IDENTIFICATION AND MANAGEMENT AFTER FAILURE OF LOCAL PROSTATE TREATMENTS

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DISCLOSURES

SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

Guideline Panel

Todd M. Morgan, MD; Stephen A. Boorjian, MD; Mark K. Buyyounouski, MD, MS; Brian F. Chapin, MD; David Y.T. Chen, MD; Heather H. Cheng, MD, PhD; Heather A. Jacene, MD; Sophia C. Kamran, MD; Amy N. Luckenbaugh, MD; Ben J. Nathanson; Yaw A. Nyame, MD, MS, MBA; Edwin M. Posadas, MD; Phuoc T. Tran, MD, PhD; Ronald C. Chen, MD, MPH

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OUTLINE OF TALK

- Biochemical recurrence (BCR)
  - How to define
  - Natural history/risk stratification/imaging evaluation
- Salvage RT for BCR
  - Early salvage RT
  - What about concurrent ADT?
- Salvage systemic therapy for BCR

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Adjuvant and Salvage Radiotherapy After Prostatectomy: AUA/ASTRO Guideline

Ian M. Thompson,* Richard K. Valicenti,* Peter Albertsen, Brian J. Davis, S. Larry Goldenberg, Carol Hahn, Eric Klein, Jeff Michalski, Mack Roach, Oliver Sartor, J. Stuart Wolf, Jr. and Martha M. Faraday

5. Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is ≥0.2 ng/ml with a second confirmatory level ≥0.2 ng/ml. (*Recommendation; Evidence Strength: Grade C*)

J Urol 2013

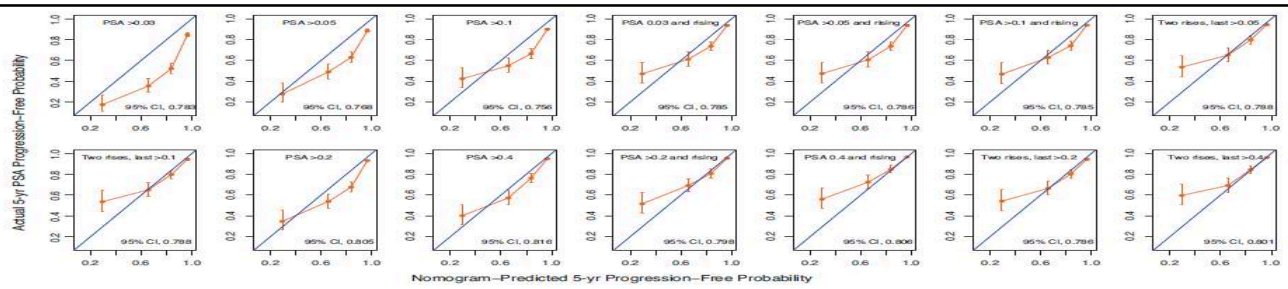

Fig. 1 – Discrimination and calibration of observed 5-yr risk of prostate-specific antigen (PSA) progression after the time of biochemical recurrence compared with 5-yr progression-free probability by a validated postoperative nomogram for 14 definitions of biochemical recurrence. CI = confidence interval.

- Optimal definition of BCR, per predicted 5-yr PFS:
  - <50% (high risk disease) → single PSA ≥ 0.05
  - >90% (low risk disease) → PSA ≥ 0.4 and rising
- **MAY USE LOWER THRESHOLD TO DEFINE BCR WITH HIGHER RISK DISEASE!**

Eur Urol 2014

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A WORD ABOUT BCR AFTER RT

- Definition:
  - Phoenix criteria = nadir PSA+ ≥ 2 ng/ml

Roach M et al, Int J Radiation Oncology Biol Phys 2006

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER RADIATION THERAPY

23. For patients with BCR following primary RT or ablative therapy who have no evidence of metastatic disease and are candidates for local salvage therapy, clinicians should perform a prostate biopsy to evaluate for local recurrence. (*Clinical Principle*)

24. In patients with a biopsy-documented prostate cancer recurrence after primary RT who are candidates for salvage local therapy, clinicians should offer RP, cryoablation, high-intensity focused ultrasound (HIFU), or reirradiation as part of an SDM approach. (*Moderate Recommendation; Evidence Level: Grade C*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

AND AFTER FOCAL THERAPY…

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER FOCAL THERAPY

GUIDELINE STATEMENT 25

In patients for whom salvage local therapy is being considered following focal ablation, clinicians should offer whole gland treatment by RP or RT. (*Expert Opinion*)

NATURAL HISTORY OF BCR

- BCR occurs in up to 35% of patients after RP
- Heterogeneous biology of BCR:
  - Nearly always precedes systemic progression/death from prostate cancer
  - Does not always result in systemic progression/death from prostate cancer
    - Men with prostate cancer > 60 years old → competing risks of mortality
  - Men with BCR as likely to die in 15 years from competing risks as prostate cancer*

***Bianco et al, Urology 2005;66:83**

Natural History of Progression After PSA Elevation Following Radical Prostatectomy

Charles R. Pound, MD
Alan W. Partin, MD, PhD
Mario A. Eisenberger, MD
Daniel W. Chan, PhD
Jay D. Pearson, PhD
Patrick C. Walsh, MD

Context In men who develop an elevated serum prostate-specific antigen level (PSA) after having undergone a radical prostatectomy, the natural history of progression to distant metastases and death due to prostate cancer is unknown.

