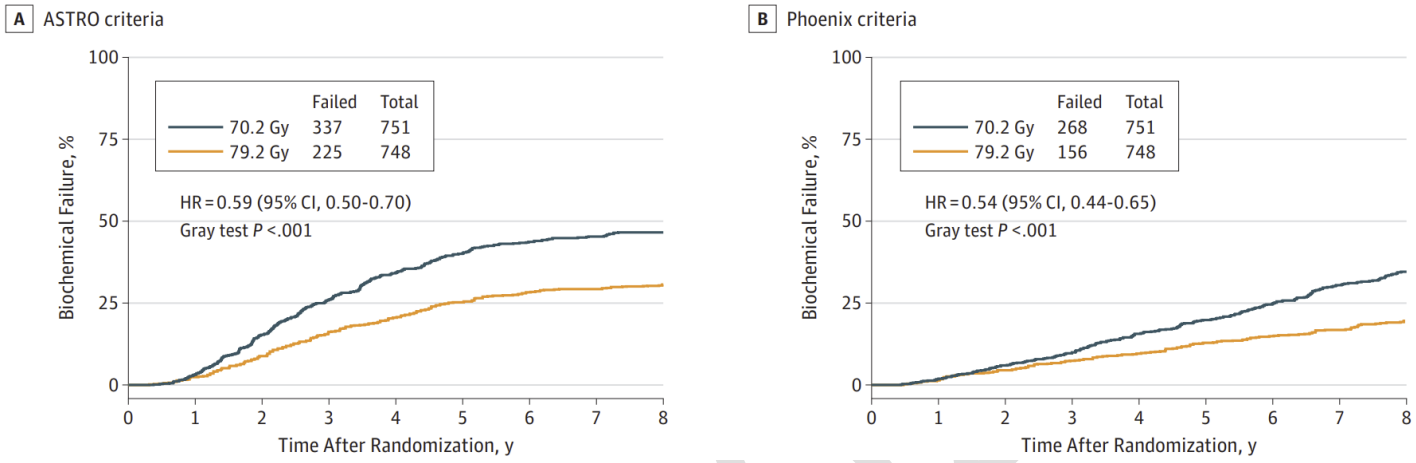


Table 2. Gastrointestinal (GI) and Genitourinary (GU) Toxic Effects[a]

Toxic Effects	No. (%)									
	70.2 Gy					79.2 Gy				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute	(n = 733)					(n = 728)				
GU[b]	146 (20)	113 (15)	10 (1)	0	0	136 (19)	116 (16)	10 (1)	0	0
GI[c]	61 (8)	33 (5)	2 (<1)	0	0	50 (7)	50 (7)	1 (<1)	0	0
Late	(n = 741)					(n = 736)				
GU	21 (3)	52 (7)	15 (2)	0	0	16 (2)	81 (11)	19 (3)	3 (<1)	0
GI	23 (3)	93 (13)	23 (3)	0	1 (<1)	26 (4)	119 (16)	34 (5)	3 (<1)	2 (<1)

PENDING WPRT Dose Escalation
RTOG 09-24.
Standard 7920 cGy for prostate.
Whole pelvis CTV from L4/L5. L5/S1-S3 presacral can be included depending on rectal dose. ADT + prostate high dose RT ± WPRT.

Brachytherapy Alone

ABS Contraindication	Relative Containdication
< 5-year life expectancy	IPSS >15-20
Distant Mets	Prior pelvic RT
Absence of rectum	Prior TURP
Prior large TURP	Large gland > 60 cc (give 3 months of ADT and then reevaluate prostate)
Ataxia telangiectasia	Enlarged median lobe into bladder neck (higher risk of urinary retention)
Non-operative patient	IBD

LDR Series: All these studies are retrospective, single-institution experiences. Initial PSA (iPSA).

Series	N	Stage	% GS 7	Med iPSA	Treatment	Med FU (mo.)	PSA Outcome
Lawton RTOG 98-05	101	T1-T2	0	≤ 10	I-125	96	8% BcF at 8 years
Beyer and Priestly	480	T1-T2	13	7.3	I-125	35	79% <4 at 5 years
Blasko	197	T1-T2	0	7	I-125	36	93% PFS at 5 years
Blasko	97	T1-T2	28	8.6	Pd-103	37	86% <1 at 4 years
Grado	241	T1-T2	--	11.3	I-125/Pd-103	24	88% <4 at 3 years
Kaye	45	T1-T2	0	11	I-125	24	98% <4 at 2 years

Low dose rate 0.4 to 2 Gy per hr Medium Dose Rate 2-12 High Dose Rate ≥ 12
Pulse dose rate, short pulses typically once an hour and replaces LDR.

2010s: LDR $17,000 vs IMRT $31,000. HDR probably cheaper.

HDR: ABS 2012 Yamada Prostate Brachytherapy Guidelines

Table 3
Current dose fractionation schedules

Institution	Dose fractionation	Bladder	Urethra	Rectum
MSKCC	Boost 7Gyx3 Mono 9.5Gyx4 Salvage 8Gyx4		<120% prescription	$D_{2\ cc} < 70\%$
UCSF	Boost 15Gyx1 Mono 10.5Gyx3 Salvage 8Gyx4*	$V_{75} < 1$ cc	$V_{125} < 1$ cc, $V_{150} = 0$ cc *(dose tunnel whenever possible)	$V_{75} < 1$ cc
WBH	Boost 10.5Gyx2 Mono 4 × 9.5 Gy (historical) 12−13.5Gyx2 (current) Salvage 7Gyx4 combined with hyperthermia	No constraint (intra-op TRUS-based dosi)	$V_{100} < 90\%$ of prescription $V_{115} < 1\%$ of prescription	$V_{75} < 1\%$ of prescription
TCC	Boost 6Gyx2 ×2 implants	<80% of Rx	<125% of prescription	<80% of Rx to outer wall
GW	Boost 6.5Gyx3 Mono two sessions of 6.5Gyx3	<100% prescription	<110% prescription	mucosa <60%, outer wall <100%
Toronto	Boost 15Gyx1	n/a	$D_{10} < 118\%$ Max < 125%	$V_{80} < 0.5$ cc
UCLA-CET	Boost 6Gyx4 Mono7.25Gyx6	90−100% wall 80% balloon	120% combo 105% any TUR 110% mono	Rectal wall 80% Rectal wall 80−85%

Table 4
Grade 3 late GU complications

Author	N	Followup (mo)	Dose	Type of treatment	Comments
Astrom (60)	214	48	10Gyx2	Boost	13 patients experienced urethral strictures
Demanes (17)	209	86	5.5 Gy−6.0Gyx4	Boost	6.7% late Grade 3 and 1% Grade 4 GU toxicity (TUR related)
Hsu (7)	112	30	9.5Gyx2	Boost	Less than 3% Grade 3 toxicity at 18 mo
Phan (49)	309	59	6Gyx4	Boost	4% late Grade 3 GU
Deger (50)	442	60	9−10 Gyx2	Boost	9% late Grade 3 GU toxicity
Martinez (77)	207	66	5.5−11Gyx2	Boost	8% late Grade 3 GU toxicity
Sullivan (52)	425	41	4−5Gyx46.5 Gyx3	Boost	8% late Grade 3 GU toxicity
Zwahlen (73)	587	66	5Gyx4−6Gyx3	Boost	7% late Grade 3 GU toxicity
Demanes (57)	298	62	7Gyx6 9.5Gyx4	Mono	3% late Grade 3 GU toxicity
Ghilizan (51)	173	17	12−13.5Gyx2	Mono	1% late GU Grade 3 toxicity
Hoskin (78)	197	37	8.5Gyx4 9Gyx4 10.5Gyx3 13Gyx2	Mono	3−7% strictures

GU = genitourinary; TUR = transurethral resection.

Retrospective THRESHOLD PSA < 0.2 Cure Study LDR Study
14220 patients either LDR alone (8552), LDR+EBRT (1175), LDR+ADT (3165), LDR+EBRT+ADT (1328).
Risk distribution was 42.4% favorable, 49.2% intermediate, and 8.4% high-risk.
Patients with clinical failure before 3.5 years were excluded.

Crook, Radiother Oncol 2020
If 4-year PSA ≤ 0.2, 77.1% of these patients had 10-year FFR 98.7% and 15-year FFR 96.1%.
Three independent validation cohorts confirmed 97–99% 10-year FFR rates with 4-year PSA ≤ 0.2.
Successive PSA categories were associated with diminished disease-free rates at 10 and 15 years.
PSA category was strongly associated with treatment success ($p < 0.0005$).
Conclusions Since 98.7% of patients with PSA ≤ 0.2 ng/mL at 4 years after LDR prostate brachytherapy were disease-free beyond 10 years, we suggest adopting this biochemical definition of cure for patients with ≥4 years' follow-up after LDR brachytherapy.

HDR Monotherapy Studies

HDR Monotherapy 1 vs. 2 Fraction Phase II Trial
←R→ 170 patients low or intermediate risk prostate cancer w/ prostate volume < 60 cc | 1. HDR 19 Gy x 1 | 2. 13.5 Gy x 2 one week apart |.
Low 19%, fav Int 51% and unfav Int 30%.
The Phoenix definition was used to define biochemical failure, all local failures were confirmed by biopsy and toxicity was assessed using CTCAE v.4.

Morton, Radiother Oncol 2020. 5-year FU
PSA decreased more quickly in the 2-fraction arm ($p = 0.009$).
5-years Median PSA 0.65 ng/ml vs. 0.16 ng/ml.
5-year BcDFS 73.5% vs. 95% ($p = 0.001$) 5-year LF 29% vs. 3% ($p < 0.001$).
Recurrence was not associated with initial stage, grade group, or risk group.
Grade 2 late rectal toxicity occurred in 1% while the incidence of grade 2 and 3 urinary toxicity was 45% and 1%, respectively, with no difference between arms.
Conclusions HDR monotherapy delivered as two fraction of 13.5 Gy is well tolerated with a high cancer control rate at 5 years. Single fraction monotherapy is inferior and should not be used.

TWO Phase II Trial Evaluation HDR Monotherapy DE
←R→ low intermediate risk disease w/ MRI-guided focal DE to the dominant intraprostatic lesion (DIL).
Outcomes from two phase II clinical trials with and without a focal boost.
Trial1 (n=87) single 19 Gy HDR. Trial2 (n=60) + additional MRI-guided focal DIL boost to ≥ 23 Gy.
ADT was not allowed. Biochemical failure (BF) was defined as nadir +2.

Alayed, Radiother Oncol 2020.
5-year BcF 31-32% both trials.
77.5% of failures were biopsy-confirmed local failures, all of which underwent local salvage therapy.
The addition of a DIL boost was not associated with worse toxicity or QOL.
Baseline PSA and Gleason score correlated with BF, but none of the dosimetric parameters was a significant predictor of BF.
Conclusions MRI-guided focal boost was safe and well tolerated, but did not improve local control after 19 Gy single-fraction HDR monotherapy, and the control rates were unacceptable. Single-fraction HDR monotherapy for prostate cancer should not be offered outside of clinical trials.

Review: https://tau.amegroups.com/article/view/17950/19867

Table 2 Dose fractionation, late genito-urinary (GU) and Gastrointestinal (GI) toxicity, and biochemical disease-free survival (DFS) by risk groupings in HDR monotherapy series.

Author	N	Dose (Gy)/no. of fractions	Median FU (yrs)	Late Grade 3 toxicity (%)		Biochemical DFS (%)		
				GU	GI	Low	Intermediate	High
Yoshioka (55)	190	48/8	7.6	1	1	–	93	81
		54/9						
		45.5/7						
Hauswald (56)	448	42–43.5/6	6.5	5	0	99	95	–
Rogers (57)	284	39/6	2.7	1	0	–	94	–
Demanes (58)	157	42/6	5.2	3	0	97	–	–
Patel (59)	190	43.5/6	6.2	4	0	–	90	–
Zamboglou (60)	492	38/4	5–7.7	6	1	95	93	93
Barkati (61)	79	30–34.5/3	3.3	9	0	85	85	–
Strouthos (62)	450	34.5/3	4.7	1	0	96	96	92
Kukielka (63)	77	45/3	4.7	1	0	97	97	–
Jawad (64)	319	38/4	5.5	6	0	98	98	–
	79	24/2	3.5	0	0	92	92	
	96	27/2	2.9	8	0	100	100	
Hoskin (65)	30	34/4	5	3–16	1	–	99	91
	25	36/4	4.5					
	109	31.5/3	3					
Hoskin (66)	106	31.5/3	9	11	1	–	91	91
	138	26/2	5.25	2	0		93	93
	50	19–20/1	4.1	2	0		94	94
Krauss (67)	63	19/1	2.9	0	0		93 (3 yrs)	–
Prada (68)	60	19/1	6	0	0		66 (6 yrs)	–

FU, follow-up; HDR, high dose-rate.

AZ 2022

Hypofractionation

Excellent Summary (2021 Nature Reviews Urology): https://www.nature.com/articles/s41585-021-00498-6

- Moderate hypofractionation should be offered to men with low-risk, intermediate-risk and high-risk prostate cancer.
- RT schedules typically administer 60–72 Gy over 4–6 weeks.
    - Bulk of current evidence supports equivalent results with the use of 60 Gy in 20 fractions over 4 weeks to the prostate with or without the inclusion of seminal vesicles and omission of pelvic lymph nodes compared with conventional fractionation.
    - CHHiP and PROFIT drive this recommendation with predominantly low-risk and intermediate-risk disease.

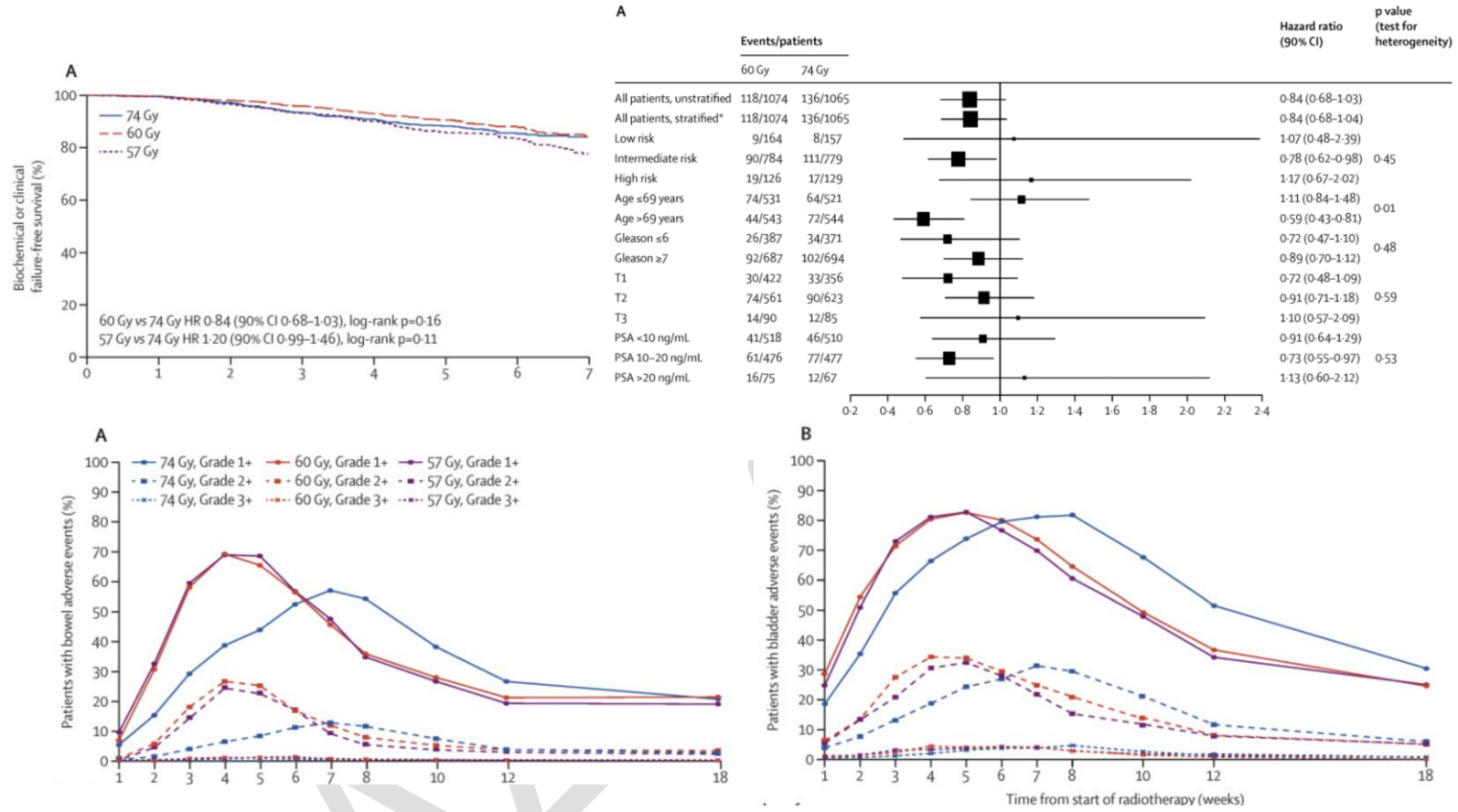
	Publication	N	Eligibility	Study design	Oncological outcome	Toxic effects
Trials comparing conventional and moderate hypofractionation						
Pollack et al. 12	2013	303	Any risk	76 Gy/38 vs 70.2 Gy/26 All ADT (HR = 24 months, Other = 4 months). Superiority design	5-year BCDF 21.4% vs. 23.3% (p = 0.745) 5-year bRFS ~76-79% (NS) NS between arms	5-year bRFS ~76-79% (NS) No Δ late toxicity. SUBSET: ↑ urinary tox in HYPOFX if IPSS > 12.
Hoffman et al. 13	2014	222	Any risk	75.6 Gy/42 vs 72 Gy/30 25% received ADT. Superiority design	8-year bRFS 76.3% vs. 89.3% (SS) Better control emerged after 5 years.	NS (≥ G2 GI or GU) No Δ OS or Δ late GI/GU tox. NS ↑ with hypofractionation of rectal bleed.
RTOG-0415 14	2016	1,115	Low risk	73.8 Gy/41 vs **70 Gy/28** No ADT Non-inferiority design	5-year DFS 85.3% in the 73.8 Gy arm and 86.3% in the 70 Gy arm (HR 0.85, 95% CI 0.64–1.14); hypofractionation was non-inferior	Worse grade 2 and 3 late GI and GU toxicities in the hypofractionation arm
HYPRO 38	2016	820	Intermediate and high risk	78 Gy/39 vs 64.6 Gy/19 ADT institutional protocol (2/3 of patients) Superiority design	5-year RFS 77.1% vs. 80.5% (p = 0.36) No significant difference between arms	Hypofx ↑ late GI G2 toxicity 18% vs 11% (SS) Could not prove non-inferior late toxicity in hypofractionation arm15
CHHiP 16	2016	3,216	Any risk	74 Gy/37 vs **60 Gy/20** vs 57 Gy/19 fractions All 3–6 months of ADT (except low risk) Non-inferiority design	5-year BCFS 88.3%, 90.6%, 85.9%. 60 Gy/20 was non-inferior to 74 Gy/37 fractions (HR 0.84, 90% CI 0.68–1.03)	60 Gy non-inferior to Conv. 57 is NOT Non-inf to Conv. No Δ GI/GU.
PROFIT 18	2017	1,206	Intermediate risk	78 Gy/39 vs **60 Gy/20** No ADT Non-inferiority design	5-year BCFS was 85% in both arms (HR 0.96, 90% CI 0.77–1.2). hypofractionation was non-inferior	No significant difference in grade 3 or greater late GI or GU toxicity
Arcangeli et al. 17	2017	168	High risk	80 Gy/40 vs 62 Gy/20 All patients 9 mo ADT Superiority design	10-year BCFS 65% vs. 72% (p = 0.148) NS between arms.	No significant difference in clinician-assessed grade 2 or greater late GI or GU toxicity[a]
*Trials comparing moderate conventional, hypofractionated and **SBRT***						
PACE-B 19	2019	874	Low and intermediate risk	78 Gy/39 vs 62 Gy/20 vs **SBRT** 36.25 Gy/5 No ADT Non-inferiority design	Pending	No difference in acute GI or GU toxicity
HYPO-RT-PC 20	2019	1,200	Intermediate and high risk	78 Gy/39 vs **SBRT** 42.7 Gy/7 No ADT Non-inferiority design	5-year RFS was 84% in both arms (HR 1.002, 95% CI 0.758–1.325); SBRT was non-inferior	G ≥ 3 GU 19% vs. 12% (SS). GI no Δ 3%. ∴ NO ONE USES THIS FRACTIONATION of 3.4 Gy.

HR-PCa Pelvic Node Hypofractionation
Phase I/II 105 HR prostate cancer 2010-2014 s/p 60 Gy in 20 fractions to prostate + 44 Gy in 20 fractions to WPRT. SIB technique.
ADT was given 2-3 months prior to RT.

Faria, PRO 2020 Median follow-up was 74 months.
≥ G2 late GI 7% and GU 9%. There was no grade 4 or 5 toxicity.
At the last follow-up, G ≥2 GI and GU were 2% and 3%. No residual grade ≥3 toxicity.
5-year OS 91%. 7-year OS 85%
5-year RFS 87%. 7-year RFS 81%.
Conclusions: The longest follow-up report of moderate HypoRT (plus ADT) to the prostate and pelvic nodes shows that this approach is feasible, well tolerated, and effective. It is convenient for patients and the health system. A larger randomized trial using this approach is warranted.

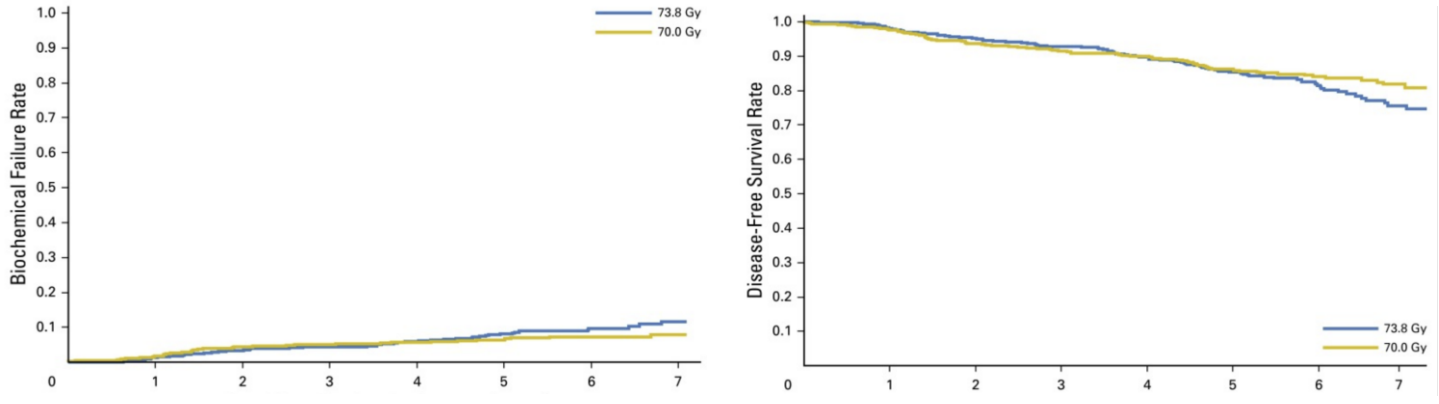
CHHiP
←R→ 3216 pT1b–T3aN0M0 | 1. Conventional 74 Gy / 37 fx | 2. 60 Gy / 20 fx | 3. 57 Gy / 19 fx |.
Most patients were given radiotherapy with 3–6 months of neoadjuvant and concurrent androgen suppression.
Risk SV+ < 30%
1^{O} Time to biochemical or clinical failure.

Dearnaley, Lancet Oncology 2016.
5 year bFF 88% , 90%, 86%. Non-inferior between 1 and 2, but cannot be claimed between 1 and 3.
Adverse events ≥ 2 bowel and bladder 1. 14%, 9.1% 2. 12%, 12%, 3. 11%, 7%.
Acute bowel toxicity 25% vs. 38% vs. 48% (SS). THIS IS THE ONLY THING THAT WAS SIGNIFICANT.
Interpretation Hypofractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localised prostate cancer.
Note: for some reason, the ACUTE toxicity was increased with hypofractionation.



NRG RTOG 04-15. **Low-Risk PCa**
←R→ 1092 men. Phase 3, non-inferiority trial. cT1c-T2c, PSA < 10. | 1. 73.8 Gy = 1.8 x 41 | 2. 70 Gy = 2.5 x 28 |
No ADT.

Lee, JCO 2016. Median follow-up was 5.8 years.
5-year DFS 85.3% vs. 86.3% (HR 0.85, NS).
70 Gy ↑ Late G2-3 GI and GU.
Conclusion: In men with low-risk prostate cancer, the efficacy of 70 Gy in 28 fractions over 5.6 weeks is not inferior to 73.8 Gy in 41 fractions over 8.2 weeks, although an increase in late GI/genitourinary adverse events was observed in patients treated with H-RT.



Italian HR-PCa.
←R→ 168 patients with 3D CRT localized high risk prostate CA. | 1. Standard 80 Gy in 2 Gy fx | 2. 62 Gy in 3.1 Gy fx |
Median Followup 70 months.

Arcangeli, JCO 2017.
10-yr FFBF 65% vs. 72% (NS). 10-yr OS 64% vs. 75% (NS). 10-yr PCaSS 88% vs. 95% (NS).
Hypofractionation, pretreatment prostate-specific antigen level, Gleason score, and clinical tumor stage for FFBF, and hypofractionation and Gleason score for PCaSS were significant prognostic variables on the multivariate analysis.

Table 3. Multivariate Analysis* for FFBF, PCaSS, and OS

End Point	Parameter	HR	Lower 95% CI	Upper 95% CI	*P*
FFBF	Arm (conv *v* hypo)	0.4661	0.2437	0.8914	.021
	iPSA (continuous)	1.0220	1.0128	1.0313	< .001
	GS (≤ 3 + 3/3 + 4/4 + 3/≥ 8)	1.4453	1.0461	1.9969	.025
	cT stage (T2/T3a/T3b)	1.9811	1.0357	3.7897	.039
PCaSS	Arm (conv *v* hypo)	0.3012	0.08144	1.114	.072
	GS (≤ 3 + 3/3 + 4/4 + 3/≥ 8)	2.7041	1.30290	5.612	.008
OS	Age (continuous)	0.067	1.070	0.036	.059

Abbreviations: conv, conventional fractionation; cT stage, clinical T stage; FFBF, freedom from biochemical failure; GS, Gleason score; HR, hazard ratio; hypo, hypofractionated radiotherapy; iPSA, initial (pretreatment) prostate-specific antigen; OS, overall survival; PCaSS, prostate cancer–specific.
*Factors included in the multivariate analysis were fractionation (conv *v* hypo), iPSA (continuous), GS (≤ 3 + 3/3 + 4/4 + 3/≥ 8), cT-stage (≤ T2/T3a/T3b), and age.

Conclusion: Long-term findings showed that hypofractionated radiotherapy failed the intent of either reducing physician-assessed late toxicity or maintaining the same efficacy. A postrandomization analysis, however, revealed that hypofractionation was a significant prognostic factor for FFBF and PCaSS, when adjusted for clinical prognostic variables.

Fox Chase.
Pollack, JCO 2013. 307 patients. Long-term ADT 2 years for: high risk (PSA > 20, GS 8-10, cT3, or GS 7 ≥ 4 cores +).
Short term planned for up to 4 months of ADT starting 4 months before random assignment.
Phase III randomization of 1. 76 Gy in 38 fractions at 2.0 Gy per fraction | 2. 70.2 Gy in 26 fractions at 2.7 Gy per fraction.
Conclusions: There were no statistically significant differences in late toxicity between the arms; however, in subgroup analysis, patients with compromised urinary function before enrollment had significantly worse urinary function after HIMRT.

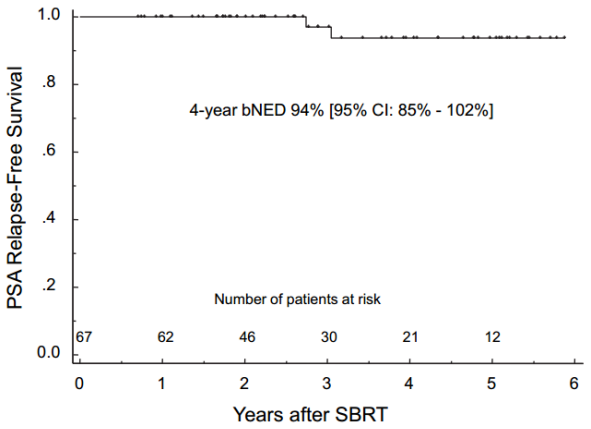
King, IJROBP 2010. 2.7 years.
67 patients with low and favorable intermediate risk prostate cancer. Every other day. Treatment (Nisha: Brachy therapy: AUA size of 15 or less. Size prostate 40-60 cc. For SBRT the bigger ones are OK. No pubic arch interference with EBERT, but the small ones be careful of urethra dose). Gold fiducials. Thin cut 1.25 mm. Ultrasound. Some do foley with contrast (this unfortunately straightens the prostate, but you can do more stringent foley dose. With VMAT or MRI, you probably don't need it. If you have 105% hot spots around the urethra, you probably will not run into problems) or retrograde urethrogram. Enema. 7.25 Gy x 5 fx = 36.25 Gy. Cyberknife. Prescribe to around 70%. Heterogeneity is around 10-20%. VMAT is more homogeneous than cyberknife.

Changes in quality of life. 20% in grade 3 IMRT. But regarding SBRT, the % is much lower around like 3-5%. (3-5% is also requiring to instrumented). Stool is only grade 1 toxicity in 12% patients. BIG takeaway, it is qD is much more toxic than qOD.

Table 3. Comparison of late urinary (GU) and rectal (GI) toxicity on the RTOG scale from the dose-escalation arm of randomized trials and intensity-modulated radioterhapy–based hypofractionated studies

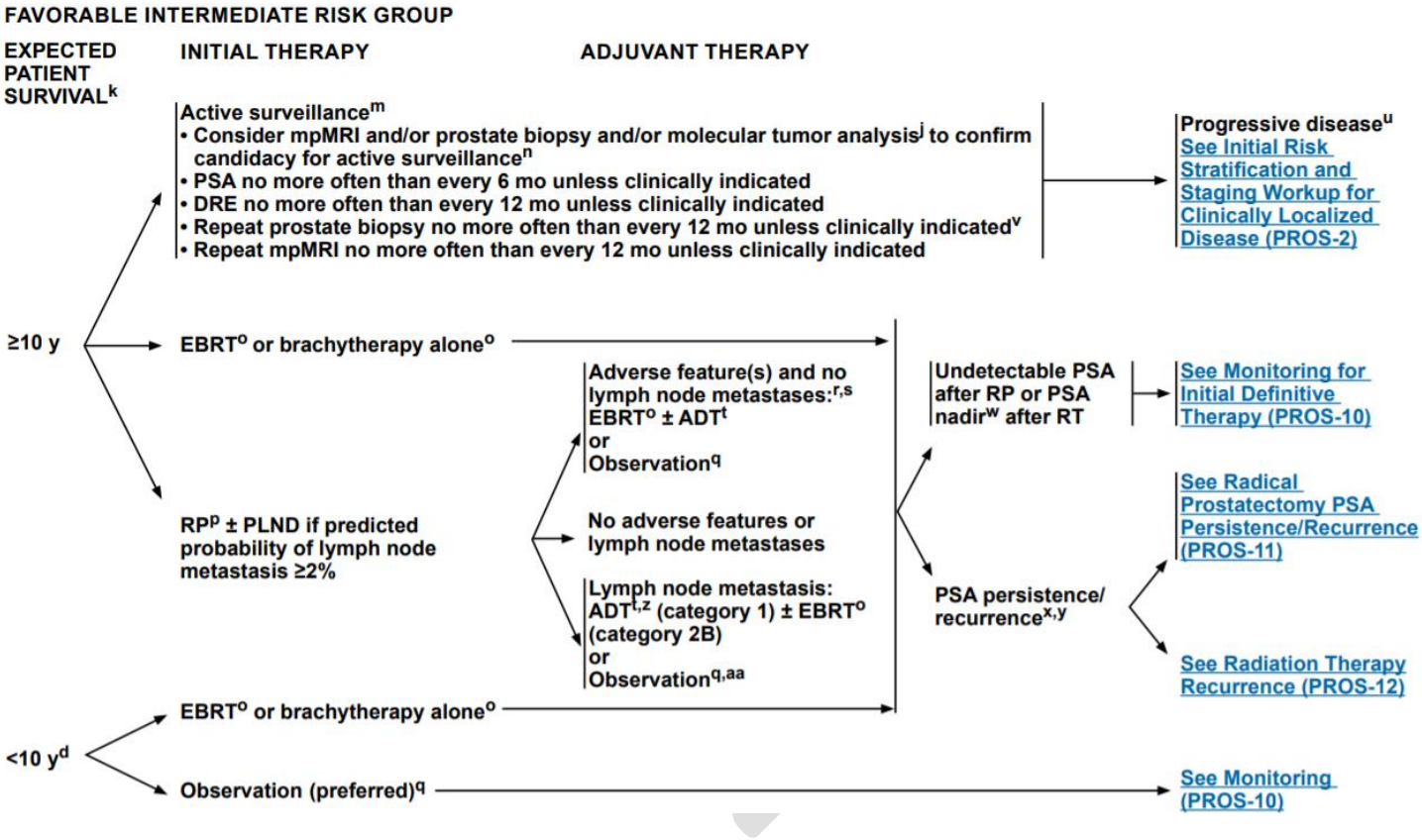
Series	*n*	Dose/no. fx and median FU	GI Gr. 2	GI Gr. 3	GI Gr. 4	GU Gr. 2	GU Gr. 3	GU Gr. 4
Dutch†	333	78/39 and 4.2 yr	27%	5%	0%	26%	13%	0%
MDA‡	151	78/39 and 8.7 yr	19%	7%	0%	7%	3%	0%
MGH§	196	79.2/44 and 8.9 yr	24%	1%	0%	27%	2%	0%
RT01¶	422	74/37 and 5.2 yr	20%	6%	0%	4%	4%	0%
Kupelian‖	770	70/28 and 3.7 yr	3.1%	1.3%	0.1%	5.1%	0.1%	0%
Martin**	92	60/20 and 3.2 yr	4%	NR	0%	3%	NR	0%
Coote††	60	60/20 and 2 yr*	4%	NR	0%	4.2%	1.6%	0%
Lock‡‡	66	63.2/20 and 3 yr	25%	3.1%	1.5%	14.1%	4.7%	0%
SBRT§§	67	40/5 and 2.7 yr	2%	0%	0%	5%	3.5%	0%

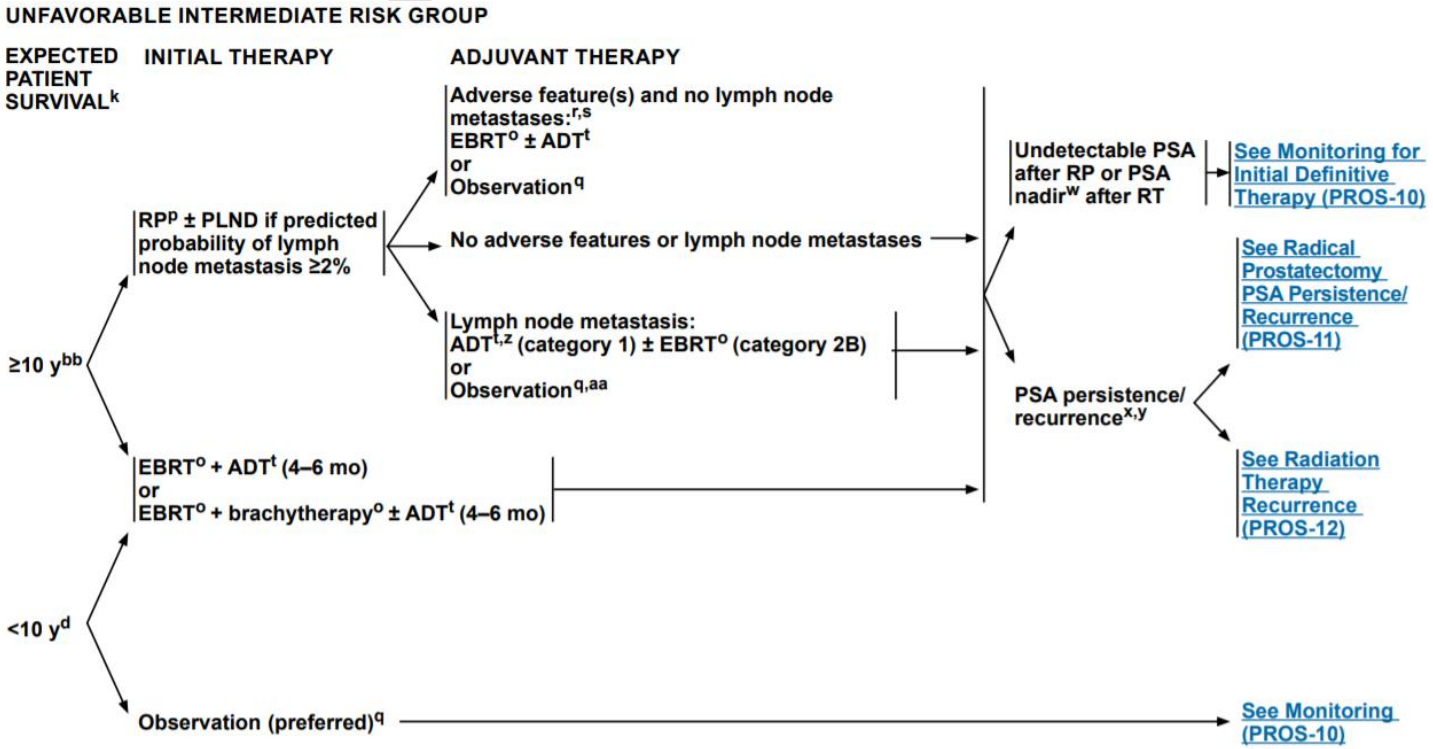
Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; CGE = cobalt gray equivalent (dose equivalent to Gy); GI = gastrointestinal; Gr. = Grade; GU = genitourinary; IMRT = intensity-modulated radiotherapy; NR: not reported; RTOG = radiation therapy oncology group.
* Reported at exactly 2 years follow-up.
† Dutch Multicenter Dose Escalation Trial (16), 78 Gy 3DCRT (90% of patients treated with three-field technique).
‡ M.D. Anderson Dose Escalation Trial (17), 78 Gy 3DCRT (four-field technique 46 Gy followed by six-field technique for boost dose).
§ MGH Proton Radiation Oncology Group (18), 79.2 CGE (50.4 Gy 3DCRT with four-field technique + 28.8 Gy with 1- or 2-field technique for proton boost).
¶ UK MRC RT01 Dose Escalation Trial (19), 74 Gy 3DCRT (four-field technique).
‖ Kupelian *et al.* (20); IMRT with daily transabdominal ultrasound image guidance.
** Martin *et al.* (21); IMRT with fiducial-based daily image guidance.
†† Coote *et al.* (22); IMRT with two-dimensional portal imaging setup.
‡‡ Lock *et al.* (24); IMRT with daily fiducial-based image guidance.
§§ Current study.



Intermediate Risk Disease: T2b-T2c, GS 7, PSA 10-20

Zelefsky UNFAVORABLE = (4+3, ≥ 50% cores, "multiple intermediate risk factors" ie cT2b-c, PSA 10-20).
Note: IF YOU HAVE 4+3, and any core ≥ 70%, then → consider MRI biopsy since you might have occult high grade disease.





ADT General

Metaanalysis of ADT Benefit
←M→ 12 trials median FU of 11.4 years.

Kishan, Lancet 2022.
Addition ADT to RT ↑ SS metastasis-free survival (HR 0·83 [95% CI 0·77–0·89], p<0·0001)
Adjuvant ADT prolongation ↑ SS MFS as well (HR 0·84 [95% CI 0·78–0·91], p<0·0001)
Neoadjuvant ADT extension NS (HR 0·95 [95% CI 0·83–1·09], p=0·50).
Treatment effects were similar irrespective of radiotherapy dose, patient age, or NCCN risk group.
Interpretation
Our findings provide the strongest level of evidence so far to the magnitude of the benefit of ADT treatment intensification with radiotherapy for men with localised prostate cancer. Adding ADT and prolonging the portion of ADT that follows radiotherapy is associated with improved metastasis-free survival in men, regardless of risk group, age, and radiotherapy dose delivered; however, the magnitude of the benefit could vary and shared decision making with patients is recommended.

NCB ADT Real-Time Use Study
Purpose: NCCN recommended ADT for all men with intermediate risk prostate cancer who underwent radiotherapy until 2018.
Intermediate risk was stratified as favorable and unfavorable in 2018 and ADT recommendation was limited to men with unfavorable.
Retrospective. 108,185 men intermediate risk prostate cancer from 2004 to 2016 in the National Cancer Database NCB.

Agrawal, Adv Rad Oncol 2022.
Of the men, 41.09% received ADT. Among 60,705 favorable risk, 32.06% received ADT.
Among 47,480 unfavorable risk, 52.64% received ADT.
MVA, use of ADT was associated with age and year of diagnosis, being non-white with government-based insurance, having higher PSA, tumor stage and Gleason score, treatment at a non-academic center and receiving external beam radiotherapy alone.
Conclusions: Our findings highlight androgen deprivation therapy use is variable in men undergoing definitive radiotherapy for intermediate risk prostate cancer with data suggesting several clinical and socioeconomic disparities influencing its use. A significant proportion of men with favorable intermediate risk prostate cancer receive ADT and remain candidates for treatment de-escalation while a significant proportion of men with unfavorable intermediate risk prostate cancer may be undertreated when ADT is omitted.

AZ 2024

ADT alone ± EBRT

Lu-Yao 2008. Observation vs ADT alone.
Age ≥ 66 yo. Medicare patients. NO difference in OS 17.3 vs 15.3%
Improved PCa SS. 60% vs 54.3%.

SPCG-7/SFU0-3
←R→ 875 patients (T3; 78%; PSA<70; N0; M0) | 1. 3 months of total androgen blockade → continuous flutamide | 2. Same as 1 + EBRT |. 1^{O} PCSS.
EBRT is to 70 Gy to prostate and SV.

Widmark, Lancet 2009.

10-year	bPFS	CSS	OS	ED	Urethral Stricture	Urgency	Incontinence
ADT	25%	76%	61%	81%	0%	8%	3%
ADT + EBRT	74%	88%	70%	89%	2%	15%	7%
All results significant							

INTERPRETATION: In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved the 10-year prostate-cancer-specific mortality, and substantially decreased overall mortality with fully acceptable risk of side-effects compared with endocrine treatment alone. In the light of these data, endocrine treatment plus radiotherapy should be the new standard.

NCIC CTV PR.3 / MRC UK PR07
←R→ 1205 locally advanced (T3 or T4) prostate cancer (n=1057); or organ-confined disease (T2) with either a PSA > 40 (n=119) or PSA >20 + GS ≥ 8 (n=25).
| 1. Lifelong ADT | 2. Lifelong ADT + EBRT |. RT (65-69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes).
ADT is bilateral orchiectomy or GnRH agonist.

Warde, Lancet 2011.
RESULTS: Median follow-up was 6·0 years (IQR 4·4-8·0).
7-year OS 66% vs. 74% (p=0·033). Both toxicity and health-related quality-of-life results showed a small effect of RT on late gastrointestinal toxicity (rectal bleeding grade >3, three patients (0·5%) in the ADT only group, two (0·3%) in the ADT and RT group; diarrhoea grade >3, four patients (0·7%) vs eight (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups).
Conclusion: Addition of EBRT increases OS in patients with high-risk prostate cancer.

Mason, JCO 2012. Supplement Abstract Only. Median follow-up is 8.0 years and 465 patients have died (260 ADT, 205 ADT+RT).
ADT + RT ↓ risk of death (HR 0.70, SS). 199 patients died of disease and/or treatment (134 on ADT alone and 65 on ADT+RT).
ADT + RT ↓ chance of dying of disease related causes than those treated with ADT (10 yr DSS 26% ADT → 15% ADT + RT, SS).
ADT + RT small ↑ late gastrointestinal toxicity (> grade II proctitis, 0.3% → 1.0% ADT+RT; -0.3 ADT vs 1.7 ADT + RT, p=0.54).
Conclusions: Mature data indicate a sustained and ↑ OS and DSS benefit for ADT+RT.

Brundage, JCO 2015. Baseline questionnaires were completed by 1,028 patients (88%).
At 6 months, RT ↑ bowel symptoms (P .02), diarrhea (P .001), urinary function (P .003), and erectile dysfunction (P .008).
By 3 years, however, there were no significant between-group differences in any domain.
Therefore, RT Δ are temporary and transient. The effects are no difference after 2 year.

Table 1. QOL Scores for Selected EORTC Core Questionnaire and FACT-P Domains at Baseline and Change From Baseline

	Baseline QOL Score				Change From Baseline													
					6 Months					12 Months				36 Months				
	ADT		ADT + RT		ADT		ADT + RT			ADT		ADT + RT			ADT		ADT + RT	
Domain	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P*	Mean	SD	Mean	SD	P*	Mean	SD	Mean	SD	P*
Global and Function Scales																		
EORTC physical function	92.5	11.9	91.5	15.9	−3.5	14.3	−3.8	14.7	.73	−5.1	12.9	−5	18.6	.79	−9	18	−10	18.5	.63
EORTC role function	95.0	11.7	94.8	13.8	−2.9	15.7	−6.9	22.6	.62	−4.9	16.4	−6	17	.66	−11.5	20.1	−13.3	26.7	.75
EORTC emotional function	85.3	14.2	83.1	17.7	0.2	12.7	3	17.9	.31	1.7	14.2	4.4	19.1	.13	0.3	14.9	0.8	21	.62
EORTC cognitive function	87.2	15.9	91	11.1	−1.8	16.3	−2.6	16.2	.9	−2.2	17.3	−4.7	18.2	.43	−4.6	22.2	−6.7	20.2	.41
EORTC social function	95	12.2	94.1	14.4	−4.7	19.9	−6.2	19.7	.33	−6	15.4	−4.7	19.8	.61	−14	26.2	−14	28.6	.87
EORTC global function	77.8	18.2	77.4	17.5	−1.8	14.4	−9	21.4	.03	−5.7	16.9	−7.9	20.6	.78	−10	16.8	−11.1	18.9	.73
FACT-P physical well-being	90.7	9.5	90.3	11.5	−1.1	3.5	−2.1	4	.001	−1.4	3.8	−1.6	3.7	.39	−1.7	3.8	−1.5	4	.78
FACT-P social/family	80.4	17	80.7	16.4	−0.5	4.7	−0.5	4.6	.85	−0.9	4.8	−0.6	4.5	.41	−1.4	5.1	−0.9	5.1	.53
FACT-P emotional function	81.3	16.7	81.8	16.1	0.9	3.1	0.8	2.9	.88	0.9	3.5	1	3.4	.69	0.6	3.2	1.1	3.3	.15
FACT-P functional well-being	81.1	18	80.2	18.6	−3.2	17.3	−6.4	16.9	.004	−3.8	17	−5.1	18.5	.42	−7.2	20.3	−6.8	17	.97
FACT-P global assessment	55.3	28.6	58.1	29.7	4.3	27.6	−3	31	.002	3.3	31.2	−0.7	30.4	.35	2.6	31.6	−1.1	29.6	.17
FACT-P total score	121.5	16.1	121.5	11.6	−1.7	14.9	−6.0	13.9	.001	−3.6	15.4	−4.3	14.7	.95	−5.9	16.4	−5.2	15.4	.56
FACT-P TOI	82.7	12.3	82.5	13	−2.1	11.8	−6.4	11.7	< .001	−3.4	12	−5	12.3	.22	−5	13.4	−5.4	12.3	.71
FACT-P prostate cancer subscale	34.7	7.1	34.8	7.1	−0.1	6.7	−2.4	6.9	< .001	−1	6.8	−1.9	7.3	.14	−1.2	7.0	−1.9	7.3	.35
Symptom/Organ Domains																		
EORTC bowel symptoms	3.6	7.3	3.3	8.4	−1.3	7.1	3.3	14.8	.02	−0.9	10.6	3.8	14.2	.02	−0.3	10.1	1.7	15.3	.55
EORTC diarrhea	4.3	11.2	5.8	17.1	−1.8	12	7.7	21.8	< .001	−2.2	9.9	3.3	20.6	.03	1	16.8	1.7	19	.32
FACT-P urinary function	28.7	24.8	29.7	23.5	−6.1	22.2	0.1	25.3	.003	−5.8	25.4	−5.5	24.9	.97	−5.2	25.6	−5.2	25.5	.89
EORTC urinary frequency	23.4	26.3	25.7	29.9	−1.8	28.9	5.3	32.9	.19	−3.5	32	−7	33.3	.62	−2	30.9	1.1	35.8	.65
EORTC urinary incontinence	5	13.8	8.1	15.2	0	17.3	0.9	12.2	.7	1.3	13.9	0	16.1	.48	1	17.5	3.3	27	.94
FACT-P erections	74.6	33	69.4	35.1	14.6	34.9	22.8	36	.008	18	35	25	36.5	.03	18	37.9	24.8	38	.1
EORTC fatigue	14	13.8	14.3	18	4	17.7	7.6	23.6	.06	7.1	17	6.7	18.9	.75	9.1	15.9	10.6	24.9	.45
EORTC hot flashes	3.6	11.5	3.1	14.1	47.7	29	38.7	32.4	.05	43.6	33.8	37.7	37	.24	38	33.5	33.3	31	.36
EORTC sleep	15.3	23.8	16.1	24.8	11	35	8	31.4	.39	8.7	29.8	7.5	31.5	.8	13.1	29.2	11.7	28.7	.81

Abbreviations: ADT, androgen-deprivation therapy; EORTC, European Organisation for Research and Treatment of Cancer; FACT-P, Functional Assessment of Cancer Therapy–Prostate questionnaire; QOL, quality of life; RT, radiotherapy; SD, standard deviation.
*P values reflect between–treatment arm comparisons of mean change scores for each time point.

Sequencing ST-ADT

MARCAP (Meta-Analysis of Randomized Trials in Cancer of the Prostate)
←M→ 10,131 patients across 11 RTCs.
"Group 1" RT → RT **+ ADT** (5 trials)
"Group 2" ST-ADT → ST-ADT **+ LT-adjADT** (4 trials)
"Group 3" ST-ADT → **neoadj ADT** + ST-ADT (3 trials)

Kishan, IJROBP 2021. 12-year FU
Group 1 12-year OS ↑ absolute 7.2% (HR 0.87, SS)
12-year MFS ↑ absolute 8.3% (HR 0.85, SS).
Group 2 12-year OS ↑ absolute 6.3% (HR 0.86, SS)
12-year MFS ↑ absolute 6.3% (HR 0.83, SS)
Group 3 12-year OS NS
12-year MFS NS
On subgroup analysis, there was no evidence of a treatment effect interaction between RT dose and ADT use (OS P-interaction 0.59) or adjuvant ADT prolongation (OS P-interaction 0.13). In the setting of dose-escalated RT, adjuvant ADT prolongation significantly improved OS (HR 0.70, 95% CI 0.53-0.92).
Conclusion This study represents the strongest evidence to support ADT use and prolongation of adjuvant ADT to at least 18 months in localized prostate cancer in conjunction with definitive RT. The relative benefit of ADT use and adjuvant ADT prolongation was consistent irrespective of RT dose-escalation. In contrast, prolongation of neoadjuvant ADT beyond 2 months did not improve survival outcomes and should not routinely be employed.

TROG RADAR 03.04
←R→ 1071 locally advanced prostate cancer (either T2b-4N0M0 OR T2a with GS ≥ 7 and PSA ≥ 10) 2x2 trial.
| 1. STAS | 2. ITAS | 3. STAS + Z | 4. ITAS + Z | STAS = 6-month ST-ADT Leuprorelin + RT ITAS = STAS → 12-month ADT Leuprorelin
Z = Zoledronic acid
RT = Prostate and SV starting from the end fo the FIFTH month of ADT.
Dose = EBRT alone (66, 70, 74 Gy / 2 Gy) or EBRT (46 Gy / 2 Gy) + Brachy boost (19.5 Gy / 3 fx).
1^{O} CSM

Denham, Lancet 2018. 10-year FU
10-year follow-up, no interactions were observed between androgen suppression and zoledronic acid so the **treatment groups were collapsed** to compare treatments according to duration of androgen suppression. | 1. STAS ALL | 2. ITAS ALL |.
10-year PCaSM 13·3% vs. 9·7% (Abs Δ 3·7%, HR 0.7, adjusted p=0·035).
The addition of zoledronic acid did not affect prostate cancer-specific mortality.
Although safety analysis was not prespecified for this 10-year analysis, one new serious adverse event (osteonecrosis of the mandible, in a patient who received 18 months of androgen suppression plus zoledronic acid) occurred since our previous report, bringing the total number of cases of this serious adverse event to three (<1% out of 530 patients who received zoledronic acid evaluated for safety) and the total number of drug-related serious adverse events to 12 (1% out of all 1065 patients evaluable for safety).
Interpretation 18 months of androgen suppression plus radiotherapy is a more effective treatment option for locally advanced prostate cancer than 6 months of androgen suppression plus radiotherapy, but the addition of zoledronic acid to this treatment regimen is not beneficial.

Retrospective Sequencing 2021
37,606 HR-PC s/p definitive external RT (≥60 Gy) + ADT starting either before or within 14 days after RT start.
Patients were grouped on the basis of ADT initiation | 1. >11 weeks before RT (30%) | 2. 8-11 weeks before RT (35%) | 3. <8 weeks before RT (35%) |.

McCall, Adv Rad Onc 2021. 70 months FU
Unadjusted 10-year OS 49.9% vs. 51.2% vs. 46.9% P = .002.
MVA + Weighting SS OS advantage for patients in the 8-11 weeks neoadjuvant ADT group (adjusted HR 0.90, P < .001)
NS OS advantage for patients in the >11 weeks group.
Conclusions Neoadjuvant ADT initiation 8 to 11 weeks before RT is associated with significantly improved OS compared with shorter neoadjuvant ADT duration. Although prospective validation is warranted, this analysis is the largest retrospective study suggesting an influence of timing between ADT and RT initiation in HR-PC.

AZ 2022

Sequencing with ADT CANADIAN Trial **NeoAdj + Concurrent vs. Concurrent + Adj**

←R→ 432 patients with Gleason score ≤ 7, clinical stage T1b to T3a, and prostate-specific antigen < 30 ng/mL.

| 1. Neoadjuvant (4 months) ADT → Concurrent RT+ADT (2 months) + RT | 2. Concurrent RT+ADT (2 months) → Adjuvant ADT (4 months) |.

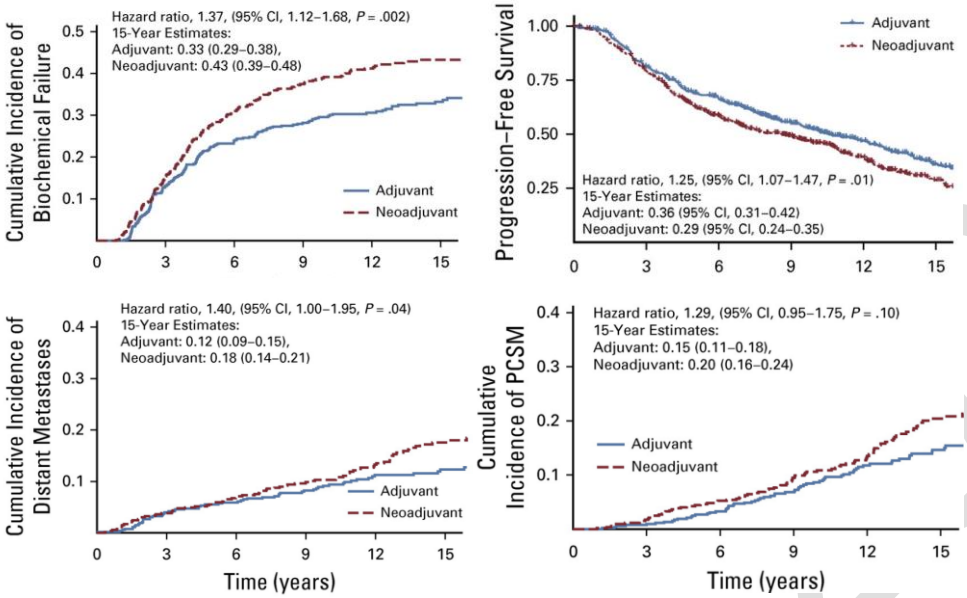
Malone, JCO 2019.

10-year bRFS 80.5% and 87.4% (NS). 10-year OS 76.4% and 73.7% (NS).

3-year incidence of late RT-related grade ≥ 3 GI (2.5% v 3.9%) or genitourinary toxicity (2.9% v 2.9%).

CONCLUSION In our study, there was no statistically significant difference in bRFS between the two treatment groups. Similarly, no difference was seen in OS or late RT-related toxicities. On the basis of these results, both neoadjuvant and concurrent initiations of short-term ADT with dose-escalated PRT are reasonable standards of care for LPCa.

POOLED RTOG 94-13 + Canadian



Spratt, JCO 2020; **Spratt, ASTRO 2020**

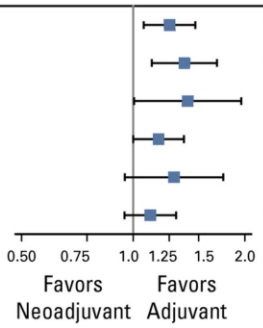
Median FU 14.9 years. N=1065 (531 NA, 534 adjuvant).

15-year BcF 33% Adj vs. 43% Neoadj (HR: 1.37, p = 0.002)
15-year DM 12% vs 18% (HR: 1.40, p = 0.04)
15-year PFS 36% vs 29% (HR: 1.25, p = 0.01).
15-year PCSM 15% vs 20% (HR: 1.29, NS, p = 0.10).
This only trend in high risk PCa (HR 1.39, p = 0.053).

15-year OS NS 39% vs 34% (HR: 1.11, p = 0.20).
NS late grade ≥ 3 GI (2-3%) or GU toxicity (~5%).
This analysis met all credibility criteria proposed by Murad (JAMA 2014).

Conclusions: Sequencing of ADT with RT significantly impacts long-term oncologic outcomes in localized PCa, favoring an adjuvant rather than neoadjuvant-based approach, without increasing late toxicity.

End Point	Neoadjuvant Incidence/N	Adjuvant Incidence/N	15-yr Absolute Benefit of Adjuvant ADT (%, CI 95%)	15-yr RMST Benefit of Adjuvant ADT (Months, CI 95%)	HR (95%)	*P* value
Progression-free survival	316/531	292/534	7.4 (−0.1, 14.8)	10.8 (2.7, 18.8)	1.25 (1.07, 1.47)	.01
Biochemical failure	214/531	168/534	10.1 (3.8, 16.3)	12.4 (3.7, 21.1)	1.37 (1.12, 1.68)	.002
Distant metastasis	82/531	60/534	5.3 (0.5, 10.1)	2.9 (−2.6, 8.4)	1.40 (1.00, 1.95)	.04
Metastasis-free survival	324/531	298/534	7.2 (0.3, 14.1)	3.9 (−3.1, 10.8)	1.17 (1.00, 1.37)	.050
Prostate cancer-specific mortality	91/531	73/534	5.8 (0.5, 11.0)	3.5 (−1.6, 8.6)	1.29 (0.95, 1.75)	.10
Overall survival	307/531	291/534	5.4 (−1.6, 12.3)	2.7 (−4.0, 9.3)	1.11 (0.95, 1.30)	.20



NCDB Retrospective Sequencing 2020

63,858 unfavorable intermediate-risk PC or high-risk or very high-risk PC.

All external beam RT and ADT.

Grouped by ADT | 1. (ref) 0-60 days AFTER RT (5%) | 2. 0-60 days before RT (35%) | 2. 61-120 d before RT (50%) | 3. 121-180 d before RT (10%) |.

79.2% were White individuals, 16.8% were Black individuals, 2.2% were Asian American individuals, and 0.2% were Native American individuals.

Dee, JAMA Oncol 2020.

Unfavorable intermediate-risk PC (4220 total deaths)

10-year OS 59.2% vs. 57.9% vs. 62.3% vs. 58.9%. All NS.

High-risk or very high-risk PC (10 959 total deaths).

10-year OS 58.9% vs. 51.7% vs. 54.8% vs. 52.4%. All NS.

Discussion Based on analysis of a large database of patients with unfavorable intermediate-risk, high-risk, or very high-risk PC, later RT initiation up to 6 months after ADT initiation was not associated with worse OS compared with initiating RT before ADT. These results validate the findings of 2 prior randomized trials2,3 and possibly justify the delay of prostate RT for patients currently receiving ADT until COVID-19 infection rates in the community and hospitals are lower. Limitations of this study included the short follow-up period, retrospective design, lack of information about ADT duration, and possible data entry errors in the database. Nonetheless, if COVID-19 outbreaks continue to occur sporadically during the coming months to years, these data could allow future flexibility about the timing of RT initiation.

RTOG 08-15 Dose Escalated ± STADT

←R→ 1538 patients with intermediate risk prostate cancer (≥ risk factors: cT2b-T2c, GS 7, PSA 10-20) | 1. DE-RT alone | 2. DE-RT + STADT |.
Ineligible: if you have all THREE factors + ≥ 50% cores+.
STADT = LHRH agonist/antagonist in combination with oral antiandrogen for 6 months.
Sequencing ADT 2 months started prior to RT. Then concurrent 2 months. Then 2 months afterwards
DE-RT = EBRT 79.2 Gy or EBRT 45 Gy + HDR/LDR boost. Pelvic nodes were NOT permitted to be treated.
67% had a single intermediate risk factor. 88% had EBRT with 11% receiving EBRT + Brachy boost. 33% had an ACE-27 score ≥ grade 2.
6.2 years median follow-up.
Powered to show OS 90% → 93%. So far, this is a negative primary trial.

Krauss, ASTRO 2021.
5-year OS 90-91% NS. 5-year CSM 0-1% NS.
PSA Failure 16% (125/750) vs. 9% (68/742) (SS). This persisted across subgroups, even Gleason 3+4 disease.
ADT also delayed salvage therapy.
Distant mets ↓3% vs. 0.6% as well (SS).
Conclusion: While the addition of TAS to dose-escalated RT did not improve overall survival for men with intermediate risk prostate cancer, significant improvements in rates of metastases, deaths due to prostate cancer, and PSA failures support the continued use of combination dose-escalated RT and TAS. Benefits will need to be weighed against the increased risk of adverse events and the patient reported outcomes analysis.
Next Steps: How do we amplify the benefits of ADT? In terms of distant mets, can we also do advanced imaging?

Movsas, ASTRO 2021.
While EPIC urinary and bowel scores decreased significantly by the end of RT in both arms, no clinically meaningful differences between arms were detected over time. For the EPIC hormonal and sexual domains, however, there were clinically meaningful differences between the two arms with greater ($p<0.0001$) deficits in the RT + TAS arm. These differences improved over time, with ~50% resolution by one year after treatment and no clinically meaningful differences by 5 years between arms. PROMIS-fatigue scores increased from baseline in both arms and were significantly higher in arm 2 at the end of RT ($p=0.016$), though slightly lower at 12 and 60 months.
Conclusion: The addition of TAS to dose-escalated RT demonstrated significant clinically meaningful declines in the EPIC hormonal and sexual domains, and increases in the PROMIS-fatigue scores, compared to RT alone. These scores gradually improved over time, with no clinically meaningful differences between arms in fatigue by one year, or in hormonal and sexual domains by 5 years. Beyond the clinical outcomes, these PRO results directly from patients provide added value to help patients make informed decisions among treatment options.

"Dose Escalated" Canadian
←R→ 600 patients with intermediate risk prostate cancer | 1. 70 Gy + ADT | 2. 76 Gy + ADT | 3. 76 Gy alone |
EBRT = as described above. ADT = short term 6 months bicalutamide + goserelin. RT (2 Gy per fraction) started four months after STADT.
Median age 71 years, median PSA 10 ng/ml, median Gleason score 7 and clinical stage

Nabid, GU ASCO 2015.
6-year bFreedom in all = 84% |1. 86.5% | 2. 89% | 3. 76.5% |. 1 vs. 3 ($p = 0.01$) and 2 vs. 3 ($p < 0.001$).
6-year DFS also significant between and 1 vs. 3 and 2 vs. 3.
Conclusions: In patients with IRPC, the use of STADT in association with RT, even at lower doses, leads to a superior biochemical control and DFS as compared to dose-escalated RT alone. These outcomes did not translate into an improved OS. Source of Funding:

AZ 2024

"BULKY PALPABLE" RTOG 86-10

←R→ 456 patients. PALPABLE T2-4 (> 25 cc) N0-1 | 1. EBRT + ADT | 2. EBRT |
44 Gy WPRT → 66-70 Gy ± 4 mo ADT (2 N and 2 C). (Non-Bulky pts were enrolled on parallel study 85-31 with LIFELONG ADT.)
Think: Bulky is RTOG 86 and Non-bulky is 85.

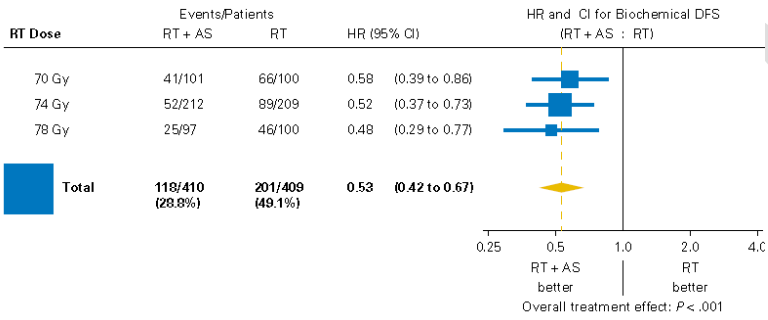
Roach, JCO 2008

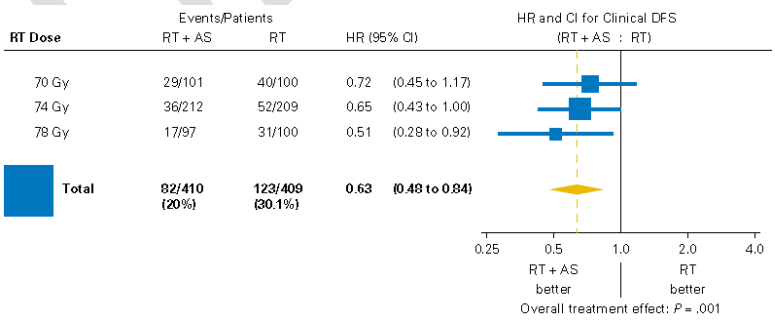
Results: 10-year CSS: 64 → 77% (SS). | DM: 47 → 35%. (SS) | OS trend for all patients: 34 → 43% (p = 0.12). |
| 8 year OS for GS 2-6 subset 52→70%. | However, the subset of 7-10 had NO OS benefit ∴ STADT may not be enough.
No difference in fatal cardiac events ~9-12% CV Mortality.

Pilepich, IJROBP 2001. 6.7 yr FU all patients, 8 yr alive patients.
8-year LC 42% vs. 30% (p = 0.016). 8-year DM 34% vs. 45% (p = 0.04) 8-yr DFS 33% vs. 21% (p = 0.004)
8-year BcDFS (PSA <1.5) 24% vs. 10%(p < 0.0001) 8-year CSM 23% vs. 31% (p = 0.05)
Subset analysis → beneficial effect of ST-ADT preferentially in patients with Gleason score 2--6.
GS 2-6 Subgroup SS ALL endpoints, including OS (70% vs. 52%, p = 0.015).
GS 7-10 Subgroup, NS in either locoregional control or survival.
Conclusion: In patients with Gleason score 2--6 carcinoma of the prostate, a short course of androgen ablation administered before and during radiotherapy has been associated with a highly significant improvement in local control, reduction in disease progression, and overall survival.

"Dose Escalated Bolla" EORTC 22991. Which is NOT the same as the "ADT DURATION Bolla" EORTC 22961
PURPOSE: Up to 30% of patients who undergo RT for int- or high-risk localized pCa relapse biochemically within 5 years. We assessed if bDFS is improved by adding 6 months of androgen suppression (AS = two injections of every-3-months depot of LHRH agonist) to RT.
←R→ 819 int- or high-risk (T1b-c + PSA > 10 or GS ≥ 7 or cT2aN0 + PSA ≤ 50). | 1. EBRT alone | 2. EBRT + ADT |.
EBRT = 70 Gy (25%), 74 Gy (50%) or 78 Gy (25%) dose escalated (institutional preference) ADT = LHRH agonist 6 months. 1° bDFS per Phoenix.
The % above indicate how many patients got that RT dose.
Mean patient age 70. 75% int 25% high risk.

Bolla, JCO 2016





	bDFS	cDFS	Total LF	DM	OS
EBRT	70%	81%	6.6%	8%	88%
EBRT + ADT	83%	89%	2.1%	4%	91%
P	< 0.001	0.001	0.001	0.05	Immature

CONCLUSION: Six months of concomitant and adjuvant AS improves biochemical and clinical DFS of intermediate- and high-risk cT1b-c to cT2a (with no involvement of pelvic lymph nodes and no clinical evidence of metastatic spread) prostatic carcinoma, treated by radiation.

Bolla, JCO 2021 Long term 12.2 years

Data for intermediate risk disease s/p at least 74 Gy (some received 78 Gy) (about 60% of the 819 men enrolled).

10-year DMFS 72.7% vs. 79.3% (HR = 0.74; P = .065).
10-year OS 74.3% vs. 80.0% (HR = 0.74; P = .082).
CONCLUSION Six months of concomitant and adjuvant AS statistically significantly improves EFS and DFS in intermediate-risk prostatic carcinoma, treated by irradiation at 74 or 78 Gy. The effects on OS and DMFS did not reach statistical significance.

Aug 22

TROG "3-6-9" 9601 - NOT THE SAME AS TROG "TOAD" 0306
←R→ 802 with cT2b-4 N0 stratified by stage (T2b/c vs. T3-4) and PSA (< 20 and ≥ 20) | 1. EBRT | 2. N 2mo → C1 ADT + RT | 3. N 5mo → 1C ADT + RT |. RT all groups 66 Gy (P + SV) No pelvic nodes in 2 Gy. NADT 3·6 mg goserelin given subcu qmonth + 250 mg flutamide PO TID. ADT total either 3 or 6 mo. NADT began 2 months before radiotherapy for the 3-month NADT group and 5 months before radiotherapy for the 6-month NADT group.
1º PCSM and ACM.

10-year PSA progression rates: 73.8% RT alone vs. 60.4% 3 months NADT vs. 52.8% 6 months NADT (p-SS for both 3 months NADT and 6 months NADT vs. RT alone).

10-year local progression: 28.2% RT alone vs. 15.7% 3 months NADT vs. 13.3% 6 months NADT (p-SS for both 3 months NADT and 6 months NADT vs. RT alone).

10-year event free survival: 12.7% RT alone vs. 28.8% 3 months NADT vs. 36.0% 6 months NADT (p-SS for both 3 months NADT and 6 months NADT vs. RT alone).

10-year prostate cancer specific mortality: 22.0% RT alone vs. 18.9% 3 months NADT vs. 11.4% 6 months NADT (p-0.0002 for 6 months NADT vs. RT alone).

10-year all cause mortality: 42.5% RT alone vs. 36.7% 3 months NADT vs. 29.2% 6 months NADT (p-0.0005 for 6 months NADT vs. RT alone).

Clinical Pearl: 6 months NADT plus 66 Gy is superior to RT alone for patients with intermediate and high risk prostate cancer.

Denham, Lancet 2011. Arms 2 and 3 were compared to arm 1.

3 months of NADT	↓ PSA progression HR 0·72, ↓ local progression HR 0·49, ↑ EFS HR 0·63.	
6 months of NADT	↓ PSA progression HR 0·57, ↓ local progression HR 0·45, ↑ EFS HR 0·51.	MORE OF IMPACT THAN 3 months.
3-month NADT	NS distant progression NS ACM.	NS PCSM
6-month NADT	↓ distant progression HR 0·49 ↓ ACM HR 0·63.	↓ PCSM HR 0·49

Tox: Treatment-related morbidity was not increased with NADT within the first 5 years after randomisation.
INTERPRETATION: 6 months of neoadjuvant androgen deprivation combined radiotherapy is an effective treatment option for locally advanced prostate cancer, particularly in men without nodal metastases or pre-existing metabolic comorbidities that could be exacerbated by prolonged androgen deprivation.

AZ 2022

D'Amico 6-month ADT trial. ←R→ 206 patients. T1-2b + G7-10 or PSA 10-40 (or lower PSA or GS if ECE or SVI on MRI). 80% int. risk. 15% G8-10.

1. 3D-CRT P+ SV +1.5 cm → 45/1.8. Boost P+1.5 cm → 22/2.0 No dose to LNs.
2. Same RT as Arm 1 + 6 mo. (LHRHa + flutamide) (med. follow-up = 4.52 years)

Hormones are given 2 months neoadjuvantly, 2 months concurrently, and 2 months adjuvant.

5 years (JAMA 2004): 5-year OS RT+AST 88% vs RT alone 78% (SS). 5-year survival-free of salvage androgen suppression 82% vs 57% (SS).
8 years (JAMA 2008): 8-year OS RT+AST 74% vs RT alone 61% (SS)
15 year (JAMA 2015): 15-yr OS RT+AST 36% vs RT alone 28% (NS)
SUBSET Low-Minimal comorbidity 44% vs. 31% (SS). High comorbidity 8% vs. 20% (NS).

Conclusion: At a median follow-up of 16.62 years, RT alone (vs RT+ADT) was associated with significantly ↓ overall and cardiac mortality in men with moderate or severe comorbidity, in contrast to no association with overall mortality at a median follow-up of 7.6 years (HR, 0.54 [95% CI, 0.27-1.10]; P = .08).[1] Although RT alone (vs RT+ADT) was associated with increased mortality in men with none or minimal comorbidity, mortality among all men randomized to RT alone was not significantly increased.

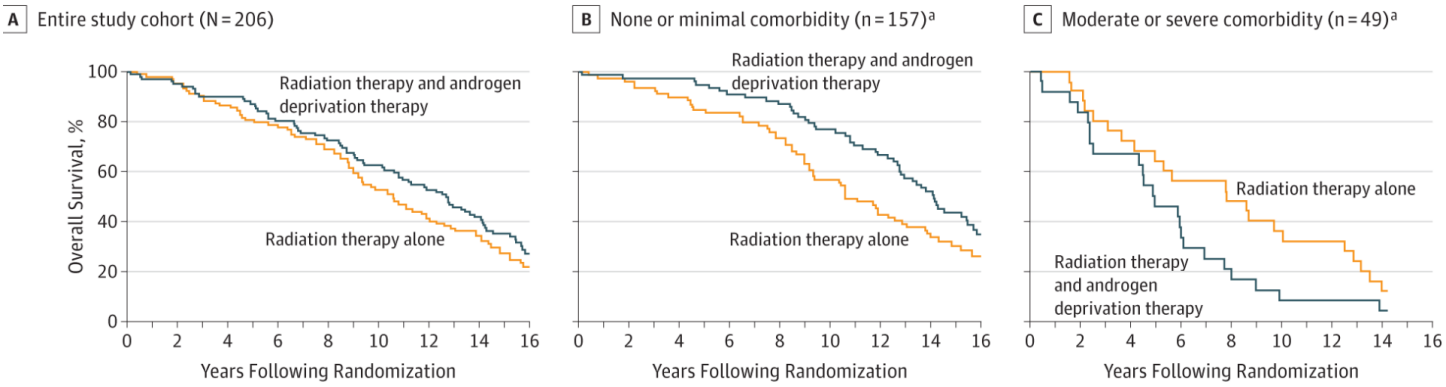


Table. All-Cause, Prostate Cancer, Cardiac, and Other-Cause Mortality Hazard Ratios by Patient, Prostate Cancer, and Treatment Factors

		Type of Mortality																			
		Overall					Prostate Cancer					Cardiac					Other Cause				
	No. of Men	No. of Deaths	Bivariable Analysis HR (95% CI)	P Value	Multivariable Analysis AHR (95% CI)	P Value	No. of Deaths	Bivariable Analysis HR (95% CI)	P Value	Multivariable Analysis AHR (95% CI)	P Value	No. of Deaths	Bivariable Analysis HR (95% CI)	P Value	Multivariable Analysis AHR (95% CI)	P Value	No. of Deaths	Bivariable Analysis HR (95% CI)	P Value	Multivariable Analysis AHR (95% CI)	P Value
Age at randomization, per year	206[a]	156	1.08 (1.05-1.12)	<.001	1.09 (1.05-1.12)	<.001	29	1.01 (0.96-1.07)	.64	1.02 (0.96-1.08)	.58	39	1.02 (0.97-1.07)	.45	1.02 (0.96-1.08)	.62	88	1.08 (1.03-1.13)	.001	1.08 (1.03-1.13)	.002
Interaction Terms																					
None or minimal comorbidity[b]																					
RT and ADT	78	53	1 [Reference]	.04	1 [Reference]	.04	5	1 [Reference]	.002	1 [Reference]	.004	7	1 [Reference]	.27	1 [Reference]	.28	41	1 [Reference]	.04	1 [Reference]	.04
RT alone	79	57	1.47 (1.01-2.15)		1.51 (1.03-2.21)		20	4.52 (1.71-12.0)		4.30 (1.60-11.50)		11	1.69 (0.67-4.26)		1.72 (0.64-4.58)		26	0.60 (0.37-0.98)		0.60 (0.36-0.99)	
Moderate or severe comorbidity[b]																					
RT and ADT	24	23	1 [Reference]	.08	1 [Reference]	.001	1	1 [Reference]	.35	1 [Reference]	.46	15	1 [Reference]	.003	1 [Reference]	<.001	7	1 [Reference]	.08	1 [Reference]	.05
RT alone	25	23	0.59 (0.32-1.06)		0.36 (0.19-0.67)		3	2.94 (0.31-27.60)		2.41 (0.23-25.21)		6	0.26 (0.10-0.64)		0.17 (0.06-0.46)		14	2.26 (0.92-5.56)		2.79 (1.02-7.60)	
ADT × comorbidity	206	156	0.35 (0.17-0.70)	.003	0.24 (0.12-0.50)[c]	<.001	29	0.63 (0.05-7.33)	.71	0.56 (0.04-7.11)[d]	.66	39	0.15 (0.04-0.55)	.004	0.10 (0.03-0.40)[e]	.001	88	3.89 (1.30-11.62)	.02	4.67 (1.56-14.04)[f]	.006
Prostate Cancer Prognostic Factors																					
PSA level, ng/mL	206	156	1.11 (0.87-1.40)	.41	1.26 (0.99-1.60)	.06	29	1.31 (0.54-3.22)	.55	1.12 (0.50-2.52)	.78	39	0.94 (0.64-1.38)	.75	1.17 (0.75-1.82)	.49	88	1.05 (0.80-1.38)	.73	1.12 (0.81-1.55)	.50
AJCC clinical tumor category																					
T1	99	76	1 [Reference]		1 [Reference]		9	1 [Reference]		1 [Reference]		20	1 [Reference]		1 [Reference]		47	1 [Reference]		1 [Reference]	
T2a	46	31	0.90 (0.59-1.37)	.63	0.74 (0.48-1.15)	.18	4	0.98 (0.31-3.13)	.97	0.87 (0.25-2.98)	.82	6	0.64 (0.26-1.57)	.33	0.37 (0.13-1.07)	.07	21	1.05 (0.63-1.76)	.86	1.11 (0.66-1.86)	.71
T2b	61	49	1.08 (0.75-1.56)	.66	1.04 (0.71-1.53)	.84	16	3.06 (1.36-6.91)	.007	2.94 (1.25-6.90)	.01	13	1.02 (0.51-2.05)	.95	0.68 (0.33-1.40)	.29	20	0.58 (0.35-0.98)	.04	0.63 (0.36-1.10)	.10
Highest Gleason score																					
≤3 + 4[g]	130	91	1 [Reference]		1 [Reference]		15	1 [Reference]		1 [Reference]		19	1 [Reference]		1 [Reference]		57	1 [Reference]		1 [Reference]	
4 + 3[h]	46	39	1.70 (1.16-2.48)	.006	1.73 (1.17-2.57)	.01	6	1.14 (0.45-2.90)	.78	1.03 (0.41-2.56)	.95	12	1.99 (0.97-4.08)	.06	1.86 (0.87-3.97)	.11	21	1.11 (0.67-1.83)	.69	1.23 (0.76-1.99)	.40
8-10	30	26	1.97 (1.27-3.06)	.002	1.56 (0.98-2.48)	.06	8	2.65 (1.11-6.33)	.03	2.52 (1.00-6.39)	.05	8	2.08 (0.90-4.82)	.09	1.97 (0.87-4.47)	.10	10	0.73 (0.37-1.43)	.35	0.68 (0.33-1.38)	.28

Abbreviations: ADT, androgen deprivation therapy; AHR, adjusted hazard ratio; AJCC, American Joint Commission on Cancer; HR, hazard ratio; PSA, prostate-specific antigen; RT, radiation therapy.

[a] There were 206 men randomized to ADT. The event rate was 76% for all-cause death, 14% for prostate cancer death, 19% for cardiac death, and 43% for other cause death.

[b] Description of comorbidity based on the 4 grades (grade 0, none; grade 1, minimal; grade 2, moderate; and grade 3, severe) of the Adult Comorbidity Evaluation 27; the grade corresponds to the severity of the individual organ system decompensation and prognostic effect.

[c] The effect size was 0.24 and the power of detecting the observed interaction was 96.7%.

[d] The effect size was 0.56 and the power of detecting the observed interaction was 9.8%.

[e] The effect size was 0.10 and the power of detecting the observed interaction was 86.5%.

[f] The effect size was 4.67 and the power of detecting the observed interaction was 86.8%.

[g] The possible scores are 3 plus 3 or 3 plus 4.

[h] The only possible score is 4 plus 3.

RT+ADT (Int + Low Risk)

RTOG 94-08.
←R→ 1979. clinical T1b-T2b, PSA ≤ 20. | 1. EBRT | 2. ADT + EBRT | Low risk 35%, int 55%, < 10% high.
RT = 46.8 Gy delivered to the WPRT pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate, for a total dose of 66.6 Gy.
ADT = 2 HT neoadjuvant + 2 concurrent HRT.
Short-term ADT received flutamide at a dose of 250 mg PO TID and either:
1. monthly subcutaneous goserelin at a dose of 3.6 mg or 2. intramuscular leuprolide at a dose of 7.5 mg for 4 months.
Radiotherapy commenced after 2 months of androgen deprivation. Median FU 9 years.
RT DOSE: 46.8 Gy WPRT → CD Boost prostate of 19.8 Gy = total of 66.6 Gy in 37 fractions
The 4 months were historically from RTOG 8610 (2 months before and 2 months concurrently).

Jones, IJROBP 2018.
Results: 10 yr rate OS = 57.2% | 62.8 HRT (SS). DSM 8% | 4% (SS).
BcF, distant metastases, and the rate of positive findings on repeat prostate biopsy at 2 years were all SS ↑ with HRT.
Toxicity: The incidence of grade 3 or higher hormone-related toxic effects was less than 5%.
NOTE: Reanalysis according to risk showed ↓in OS and DSM primarily among intermediate-risk patients, with NS ↓ among low-risk patients.
Reanalysis 10-year OS = 54% → 61%
Conclusion: ADT only really for intermediate risk patients.
Compared to D'Amico, this had more 3+4 vs 4+3.

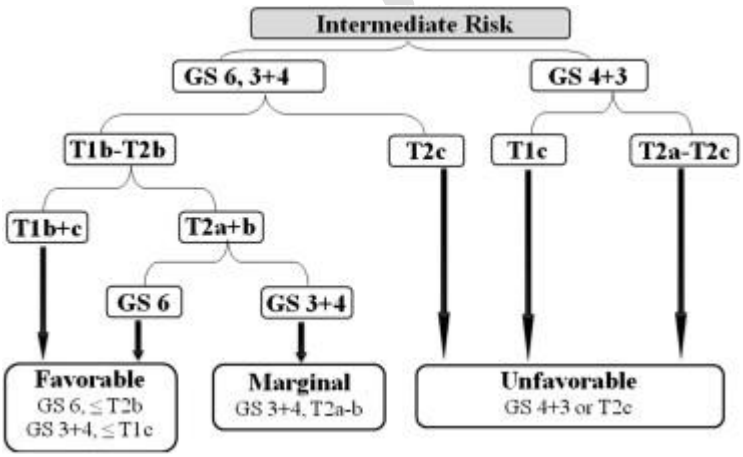
Jones IJROBP 2021.

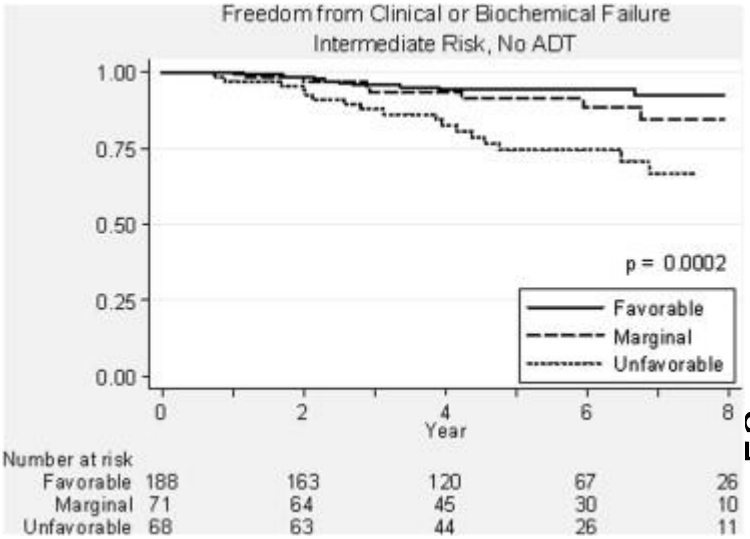
		RT+ADT (10y)	RT alone (10y)	RT+ADT (18y)	RT alone (18y)	HR	p-value
OS	**(1974 pts)**	**63%**	**56%**	**23%**	**23%**	**0.94**	**0.28**
Low Risk	*(703 pts)*	*69%*	*62%*	*26%*	*31%*	*1.01*	*0.93*
Int. Risk	*(1086 pts)*	*60%*	*53%*	*21%*	*20%*	*0.92*	*0.22*
High Risk	*(185 pts)*	*55%*	*52%*	*19%*	*16%*	*0.88*	*0.48*
Age<=70	*(972 pts)*	*71%*	*64%*	*35%*	*34%*	*0.93*	*0.37*
Age>70	*(1002 pts)*	*55%*	*49%*	*11%*	*14%*	*0.99*	*0.89*
BF		**32%**	**46%**	**37%**	**51%**	**0.66**	**<0.01**
DM		**5%**	**8%**	**8%**	**12%**	**0.66**	**0.01**
LP		**11%**	**16%**	**12%**	**18%**	**0.68**	**<0.01**

Conclusions
Further follow-up demonstrates that OS converges at approximately 15 years, by which point the administration of 4 months of ADT had conferred an estimated additional 6 months of life.

Castle, IJROBP 2013. Favorable outcomes with higher dose RT and no HT given favorable intermediate risk prostate Cancer. 1^{O} FFF.
Retrospective. 3 groups tx with IMRT or 3D CRT (75.6-78 Gy) from 1993-2008
| 1. 326 int risk w/ RT alone | 2. 218 int risk RT and ≤6 mo of ADT | 3. 274 low risk patients tx with definitive RT |. Median follow-up 58 months.
These 3 int. risk groups were analyzed after divided into 3 prognostic groups:
| 1. 188 favorable patients: GS 6, ≤T2b or GS 3+4, ≤T1c | 2. 71 marginal: GS 3+4, T2a-b | 3. 68 unfavorable: GS 4+3 or T2c disease |.

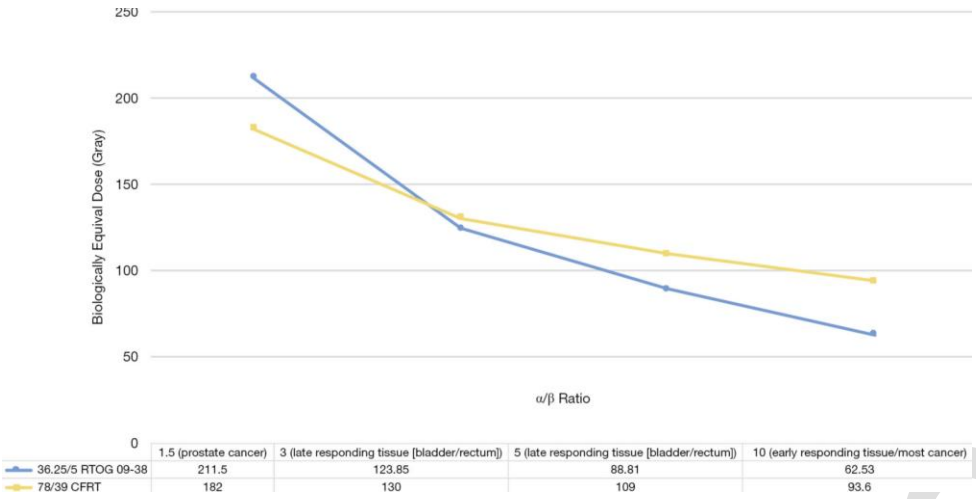
Results: HR for recurrence in each group were 1.0, 2.1, and 4.6, respectively. When int risk patients TX with RT compared to int risk TX with RT and ADT, the greatest benefit from ADT was seen for the unfavorable intermediate-risk patients (FFF, 74% vs 94%, respectively; P =.005).
Favorable had no significant benefit from the addition of ADT to RT (FFF, 94% vs 95%, respectively; P =.85).
Note: When multivariate Cox proportional hazards analysis was performed in the favorable intermediate-risk subset using the same variables, the only predictor of increased failure was younger age but not the use of ADT.

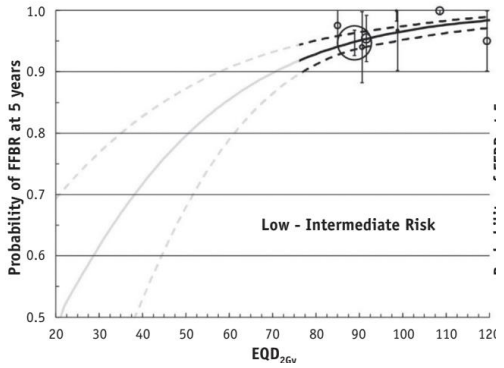


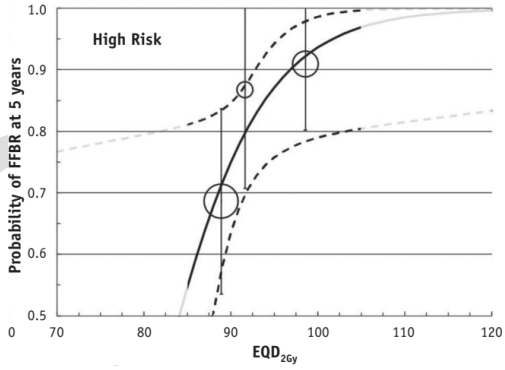


AZ 2021

SBRT







Studies on Definitive SBRT and SBRT Boost (HyTEC and https://cco.amegroups.com/article/view/16080/16541#B23)

Table 1 Summary of included SBRT series

	Cohort	N	Risk category (%)			Platform	Dose/fractionation				ADT (%)	Med f/u (y)	FFBR (%)	
			Low	Int	High		Gy	Fx	EQD2Gy	Schedule			2-y	5-y
1	RSSR[39]	437	43	49	8	CK, LINAC	35-38	4-5	85.0-119.4	NA	11	1.7	96.1	-
2	RPCR[40]	1743*	41	42	10	CK	35-40	4-5	102.5-108.6	NA	-	2.0	92.0	-
3	McBride et al[41]	45	100	0	0	CK	36.25-37.5	5	90.6-96.4	4-20 d	0	3.7	97.7	-
4†	Hannan et al[42]	91	36	64	0	Tomo, LINAC	45-50	5	135.0-164.3	NA	17	4.5	100	98.6
5	Jackson et al[43]	66	49	51	0	LINAC	37	5	94.1	Q3D	0	3.0	100	-
6	Virginia Mason[51]	40	100	0	0	LINAC	33.5	5	78.5	QD	-	3.4	90.0	-
7	Royal Marsden[44,‡]	51	20	69	12	CK	36.25	5	90.6	NA	0	1.2	-	-
8	Western Australia[34]	45	24	62	13	CK	36.25	5	90.6	QOD	16	1.5	100	-
9†	pHART3[37]	84	100	0	0	LINAC	35	5	85.0	QW	1	9.6	100	97.5
10†	pHART6[37]	30	60	40	0	LINAC	40	5	108.6	QW	0	6.9	100	96.7
11†	21st Century Oncology[46]	102	100	0	0	LINAC	40	5	108.6	QOD	-	5.0§	100	100
12†	Genesis Health Care Partners[47]	79	51	49	0	CK	38	4	119.4	NA	-	5.0§	100	95
13†	Stanford[60]	67	100	0	0	CK	36.25	5	90.6	QD/QOD	0	2.7	100	94
14	Erasmus MC[52]	50	60	40	0	CK	38	4	119.4	QD	0	1.9	100	-
15	Milan[55]	90	59	41	0	LINAC	35	5	85.0	QOD	13	2.3	97.8	-
16	Gliwice[50]	400	53	47	0	CK	36.25	5	90.6	QOD	58	1.3	99.5‖	-
17	Olsztyn[49]	68	10	90	0	LINAC	33.5	5	78.5	BIW	77	2.0	100	-
18	Naples[45]	112	NA	NA	NA	CK	35-36	5	85.0-92.6	QD	19	2.0	97.4	-
19†	Seoul[61]	44	11	23	66	CK	32-36	4	86.9-108.0	QD	89	3.3	100 (Low/int risk) 96.0 (High risk)	100 (Low/int risk) 90.9 (High risk)
20	Finland[56]	218	22	27	51	CK	35-36	5	85.0-92.6	QOD	65	1.9	95.4	-
21	Georgetown[54]	100	37	55	8	CK	35-36.25	5	85.0-90.6	QOD	11	2.3	99.0	-
2†	Flushing[48]	515	63	30	7	CK	35-36.25	5	85.0-90.6	QD	14	7.0	98.0 (Low/int risk)¶ 72.0 (High risk)¶	94.7 (Low/int risk)¶ 68.6 (High risk)¶
23	Vicenza[53]	100	41	42	17	CK	35	5	85.0	QD	29	3.0	96.0#	94.4#
24†	Philadelphia[62]	142	43	44	13	CK	35-37.5	5	85.0-96.4	QOD	28	3.3	97.9 (Low/int risk) 86.7 (High risk)&	94.4 (Low/int risk) 86.7 (High risk)&
25	Virginia Hospital Center[57]	102	36	55	8	CK	36.25	5	90.6	QD	9	4.3	100	-

Table 1 Photon-based stereotactic body radiation therapy for localized prostate cancer

Study	Number of patients	Radiation therapy device	Study type	Median follow up time (months)	Dose and fractionation	Actuarial FFBF	RTOG/CTCAE late GI toxicity ≥ grade 3 (%)	RTOG/CTCAE late GU toxicity ≥ grade 3 (%)
King *et al.* (25)	1,100 (641 L, 334 I, 125 H)	Robotic arm	Phase II	36	35–40 Gy in 5 fx	5 years: 93% (95% L, 84% I, 81% H)	NR	NR
Katz *et al.* (26)	477 (324 L, 153 I)	Robotic arm	Retrospective	72	35–36.3 Gy in 5 fx	7 years: 93.7% (95.9% L, 89.3% I)	0	1.70
Meier *et al.* (27)	309 (172 L, 137 I)	Robotic arm	Phase II	61	40 Gy in 5 fx	5 years: 87.1% (97.3% L, 97.1% I)	0	2
Bernetich *et al.* (28)	142 (61 L, 63 I, 18 H)	Robotic arm	Retrospective	38	35–37.5 Gy in 5 fx	5 years: 92.7% (94.4% L, 94.2% I, 83.9% H)	0	2
Friedland *et al.* (29)	112	Robotic arm	Retrospective	24	35–36 Gy in 5 fx	97% FFBF (actuarial value not reported)	1	0
Mantz *et al.* (30)	102 (L)	Gantry	Retrospective	48	40 Gy in 5 fx	5 years: 100%	0	0
Bolzicco *et al.* (31)	100 (41 L, 42 I, 17 H)	Robotic arm	Prospective, single institution	36	35 Gy in 5 fx	3 years: 94.4%	0	1
Hannan *et al.* (32)	91 (33 L, 58 I)	Gantry	Phase I–II	54	45–50 Gy in 5 fx	5 years: 98.6% (100% L, 98% I)	6.80	6
D'Agostino *et al.* (33)	90 (53 L, 37 I)	Gantry	Phase II	27	35 Gy in 5 fx	100 % FFBF for L, 94.5% FFBF for I (actuarial not reported)	0	0
Loblaw *et al.* (34)	84 (L)	Gantry	Phase I–II	55	35 Gy in 5 fx	5 years: 98%	1	1
Fuller *et al.* (35)	79 (40 L, 39 I)	Robotic arm	Retrospective	60	38 Gy in 4 fx	5 years: 100% L, 92% I	0	6
Rucinska *et al.* (36)	68 (7L, 61 I)	Gantry	Prospective, single institution	24	33.5 Gy in 5 fx	100 % FFBF (actuarial value not reported)	0	0
McBride *et al.* (37)	45 (L)	Robotic arm	Phase I	44.5	36.3–37.5 in 5 fx	3 years: 97.7%	4.40	2.20
Lee *et al.* (38)	45 (6 L, 26 I, 13 H)	Robotic arm	Retrospective	63	36 Gy in 5 fx	5 years: 89.7%	0	4.40
Kang *et al.* (39)	44 (5 L, 28 I, 11 H)	Robotic arm	Retrospective	40	34–36 Gy in 4 fx	5 years: 100% L, 100% I, 90.8% H	0	0
Madsen *et al.* (40)	40 (L)	Gantry	Phase I/II	41	33.5 in 5 fx	4 years: 90%	0	0
Jeong *et al.* (41)	39 (16 L, 23 I)	Robotic arm	Retrospective	30	37.5 Gy in 5 fx	3 years: 93.9%	2.60	0
Park *et al.* (42)	39 (6L, 20 I, 3 H)	Robotic arm	Retrospective	42	3–36.3 Gy in 5 fx	5 years: 100% L, 83.9% I, 33.3% H	NR	NR
Kim *et al.* (43)	33 (9 L, 24 I)	Robotic arm	Retrospective	51	36.3 Gy in 5 fx	5 years: 100%	0	0
Kotecha *et al.* (44)	24 (11 I, 13 H)	Gantry	Retrospective	25	36.3 in 5 (50 Gy in 5 fx boost)	95.8% FFBF at 2 years (actuarial not reported)	0	0

Data regarding the use of definitive prostate stereotactic body radiation therapy for treatment of localized prostate cancer. L, low-risk prostate cancer; I, intermediate-risk prostate cancer; H, high-risk prostate cancer; Gy, Gray; fx, fractions; NR, not reported; RTOG, Radiation Therapy Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, genitourinary.

Table 2 Photon-based stereotactic body radiation therapy in conjunction with external beam radiation therapy for localized prostate cancer

Study	Number of patients	Study type	Median follow up time (months)	Dose and fractionation	Actuarial FFBF	RTOG/CTCAE late GI toxicity ≥ grade 3 (%)	RTOG/CTCAE late GU toxicity ≥ grade 3 (%)
Mercado *et al.* (46)	108 (4 L, 45 I, 59 H)	Retrospective	41	19.5 Gy in 3 fx (SBRT) and 45–50.4 Gy in 35–28 fx (CF-EBRT)	3 years: 100% I, 89.8% H	NR	NR
Katz *et al.* (47)	73 (41 I, 32 H)	Retrospective	33	18–21 Gy in 3 fx (SBRT) and 45 Gy in 25 fx (CF-EBRT)	3 years: 89.5% I, 77.7% H	0	1.40
Anwar *et al.* (48)	48 (14 I, 34 H)	Retrospective	42.7	19–21 Gy in 2 fx (SBRT) and 45 Gy in 25 fx (CF-EBRT)	5 years: 90%	0	1
Lin *et al.* (49)	41 (H)	Retrospective	42	21 Gy in 3 fx (SBRT) and 45 Gy in 25 fx (CF-EBRT)	4 years: 91.9%	0	0
Kim *et al.* (50)	39 (20 I, 19 H)	Retrospective	53.6	21 Gy in 3 fx (SBRT) and 45 Gy in 25 fx (CF-EBRT)	5 years: 100% I, 89.5% H	0	0

Note: Cyberknife has increased inhomogeneity. VMAT has quite a uniform dose.

Table 1 Selected studies analyzing factors associated with late urinary side effects

Study	n	Treatment details	Med. f/u (y)	Urinary endpoint	Dosimetric factors associated* with worse urinary outcomes	Nondosimetric factors associated* with worse urinary outcomes
King et al,[20] 2012 (Stanford)	67	36.25 Gy (5 fx), QD/QOD	2.7	RTOG G2: 5.0% G3: 3.5%		QD (vs QOD) treatment schedule (for RTOG ≤G2 toxicity) Urologic instrumentation
Bolzicco et al,[21] 2013 (Vicenza)	100	35 Gy (5 fx), QD	3.0	RTOG G2: 3.0% G3: 1.0%		Prior procedure for BPH
Elias et al,[22] 2014 (Sunnybrook)	84	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 17.9%	Bladder D5cc >34 Gy	Bladder volume
Katz et al,[23] 2014 (Flushing)	515	35-36.25 Gy (5 fx), QD	6.0	RTOG G2: 9.1% G3: 1.7%	Prescription dose 36.25 Gy (vs 35 Gy)	Prostate volume >60 cc
Bernetich et al,[24] 2014 (Drexel)	142	79%: 35-36.25 Gy (5 fx), QOD 21%: 37.5 Gy (5 fx), QOD	3.0	CTCAE v3 G2: 14% G3: 2%	Prescription dose 37.5 Gy (vs 35-36.25 Gy)	
Gurka et al,[25] 2015 (Georgetown)	208	35-36.25 Gy (5 fx), QOD	4.0	CTCAE v4 ≥G2 bleed: 2.4%		Prostate volume Prior procedure for BPH Alpha antagonist use
Gomez et al,[26] 2015 (UCLA)	75	40 Gy (5 fx), QOD	1.0	EPIC QOL (avg of obs/irrit and incont)	Bladder V40 Gy >5.5 cc	Larger prostate volume
Seymour et al,[27] 2015 (UCSF)	56	38 Gy (4 fx), QD/QOD	3.0	CTCAE v4 G2: 19.6% G3: 3.6%	Urethra Dmax >47 Gy Urethra V44 Gy Bladder V19 Gy More heterogeneous plan	Prostate volume ≥50 cc
Qi et al,[28] 2016 (UCLA)	86	40 Gy (5 fx), QOD	1.0	EPIC QOL Obs/irrit MID: 46% Incont MID: 28%	Bladder mean (obs/irrit, incont) Bladder V34-40 Gy (obs/irrit) Bladder D2-10cc (obs/irrit)	Larger prostate volume (incont)
Kole et al,[29] 2016 (Georgetown)	216	35-36.25 Gy (5 fx), QOD	4.0	IPSS Late urinary flare: 13%	Bladder D12.7% >33.5 Gy	Age <65
Helou et al,[30] 2017 (Sunnybrook)	259	32%: 35 Gy (5 fx), QW 39%: 40 Gy (5 fx), QW 29%: 40 Gy (5 fx), QOD	3.2	RTOG G2: 32.6% G3: 1.9%	Prescription dose 40 Gy (vs 35 Gy)	Higher age Shorter treatment duration
Zhang et al,[31] 2017 (UCSF)	78	38 Gy (4 fx), QD/QOD	3.0	CTCAE v4 G2: 19.2% G3: 2.6%	Urethra V42 Gy	Shorter treatment duration More heterogeneous plan
Jackson et al,[32] 2018 (Multicenter)	66	37 Gy (5 fx), QOD	3.1	EPIC QOL Obs/irrit MID: 25% Incont MID: 24%	Bladder Dmax (obs/irrit) Bladder V3.7-37 Gy (incont)	

Table 2 Selected studies analyzing factors associated with late bowel side effects

Study	n	Treatment details	Med. f/u (y)	Bowel endpoint	Dosimetric factors associated* with worse bowel outcomes	Nondosimetric factors associated* with worse bowel outcomes
King et al,[20] 2012 (Stanford)	67	36.25 Gy (5 fx), QD/QOD 16%: 45 Gy (5 fx), QOD	2.7 2.0	RTOG G2: 2.0% CTCAE v3	Rectum V50 Gy >3 cc Rectum Circumference V39 Gy	QD (vs QOD) treatment schedule
Kim et al,[33] 2014 (multicenter)	91	16%: 47.5 Gy (5 fx), QOD 67%: 50 Gy (5 fx), QOD		G2: 23.1% G3: 3.3% G4: 2.2%	>35%	
Elias et al,[22] 2014 (Sunnybrook)	84	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 26.2%	Rectum V31.8 Gy >10% Rectum D1cc >35 Gy	
Gomez et al,[26] 2015 (UCLA)	75	40 Gy (5 fx), QOD	1.0	EPIC QOL	Rectum V40 Gy >1.5 cc Rectum V36 Gy >4.2 cc	
Musunuru et al,[34] 2016 (Sunnybrook)	258	33%: 35 Gy (5 fx), QW 67%: 40 Gy (5 fx), QW or QOD	2.5	CTCAE v3 G2 bleed: 16.2% G3 bleed: 1.6% G4 bleed: 1.6%	Rectum V38 Gy >2 cc Prescription dose 40 Gy (v 35 Gy)	SV treatment (vs prostate only) PTV margin 5 mm (vs 4 mm) Hemorrhoids Anticoagulant use
Miszczyk et al,[35] 2017 (Poland)	400	36.25 Gy (5 fx), QOD	1.3	RTOG G1: 4.7% G2: 0.6%		Diabetes

Table 3 Selected studies analyzing factors associated with late sexual side effects

Study	n	Treatment details	Med. f/u (y)	Sexual endpoint	Dosimetric factors associated* with worse sexual outcomes	Nondosimetric factors associated* with worse sexual outcomes
Wiegner et al,[36] 2010 (Stanford)	32 (no ADT)	36.25 Gy (5 fx), QD/QOD	3.0	EPIC QOL 20M impotency: 61% (23% if potent at baseline)	(PB not associated)	Older age
Obayomi-Davies et al,[37] 2013 (Georgetown)	97 (potent at baseline, no ADT)	35-36.25 Gy (5 fx), QOD	2.7	EPIC QOL 2Y impotency: 45.6%	(PB not associated)	Charlson Comorbidity Index ≥1
Elias et al,[22] 2014 (Sunnybrook)	84 (4% ADT)	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 37.5%	PB V20 Gy >40% PB V35 Gy >4%	
Dess et al,[38] 2018 (Georgetown)	373 (no ADT)	35-36.25 Gy (5 fx), QOD	4.7	EPIC QOL 2Y impotency: 66% (43% if potent at baseline)	(PB not analyzed)	Older age Higher body mass index Diabetes Hypertension Coronary artery disease

Meta-Analysis 2020
←M→ 7 studies of 6795 patients (3 were randomized). 42% CRFT (≥40 fractions), 49% HFRT (15-25 fractions), and only 9% UFRT (7 fractions). Across all cohorts, 73-90% of patients had intermediate risk disease. No patients receiving ultra-hypofractionation had low-risk disease (all ultra-hypofx were from HYPO-RT-PC).
1^{O} 5-year DFS (defined as alive without evidence of biochemical failure (PSA nadir + 2 ng/mL)).