Objective To characterize the time course of disease progression in men with biochemical recurrence after radical prostatectomy.

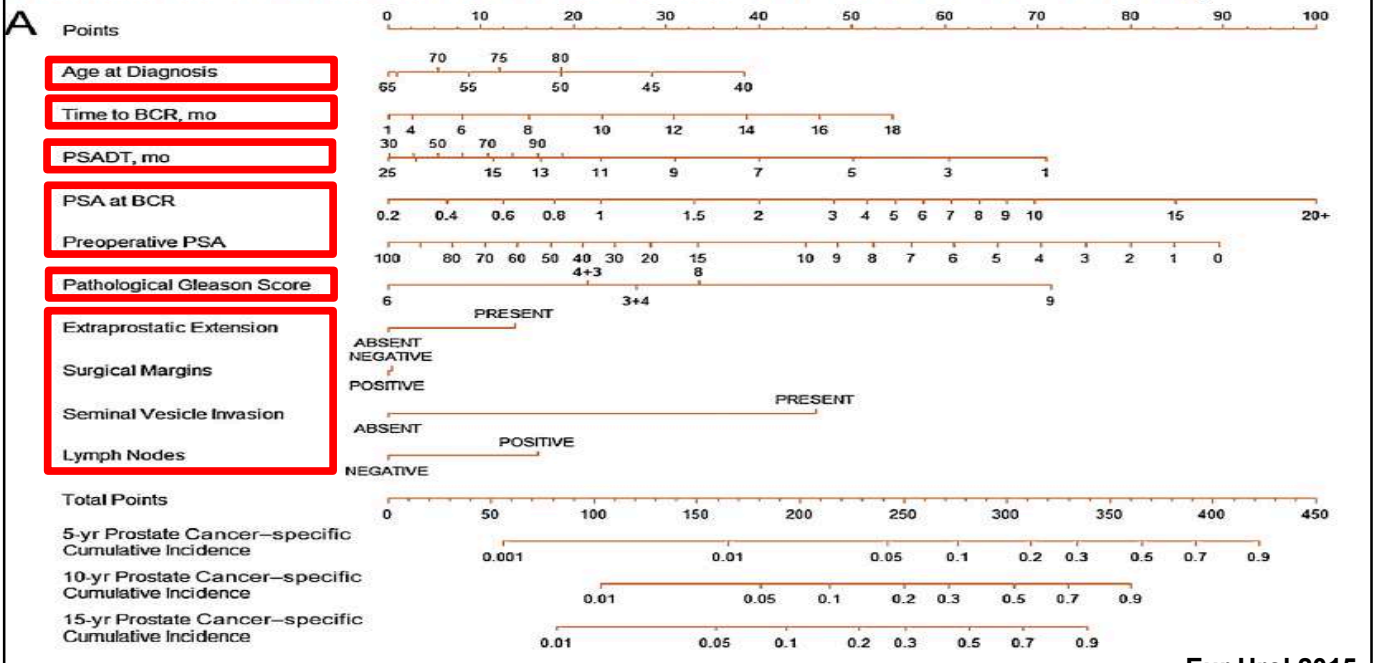
Design A retrospective review of a large surgical series with median (SD) follow-up of 5.3 (3.7) years (range, 0.5-15 years) between April 1982 and April 1997.

Setting An urban academic tertiary referral institution.

- 304 men with BCR after RP
- Mean follow-up = 5.3 years
- 34% of BCR patients → metastatic disease
  - Median **8 years** from BCR to metastasis
  - Median **5 years** from metastasis to death
    13 years
  - *Must consider competing risks of mortality!*

JAMA 1999

Nomogram Predicting Prostate Cancer–specific Mortality for Men with Biochemical Recurrence After Radical Prostatectomy



Eur Urol 2015

EAU BCR RISK GROUPS

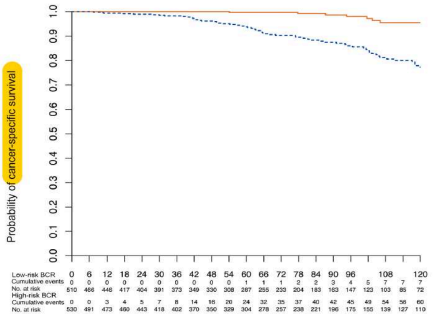
Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review

- Low-risk BCR
  - RP: PSA DT > 1 year and pGS<8
  - RT: Interval to BCR > 18 months and biopsy GS < 8
- High-risk BCR
  - RP: PSA DT ≤ 1year or pGS 8-10
  - RT: Interval to BCR < 18 months or biopsy GS 8-10