Leher, Radiother Oncol 2020
5-year DFS 85%, 86% and 85% (NS).
5-year late ≥ G2 GI toxicity 12.1%, 14.6%, 10%. NS when CFRT is compared with HFRT or UFRT.
5-year late ≥ G2 urinary tox 19.4%, 20.4%, 18%. NS when CFRT is compared with HFRT or UFRT.
Conclusion
Ultrahypofrationated regimens appear to offer similar levels of safety and efficacy to CFRT and HFRT. These findings are hypothesis-generating and require further validation by ongoing prospective trials.

RTOG 09-38
PENDING

HYPO-RT-PC
←R→ 1200 patients 89% int risk and 11% high risk. ≤ 75 yo. | 1. 42.7 Gy in 7 fx, 3 days per week | 2. 78 Gy in 39 fractions, daily |.
No ADT was allowed. cT3a was allowed by only 5% had it.
5-year median FU. 1^{O} time to BcF or clinical F.

Widmark, Lancet 2019
5-year FFS ~84% (NS).
Side effects: ↑ acute physician-reported RTOG ≥ G2 urinary tox 28% vs. 23%; (p=0·057).
↑ late toxicity urinary ≥ G2 6% vs. 2% (p=0.0037).
Erection before RT was 70% and dropped to 35% after 5 years in both arms.
NS late tox ≥ G2 bowel late toxicity between the two treatment groups at any point after radiotherapy.
Interpretation: Ultra-hypofractionated radiotherapy is non-inferior to conventionally fractionated radiotherapy for intermediate-to-high risk prostate cancer regarding failure-free survival. Early side-effects are more pronounced with ultra-hypofractionation compared with conventional fractionation whereas late toxicity is similar in both treatment groups. The results support the use of ultra-hypofractionation for radiotherapy of prostate cancer.

IMPT (SBRT)
Retrospective 284 patients low IMPT (36.25 GyE in 5 fx) in 1. Low (43%), 2. fav int (45%), and 3. unf int risk (12%) prostate Ca.
Median TX time = 9 days.
In addition, 49 (17.6%) patients underwent neoadjuvant hormonal therapy. No patients had adjuvant hormonal therapy.

Kubes, IJROBP 2021. 56 months.
5-year bDFS 96.9%, 91.7%, 83.5%.
Late toxicity GI G1 22%, G2 7.2%, and G3 0.36%
Late toxicity GU G1 29%, G2 5.0%, and G3 0%.
PSA relapse was observed in 17 patients (6.1%), and lymph node or bone recurrence was detected in 11 patients.
Four (1.4%) local recurrences were detected.
Nine patients (3.2%) died of causes unrelated to prostate cancer. No deaths related to prostate cancer were reported.
Conclusion Ultrahypofractionated proton beam radiation therapy for prostate cancer is effective with long-term bDFS comparable with other fractionation schedules and with minimal serious long-term GI and GU toxicity.

PATRIOT Study Weekly vs. QoD SBRT
Phase II 152 low and intermediate-risk prostate cancer | 1. 40 Gy in 5 fx delivered once per week (QW) | 2. every other day |.
1^{O} proportion with a minimum clinically important change (MCIC) in bowel QOL during the acute (≤12 week) period.

Quon, Radiother Oncol 2018.
Acute bowel MCIC reporting 68% vs. 90% (p=0.002)
Acute moderate–severe problems with bowel QOL 20% vs. 57% (p < 0.001).
Acute urinary MCIC reporting 78% vs. 94% (p = 0.006).
Late Δ NS in urinary or bowel QOL at 2 years or last follow-up.
Conclusion Prostate SBRT delivered QW improved acute bowel and urinary QOL compared to EOD. Patients should be counselled regarding the potential for reduced short-term toxicity and improved QOL with QW prostate SBRT.

Alayed, Radiother Oncol 2020. 62 month long term
Late changes in QOL were not significantly different between the two arms.
Late ≥G3 GI toxicity 1 (1.3%) vs 3 (2.7%). Late ≥G3 GU toxicity 5 (6.7%) vs 2 (2.7%).
5-year BF 3.0 vs 7.2% (p = 0.22). 5-year Salvage Therapy n=0 vs. n=4 (p = 0.04).
5-Year OS and CSS was 95.8% and 98.6% with no difference between arms (p = 0.49, p = 0.15).
3 patients in the QW arm developed metastases.
Interpretation Although we previously reported that weekly prostate SABR had better bowel and urinary QOL compared to EOD, the updated results show no difference in late toxicity, QOL, BF, or PSA kinetics. Patients should be counseled that QW SABR reduces short-term toxicity compared to QW SABR.

AZ 2021

Georgetown SBRT IPSS ≥ 15 Study https://www.frontiersin.org/articles/10.3389/fonc.2020.01060/full
53 patients prospective with IPSS ≥ 15 s/p SBRT35-36.25 Gy in 5 fractions via Cyberknife.
Median prostate size 37 cc. 30% patients received ADT.

Aghdam, Frontiers 2020
3-yr G3 GU toxicity 7.5%.
A mean baseline IPSS score of 19.8 significantly decreased to 12.9 at 3 months post-SBRT (p = 0.002) and remained stable at 36 months (13.7).
A mean baseline EPIC-26 obstructive/irritative score of 64.1 significantly improved to 80.2 at 3 months (p = 0.002).
This improvement was maintained to 36 months.
There was no significant change from the mean baseline EPIC-26 urinary incontinence score at any point during follow up.
Conclusions: SBRT for clinically localized prostate cancer was well-tolerated in men with baseline IPSS ≥ 15 (1). Grade 3 toxicities occurred but resolved with time. Our data suggest that poor baseline urinary function does not worsen following SBRT and may even improve. High baseline IPSS score should not be considered a contraindication to SBRT.

Mirage MRI vs. CT Trial
←R→ 100 patients s/p SBRT | 1. CT-guidance | 2. MRI-guidance |. Planning margins of 4 mm (CT-arm) and 2 mm (MRI-arm) with P+SV.
RT = P+SV 40 Gy in five fractions. ENI and SpaceOARS allowed per physician discretion.
1^{O} acute (i.e., within 90 days of SBRT) grade ≥2 GU physician-reported toxicity (by CTCAE version 4.03).

Kishan, ASCO 2022.
Acute grade ≥2 GU toxicity 24 (47.1%) vs. 11 (22.4%) (p = 0.01).
Acute grade ≥2 GI toxicity 7 (13.7%) vs. 0 (0%), p = 0.01.).
↑ IPSS scores from baseline 1-month post-SBRT (median change of 10 vs. 6, p = 0.03)
3-month post SBRT (median change of 3 vs. 2, p = 0.3).
↓ EPIC-26 bowel domain scores 1-month post-SBRT (median change of -8.3 vs. 0, p = 0.03)
3-months post-SBRT (median change of -2.3 vs. 0, p = 0.4).
Given the large primary endpoint signal seen, our protocol was amended to reduce the projected sample size to 154 while still maintaining 89% power to detect a difference.
Conclusions: This interim analysis demonstrates a statistically significant reduction in acute grade ≥2 GU toxicity with MRI-guidance versus CT-guidance in the context of prostate SBRT. Patient-reported urinary and bowel function metrics are also better preserved at the 1 month time point with MRI-guidance, though this difference dissipates (potentially due to side-effect management) at the 3 month time point. Accrual has been completed as of October 2021 and a final analysis for the primary endpoint is anticipated in early 2022.

Pilot Trials

UTSW Phase I ADT + SBRT **HR-PCa**
55 patients with ≥ T3, ≥ GG4, PSA ≥ 20. All patients received mpMRI, SpaceOAR, and fiducials.
s/p hormones (bicalutamide + GnRH agonist/antagonist) 10-20 weeks → SBRT → continuation for 2 years or hormones.
Alpha blockers used during SBRT and 4mg dex given prior to each treatment.
SBRT = CTV (Prostate + 1 cm SVs) + 3 mm = 4750 cGy in 5 fractions.
Elective LN 2250 cGy → (LN+ Dose Escalation) 2500 cGy and intraprostatic lesions 5000 → 5250 → 5500 cGy.

Hannan, IJROBP 2021
Grade 2 GI 13% Grade 2 GU 25%. No grade 3+ toxicity.
NS ↑ toxicity across dose-escalation cohorts.
Late G2 GI 7%. Late 2 GU 20%. Late 1 grade 3+ late urinary retention requiring TURP.

MSK Pilot Study LDR + SBRT **IntR-PCa**
40 patients with intermediate risk LDR Pd-103 (prescription dose, 100 Gy) → 1 month later with SBRT (25 Gy in 5) to the P+SV.
1^{O} rate of grade 2+ genitourinary toxicity at 12 months.
Biochemical failure was defined as prostate-specific antigen nadir +2 ng/mL.
Posttreatment biopsies were performed at between 24 and 36 months; median follow-up was 36 months.

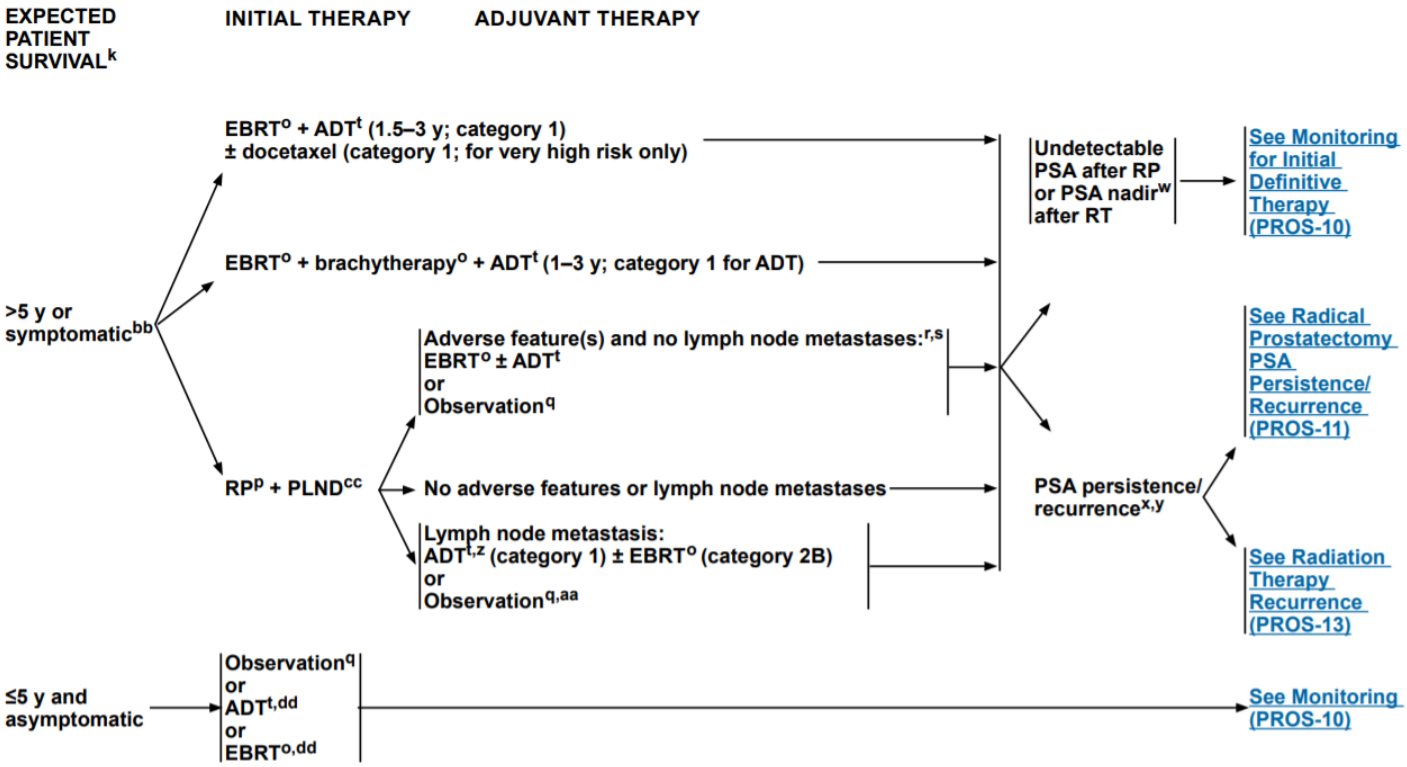
Kollmeier, IJROBP 2020.
12-month G2 GU 25%. No G3.
Baseline → RT → 12-month → 24 month **Mean IPSS** 5 → **RT** → 10 → 6.2.
12-month G2 GI 5%. No G3.
One patient without a PPB developed osseous metastases at 18 months posttreatment in the absence of biochemical failure.
Conclusion Low-dose-rate brachytherapy in combination with ultrahypofractionated stereotactic RT was safe and effective for intermediate-risk prostate cancer in early results of this trial.

AL 2022

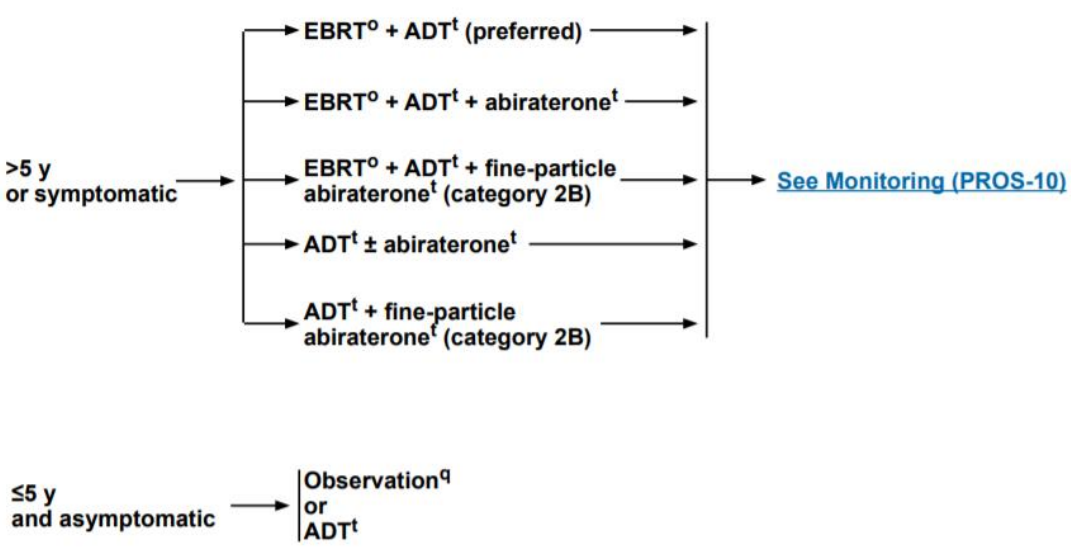
High Risk Disease: Stage Group ≥ IIIA

- Survival
  - 5-10 year bPFS: T1 or 2: 60% T3 or N+: 20%
  - 5-10 year CSS: T1 or 2: 80-85% N+: 60%
-

HIGH OR VERY HIGH RISK GROUP



REGIONAL RISK GROUP



Surgery / LND (vs. RT)

Australian Referral Patterns (High Risk Prostate s/p Prostatectomy)
1071 high risk prostate cancer s/p RP (2013-2015) with ≥ 1 high-risk pathological feature of ECE, SVI, SM+.
1^{O} outcomes were as follows: (i) referral to a radiation oncologist within 4 months after RP ('referred'); (ii) commencement of radiotherapy within 6 months after RP among those who consulted a radiation oncologist ('radiotherapy after consultation').

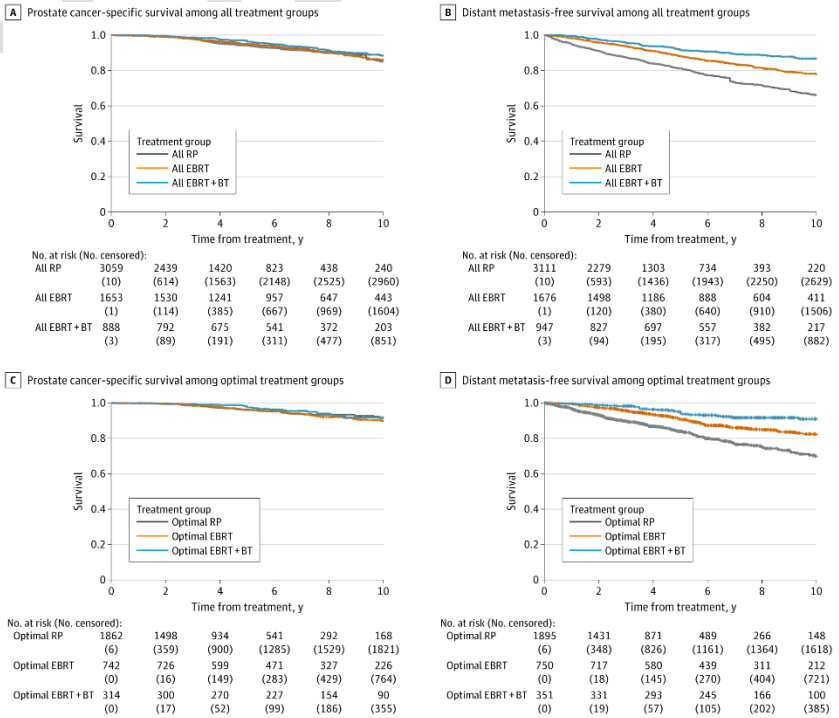
Egger, J Med Imaging and Rad Onc 2019.
325 (30%) of 1071 patients were 'referred'. 74 (61%) of 121 patients 'radiotherapy after consultation'.
Overall, the probability of receiving radiotherapy within 6 months after RP was 15%.
The probability of being 'referred' increased according to higher 5-year risk of cancer-recurrence (P < 0.001).
Conclusion Only 30% of patients with high-risk features are referred to a radiation oncologist with the likelihood of referral being influenced by the perceived risk of cancer-recurrence as well as the urologist's institutional/personal preference. When patients are seen by a radiation oncologist, 61% receive radiotherapy within 6 months after RP with the likelihood of receiving radiotherapy not being heavily influenced by increasing risk of recurrence. This suggests many suitable patients would receive radiotherapy if referred and seen by a radiation oncologist.

UCLA Pooled RT vs. Surgery Retrospective
6004 High Risk Prostate Ca (any GS5, cT3b-4, ≥ 50% core biopsy, or NCCN ≥ 2 high risk feature). TX between 2000-2014.
Treatments: 1. RP + adj TX (53%) 2. EBRT + ADT ≥ 2 years (30%) 3. EBRT + BT + ADT ≥ 1 year (17%).
Only about 50% of patients received "optimal" (addition of RT+ADT or RP+adjRT/ADT in GG5/LN+) care.

Kishan, JAMA 2021
5-year PCaSM (ALL)
5-year PCaSM ("Optimal") 3.4% vs. 3.3%, vs. 3.4% (NS).
Conclusions and Relevance These findings suggest that among patients with high-risk prostate cancer and additional unfavorable clinicopathologic features receiving guideline-concordant multimodal therapy, prostate cancer–specific mortality outcomes were equivalent among those treated with RP, EBRT, and EBRT with BT, although distant metastasis outcomes were more favorable among patients treated with EBRT and EBRT with BT. Optimal multimodality treatment is critical for improving outcomes in patients with high-risk prostate cancer.

Table 3. Competing Risk Models of Time Until Prostate Cancer-Specific Mortality and Distant Metastasis

Comparison	Subdistribution hazard ratio (95% CI)[a]	*P* value
All patients		
Prostate cancer specific mortality		
All EBRT vs all RP	0.78 (0.63-0.97)	.03
All EBRT+BT vs all RP	0.70 (0.53-0.92)	.01
All EBRT+BT vs all EBRT	0.89 (0.67-1.18)	.43
Distant metastasis		
All EBRT vs all RP	0.50 (0.44-0.58)	<.001
All EBRT+BT vs all RP	0.29 (0.23-0.36)	<.001
All EBRT+BT vs all EBRT	0.58 (0.46-0.73)	<.001
Optimal treatment		
Prostate cancer specific mortality		
Optimal EBRT vs optimal RP	0.76 (0.52-1.09)	.14
Optimal EBRT+BT vs optimal RP	0.86 (0.55-1.34)	.50
Optimal EBRT+BT vs optimal EBRT	1.13 (0.69-1.85)	.62
Distant metastasis		
Optimal EBRT vs optimal RP	0.48 (0.38-0.61)	<.001
Optimal EBRT+BT vs optimal RP	0.25 (0.16-0.37)	<.001
Optimal EBRT+BT vs optimal EBRT	0.52 (0.33-0.80)	.003



High Risk Pca **Limited vs. Extended LND**.
←R→ 300 patients intermediate- or high-risk clinically localized PCa.
| 1. LPLND (obturator nodes) | 2. EPLND (obturator, external iliac, internal iliac, common iliac, and presacral nodes) |.
1^{O} BcRFS.

Lestingi, Euro Urol 2020.
Median BRFS 61.4 mo vs. not reached (HR 0.91, p = 0.6). Median MFS was not reached in either group (HR 0.57, p = 0.3).
CSS data were not available because no patient died from PCa before the cutoff date.
In exploratory subgroup analysis, patients with preoperative biopsy International Society of Urological Pathology (ISUP) grade groups 3-5 who were allocated to EPLND had better BRFS (HR 0.33, 95% CI 0.14-0.74, interaction p = 0.007). The short follow-up and surgeon heterogeneity are limitations to this study.
Conclusion: This RCT confirms that EPLND provides better pathological staging, while differences in early oncological outcomes were not demonstrated. Our subgroup analysis suggests a potential BCRFS benefit in patients diagnosed with ISUP grade groups 3-5; however, these findings should be considered hypothesis-generating and further RCTs with larger cohorts and longer follow up are necessary to better define the role of EPLND during RP.

CALGB 90203
←R→ 788 high-risk (<60% chance of BPFS at 5 years per the Kattan Nomogram) prostate cancer | 1. RP alone | 2. ADT + docetaxel → RP |.
Docetaxel (75 mg/m2 body surface area every 3 weeks for 6 cycles).
ADT (18-24 weeks of an LHRH agonist or antagonist)
1^{o} 3-year BPFS. Biochemical failure = PSA > 0.2 ng/mL that ↑ on 2 consecutive occasions that were at least 3 months apart.

Eastham, JCO 2020. 6-year FU
Overall rates of grade 3 and 4 adverse events during chemotherapy were 26% and 19%, respectively.
3-year BPFS (0.89 v 0.84, NS).
Neoadjuvant CHT was associated with ↑ overall BPFS (HR 0.69; SS), ↑ MFS (HR 0.70; SS), and ↑ OS (HR 0.61; SS) compared with RP alone.
CONCLUSION The primary study end point, 3-year BPFS, was not met. Although some improvement was seen in secondary end points, any potential benefit must be weighed against toxicity. Our data do not support the routine use of neoadjuvant CHT and RP in patients with clinically localized, high-risk PC at this time.
Notes: 6% of the neoadjuvant arm and 11% of the surgery alone arm received adjuvant radiation ≤6 months post-op, and roughly half received salvage therapy >6 months post-op but before meeting the definition of the primary endpoint. When salvage therapy was counted as an event, median event-free survival was more than doubled with neoadjuvant therapy (4.5 years) versus without (1.8 years), and there were significantly fewer metastatic events. And while risk of death was technically lower after neoadjuvant therapy (HR 0.61), most mortality events were not related to prostate cancer.

AZ 2022

RT ± LT-ADT

"LONG ADT BOLLA" EORTC 22863 (1987-1995) -- RT +/- concurrent/adjuvant ADT x3 years
←R→. 415 patients with T1-4 (80% T3), GS 2-10 (40% not documented), PSA < 4 - > 40 (30%). N0-1 (N0 88%). | RT alone | RT + concur/adj goserelin |.
RT pelvis 50/25 + boost 20/10. Goserelin monthly starting on first day of RT, total of 3 years.
Remember, back in the day they did not have 3D conformality Eclipse. They used X-rays and carved out blocks.

Bolla, Lancet 2010. ALL RESULTS ARE SIGNIFICANT.
Outcome: 10 yr OS: RT+ADT 39.8% → 58.1% (SS). Clinical DFS: 22.7% → 47.7% (SS); PSA was not used routinely then.
Prostate cancer mortality: 30.4% → 10.3% (SS).
Cardiovascular toxicity: No difference between the 2 arms.

Increase benefit LOCAL and DISTANT table 2 Must add.

"Lifelong ADT non-bulky" RTOG 85-31
←R→ 977 high risk cT3 or pT3 or N1. | 1. XRT alone | 2. XRT + lifelong ADT | ADT= adjuvant goserelin (Zoladex) .
N+ regional nodes (including common iliac or paraaortics).
Bulky patients (primary tumor volume > 25 cm by product of two dimensions) not allowed unless +LN outside of the pelvis (i.e. common iliac or PA).
(Bulky pts were enrolled on parallel study 86-10.)
Hormones: Goserelin started during last week of XRT and continued monthly until progression.
Radiation technique: For patients with LN+ disease within the pelvis: upper border at L5/S1 interspace, lower border 5-6 cm below pubic symphysis, lateral borders for AP/PA 2cm lateral to pelvic brim. For positive common iliac nodes, extended up to L2/L3 interspace to include paraaortic nodes. For positive periaortic LN, extend to body of T11.
Dose: 65-70 Gy definitive. 60 Gy for post-op. 44-46 Gy to WPRT pelvic field followed by boost.

Pipepich, IJROBP 2005. 10-years. ALL RESULTS ARE SIGNIFICANT.
10-year OS 39% → 49% (SS) LF 38% → 24% (SS) DM 39%→ 24% (SS) bNED 9% → 31% (SS)
Conclusion: In unfavorable prognosis, adjuvant AST improves survival
The OS benefit REALLY COMES OUT in GS 7-10.

Table 3. Multivariate analysis results

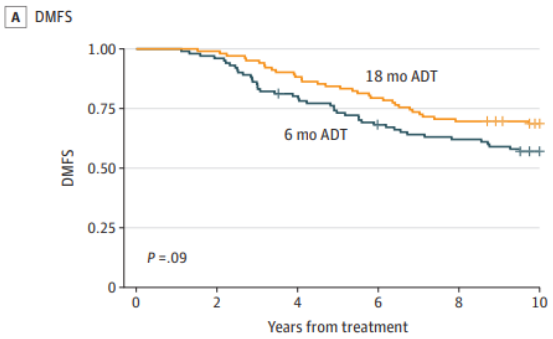
	Absolute survival		Local failure		Distant failure		NED survival (PSA <1.5 ng/mL)		Disease-specific death	
Variable	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Treatment (Arm I vs. Arm II)	1.3	0.001	1.9	<0.0001	1.9	<0.0001	2.2	<0.0001	1.7	0.0003
Prostatectomy (yes vs. no)	1.8	0.0004	3.4	NS	2.2	<0.0001	2.1	<0.0001	2.3	0.0005
Nodal involvement (no vs. yes)	1.6	<0.0001	NS	<0.0001	1.8	<0.0001	1.7	<0.0001	2.1	<0.0001
Central Gleason score (2–6 vs. 7–10)	1.7	<0.0001	1.5	0.0015	2.2	<0.0001	1.6	<0.0001	3.2	<0.0001
Age (<70 vs. ≥70 y)	1.5	<0.0001	NS	NS	NS	NS	1.3	0.0039	NS	NS
Clinical stage (A-B vs. C)	1.4	0.027	NS	NS	NS	NS	1.3	0.038	NS	NS

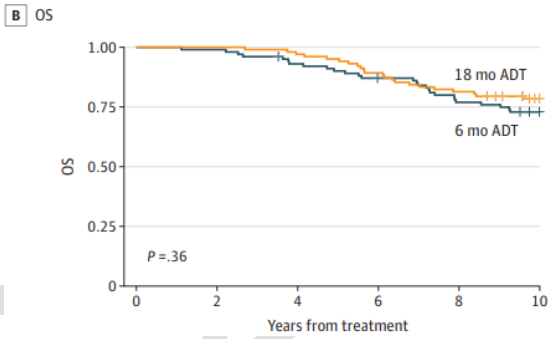
Lawton, JCO 2005 Subgroup pLN+ adenocarcinoma of the prostate.
98 RT + ADT (LHRH agonist) vs. 75 RT alone (with delayed) hormonal manipulation instituted at the time of relapse).
RESULTS: Median follow-up of 6.5 years for all patients and 9.5 years for living patients.
5-year PFS 54% vs. 10% (SS). 9-year PFS 33% vs. 4% (SS).
MVA revealed RT + immediate ADT SS impact on all end points analyzed: absolute survival, disease-specific failure, metastatic failure, and biochemical control with PSA less than 4 ng/mL and less than 1.5 ng/mL.
CONCLUSION: Pending the results of randomized trials, patients with adenocarcinoma of the prostate who have pathologically involved pelvic lymph nodes (pathologic node-positive or clinical stage D1) should be considered for external-beam irradiation plus immediate hormonal manipulation rather than radiation alone with hormone manipulation at the time of relapse.

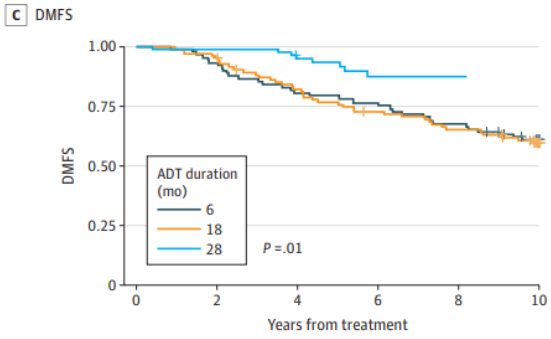
ADT Duration Trials

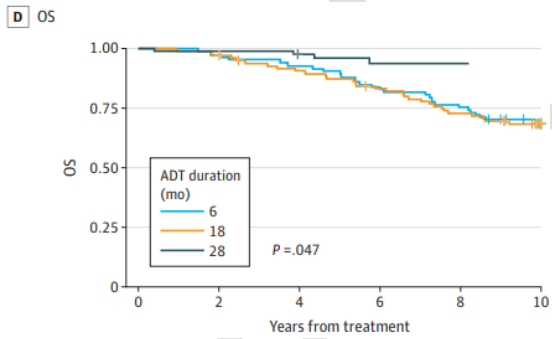
Combined 3 Study HR-PCa 18 mo Cutoff Study
Cohorts 3410 men of 3 studies (←R→ DART, post-hoc RADAR, and RR).
High-dose EBRT or EBRT+BT for an ADT duration determined by patient-physician choice (retrospective) or by randomization (RCTs).
1^{O} DMFS.

Kishan, JAMA Network 2022.
A+B Unadjusted Kaplan-Meier curves for DMFS and OS for EBRT+BT on RADAR (6 vs. 18 months of ADT).
C+D Adjusted survival curves for DMFS and OS for the cross-trial comparison RADAR (6-mo, 18-mo ADT) and DART (28 months).
Conclusions and Relevance These cohort study findings suggest that the optimal minimum ADT duration for treatment with high-dose EBRT alone is more than 18 months; and for EBRT+BT, it is 18 months or possibly less. Additional studies are needed to determine more precise minimum durations.









"Dose Escalated" **DART** 01 / 05 GICOR (Spanish Trial). 4 months ± 2 years ADT (YES dose escalated) ALL RESULTS ARE SIGNIFICANT.
←R→ 355 cT1c–T3b N0M0 with int (45%) / high-risk (55%) factors. PSA = all range even (none > 100); GS 7 or T2, = 60%.
| 1. four mo. (2 NA + 2 C) ADT w/ 3DCRT 76-82 Gy | same treatment → 24 months of adjuvant ADT |.
4 months of neoadjuvant and concomitant androgen deprivation with subcutaneous goserelin (2 mo before and 2 mo. with high-dose RT).
Anti-androgen therapy (flutamide 750 mg per day or bicalutamide 50 mg per day) was added during the first 2 mo. of treatment.
Long term ADT = continued luteinising hormone-releasing hormone analogue every 3 months for another 24 months.
1^{O} endpoint was biochem DFS.

Zapatero, Lancet Oncology 2015. 5 year follow up.
5-year biochemical DFS ↑ with LT ADT vs ST ADT: 81% → 90%, SS.
OS 86% → 95%, SS. MetFS 83% → 94%, SS.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTAD (n=177)					
Rectal	39 (22%)	18 (10%)	3 (2%)	0	0
Urinary	32 (18%)	13 (7%)	3 (2%)	2* (1%)	0
STAD (n=178)					
Rectal	35 (20%)	13 (7%)	2 (1%)	0	0
Urinary	31 (17%)	12 (7%)	4 (2%)	1* (<1%)	0

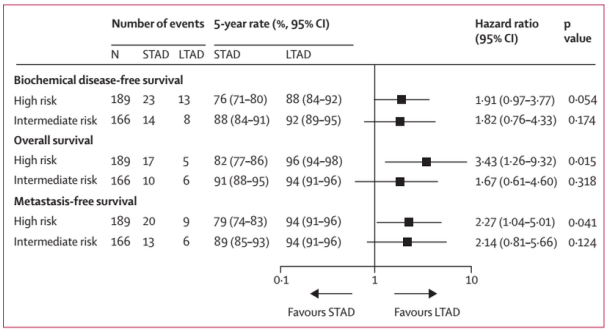


Figure 3: **Effects of duration of androgen deprivation stratified by risk group**
STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation.

An unexpected finding of our trial was that almost 5 times as many patients died of cancers other than of the prostate in the short-term androgen deprivation group than in the long-term androgen deprivation group. We cannot provide a satisfactory explanation for this finding, although we do recognize its potential effect on the interpretation of the results. An association between the hormonal environment, immune tolerance, and the immune response to cancer cannot be excluded.
Criticism: 63 months follow up. Short follow up. Also small sample size. ∴ cannot say enough about intermediate risk. Not long enough and not enough patients.

Zapatero, IJROBP 2016
5-year grade ≥2 rectal and urinary toxicity was 11.1% and 8.2% for LTAD and 7.6% and 7.3% for STAD, respectively.
Risk of late grade ≥2 rectal toxicity (NS) between LTAD vs. STAD.
Long-term AD (HR 2.090; SS) and a history of MI (HR 2.08, SS) were significantly correlated with a higher probability of CV events.
CONCLUSION: Long-term AD did not significantly impact urinary or rectal radiation-induced toxicity, although it was associated with a higher risk of cardiovascular events. Longer follow-up is needed to measure the impact of AD on late morbidity and non-PCa mortality.

Non-Linear ADT RR. Williams, IJROBP 2011.
RR 3,666 PCa ADT + EBRT or EBRT alone. The primary endpoint was time to biochemical failure (nadir plus 2 ng/ml), assessed from the end of therapy.
RESULTS: ↑ ADT duration was nonlinear. 6 mo ADT ↓ RR bR 38% vs. 12 mo ↓ 58% vs. 24 mo ↓ 66% vs. 36 mo ↓ 66%.
Higher T stage cancers and those treated with lower radiation doses had a significantly greater benefit for increasing ADT duration (SS).

"2+2=4" **RTOG 92-02**. -- 4 months ± 2 years ADT (NON-dose escalated)
←R→. 1554 patients with locally advanced PCA. T2c-T4 (T2 45%, T3 50%); PSA < 150 (PSA ≤ 30 in 67%), allowed N+ (N+ 4%, Nx 87%) but excluded LN+ at common iliac or higher chains. Goserelin 3.6 mg SC qM + flutamide 250 mg TID for 2 months before and 2 months during XRT.
THEN | 1. Observation (ST-ADT) | 2. Two years of goserelin (LT-ADT) |. XRT WPRT pelvis 45 Gy, followed by a boost to 65-70 Gy.

Hanks, JCO 2003. Median F/U 5.8 year.
Results: 5-year DFS ST-AST 28% vs. LT-AST 46% (SS); LR 12% vs. 6% (SS); OS 78% vs. 80% (NS)
Subset analysis (GS 8-10): OS ST-AST 71% vs LT-AST 81% (SS); all other points also (SS
Conclusion: Long-term ADT improves DFS over short-term ADT, survival benefit for GS 8-10 subset

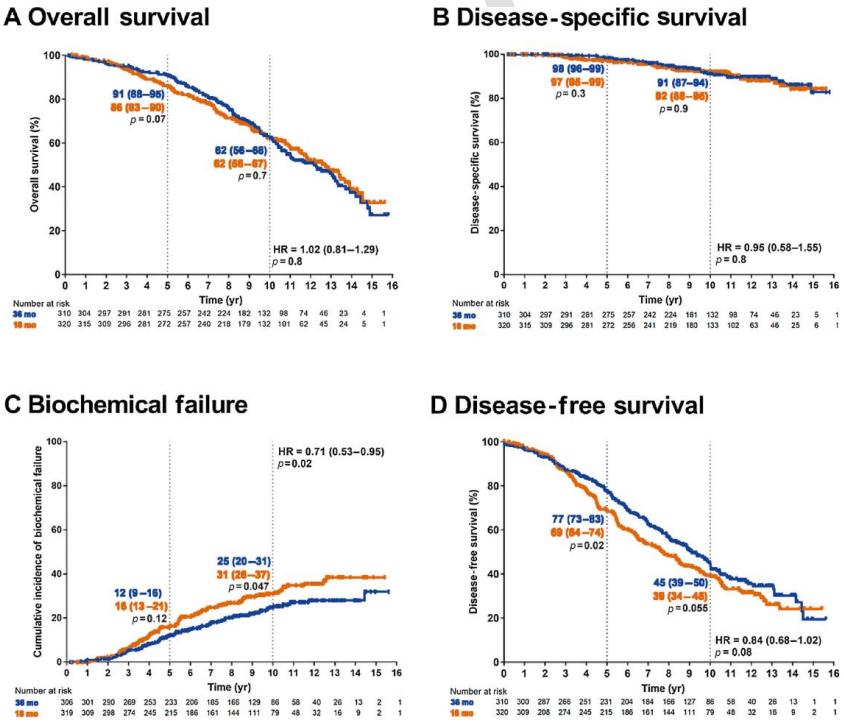
Horwitz, JCO 2008. Median F/U 11.3 years
Results: 10-year DFS ST-ADT 13% vs. LT-ADT 22% (SS), DSS 84% vs. 89% (SS), LR 22% vs. 12% (SS); OS 52% vs. 54% (NS)
Subset analysis (GS 8-10): OS ST-AST 32% vs. LT-AST 45%; all other points also SS.
Conclusion: LT-ADT is superior to ST-ADT for DFS; not powered for OS. On subgroup analysis, GS 8-10 has survival advantage

"ADT Non-Inferiority Bolla" EORTC 22961. -- AST 6 months vs. AST 3 years (Concurrent ± adjuvant)
←R→ Non-inferiority trial trying to see if 6 months is as good as 3 years. 970 men.
Locally advanced prostate cancer (T1c-T2b pN1-N2 M0 or cT2c-T4 N0-N2 M0), PSA up to 40x normal, Hb >10.
3D-CRT pelvis 50 Gy + prostate boost 70 Gy. AST 6 months (complete androgen blockade) initiated 1st day of RT.
Flutamide / bicalutamide 1 week before and then for 3 months after. +/- 3 years after.
If no progression | 1. observation | 2. AST 3 years (LHRH triptorelin) |. 72% completed full 3 years. Median F/U 6.4 year.

Bolla, NEJM 2009. Closed early. Futility. ALL RESULTS ARE SIGNIFICANT.
Results: 5-year OS 6-months 81% vs. 3-years 85% (HR 1.4, SS) 5-year CSS 95% vs. 97% (HR 1.7, SS). 5-year bPFS 59% vs. 78% (SS).
Toxicity: Hot flashes 29% vs. 39% Gynecomastia 7% vs. 18% (SS). Incontinence 10% vs. 18% (SS).
Quality of life comparable between arms. No difference in fatal cardiac events (4% vs. 3%).
Conclusion: Combination of RT + 3 years AST provides superior EVERYTHING to 6-month AST in locally advanced cancer
Note: This was designed as a non-inferiority trial.

"Intermediate Risk" RTOG 99-10
←R→ 1579 INTERMEDIATE RISK | 1. EBRT + ADT (neo 2 + concurrent 2) months | 2. EBRT + ADT (7 + 2) | 85% int 15% high risk.

Pisansky, JCO 2015. ALL RESULTS NEGATIVE.
10-year bFreedom 73% (NS) 10-year CSS 95-96% (NS) 10-year OS 66-67% (NS).



PCS IV (Canadian Phase III)
←R→ 630 high risk patients with prostate RT + PELVIS RT
| 1. 3-year ADT | 2. 1.5-year ADT |.
1°OS and QoL were primary end points.

Nabid, Eur Urol 2018.
5-yr OS rates 91% vs. 86% (NS).
QoL SS (p<0.001) in six scales and 13 items favoring 18 mo ADT with two of them presenting a clinically relevant difference in mean scores of ≥10 points.

18 MONTHS HAD WORSE BIOCHEMICAL FAILURE (SS).
10-year biochemical failure rate 25% vs. 31% (p=0.047)

CONCLUSIONS: In localized HRPC, our results support that 36 mo is not superior to 18 mo of ADT. ADT combined with RT can potentially be reduced to 18 mo in selected men without compromising survival or QoL. Thus, 18 mo of ADT appears to represent a valid option in HRPC.

CRITICISM: NOT designed as non-inferiority. Median age is 71. Caution against applying this to younger patients. 36 month completion was only 53% compared to 88% at 18 months. RT was only 70 Gy, NOT dose escalated.

Brachy Boost

Morton, J Contemp Brachytherapy 2014 Summary Table 1.

Author	*N*	Median; follow-up (months)	Late grade 3 toxicity		bDFS by risk group			Dose/fraction (EBRT + HDR) in Gy
			GU	GI	Low	Intermediate	High	
Agoston [25]	100	62	14%	2%		84%	82%	60/30 + 10/1
Aluwini [26]	264	75	4%	1%	97%			45/25 + 18/3
Bachand [27]	153	44				96%		44/22 + 18/2-20/2
Cury [28]	121	63	2%	2%		91%		50/20 + 10/1
Deutsch [29]	160	53			100%	98%	93%	50.4/28 + 21/3
Galalae [30]	122	117	5%	3%	88%	71%	72%	50/25 + 18-30 Gy*/2
Ghadjar [31]	64	61	14%	0%		100%	91%	50/25 + 21/3
Kaprealian [32]	64 101	105 43	1%	0%		84% 94%	80% 82%	45/25 + 18/3 45/25 + 19/2
Khor [33]	344	61	2%	0%		84%	74%	46/23 + 19.5/3
Kotecha [34]	229	61	5%	0.4%	95%	90%	57%	50.4/28 + 16.5-22.5/3
Lilleby [35]	275	44				100%	98.8%	50/25 + 20/2
Marina [36]	282	96				91%		46/23 + 19-23 Gy/2
Martínez-Monge [37]	200	44	5%	2%			85%	54/27 + 19/4
Morton [38]	60 123	72 45	4% 1%	0% 0%		98% 95%		45/25 + 20/2 37.5/15 + 15/1
Neviani [39]	455	48	8%	1%	92%	88%	85%	45/25 + 16.5/3-21/3
Pellizon [40]	209	64			92%	90%	89%	45/25 + 20/2
Phan [41]	309	59	4%	0.3%	98%	90%	78%	36/18-50.4/28 + 15/3-26/4
Pistis [42]	114	32					97%	60/30 + 10/1
Prada [43]	313	68	2%	0%	100%	88%	79-91%	46/23 + 23/2
Savdie [44]	90	95					80%	45/25 + 16.5/3
Whalley [45]	101	56	2%	0%		95%	66%	46/23 + 19.5/3-17/2
Zwahlen [46]	196	66	7%	0%		83%		46/23 + 20/4-18/3

**30 Gy to peripheral zone, 18 Gy to anterior prostate.*

Summary of studies showing freedom from biochemical relapse after high dose rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT), according to risk group

Reference	Dose schedule	No. of patients	Low risk (%)	Intermediate risk (%)	High risk (%)	End point (years)
Aström et al [34]	EBRT: 50 Gy @ 2 Gy per fraction HDR: 2×10 Gy per fraction	214	100	100	86	4
Flynn et al [38]	NAHT: 86% EBRT: 45 Gy @ 1.8 Gy per fraction HDR: 15.5–21.0 Gy in 3 or 4 fractions	674	97	92	72	5
Galalae et al [33]	EBRT: 45.6–50.0 Gy @ 1.8–2.0 Gy per fraction HDR: BED 79.6–123.0 Gy	611	96	88	69	5
Galalae et al [39]	NAHT: 0% BED: ≤94 Gy *vs* >94 Gy	324	–	85	81	5
Guix et al [41]	EBRT: 46–66 Gy @ 2 Gy per fraction HDR: 2×5–8 Gy	445	–	95	94	5
Izard et al [43]	NAHT: median 6 months EBRT: 45.0–59.4 Gy @ 1.8 Gy per fraction PDR BRT: 18 Gy in 3 fractions	165	100	95	67	5
Martinez et al [44]	NAHT: no HDR: 5.5–11.5 Gy per fraction	207	–	85	75	5
Phan et al [46]	NAHT: 36% EBRT: 36.0–50.4 @ 1.8–2.0 Gy per fraction HDR: 22–24 Gy	309	100	100	97	5

Brachytherapy doses using Iodine-125 are as follows 145 Gy as monotherapy 110 Gy as a boost dose following external beam radiation.
Brachytherapy doses using Palladium-103 are as follows 125 Gy as monotherapy 90-100 Gy as a boost dose following external beam radiation.

An ideal LDR prostate implant should have a D90(the dose that covers 90% of the volume of the CTV) larger than the prescription dose (D90> 100% of prescription dose). As well, V100 (the percentage of the CTV that receives at least the prescribed dose) must be at least 95% (V100> 95% of CTV). The V150 (the percentage of the CTV that receives at least 150% of the prescription dose), should be equal to or less than 50% (V150≤50% of CTV). For the rectum, the D0.1cc should be < 150% of reference prescription dose.

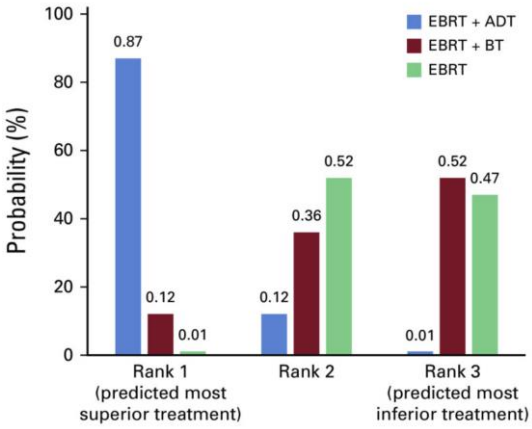
1 fraction HDR boost. Helou, Radiotherapy and Oncology 2015.
Results of 2 sequential phase II trials: 1. Single 15 Gy HDR-boost → EBRT 37.5 Gy / 15 fx 2. Two HDR fx of 10 Gy → EBRT 45 Gy/25.
Results: n = 183 patients were accrued; 1. N=123, 2. N= 60. 5 year bRFS 97.4% and 92.7%, respectively (p = 0.995). Median nPSA was 0.08 ng/ml. Failure to achieve a nPSA <0.4 ng/ml was associated with a significantly higher rate of biochemical relapse (5-year bDFS: 100% vs. 72%; p < 0.0001).
Conclusion: HDR boost with single fraction 15 Gy provides durable long-term biochemical disease-free survival. PSA nadir <0.4 ng/ml is associated with very low risk of biochemical failure.

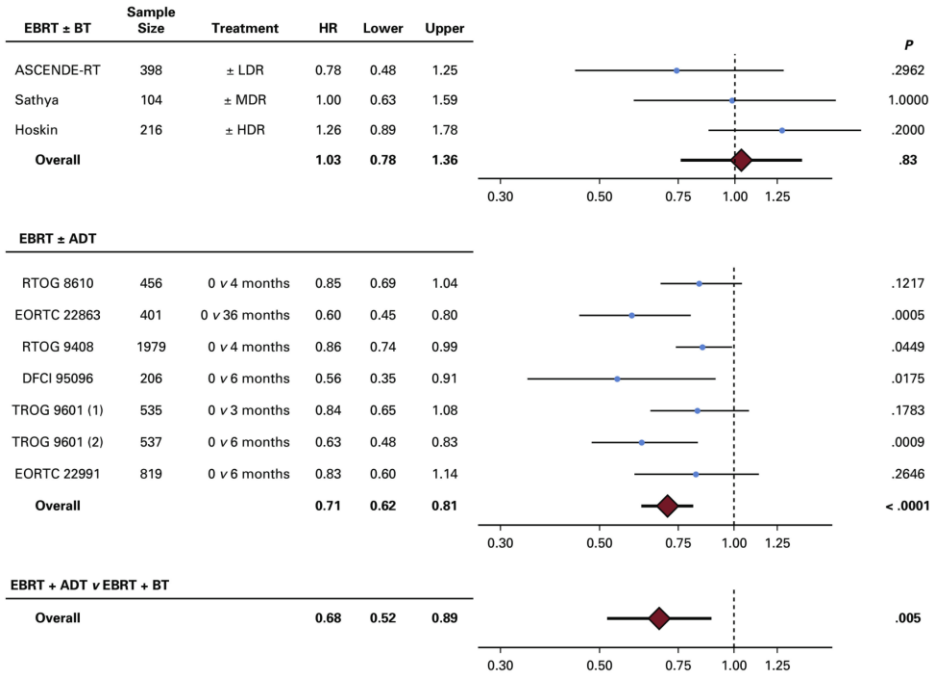
THEPCA Sequencing Trial
←R→ 100 intermediate/high risk localized prostate cancer = NAC + Adj Hormones (LT-ADT 2 years) + | 1. HDR → EBRT | 2. EBRT → HDR |.
Radiation: HDR boost 15Gy + EBRT 46Gy in 23 fractions. Median IPSS 6.6.

Ahmed, JCO 2021.
1-year Grade 1 GU 22.88% vs. 19.36% (NS). 1-year Grade 2 GU 5.28% vs. 2.64% (NS).
1-year Grade 1 GI 21.2% vs. 23.76% (NS) 1-year Grade 2 GI 5.28% vs 3.52% (NS).
Baseline mean IIEF scores were 10.9 and 10.53 in Arm A and B respectively.
The PTV, CTV & OAR dose were compared and no significant differences were found.
Conclusions: There were no significant differences in GI and GU related toxicities up to a year between patients receiving HDR brachytherapy before or after EBRT. There were no grade 3 or 4 toxicities. Treatment was well tolerated in both arms with good QOL scores. Longer follow up and a phase III multicenter RCT would be needed to validate findings

Meta-analysis EBRT ± 1. ADT or 2. BT
←M→ 6 trials EBRT ± ADT (4663) and 3 trials EBRT ± BT (718).

Jackson, JCO 2020
OS ADT ↑ HR 0.71, SS
BT ←→ HR 1.03, NS





Conclusion: Our findings suggest that current practice patterns of omitting ADT with EBRT plus BT may result in inferior OS compared with EBRT plus ADT in men with intermediate- and high-risk prostate cancer. ADT for these men should remain a critical component of treatment regardless of radiotherapy delivery method until randomized evidence demonstrates otherwise.

ASCENDE-RT Asco GU 2015 trial. Morris ASCO GU 2015.
Inclusion criteria: high (69%) and intermediate (31%) risk patients having a total of 12 mo ADT LHRH agonist + at least 1 mo nonsteroidal antiandrogen.
Randomization: After 8 mo of neoadj ADT, pelvis EBRT (46 Gy, 23 fx). → 1. DE-EBRT boost (32 Gy, 16 fx) or 2. LDR-B (I-125 to min peripheral tx 115 Gy).
Exclusion criteria: PSA > 40, clinical stage T3b or higher, prior TURP, prostate volume greater than 75cm3, and inability to tolerate anesthesia.
Randomization (p<0.001), % positive cores (p=0.005), initial PSA (p=0.006) and clinical T-stage (p=0.013) were predictive RFS multivariable Cox model.
The median PSA at latest FU for non-relapsing patients assigned to LDR-B is 0.02 vs 0.24 ng/mL for DE-EBRT.

Rodda, IJROBP 2017.
Results: Relapse free survival (RFS): 3, 5, 7, 9. | EBRT vs. LDR | 94%, 77%, 71%, 63% | 94%, 89%, 86%, 83% (p=0.001).
The LDR-PB boost increased the risk of needing temporary catheterization and/or requiring incontinence pads.
5-year G3 GU total incidences 18.4% for LDR-PB vs. 5.2% for DE-EBRT (P<.001).
5-year G3 GU morbidity was 8.6% vs 2.2%, (P=.058).
5-year G3 GI total incidence 8.1% for LDR-PB, versus 3.2% for DE-EBRT (P=.124).
Among men reporting adequate baseline erections, 45% of LDR-PB similar erectile function at 5 years, versus 37% after DE-EBRT (P=.30).
Conclusion: 1st paper to show that brachytherapy boost is beneficial for int-high risk patients.
NO OVERALL SURVIVAL BENEFIT.

RTOG 02-32. 1^{O} = PFS.
←R→ 588 T1c-N2b. GS 6 + PSA 10-20 or GS 7 + PSA < 10. | 1. Brachytherapy alone | 2. 45 Gy to pelvic area + Brachy boost |.
Boost Brachy = I-125 (110 Gy) or Pd-103 (100 Gy). Brachy = 145 Gy or 125 Gy. 45 Gy EBRT = IMRT or 3D CRT.

Prestige, ASTRO press release 2016
5-year PFS 86% vs 85%.
Overall toxicity acutely was similar for grade ≥3 (8%).
Late toxicity more common for combined: G2 (37% vs. 52%) and G3 (7% vs. 12%) were more for combined (SS).

Mount Vernon, UK.
←R→ 106 patients, T1-3 M0 (T3 26%), PSA < 50. | 1. EBRT 55 Gy = 2.75 x 20 | 2. EBRT 35.75 = 2.75 x 13 + HDR 17/2 |. ADT 76%

Hoskin, Radiother Oncol. 2020.
Median time to relapse was 82 vs. 137 months (p = 0·01).
A 27% risk of recurrence with EBRT alone was observed (p = 0·001), resulting in a 21% improvement in RFS at 12 years with EBRT + HDR-BTb.
MVA, risk category and no androgen deprivation therapy were significant covariates for risk of relapse.
Differences in overall survival were not significant.
Conclusion: At 12 years there remains a significant improvement in RFS after EBRT + HDR-BTb; both treatments were equitoxic for severe late urinary and bowel events and urethral strictures.

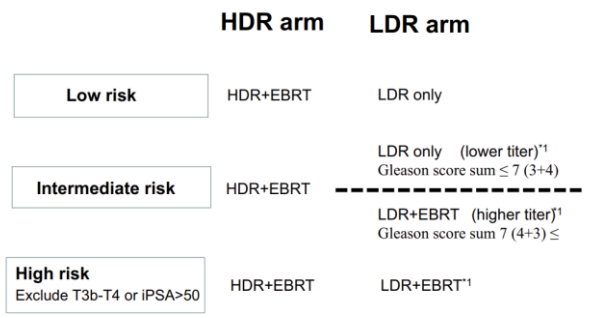
RTOG 00-19. Phase II. EBRT + I-125 Permanent Boost of 108 Gy.
138 men intermediate risk PSA 10-20, GS <7 or PSA < 20 GS 7.
45 EBRT → 108 Gy I-125 brachy.

Lawton, IJROBP 2012. 8-year FU
8-year late grade >3 genitourinary and/or gastrointestinal toxicity was 15%.
Most common grade >3 toxicities were urinary frequency, dysuria, and proctitis.
There were two grade 4 toxicities, both bladder necrosis, and no grade 5 toxicities.
In addition, 42% of patients complained of grade 3 impotence (no erections) at 8 years.
The 8-year estimate of biochemical failure was 18% and 21% by the Phoenix and ASTRO consensus definitions, respectively.

Conclusion: Biochemical control for this treatment seems durable with 8 years of follow-up and is similar to high-dose external beam radiation alone or brachytherapy alone. Late toxicity in this multi-institutional trial is higher than reports from similar cohorts of patients treated with high-dose external-beam radiation alone or permanent low-doserate brachytherapy alone, perhaps suggesting further attention to strategies that limit doses to normal structures or to unimodal radiotherapy techniques.

RT 2022

"Old Unbalanced 3D-CRT Era" Japanese RR HDR + EBRT vs. LDR ± EBRT
RR 924 patents | 1. HDR-BT + EBRT | 2. LDR-BT ± EBRT |.
Non-Randomized. RT was 3D-CRT (IMRT only < 2%).
LDR: Prostate CTV 145 Gy (LDR-BT alone) or 110 Gy (LDR-BT with 40 Gy/ 20 fx EBRT).
HDR: Median dose HDR 31.5 Gy (11–31.5 Gy) and that of EBRT was 39 Gy (39–51 Gy).
Excluded patients with T3b-4 disease/ initial PSA > 50 ng/ml.



Yamazaki, Sci Rep 2021.

5-year BcNED	All	96.3% vs. 95.7%.
5-year BcNED	Low Risk	100% and 96.5%
	Int Risk	97.4% and 97.1%
	High Risk	95.7% and 94.9%

5-year BcNED	HDR-BT+EBRT	96.3%
	LDR-BT+EBRT	95.5%
	LDR-BT alone	97%

Acute grade ≥2 GU toxicities were ↑ in the LDR-BT group (42.2%) than in the HDR-BT group (9%, P<0.0001).
Late grade 3 GU "obstruction" were ↑ in the HDR-BT group (6.1%) than in the LDR-BT group (0.6%).
"It would be interesting to know if the higher rate of grade 3 late GU obstruction in the HDR-BT with EBRT group was mainly due to simple strictures that were easily dilated; this is a problem related to the toxicity grading system."

Variables	Strata	HDR-BT n = 924			LDR-BT n = 500		P value
		No. or Median (range)	(%)		No. or Median (range)	(%)	
Age		71 (47–86)			69 (45–83)		**0.0029**
T category	1	228	(25%)		241	(48%)	**< 0.0001**
	2	379	(41%)		245	(49%)	
	3	317	(34%)		14	(3%)	
iPSA	ng/ml	12 (2.682–50)			7(1.4–46)		**< 0.0001**
Gleason score	-6	11	(1%)		284	(57%)	**< 0.0001**
	7	236	(26%)		193	(39%)	
	8-	382	(41%)		23	(5%)	
NCCN risk classification	Low	11	(1%)		200	(40%)	**< 0.0001**
	Intermediate	269	(29%)		259	(52%)	
	High	644	(70%)		41	(8%)	
Prescribed dose	11 Gy / 1fr + EBRT 45 Gy /15 fr or 51 Gy /17fr	145	(16%)	110 Gy + EBRT (40 Gy / 20fr)	69	(14%)	NA
	18 Gy / 2 fr + EBRT 39 Gy /13 fr or 51 Gy / 17fr or 48 Gy/16fr	233	(25%)	145 Gy	431	(86%)	
	20 Gy / 2fr + EBRT 30 Gy /15 fr or 46 Gy /23fr	13	(1%)				
	21 Gy / 3fr or 21 Gy /2 fr + EBRT 51 Gy / 17 fr or 45 Gy /15fr or 42 Gy/14fr	54	(6%)				
	25 Gy / 5fr + EBRT 51 Gy /17 fr	5	(1%)				
	31.5 Gy / 5fr + EBRT 30 Gy /10fr	468	(51%)				
Hormonal therapy	Yes	872	(94%)		399	(80%)	**< 0.0001**
Neoadjuvant	Months	10 (1–89)			6 (1–24)		
Adjuvant	Months	36 (1–93)			3 (1–19)		
	No	52	(6%)		101	(20%)	
Follow-up	Months	70 (2–177)			84 (17–148)		**< 0.0001**

Toxicities	Grade	HDR-BT n = 924		LDR-BT n = 500		P-value	LDR-BT alone n = 431		LDR-BT plus EBRT n = 69		P-value
		No	(%)	No	(%)		No	(%)	No	(%)	
(a) Acute toxicity											
Gastrointestinal	0	827	(90%)	436	(87%)	0.4588	388	(90%)	48	(70%)	* < 0.0001
	1	94	(10%)	62	(12%)		43	(10%)	19	(28%)	
	2	2	(0.2%)	2	(0.4%)		0	(0%)	2	(3%)	
	3	1	(0.1%)	0	(0%)		0	(0%)	0	(0%)	
Genitourinary	0	340	(37%)	37	(7%)	< 0.0001	33	(8%)	4	(6%)	0.8915
	1	499	(54%)	252	(50%)		218	(51%)	34	(49%)	
	2	82	(9%)	210	(42%)		179	(42%)	31	(45%)	
	3	3	(0%)	1	(0.2%)		1	(0%)	0	(0%)	

Toxicities	Grade	HDR-BT n = 924		LDR-BT n = 500		P-value	LDR-BT alone n = 431		LDR-BT plus EBRT n = 69		P-value
		No	(%)	No	(%)		No	(%)	No	(%)	
(b) Late toxicity											
Gastrointestinal	0	766	(83%)	446	(89%)	0.0142	396	(92%)	50	(72%)	* < 0.0001
	1	130	(14%)	46	(9%)		31	(7%)	16	(23%)	
	2	27	(3%)	8	(2%)		4	(1%)	3	(4%)	
	3	1	(0.1%)	0	(0%)		0	(0%)	0	(0%)	
Genitourinary	0	418	(45%)	202	(40%)	< 0.0001	176	(41%)	26	(38%)	0.7413
	1	361	(39%)	215	(43%)		182	(42%)	33	(49%)	
	2	87	(9%)	78	(16%)		68	(16%)	10	(15%)	
	3	58	(6%)	5	(1%)		5	(1%)	0	(0%)	

Opinion: Even in the era of non-dose escalated 3D-CRT, HDR is an excellent option that is as good (if not better) as LDR since as it can not only provide excellent BcNED for a higher-risk patient population, but also offer less acute and long-term side effects (particularly GU).

Brachy Boost ± ADT

General Notes:

1. Generally, historical and retrospective studies have suggested that Brachytherapy may obviate the need for ADT.
    a. Cleveland Clinic Data 2020 showed that across all subgroups, ADT was NOT beneficial.
2. Contemporary prospective studies suggest that ADT can be beneficial.
    a. MARCAP showed that with a 12-year follow-up, ADT (when added to RT) ↑ 12-year OS abs 7.2%. This was irrespective of RT dose.
    b. TROG RADAR 03.04 → addition for LT-ADT over ST-ADT in LA-PCa patients getting either EBRT or combined EBRT + Brachy bst, there is a ↑ OS.
    c. RTOG 08-15 → addition of ADT improved BCF rates and DM across subgroups regardless of RT (EBRT 79.2 Gy or EBRT 45 Gy + HDR/LDR boost).
    d. HDR/LDR boosts do not improve any survival outcomes. However, ADT trials nearly always shows a survival benefit. Choosing BT over ADT can be seen as choosing a worse oncologic outcome of the two. ASCENDE-RT shows that giving both ↑ toxicity.

Historical Studies:

Cleveland Clinic Single Institution
2705 men all I-125 LDR brachytherapy monotherapy → 756 (50%) favorable-IR vs. 754 (50%) unfavorable-IR.

Tom, Brachytherapy 2020.	Median follow up was 48 months.		
5-year BcF 4.3% vs. 17.0% (SS)	5-year DM 1.6% vs. 5.4% (SS).		
HR for BcF (vs. UnF-I)	Patients with only 1 UnF-Risk Factor	HR 2.27	SS
	Patients with 2-3 UnF-Risk Factors	HR 4.42	SS.
HR for DM (vs. UnF-I)	Patients with only 1 UnF-Risk Factor	HR 2.46	SS
	Patients with 2-3 UnF-Risk Factors	HR 4.76	SS.

Conclusions These findings validate the prognostic utility of the 2019 NCCN favorable-IR and unfavorable-IR prostate cancer subgroups among men treated with brachytherapy. Androgen deprivation was not beneficial in any subgroup. Alternative treatment intensification strategies for unfavorable-IR patients are warranted.

HDR Boost Study
Prospective 611 patients in 3 prospective trials of EBRT + HDR Boost
177/611 received a ST-ADT (neoadjuvant/concurrent ADT).
Patients were divided into three risk groups.
Group I (n=46) ≤ T2a, GS ≤6, PSA ≤10 ng/mL.
Group II (n=188) ≥ T2b, GS ≥ 7, PSA ≥ 10, with any one factor higher.
Group III (n= 359) Any two risk factors higher.
EBRT (45-50 Gy) to prostate, SV, and pelvic LN + HDR boost (2-4 fx) during EBRT.

Table 2. Actuarial analysis at 5 years by risk factors groups

Endpoint	All (n = 593)	Group I (n = 46)	Group II (n = 188)	Group III (n = 359)
OS	85%	88%	86%	85%
CSS	96%	100%	99%	95%
BC	77%	96%	88%	69%
DFS	67%	83%	75%	61%
LR	7.4%	0%	3.5%	10%

Abbreviations: BC = biochemical control; CSS = cause-specific survival; DFS = disease-free survival; LR = local recurrence; OS = overall survival.

Galalae, IJROBP 2004. FU 5 years.
5-year BcC 77%. 10-year BcC 73%
5-year DFS 67% 10-year DFS 49%
5-year CSS 96% 10-year CSS 92%r
5-year BcC 96% vs. 88% vs. 69%.
5-year CSS 100% vs. 99% vs. 95%.
In univariate and multiple regression analyses for BC, risk group, stage, iPSA, and GS were significant in predicting failure.
However, age, follow-up interval, and ADT did not.

Conclusions: EBRT with HDR-BT produced excellent long-term outcomes in terms of BC, DFS, and CSS in patients with prostate cancer even for those at highest risk. Conformal HDR-BT is both a precise dose delivery system and an effective treatment for both favorable and unfavorable prostate cancer. The addition of a short course of neoadjuvant/concurrent ADT failed to improve outcome. The results were similar at all three institutions, giving credence to the reproducibility of the brachytherapy treatment.

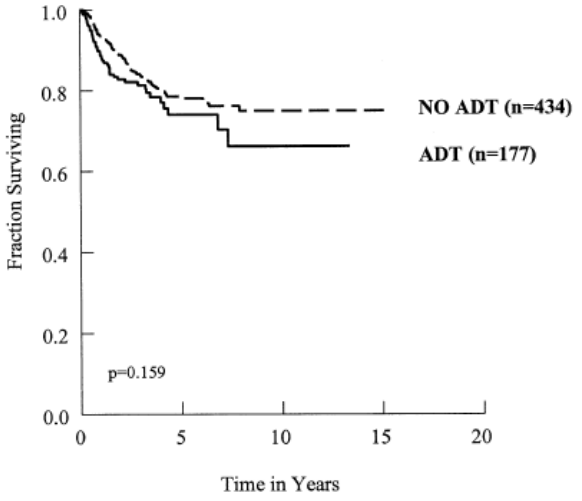


Fig. 3. Actuarial analysis of biochemical control of all patients stratified by ADT.

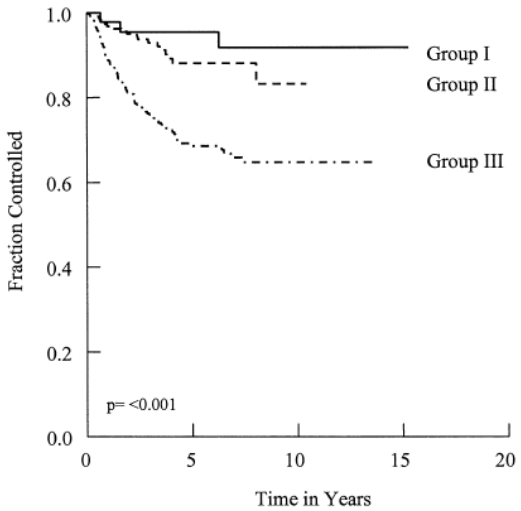


Fig. 4. Actuarial analysis of biochemical control stratified by risk groups.

Strom, Int Braz J Uro 2014. 5.2 years
120 patients EBRT 45 Gy + Pd-103 LDR boost to 100 Gy or I-125 LDR to 110 Gy. ADT = GnRH ± anti-androgen given to 29/92 (32%) intermediate-risk patients for a median duration of 4 months and 26/28 (93%) high-risk patients for a median duration of 28 months.
Results: NS (bDFS), distant metastasis-free survival (DMFS), or overall survival (OS) without or with ADT.
NS bDFS, DMFS, or OS with a palladium-103 vs. an iodine-125 LDR brachytherapy boost.
CONCLUSIONS:
There was no statistically-significant difference in outcomes with the addition of ADT, though the power of the current study was limited. The Radiation Therapy Oncology Group 0815 and 0924 phase III trials, which have accrual targets of more than 1,500 men, will help to clarify the role ADT in locally-advanced prostate cancer patients treated with EBRT and a brachytherapy boost. Palladium-103 and iodine- 125 provide similar bDFS, DMFS, and OS.

ADT ± Chemotherapy

D'Amico Docetaxel Trial
←R→ 350 prostate Ca T1c-4N0M0 unfavorable-risk | 1. RT + ADT + plus docetaxel | 2. RT + ADT |.
RT = P/SV given 1.8 Gy x 39 = 73.7 Gy normalized to 95%/95% (70.2 Gy).
ADT = LHRH agonist and antiandrogen were given for 2 months prior to radiation, 2 months during, and then 2 months after.
Docetaxel = 60 mg/m2 once every 3 weeks for three cycles before RT and 20 mg/m2 once weekly during RT.
1^{O} overall survival (OS).

D'Amico, JCO 2021. 10-year FU.
10-year OS 9.11 vs 8.82 years (P = .22).
Significantly fewer RT-induced cancers were observed (10-year estimates: 0.61% v 4.90%; age-adjusted HR 0.13; P = .046).
Subset PSA < 4 HR 0.27
Subset PSA 4-20 HR 1.51
"Less PC-specific mortality on the docetaxel arm (0.00% v 28.57%) among men with PSA < 4 ng/mL."
CONCLUSION Adding docetaxel to ADT + RT did not prolong OS in men with unfavorable-risk PC, but decreased RT-induced cancer incidence, and may prolong OS in the subgroup of men with a PSA < 4 ng/mL by reducing PC-specific mortality.

RTOG 05-21 – ADT + RT ± chemo (docetaxel and prednisone).
←R→ 562 high risk prostate (G 7-8) PSA > 20. Median age = 66, median PSA = 15.1, GS 9-10 = 53%, cT3-4 = 27%. Median follow-up = 5.5 yrs.
| ADT (LHRH agonist and PO antiandrogen) x 8 weeks → RT to 72-75.6 Gy + concurrent ADT (same) | * antiandrogen stops at end of RT. LHRH 2 yrs.
| Same as above + start 6 cycles of docetaxel + prednisone with ADT beginning 28 days after completed RT |
* Docetaxel IV over 1 hour (on day 1 of each cycle) q 21 days with premedication of dexamethasone.
* Prednisone PO daily until day 21 of the last cycle of chemo (so basically after the 6^{th} cycle, keep giving until day 21).

Sandler. 2015 ASCO meeting. 1^{O} Endpoint = OS.
4-yr OS 89% vs. 93% (p=0.04). 5-yr DFS = 66% vs. 73% (p=0.05).
Conclusions: For high-risk, localized PCa, adjuvant CT improved the OS from 89% to 93% at 4 years. Toxicity was acceptable.

GETUG 12
←R→ 207 high risk (cT3-T4 or GS ≥ 8; PSA > 20 ; pN1) | 1. ADT alone | 2. ADT + Chemo |
C = Four cycles of docetaxel on day 2 at a dose of 70 mg/m ^{2} and estramustine 10 mg/kg per day on days 1–5, every 3 weeks
All patients received RT or surgery after 3 months of systemic treatment.

Fizazi, Lancet 2015.
8-year RFS 50% vs 62% (p=0·017).
Interpretation
Docetaxel-based chemotherapy improves relapse-free survival in patients with high-risk localised prostate cancer. Longer follow-up is needed to assess whether this benefit translates into improved metastasis-free survival and overall survival.

RTOG 99-02
←R→ 397 high risk prostate cancer (68% GS 8-10 and 24% cT3-4) | 1. EBRT + ADT long term GnRH agonist 2 years | 2. EBRT + ADT + Chemo |
Chemotherapy = adjuvant paclitaxel, estramustine, oral etoposide.

Rosenthal, IJROBP 2015.
Conclusion: No Δ at all.

	BF	LF	DM	DFS	OS
EBRT + ADT	58%	11%	16%	22%	65%
EBRT + ADT + C	54%	7%	14%	26%	63%
	NS	NS	NS	NS	NS

AZ 2022

WPRT (Definitive RT)

Tata Memorial Prostate Only vs. Pelvis-RT (POP-RT)
←R→ 224 phase III, single center N0 ↑ or very ↑ risk with estimated nodal risk ≥ 20% | 1. Prostate RT 68 Gy / 25 fx | 2. (Arm1) + WPRT SIB 50 Gy / 25 |.
WPRT → pelvic nodes, including common iliac.
All patients → IGRT IMRT + ≥ 2 years ADT.
1^{O} 5-year biochemical failure-free survival (BFFS), and secondary end points were disease-free survival (DFS) and overall survival (OS).

Murthy, JCO 2021. Median FU 68 months
5-year BFFS was 81.2 vs. 95.0 (HR 0.23, P < .0001). 5-year DFS 77.2% vs. 89.5% (SS). 5-year OS NS 90 vs. 92.5%.
Distant metastasis-free survival was also higher with WPRT (95.9% v 89.2%; HR, 0.35; 95% CI, 0.15 to 0.82; P = .01).
Benefit in BFFS and DFS was maintained across prognostic subgroups.
CONCLUSION Prophylactic pelvic irradiation for high-risk, locally advanced prostate cancer improved BFFS and DFS as compared with PORT, but OS did not appear to differ.

Murthy, Rad Oncol 2020. 44.5 months
No RTOG grade IV toxicity was observed. Acute GI and GU toxicities were similar between both the arms.
Late GI ≥G2 AE 3.8% vs. 6.5% (p = 0.39). Late GU ≥G2 AE 7.5% vs. 17.7% (p = 0.03).
Bladder V30 36% vs. 60% (SS). Bladder V40 25% v. 41% (SS).
There was no difference in QOL scores of any domain between both arms.
Conclusion Pelvic irradiation using hypofractionated IG-IMRT resulted in increased grade II or higher late genitourinary toxicity as compared to prostate only RT, but the difference was not reflected in patient reported QOL.

CHIRP Hypofractionated WPRT
←R→ 111 high risk prostate cancer Prostate + WPRT | 1. 68 Gy in 25 fractions in 2.72 Gy/fx | 2. 78 Gy in 39 fractions |.
HFRT = SIB (25 fractions) 45 Gy WPRT + 68 Gy to the prostate ± SV.
CFRT = Sequential WPRT 46 Gy in 23 → CD Boost to 78 Gy in 39.
18 months of ADT given.

Wang, PRO 2021. 38 months FU
G ≥2 GI toxicity (HFRT 18.9% vs CFRT 21.8%; P = .812). Acute GU (HFRT 30.2% vs CFRT 30.9%; P = 1.00)
Late GI (HFRT 16.0% vs CFRT 10.0%; P = .554) Late GU (HFRT 16.0% vs CFRT 6.0%; P = .200)
3-year BcFS 97.3% vs. 91.0% (P = .606).
3-year OS 94.8% vs. 100.0% (P = .116).
Conclusions
HFRT and CFRT using intensity modulated radiation therapy were both well tolerated for patients with high-risk prostate cancer and resulted in similar 3-year biochemical recurrence-free survival and overall survival.

Dose Escalation LN Study
Phase 2 with 30 patients PSA 11.5, T1c-T3b, GS 6-9, LN% risk ≥ 25, KPS ≥ 70, M0
All received Prostate 70 Gy in 28 fractions SIB with WPRT 56 Gy in 28 fractions (CTV D95% ≥ 50.4 Gy).
Eligibility: LN calculated ≥25% risk.
Constraints: Bladder/Rectum V45 < 45%, V55 < 25%, V15 < 65%. SB Constraint V46.5 < 300 cc.

Hall, PRO 2021
G2 GU/GI combined 44%. 1 reported G3 (unrelated to treatment).
5-year BCFFS 80%. Mean BCPFS 8.3 years.
5-year PCaSS 95%. Mean PCaSS 8.7 years.
5-year DMFS 96%.
Conclusions In this single arm, small, prospective feasibility study, nodal radiation therapy dose escalation was safe, feasible, and seemingly well tolerated. Rates of progression free survival are highly encouraging in this population of predominately National Comprehensive Cancer Network very high-risk patients.

AX 2022

RTOG 94-13. Stratification: (T1c,T2a | T1b,T2b | T2c-T4) PSA (≤ 30 | > 30) Gleason (<7 | 7-10).
←R→ 1275 Risk LN > 15%. Median PSA 23. 23% T1c-T2a. 66% T2c-T4. 73% G 7-10. RT 70.2 (50.4 to WPRT if on WPRT arms).
Q: Consider the TIMING of HT and RT target volume: whole pelvis (WP) or prostate only RT (PO).
| 1. NHT 2 mos. before & during. RT to 50.4 Gy WP → prostate boost to 70. | 2. NHT 2 mos. before & during. RT to prostate only to 70. |
| 3. RT consisting of 50.4 Gy to WP → prostate boost to 70. → 4 mo. AHT | 4. RT to the prostate only → 4 mos. of AHT. |
ALL OTHER HIGH-RISK PROSTATE TRIALS WERE WITH WHOLE PELVIS TREATMENT.

Roach, JCO 2003. WP RT vs PO RT- 4 yr PFS 56% vs 40% (SS). WP RT + N&C HT vs other 3 arms- PFS 61% vs 45-49% (SS).
No differences in overall survival. Where we get PLN XRT for LN risk > 15%
Conclusions: Initial benefit seen for WPRT + NCHT arm as well as WP vs. PO rt. The initial benefit seen for WPRT + N&CHT is that the ADT helped with the low dose given to the pelvic LN.
Problems: study not designed to compare all 4 treatment arms individually. Assumed no interactions between hormonal therapy and extent of radiation treatments (this turns out to be untrue).

Roach, IJROBP 2006. WP vs. Mini pelvis vs. PORT for N&CHT pts. MP defined as >/= 10 x 11 cm but < 11 x 11 cm
Conclusions: WP RT is associated with an improvement in PFS compared to MP and PORT in patients with a risk of LN involvement >15%
Late grade 3+ GI toxicity was similar with WP RT compasred to MP RT, however both were higher than PORT.
This study supports WP RT as the standard of care for this patient population when treating with RT & N&C HT.

Roach, ASTRO 2013.

	PFS	BFreedom	OS
Neo/concur ADT + WPRT	40%	70%	88%
Neo/concur ADT + PO	56%	57%	83%
WPRT → adj ADT	51%	63%	81%
PO → adj ADT	50%	63%	82%
	0.03	0.01	NS

Comment: Perhaps the high-risk patients did not benefit from WPRT due to metting out. The low risk patients probably have no benefit from WPRT. ∴ you need to choose the right patient → RTOG 09-24. Also strong with 2x2 design.

Roach IJROBP 2006 SUBSET
Secondary analysis of RTOG to determine if pelvic field size influenced PFS. A "mini-pelvis" MP field defined as ≥ 10 x 11 cm but < 11 x 11cm.
7-year PFS was WP 40%, MP 35%, PO 27% (p=0.02).

Commentary on the use of WPRT: Zaorsky, IJROBP 2021

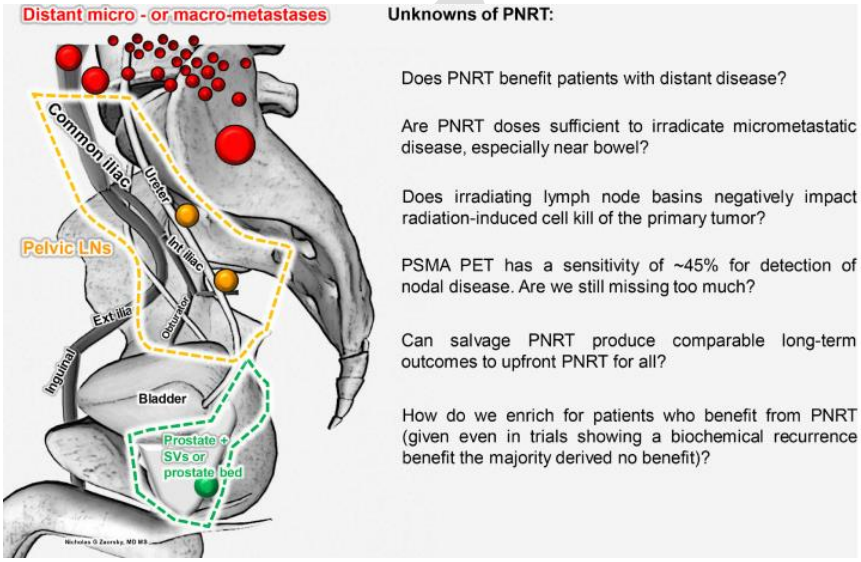


Fig. 1. The fundamental premise for recommending PNRT is that a subset of patients with radiographic node negative disease will harbor pathologically node positive disease, and PNRT would translate into improved oncologic outcomes with minimal additional toxicity. In the left panel, one would only be irradiating the pelvic nodes, and there would not be occult metastases. As of 2021, several unanswered questions about PNRT remain (right panel).

In summary, although we have new data to support the use of PNRT for biochemical control in select subsets of patients (PSMA PET negative high-risk localized and post-RP BCR PSA >0.34 ng/mL), we still await the results of the definitive trial in the use of PNRT in localized prostate cancer, RTOG 0924. We must remember that we have evidence that PNRT has zero level 1 evidence of any impact on survival,1,2,5,11 and significantly increases toxicity, even with improved techniques.5 There remains concern that PNRT doses are inadequate for micrometastatic disease, the clear negative impact of PNRT on hematologic toxicity and depletion of lymphocytes, and it remains challenging to identify the subset of patients who will have occult disease outside of the pelvis.8,9 Adoption of the experimental arm of RTOG 0924, use of PNRT, we accept is "a" standard of care, but it fundamentally begs the question why RTOG 0924 was conducted if we are to ignore our prior phase III trial results.1,2 Thus, we caution the ubiquitous use of PNRT until RTOG 0924 is reported. If the results of RTOG 0924 are negative, and the use of PNRT was appropriately experimental as deemed by the trial protocol, millions of men will have received this treatment without clear benefit and potential harm.

See "Salvage SPPORT RTOG 05-34."

GETUG-01
←R→ 446 cT1b-3N0 | 1. WPRT 46 Gy → 66-70 Gy | 2. Prostate Only 66-70 Gy |.
Stratified with low risk (cT1-2 ,GS 6, PSA < 3x ULN) vs. high (cT3, GS > 6, PSA > 3x ULN). If high risk, then 6-month ADT.

Pommier, IJROBP 2016.
10-year OS 71% (NS) 10-year EFS 52-54% (NS)
Criticism: RT low dose, ADT not enough, poor RT coverage S1/S2.
Note: A rather useless trial showing that WPRT vs. PO makes no difference if you don't give proper RT or ADT = you just don't cure the patient.

NCDB Review
RR 3450 cN+ without DM.

Lin, JCNI 2015.
ADT+EBRT associated with a 50% ↓ risk of 5-year ACM ($p < 0.001$).

SEER
RR 796 cN+ and 2991 pN+.

Rusthoven (IJROBP 2014)
In Clinical cohort, 43% were treated with EBRT and 57% were not. 10-year OS 45% vs. 29% ($p < 0.001$).
Results similar in pathologic N+ cohort.

AZ 2022

Postop RT (Adj vs. Salv)

Historical Adj-RT Trials (3)

- RP is most the common treatment for early-stage prostate cancer.
- Undetectable levels are ≤ 0.05.
- 20-35% positive margin rates.
- 25-35% biochemical recurrence after RP.
  - 50% if pT3 and/or + margins.
- Sites of relapse:
  - 60% anastomosis.
  - 15% retrovesicle space
  - 10% bladder neck
  - 10% other (residual SV, etc).

- Adjuvant is RT when PSA is still undetectable (usually 4 weeks after RT), < 0.1 .
- Salvage is RT when PSA is detectable.
- EARLY SALVAGE based on GETUG AFU 17, RADICALS, RAVES is either 0.1 or 0.2.
- RT = 66 Gy in 2 Gy fx and (if LNS) 46 Gy in 2 Gy fx.
  - PTV prostate is 8-10 mm all around and 6 mm posteriorly.

- Definition of bRecurrence

[y] PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).

[z] RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA persistence/ recurrence after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

AZ 22

SWOG-8794 (RTOG 90-19 / INT-0086) (1988-95) -- Adjuvant RT vs. observation
←R→ within 16 weeks of RP. 473 patients, radical prostatectomy with extraprostatic disease (ECE, SV+, or SM+). Pelvic LND required until 1995, when very low risk patients were exempt. | 1. Prostatic fossa RT 60-64 Gy | 2. Observation |. No concurrent hormones.
RT field non-3D, 4-field. 1^{O} endpoint mets-free survival (MFS). Both detectable and non-detectable PSA (AKA Both adj and salvage study).
Number needed to treat was 9.1 for OS and 12.2 for MFS at 12.6 years.
NOTE: 30% patients had detectable PSA > 0.2 so salvage!

Swanson, IJROBP 2005. ASTRO Abstract Plenary #1 Webcast.
Median f/u 9.7 yrs. RT improved bDFS 10-yr 47% vs 23%, metastasis free survival 83% vs 61%, OS 74% v 63%.

Thompson, JAMA 2006. 10-years.
Outcome: MFS RT 65% vs. obs 57% (NS), median 14.7 vs. 13.2 years. 33% of obs → salvage RT for disease relapse instead of observation alone.
Biochemical progression (defined as PSA ≥ 0.4) RT 35% vs. 64% (SS), median TTF 10.3 yrs vs observation 3.1 yrs (SS).
Recurrence free survival 61% vs. 47% (SS). Hormones initiated in 10% vs 21% (SS). No difference in OS.
Rectal complications 3% vs 0%, urethral strictures 18% vs 9%, total urinary incontinence 6% vs 3%.
Conclusion: Adjuvant RT decreases PSA and clinical recurrence by ~50%. However, while ~ 70% of pts have biochemical relapse, after censoring for death without mets, mets free survival ~ 78% at 13.2 years (rate of events was lower than anticipated).

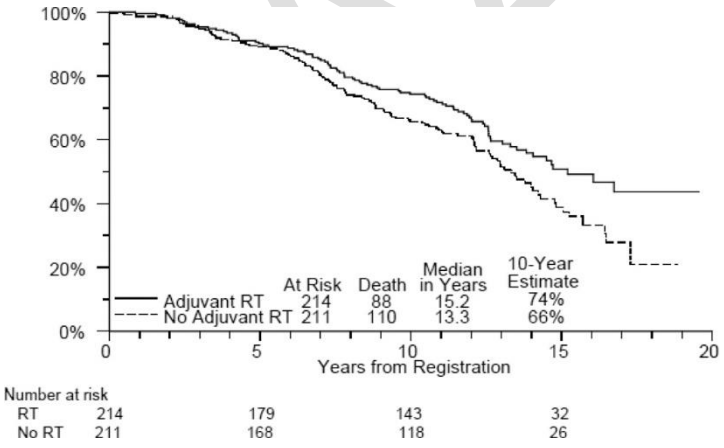
Based on other trials. Biochemical failure → mets in 8 years Johns Hopkin.

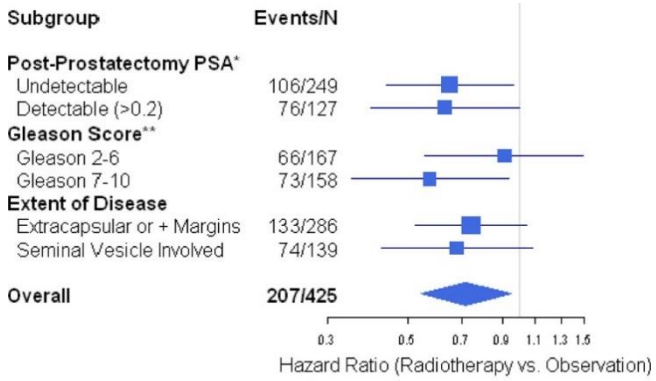
Swanson, JCO 2007. Failure analysis. Biochemical progression defined as PSA ≥ 0.2.
10-year PSA failure: Postsurgical PSA <0.2: Biochemical Progression: Obs 72% vs. RT 42%; local failure 20% vs. 7%; DM 12% vs. 4%
Postsurgical PSA 0.2-1.0: Biochemical Progression: Obs 80% vs. RT 72%; local failure 25% vs. 9%; DM 16% vs. 12%
Postsurgical PSA >1.0: Biochemical Progression: Obs 100% vs. RT 94%; local failure 28% vs. 9%; DM 44% vs. 18%
Conclusion: Failure in high risk patients predominately local; adjuvant RT reduces risk of failure.

Moinpour, JCO 2008. QOL. 217 patients registered on HRQL study. Questionnaire for GI/GU symptoms, and physical/emotional function.
Outcome: Global QOL initially worse for RP+RT, but improved over time and eventually exceeded RP alone (SS). RP+RT worse bowel function through 2 years, and worse GU function. No difference on ED.
Conclusion: Adding RT to surgery resulted in more frequent urination, and early bowel dysfunction, but long-term QoL better
uber
Swanson, J Urology 2008. SVI. Subset analysis. 139 patients with SVI, regardless of ECE or SM. Compared with SVI-, SVI+ had worse 10-year bFFS (22% vs 33%, SS), mets-free survival (56% vs. 70%, SS), and overall survival (61% vs. 74%, SS)
Outcome: Adjuvant RT ↑ 10-year bFFS (12% to 36%, SS). Trend for MFS (47% to 66%, NS), and OS (51% to 71%, p=0.08)
Conclusion: SVI involvement is a negative prognostic factor, but long-term control possible with adjuvant RT

2008 ASTRO "Update of SWOG 8794: Adjuvant Radiotherapy for pT3 Prostate Cancer Improves Metastasis Free Survival" Swanson GP et al. IJROBP Volume 72, Issue 1, Supplement 1, 1 September 2008, Page S31. Confirmed 15-year metastasis-free survival advantage (46% vs. 38%, p=0.036) and suggested an overall survival advantage (47% vs. 37%, p=0.053) favoring adjuvant RT.

Thompson, J Urology 2009. 15-year update.
RT improved metastasis free survival 43% vs 54% (HR 0.71, 93/214 vs. 114/211)
RT improved overall survival: HR 0.72, 59% vs 48%, p=0.023. # of Deaths 88/214 vs 110/211.
Median f/u of ~12.5y in both arms
70 of 211 pts on observation arm ultimately received RT.





* Missing for 49 patients, ** Missing for 100 Patients
Size of box and diamond symbols are proportionate to sample size

"Post-op Bolla" EORTC 22911. Same arms as SWOG. Adjuvant and Salvage. Initially the endpoint is LC, then clinical PFS. NOT biochemical free survival
56 men need to treat to prevent 1 death at 10.6

POOLED FROM both NTT from above to prevent b recurrence is 4.2.

←R→ . 1005 patients. Radical prostatectomy pT2-3N0, ilio-obturator LND, with extracapsular disease (ECE, SV+, SM+). Arm 1) observation vs. Arm 2) RT 60/30, start within 16 weeks of RP. RT technique conventional (non-3D), 50/25 + 10/5 boost with smaller margins. Borders surgical limits SV to apex. No Gleason scoring (used WHO grade). Biochemical failure increase of 0.2 from postop nadir measured on 3 occasions at least 2 weeks apart and is dated from first day of rise. After biochemical or clinical failure, could get salvage RT. By risk: 43% had one RF only, 43% had two RFs, 12% had all three RFs. Primary endpoint clinical PFS, ammended to bNED in 2003
NOTE: similar to above, about 30% had > 0.2 PSA so salvage.

Bolla, Lancet 2005. Median F/U 5 years
Outcome: 5-year bNED RT 74% vs observation 53% (SS), regardless of risk factors. Most failures loco-regional. Clinical PFS 85% vs. 78% (SS) the major factors are below. OS 91-92% (NS).
Late toxicity: Grade 3 RT 4% vs. observation 3% (p=0.07)
Conclusion: Post-operative radiotherapy results in improved biochemical and clinical PFS, but its benefit should be weighed against the risk of increased toxicity.

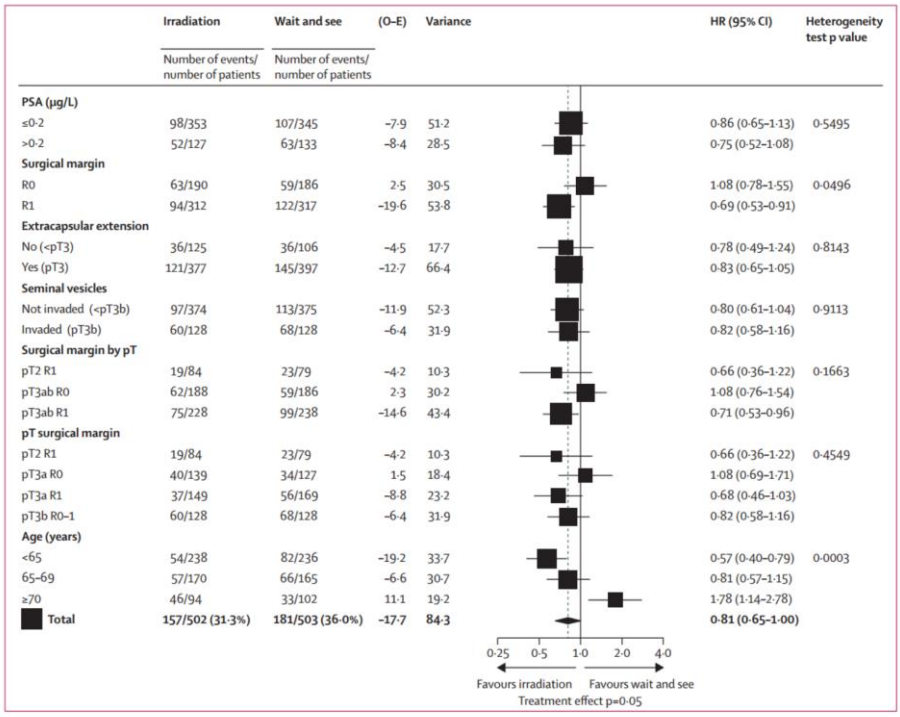


Figure 3: **Effects of baseline factors on clinical progression-free survival**
O=observed. E=expected. HR=hazard ratio. PSA=prostate-specific antigen.

Van der Kwast, JCO 2007. Subset analysis.
Pathology data review. 552 patients
Surgical margin impact: if SM+, RT prevents 291 events/1000 patients (SS); need to treat 3 patients to prevent 1 recurrence. If SM-, RT prevents 88 events/1000 patients (NS).
Conclusion: After careful central path review, RT beneficial only for patients with positive margins (this effect was not seen when using the local pathology data), no benefit if negative margins

Bolla, Lancet 2012. Median F/U 10.6 years

	10-year bRFS	5-year cPFS	10-year LRF	10-year DM	10-year OS	10-year Tox	G 3 Acute Tox
Adj EBRT	62%	70%	7%	10.1%	77%	70.8%	5.3%
Obs	39%	65%	16%	11%	80%	59.7%	2.5%
p	< 0.001	0.054	< 0.001	NS	NS	0.001	0.052

ARO 9602 RP alone vs ± adjuvant RT. Only the trial that is PURE adjuvant RT: EXCLUDED PATIENTS if DETECTABLE (≥ 0.1) post-op PSA.

Randomized. 388 men. 1. Observation (192). 2. Radiation (193). THIS WAS NOT POWERED PROPERLY for endpoints.
Radical prostatectomy (open RP and PLND, nerve sparing allowed) ONLY pT3 pN0, age <76 years. Randomization was prior to determination of post-op PSA. If undetectable PSA was not achieved, pts were removed from protocol and scored as having progressive disease. Pts with undetectable post-op PSA (<0.1) assigned treatment (n=80%).

Arm 1) observation vs. Arm 2) RT 60/30 Gy. RT 3D plan prostatic fossa + SV + 1cm. Start 6-12 weeks after RP. Primary endpoint PSA control (PSA relapse defined as undetectable to detectable, followed by another increase). Patients not reaching undetectable PSA (20%) treated with 66.6 Gy. LR not investigated because DRE often false positive

2005 ASCO Abstract. Weigel.
Outcome: Patients treated per protocol bNED 81% vs. 60% (SS). Greatest benefit SM+, PSA >10, GS <7
Late toxicity: GU grade 3 2%, GI no grade 3
Conclusion: Adjuvant RT significantly improves risk of PSA progression after RP

Weigel, JCO 2009. Median F/U 4.5 years
Outcome: 5-year bPFS observation 54% vs. RT 72% (HR 0.53, SS). DM 3% vs. 2%. Negative predictors preop PSA >10, stage ?pT3b
Toxicity: No Grade 4, 1 patient with Grade 3 bladder, Grade 2 in 3%
Conclusion: Patients with pT3 PCA who achieve undetectable PSA after surgery benefit from adjuvant RT

Weigel, Eur Oncol 2014.
10-yr PFS was 56% for ART and 35% for WS (p<0.0001). SUBSET: pT3b WS (28%) and R1 (27%).
Neither MFS or OS NS. However, the study was underpowered for these end points.
Grade ≥ Tox ↑ from 4% → 22% (SS). No grade 4 events occurred.
CONCLUSIONS: Compared with WS, ART reduced the risk of (biochemical) progression with a hazard ratio of 0.51 in pT3 PCa. With only one grade 3 case of late toxicity, ART was safe.

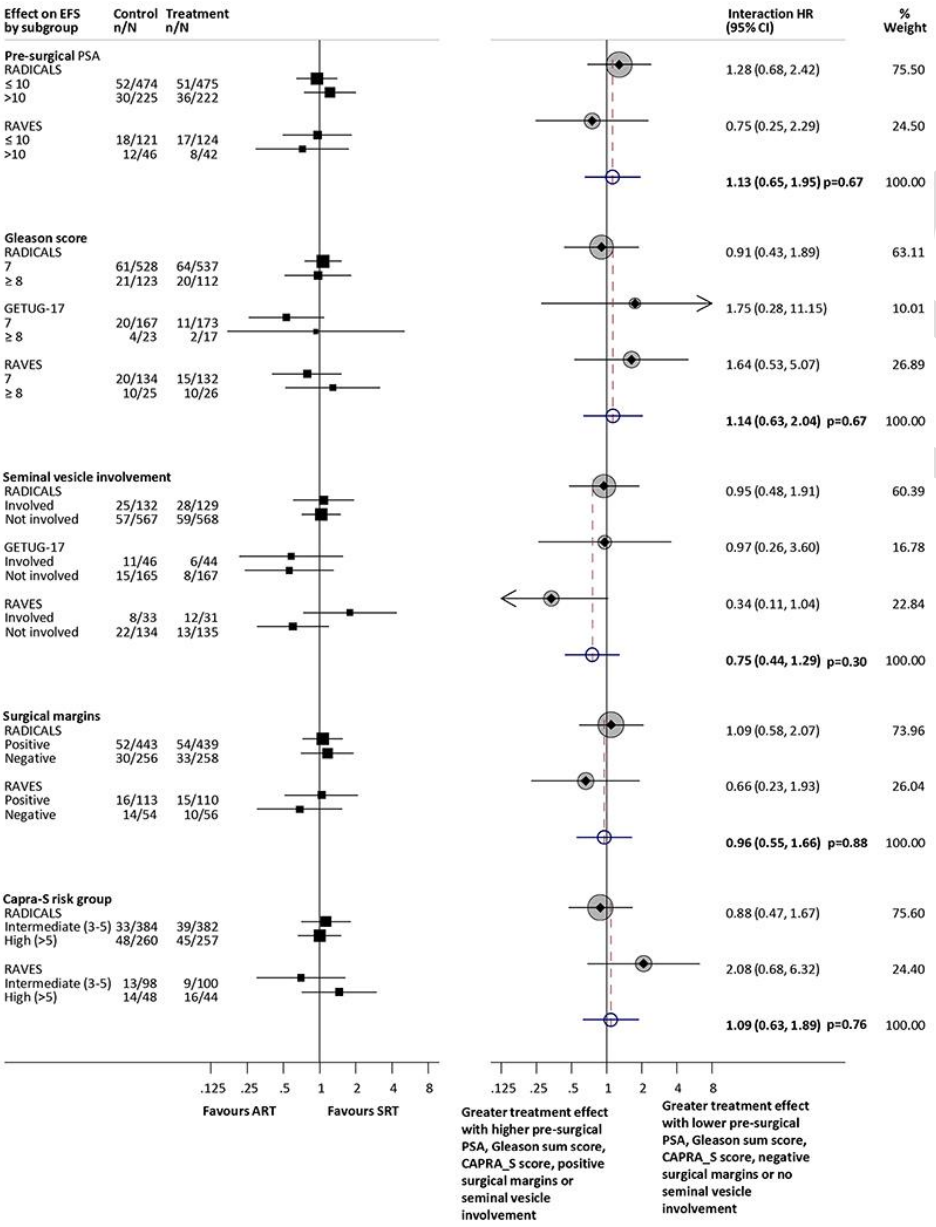
Ontario. Morgan 2008 Meta-analysis of 3 above PRT.
←M→ Three RCTs representing 1,743 patients satisfied the eligibility criteria (pT3 and or R1).
NO BENEFIT OS. NO Δ G3 Gi or GU toxicity (all < 5%)
SIGNIFICANT BENEFIT bRFS (HR 0.47, p < 0.00001). SIGNIFICANT BENEIFT in "ANY" toxicity 54-64% (SS).

Cochrane, Daly 2011 Metaanalysis with LONGER follow-up than Ontario.
←M→ Adjuvant RT SS ↑ OS and ↑ DMFS.
AUTHORS' CONCLUSIONS: Adjuvant RT after RP improves overall survival and reduces the rate of distant metastases, but these effects are only evident with longer follow up. At 5 and 10 years it improves local control and reduces the risk of biochemical failure, although the latter is not a clinical endpoint. Moderate or severe acute and late toxicity is minimal. There is an increased risk of urinary stricture and incontinence, but no detriment to quality of life, based on limited data. Given that the majority of men who have undergone a RP have a longer life expectancy, radiotherapy should be considered for those with high-risk features following radical prostatectomy. The optimal timing is unclear.

AZ 2022

Salv-RT Major Trials (3)

- PSA failures occur in about 30% of patients after RP (all comers) in 10 years.
  - 60% of patients locally fail after RP WITHOUT time limit.
- Those with ↑ PSA after RP have 60% probability of developing DM and 20% of risk of prostate CA mortality within 10 years if left untreated.
- Median time from PSA failure → DM is ~ 8 years, but only ~3 years for high GS or short PSA doubling time < 3 mo (Pound 1999, Freeland 2005).
  - Median time from DM to death is ~ 5 years.
- If PSA rises within 2 years, they will met out within 5 years.
  - If rises AFTER 2 years, met out in 10-15 years.
- Velocity: greater risk of death after prostatectomy.
- Early Salvage is NO WORSE than adjuvant RT.
  - Therefore, early salvage also gives men a chance (~50%!!!) not to receive RT at all.



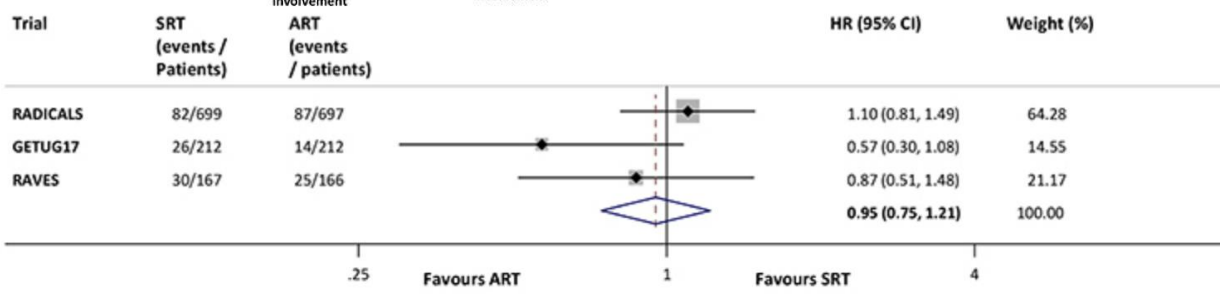
ARTISTIC meta-analysis

←M→ 2153 men through RADICALS (ISRCTN40814031), GETUG-AFU 17 (NCT00667069) and RAVES (NCT00860652).
≥ 70% of all patients had at least one of: SM+, ECE+, or pT3a/b disease.
Used a "harmonised definition" of EFS = as the time from randomisation until the first evidence of either

1. PSA Progression ≥0·4 ng/mL and rising after completion of any postoperative radiotherapy
2. Clinical or radiological progression
3. Initiation of a non-trial treatment
4. Death from prostate cancer
5. PSA level of ≥ 2·0 ng/mL at any time.