Van den Broeck T et al, Eur Urol 2019

External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort

- 1040 patients with BCR after RP
- F/u 124 mo RP/65 mo BCR



Tilki D et al, Eur Urol 2019

5. Clinicians should use prognostic factors (e.g., PSA doubling time [PSADT], Gleason Grade Group, pathologic stage, surgical margin status, validated post-prostatectomy genomic classifier and/or positron emission tomography (PET) imaging results) to counsel patients with a detectable PSA about their risk of clinical progression. (*Moderate Recommendation; Evidence Level: Grade B*)

TABLE 3: High-risk Features in the Setting of BCR to be Considered for Patient Counseling and Management**

• **Grade Group 4-5**
• **Stage pT3b-4**
• **Surgical margin status***
• **Node-positive disease**
• **Short PSADT**
• **Short interval from primary therapy to PSA recurrence (including persistent detectable PSA after prostatectomy)**
• **Higher post-prostatectomy PSA**
• **Genomic classifier risk**
• **PET imaging findings**

Boorjian SA et al, AUA Guidelines 2024

IMAGING EVALUATION OF THE PATIENT WITH BCR

“Conventional” = bone scan, CT/MRI
“Molecular; next generation” = PSMA PET

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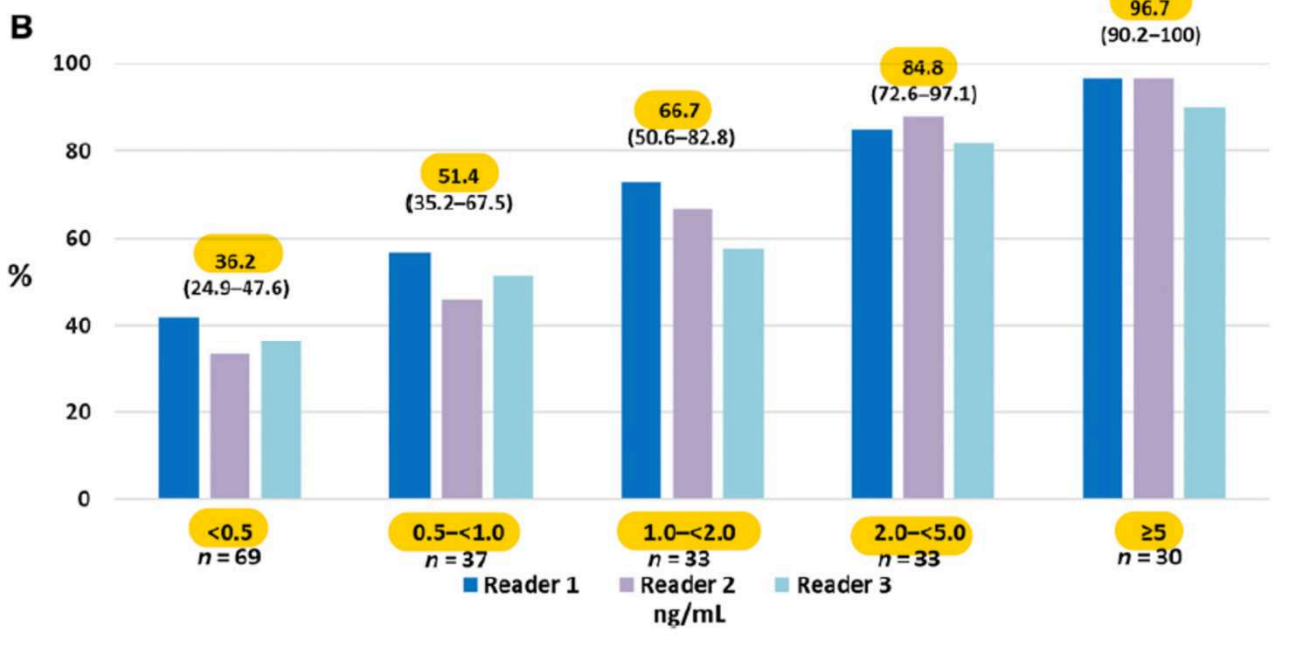

Figure 2.
CLR (**A**) and detection rate (**B**) by baseline PSA levels. Median (95% CI) for each group of three readers provided. CLR, correct localization rate; PSA, prostate-

Morris MJ et al, Clin Cancer Res 2021

SO WHAT DO OUR GUIDELINES SAY ABOUT IMAGING?

8. In patients with a BCR after local therapy, clinicians may obtain a prostate-specific membrane antigen (PSMA)-PET in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

9. For patients with BCR following RP in whom salvage radiation is being considered, the clinician should perform next generation molecular PET imaging. (*Moderate Recommendation; Evidence Level: Grade C*)

- Exclude patients with extra-pelvic disease or distant metastases from receiving salvage local therapy

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

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BUT BE VERY CAREFUL ON UTILIZING THE FINDINGS OF A PSMA PET…

12. In a patient with a BCR following RP, clinicians should not withhold salvage prostate bed RT in the setting of a negative PET/CT. (*Expert Opinion*)

- Detection rate of PET not high enough at low levels of PSA
  - Microscopic disease still may be present

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

Does addition of multiparametric MRI to PSMA PET/CT improve diagnostic accuracy for biochemical recurrence after radical prostatectomy?