Vale, Lancet 2020

Results: Across the 3 trials, 1075 men were randomised to ART and 1078 to SRT.
Based on 270 events, EFS NS (HR 0·95, 95% CI 0·75-1·21; p=0·70).
5-year EFS 88-89%.
Results were consistent across trials (heterogeneity p=0·18; I2=42%).
Interpretation: This collaborative and prospectively designed systematic review and meta-analysis suggests that adjuvant radiotherapy does not improve event-free survival in men with localised or locally advanced prostate cancer. Until data on long-term outcomes are available, early salvage treatment would seem the preferable treatment policy as it offers the opportunity to spare many men radiotherapy and its associated side-effects.



GETUG AFU 17 Early termination (due to low event rates).
←R→ 424 (planned 718) s/p radical prostatectomy, with pT3a, pT3b, or pT4a (with bladder neck invasion), pNx / pN0m, +SM. | 1. aRT | 2. Delay sRT|.
PSA must be < 0.1 after surgery. Pelvic LN COULD be included if needed.
Biochemical relapse triggering RT = 0.2 ng/mL confirmed after 4 weeks.
Biochemical progression after RT = 1. Clinical progression 2. > 1 ng/mL any time 3. > 0.4 ng/mL after any RT.
RT 7-10 mm all around and 5 mm posteriorly. PTV 1 = 66 Gy / 2 Gy, PTV 2 (LNs) 46 Gy / 2 Gy fx.
All received 6 months of triptorelin (intramuscular injection every 3 months).
1^{O} EFS.

Sargos, Lancet 2020. 6-year FU.
In the salvage radiotherapy group, 115 (54%) of 212 patients-initiated study treatment after biochemical relapse.
5-year EFS 90-92%.
Acute ≥ G3 2-3%. Late ≥ 2 GU 59% vs. 22%. Late ≥ G2 GI 27% vs. 7% (SS).
Late erectile dysfunction ≥ G2 28% vs. 8% (SS).
Interpretation Although our analysis lacked statistical power, we found no benefit for event-free survival in patients assigned to adjuvant radiotherapy compared with patients assigned to salvage radiotherapy. Adjuvant radiotherapy increased the risk of genitourinary toxicity and erectile dysfunction. A policy of early salvage radiotherapy could spare men from overtreatment with radiotherapy and the associated adverse events.

RADICALS-RT
Background: The optimal timing of RT after RP for prostate cancer (PCa) is uncertain. RADICALS-RT compared the efficacy and safety of adjuvant RT (aRT) versus an observation policy with salvage RT for PSA failure (Obs+sRT).
←R→ 1396 post-op PSA ≤ 0.2ng/ml and ≥1 risk factor (pT3/4, Gleason 7-10, positive margins or pre-op PSA ≥ 10ng/ml) ←R→ ≤22wk after surgery.
| 1. aRT | 2. Obs+sRT for PSA failure | Failure = (3 consecutive rises, or 2 consecutive rises + PSA > 0.1).
Stratification: GS, Margin, RT schedule (52.5Gy/20f, 66Gy/33f) and centre.
1^{O} freedom-from-distant metastases (FFDM) with >1200 pts needed for 80% power to detect an improvement from 90% to 95% at 10yr with aRT.
2^{O} bPFS (any of PSA≥0.4ng/ml post-RT, PSA≥2.0ng/ml at any time, local/distant progression, deferred HT, PCa death), freedom-from-non-protocol hormone therapy (HT), safety (RTOG scale), and patient reported OMs (ICSmaleSF). Standard survival analysis methods were used.

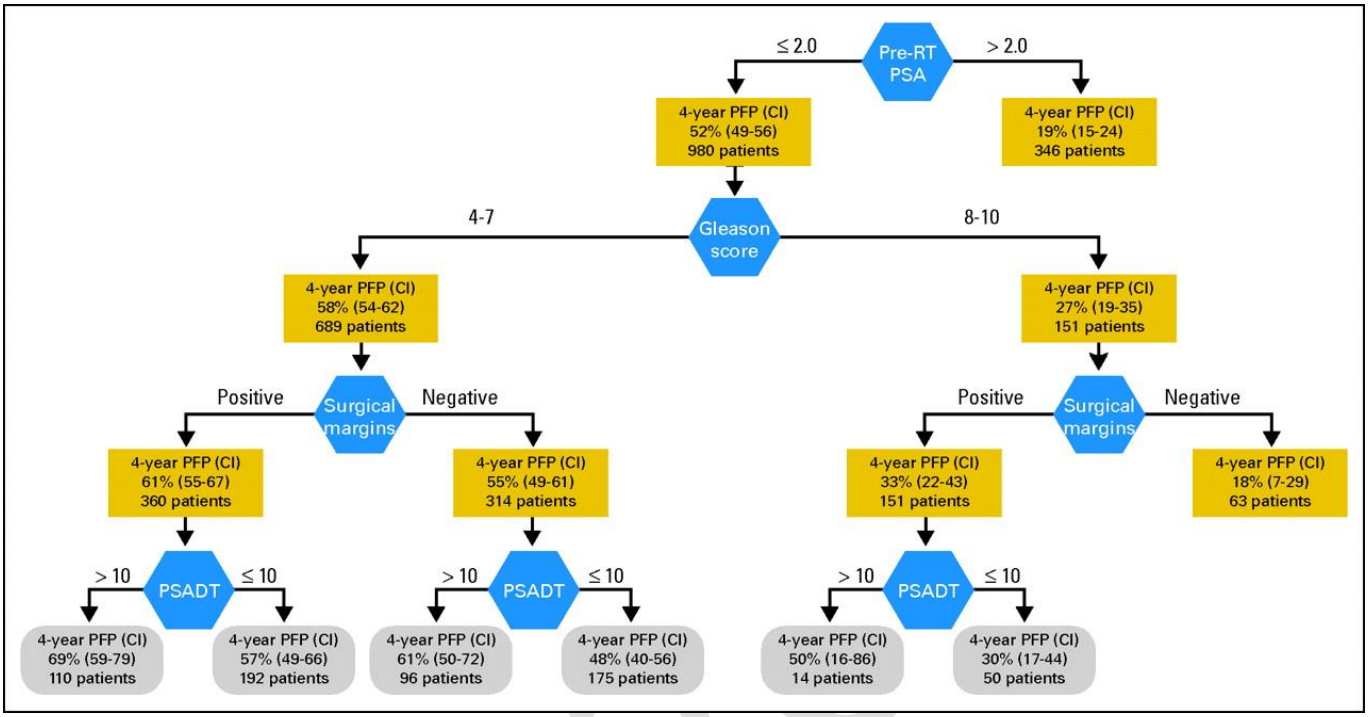
Parker, Lancet 2020.
Too early for 1^{O} results. Here to present 2^{O} results. 5-year FU.
5-year bPFS 85% v 88% (NS). Freedom-from-non-protocol HT 92% v 94% (NS).
1-year self-reported urinary incontinence 5.3% vs 2.7% (p=0.008). 5-year RTOG Grade 3/4 urethral stricture any time 8% vs 5% (p=0.03).
Conclusions: First results from RADICALS-RT do not show a benefit for aRT after RP in this patient group. Further follow-up is needed to report on long-term OMs, including FFDM. Adjuvant RT after RP increases risk of urinary morbidity. An observation policy with sRT for PSA failure should be the current standard after RP.

RAVES (TROG 08.03/ANZUP)
←R→ 333 prostate s/p prostatectomy with high risk (+SM, +EPE, +SV) and PSA ≤ 0.1 ng/mL | 1. Adj RT within 6 mo | 2. Early Salvage after PSA ≥ 0.2 |.
RT = 64 Gy in 32 fractions to the prostate bed w/o ADT.
1^{O} bFFP.

Kneebone, Lancet 2020. PREMATURE CLOSURE because of unexpectedly low event rates.
84 (50%) patients in the salvage radiotherapy group had radiotherapy triggered by a PSA of 0·20 ng/mL or more.
5-year bFFP 86% vs. 87% (NS).
≥ G2 GU toxicity rate 70% vs. 54%. ≥ G2 GI toxicity rate 14% vs. 10%.
Interpretation Salvage radiotherapy did not meet trial specified criteria for non-inferiority. However, these data support the use of salvage radiotherapy as it results in similar biochemical control to adjuvant radiotherapy, spares around half of men from pelvic radiation, and is associated with significantly lower genitourinary toxicity.

Nomograms + RR

Stephenson 2007. Is RT salvage ineffective in those who are at high risk of distant mets?
Retrospective. 1,540 patients with **PSA ≥0.2 (ALL)** followed by another higher value or single PSA ≥ 0.5 after RP. 17% of patients received neoadjuvant ADT prior to RT. Median RT = 64.8 Gy (range 37.8 – 75.6 Gy). PFP = progression free probability.



Tendulkar Nomogram Update, JCO 2016 5-year FU
RR 2460 LN- patients s/p RP with detectable post-RP PSA treated with salvage RT w/ wo ADT.
GS 6 = 599 patients (24%), GS 7 = 1,387 (56%), GS 8 = 244 (10%), GS 9-10 = 230 (9%).
EPE = 1,370 patients (56%), SVI = 452 (18%), SM+ = 1,434 (58%).
Received ADT 390 (16%) = median, 6 months.
The median pre-SRT PSA was 0.5 ng/mL (interquartile range, 0.3 to 1.1).

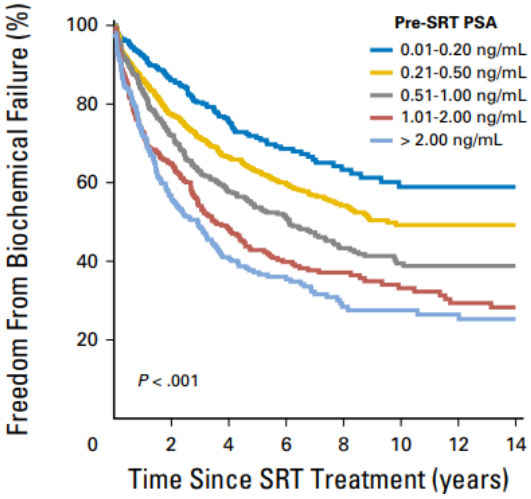
PSA at Salvage RT	0.01-0.2	0.21-0.5	0.51-1	1.01-2	> 2	P
5-year bRFS	71%	63%	54%	43%	37%	< 0.001
10-year FFDM	91%	85%	81%	80%	63%	< 0.001

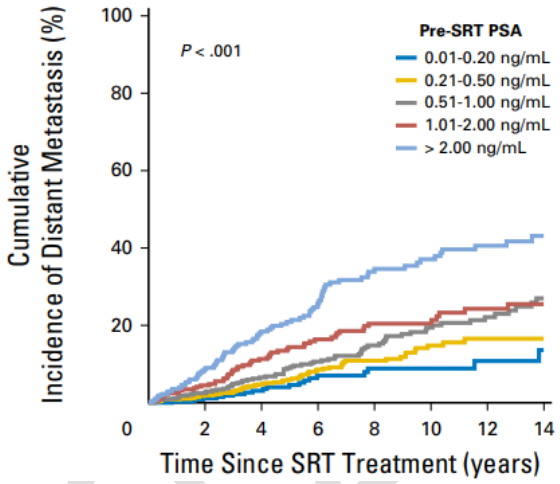
Table 2. Estimated Rates of Freedom From Biochemical Failure and Distant Metastases by Gleason Score and Preradiation PSA

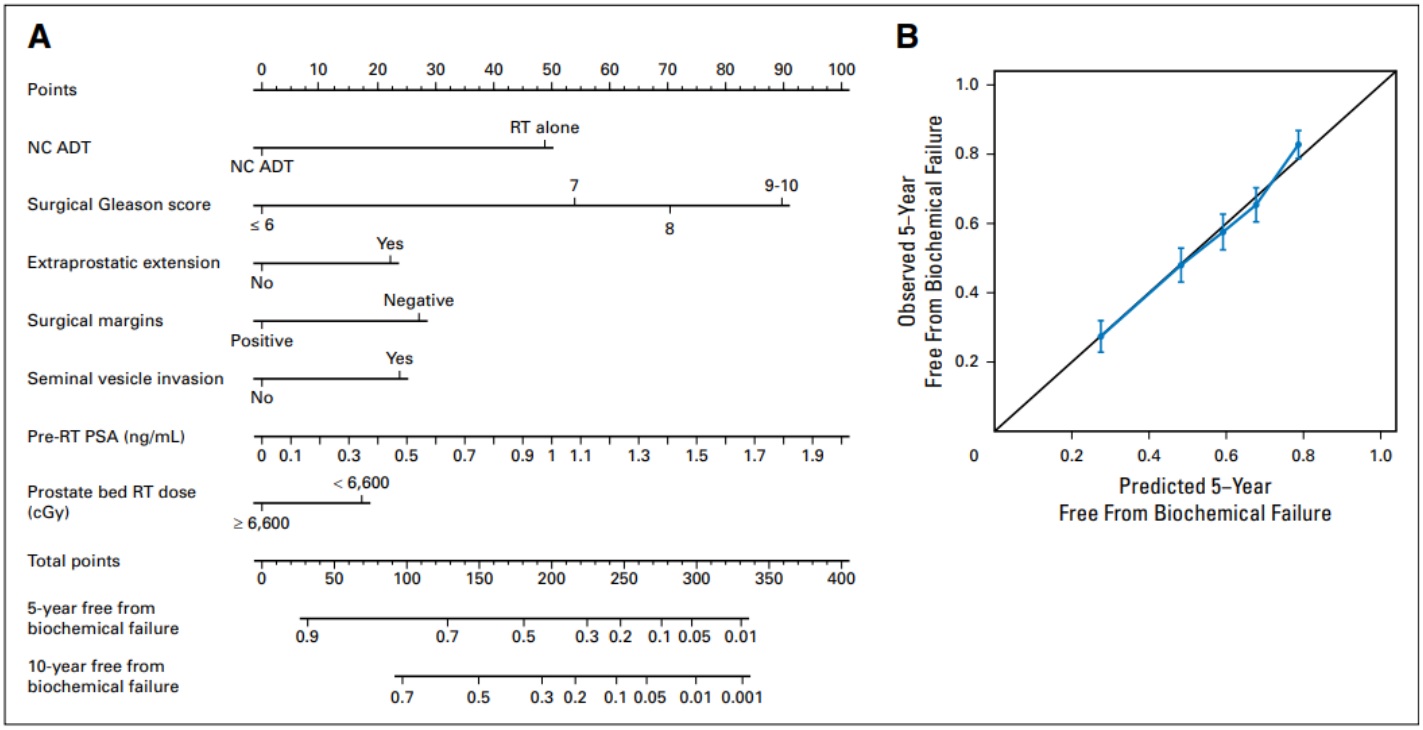
	GS ≤ 6 (grade group 1)			GS 7 (grade group 2-3)			GS 8 (grade group 4)			GS 9-10 (grade group 5)		
PSA (ng/mL)	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.
0.01-0.1	100	100 to 100	25	82	73 to 91	107	73	47 to 98	22	47	23 to 72	30
0.11-0.2	85	73 to 98	51	64	55 to 74	155	69	47 to 91	25	41	18 to 64	26
0.21-0.5	82	75 to 88	179	62	57 to 66	502	45	1 to 59	68	42	30 to 54	73
0.51-1.0	76	68 to 84	146	49	42 to 55	308	38	18 to 58	37	23	8 to 39	42
1.01-2.0	58	48 to 68	116	35	26 to 44	165	33	17 to 50	45	27	0 to 55	15
> 2.0	52	41 to 63	82	32	23 to 41	150	30	13 to 47	47	26	10 to 43	44
P	< .001			< .001			.013			.049		

	GS ≤ 6 (grade group 1)			GS 7 (grade group 2-3)			GS 8 (grade group 4)			GS 9-10 (grade group 5)		
PSA (ng/mL)	10-yr DM (%)	95% CI	No.	10-yr DM	95% CI	No.	10-yr DM	95% CI	No.	10-yr DM	95% CI	No.
0.01-0.1	0	0 to 0	25	7	0 to 14	107	16	0 to 40	22	23	0 to 45	30
0.11-0.2	0	0 to 0	51	7	0 to 16	155	7	0 to 20	25	32	0 to 68	26
0.21-0.5	3	0 to 8	179	16	10 to 22	502	22	6 to 39	68	29	16 to 43	73
0.51-1.0	3	0 to 7	146	23	16 to 30	308	36	10 to 62	37	37	16 to 58	42
1.01-2.0	10	3 to 17	116	25	17 to 33	165	21	7 to 35	45	40	11 to 69	15
> 2.0	22	12 to 32	82	33	22 to 44	150	62	39 to 85	47	65	45 to 85	44
P	< .001			< .001			.024			.009		

Abbreviations: DM, distant metastases; FFBF, freedom from biochemical failure. GS, Gleason score; PSA, prostate-specific antigen.







Conclusion: Early SRT at low PSA levels after RP is associated with improved FFBF and DM rates. Contemporary nomograms can estimate individual patient outcomes after SRT in the modern era.

UCLA King Data shows that with ever ↑ PSA 0.1 = ↓ chance of RFS by 2.6%.
With a PSA level of 0.2 ng/mL or less before SRT, the RFS approached 64%.
The dose for salvage RT in the range of 60-70 Gy seemed to be on the steep part of the sigmoidal dose-response curve
A dose of 70 Gy achieving 54% RFS compared with only 34% for 60 Gy.
∴ There was a 2% improvement in RFS for each additional Gy (95% CI, ~0.9-3.2).
CONCLUSIONS: This study provides Level 2a evidence for initiating SRT at the lowest possible PSA. Dose escalation is also suggested by the data. Progressively better tumor control rates with SRT after radical prostatectomy are achieved with a lower PSA at initiation and with a higher RT dose. Early salvage RT may be an equivalent strategy to adjuvant RT.

bRelapse → Brachy
Phase II data has demonstrated that salvage brachytherapy after external beam radiation to a median of 81 Gy is effective and safe, and results in a 5-year biochemical relapse-free survival of 68.5%. References: Yamada et al., Brachytherapy, March-Apr 2014, 13(2):111-6.

Mayo Clinic
RR Single Institution. 1106 s/p RP → salvage RT. If post-op PSA ≥ 0.1 = excluded.

Stish, JCO 2016

	10-year		
	PSA ≤ 0.5	PSA > 0.5	p
bFreedom	40%	32%	SS
FFDM	87%	75%	SS
PCSS	94%	87%	SS
OS	83%	73%	NS

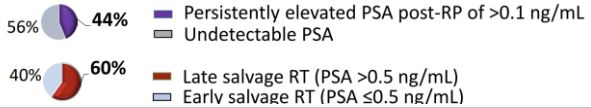
Conclusion: The use of SRT at lower PSA levels and delivery of higher doses are each strongly associated with a ↓ incidence of further BcR.

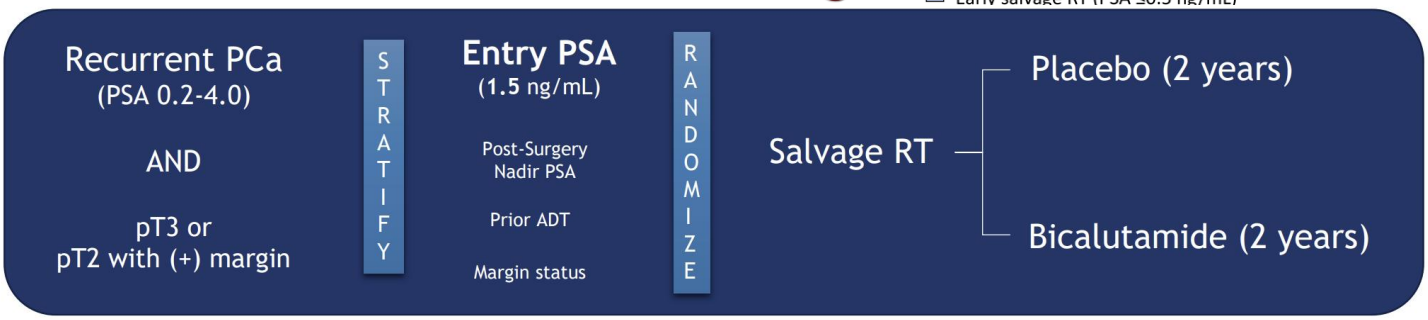
Table 2. Cumulative Incidence of Biochemical Recurrence According to Exploratory Patient Subsets

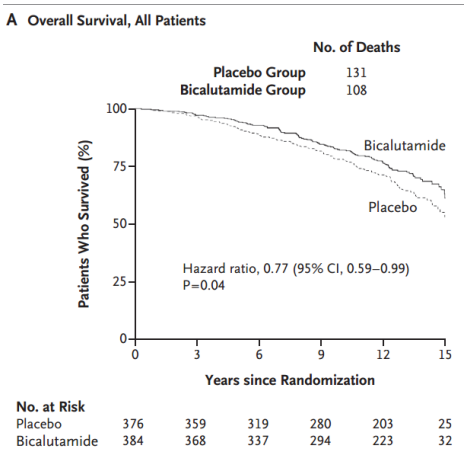
Characteristic	Events (No.)*	5-Year (%)	10-Year (%)	Single Variable HR (95% CI)	P	Multiple Variable HR (95% CI)†	P
Pathologic tumor stage							
T2	287	41	57	1.0 (Ref)	—	1.0 (Ref)	—
T3a	175	54	67	1.37 (1.14 to 1.65)	.001	1.27 (1.04 to 1.55)	.02
T3b	128	72	83	2.29 (1.86 to 2.82)	<.001	2.05 (1.64 to 2.56)	< .001
T4	7	71	100	2.03 (0.84 to 4.93)	.12	1.15 (0.42 to 3.15)	.78
Pathologic nodal stage							
N0	584	49	64	1.0 (Ref)		1.0 (Ref)	—
N1	10	82	82	2.11 (1.13 to 3.94)	.02	1.48 (0.75 to 2.95)	.26
Gleason score							
≤ 6	136	35	52	1.0 (Ref)	—	1.0 (Ref)	—
7	301	51	66	1.63 (1.33 to 2.00)	<.001	1.7 (1.38 to 2.09)	< .001
8	59	70	80	2.44 (1.80 to 3.32)	<.001	2.67 (1.95 to 3.65)	< .001
9-10	71	71	81	2.85 (2.14 to 3.80)	<.001	3.34 (2.47 to 4.52)	< .001
Pre-RP PSA, ng/mL							
< 10	345	46	62	1.0 (Ref)	—	1.0 (Ref)	—
10-20	136	51	68	1.18 (0.97 to 1.44)	.11	1.01 (0.81 to 1.26)	.91
> 20	84	66	71	1.55 (1.22 to 1.97)	<.001	1.11 (0.84 to 1.47)	.46
RP to detectable PSA							
< 1.0 year	255	56	66	1.0 (Ref)	—	1.0 (Ref)	—
≥ 1.0 years	310	45	62	0.77 (0.65 to 0.91)	.002	0.86 (0.72 to 1.03)	.10
Pre-SRT PSA (per doubling)				1.18 (1.11 to 1.25)	<.001	1.30 (1.21 to 1.39)	< .001
Androgen suppression							
None	527	51	66	1.0 (Ref)	—	1.0 (Ref)	—
≤ 1.0 year	51	48	62	0.81 (0.61 to 1.08)	.14	0.59 (0.43 to 0.81)	< .001
> 1.0 years	22	35	50	0.52 (0.34 to 0.79)	.002	0.26 (0.16 to 0.41)	< .001
SRT dose (Gy)							
< 66	224	54	70	1.0 (Ref)	—	1.0 (Ref)	—
66-67.99	119	56	66	1.03 (0.82 to 1.29)	.80	1.09 (0.86 to 1.38)	.50
68-71.99	187	47	59	0.80 (0.65 to 0.97)	.021	0.77 (0.60 to 0.98)	.04
≥ 72	70	39	70	0.68 (0.52 to 0.89)	.005	0.60 (0.43 to 0.86)	.005
SRT year							
1987-2002	253	57	70	1.0 (Ref)	—	1.0 (Ref)	—
2003-2007	203	44	61	0.76 (0.63 to 0.92)	.004	1.08 (0.86 to 1.35)	.52
2008-2013	144	48	—	0.79 (0.64 to 0.98)	.03	1.49 (1.10 to 2.01)	.009

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; Ref, referent; RP, radical prostatectomy; SRT, salvage radiotherapy.
*Six hundred events total; number of events not shown for patients with missing variables.
†Multiple variable analyses limited to patients in whom all characteristics are known.

Salvage RT + ADT





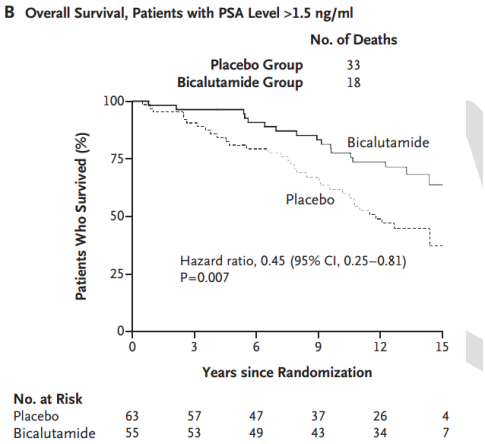


RTOG 96-01. Salvage prostate. RT +/- ADT 13 year F/U
←R→ 760 patient prostatectomy + PLND (but no WPRT).
INCLUSION: KPS 80-100, pT2 (+SM) or pT3, pN0, detectable PSA 0.2 to 4.0 ng/mL at least 8 wk after surgery.
| 1. RT + ADT | 2. RT + placebo |. ADT = 24 months of bicalutamide at a dose of 150 mg daily.
Different Medication Dose → Many centers now use 50 mg daily.
RT 64.8 Gy in 36 fx 1.8 Gy. Regional pelvic lymph-node treatment was omitted since all pLN-.

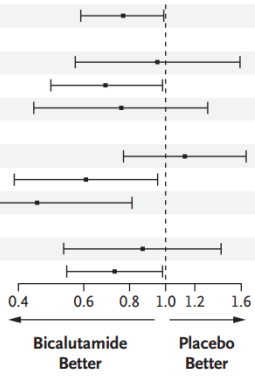
A lot of patients had high PSAs on this trial. 50% < 0.7. And 50% > 0.7.

Shipley, NEJM 2017. 13-year F/U.
OS_{12} 76.3% vs 71.3% (p=0.04). Death from PCa 5.8% vs 13.4% (P < 0.001).
The cumulative incidence of metastatic prostate cancer at 12 years 14.5% vs 23.0% (P = 0.005).
Incidence of late adverse events associated with RT was similar.
Gynecomastia 69.7% vs 10.9% of those in the placebo group (P<0.001).

ADT concurrently, not neo-adjuvant.
Patients for preventing metastatic disease. GS 8-10 benefited from ADT!!! 23% → 14% distant mets ADT.
Practice: 0.2-0.7 consider STADT especially for GS 8-10. For > 0.7, LTADT ADT GS 8-10. For > 1.5, LTADT.



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

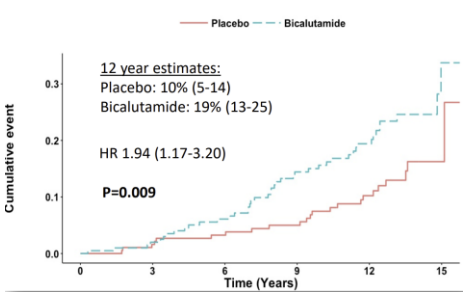


Secondary Analysis. Other Cause Mortality by PSA.
Spratt, ASTRO 2019
760 patients, 85% (n=642/760) pre-SRT PSA of ≤1.5 ng/mL stratum.
OS NS Δ men with PSA ≤1.5 ng/mL (HR 0.87)
OS Benefit PSA >1.5 ng/mL (n=118) (HR 0.45 [0.25-0.81]).
pre-SRT PSA ≤0.6 ng/mL (n=389) had ↑ OCM (sHR:1.94, [1.17-3.20]) from bicalutamide (greatest in PSA 0.2-0.3 (n=148; sHR:4.14 [1.57-10.89]).
Bicalutamide ↑ grade 3-5 cardiac events (p=0.04).

SEE DECIPHER ANALYSIS under Genetic Testing.

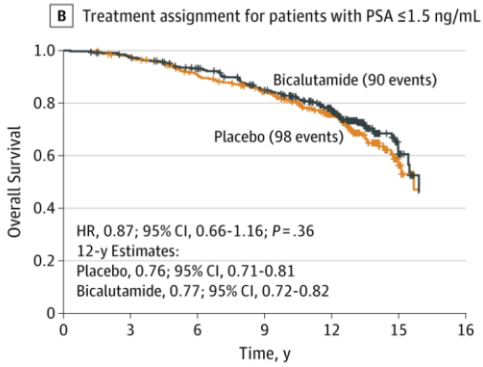
Other-Cause Mortality

PSA 0.2-0.6 ng/mL

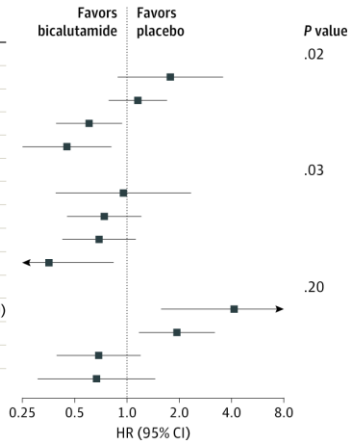


Dess, JAMA Oncol 2020. Secondary Analysis.
760 men SM+ or pT3 disease + a pre-SRT PSA of 0.2-4.0 ng/mL were included.
Age median 65 (40-83) years.
12-year OS in patients > 1.5 PSA absolute Δ 25% (ss). NS if PSA < 1.5 of only 1%.
The PSA ≤ 1.5 group was further categorized as receiving early salvage RT (PSA 0.2-0.6) or late salvage RT (0.61-1.5).
IF subanalysis PSA 0.61 - 1.5 (n = 253), ALSO OS benefit (SS). Vs. early SRT (PSA ≤0.6 ng/mL, n = 389), OS NS
Early SRT also unfortunately ↑ other cause mortality (SS).
(subdistribution HR, 1.94; 95% CI, 1.17-3.20; P = .01), and an increased odds of late grades 3 to 5 cardiac and neurologic toxic effects (odds ratio, 3.57; 95% CI, 1.09-15.97; P = .05).
There was a strong interaction between PSA (as a continuous variable) and OS benefit from ADT.

Conclusions and Relevance These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of antiandrogen treatment with SRT. In patients receiving late SRT (PSA >0.6 ng/mL, hormone therapy was associated with improved outcomes. In men receiving early SRT (PSA ≤0.6 ng/mL), long-term antiandrogen treatment was not associated with improved OS. Future randomized clinical trials are needed to determine hormonal therapy benefit in this population.



End point, PSA	Bicalutamide incidence/N	Placebo incidence/N	12-Year absolute difference bicalutamide vs placebo (CI 95%)	HR (95% CI)
Overall survival				
0.20-0.30	20/74	13/74	-0.13 (-0.27 to 0.01)	1.78 (0.88-3.57)
0.20-0.60	56/201	48/188	-0.04 (-0.12 to 0.05)	1.16 (0.79-1.70)
0.61-1.50	34/128	50/125	0.09 (-0.03 to 0.20)	0.61 (0.39-0.94)
≥1.51	18/55	33/63	0.25 (0.07 to 0.42)	0.45 (0.25-0.81)
Distant metastasis				
0.20-0.30	9/74	10/74	0.01 (-0.10 to 0.13)	0.95 (0.39-2.34)
0.20-0.60	28/201	36/188	-0.04 (-0.12 to 0.03)	0.74 (0.45-1.21)
0.61-1.50	28/128	37/125	-0.10 (-0.21 to 0.01)	0.69 (0.43-1.12)
≥1.51	7/55	20/63	-0.18 (-0.33 to -0.03)	0.36 (0.15-0.84)
Other-cause mortality				
0.20-0.30	17/74	5/74	0.18 (0.06 to 0.31)	4.14 (1.57-10.89)
0.20-0.60	43/201	23/188	0.09 (0.02 to 0.17)	1.94 (1.17-3.20)
0.61-1.50	21/128	29/125	-0.03 (-0.13 to 0.08)	0.69 (0.39-1.20)
≥1.51	10/55	15/63	-0.09 (-0.23 to 0.06)	0.67 (0.31-1.45)



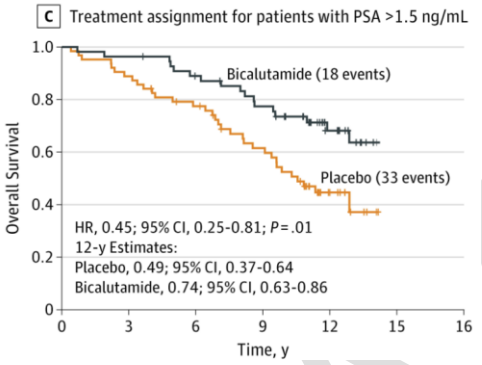


Table 2. Multivariable Analysis for Overall Survival, Distant Metastasis, and Other-Cause Mortality for Patients With PSA Levels of 0.2 to 0.6 ng/mL

	Overall survival (n = 383)		Distant metastasis (n = 383)		Other-cause mortality (n = 383)	
Variable	HR (95% CI)	*P* Value	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
Bicalutamide vs placebo	1.07 (0.72-1.59)	.73	0.69 (0.43-1.13)	.14	1.87 (1.12-3.12)	.02
Age	1.10 (1.06-1.13)	<.001	1.00 (0.96-1.04)	.91	1.12 (1.07-1.16)	<.001
Gleason score						
7 vs ≤6	1.09 (0.68-1.75)	.71	1.47 (0.75-2.87)	.26	0.86 (0.49-1.49)	.59
8-10 vs ≤6	1.91 (1.09-3.34)	.02	2.68 (1.27-5.64)	.01	0.77 (0.38-1.58)	.48
T2 vs T3	0.91 (0.58-1.43)	.69	0.71 (0.37-1.38)	.31	1.20 (0.71-2.03)	.49
Margin, positive vs negative	1.02 (0.64-1.65)	.92	0.47 (0.26-0.82)	.01	1.24 (0.67-2.32)	.49
Nadir PSA, <0.5 vs ≥0.5 ng/mL	1.74 (0.63-4.83)	.29	1.88 (0.64-5.57)	.25	2.80 (1.11-7.08)	.03

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; sHR, subdistribution hazard ratio.

Feng, JAMA Oncol 2021 Genomic Classifier (GC) DECIPHER SUBSET
GC scores generated from 486 of 760 randomized patients with a median follow-up of 13 years. 314 White [89.2%].
MVA, GC (continuous variable, per 0.1 unit) was independently associated with DM (HR 1.17; P = .006), PCSM (HR, 1.39; P < .001), OS (HR, 1.17; P = .002).
Estimated absolute effect of bicalutamide on 12-year OS was less when comparing patients with lower vs higher GC scores (2.4% vs 8.9%), which was further demonstrated in men receiving early sRT at a prostate-specific antigen level lower than 0.7 ng/mL (−7.8% vs 4.6%).
Conclusions and Relevance This ancillary validation study of the Decipher GC in a randomized trial cohort demonstrated association of the GC with DM, PCSM, and OS independent of standard clinicopathologic variables. These results suggest that not all men with biochemically recurrent prostate cancer after surgery benefit equally from the addition of hormone therapy to sRT.

Table 2. Multivariable Analysis of GC for Distant Metastasis, Death From Prostate Cancer, and Overall Survival[a]

	DM		PCSM		OS	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
GC score	1.17 (1.05-1.32)	.006[b]	1.39 (1.20-1.63)	<.001[b]	1.17 (1.06-1.29)	.002[b]
Treatment vs placebo	0.62 (0.39-0.97)	.04[b]	0.53 (0.30-0.92)	.02[b]	0.82 (0.57-1.19)	.29
Age ≥65 vs <65, y	1.30 (0.83-2.06)	.25	1.52 (0.88-2.66)	.14	1.95 (1.33-2.91)	<.001[b]
African American vs non-African American	0.88 (0.28-2.13)	.80	0.86 (0.17-2.73)	.83	1.35 (0.57-2.77)	.47
Gleason 8-10 vs ≤7	2.11 (1.24-3.47)	.007[b]	2.53 (1.38-4.49)	.003[b]	1.87 (1.20-2.85)	.007[b]
T3 vs T2	1.42 (0.82-2.58)	.22	2.01 (0.97-4.62)	.06	1.24 (0.79-1.97)	.35
PSA level at trial entry	1.16 (0.88-1.49)	.26	1.37 (1.01-1.80)	.04[b]	1.08 (0.84-1.35)	.53
Positive surgical margins	0.71 (0.44-1.16)	.17	1.26 (0.68-2.44)	.46	0.98 (0.64-1.53)	.92
Non-nadir vs nadir (<0.5 ng/mL)	1.31 (0.62-2.51)	.46	2.10 (0.92-4.26)	.07	1.98 (1.13-3.30)	.02[b]

"TOAD" TROG 0306 - NOT THE SAME AS TROG "3-6-9" 9601
←R→ 293 patients with 1. PSA relapse after curative Tx (RT or surgery, w/wo postop RT) 2. not suitable for curative tx (age, comorbidity, or advanced dx).
| 1. immediate ADT | 2. delayed ADT | Arm 2 has a recommended interval of at least 2 years unless clinically contraindicated.
261 fit the first category and 32 fit the non-curable disease.
Excluded patients with overt mets, those who received ≥ 12 months of ADT as part of up-front tx.

Duchesne, Lancet 2016.
5-year OS 91.2% vs. 86·4% (p=0·047).
Interpretation
Immediate receipt of androgen-deprivation therapy significantly improved overall survival compared with delayed intervention in men with PSA-relapsed or non-curable prostate cancer. The results provide benchmark evidence of survival rates and morbidity to discuss with men when considering their treatment options.
NOTE: survival is NOT significant if you only consider post-op patients and NOT the other patients. Curves did NOT separate until 5 years.

GETUG-AFU 16
←R→ 743 s/p RP with INITIALLY UNDETECTABLE and subsequently rising PSA 0.2 – 2. | 1. Salvage RT alone | 2. RT + ADT |
ADT = 6 mo goserelin day 1 and 3 months later. RT = 66 Gy in 33 fx via 3DCRT or IMRT.
WPRT allowed if >15% prostate node + risk or if nodes were not assessed at surgery.

Carrie, Lancet 2016.
5-year bRFS 62% vs. 80% (SS).
No additional late adverse events occeleurred in patients receiving short-term ADT vs. RT alone.
Interpretation Adding short-term androgen suppression to salvage radiotherapy benefits men who have had radical prostatectomy and whose PSA rises after a postsurgical period when it is undetectable. Radiotherapy combined with short-term androgen suppression could be considered as a reasonable option in this population.

Retrospective Trock, JAMA 2008
RR 635 s/p prostatectomy with bFailure and/or LR and received NO salvage treatment (n = 397), salvage RT alone (n = 160), or salvage RT + ADT (n = 78).
1^{O} PCSS = time of recurrence until death from disease.

RESULTS: Median follow-up of 6 years after recurrence and 9 years after prostatectomy.
116 men (18%) died from prostate cancer | none 89 (22%) | RT 18 (11%) | RT+ADT 9 (12%) |.
Salvage RT alone 3x ↑ PCSS (SS).
Addition of ADT + RT no Δ PCSS.
Salvage radiotherapy initiated more than 2 years after recurrence provided no Δ ↑ PCSS.
Salvage radiotherapy also was associated with a significant increase in OS.
CONCLUSIONS: Salvage radiotherapy administered within 2 years of biochemical recurrence was associated with a significant increase in prostate cancer-specific survival among men with a prostate-specific antigen doubling time of less than 6 months, independent of other prognostic features such as pathological stage or Gleason score. These preliminary findings should be validated in other settings, and ultimately, in a randomized controlled trial.

AZ 2022

Salv-RT + Systemic

NRG GU002 – SRT + 6mo ADT ± Docetaxel
FORMULA 509 – SRT + 6 mo ADT ± abiraterone/apalutamide
STEEL Men specifically at high PSA over 0.7 to SRT + 2 years ADT ± enzalutamide.

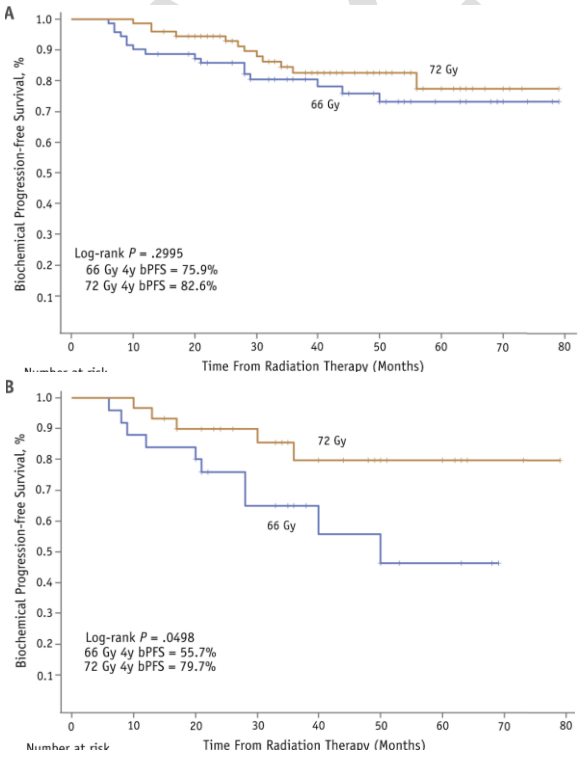
Δ RT Dose/Fx

SAKK 09/10 UK Salvage RT Trial
←R→ 350 BcR after RP | 1. conventional-dose (64 Gy) | 2. dose-intensified SRT (70 Gy) | to the prostate bed without hormonal therapy.
Median PSA 0.3 at randomization.
1^{O} FFBcP

Ghadjar, Euro Ur 2021. 6.2 years
6-year FFBcP ~62% NS Median FFBP ~8 years.
Late G2/3 GU 7.9%/21% vs. 4.0%/26% (p = 0.8).
Late G2/3 GI 4.2%/7.3% vs. 2.3%/20% (p = 0.009).
There were no significant differences in QoL.
Conclusions Conventional-dose SRT to the prostate bed is sufficient in patients with early biochemical progression of prostate cancer after RP.

NRG GU003 Hypofractionated PORT = HYPORT
←R→ 298 men s/p RT with either 1. Undetectable PSA < 0.1 + margin-negative pT3N0 / margin-positive pT2N0, OR 2. Detectable PSA + pT2-3N0.
| 1. HYPORT 62.5 Gy / 25 fx in 2.5 Gy | 2. Conventional 66.6 Gy / 37 fx in 1.8 Gy |.
WPRT NOT ALLOWED. ADT ≤ 6 month allowed.
1^{O} non-inferiority trial EPIC GI and GU at 24 months.

Buyyounouski, ASTRO 2021.
Between July 2017 and July 2018, 298 patients were screened and 296 were randomized: 144 to HYPORT and 152 to COPORT.
Mean GU Δ scores at the end of RT were **NS** and **remained so at 6 and 12 months**.
Mean GI Δ scores at the end of RT were **SS** (HYPORT mean GI = -15.0 vs COPORT mean GI = -6.8 p ≤ 0.01).
However, both arms mean GI change scores resolved at 6 and 12 months.
24-month mean GU NS HYPORT mean GU = -5.2 vs COPORT mean GU = -3.0, p = 0.81
24-month mean GI NS HYPORT mean GI = -2.2 vs COPORT mean GI = -1.5, p = 0.12.
With a median follow-up for censored patients of 2.1 years, there was no difference between HYPORT versus COPORT for biochemical failure defined as a PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount (2-yr actuarial, 12% vs 8%, p = 0.29) or local failure (2-yr actuarial, 0.7% vs 0.8%, p = 0.35).
Conclusion: HYPORT is non-inferior to COPORT in terms of late patient-reported GU or GI toxicity. More follow-up is needed to appropriately assess disease control endpoints. In some clinic scenarios, HYPORT may be considered an acceptable practice standard.



Chinese DE-PORT Trial
←R→ 144 with RP + (pT3-4, SM+, or ↑ PSA 0.2 ng/mL)
| 1. 66 Gy in 33 fractions | 2. 72 Gy in 36 fractions |.
1^{O} bPFS

Qi, IJROBP 2019.
4-year bPFS 75.9% vs 82.6% (NS)
Subset GS 8-10, 4-year bPFS 55.7% vs. 79.7% (p=0.049).
Toxicity analysis showed no difference in 2 acute or late GI or GU toxicities between these 2 cohorts.
A total of 48 patients were scored as urinary incontinence before radiation therapy, of which 39 (81.3%) reported incontinence recovery or stable at 1-year follow-up, and only 9 (18.8%) patients reported worsening.
There was no difference between the 2 cohorts in urinary incontinence either at baseline or at 1-year follow-up.
Conclusions: Dose escalation (72 Gy) demonstrated no improvement in 4-year bPFS compared with the 66 Gy regimen. However, the dose escalation was not associated with greater acute or late GU or GI toxicities and did not increase urinary incontinence.

Phase II 15 Fx Trial
Single Arm 61 patients (57 salvage, 4 adjuvant).
All → s/p radical prostatectomy → hypofractionated RT to the prostate bed 51 Gy in 15 fractions (3.4 Gy per fraction) IMRT/IGRT.
1^{O} acute GU grade ≥2 toxicity.

Leite, IJROBP 2021. 16 months FU.
11.5% acute Grade ≥2 GU symptoms 13.1% acute grade ≥2 GI symptoms.
8.5% late Grade ≥2 GU toxicity 11.5% late grade ≥2 GI toxicity
2-year BFFS, use of subsequent salvage therapy, and the development of metastasis were 95.1%, 0%, and 0%, respectively.
Conclusions Hypofractionated RT to the prostate bed in 15 treatments was safe, with an acceptable GU and GI toxicity profile. Further study in large, randomized trials is warranted.

Metaanalysis
←M→ 1996 to 2015 factors associated with RFS after salvage RT (uniformly defined as a PSA>0.2ng/mL or rising above post-SRT nadir).
A sigmoidal dose-response curve was objectively fitted and a non-parametric statistical test used to determine significance.
71 studies (10,034 patients) satisfied the meta-analysis criteria.

King Radiother Oncol 2016.
SRT dose (p=0.0001), PSA prior to SRT (p=0.0009), ECE+ (p=0.039) and SV+ (p=0.046) had significant associations with RFS.
Statistical analyses confirmed the independence of SRT dose-response.
Omission of series with ADT did not alter results.
Dose-response is well fit by a sigmoidal curve (p=0.0001) with a TCD50 of 65.8Gy, with a dose of 70Gy achieving 58.4% RFS vs. 38.5% for 60Gy. A 2.0% [95% CI 1.1-3.2] improvement in RFS is achieved for each Gy. The SRT dose-response remarkably parallels that for definitive RT of localized disease.
CONCLUSIONS: This study provides level 2a evidence for dose-escalated SRT>70Gy. The presence of an SRT dose-response for microscopic disease supports the hypothesis that prostate cancer is inherently radio-resistant.

Multicenter RR
RR 1108 patients margin positive and pre-RT PSA ≤ 2. Without confounding of planned androgen suppression.
bcF = > 0.2.

Pisansky, IJROBP 2016.
5-year FFbcF 63.5%. 10-year FFbcF 49.8%. 10-year DM was 12.4%.
Predictors for bcF and DM GS ≥7, ↑ pre-RT PSA level, EPE, and SV+.
A salvage radiation dose of ≥66.0 Gy was associated with a reduced cumulative incidence of biochemical failure, but not of distant metastasis.
CONCLUSIONS: The use of salvage radiation doses of ≥66.0 Gy are supported by evidence presented in the present multicenter pooled analysis of individual patient data. The observational reporting method, limited sample size, few distant metastasis events, modest follow-up duration, and elective use of salvage therapy might have diminished the opportunity to identify an association between the radiation dose and this endpoint.

King, Spiotto. IJROBP 2008.
RR 122 patients with RP + pLN- → salvage RT. Median prostate bed dose was 60 Gy for 38 patients and 70 Gy for 84 patients.
ADT 4 months and WPRT given concurrently to 68 and 72 patients [sic], respectively. The median follow-up was >5 years.

5-year bRFS rate 60 Gy 25% vs. 70 Gy 58% (SS). if RT alone… 5-year bRFS 17% vs. 55% (SS). If prostate bed only RT 23% vs. 66% (SS)
MVA prostate bed 70 Gy (HR 0.48, SS), pre-RT PSA ≤ 1 ng/mL (HR 0.28, SS), and no SV involvement (HR 0.44, SS).
CONCLUSIONS: A clinically significant dose response from 60 Gy to 70 Gy was observed in the setting of salvage RT after prostatectomy. A dose of 70 Gy to the prostate bed is recommended to achieve optimal disease-free survival.

Milan RR
RR 334 hrPCa (pT3-4 and/or + SM) node-negative patients submitted to RP + PLND analyzed by early adjuvant RT to the prostatic bed, <70.2 vs. ≥ 70.2.

Cozzarini, IJROBP 2009. Note SS Δ median FU (10 vs. 7 years, respectively) owing to the gradual ↑ of early adjuvant RT over time.
Median time to bcF 38 vs. 36 months (NS).
5-year bRFS 83% vs. 94% (SS), 5-year DFS 71% vs. 88% (SS).
MVA showed EA-RT ≥ 70 Gy independently ↑ bRFS (hazard ratio 2.5, p = 0.04) and DFS (hazard ratio 3.6, p = 0.004).
NOTE 1: Similar results were obtained after the exclusion of patients receiving any androgen deprivation.
NOTE 2: After grouping the hormone-naïve patients by postoperative PSA level the SS impact of high-dose EART on both 5-year bRFS and DFS was maintained only for those with undetectable values, possibly owing to micrometastatic disease outside the irradiated area in case of detectable postoperative PSA values.
CONCLUSION: This series provides strong support for the use of EART doses >or=70 Gy after radical retropubic prostatectomy in hrCaP patients with undetectable postoperative PSA levels.

AZ 2022

Mayo RR
RR 364 rising PSA level after RP → salvage EBRT. Patients receiving pre-EBRT androgen suppression were excluded.
RT doses (low, <64.8 Gy; moderate, 64.8-66.6 Gy; high, >66.6 Gy). Median pre-EBRT PSA level was 0.6 ng/mL.

Bernard, IJROBP 2010.
5-year bcControl = 50% overall and 43%, 54%, and 61% for the low-, moderate-, and high-dose groups, respectively.
MVA = evidence of a linear trend between dose and BcF (Dose RR 0.77, p = 0.05).
Compared with the low-dose group, there was evidence of a decreased risk of BcF for the high-dose group (RR, 0.60; p = 0.04), but no difference for the moderate-dose group (RR, 0.85; p = 0.41).
CONCLUSIONS:
Our results suggest a dose response for salvage EBRT. Doses higher than 66.6 Gy result in decreased risk of BcF.

MSKCC RR The only "negative study in this group"
RR 285 pts treated with salvage RT. Median PSA before SRT 0.4. 60 pts (21%) had MRI-detected local recurrence. 42 pts had pathologic confirmation LR.
95% were treated to a dose >= 66 Gy; 72% received >= 70 Gy. ADT used in 31%.

Goenka A, IJROBP 2012. Median f/u 60 mo.
7-yr bRFS 37%, DMFS 77%. Predictors of recurrence: vascular invasion, negative margins, presalvage PSA > 0.4, no use of ADT, GS ≥ 7, +SV.
RT dose >= 70 Gy was not associated with improved biochemical control. PSA-DT < 3 months was the only indep. predictor of DM.
Trend toward benefit of dose >= 70 Gy in decreasing clinical local failure in pts who had radiographically visible local disease at the time of SRT.
Conclusion: "Salvage RT provides effective long-term biochemical control and freedom from metastasis in selected patients presenting with detectable PSA after prostatectomy. Androgen-deprivation therapy was associated with improvement in biochemical progression-free survival. Clinical local failures were rare but occurred most commonly in patients with greater burden of disease at time of SRT as reflected by either radiographic imaging or a greater PSA level. Salvage radiation doses ≥70 Gy may ultimately be most beneficial in these patients, but this needs to be further studied."