Yash Khanna[3,9], Vidyasagar Chinni[1,8], Kavitha Gnanasambantham[3], Eldho Paul[11], Richard O'Sullivan[4], Zita E. Ballok[4], Andrew Ryan[6], Shakher Ramdave[9], Dinesh Sivaratnam[2], Patrick Bowden[5], Mario Guerrieri[7], Weranja K.B. Ranasinghe[3,9,10] and Mark Frydenberg[1,2,3]

- 117 patients with BCR after RP underwent both scans
- Median PSA at imaging = 0.3 ng/mL
- Local recurrence = prostate bed or at anastomosis

BJU Int 2026

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Does addition of multiparametric MRI to PSMA PET/CT improve diagnostic accuracy for biochemical recurrence after radical prostatectomy?

Yash Khanna[3,9], Vidyasagar Chinni[1,8], Kavitha Gnanasambantham[3], Eldho Paul[11], Richard O'Sullivan[4], Zita E. Ballok[4], Andrew Ryan[6], Shakher Ramdave[9], Dinesh Sivaratnam[2], Patrick Bowden[5], Mario Guerrieri[7], Weranja K.B. Ranasinghe[3,9,10] and Mark Frydenberg[1,2,3]

- Detection of local recurrence with PSA <0.2 ng/mL:
  - MRI = 30.3% vs. PSMA = 0% (p<0.001)
- Detection of local recurrence with PSA 0.2-0.5 ng/mL:
  - MRI = 33.3% vs PSMA = 13.3% (p=0.001)

BJU Int 2026

GUIDELINES ON CONVENTIONAL IMAGING IN BCR

11. In patients with BCR, clinicians may obtain a pelvic magnetic resonance imaging (MRI) in addition to a PET/CT for evaluation of local recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

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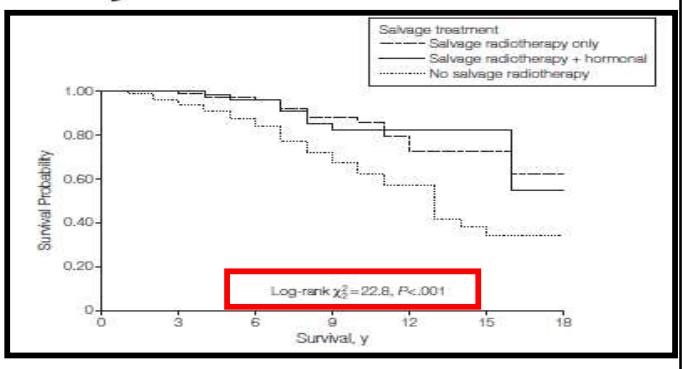
Prostate Cancer–Specific Survival Following Salvage Radiotherapy vs Observation in Men With Biochemical Recurrence After Radical Prostatectomy

- 635 men with BCR after RP
  - 238 – salvage RT (78 w/ ADT)
  - 397 – no salvage treatment
- Median follow up:
  - 6 yrs after BCR
  - 9 yrs after RP



- Salvage RT = improved CSS (HR 0.32) and OS

Trock B et al, JAMA 2008

Salvage Radiotherapy versus Observation for Biochemical Recurrence following Radical Prostatectomy for Prostate Cancer: A Matched Pair Analysis

Derya Tilki [1,2,3,*,†], Felix Preisser [4,†], Reinhard Thamm [5], Raisa S. Pompe [1], Felix K.-H. Chun [4], Markus Graefen [1], Alessandra Siegmann [6], Dirk Böhmer [6], Volker Budach [6] and Thomas Wiegel [5]

- 1832 men with BCR after RP 1989-2016
  - 603 treated with salvage RT (without ADT)
- Median follow-up 95.9 months
- Propensity-score matching used to account for differences in pathologic tumor characteristics