AZ 2024

WPRT (Salvage RT)

Salvage SPPORT RTOG 05-34. | 1. RT Prostate Bed Only | 2. RTPBO + ADT | 3. RTPBO + ADT + WPRT |
bCF after salvage prostate bed radiation therapy (PBRT) is typically 30-40% at 5-10 years.
Neoadjuvant and concurrent short term androgen deprivation therapy (STAD) is an effective addition to primary radiation therapy and in 2005 had not yet been tested with salvage PBRT.
Pelvic lymph node radiation therapy (PLNRT) has shown promise, but has never been conclusively proven to be effective in a Phase III randomized trial.
Trial hypothesis: For prostate cancer patients with a rising PSA after prostatectomy, there will be an incremental gain in freedom from progression with the addition of: • STAD to PBRT • PLNRT + STAD to PBRT
ADT 6 months.
ASTRO 2018 Results below.
Constraint Bladder – CTV V65 < 40% and V40 < 70%.

STRATIFY	RANDOMIZE
SV Involvement 1. No 2. Yes **Prostatectomy Gleason Score** 1. Gleason ≤ 7 2. Gleason 8-9 **Pre-Radiotherapy PSA** 1. PSA ≥ 0.1 and ≤ 1.0 ng/mL 2. PSA > 1.0 and < 2.0 ng/mL **Pathology Stage** 1. pT2 and margin negative 2. All others	**Arm 1: PBRT Alone** PBRT 64.8-70.2 Gy **Arm 2: PBRT + STAD** PBRT 64.8-70.2 Gy + STAD for 4-6 months beginning 2 months before RT **Arm 3: PLNRT + PBRT + STAD** PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,+ STAD for 4-6 months beginning 2 months before RT

SV = seminal vesicle; RT = radiation therapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; STAD = neoadjuvant and concurrent short-term androgen deprivation

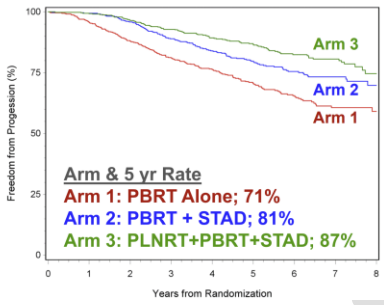
Primary endpoint: FFP at 5 years

Failure defined as first occurrence of:

- PSA ≥ Nadir+2 ng/mL
- Clinical progression (local, regional or distant)
- Death due to any cause

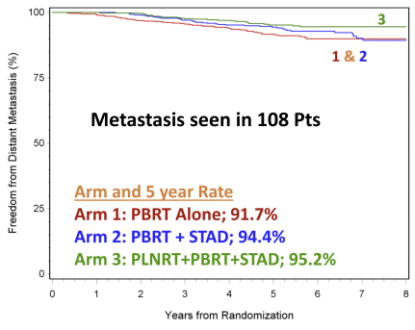
	PBRT Alone (n=574)		PBRT+STAD (n=585)		PLNRT+PBRT+STAD (n=577)		Total	
Patient/Tumor Characteristic	n	%	n	%	n	%	n	%
Zubrod Performance Status								
0	533	92.9	546	93.3	543	94.1	1622	93.4
1	41	7.1	39	6.7	34	5.9	114	6.6
Seminal Vesicle Involvement								
No	492	85.7	498	85.1	489	84.7	1479	**85.2**
Yes	82	14.3	87	14.9	88	15.3	257	14.8
Prostatectomy Stage								
pT2	304	53.0	326	55.7	312	54.1	942	**54.3**
pT3 NOS	19	3.3	17	2.9	22	3.8	58	3.3
pT3a ECE	173	30.1	160	27.4	156	27.0	489	28.2
pT3b SVI	78	13.6	82	14.0	87	15.1	247	14.2
Prostatectomy Margins								
Positive	292	50.9	292	49.9	286	49.6	870	**50.1**
Negative	273	47.6	286	48.9	288	49.9	847	48.8
Unknown	9	1.6	7	1.2	3	0.5	19	1.1

FFP: All eligible patients (1,792)



5 yr Rate Comparison
Arm 3 vs Arm 1: p<0.0001
Arm 2 vs Arm 1: p<0.0001
Arm 3 vs Arm 2: p=0.0039

HRs and 97.5% CIs
3 vs 1: 0.45 (0.34-0.61)
2 vs 1: 0.62 (0.47-0.82)
3 vs 2: 0.71 (0.52-0.98)



5 yr Rate Comparison
Arm 3 vs Arm 1: p=0.014
Arm 2 vs Arm 1: p=0.05
Arm 3 vs Arm 2: p=0.28

HRs and 97.5% CIs
3 vs 1: 0.52 (0.30-0.92)
2 vs 1: 0.81 (0.49-1.33)
3 vs 2: 0.64 (0.36-1.14)

No statistically significant differences in OS

Acute Adverse Events (CTCAEv3) Without Regard For Attribution

	PBRT Alone (n=557)		PBRT+STAD (n=568)		PLNRT+PBRT+STAD (n=567)		p-value
Type	n	%	n	%	n	%	
GI							
Grade 2+	11	2.0	22	3.9	39	6.9	**<0.001**
Grade 3+	1	0.2	5	0.9	4	0.7	0.37
Renal/GU							
Grade 2+	54	9.7	68	12.0	69	12.3	0.35
Grade 3+	5	0.9	5	0.9	8	1.5	0.70
Blood/Bone Marrow							
Grade 2+	13	2.3	10	1.8	29	5.1	**0.002**
Grade 3+	3	0.5	1	0.2	15	2.6	**<0.001**

Late Adverse Events (CTCAEv3) Without Regard For Attribution

	PBRT Alone (n=557)		PBRT+STAD (n=571)		PLNRT+PBRT+STAD (n=570)		p-value
Type	n	%	n	%	n	%	
GI							
Grade 2+	54	9.7	50	8.8	46	8.1	0.63
Grade 3+	4	0.7	2	0.4	6	1.1	0.34
Renal/GU							
Grade 2+	188	33.8	184	32.2	197	34.6	0.70
Grade 3+	24	4.4	28	4.9	34	6.0	0.44
Blood/Bone Marrow							
Grade 2+	17	3.1	9	1.6	23	4.1	**0.044**
Grade 3+	2	0.4	1	0.2	6	1.1	0.12

Conclusions: • Strongest level I evidence supporting PLNRT • For Arm 3 vs Arm 1, number needed to treat to prevent one progression within 5 years is 6 (95%CI 4.6-8.6)! o Follow-up continuing to further elucidate the magnitude of the differences between Arms 2 and 3 • Robust effect translating into a decrease in distant metastasis • Is there a PSA cutpoint below which PLNRT is not needed? • Role of PET in PLNRT decisions? • Implications for the management of primarily managed prostate cancer • Local control needed to realize the impact of PLNRT (NRG 0924)

Stanford Retrospective
RR 160 patients s/p RT → Salvage Whole Pelvis RT (WPRT) vs. Prostate Bed RT (PBRT).
ST-ADT concurrently given to 87/160 patients. 114/160 High Risk LN+ (with GS ≥8, PSA ≥20, pT3, or pLN+). Of these, 72/114 had WPRT.

Spiotto, IJROBP 2007.
For high-risk patients, 5-year bRFS 47% vs. 21% (SS).
For low-risk patients, no difference (p = 0.9) was found.
MVA, only WPRT (p = 0.02) and a preoperative PSA <1.0 ng/mL (p = 0.002) were significantly associated with bRFS.
The benefit from ADT with postoperative RT was only observed when given concurrently with WPRT (p = 0.04) and not with PBRT (p = 0.4).
Conclusion: The results of our study have indicated that WPRT confers superior bRFS compared with PBRT for high-risk patients receiving adjuvant or salvage RT after radical prostatectomy. This advantage was observed only with concurrent TAS. These results are analogous to the benefit from WPRT seen in the Radiation Therapy Oncology Group 94-13 study.

Other

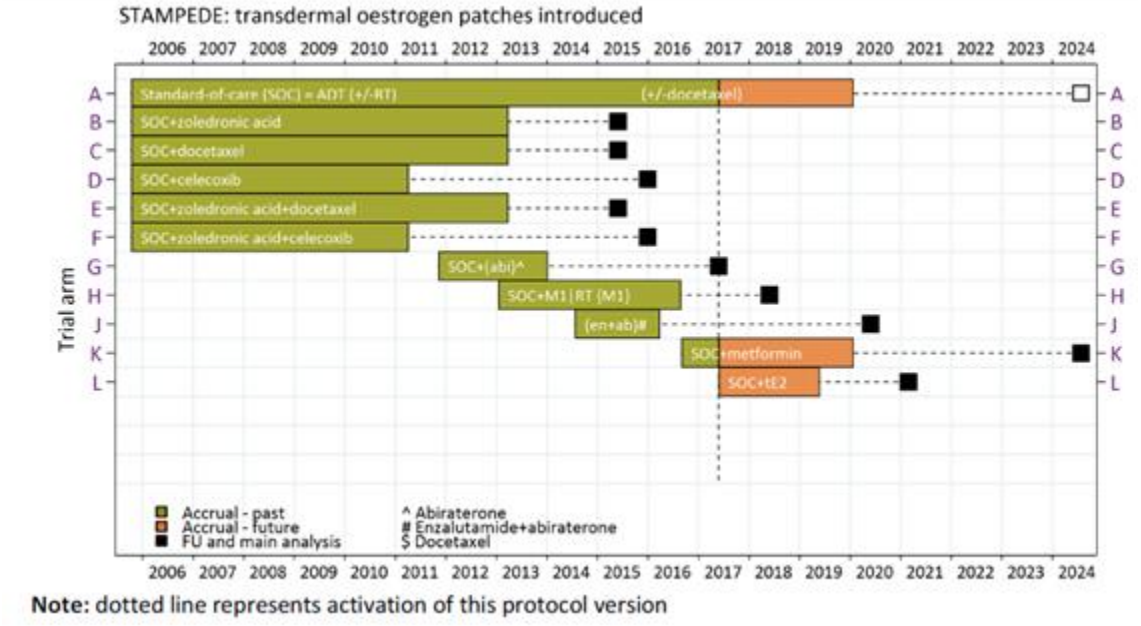
Canadian Phase II Single Arm Trial of Second Failure
Phase II. 72 patients Rising PSA (0.4-3) s/p MAX local TX (RP and PORT) with NO prior salvage ADT.
All patients had PSMA PET w/ oligorecurrent PCa → SBRT / surgery without ADT.
38 (53%) had PSMA-detected oligorecurrent-PCa amenable for MDT. 37 (51%) agreed to MDT: 10 and 27 underwent surgery and SABR, respectively.
1^{O} bCR.

Glicksman, European Urology 2021.
Median follow-up was 15.9 months (IQR 9.8-19.1).
Median time to PSA progression = 17 months.
Of patients receiving MDT, the overall response rate was 60%, including 22% rendered bNED.
One (2.7%) grade 3 toxicity (intra-operative ureteric injury) was observed.
Conclusions PSMA-defined oligorecurrent-PCa can be rendered bNED, a necessary step towards cure, in 1 of 5 patients receiving MDT alone.
Randomized trials are justified to determine if MDT +/− systemic agents can expand the curative therapeutic armamentarium for PCa.

AZ 2022

STAMPEDE Trial Info

STAMPEDE is a multi-centre, RTC for locally advanced or metastatic PCa (mCSPC) commencing LT-ADT.
For patients with newly diagnosed disease or have been previously treated with RT or RP → now have signs of progression (↑ PSA, e.g.).
The trial will assess the effects of adding different agents, both as single agents and in combinations, to the standard-of-care or substituting standard of care.

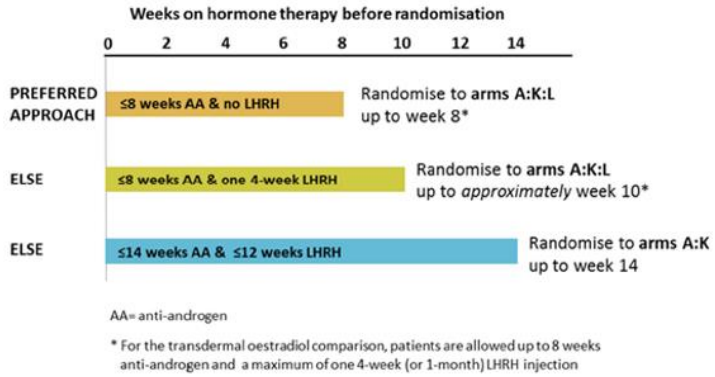


Eligibility:

ALL must have PCA and intention to tx with LT-ADT.

One of the criteria:

1. High-Risk Newly-Diagnosed Non-Metastatic Node-Negative Disease
    a. At least ≥2
        i. T category T3/4
        ii. PSA≥40ng/ml
        iii. Gleason sum score 8-10
    b. Intention to treat with radical radiotherapy
2. Newly-Diagnosed Metastatic or Node-Positive Disease
    a. At least 1
        i. Stage Tany N+ M0
        ii. Stage Tany Nany M+
3. Previously RT or RP → Now Relapsing
    a. At least 1
        i. PSA ≥4ng/ml and rising with doubling time less than 6 months
        ii. PSA ≥20ng/ml
        iii. N+
        iv. M+



LN+ Disease

Local Therapy

SEER/U. Colorado
RR 796 clinically node positive (cN+), 2991 pathologically node positive (pN+), analyzed as separate cohorts.

Rusthoven, IJROBP 2014
For cN+ patients, 43% had EBRT vs 57% had No Local Therapy (NLT). 10-yr OS 45% vs 29% (P<.001) (median OS 9.6 vs 5.9 yr)
For pN+ patients, 78% had local therapy (radical prostatectomy (RP) 57%, EBRT 10%, or both 11%) vs 22% had NLT. 10-yr OS 65% vs 42% (P<.001) (median OS 13.6 vs 8.3 years)
Local therapy beneficial across subgroups, including age >=70 years and multiple +lymph nodes
Secondary comparisons of RP vs EBRT and RP +/- Adjuvant EBRT: no significant differences between modalities. +Trend toward improved OS with RP + Adjuvant EBRT over RP alone (p=.08).
Conclusion: "RP and EBRT were associated with substantial improvements in OS and PCSS. The best available evidence suggests that patients with N1M0 PCa can achieve improved long-term survival outcomes with definitive local therapy and these strategies should be considered in appropriate candidates."

"Mixed Population Model" PMID 25680608 - authors propose a model to account for potential "under-ascertainment" of radiation data (ie, coding "no radiation" in observational databases [SEER, etc] when radiation was actually delivered to the patient [Jagsi Cancer 2012;118:333-341, Walker IJROBP 2013;86:686-693, Jagsi IJROBP 2014;90(1):11-24]):

AZ 2022

ADT Studies

STAMPEDE (Trial G and J) **HIGH RISK or LN+ Men**

←R→ 1974 non-metastatic prostate cancer upfront high-risk (LN+ or LN- and ≥ 2: T3-4, GS8-10, PSA ≥ 40) or relapsing with 1 of 3 high-risk features (1. ≤ 12 mo total ADT with interval ≥ 12 month without treatment and PSA ≥ 4 w/ DT of 6 months, 2. PSA ≥ 20, 3. Nodal relapse).

39% were N+ and 79% had Gleason ≥8 disease.

TRIAL 1 (G) | 1. ADT alone* | 2. PO abiaterone + prednisolone |.

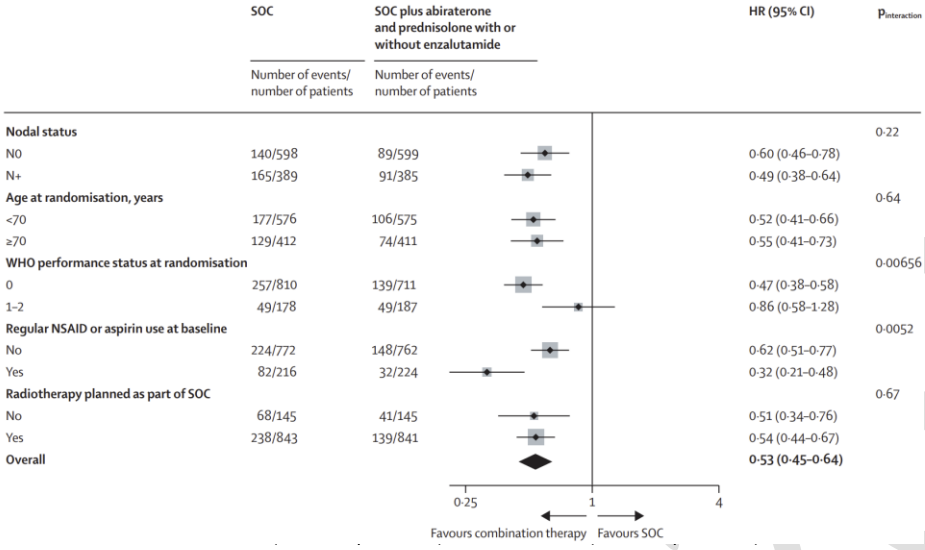
TRIAL 2 (J) | 1. ADT alone* | 3. PO abiaterone + prednisolone +enzalutamide |.

* Could include sugery and LHR agonists/antagonists. ADT given for 3 years. Combination therapy for 2 years.

RT = 74 Gy in 37 fractions to prostate and SV (or hypofractionated schedules).

85% planned to receive radiation → mandated for N0 disease and "encouraged" for N+ disease (71%)

1^{O} MFS.



Attard, Lancet 2022 6-year FU

6-year MFS 69% vs. 82% (SS)

(MFS Forest Plot See ←)

No evidence of Δ in MFS when enzalutamide and abiraterone acetate vs. abiraterone acetate alone (HR 1.02, NS).

2-year G≥3 AE TRIAL 1: 29% vs. 37% and TRIAL 2: 32% vs. 58%.

Most common events in combination-therapy groups HTN (5%) and ALT ↑ (6%).

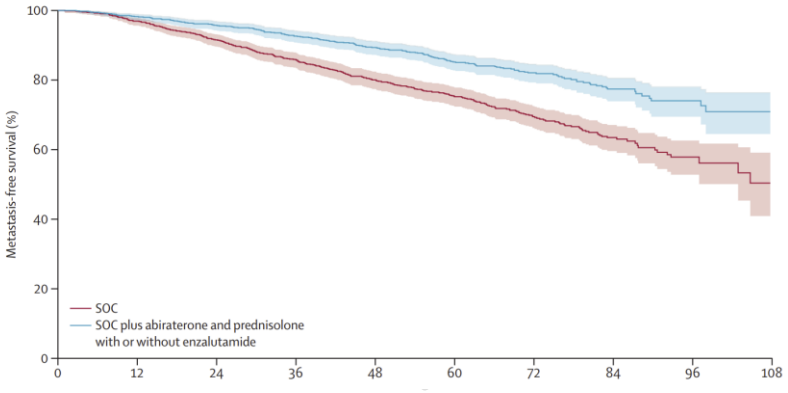
Seven G5 adverse events were reported, none in control groups.

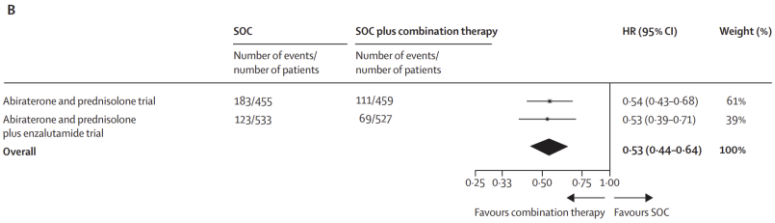
Interpretation Among men with high-risk non-metastatic prostate cancer, combination therapy is associated with significantly higher rates of metastasis-free survival compared with ADT alone. Abiraterone acetate with prednisolone should be considered a new standard treatment for this population.

BCFFS (HR 0·39, p<0·0001) PFS (HR 0·44, p<0·0001).

First 2 years ≥ G3 **Combination** 169 (37%) of 451 patients and **Control** 130 (29%) of 455 patients. Abiaterone Alone Trial

First 3 years ≥ G3 **Combination** 298 (58%) of 513 patients and Control 172 (32%) of 533 patients. Abiaterone + Enzalu. Trial.





ECOG EST-3886 (1988 - 93)
98 pts. Pts were found to have node-positive disease after radical prostatectomy + pelvic lymphadenectomy.
| 1. Adjuvant goserelin (or bilateral orchiectomy) | 2. observation until disease progression |.
Progression based on local or distant disease, not PSA.

Messing, NEJM 1999.
Median 7.1 yrs f/u. 77% (antiandrogen) vs 18% (obs) were alive with no evidence of recurrent disease and undetectable PSA.
Death from any cause in 7 of 47 men (antiandrogen) vs 18 of 51 (obs), S.S.
Conclusion: survival benefit for immediate hormonal therapy. RT not used.

Messing, Lancet 2006.
Median f/u 11.9 yr. Improved OS (HR=1.84), PCSS (HR=4.09) , and PFS (HR=3.42).

RTOG 95-31.
←R→ 173 prostate cancer with +LN | 1. EBRT + ADT upfront (n=173) | 2. EBRT alone → ADT at relapse (n=75) |.

Lawton, JCO 2005.
5-year PFS (w/ PSA < 1.5) = 54% vs. 10% (SS). 9-year PFS (w/ PSA < 1.5) 33% vs. 4% (SS).
MVA = RT + ADT SS ↑ all end points analyzed: absolute survival, disease-specific failure, metastatic failure, and biochemical control with PSA less than 4 ng/mL and less than 1.5 ng/mL.
Conclusion: Pending the results of randomized trials, patients with adenocarcinoma of the prostate who have pathologically involved pelvic lymph nodes (pathologic node-positive or clinical stage D1) should be considered for external-beam irradiation plus immediate hormonal manipulation rather than radiation alone with hormone manipulation at the time of relapse.

AZ 2022

Surg → Adj RT

German LN+ Adjuvant vs. Salvage RT Study
Prospective Cohort pN+ prostate cancer s/p RP (1995-2017) → 9% had LN+, 82% had 1-3 LNs+. | 1. Adj RT | 2. Early Salvage |.
Among LN+ patients, 25.5% adj RT, 41% salv RT, 33.5% no RT.
1^{O} ACM.

Tilki, JCO 2022. 7 years.
7-year ACM (≥ 4 LNs) 7.74% vs 23.36% (SS).
7-year ACM (1-3 LNs) 14.27% v 13.89% (NS).
CONCLUSION Adjuvant compared with early sRT in men with pN1 PC was associated with a decreased ACM risk, and this reduction increased with each additional positive pelvic LN.

TABLE 2. Treatment Propensity Score Adjusted HRs for the Risk of Death

Covariate	No. of Men	No. of Deaths	No. of PC deaths	Univariable Analysis		Multivariable Analysis	
				ACM HR (95% CI)	*P*	ACM AHR (95% CI)	*P*
aRT(t) *v* early sRT(t)	3,891	286	136	0.90[a] (0.84 to 0.96)	.003	0.92[a] (0.85 to 0.99)	.03
No RT(t) *v* early sRT(t)	17,062	923	192	1.00[a] (0.95 to 1.04)	.84	0.99[a] (0.94 to 1.04)	.68
Treatment propensity score							
Propensity score for selection of aRT *v* (early sRT or no RT)	17,913	986	223	1.029 (1.024 to 1.034)	< .001	1.016 (1.010,1.022)	< .001
Propensity score for selection of early sRT *v* (aRT or no RT)	17,913	986	223	1.028 (1.025,1.031)	< .001	1.015 (1.011 to 1.018)	< .001
Patient and PC prognostic factors							
Age at RP in years	17,913	986	223	1.07 (1.05 to 1.08)	< .001	1.05 (1.04 to 1.07)	< .001
No. of positive LNs	17,913	986	223	1.24 (1.18 to 1.29)	< .001	1.13 (1.08,1.19)	< .001
No. of pelvic LNs sampled	17,913	986	223	1.02 (1.01 to 1.03)	< .001	0.996 (0.99 to 1.003)	.27
Time-dependent ADT use							
Adjuvant ADT (t)	440	64	38	2.97 (2.28 to 3.86)	< .001	1.64 (1.21 to 2.23)	.002
Salvage ADT (t)	1,819	270	166	4.20 (3.64 to 4.86)	< .001	3.11 (2.60 to 3.72)	< .001

Multicenter Matched Study
RR, 1107 pts, all N+ after radical prostatectomy with extended LN dissection (obturator, ext iliac, and hypogastric); median 15 nodes removed.
Treated at Mayo Clinic or San Raffaele (Milan). Lifelong ADT (100%), prostate adjuvant RT (34.9%), WPRT (70-85%).
RT median dose to prostate bed: 66.6 - 70.2 Gy; whole pelvis 45-50.4 Gy.
Developed stratification into 5 risk groups based on 4 parameters (number of positive nodes, pathologic Gleason score, tumor stage, surgical margin status). Validated using SEER database.

Abdollah, JCO 2014
Adjuvant RT associated with more favorable CSM (HR 0.37). Only 2 risk groups benefitted from RT: intermediate risk (1-2 LN, G 7-10, pT3b/pT4 or +SM) and high risk (3-4 LN).
Conclusion: "The beneficial impact of aRT on survival in patients with pN1 prostate cancer is highly influenced by tumor characteristics. Men with low-volume nodal disease (≤ two PLNs) in the presence of intermediate- to high-grade, non-specimen-confined disease and those with intermediate-volume nodal disease (three to four PLNs) represent the ideal candidates for aRT after surgery."

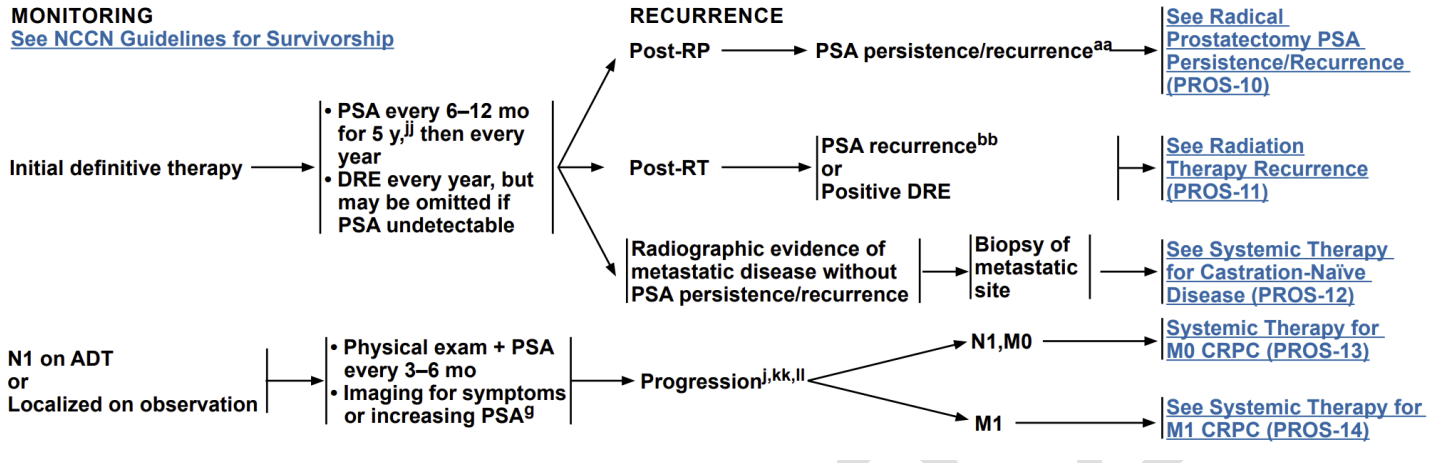
Risk Group	Criteria			8-yr CSM-Free Survival (%)		
				Entire Cohort	aHT alone	aHT + aRT
Very low risk	1-2 LN	G 2-6	-	98.6	98.4	100 (p=0.7)
Low risk	1-2 LN	G 7-10	pT2/pT3a and SM-	96.6	96.8	96.3 (p=0.4)
Int risk	1-2 LN	G 7-10	pT3b/pT4 or SM+	86.7	84.2	93.1 (p=0.03 *)
High risk	3-4 LN	-	-	85.3	78.8	96.5 (p=0.02 *)
Very high risk	≥ 5 LN	-	-	72.2	72.0	74.7 (p=0.9)
* denotes statistically significant difference						

European Association of Urology
RR 1338 patients with LN+ after RP from three tertiary care centers. 49% lifelong ADT, 23% adj EBRT + ADT.

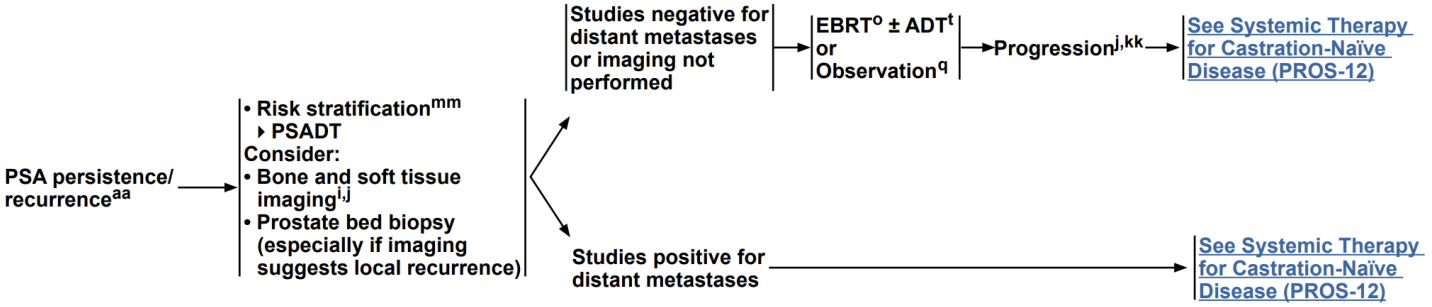
Touijer, Eur Urol 2017.
ADT+EBRT vs. ADT alone OS HR 0.46, SS. or observation HR: 0.41, SS.
Higher-risk patients benefited more from ADT+EBRT than lower-risk patients. 10-year OS Δ 5% in low-risk to Δ 40% in high-risk.
ADT+EBRT also ↑ CSS, SS.
However, ADT (vs. OBS) ↑ other-cause mortality (HR: 3.05, SS), resulting in similar OS between ADT and observation (NS).
While selection bias might remain, its effect would operate in the opposite direction to our findings.
CONCLUSIONS: In men with LNM after RP, ADT+EBRT improved survival over either observation or adjuvant ADT alone. This survival benefit increases with higher-risk disease.

Recurrence

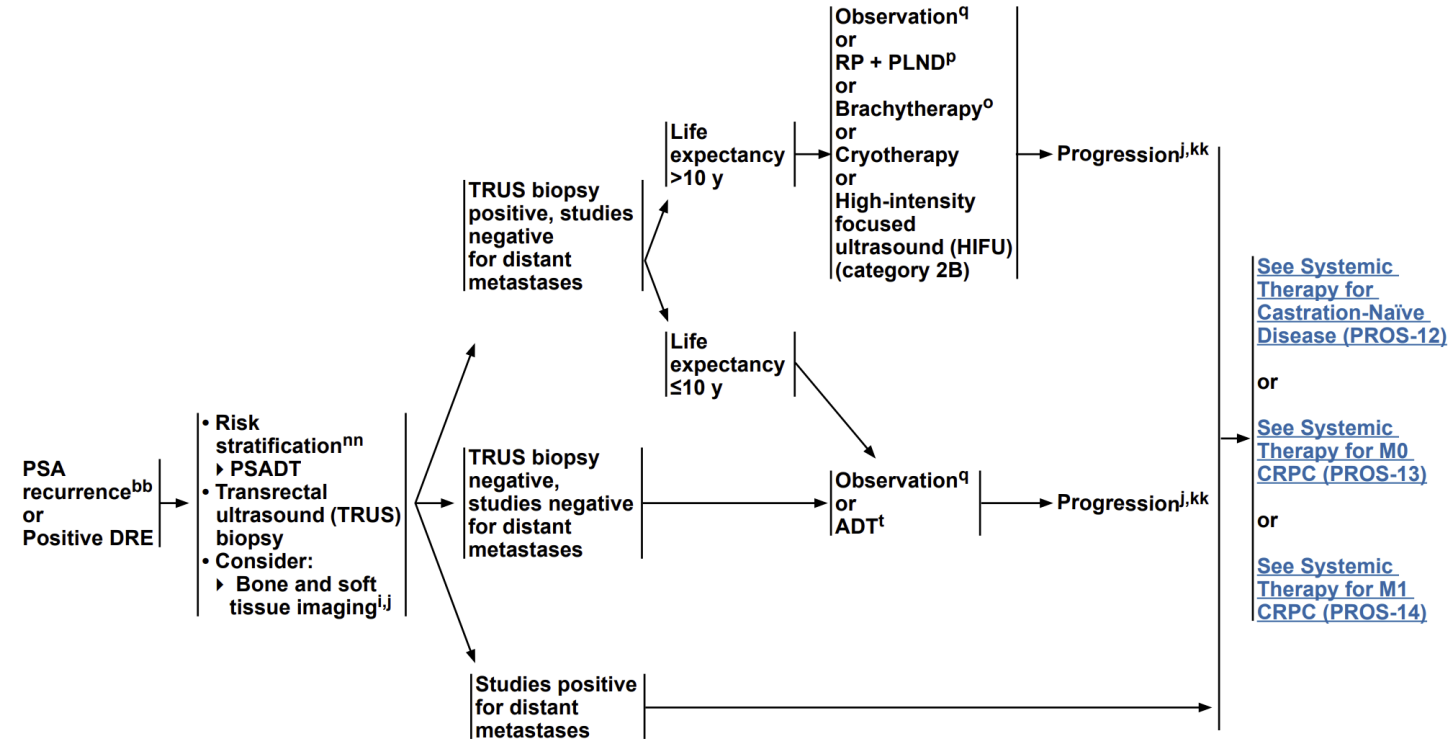
Workflow NCCN



RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE



RADIATION THERAPY RECURRENCE



Salvage Therapies

MASTER **Meta-analysis Salvage RT vs. RP**
←M→ 150 studies with 11332 patients.
Two- and 5-yr recurrence-free survival (RFS) rates and crude incidences of severe GU and GI toxicity were extracted as endpoints of interest.

Valle, Euro Urology 2020.
A total of 150 studies were included for analysis.
5-yr RFS = 50% cryotherapy, 60% HDR brachytherapy and SBRT, with no significant differences between any modality and RP.
Severe GU toxicity 5.6% SBRT, 9.6% HDR, 9.1% LDR vs. 20% RP ($p \leq 0.001$ for all).
Severe GI toxicity 0% HDR vs. 1.8% RP ($p < 0.01$), with no other differences identified.
Conclusions Large differences in 5-yr outcomes were not uncovered when comparing all salvage treatment modalities against RP. Reirradiation with SBRT, HDR brachytherapy, or LDR brachytherapy appears to result in less severe GU toxicity than RP, and reirradiation with HDR brachytherapy yields less severe GI toxicity than RP. Prospective studies of local salvage for radiorecurrent disease are warranted.

Table 3 – Covariate-adjusted meta-regression comparing efficacy and toxicity between salvage modalities and radical prostatectomy

	2-yr RFS	5-yr RFS	Severe GU toxicity	Severe GI toxicity
Radical prostatectomy				
Adjusted percent[a] (95% CI)	72% (66–78%)	53% (46%–59%)	21% (16%–26%)	1.5% (0.4%–3.2%)
Odds ratio (95% CI)	1.0	1.0	NA	NA
p value	Reference	Reference	Reference	Reference
R^2 (%)	0.0	0.0	0.0	0.0
Cryotherapy				
Adjusted percent[a] (95% CI)	66% (59–72%)	57% (49–65%)	15% (8–23%)	0.9% (0.3–1.8%)
Odds ratio (95% CI)	0.74 (0.49–1.12)	1.20 (0.80–1.79)	NA	NA
p value	0.2	0.4	0.2	0.5
R^2 (%)	25	0.0	8.2	27
HIFU				
Adjusted percent[a] (95% CI)	52% (45%–59%)	46% (37%–55%)	23% (17%–30%)	0.8% (0.1%–2.1%)
Odds ratio (95% CI)	0.42 (0.28–0.64)	0.76 (0.48–1.21)	NA	NA
p value	**<0.001**	0.2	0.5	0.4
R^2 (%)	0.0	41	15	22
SBRT				
Adjusted percent[a] (95% CI)	58% (46–69%)	56% (37–73%)	5.6% (1.4–12%)	0.0% (0.0–1.2%)
Odds ratio (95% CI)	0.52 (0.30–0.93)	1.13 (0.50–2.58)	NA	NA
p value	0.03	0.8	**<0.001**	0.07
R^2 (%)	55	4.2	0.00	0.0
HDR				
Adjusted percent[a] (95% CI)	77% (69–83%)	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	**0.002**	**0.003**
R^2 (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent[a] (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	**0.001**	0.6
R^2 (%)	4.3	5.2	12	20%

Italian Salvage RP
Single arm 189 s/p RP → rising PSA → salvage LND between 2002-2011 (145 of 189 received ADT after sLND).
LN recurrence detected via PET/CT (11-choline or PSMA).
1^{O} CSM.

Bravi, Euro Urol 2020.
10-year RFS 31% 10-year BcRFS 11%.
10-year FFCSM 66% 10-year FFAllCD 64%.
MVA showed ↓ PCaSM = PSA response after sLND (HR 0.45; p = 0.001), ADT within 6 mo from sLND (HR: 0.51; p = 0.010).
Conclusions A third of men treated with sLND for PET-detected nodal recurrence of PCa died at long term, with PCa being the main cause of death. Salvage LND alone was associated with durable long-term outcomes in a minority of men who significantly benefited from additional treatments after surgery. Taken together, all these data argue against the use of metastasis-directed therapy alone for patients with node-only recurrent PCa. These men should instead be considered at high risk of systemic dissemination already at the time of sLND.

RTOG 05-26 Salvage LDR
Phase II 100 patients (low-int PCa) s/p EBRT and local failure (> 30 months after EBRT, with PSA < 10) → salvage LDR brachytherapy.
Median RT 74 Gy. ADT + BT was used in 16%.
Overall: 92 patients evaluable → either Iodine-125 (140 Gy minimum) or Palladium-103 (120 Gy minimum) to entire prostate.

Crook, IJROBP 2021. 5-year FU
10-year OS 70%. 19 died (5 PCa, 10 other, 4 unknown). 10-year failures = local 5%, distant 19%, and biochemical 46%.
5-year DFS is 61% 10-year DFS 33%.
1^{O} late GI and GU grade ≥3 were 14%.
No baseline characteristic was significantly associated with any clinical outcome.
Conclusions This is the first prospective multicenter trial reporting outcomes of salvage LDR BT for LF after EBRT. Five-year freedom from BF is 68%, comparable to other salvage modalities. Although further LF is rare (5%), BF climbs to 46% by 10 years.

CONDOR PSMA-PET Trial

Purpose: Current FDA-approved imaging modalities are inadequate for localizing prostate cancer biochemical recurrence (BCR). 18F-DCFPyL is a highly selective, small-molecule prostate-specific membrane antigen-targeted PET radiotracer. CONDOR was a prospective study designed to determine the performance of 18F-DCFPyL-PET/CT in patients with BCR and uninformative standard imaging.

208 men with rising PSA ≥0.2 ng/mL s/p RP or ≥2 ng/mL above nadir after radiotherapy were eligible.

Median baseline PSA of 0.8 ng/mL (range: 0.2-98.4 ng/mL)

1^{O} correct localization rate (CLR), defined as PPV + additional requirement of anatomic lesion colocalization between 18F-DCFPyL-PET/CT and a composite standard of truth (SOT). The SOT consisted of, in descending priority (i) histopathology, (ii) subsequent correlative imaging findings, or (iii) post-radiation PSA response.

The trial was considered a success if the lower bound of the 95% confidence interval (CI) for CLR exceeded 20% for two of three ^{18}F-DCFPyL-PET/CT readers. Secondary endpoints included change in intended management and safety.

Morris, Clin Cancer Res 2021.

Median baseline PSA of 0.8 ng/mL (range: 0.2-98.4 ng/mL) underwent 18F-DCFPyL-PET/CT.

The CLR was 84.8%-87.0% (lower bound of 95% CI: 77.8-80.4). A total of 63.9% of evaluable patients had a change in intended management after 18F-DCFPyL-PET/CT. The disease detection rate was 59% to 66% (at least one lesion detected per patient by 18F-DCFPyL-PET/CT by central readers).

Conclusions: Performance of 18F-DCFPyL-PET/CT achieved the study's primary endpoint, demonstrating disease localization in the setting of negative standard imaging and providing clinically meaningful and actionable information. These data further support the utility of 18F-DCFPyL-PET/CT to localize disease in men with recurrent prostate cancer.See related commentary by True and Chen, p. 3512.

Canadian Prospective Pylarify PSMA Study

79 men T1 (62%) and GS < 7 (95%). Median PSA 7.4 and at relapse PSA 4.8. Comparing 18F-DCFPyL PET/CT when added to diagnostic imaging (DI; CT abdomen and pelvis, bone scan, multiparametric MRI pelvis) for men with **radio-recurrent prostate cancer**.

All men were imaged with DI and subsequently underwent 18F-DCFPyL PET/CT with local and central reads.

Discordance in patterns of disease detected with 18F-DCFPyL PET/CT versus DI and changes in management were characterized.

Liu, IJROBP 2020.

DI detected → isolated intraprostatic recurrence in 38 (48%), regional LN+ 9 (11%), distant disease in 12 (15%), and no disease in 26 (33%).

18F-DCFPyL PET/CT → isolated P recurrence in 38 (48%), regional LN+ in 21 (27%), distant disease in 24 (30%), and no disease in 10 (13%).

DI identified 8 out of 79 (10%) patients to have oligometastatic disease, compared with 21 out of 79 (27%) with 18F-DCFPyL PET/CT.

18F-DCFPyL PET/CT changed proposed management in 34 out of 79 (43%) patients.

Conclusions 18F-DCFPyL PET/CT identified extraprostatic disease in twice as many men with radio-recurrent prostate cancer compared with DI and detected a site of recurrence in 87% of men compared with 67% with DI. Furthermore, 18F-DCFPyL PET/CT identified potentially actionable disease (prostate only recurrence or oligometastatic disease) in 75% of men and changed proposed management in 43% of men.

AZ 2021

nmCRPC

ARAMIS nmCRPC

←R→ 1509 men with mCRPC received 2:1 | 1. Darolutamide | 2. Placebo |.

After the results of the primary end-point analysis were found to be positive, unblinding of the treatment assignments occurred, and patients in the placebo group were permitted to cross over to receive open-label darolutamide treatment.

1^{O} OS.

Table 2. **Secondary and Exploratory End Points at 3 Years in the Intention-to-Treat Population.**

End Point	Darolutamide (N=955)	Placebo* (N=554)	Hazard Ratio (95% CI)†	P Value
Secondary end points				
Overall survival				
Patients who were alive — % (95% CI)	83 (80–86)	77 (72–81)	0.69 (0.53–0.88)	0.003
No. who died	148	106		
Time to pain progression‡				
Patients who had not had event — % (95% CI)	53 (47–60)	32 (22–43)	0.65 (0.53–0.79)	<0.001
No. of events	251	178		
Time to first use of cytotoxic chemotherapy				
Patients who had not received cytotoxic chemotherapy — % (95% CI)	83 (80–86)	75 (69–80)	0.58 (0.44–0.76)	<0.001
No. of events	127	98		
Time to first symptomatic skeletal event				
Patients who had not had event — % (95% CI)	96 (95–98)	92 (89–96)	0.48 (0.29–0.82)	0.005
No. of events	29	28		
Exploratory end points				
Time to first prostate cancer–related invasive procedure				
Patients who had not had event — % (95% CI)	94 (92–96)	87 (83–90)	0.42 (0.28–0.62)	
No. of events	45	53		
Time to initiation of subsequent antineoplastic therapy				
Patients who had not had event — % (95% CI)	88 (85–91)	70 (64–76)	0.36 (0.27–0.48)	
No. of events	85	105		

Adverse Event	Darolutamide (N=954)			Placebo (N=554)		
	Any Grade	Grade 3 or 4	EAIR for Any Grade per 100 Patient-Yr	Any Grade	Grade 3 or 4	EAIR for Any Grade per 100 Patient-Yr
	no. of patients (%)			*no. of patients (%)*		
Fatigue	126 (13.2)	4 (0.4)	8.3	46 (8.3)	5 (0.9)	7.4
Bone fracture†	52 (5.5)	10 (1.0)	3.4	20 (3.6)	5 (0.9)	3.2
Fall, including accident	50 (5.2)	9 (0.9)	3.3	27 (4.9)	4 (0.7)	4.3
Weight decrease, any event	40 (4.2)	0	2.6	14 (2.5)	0	2.2
Asthenic condition‡	38 (4.0)	2 (0.2)	2.5	17 (3.1)	2 (0.4)	2.7
Rash§	30 (3.1)	2 (0.2)	2.0	6 (1.1)	1 (0.2)	1.0
Seizure, any event	2 (0.2)¶	0	0.1	1 (0.2)	0	0.2
Mental-impairment disorder‖	19 (2.0)	3 (0.3)	1.3	10 (1.8)	0	1.6
Depressed-mood disorder‖	21 (2.2)	1 (0.1)	1.4	10 (1.8)	0	1.6
Hypertension	74 (7.8)	33 (3.5)	4.9	36 (6.5)	13 (2.3)	5.8
Hot flush	57 (6.0)	0	3.8	25 (4.5)	0	4.0
Cardiac arrhythmia‖**††	70 (7.3)	17 (1.8)	4.6	24 (4.3)	4 (0.7)	3.8
Coronary-artery disorder‖‡‡	38 (4.0)	19 (2.0)	2.5	15 (2.7)	2 (0.4)	2.4
Heart failure‖§§	18 (1.9)	4 (0.4)	1.2	5 (0.9)	0	0.8

Fizazi, NEJM 2020.

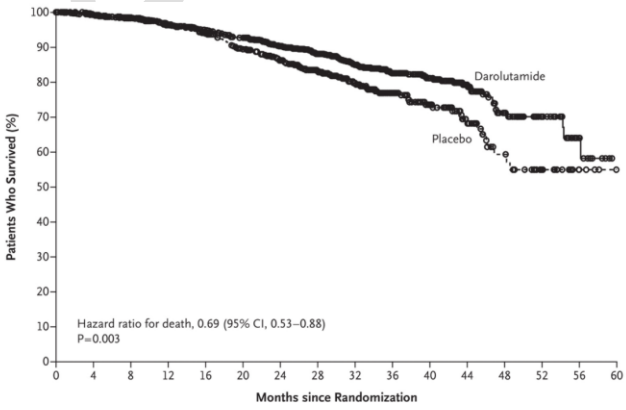
3-year OS 83% vs. 77% (SS).

Risk of death SS ↓ by 31% (HR for death, 0.69; P=0.003).

Darolutamide was also associated with a significant benefit with respect to all other secondary end points, including the time to first symptomatic skeletal event and the time to first use of cytotoxic chemotherapy.

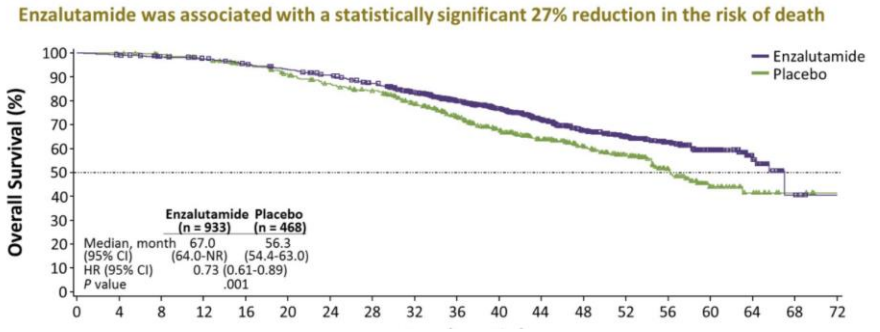
The incidence of adverse events after the start of treatment was similar in the two groups; no new safety signals were observed.

CONCLUSIONS Among men with nonmetastatic, castration-resistant prostate cancer, the percentage of patients who were alive at 3 years was significantly higher among those who received darolutamide than among those who received placebo. The incidence of adverse events was similar in the two groups.

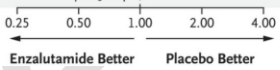


PROSPER nmCRPC

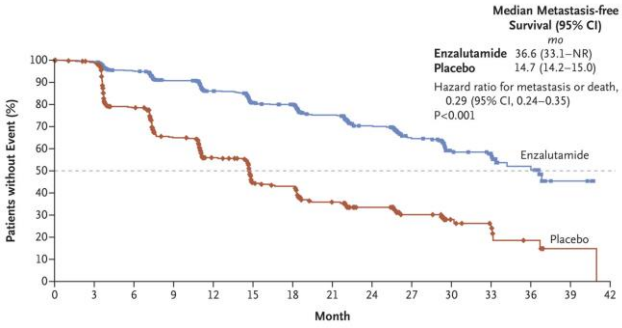
←R→ 1401 nonmetastatic, castration-resistant prostate cancer (nmCRPC) and a rapidly rising prostate-specific antigen (PSA) = DT ≤ 10 months.
All continuing ADT → 2:1 ratio | 1. enzalutamide (160 mg) | 2. placebo once daily |.
1^{O} metastasis-free survival.



Subgroup	No. of Patients		No. of Events		Hazard Ratio for Death (95% CI)
	Enzalutamide	Placebo	Enzalutamide	Placebo	
All patients	933	468	288	178	0.73 (0.61–0.88)
Geographic region					
North America	141	63	43	24	0.76 (0.46–1.25)
European Union	458	232	119	95	0.55 (0.42–0.73)
Rest of the world	334	173	126	59	1.00 (0.73–1.36)
Age at baseline					
≤Median	489	267	126	97	0.64 (0.49–0.84)
>Median	444	201	162	81	0.81 (0.62–1.05)
ECOG performance-status score at baseline					
0	747	382	203	134	0.71 (0.57–0.88)
1	185	85	85	44	0.76 (0.52–1.09)
PSA doubling time at baseline					
<6 Mo	719	361	222	145	0.69 (0.56–0.86)
≥6 Mo	214	107	66	33	0.90 (0.59–1.36)
PSA value at baseline					
≤Median	456	243	110	73	0.72 (0.54–0.97)
>Median	475	224	177	105	0.72 (0.57–0.92)
Baseline use of bone-targeting agent					
Yes	96	49	37	15	1.17 (0.64–2.13)
No	837	419	251	163	0.69 (0.57–0.84)
Total Gleason score at diagnosis					
≤7	512	242	149	89	0.71 (0.55–0.93)
≥8	381	207	128	85	0.76 (0.58–1.00)
LDH value at baseline					
≤Median	458	228	144	92	0.70 (0.54–0.91)
>Median	450	233	135	85	0.75 (0.57–0.99)
Hemoglobin value at baseline					
≤Median	474	238	164	89	0.82 (0.63–1.06)
>Median	457	229	123	89	0.64 (0.49–0.84)



Sternberg, NEJM 2020
Median OS 67.0 months vs. 56.3 months (HR 0.73; P=0.001).
CONCLUSIONS
Enzalutamide plus androgen-deprivation therapy resulted in longer median overall survival than placebo plus androgen-deprivation therapy among men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising PSA level. The risk of death associated with enzalutamide was 27% lower than with placebo. Adverse events were consistent with the established safety profile of enzalutamide.



Hussain, NEJM 2018.
Median MFS 36.6 months vs. 14.7 months (HR 0.29; P<0.001).
Time to the 1st use of a subsequent antineoplastic therapy 39.6 vs. 17.7 months (HR 0.21; P<0.001).
Such therapy was used in 15% vs. 48% of patients as was the time to PSA progression (37.2 vs. 3.9 months; HR 0.07; P<0.001).
Progression occurred in 22% vs. 69% of patients.
1st interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died.
Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo.
CONCLUSIONS Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo. Adverse events were consistent with the established safety profile of enzalutamide.

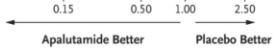
SPARTAN nmCRPC

←R→ 1207 nonmetastatic castration-resistant prostate cancer w/ PSA-DT ≤ 10 months.
2:1 ratio | 1. apalutamide (240 mg per day) | 2. Placebo |. All the patients continued to receive ADT.
1^{O} MFS.

Smith, NEJM 2018.
Median MFS 40.5 months vs. 16.2 months (HR 0.28; P<0.001).
Time to symptomatic progression HR 0.45; SS.
Rate of adverse events leading to discontinuation of the trial regimen was 10.6% vs. 7.0%.
Adverse events rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).
CONCLUSIONS Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo.