Cancers 2022

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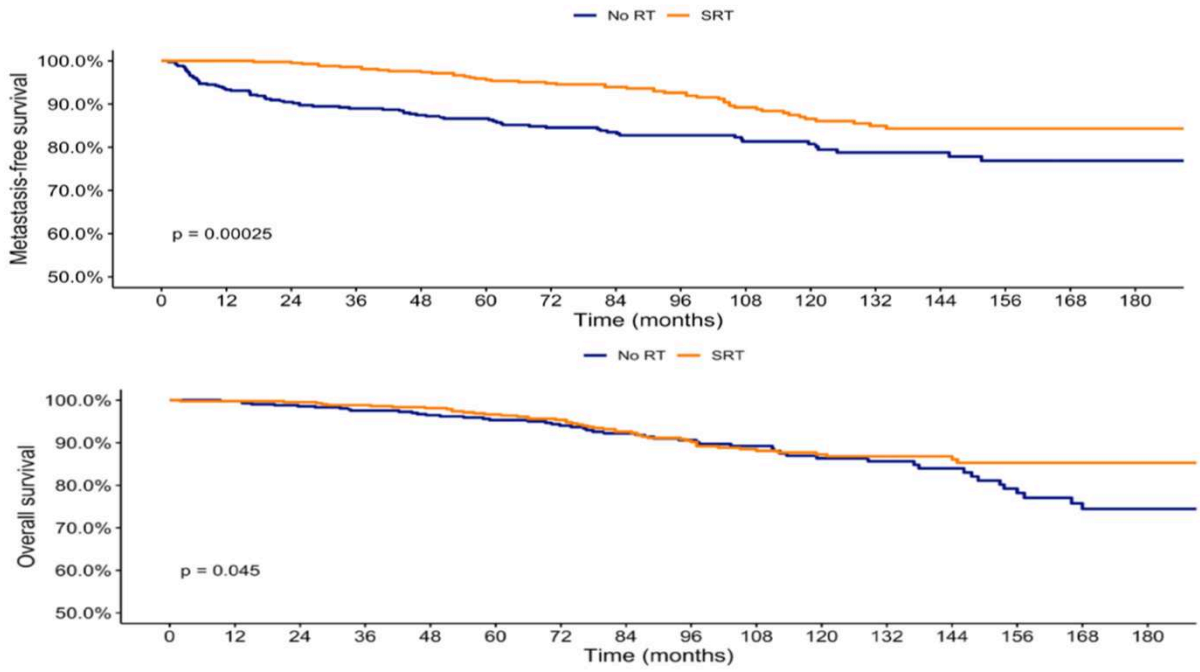

- Results maintained on multivariable analysis

Tilki D et al, Cancers 2022

(EARLY) SALVAGE RT

1. Clinicians should inform patients that salvage radiation for a detectable prostate-specific antigen (PSA) after RP is more effective when given at lower levels of PSA. (*Strong Recommendation; Evidence Level: Grade B*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

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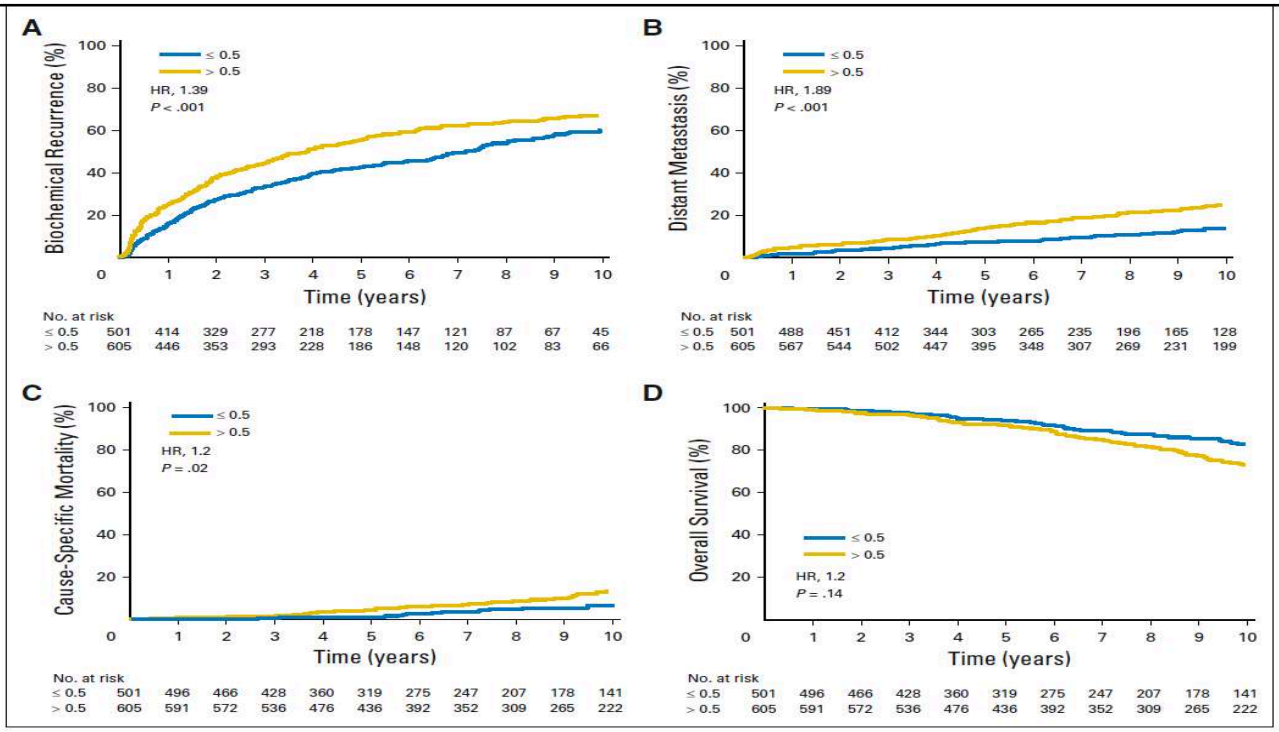