B Subgroup Analyses

Subgroup	Apalutamide	Placebo	Hazard Ratio (95% CI)
	median metastasis-free survival (mo)		
All patients	40.5	16.2	0.30 (0.24–0.36)
Age			
<65 yr	NR	7.3	0.14 (0.08–0.27)
65 to <75 yr	NR	14.6	0.25 (0.18–0.34)
≥75 yr	40.5	18.5	0.42 (0.31–0.56)
Race			
White	40.5	14.6	0.26 (0.21–0.34)
Black	25.8	36.8	0.63 (0.23–1.72)
Asian	NR	18.5	0.33 (0.16–0.67)
Other	30.0	18.4	0.40 (0.24–0.65)
Region			
North America	40.5	15.7	0.30 (0.21–0.42)
Europe	NR	14.8	0.29 (0.22–0.39)
Asia–Pacific	NR	18.5	0.30 (0.17–0.54)
No. of previous hormonal therapies			
1	NR	16.6	0.34 (0.21–0.53)
≥2	40.5	16.2	0.29 (0.23–0.36)
Baseline ECOG performance status			
0	40.5	15.7	0.27 (0.21–0.34)
1	27.8	18.4	0.40 (0.27–0.60)
Baseline PSA level			
At or below median	NR	18.4	0.28 (0.20–0.39)
Above median	30.0	14.5	0.29 (0.23–0.38)
PSA doubling time			
≤6 mo	40.5	14.6	0.29 (0.23–0.36)
>6 mo	NR	22.8	0.30 (0.20–0.47)
Use of bone-sparing agent			
Yes	NR	22.0	0.38 (0.19–0.76)
No	40.5	14.8	0.29 (0.23–0.36)
Classification of local or regional nodal disease			
N0	40.5	18.3	0.33 (0.26–0.41)
N1	NR	10.8	0.15 (0.09–0.25)



Metastatic Prostate Cancer

General Survival

SEER Analysis Survival
Retrospective 26,168 metastatic PCa. 50% age 50-70, 75% White, 70% M1b.

Elmehrath, JAMA Net Open 2021
Most deaths (59.0%) occurred within the latency period of 2 years after diagnosis of metastatic PC, whereas 31.6% occurred 2 to 5 years after diagnosis and 9.4% occurred more than 5 years after diagnosis. Of the total deaths, 13 011 (77.8%) were from PC, 924 (5.5%) were from other cancers, and 2797 (16.7%) were from noncancer causes.
During all latency periods, the most common noncancer causes of death were cardiovascular diseases (SMR, 1.34; 95% CI, 1.26-1.42), chronic obstructive pulmonary disease (SMR, 1.19; 95% CI, 1.03-1.36), and cerebrovascular diseases (SMR, 1.31; 95% CI, 1.13-1.50).
Conclusions and Relevance In this cohort study, deaths from noncancer causes, including cardiovascular disease, constituted a substantial number of deaths among men with metastatic PC. Therapy and follow-up should be tailored to the needs of each patient with metastatic PC, and counseling regarding future health risks should be provided.

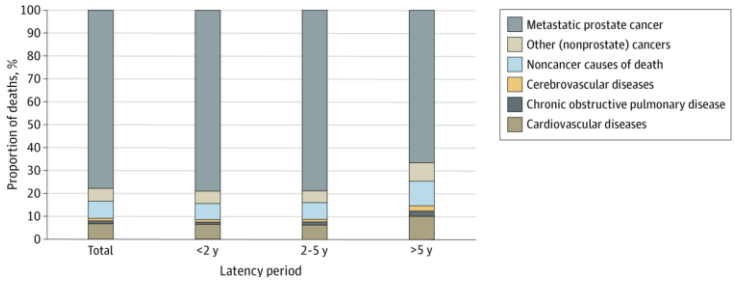


Table 1. Baseline Characteristics of Patients With Metastatic Prostate Cancer and of Those Who Died According to the Time of Death After Diagnosis

Characteristic	Diagnosed cases, No.	Deaths, No.	Age at death, mean (SD), y	Deaths by time after diagnosis, No. (%)		
				<2 y	2-5 y	>5 y
All patients	26 168	16 732	74.13	9869 (59.0)	5290 (31.6)	1573 (9.4)
Age at diagnosis, y						
<50	625	384	49.24	190 (49.5)	156 (40.6)	38 (9.9)
50-70	12 797	7393	64.94	3965 (53.6)	2616 (35.4)	812 (11.0)
>70	12 746	8955	82.79	5714 (63.8)	2518 (28.1)	723 (8.1)
Race						
White	19 486	12 592	74.96	7361 (58.5)	4036 (32.1)	1195 (9.5)
Black	4989	3246	70.52	2004 (61.7)	960 (29.6)	282 (8.7)
American Indian or Alaska Native	162	104	73.51	67 (64.4)	28 (26.9)	9 (8.7)
Asian or Pacific Islander	1531	790	75.87	437 (55.3)	266 (33.7)	87 (11.0)
Cancer stage						
M1a	1604	794	73.09	349 (44.0)	342 (43.1)	103 (13.0)
M1b	19 017	12 004	74.40	6903 (57.5)	3945 (32.9)	1156 (9.6)
M1c	5547	3934	73.54	2617 (66.5)	1003 (25.5)	314 (8.0)
Treatment						
Cancer-directed surgery	2949	1826	75.74	1057 (57.9)	577 (31.6)	192 (10.5)
Radiotherapy	6108	3793	71.29	2296 (60.5)	1152 (30.4)	345 (9.1)
Chemotherapy	2780	1290	67.36	828 (64.2)	377 (29.2)	85 (6.6)

Table 2. Observed Deaths and SMRs for Causes of Death After Diagnosis of Metastatic Prostate Cancer

Cause of death	Deaths by time after diagnosis						Total deaths	
	<2 y		2-5 y		>5 y			
	Observed, No. (%)	SMR (95% CI)[a]	Observed, No. (%)	SMR (95% CI)[a]	Observed, No. (%)	SMR (95% CI)[a]	Observed, No. (%)	SMR (95% CI)[a]
All	9869 (100)	6.43 (6.30-6.56)[b]	5290 (100)	6.07 (5.90-6.23)[b]	1573 (100)	3.63 (3.45-3.81)[b]	16 732 (100)	5.89 (5.80-5.98)[b]
Prostate cancer	7792 (79.0)	NA	4171 (78.8)	NA	1048 (66.6)	NA	13 011 (77.8)	NA
Other cancers	527 (5.3)	1.68 (1.54-1.82)[b]	271 (5.1)	1.52 (1.35-1.72)[b]	126 (8.0)	1.50 (1.25-1.78)[b]	924 (5.5)	1.60 (1.50-1.71)[b]
Noncancer causes[c]	1550 (15.7)	1.32 (1.26-1.39)[b]	848 (16.0)	1.27 (1.19-1.36)[b]	399 (25.4)	1.19 (1.08-1.31)[b]	2797 (16.7)	1.29 (1.24-1.33)[b]
Septicemia	69 (4.5)	3.00 (2.34-3.80)[b]	31 (3.7)	2.37 (1.61-3.36)[b]	8 (2.0)	1.21 (0.52-2.38)	108 (3.9)	2.53 (2.08-3.05)[b]
Infectious and parasitic diseases including HIV infection	21 (1.4)	1.55 (0.96-2.38)	9 (1.1)	1.20 (0.55-2.28)	3 (0.8)	0.87 (0.18-2.54)	33 (1.2)	1.35 (0.93-1.90)
Diabetes	58 (3.7)	1.23 (0.93-1.59)	34 (4.0)	1.27 (0.88-1.77)	10 (2.5)	0.75 (0.36-1.38)	102 (3.6)	1.17 (0.95-1.42)
Alzheimer disease[d]	27 (1.7)	0.57 (0.37-0.83)[b]	21 (2.5)	0.76 (0.47-1.15)	16 (4.0)	1.03 (0.59-1.67)	64 (2.3)	0.70 (0.54-0.90)[b]
Cardiovascular diseases	653 (42.1)	1.40 (1.29-1.51)[b]	335 (39.5)	1.28 (1.14-1.42)[b]	159 (39.8)	1.23 (1.05-1.44)[b]	1147 (41.0)	1.34 (1.26-1.42)[b]
Cerebrovascular diseases	107 (6.9)	1.30 (1.07-1.58)[b]	55 (6.5)	1.19 (0.90-1.55)	36 (9.0)	1.56 (1.10-2.17)[b]	198 (7.1)	1.31 (1.13-1.50)[b]
Pneumonia and influenza	51 (3.3)	1.28 (0.96-1.69)	30 (3.5)	1.34 (0.91-1.92)	10 (2.5)	0.90 (0.43-1.66)	91 (3.3)	1.24 (1.00-1.53)[b]
COPD and associated conditions	99 (6.4)	1.05 (0.86-1.28)	72 (8.5)	1.34 (1.05-1.69)[b]	36 (9.0)	1.35 (0.95-1.88)	207 (7.4)	1.19 (1.03-1.36)[b]
Chronic liver disease and cirrhosis	19 (1.2)	1.46 (0.88-2.28)	4 (0.5)	0.56 (0.15-1.42)	2 (0.5)	0.63 (0.08-2.28)	25 (0.9)	1.07 (0.69-1.58)
Nephritis, nephrotic syndrome, and nephrosis	36 (2.3)	1.00 (0.70-1.39)	19 (2.2)	0.93 (0.56-1.45)	16 (4.0)	1.54 (0.88-2.50)	71 (2.5)	1.06 (0.83-1.34)
Accidents and adverse effects of medications	72 (4.6)	1.70 (1.33-2.14)[b]	37 (4.4)	1.55 (1.09-2.13)[b]	13 (3.3)	1.10 (0.59-1.89)	122 (4.4)	1.56 (1.30-1.86)[b]
Suicide and self-inflicted injury	30 (1.9)	2.97 (2.00-4.24)[b]	19 (2.2)	3.42 (2.06-5.34)[b]	5 (1.3)	2.01 (0.65-4.68)	54 (1.9)	2.97 (2.23-3.88)[b]
Other	308 (19.9)	1.20 (1.07-1.34)[b]	182 (21.5)	1.22 (1.05-1.41)[b]	85 (21.3)	1.08 (0.86-1.33)	575 (20.6)	1.18 (1.09-1.28)[b]

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable; SMR, standardized mortality ratio.

[c] Percentages for individual noncancer causes of death reflect the percentage of total noncancer causes of death. Percentages may not sum to 100 owing to rounding.

Oligo MDT

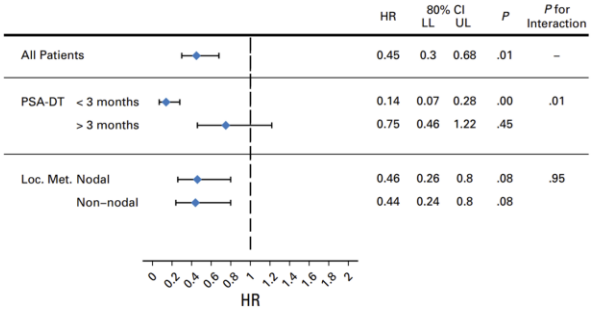
Phase II **STOMP** mCSPC
←R→ 62 asymptomatic PCa BcR s/p 1^{O} PCa treatment with curative intent + ≤ 3 extracranial mets on PET/CT + serum testo. > 50 ng/mL.
| 1. surveillance | 2. MDT of all detected lesions (surgery or SBRT) |.
Surveillance = PSA q3 months + repeated imaging at PSA or clinical progression.
Randomization balanced for PSA-DT (≤ 3 v > 3 months) and LN versus non-LN mets.
1^{O} ADT-free survival.
ADT was started at symptomatic progression, progression to more than three metastases, or local progression of known metastases.

Table 2. Indications for Starting Androgen Deprivation Therapy

Indication	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Not started yet	6 (19)	12 (39)
Polymetastatic progression	16 (55)	19 (61)
Local progression	6 (23)	0 (0)
Symptomatic progression	3 (10)*	0 (0)

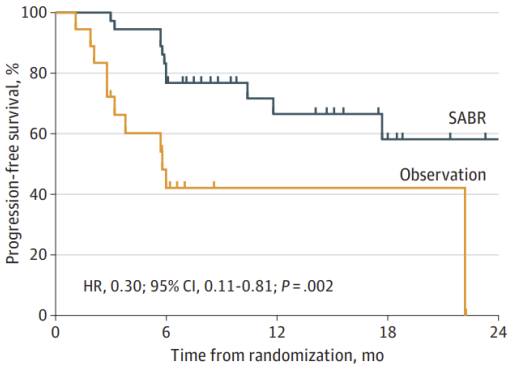
NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and polymetastatic progression.

B IntToTx – Association MDT & ADT-FS



Ost, JCO 2018. 3-year FU
Median ADT-free survival 13 months vs. 21 months (HR 0.60, P = .11).
Quality of life was similar between arms at baseline and remained comparable at 3-month and 1-year follow-up.
Six patients developed grade 1 toxicity in the MDT arm. No grade 2 to 5 toxicity was observed.
Conclusion
ADT-free survival was longer with MDT than with surveillance alone for oligorecurrent PCa, suggesting that MDT should be explored further in phase III trials.

Phase II **ORIOLE** **"**Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer" mCSPC
←R→ 54 recurrent hormone-sensitive PCa + 1 to 3 metastases w/o any ADT within 6 months of enrollment or 3 or more years total.
| 1. SABR | 2. Obs |. Randomization 2:1.
1^{O} 6-month Progression = PSA ↑, imaging detect, ADT for any reason, or death.



Phillips, JAMA Oncol 2020.
6-month progression 7 of 36 patients (19%) vs. 11 of 18 patients (61%), (P = .005).
SABR ↑ median PFS not reached vs 5.8 months (HR 0.30; P = .002).
Total consolidation of PSMA radiotracer-avid disease decreased the risk of new lesions at 6 months (16% vs 63%; P = .006).
No toxic effects of grade 3 or greater were observed.
T-cell receptor sequencing identified significant increased clonotypic expansion following SABR and correlation between baseline clonality and progression with SABR only (0.082085 vs 0.026051; P = .03).
Conclusions and Relevance Treatment with SABR for oligometastatic prostate cancer improved outcomes and was enhanced by total consolidation of disease identified by PSMA-targeted positron emission tomography. SABR induced a systemic immune response, and baseline immune phenotype and tumor mutation status may predict the benefit from SABR. These results underline the importance of prospective randomized investigation of the oligometastatic state with integrated imaging and biological correlates.

Phase II **OLIGOPELVIS GETUG P07** mCSPC
67 patients (2014-2016) 50% received prior Prostate RT → oligorecurrence (≤ 5 pelvic LN via PET) → IMRT + ADT (6 months).
WPRT 54 Gy in 30 fx → 66 Gy SIB to gross nodes. Prostate bed (if no prior RT) 66 Gy in 33 fractions → 72 Gy in 36 fractions for gross disease.
1^{O} 2-year "PFS" - - defined as 2 consecutive PSA above level at inclusion ± clinical evidence of progression ± death from any cause.

Supiot, Euro Urol 2021.
2-PFS 81%. 3-year PFS 58%. Median PFS 45.3 mo.
2-year BcRFS 58% 3-year BcRFS 46%. Median BcRFS 25.9 mo.
Grade 2 + 2-yr genitourinary and gastrointestinal toxicities were 10% and 2%, respectively.
Recurrences: 80% were outside the pelvis (50% non-regional nodes).
Conclusions Combined high-dose salvage pelvic radiotherapy and ADT appeared to prolong tumor control in oligorecurrent pelvic node relapses in prostate cancer with limited toxicity. After 3 yr, nearly half of patients were in complete remission. Our study showed initial evidence of benefit, but a randomized trial is required to confirm this result.

Pre-2022

MDT and Patterns of Recurrence mCSPC

RR 258 castrate sensitive oligomets (5 lesions at staging) w/ 474 mets.

Median follow-up was 25.2 months, and 50.4% of patients received concurrent ADT.

Table 4 Multivariable analysis for factors associated with biochemical progression-free survival

Variable	Comparison	HR (95% CI)	*P* value
Age		1.03 (1.001-1.05)	.04
T stage	Tx vs T1/2	0.35 (0.08-1.50)	.16
	T3/4 vs T1/2	1.33 (0.90-2.00)	.15
N stage	Nx vs N0	1.40 (0.54-3.57)	.49
	N1 vs N0	2.00 (1.12-3.55)	.02
M stage	Mx vs M0	0.86 (0.55-1.35)	.51
	M1 vs M0	0.44 (0.23-0.83)	.01
Gleason grade group		1.01 (0.83-1.24)	.91
iPSA		1.002 (1.0008-1.003)	<.001
ADT	Yes vs No	0.41 (0.26-0.67)	<.001
Number met		0.99 (0.83-1.20)	.94
Tx location	Bone vs Node	1.42 (0.93-2.17)	.11
	Multiple vs Node	0.50 (0.22-1.12)	.09
Pre-SABR PSA		1.02 (1.01-1.04)	.01
Enhanced imaging		2.81 (1.55-5.12)	.001

Deek, IJROBP 2020.

Median time PSA recurrence 15.7 months.
Next intervention 28.6 months
DMFS 19.1 months.
bPFS 16.1 months.

2-year OS 96.8%.

MVA factors → bPFS included age (HR 1.03; P Z .04), N1 disease at diagnosis (HR, 2.00; P Z .02), M1 disease at diagnosis (HR, 0.44; P Z .01), initial PSA at diagnosis (HR, 1.002; P Z < .001), pre-SABR PSA (HR, 1.02; P Z .01), and use of enhanced imaging for staging (HR, 2.81; P Z .001).

Patterns progression → If Tx to a bone lesion alone → 86.5% recur included an osseous site.
→ If Tx initially to a LN alone → 65.5% recur in a node only, but also 32.3% recur in bone.

Class progression I (no recurrence 18 months after therapy) 40.9%
II (oligoprogressors 3 lesions at recurrence) 36% (7.9% PSA recur but no metastatic disease)
III (polyprogressors >3 lesions at recur) 23.1%.

Conclusions: After MDT, the majority of patients have long-term control or oligoprogression (class I or II). Recurrence tended to occur in osseous sites. These findings, if validated, have implications for future integration of MDT and clinical trial design.

Table 2 Patterns of recurrence after metastasis-directed therapy

	Original treatment site			
Failure location	Bone (N = 74)	Node (N = 31)	Bone/Node (N = 8)	*P* value
Bone component, n	64 (86.5%)	10 (32.3%)	4 (50%)	<.001
Node, n	7 (9.5%)	20 (64.5%)	3 (37.5%)	
Other, n	3 (4.0%)	1 (3.2%)	1 (12.5%)	

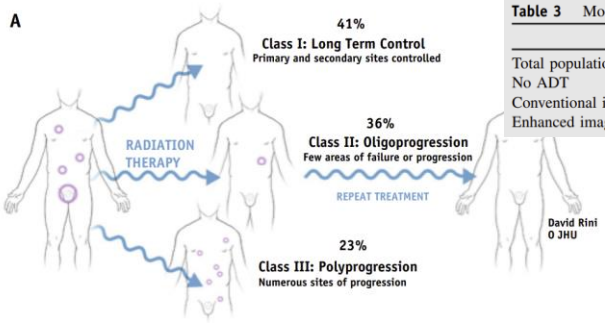
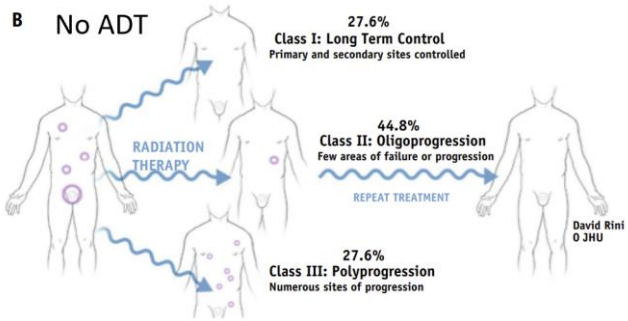


Table 3 Modes of progression

	LTC	Oligoprogressor	Polyprogressor
Total population	40.9%	36%	23.1%
No ADT	27.6%	44.8%	27.6%
Conventional imaging	46.1%	36.2%	17.7%
Enhanced imaging	36.3%	37.7%	26%



Retrospective Salvage RT and ADT Timing

305 patients with bCR and PSMA PET+ oligorecurrence. 96% of the patients initially had high-risk PCa. A median of one (range 0–19) nodal metastases and one (range 0–5) distant metastases were treated.

Treatment: MDT with fractionated or SBRT for all PSMA-positive metastatic sites; 37.8% received concurrent ADT.

The primary outcome is bRFS.

Kroeze, Euro Urology 2021. The median follow-up was 16 mo.

MDT + ADT significantly improved bRFS and remained an independent factor (HR 0.28, p < 0.0001).

bRFS was not significantly different between MDT + ≤6 mo of ADT and MDT alone (p = 0.121).

Patients receiving MDT had 1- and 2-yr ADT-free survival of 93% and 83%, respectively.

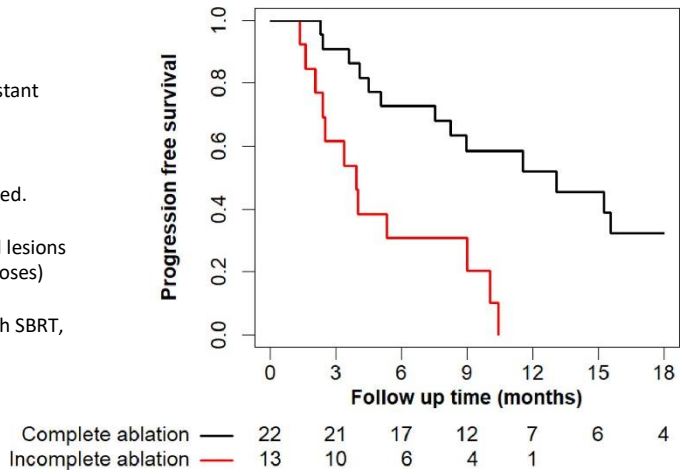
New therapies, most frequently MDT (23%), were required more frequently after MDT (85% vs 29%; p < 0.001).

Grade ≥3 acute toxicity was observed in 0.9% of patients and late toxicity in 2.3%.

Conclusions In this cohort of patients with oligorecurrent PCa, concurrent ADT with MDT improved bRFS significantly, but a large number of patients treated with MDT were spared from ADT for 2 yr, although a greater need for other salvage therapies was observed.

Harvard Retrospective SABR
RR 35 men CRPC s/p androgen receptor signaling inhibitor (ARSI) resistant w/ oligomets → 65 lesions SBRT treated.

Brennan, Adv Rad Onc 2021.
In 63% of men PSA reduction greater than 50% was achieved.
Median PFS was 9.0 months.
Incomplete ablation (defined as the presence of untreated lesions after SBRT or receipt of prior palliative radiation therapy doses) was associated with worse PFS (HR 4.21; P < .01).
Subgroup of 22 men with complete oligomets ablation with SBRT, the median PFS was 13.1 months.
1-year OS was 93.1%.



BR001 Phase I Safety
Prospective 42 patients. Twelve patients (34.3%) had breast cancer, 10 (28.6%) had non–small cell lung cancer, and 13 (37.1%) had prostate cancer; there was a median of 3 metastases treated per patient. Metastases to 7 anatomic locations were included: bone/osseous (BO), spinal/paraspinal (SP), peripheral lung (PL), central lung (CL), abdominal-pelvic (AP), mediastinal/cervical lymph node (MC), and liver (L). Six patients could be enrolled per anatomic site. Patients with breast, prostate, or non–small cell lung cancer with 3 to 4 metastases or 2 metastases in close proximity (≤5 cm) amenable to SBRT were eligible for this phase 1 study.
SBRT = The starting dose was 50 Gy in 5 fractions (CL, MC), 45 Gy in 3 fractions (PL, AP, L), and 30 Gy in 3 fractions (BO, SP).

Chmura, JAMA Network 2021.
This phase 1 trial demonstrated the safety of SBRT for patients with 3 to 4 metastases or 2 metastases in close proximity.
There were no treatment-related deaths.
Late grade 3 AEs demonstrate the need for extended follow-up in long-surviving patients with oligometastatic disease.
Treatment with SBRT for multiple metastases has been expanded into multiple ongoing randomized phase 2/3 National Cancer Institute–sponsored trials (NRG-BR002, NRG-LU002).

AZ 2022

New-Gen Hormones

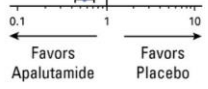
ARASENS mCSPC Darolutamide (AR inhibitor) Trial
←R→ 1306 patients mCSPC | 1. Darolutamide | 2.placebo |.
86.1% of the patients had disease that was metastatic at the time of the initial diagnosis (78.2% GS ≥8, 79.5% bone mets, 17.5% visceral mets).
All patients received ADT + docetaxel.
1^{O} OS

Smith, NEJM 2022
4-year OS 62.7% vs. 50.4% (SS). HR death ↓ by 32.5% (HR 0.68; P<0.001).
Time to castration resistance, painful skeletal events, and subsequent therapy all Prolonged.
Frequency of grade 3 or 4 adverse events was 66.1% in the darolutamide group and 63.5% in the placebo group; neutropenia was the most common grade 3 or 4 adverse event (in 33.7% and 34.2%, respectively).
CONCLUSIONS
In this trial involving patients with metastatic, hormone-sensitive prostate cancer, overall survival was significantly longer with the combination of darolutamide, androgen-deprivation therapy, and docetaxel than with placebo plus androgen-deprivation therapy and docetaxel, and the addition of darolutamide led to improvement in key secondary end points. The frequency of adverse events was similar in the two groups.

TITAN mCSPC Apalutamide
←R→ 1052 all received ADT + | 1. Apalutamide | 2. Placebo |.

C

Subgroup	Events/No. Apalutamide	Events/No. Placebo	Median OS (months) Apalutamide	Median OS (months) Placebo	HR (95% CI)
All patients	170/525	235/527	NR	52.2	0.65 (0.53 to 0.79)
Baseline ECOG performance status					
0	94/328	134/348	NR	52.2	0.68 (0.52 to 0.89)
1	76/197	101/178	NR	32.3	0.56 (0.42 to 0.76)
Geographic region					
EU/NA	53/173	66/173	NR	52.2	0.75 (0.52 to 1.07)
Other	117/352	169/354	NR	44.0	0.62 (0.49 to 0.78)
Bone metastasis only at baseline					
Yes	70/289	115/269	NR	NR	0.50 (0.37 to 0.67)
No	100/236	120/258	NR	48.7	0.85 (0.65 to 1.11)
Visceral disease at baseline					
Yes	27/56	43/72	40.8	30.1	0.76 (0.47 to 1.23)
No	143/469	192/455	NR	52.2	0.65 (0.52 to 0.80)
Gleason score at baseline					
≤ 7	48/174	63/169	NR	NR	0.67 (0.46 to 0.98)
> 7	122/351	172/358	NR	43.7	0.64 (0.51 to 0.81)
Prior docetaxel use					
Yes	21/58	17/55	NR	NR	1.12 (0.59 to 2.12)
No	149/467	218/472	NR	48.7	0.61 (0.50 to 0.76)
Age (years)					
< 65	49/149	90/182	NR	41.7	0.57 (0.40 to 0.80)
65-74	81/243	95/232	NR	NR	0.74 (0.55 to 0.99)
≥ 75	40/133	50/113	NR	52.2	0.65 (0.43 to 0.99)
Baseline PSA above median					
Yes	115/286	126/240	NR	38.9	0.67 (0.52 to 0.86)
No	55/239	109/287	NR	NR	0.54 (0.39 to 0.75)
Baseline LDH above ULN					
Yes	34/60	34/60	38.2	28.4	0.91 (0.57 to 1.47)
No	128/443	188/442	NR	52.2	0.61 (0.49 to 0.77)
Baseline ALP above ULN					
Yes	79/177	119/180	NR	28.7	0.55 (0.42 to 0.74)
No	90/346	115/345	NR	52.2	0.72 (0.55 to 0.95)
Disease volume					
High	134/325	175/335	NR	38.7	0.70 (0.56 to 0.88)
Low	36/200	60/192	NR	NR	0.52 (0.35 to 0.79)
No. of bone lesions					
≤ 10	76/318	108/331	NR	NR	0.69 (0.52 to 0.93)
> 10	94/207	127/196	NR	26.9	0.54 (0.42 to 0.71)
Metastasis stage at diagnosis					
M0	20/85	29/59	NR	41.2	0.39 (0.22 to 0.69)
M1	140/411	199/441	NR	48.7	0.68 (0.55 to 0.85)
Disease risk					
Low	58/236	75/241	NR	NR	0.76 (0.54 to 1.07)
High	112/289	160/286	NR	34.0	0.57 (0.45 to 0.73)



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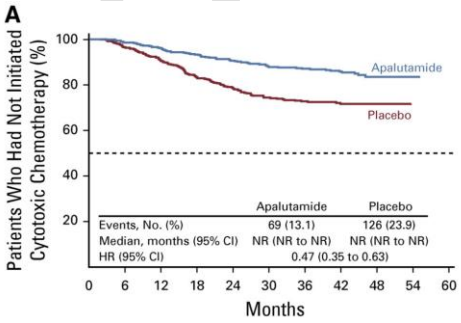
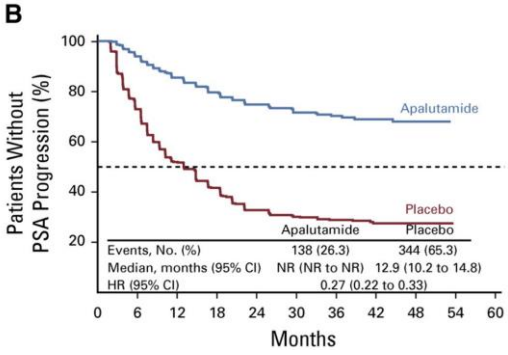


Chi, JCO 2021. FU 44 months.
405 OS events had occurred and 208 placebo-treated patients (39.5%) had crossed over to apalutamide.
Median treatment duration was 39.3 (apalutamide), 20.2 (placebo), and 15.4 months (crossover).
Apalutamide plus ADT SS ↓ risk of death by 35% (and by 48% after adjustment for crossover).
Median OS NR v 52.2 months (HR 0.65, P < .0001).
Apalutamide plus ADT delayed second progression-free survival and castration resistance (P < .0001 for both).
CONCLUSION The final analysis of TITAN confirmed that, despite crossover, apalutamide plus ADT improved OS, delayed castration resistance, maintained health-related quality of life, and had a consistent safety profile in a broad population of patients with mCSPC.

B



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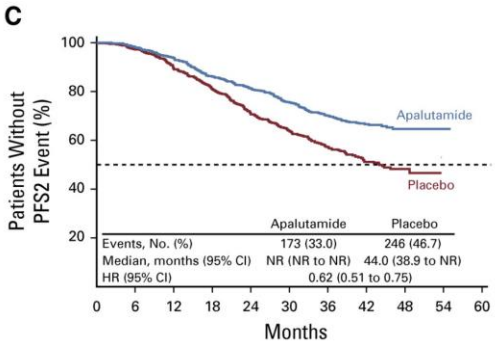

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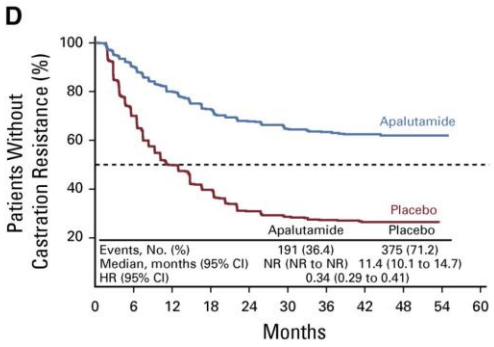


ACIS Trial mCRPC

←R→ 982 chemotherapy-naive men with mCRPC not previously treated with androgen biosynthesis signalling inhibitors and were receiving ongoing ADT. All received PO abiraterone+placebo WITH | 1. apalutamide 240 mg once daily | 2. Placebo |.

1^{O} radiographic PFS in the intention-to-treat population.

Saad, Lancet 2021. 54.8 mo FU final analysis.

Median radiographic PFS 22·6 vs. 16·6 months (HR 0·69, p<0·0001).

Median OS 36.2 vs 33.7 months (NS).

Grade 3–4 AE HTN 82 [17%] of 490 vs. 49 [10%] of 489.

Serious AE 195 (40%) vs. 181 (37%).

Drug-related treatment-emergent adverse events with fatal outcomes occurred in three (1%) patients in the apalutamide plus abiraterone–prednisone group (2 pulmonary embolism, 1 cardiac failure) and five (1%) patients in the abiraterone–prednisone group (1 cardiac failure and 1 cardiac arrest, 1 mesenteric arterial occlusion, 1 seizure, and 1 sudden death).

Interpretation Despite the use of an active and established therapy as the comparator, apalutamide plus abiraterone–prednisone improved radiographic progression-free survival. Additional studies to identify subgroups of patients who might benefit the most from combination therapy are needed to further refine the treatment of mCRPC.

TRANSFORMER Bipolar Androgen Therapy (BAT) Trial mCRPC

Name: (Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance)

Background: Prostate cancer (PCa) becomes resistant to androgen ablation through adaptive upregulation of the androgen receptor in response to the low-testosterone microenvironment. Bipolar androgen therapy (BAT), defined as rapid cycling between high and low serum testosterone, disrupts this adaptive regulation in castration-resistant PCa (CRPC).

←R→ | 1. Monthly BAT | 2. Enzalutamide |.

Both arms received ADT. BAT = 400 mg IM testosterone monthly.

1^{O} PFS

Denmeade, JCO 2021.

Median PFS 5.7 for both arms.

PSA50 (50% ↓ in PSA) = 28.2% vs. 25.3%.

PSA50 (at crossover) = BAT→E **77.8%** vs. E→BAT **23.4%**.

PFS2 (PFS from randomization through crossover) BAT→E **28.2 mo** vs. E→BAT **19.6 mo** (HR, 0.44; P = .02).

Median OS was 32.9 months for BAT versus 29.0 months for enzalutamide (NS)

Median OS BAT→E 37.1 mo vs. E→BAT 30.2 mo (HR, 0.68; P = .225).

BAT adverse events were primarily grade 1-2.

Patient-reported QoL consistently favored BAT.

CONCLUSION This randomized trial establishes meaningful clinical activity and safety of BAT and supports additional study to determine its optimal clinical integration. BAT can sensitize CRPC to subsequent antiandrogen therapy. Further study is required to confirm whether sequential therapy with BAT and enzalutamide can improve survival in men with CRPC.

Enzalutamide Crossover Phase II mCRPC

←R→ 202 patients | 1. Abiraterone → Crossover Enzalutamide| 2. Opposite sequence |.

Treatment was not masked to investigators or participants.

1^{O} time to second PSA progression and PSA response (≥30% decline from baseline) on second-line therapy.

Khalaf, Lancet 2019. 23 months.

At the time of data cutoff, 73 (72%) patients in group A and 75 (74%) patients in group B had crossed over.

Median Time to 2nd PSA progression 19·3 months vs. 15·2 months [HR 0·66, p=0·036).

PSA responses to second-line therapy: Enzalutamide 26/73 (36%) vs. Abiraterone 3/75 (4%) (χ2 p<0·0001).

Grade 3–4 AE hypertension (27 [27%] of 101 patients in group A vs 18 [18%] of 101 patients in group B) and fatigue (six [10%] vs four [4%]).

Serious adverse events were reported in 15 (15%) of 101 patients in group A and 20 (20%) of 101 patients in group B.

There were no treatment-related deaths.

Interpretation

Enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor, whereas abiraterone acetate did not, leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence. Our data suggest that using a sequencing strategy of abiraterone acetate followed by enzalutamide provides the greatest clinical benefit.

PLATO mCRPC

←R→ 251 patients with chemotherapy-naïve mCRPC received open-label enzalutamide 160 mg daily. Men with no PSA ↑ at weeks 13 and 21 were treated until PSA progression (≥ 25% increase and ≥ 2 ng/mL above nadir), then randomly assigned abiraterone+prednisone | 1. w/ enzalutamide | 2. w/ placebo | until disease progression.

1^{O} PFS (radiographic or unequivocal clinical progression or death during study).

Attard, JCO 2018.

Median PFS 5.7 vs. 5.6 months (NS). There was no difference in the secondary end points (time to PSA progression and PSA response).

Grade 3 hypertension (10% v 2%) and increased ALT (6% v 2%) or AST (2% v 0%).

Conclusion Combining enzalutamide with abiraterone acetate and prednisone is not indicated after PSA progression during treatment with enzalutamide alone; hypertension and elevated liver enzymes are more frequent with combination therapy.

JAN 2022

Abiraterone

Mechanism: Abiraterone is a steroid genesis inhibitor at 17α hydrolase and 17,20 lyase. This causes the upstream mineralcorticoid count to increase, leading into potassium wasting (hypokalemia) and hypertension, which is similar to CYP17 deficency. Glucocorticoids are given to 1. ↓ the upstream mineralcorticoids, 2. ↓ adverse events, 3. ↑ anticancer activity.

STAMPEDE. mCSPC

| **ARM C** 1. SOC + DocP (Docetaxel Prednisone) | **ARM G** 2. SOC + AAP (abiraterone acetate Prednisone) | .
SOC was long-term ADT or, for most non-metastatic cases, ADT for ≥2 years and RT to the primary tumour.
←R→ hormone naïve. 566 patients 1 : 2 to SOC + docetaxel 75 mg/m2 3-weekly×6 + prednisolone 10 mg daily; or SOC + abiraterone acetate 1000 mg + prednisolone 5 mg daily. AAP duration depended on stage and intent to give radical RT.
The primary outcome measure was death from any cause.

Sydes, Ann Oncol 2018.
342 (60%) M1; 429 (76%) Gleason 8-10; 449 (79%) WHO performance status 0; median age 66 years and median PSA 56 ng/ml.

BENEFIT SEEN IN ABIRATERONE in FFS and PFS.
OS (NS), FFS HR = 0.51 (SS), PFS HR = 0.65 (SS), MetFS (NS), PCaSS (NS), symptomatic skeletal events (NS).
4-year FFS 48% vs. 67% (SS). 4-year PFS 60% vs. 72% (SS).
≥1 grade 3, 4 or 5 adverse events ever was 36%, 13% and 1% SOC + DocP, and 40%, 7% and 1% SOC + AAP; prevalence 11% at 1 and 2 years on both arms. Relapse treatment patterns varied by arm.
CONCLUSIONS: This direct, randomised comparative analysis of two new treatment standards for hormone-naïve prostate cancer showed no evidence of a difference in overall or prostate cancer-specific survival, nor in other important outcomes such as symptomatic skeletal events. Worst toxicity grade over entire time on trial was similar but comprised different toxicities in line with the known properties of the drugs.

STAMPEDE locally advanced or metastatic prostate cancer. mCSPC
←R→ 1917 | **ARM A** 1. ADT | **ARM G** 2. ADT + Abiraterone |. Abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy).
RT mandated if patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes.
The median age was 67 years, and the median PSA level was 53 ng per milliliter.
52% M+, 20% N+/NX, 95% had newly diagnosed disease. The median follow-up was 40 months.

James, NEJM 2017.
3-year OS 76% vs. 83% (SS). 3-year FFS 45% vs. 75% (SS). Mean FFS time: 30 mo vs. 43.9 mo (SS).
3-year PFS 62% vs. 80% (SS). 3-year FF symptomatic skeletal events 78% vs. 88% (SS).
CONCLUSIONS Among men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone.

LATITUDE mCSPC

Background: Abiraterone acetate, a drug that blocks endogenous androgen synthesis, plus prednisone is indicated for metastatic castration-resistant prostate cancer. We evaluated the clinical benefit of abiraterone acetate plus prednisone with androgen-deprivation therapy in patients with newly diagnosed, metastatic, castration-sensitive prostate cancer.

←R→ 1199 patients | 1. ADT + abiraterone acetate | 2. ADT + placebo |.
Abiraterone (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group).

Fizazi, NEJM 2017.
Median OS (not reached) vs. 34.7 months (SS) . Median length of radiographic PFS 33.0 vs. 14.8 months (SS).
Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostate-specific antigen progression (SS all), along with next symptomatic skeletal events (P=0.009). These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.
CONCLUSIONS The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer. (Funded by Janssen Research and Develop

NZ 2024

COU-AA-302 mCRPC

Background: Abiraterone acetate, an androgen biosynthesis inhibitor, improves overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy. We evaluated this agent in patients who had not received previous chemotherapy.

←R→ 1088 mCRPC in chemotherapy-naïve | 1. abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) | 2. or placebo plus prednisone |.
The study was unblinded after a planned interim analysis that was performed after 43% of the expected deaths had occurred.
1º radiographic PFS and OS.

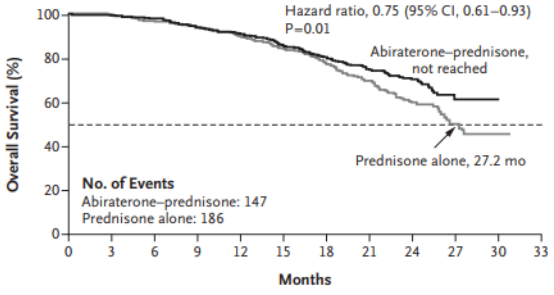
Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

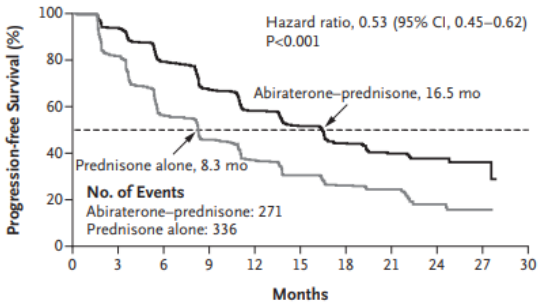
End Point	Abiraterone–Prednisone (N=546)	Prednisone Alone (N=542)	Value (95% CI)†	P Value
Secondary end points				
Median time to opiate use for cancer-related pain — mo	NR	23.7	0.69 (0.57–0.83)	<0.001
Median time to initiation of cytotoxic chemotherapy — mo	25.2	16.8	0.58 (0.49–0.69)	<0.001
Median time to decline in ECOG performance score by ≥1 point — mo	12.3	10.9	0.82 (0.71–0.94)	0.005
Median time to PSA progression — mo‡	11.1	5.6	0.49 (0.42–0.57)	<0.001
Exploratory end points§				
Median time to increase in pain — mo¶	26.7	18.4	0.82 (0.67–1.00)	0.049
Median time to functional-status decline measured as FACT-P total score — mo‖	12.7	8.3	0.78 (0.66–0.92)	0.003
Patients with decline of ≥50% in PSA level — %**	62	24	2.59 (2.19–3.05)††	<0.001
Patients with a RECIST response — %‡‡				
Defined objective response	36	16	2.27 (1.59–3.25)††	<0.001
Stable disease	61	69		
Progressive disease	2	15		

Ryan, NEJM 2013. 22.2 months
Median radiographic PFS 16.5 vs. 8.3 months (HR 0.53; P<0.001).
Median OS NR vs. 27.2 months (HR 0.75; P=0.01) *but did not cross the efficacy boundary*.

Abiraterone–prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status. Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver-function testing were more common with abiraterone–prednisone.

CONCLUSIONS Abiraterone improved radiographic progression-free survival, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer.





D Overall Survival

Subgroup	Abiraterone–Prednisone (median, mo)	Prednisone Alone (median, mo)	Hazard Ratio (95% CI)
All patients	NR	27.2	0.75 (0.61–0.93)
Baseline ECOG			
0	NR	27.2	0.71 (0.55–0.92)
1	NR	26.4	0.86 (0.58–1.28)
Baseline BPI-SF			
0–1	NR	27.2	0.71 (0.54–0.94)
2–3	25.5	NR	0.87 (0.59–1.29)
Bone metastases only at entry			
Yes	NR	27.2	0.68 (0.48–0.96)
No	NR	27.5	0.81 (0.61–1.06)
Age			
<65 yr	NR	NR	0.80 (0.51–1.24)
≥65 yr	NR	26.4	0.73 (0.57–0.94)
≥75 yr	NR	23.8	0.71 (0.51–1.00)
Baseline PSA above median			
Yes	26.9	23.8	0.72 (0.43–0.94)
No	NR	NR	0.77 (0.38–1.09)
Baseline LDH above median			
Yes	NR	23.6	0.69 (0.53–0.91)
No	NR	27.5	0.79 (0.55–1.12)
Baseline ALK-P above median			
Yes	NR	23.6	0.79 (0.60–1.04)
No	NR	27.5	0.66 (0.46–0.94)
Region			
North America	NR	27.2	0.66 (0.49–0.88)
Other	NR	NR	0.89 (0.65–1.22)

0.20 0.75 1.00 1.50
Abiraterone–Prednisone Better Prednisone Alone Better

C Radiographic Progression-free Survival

Subgroup	Abiraterone–Prednisone (median, mo)	Prednisone Alone (median, mo)	Hazard Ratio (95% CI)
All patients	16.5	8.3	0.53 (0.45–0.62)
Baseline ECOG			
0	16.4	8.3	0.56 (0.47–0.67)
1	18.0	7.4	0.43 (0.30–0.61)
Baseline BPI-SF			
0–1	16.7	8.3	0.53 (0.43–0.65)
2–3	10.7	7.4	0.61 (0.44–0.83)
Bone metastases only at entry			
Yes	20.7	11.1	0.55 (0.42–0.71)
No	11.2	5.7	0.51 (0.41–0.62)
Age			
<65 yr	16.6	8.1	0.48 (0.35–0.66)
≥65 yr	16.5	8.3	0.55 (0.46–0.67)
≥75 yr	14.9	8.2	0.64 (0.48–0.84)
Baseline PSA above median			
Yes	12.8	5.8	0.54 (0.43–0.68)
No	19.4	10.2	0.48 (0.38–0.61)
Baseline LDH above median			
Yes	14.1	5.6	0.47 (0.38–0.60)
No	16.6	10.8	0.57 (0.45–0.71)
Baseline ALK-P above median			
Yes	13.6	5.6	0.54 (0.43–0.68)
No	19.4	9.7	0.48 (0.38–0.61)
Region			
North America	16.6	8.2	0.51 (0.40–0.63)
Other	16.3	8.3	0.56 (0.45–0.71)

0.20 0.75 1.00 1.50
Abiraterone–Prednisone Better Prednisone Alone Better

Saad, Euro Urol 2015 Post Hoc Analysis of Bone-Targeted Therapy (BTT) + 3rd interm analysis
Patients were grouped by concomitant BTT use or no BTT use.
Concomitant BTT SS ↑ OS (HR 0.75; p = 0.01), ↑ time to ECOG PS↓ (HR 0.75; p < 0.001), and ↑ time to opiate use pain (HR 0.80; p = 0.036).
Osteonecrosis of the jaw (all grade 1/2) with concomitant BTT use was reported in <3% of patients.
Conclusions AA with concomitant BTT was safe and well tolerated in men with chemotherapy-naïve mCRPC. The benefits of AA on clinical outcomes were increased with concomitant BTT.

Abiraterone + Bisphosphonates mCRPC

RR 745 men began receiving abiraterone acetate + prednisone as first-line therapy for mCRPC + bone mets.

Patients classified by ± concomitant BRIs (bone reabsorption inhibitors) and subclassified by volume of disease.

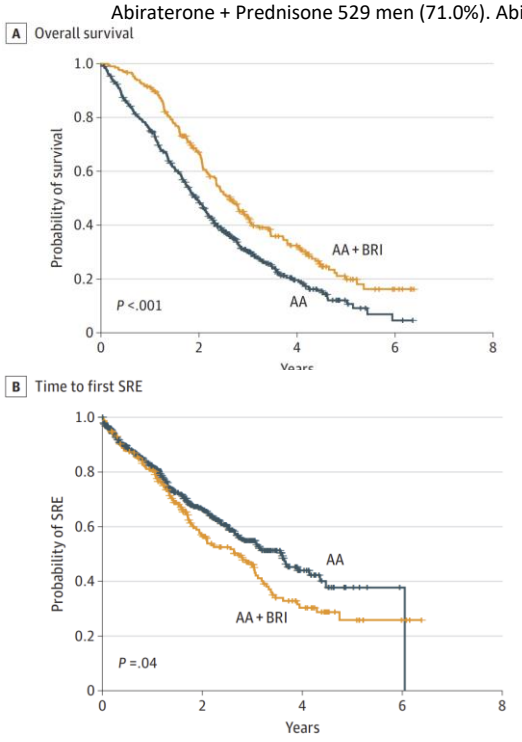
High volume or low volume, using CHAARTED E3805 study definitions.

***High-volume** = **1.** visceral metastases or **2.** ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.*

Xgeva (61%) or Zometa (39%).

420 men (56.4%) had high-volume disease, and 276 men (37.0%) had low-volume disease.

Abiraterone + Prednisone 529 men (71.0%). Abiraterone + Prednisone + BRI 216 men (29.0%).



Francini, JAMA Network 2021.

Median OS 23 vs. 31.8 month (HR 0.65; P < .001).

OS benefit in the BRI cohort (high-volume vs L-V disease) = 33.6 vs 19.7 months (HR, 0.51; P < .001).

Shorter time to first SRE 42.7 vs. 32.4 (HR, 1.27; P = .04).

First risk of a first SRE was more than double in subgroup with L-V disease (HR, 2.29; P < .001).

MVA, concomitant BRIs use was independently associated with longer OS (HR, 0.64; P < .001).

Conclusions and Relevance In this study, the addition of BRIs to abiraterone acetate with prednisone as first-line therapy for the treatment of patients with mCRPC and bone metastases was associated with longer OS, particularly in patients with high-volume disease. These results suggest that the use of BRIs in combination with abiraterone acetate with prednisone as first-line therapy for the treatment of mCRPC with bone metastases could be beneficial.

Table 2. Clinical Outcomes Among Overall Population by Receipt of Bone Resorption Inhibitors

Outcome	Abiraterone acetate cohort (n = 529)	BRI cohort (n = 216)	HR (95% CI)	*P* value
Deaths, No.	369	147	NA	NA
OS, median (95% CI), mo	23.0 (21.0-25.7)	31.8 (28.2-36.4)	0.65 (0.54-0.79)	<.001
SREs, No.	188	116	NA	NA
Time to first SRE, median (95% CI), mo	42.7 (33.2-52.2)	32.4 (24.1-37.3)	1.27 (1.0-1.60)	.04

Table 3. Clinical Outcomes for Disease Volume Subgroups by Receipt of Bone Resorption Inhibitors

	High-volume disease (n = 420)[a]				Low-volume disease (n = 276)[b]			
Outcome	Abiraterone acetate cohort (n = 336)	BRI cohort (n = 84)	HR (95% CI)	*P* value	Abiraterone acetate cohort (n = 179)	BRI cohort (n = 97)	HR (95% CI)	*P* value
Deaths, No.	268	53	NA	NA	114	63	NA	NA
OS, median (95% CI), mo	19.7 (17.3-21.8)	33.6 (24.8-46.3)	0.51 (0.38-0.68)	<.001	33.0 (29.2-41.4)	31.8 (28.2-37.1)	0.93 (0.68-1.26)	.62
SREs, No.	135	34	NA	NA	49	59	NA	NA
Time to first SRE, median (95% CI), mo	31.7 (25.2-38.1)	51.5 (31.6-NA)	0.70 (0.48-1.03)	.07	NA (43.9-NA)	25.2 (20.9-40.0)	2.29 (1.57-3.35)	<.001

Abbreviations: BRI, bone resorption inhibitor; HR, hazard ratio; NA, not available/not applicable; OS, overall survival; SRE, skeletal-related event.

[a] High-volume disease was defined as visceral metastases and/or at least 4 bone metastases, including 1 or more metastases out of the axis and pelvis.

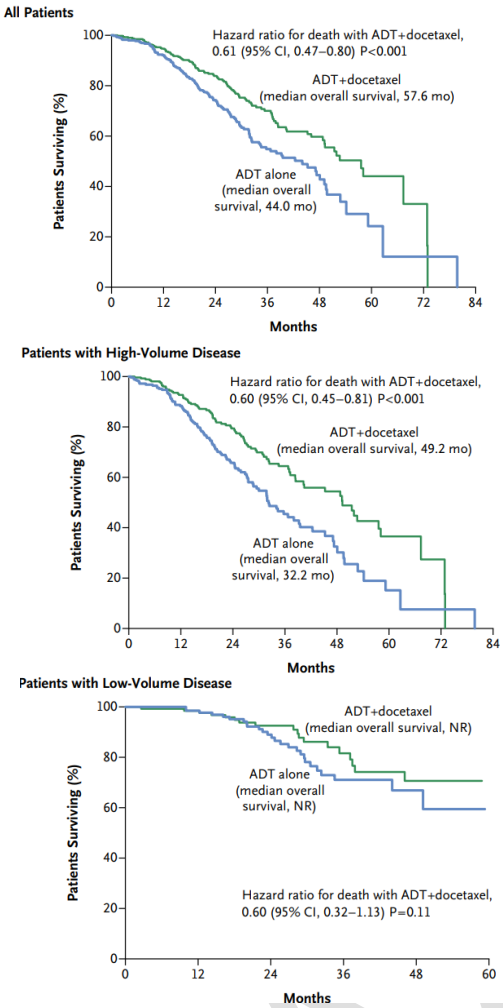
[b] Low-volume disease was defined as the absence of high-volume disease.

Chemotherapy

CHAARTED E3805 Docetaxel Trial ADT + Docetaxel vs. ADT mCSPC

←R→ 790 patients metastatic castrate sensitive. | 1. ADT + docetaxel 75 mg/m^2 every 3 weeks x 6 cycles | 2. ADT alone |.

High-volume = **1.** visceral metastases or **2.** ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.



Sweeny, NEJM 2015 Median FU 29 months.

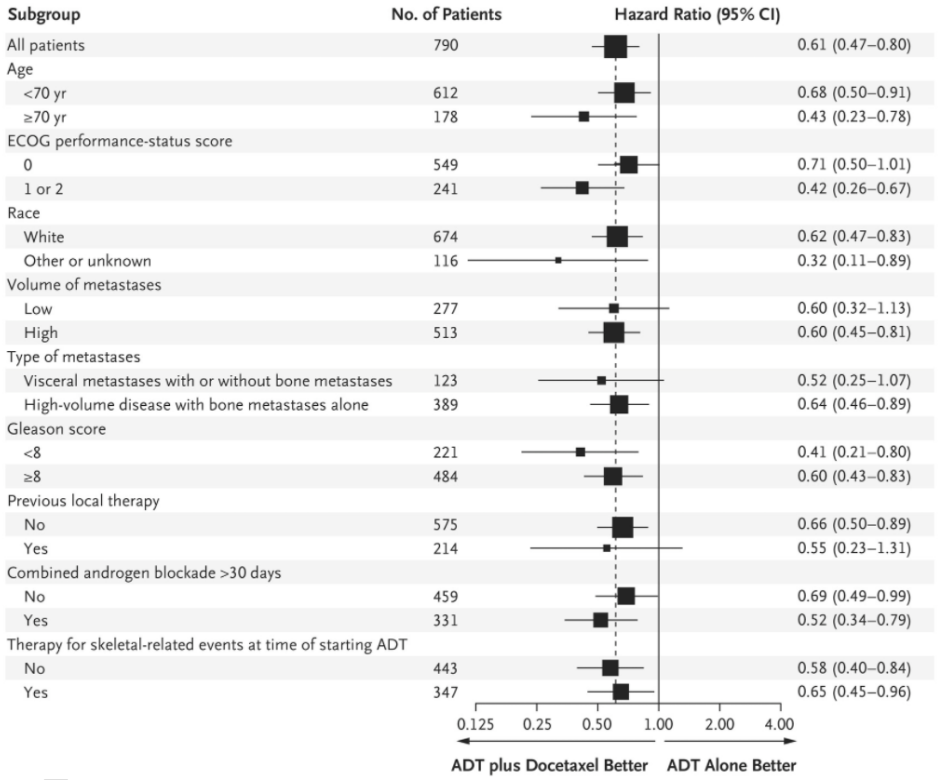
Median OS 57.6 months vs. 44.0 months (HR 0.61; P<0.001).

Median time to "progression" (PSA, symptomatic, imaging) 20.2 months vs. 11.7 (HR 0.61; P<0.001).

1-year PSA ↓ (≤ 0.2) 27.7% vs. 16.8% (P<0.001).

Combination group = G3-4 febrile neutropenia 6.2%, G3-4 infection w/ neutropenia 2.3%.

Conclusions: Six cycles of docetaxel at the beginning of ADT for metastatic prostate cancer resulted in significantly longer overall survival than that with ADT alone.

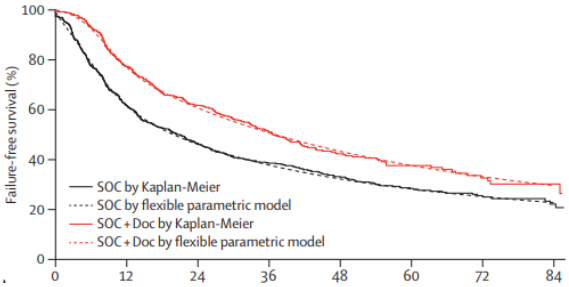


STAMPEDE Trial. ARM A (SoC), B (SoC+ZA), C (SoC+Doc), E (SoC+ZA+Doc) mCSPC

←R→ 2962 men. 1817 (61%) men had M+ disease, 448 (15%) had N+/X M0, and 697 (24%) had high risk N0M0 (at least 2 of: T3/4, GS 8-10, PSA ≥ 40). 165 (6%) men were previously treated with local therapy, and median PSA was 65 ng/mL (IQR 23–184).
All patients: LTHT, started no longer than 12 weeks before randomization. No age restriction. Fit for chemo.
Standard of care (SOC): LTHT (GRH agonists or antagonists) at least 2 years. No recs for GCSF with docetaxel.

RT was optional for men with N+M0. Randomized 2:1:1:1 A, B, C, E

ZA 4mg given for six 3-weekly cycle → 4-weekly until 2 years. DOC (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. There was no blinding to treatment allocation.
1^{O} OS.



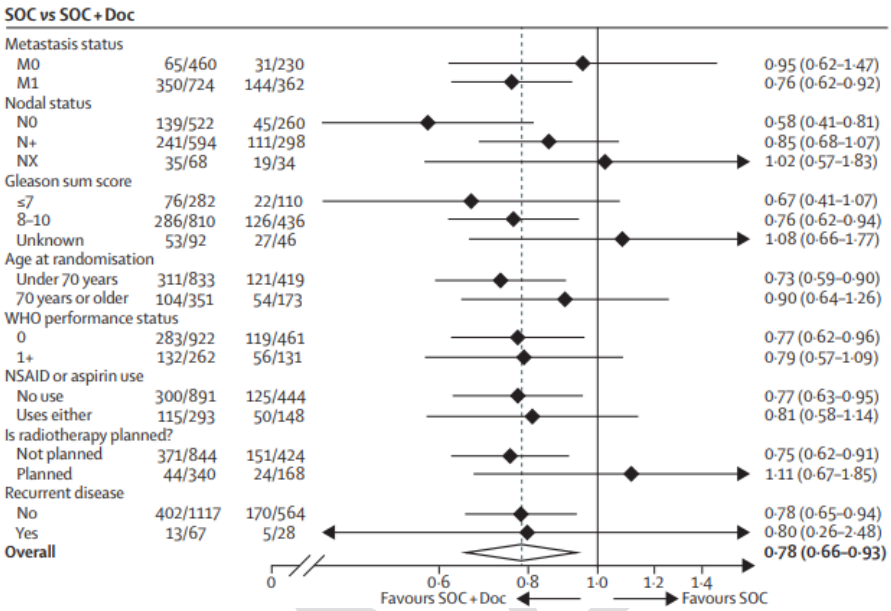
James, Lancet 2016. Median follow-up was 43 months (IQR 30–60).
There were 415 deaths in the control group (347 [84%] prostate cancer).

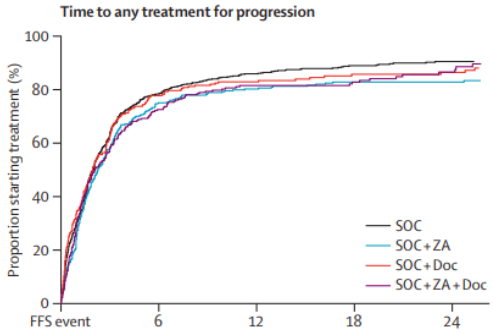
Median OS:		
	SOC	71 mo
	SOC + ZA	NR (HR 0·94, p=0·450)
	SOC + Doc	81 mo (0·78, p=0·006)
	SOC + Doc/ZA	76 mo (0·82, p=0·022).

G3–5 SOC 399 (32%), SOC + ZA 197 (32%), SOC + Doc 288 (52%), SOC + Doc/ZA 269 (52%).

Conclusion: ZA = no evidence of survival improvement and should not be part of SOC for this population.

Docetaxel = given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Docetaxel treatment should become part of standard of care for adequately fi t men commencing long-term hormone therapy.





Archive

Radioligands

ALSYMPCA Radium-223 mCRPC

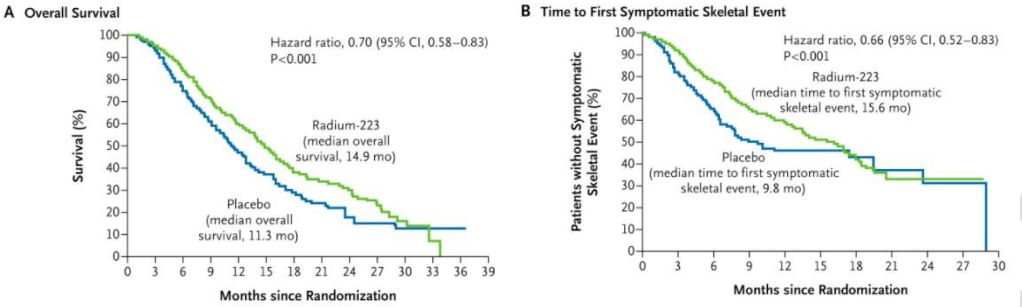
BACKGROUND: Xofigo aka Radium-223 dichloride (radium-223), an alpha emitter. Efficacy and safety of radium-223 as compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases.

←R→ 921 who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, |

SOC + | 1. six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) | 2. matching placebo |.

1 injection was administered every 4 weeks.

1^{O} OS. 2^{O} time to the first symptomatic skeletal event and various biochemical end points.



Parker, NEJM 2013.

Median OS 14.0 vs. 11.2 months (HR 0.70; P=0.002).

Median time to first skeletal mets 15.6 vs. 9.8 (SS).

Requirement: ANC > 1.5, Platelet > 100, Hbg > 10.

Radium-223 was associated with low myelosuppression rates and fewer adverse events.

CONCLUSIONS: In this study, which was terminated for efficacy at the prespecified interim analysis, radium-223 improved overall survival.

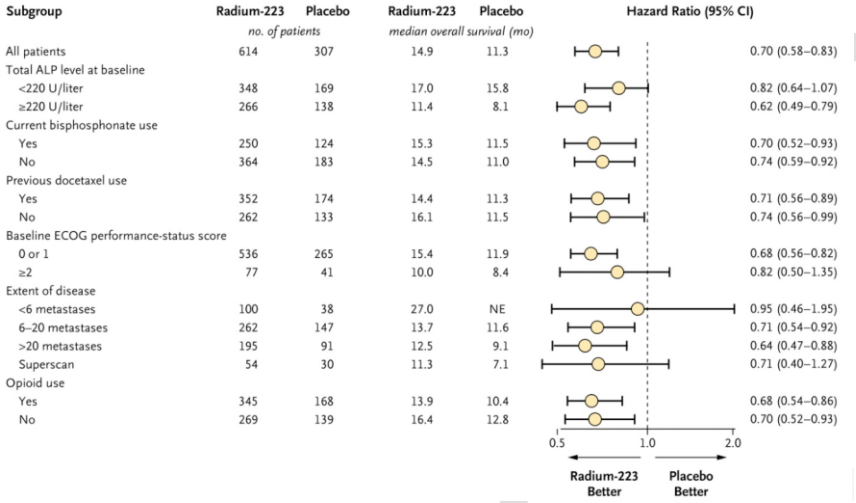


Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

ERA 223 Radium-223 mCRPC

←R→ 806 chemotherapy-naive, asymptomatic or mildly symptomatic mCRPC + bone metastases.

All PO Abiraterone + | 1. Xofigo | 2. Placebo |.

PO abiraterone acetate 1000 mg once daily + PO prednisone or prednisolone 5 mg twice daily during and TX.

1^{O} symptomatic skeletal EFS.

Smith, Lancet 2019. Primary analysis 21.2 months.

Median symptomatic SkEFS 22·3 vs. 26·0 months (HR 1·122, p=0·2636).

Fractures (any grade) 112 (29%) of 392 vs. 45 (11%) of 394 patients.

Most common G3–4 AE = hypertension (43 [11%] vs 52 [13%]), fractures (36 [9%] vs 12 [3%]), ↑ ALT (34 [9%] vs 28 [7%]).

Serious treatment-emergent AE 160 (41%) vs. 155 (39%).

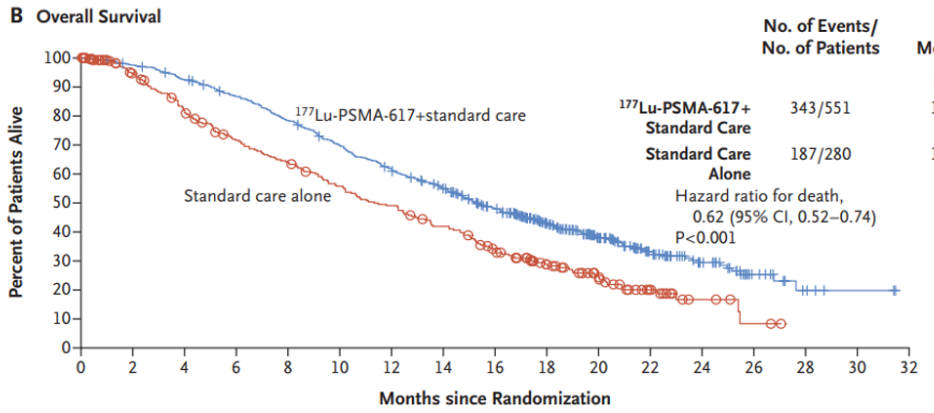
Treatment-related deaths occurred in two (1%) patients in the radium-223 group (acute myocardial infarction and interstitial lung disease) and one (<1%) in the placebo group (arrhythmia).

Interpretation The addition of radium-223 to abiraterone acetate plus prednisone or prednisolone did not improve symptomatic skeletal event-free survival in patients with castration-resistant prostate cancer and bone metastases, and was associated with an increased frequency of bone fractures compared with placebo. Thus, we do not recommend use of this combination.

VISION Trial Lutetium-177 (177Lu)–PSMA-617 mCRPC

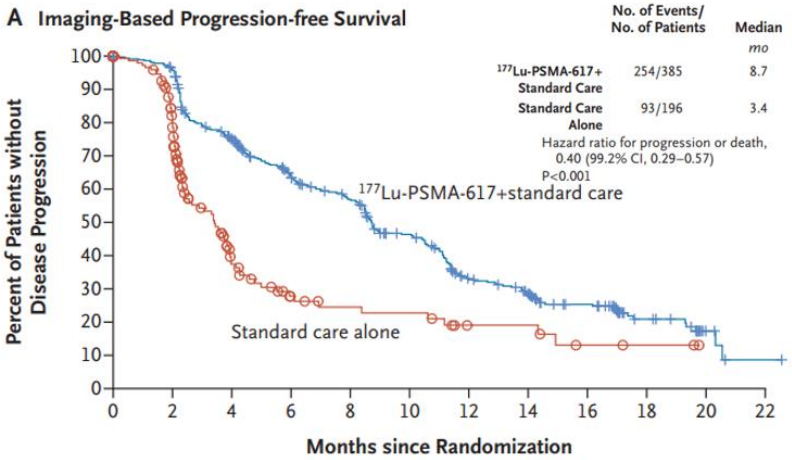
Background: Metastatic castration-resistant prostate cancer remains fatal despite recent advances. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 (177Lu)–PSMA-617 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

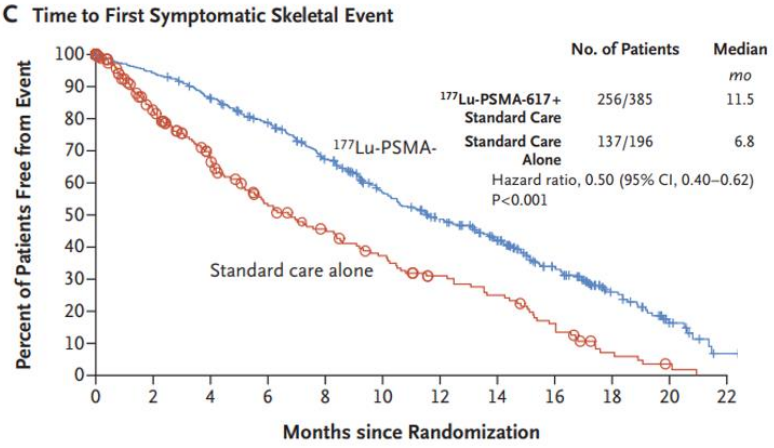
←R→ 831 patients mCRPC previously tx ≥ AR–pathway inhibitor and 1-2 taxane regimens. All received 68Ga PET scans.
Majority was PSMA positive, but 8.7% had a PSMA negative met.
| 1. 177Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus protocol-permitted SoC | 2. SoC alone |.
Protocol-permitted SoC excluded chemotherapy, immunotherapy, radium-223 (223Ra), and investigational drugs.
1^{O} imaging-based PFS / OS.



Sartor, NEJM 2021. 20.9 months.
Median imaging-based PFS
8.7 vs. 3.4 months (HR 0.40; P<0.001)
Median imaging-based OS
15.3 vs. 11.3 months (HR 0.62; P<0.001).
All the key 2^{O} end points SS favored 177Lu-PSMA-617.
AE ≥G3 52.7% vs. 38.0% (SS).
but QoL was not adversely affected.

CONCLUSIONS Radioligand therapy with 177Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer.





Immunotherapy

IPTential150 Ipatasertib (AKT inhibitor) Trial mCRPC

Background: Prostate Cancer often have PTEN Δ → dysregulates PI3K/AKT pathway. Dual pathway inhibition with AKT inhibitor ipatasertib plus abiraterone might have greater benefit than abiraterone alone. We aimed to compare ipatasertib plus abiraterone with placebo plus abiraterone in patients with previously untreated mCRPC with or without tumour PTEN loss.

←R→ 1101 patients previously untreated asymptomatic or mildly symptomatic mCRPC → progressive disease received abiraterone+prednisone WITH
| 1. ipatasertib (400 mg qd PO) | 2. Placebo |. Abiraterone (1000 mg qd PO) and prednisolone (5 mg BID PO).
1^{O} radiographical PFS in patients with PTEN loss (521 (47%) PTEN loss by IHC)).

Sweeney, Lancet 2021. **FU 19 months.**

Median radiographical PFS (Δ PTEN n=521) 18.5 vs. 16·5 months (HR 0·77, p=0·034; yes significant at α=0·04).
Median radiographical (ITT population 19·2 vs. 16.6 months (HR 0·84, p=0·043; not significant at α=0·01).
Grade ≥3 AE 386 (70%) of 551 vs. 213 (39%) of 546.
Discontinuation 116 (21%) vs. 28 (5%).
Deaths due to adverse events deemed related to treatment occurred in two patients (<1%; acute myocardial infarction [n=1] and lower respiratory tract infection [n=1]) in the placebo–abiraterone group and in two patients (<1%; hyperglycaemia [n=1] and chemical pneumonitis [n=1]) in the ipastasertb–abiraterone group.

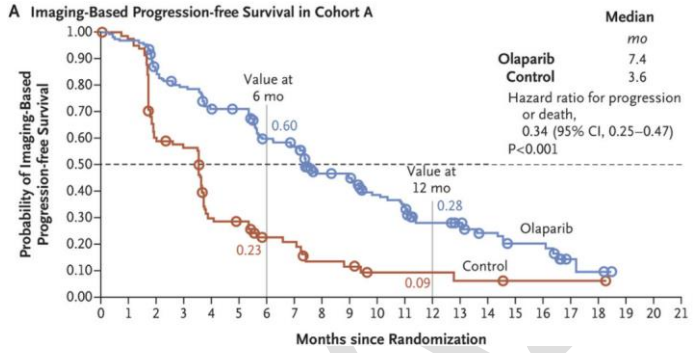
Interpretation

Ipatasertib plus abiraterone significantly improved radiographical progression-free survival compared with placebo plus abiraterone among patients with mCRPC with PTEN-loss tumours, but there was no significant difference between the groups in the intention-to-treat population. Adverse events were consistent with the known safety profiles of each agent. These data suggest that combined AKT and androgen-receptor signalling pathway inhibition with ipatasertib and abiraterone is a potential treatment for men with PTEN-loss mCRPC, a population with a poor prognosis.

PROfound Trial Phase II Olaparib (PARP inhibitor) mCRPC

Background: Multiple LoF Δ in genes that are involved in DNA repair, including homologous recombination repair, are associated with response to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition in patients with prostate and other cancers.

←R→ two cohorts A (n=245) ≥ 1 Δ in BRCA1, BRCA2, ATM and cohort B (n=142) any Δ of 12 prespecified genes.
Evaluating the PARP inhibitor olaparib in men with mCRPC → disease prog. while receiving a new hormonal tx (e.g., enzalutamide or abiraterone) →
| 1. Olaparib | 2. Physician's choice of enzalutamide or abiraterone (control) |.
1^{O} imaging-based PFS progression-free survival in cohort A according to blinded independent central review.



De Bono, NEJM 2020

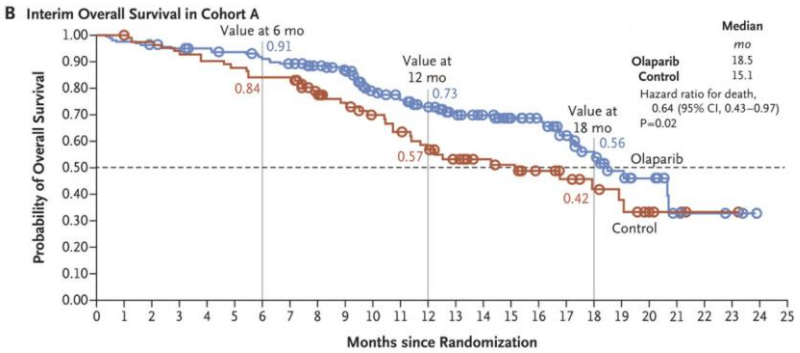
Median imaging PFS (in cohort A), 7.4 months vs. 3.6 months (HR 0.34; P<0.001).

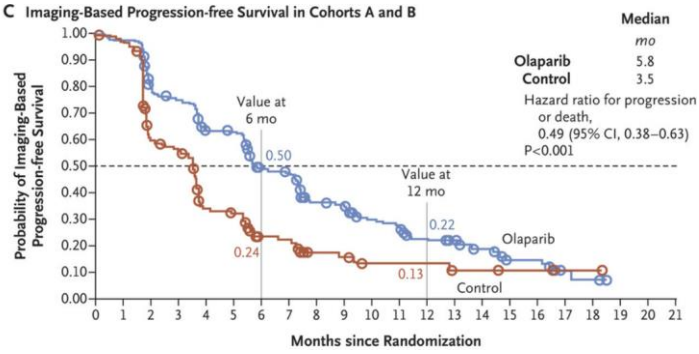
A significant benefit was also observed with respect to the confirmed objective response rate and the time to pain progression.

Median OS (in cohort A) 18.5 months vs. 15.1 months (SS).

81% patients in the control group who had progression crossed over to receive olaparib. A significant benefit for olaparib was also seen for imaging-based progression-free survival in the overall population (cohorts A and B). Anemia and nausea were the main toxic effects in patients who received olaparib.

CONCLUSIONS In men with metastatic castration-resistant prostate cancer who had disease progression while receiving enzalutamide or abiraterone and who had alterations in genes with a role in homologous recombination repair, olaparib was associated with longer progression-free survival and better measures of response and patient-reported end points than either enzalutamide or abiraterone.





TRITON II Phase II Rucaparib (PARP inhibitor) mCRPC

Background: BRCA1 or BRCA2 (BRCA) alterations are common in men with metastatic castration-resistant prostate cancer (mCRPC) and may confer sensitivity to poly(ADP-ribose) polymerase inhibitors. We present results from patients with mCRPC associated with a BRCA alteration treated with rucaparib 600 mg twice daily in the phase II TRITON2 study.

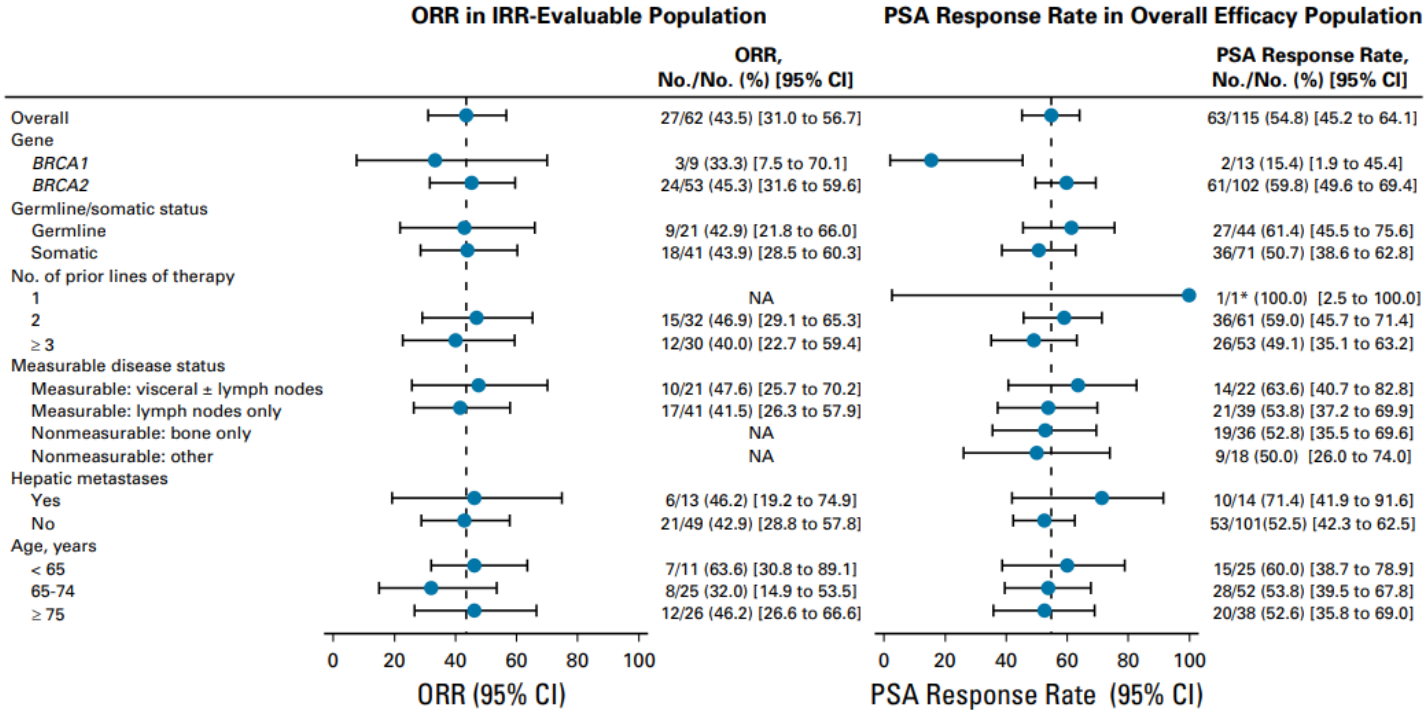
←R→ 115 mCRPC WITH BRCA who progressed s/p 1-2 lines of next-generation AR-directed therapy AND one taxane-based chemotherapy.
Efficacy and safety populations WITH BRCA alteration with and without measurable disease.
Received ≥ 1 dose of rucaparib.
1^{O} ORR (RECIST) and locally assessed PSA response (≥ 50% ↓ from baseline).

Abida, JCO 2020

Confirmed ORRs 43.5%.
Confirmed PSA response rate was 54.8%.
Median Time to PSA progression 6.5 months.

ORRs were similar for patients with a germline or somatic BRCA alteration and for patients with a BRCA1 or BRCA2 alteration, while a higher PSA response rate was observed in patients with a BRCA2 alteration. The most frequent grade ≥ 3 treatment-emergent adverse event was anemia (25.2%; 29 of 115 patients).

CONCLUSION Rucaparib has antitumor activity in patients with mCRPC and a deleterious BRCA alteration, but with a manageable safety profile consistent with that reported in other solid tumor types.



PENDING TRITON III : A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3)

TOPARP Phase 2 Trials **Olaparib** mCRPC

Background: A subset of prostate cancers are driven by defects in DNA damage repair (DRR), which includes BRCA mutations. That proportion is enriched among men with metastatic, castrate resistant prostate cancer (mCRPC). As we've seen in ovarian cancer, DRR can lead to sensitivity to PARP inhibition due to an overwhelming buildup of sublethal DNA damage that becomes lethal in cells with DRR.

TOPARP-A

Phase II. 50 mCRPC treated with olaparib 400 mg PO BID. All had received prior treatment with docetaxel, 49 (98%) had received abiraterone or enzalutamide, and 29 (58%) had received cabazitaxel. Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumor biopsies.

1^{O} response rate based on 1 of 3 criteria:

1. Objective response RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1
2. ↓ at least 50% in PSA
3. Confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 ml of blood to less than 5 cells per 7.5 ml).

Mateo, NEJM 2015

Response rate: 16/49 (1 could not be evaluated) = 33%.

Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes — including BRCA1/2, ATM, Fanconi's anemia genes, and CHEK2.

Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with BRCA2 loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 with ATM aberrations.

Anemia (in 10 of the 50 patients [20%]) and fatigue (in 6 [12%]) were the most common grade 3 or 4 adverse events, findings that are consistent with previous studies of olaparib.

CONCLUSIONS: PARP inhibitor olaparib in patients whose prostate cancers were no longer responding to standard treatments and who had defects in DNA-repair genes led to a high response rate.

TOPARP-B

Phase-II Dose Study.

←R→ 711 screened, but only 92 evaluable. progressing mCRPC. Previously treated with 1-2 taxane chemotherapy regimens. Tumour biopsies tested with targeted sequencing. Patients with DDR gene aberrations were randomly assigned (1:1) to | 1. 400 mg | 2. 300 mg | olaparib BID, given continuously in 4-week cycles until disease progression or unacceptable toxicity. Neither participants nor investigators were masked to dose allocation. 1^{O} same as TOPARP-A.

Mateo, Lancet 2019. 25-month FU.

Confirmed composite response 54.3% vs. 39·1%.

Radiological response 24·2% vs. 16·2%.

PSA50 achieved 37·0% vs. 30·2%.

Circulating tumour cell achieved 53·6% vs. 48·1%.

The most common grade 3–4 adverse event in both cohorts was anaemia (15 [31%] of 49 patients in the 300 mg cohort and 18 [37%] of 49 in the 400 mg cohort).

19 serious adverse reactions were reported in 13 patients.

One death possibly related to treatment (myocardial infarction) occurred after 11 days of treatment in the 300 mg cohort.

Interpretation

Olaparib has antitumour activity against metastatic castration-resistant prostate cancer with DDR gene aberrations, supporting the implementation of genomic stratification of metastatic castration-resistant prostate cancer in clinical practice.

Funding

AL 2021

Benefit RT to Prostate

STOPCAP Metaanalysis
INTERVENTION: We included trials that randomised men to prostate radiotherapy and androgen deprivation therapy (ADT) or ADT only.
RESULTS AND LIMITATIONS: We identified one ongoing (PEACE-1) and two completed (HORRAD and STAMPEDE) eligible trials.
OS NS. ↑ bPFS and FFS, equivalent to ~10% benefit at 3yr.
The effect of prostate RT varied by metastatic burden. 3-year OS < 5 77% vs. ≥ 5 70% (SS).
CONCLUSIONS: Prostate radiotherapy should be considered for men with mHSPC with a low metastatic burden.

STAMPEDE
←R→ 2061 newly diagnosed metastatic prostate cancer | 1. standard of care (control group) | 2. standard of care + RT |
Standard of care = lifelong ADT + up-front docetaxel permitted. RT = daily (55 Gy in 20 fx over 4 weeks) or weekly (36 Gy in 6 fx over 6 weeks).
1^{O} OS.

Table 2

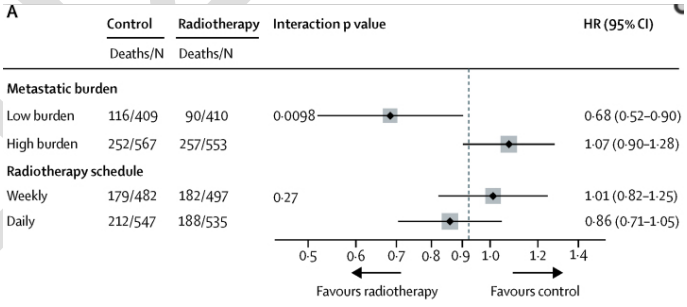
Summary of estimated treatment effect for main outcome measures, for all patients and by metastatic burden

	Adjusted hazard ratio (95% CI)	Survival at 3 years*		Restricted mean survival time (months)*		
		Control	Radiotherapy	Control	Radiotherapy	Difference (95% CI)
Overall survival						
All patients	0·92 (0·80–1·06)	62%	65%	41·6	42·5	1·0 (−0·6 to 2·5)
Low metastatic burden	0·68 (0·52–0·90)	73%	81%	45·4	49·1	3·6 (1·0 to 6·2)
High metastatic burden	1·07 (0·90–1·28)	54%	53%	38·8	37·6	−1·2 (−3·5 to 1·1)
Failure-free survival						
All patients	0·76 (0·68–0·84)	23%	32%	21·4	26·2	4·8 (2·8 to 6·7)
Low metastatic burden	0·59 (0·49–0·72)	33%	50%	27·4	36·1	8·6 (5·6 to 11·7)
High metastatic burden	0·88 (0·77–1·01)	17%	18%	17·3	18·8	1·5 (−0·7 to 3·6)
Progression-free survival						
All patients	0·96 (0·85–1·08)	44%	44%	32·4	33·1	0·7 (−0·9 to 2·3)
Low metastatic burden	0·78 (0·63–0·98)	58%	63%	39·4	42·9	3·5 (0·4 to 6·7)
High metastatic burden	1·09 (0·94–1·26)	35%	30%	28·0	26·2	−1·8 (−4·3 to 0·8)
Metastatic progression-free survival						
All patients	0·97 (0·86–1·10)	47%	47%	33·9	34·4	0·4 (−1·5 to 2·4)
Low metastatic burden	0·80 (0·63–1·01)	62%	67%	41·1	44·2	3·1 (0·2 to 6·0)
High metastatic burden	1·10 (0·95–1·28)	37%	33%	29·3	27·3	−2·0 (−4·7 to 0·7)
Prostate cancer-specific survival						
All patients†	0·93 (0·80–1·09)	66%	69%	43·9	44·6	0·7 (−1·1 to 2·5)
Low metastatic burden	0·65 (0·47–0·90)	79%	86%	48·6	51·8	3·3 (1·0 to 5·5)
High metastatic burden	1·10 (0·92–1·32)	58%	56%	40·6	39·0	−1·6 (−3·9 to 0·7)
Symptomatic local event-free survival						
All patients	1·07 (0·93–1·22)	57%	55%	38·2	37·2	−1·1 (−3·1 to 0·9)
Low metastatic burden	0·82 (0·64–1·05)	65%	72%	41·6	44·0	2·4 (−0·7 to 5·4)

Parker, Lancet 2018
40% low metastatic burden (≤ 3 mets without peritoneal), 54% high, 6% unknown.

ALL COMERS:
3-year FFS 23% vs. 32% (SS).
Median FFS 13 mo vs 17 mo (SS).
3-year OS NS.
HOWEVER, there was a benefit in low burden disease.

INTERPRETATION: NO OS Δ except in low burden.



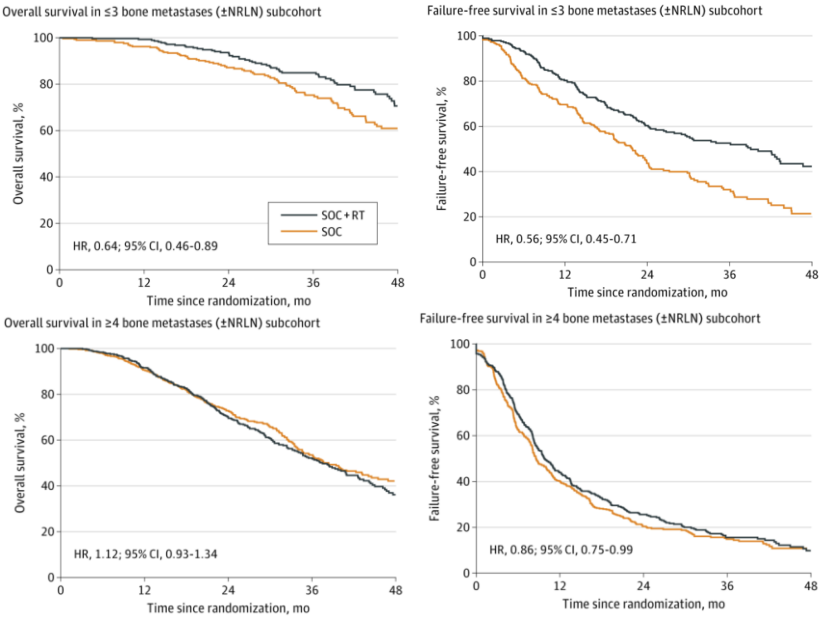
Ali, JAMA Oncol 2021. Exploratory Secondary Analysis
1939 of 2061 men were included (median age, 68 years); 1732 (89%) had bone metastases.

Bone metastasis counts were associated with OS and FFS benefit from prostate RT.

Survival benefit ↓ continuously as the number ↑ of bone metastases (Benefit most pronounced up to 3 bone metastases).

Prostate RT benefit on subgroup if 1. low metastatic burden with only nonregional lymph nodes (M1a) or 2. ≤ 3 bone metastases without visceral metastasis.

Conclusions and Relevance In this exploratory analysis of a randomized clinical trial, bone metastasis count and metastasis location based on conventional imaging were associated with OS and FFS benefit from prostate RT in M1 disease.



HORRAD

←R→ 432 patients with PSA >20 + and primary bone mPCa on bone scan between 2004 and 2014.

| 1. ADT + RT | 2. ADT | 1^{O} OS.

Median PSA level was 142ng/ml and 67% of patients had more than five osseous metastases.

Boeve, Eur Urol 2018.

Median OS 45 mo vs. 43 mo (NS). Median time to PSA progression 15 mo vs. 12 mo (SS).

CONCLUSIONS: The current RCT comparing ADT to ADT with EBRT to the prostate in patients with primary bone mPCa did not show a significant difference in overall survival, although the CI cannot exclude a substantial survival benefit. Further research is needed to confirm our findings.

SIGNIFICANT CRITICISM: HIGH median PSA 142. HIGH cutoff of low burden ≤ 4 vs. > 5 Inclusion visceral met without stratification.

Also, unexplained much better OS for ADT alone arm (should be about~ 28 mo but in this trial it was ~43 mo).

Takeaway: No benefit with RT to prostate only applicable in patients with exceptional amounts of metastatic disease.

Most newly diagnosed metastatic patients do not fall in this category.

AZ 2022

Side effects

ADT + Exercise
Secondary analysis from 2 RTC → evaluating role of exercise on treatment-related side effects in patients with PCa receiving ADT.
115 patients → s/p ADT + RT. Patient-reported quality of life and functional and symptom scales were assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and PR25 before and after | 1. 6 months of exercise | 2. usual care (UC) |.

Schumacher, PRO 2021.
SS ↓ in physical functioning (P = .019) and increased fatigue (P = .007) in the control group.
No Δ observed in the exercise group.
NS Trend ↓ sexual activity in the control group (P = .064), with a mean adjusted change of -7.1 points.
6-month ↓ clinically important pain 18.1 vs 37.2%, (P = .022).
No between-group differences were found for urinary (P = .473) or hormonal treatment-related symptoms (P = .552).
Conclusions Exercise during concomitant hormone and radiation treatment for men with PCa may mitigate some adverse changes in patient-reported fatigue, physical functioning, and possibly sexual activity. The promotion and provision of exercise to counter a range of treatment-related adverse effects in patients with PCa undergoing radiation therapy and ADT should be actively encouraged.

Bicalutamide Side Effects (Exploratory Analysis of CHHiP trial)
| 1. 2700 had LHRHa | 2. 403 had bicalutamide (150 mg daily) |.
1^{O} BCF. Groups were compared with Cox regression adjusted for various prognostic factors and stratified by radiotherapy dose. A key secondary endpoint was erectile dysfunction (ED) assessed by clinicians (LENT-SOM subjective erectile function for vaginal penetration) and patients (single items within UCLA-PCI and EPIC-50 questionnaires) at 2 years and compared between HT regimens by chi square trend test.
Bicalutamide patients were significantly younger (median 67 vs 69 years LHRHa).

Tree, IJROBP 2022 Median follow-up is 9.3 years.
5-year BCF Survival ~87% NS.
2-years G ≥ 2 LENT-SOM ED 313/590 (53%) vs. 17/68 (25%) (p<0.0001).
2-year ED patient reported scale NS
Breast Tenderness 2.8% vs. 26%.
Conclusions In this non-randomised comparison, there was no evidence of a difference in efficacy according to type of HT received.
Bicalutamide preserved clinician assessed (LENT-SOM) erectile function at 2 years but patient reported outcomes were similar between groups.

QoL Fox Chase (Max 1 Week Treatment)
342 low/intermediate prostate cancer → 342 LDR, 159 HDR, 112 SBRT treated from 2001 to 2018
Prospectively collected International Prostate Symptom Score (IPSS), Sexual Health Inventory For Men (SHIM), and Expanded Prostate cancer Index Composite Short Form (EPIC-26).
Early (3 to 6 mo) or late (1 to 2 y) PRQOL scores.

Paly, Am JCO 2021.
Early/late time points → rates of IPSS MID after LDR were higher compared to HDR/SBRT.
No IPSS differences between SBRT and HDR.
All modalities showed early and late SHIM worsening.
No temporal differences in SHIM between SBRT and brachytherapy.
No differences in EPIC subdomains between HDR and SBRT.
Bowel symptoms worsened early after SBRT, whereas urinary irritative/obstructive symptoms worsened late after HDR.
Among all domains, MID after SBRT and HDR were similar.
Conclusions: In a cohort of patients treated with modern radiotherapy techniques, HDR and SBRT resulted in clinically meaningful improved urinary PRQOL compared with LDR.

SEER Side Effects and Regret
Prospective 2072 men SEER (2011-2012) any treatment modality (surgery, RT, AS).

Wallis, JAMA Oncol 2021
5-year treatment-related surgery 183 (16%) vs. RT 76 (11%), AS 20 (7%) undergoing active surveillance.
Surgery vs. AS ↑ regret (aOR 2.40, SS). Radiation vs. AS only trend regret (aOR, 1.53 NS).
When mediation by patient-reported functional outcomes was considered, treatment modality was not independently associated with regret.
Only sexual dysfunction (not other outcomes) SS associated with regret (aOR 0.65, SS Δ sexual function from baseline).
Subjective patient-perceived treatment efficacy (aOR, 5.40 [95% CI, 2.15-13.56]) and adverse effects (aOR, 5.83 [95% CI, 3.97-8.58]), compared with patient expectations before treatment, were associated with treatment-related regret.
Other patient characteristics at the time of treatment decision-making, including participatory decision-making tool scores (aOR, 0.80 [95% CI, 0.69-0.92]), social support (aOR, 0.78 [95% CI, 0.67-0.90]), and age (aOR, 0.78 [95% CI, 0.62-0.97]), were significantly associated with regret.
Results were comparable when assessing regret at 3 years rather than 5 years.
Conclusions and Relevance The findings of this cohort study suggest that more than 1 in 10 patients with localized prostate cancer experience treatment-related regret. The rates of regret appear to differ between treatment approaches in a manner that is mediated by functional outcomes and patient expectations. Treatment preparedness that focuses on expectations and treatment toxicity and is delivered in the context of shared decision-making should be the subject of future research to examine whether it can reduce regret.

Other

Hypofractionated Proton Therapy vs. IMRT
1850 patients from 7 tertiary referral centers treated from 1998 to 2018.
All moderately hypofractionated radiation (250 to 300 cGy per daily fraction → 4 to 6 weeks).
1282 IMRT (median follow-up 80.0 months) and 568 PBT (median follow-up 43.9 months)
1^{O} late genitourinary (GU) and gastrointestinal (GI) toxicity.

Vapiwala, IJROBP 2021.
Overall toxicity rates were low, with the majority of patients experiencing no late GU (56.6%, n = 1048) or late GI (74.4%, n = 1377) toxicity.
Late grade ≥3 GU toxicity of PBT 2.0% vs. IMRT 3.9% (OR 0.47; NS) Late grade ≥2 GI PBT 14.6% vs. IMRT 4.7% (OR 2.69; NS).
MVA No factors were significantly predictive of GU toxicity.
Only anticoagulant use was significantly predictive of GI toxicity (OR 1.90; P = .008).
Conclusions In this large, multi-institutional analysis of 1850 patients with early-stage prostate cancer, treatment with moderately hypofractionated IMRT and PBT resulted in low rates of toxicity. No difference was seen in late GI and GU toxicity between the modalities during long-term follow-up. Both treatments are safe and well tolerated.
Justified | Vapiwala, Int J Radiat Oncol Biol Phys 2021

Pending Proton vs. Photon Comparison Trials
COMPPARE
PARTIQoL

Chemoprevention Trial

PCPT Trial Thompson, NEJM 2013. ←R→ 18,882 men (> 55 yo, normal DRE, PSA < 3) | 1. finasteride (5 mg daily) | 2. placebo | for 7 years.
Results: Diagnosed pCa 10.5% vs. 14.9% (P<0.001). High Risk Diagnosed 3.5% vs. 3.0% (Gleason score, 7 to 10) (P=0.05).

25% ↓ in prevalence of prostate cancer over 7-year period from 30.6% to 18.6%. More aggressive cancers (GS 7-10) were seen in patients who took finasteride (37% of all tumors, and 6.4% of men on finasteride) than placebo (22% of all tumors, and 5.1% of men on placebo). Finasteride did reduce urinary symptoms compared to placebo. More sexual side effects: gynecomastia, loss of libido, ED. Not powered for PCaSS or OS.
Conclusion: Finasteride ↓ risk of prostate cancer by nearly 50% due entirely to a relative reduction of low-grade cancer.

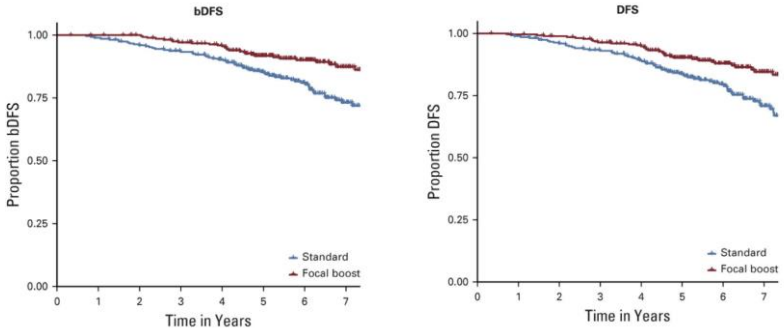
There is a study of REDUCE trial (Reduction by Dutasteride of Prostate Cancer Events) Phase III inhibition of I and II 5a-reductase. 22.8% reduction of being diagnosed with prostate cancer 4 years after starting

UK PATCH Estrogen Trial
←R→ Phase II/III 1694 men w/ locally advanced or metastatic PCa prostate cancer | 1. LHRHa according to local practice | 2. tE2 patches |.
Patches = four 100 µg patches per 24 h, changed twice weekly, ↓to 3 patches twice weekly if castrate at 4 weeks [aka testosterone ≤1·7 nmol/L]).

Langley, Lancet 2021. 4 year FU
1 month castration rates 65% vs. 83% 3 month castration rates 93% vs. 93%.
157 events from 145 men met predefined cardiovascular criteria, with a further ten sudden deaths with no post-mortem report (total 167 events in 153 men).
26 (2%) of 1694 patients had fatal cardiovascular events, 15 (2%) of 790 assigned LHRHa and 11 (1%) of 904 allocated tE2.
The time to first cardiovascular event did not differ between treatments (HR 1·11, p=0·54) [including sudden deaths without post-mortem report]; 1·20, 0·86–1·68; p=0·29 [confirmed group only]). 30 (34%) of 89 cardiovascular events in patients assigned tE2 occurred more than 3 months after tE2 was stopped or changed to LHRHa. The most frequent adverse events were gynaecomastia (all grades), with 279 (38%) events in 730 patients who received LHRHa versus 690 (86%) in 807 patients who received tE2 (p<0·0001) and hot flushes (all grades) in 628 (86%) of those who received LHRHa versus 280 (35%) who received tE2 (p<0·0001).
Interpretation Long-term data comparing tE2 patches with LHRHa show no evidence of a difference between treatments in cardiovascular mortality or morbidity. Oestrogens administered transdermally should be reconsidered for androgen suppression in the management of prostate cancer.

ASTRO 2022

Netherlands FLAME MRI Based Dose Escalation Trial
←R→ 571 intermediate- and high-risk PCa between 2009 and 2015
| 1. 77 Gy (fractions of 2.2 Gy) to the entire prostate |
| 2. + SIB focal boost → 95 Gy (fractions up to 2.7 Gy) to the intraprostatic lesion visible on multiparametric MRI |.
1^{O} 5-year bDFS.



Kerkmeijer, JCO 2021. Median FU 72 months.
5-year bDFS 85% vs. 92% (SS). PCaSS (P = .49) and OS (P = .50).
Late GU G≥2 23% vs. 28%. Late GI G≥2 12% vs. 13%.
Both for late toxicity as health-related quality of life, differences were small and not statistically significant.

CONCLUSION The addition of a focal boost to the intraprostatic lesion improved bDFS for patients with localized intermediate- and high-risk prostate cancer without impacting toxicity and quality of life. The Focal Lesion Ablative Microboost in Prostate Cancer study shows that a high focal boost strategy to improve tumor control while respecting organ at risk dose constraints is effective and safe.

Groen, Radiother Oncol 2021. Secondary Analysis Dosimetry
Dose parameters (D2cm3 and D50%) and GI toxicity grade ≥2 in four years of follow-up was assessed.
D_{2cm} dose–effect relation adjusted OR 1.17 ($p < 0.0001$) and $D_{50\%}$ adjusted OR 1.20 ($p < 0.0001$).
Conclusion Although there was no difference in toxicity between study arms, a higher radiation dose to the anorectum was associated with a statistically significant increase in GI toxicity following EBRT for prostate cancer. This dose–effect relation was present for both large and small anorectal volumes. Therefore, further increase in dose to the anorectum should be weighed against the benefit of focal dose escalation for prostate cancer.

Phase I Prostate Fossa SBRT
24 patients indicated for adjuvant or salvage RT → SBRT 3.6 Gy × 15 fx (DL1); 4.7 Gy × 10 fx (DL2); and 7.1 Gy × 5 fx (DL3).
Escalation followed a 6 + 6 rules-based design with 12 patients required at the maximum tolerated dose.
Dose-limiting toxicity was defined as grade (G) ≥3, gastrointestinal (GI) or genitourinary (GU) toxicity.
4 patients received ADT.

Kishan, IJROBP 2018.
No G ≥ 3 GI or GU toxicity was seen at any DL.
A few G2 GI symptoms: 2 of 6 patients in the DL1 group, 3 of 6 in DL2, and 7 of 12.
Except in 1 patient, all acute G2 GI toxicity resolved by 10 weeks.
Three of 12 patients reported an increase to G1 and G2 GU toxicity in the 2 weeks after RT in groups DL1 and DL2 and 1 of 12 patients in DL3.
At week 2 after RT, decline in the 26-item Expanded Prostate Cancer Index Composite bowel domain met criteria for a minimally important difference in 71% of patients. At week 10, 1 of 6, 2 of 6, and 7 of 11 patients at DLs 1, 2, and 3, respectively, still met minimally important difference criteria. International Prostate Symptom Scores worsened 2 weeks after treatment but improved by 6 to 10 weeks.
Conclusions
Dose escalation up to 7.1 Gy × 5 fx to the PF was completed without acute G ≥ 3 toxicity. There was transient G2 rectal toxicity at all DLs during and immediately after RT. We must perform long-term follow-up and assessment of late toxicity of SBRT to the PF.

City of Hope Phase I Prostate Fossa SBRT
26 patient organ-confined, node-negative prostate cancer who had biochemical failure (PSA < 2).
Doses delivered were 35 Gy (n=3), 40 Gy (n=8), and 45 Gy (n=15) in 5 fractions, given every other day.
Dose-limiting toxicity (DLT) = CTCAE (V4) ≥ G3 GI/GU toxicity within 90 days of treatment.
Maximum tolerated dose was the highest dose to be tested where fewer than 2 of the patients experienced DLT. Patients completed quality-of-life questionnaires at regular time intervals.

Sampath, IJROBP 2019.
Late grade ≥2 and ≥3 GI occurred in 11% and 0%, respectively, and late grade ≥2 and ≥3 GU toxicity occurred in 38% and 15%, respectively.
No difference was observed in late GU toxicity between 40 Gy and 45 Gy.
Sexual function scores were significantly lower in the patients receiving androgen deprivation therapy (P < .01). In all patients, the crude rate of PSA control (<0.2 ng/mL) was 11 out of 26 (42%).
Conclusions
Dose escalation to 45 Gy did not result in acute DLT events, had similar rates of late grade 3 toxicity, and did not demonstrate higher rates of PSA control, compared with 40 Gy. While allowing for higher plan heterogeneity, the recommended dose for phase 2 study will be 40 Gy in 5 fractions.

AE 2022

MEAL (Men's Eating and Living) Study CALGB 70807
←R→ 478 patients 50 to 80 years, stage ≤ cT2a, and PSA < 10 | 1. Telephone consulting | 2. Control |.
Telephone consulting = promoting consumption of 7 or more daily vegetable servings.
1^{O} = time to progression (progression = PSA ≥ 10, PSA doubling time < 3 years, or upgrading (defined as increase in tumor volume or grade) on follow-up prostate biopsy).

Parsons, JAMA Network 2020.
There were no significant differences in time to progression (unadjusted HR, 0.96, adj hazard ratio, 0.97).
The 24-month progression-free = 43.5% vs. 41.4% (NS).
Conclusions and Relevance Among men with early-stage prostate cancer managed with active surveillance, a behavioral intervention that increased vegetable consumption did not significantly reduce the risk of prostate cancer progression. The findings do not support use of this intervention to decrease prostate cancer progression in this population, although the study may have been underpowered to identify a clinically important difference.

AZ 2022