J Clin Oncol 2016

Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy

Rahul D. Tendulkar, Shree Agrawal, Tianming Gao, Jason A. Efstathiou, Thomas M. Pisansky, Jeff M. Michalski, Bridget F. Koontz, Daniel A. Hamstra, Felix Y. Feng, Stanley L. Liauw, Matthew C. Abramowitz, Alan Pollack, Mitchell S. Anscher, Drew Moghanaki, Robert B. Den, Kevin L. Stephans, Anthony L. Zietman, W. Robert Lee, Michael W. Kattan, and Andrew J. Stephenson

- 2460 (N0) patients treated with SRT (median 66 Gy)
  - Median follow-up = 5 years
- 5-year post SRT BCR-free survival = 56%
  - If pre-SRT PSA 0.01-0.2 = 71%
  - If pre-SRT PSA 0.21-0.5 = 63%
  - If pre-SRT PSA 0.51-1.0 = 54%
  - If pre-SRT PSA 1.01-2.0 = 43%
  - If pre-SRT PSA > 2.0 = 37%

J Clin Oncol 2016

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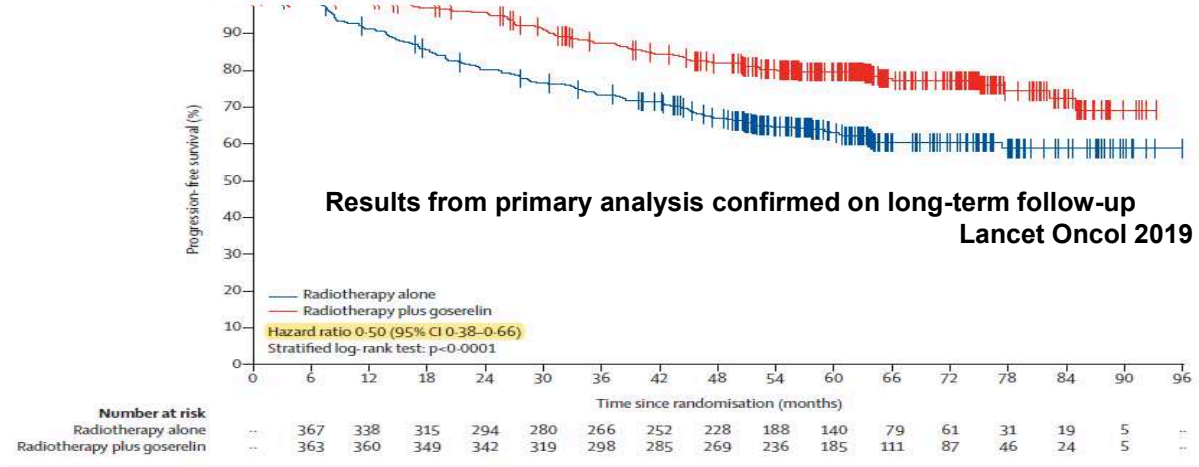
SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

2. For patients with a detectable PSA after RP in whom salvage radiation therapy (RT) is being considered, clinicians should provide salvage radiation when the PSA is ≤0.5 ng/mL. (*Moderate Recommendation; Evidence Level: Grade B*)

3. For patients with a detectable PSA after RP who are at high risk for clinical progression, clinicians may offer salvage radiation when PSA values are <0.2 ng/mL. (*Conditional Recommendation; Evidence Level: Grade C*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial



Results from primary analysis confirmed on long-term follow-up
Lancet Oncol 2019

Lancet Oncol 2016

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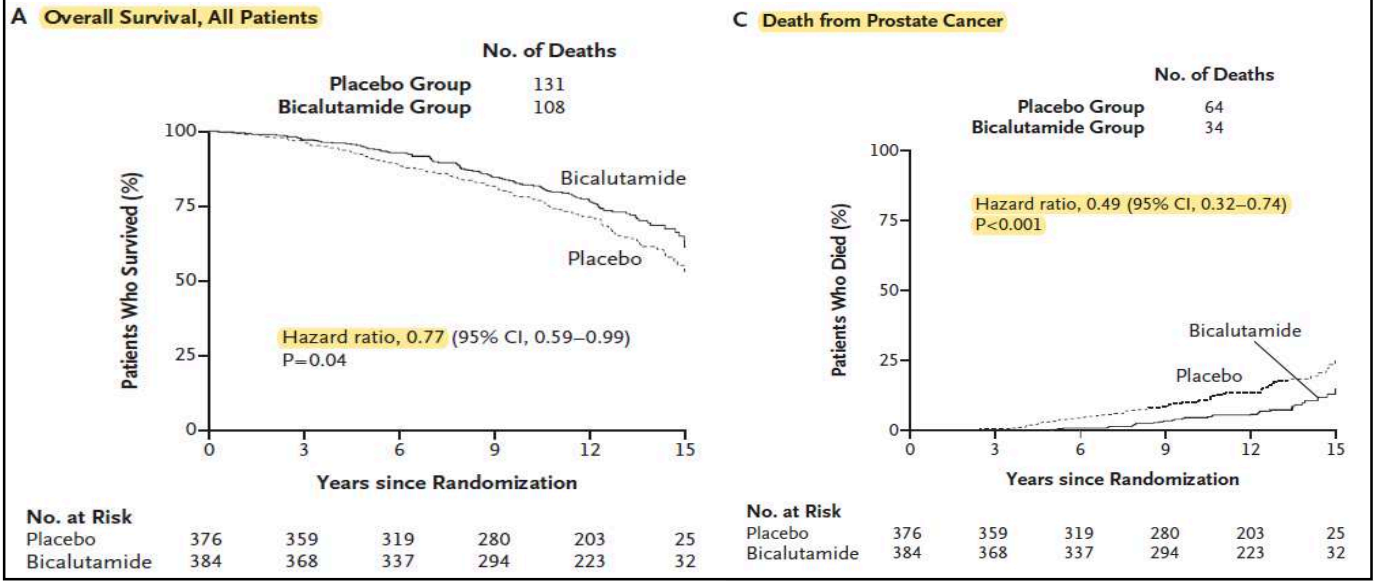
Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

W.U. Shipley, W. Seiferheld, H.R. Lukka, P.P. Major, N.M. Heney, D.J. Grignon, O. Sartor, M.P. Patel, J.-P. Bahary, A.L. Zietman, T.M. Pisansky, K.L. Zeitzer, C.A.F. Lawton, F.Y. Feng, R.D. Lovett, A.G. Balogh, L. Souhami, S.A. Rosenthal, K.J. Kerlin, J.J. Dignam, S.L. Pugh, and H.M. Sandler, for the NRG Oncology RTOG*



SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

13. Clinicians should offer androgen deprivation therapy (ADT) in addition to salvage RT for patients with BCR following RP and any high-risk features (e.g., higher post-prostatectomy PSA such as PSA ≥0.7ng/mL, Gleason Grade Group 4 to 5, PSADT ≤6 months, persistently detectable post-operative PSA, seminal vesicle involvement). (*Moderate Recommendation; Evidence Level: Grade B*)

16. For patients with pN1 disease being treated with post-operative RT, clinicians should include ADT rather than treating with RT alone. (*Clinical Principle*)

15. Clinicians should discuss treatment side effects and the impact of medical comorbidities when patients are being considered for ADT (as well as duration) with salvage RT, utilizing a shared decision-making approach. (*Clinical Principle*)

14. For patients with BCR following RP without any high-risk features, clinicians may offer radiation alone. (*Conditional Recommendation; Evidence Level: Grade C*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

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SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

17. When providing ADT to patients undergoing salvage RT, clinicians should provide a minimum of four to six months of hormonal therapy. (*Clinical Principle*)

18. For patients with high-risk features, clinicians may extend ADT to 18 to 24 months. (*Expert Opinion*)

Morgan TM, Boorjian SA et al, AUA Guidelines 2024

AND WHAT ABOUT SYSTEMIC THERAPY ALONE (ADT…AND MORE?) FOR BCR?

Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study

X. Garcia-Albeniz[a,*], J.M. Chan[b,c], A. Paciorek[b], R.W. Logan[a], S.A. Kenfield[c], M.R. Cooperberg[b,c], P.R. Carroll[c], M.A Hernán[a,d,e]

- 2096 men with PSA relapse after RP or RT
- No difference in ACM or PSCM with "Immediate" ADT (within 3 mo. of PSA relapse) vs. "Delayed" ADT (at metastasis, symptoms, or short PSA DT)

Eur J Cancer 2015

Mortality and Androgen Deprivation Therapy as Salvage Treatment for Biochemical Recurrence after Primary Therapy for Clinically Localized Prostate Cancer

Alex Z. Fu,* Huei-Ting Tsai, Reina Haque, Marianne Ulcickas Yood, Andrea E. Cassidy-Bushrow, Stephen K. Van Den Eeden,† Nancy L. Keating, Matthew R. Smith, Yingjun Zhou, David S. Aaronson and Arnold L. Potosky

- 5,904 men with BCR after RP or RT
- Salvage ADT not associated with ACM or PCSM (overall cohort)
- With PSA DT < 9 months:
  - Salvage ADT associated with decreased ACM and PSCM
    - For both RP and RT patients

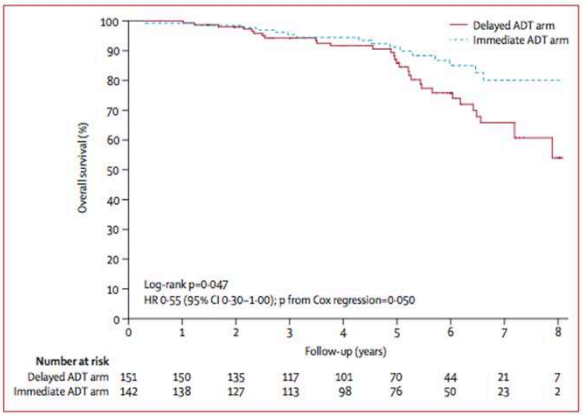
J Urol 2017

Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial

Gillian M Duchesne, Henry H Woo, Julie K Bassett, Steven J Bowe, Catherine D'Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stockler, Rodney A Syme, Keen Hun Tai, Sandra Turner*

- 293 patients
  - 261 w/ PSA relapse after potentially curative surgery and/or RT (mostly post-RT)
  - 32 "unsuitable" for primary therapy
- Trial closed early to accrual
- Randomized to immediate vs delayed (>2 yrs) ADT
- Median follow-up = 5 years

- 5 yr OS 91.2% (immediate) vs 86.4% (delayed) (p=0.047)



Lancet Oncol 2016

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Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline (2023)

William Lowrance, MD, MPH, MBA; Rodney Breau, MSc, MD, FRCSC; Roger Chou, MD; Brian F. Chapin, MD; Tony Crispino; Robert Dreicer, MD, MS, MACP, FASCO; David F. Jarrard, MD; Adam S. Kibel, MD; Todd M. Morgan, MD; Alicia K. Morgans, MD, MPH; William K. Oh, MD; Matthew Resnick, MD, MPH, MMHC; Anthony Zietman, MD; Michael S. Cookson, MD, MMHC

Amendment: William Lowrance, MD, MPH; Robert Dreicer, MD, MS, MACP, FASCO; David Jarrard, MD; Kristen Scarpato, MD, MPH, David Buckley, MD; Jessica Griffin, MS; Sennett K. Kim; Michael S. Cookson, MD, MMHC

7. For patients with a rising PSA after failure of local therapy and no demonstrated metastatic disease by imaging, clinicians should offer observation or clinical trial enrollment. (Clinical Principle)
8. ADT should not be routinely initiated in this population (Expert Opinion). However, if ADT is initiated in the absence of metastatic disease, intermittent ADT may be offered in lieu of continuous ADT. (Conditional Recommendation; Evidence Level: Grade B)

BUT ARE WE ABOUT TO "EMBARK" ON A NEW ERA?

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Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

S.J. Freedland, M. de Almeida Luz, U. De Giorgi, M. Gleave, G.T. Gotto, C.M. Pieczonka, G.P. Haas, C.-S. Kim, M. Ramirez-Backhaus, A. Rannikko, J. Tarazi, S. Sridharan, J. Sugg, Y. Tang, R.F. Tutrone, Jr., B. Venugopal, A. Villers, H.H. Woo, F. Zohren, and N.D. Shore

- BCR after RP (~25%), RT (~25%), or RP+RT (~50%) with PSA DT ≤ 9 months
- 1:1:1 randomized trial
  - Enza + leuprolide
  - Placebo + leuprolide
  - Enza monotherapy
- Primary endpoint = MFS
- Median follow-up = 60.7 months

N Engl J Med 2023

Pfizer and Astellas' XTANDI® Approved by U.S. FDA in Earlier Prostate Cancer Treatment Setting

Thursday, November 16, 2023 - 10:20pm

XTANDI becomes the first and only androgen receptor signaling inhibitor approved for use with or without a GnRH analog therapy* in nonmetastatic castration-sensitive prostate cancer

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NEVERTHELESS…QUESTIONS REMAIN:

- Median PSA at study entry was ~ 5 ng/ml (high?)
- Staging evaluation was with conventional imaging (not PSMA PET?)
- → Was this a truly non-metastatic population?
- Impact on/benefit versus sequential therapies?
- Cost?

Original Investigation | Imaging

PSMA-PET/CT Findings in Patients With High-Risk Biochemically Recurrent Prostate Cancer With No Metastatic Disease by Conventional Imaging

Adrien Holzgreve, MD; Wesley R. Armstrong, BS; Kevyn J. Clark; Matthias R. Benz, MD; Clayton P. Smith, MD; Loïc Djaileb, MD; Andrei Gafita, MD; Pan Thin, BS; Nicholas G. Nickols, MD, PhD; Amar U. Kishan, MD; Matthew B. Rettig, MD; Robert E. Reiter, MD; Johannes Czernin, MD; Jeremie Calais, MD, PhD

- 182 patients who met EMBARK criteria and who had undergone PSMA PET in prior prospective studies
  - Median PSA at PSMA PET = 2.8
- PSMA PET (+) in 84%
  - 46% (+) for metastatic disease
  - 24% had ≥ 5 lesions identified

JAMA Netw Open 2025

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CONCLUSIONS

- BCR
  - AUA defines ≥ 0.2 with confirmatory value
  - High risk BCR
    - Gleason Grade Group 4-5, pT3b-4, node positive, short PSA DT, PSA persistence
  - Natural history heterogeneous/prolonged
    - Remember competing causes of mortality

CONCLUSIONS

- Evaluate BCR with PSMA PET, especially if considering salvage RT…but remember limitations of scan
  - Don’t use negative scan to deny prostate bed salvage RT
- Salvage RT
  - Earlier = better (≤ 0.5…maybe even ≤ 0.2?)
  - Offer with ADT for high risk features
- Systemic therapy for BCR
  - Don’t routinely utilize ADT alone; if treat, offer intermittent ADT
  - Enzalutamide now approved +/- ADT as well
    - But - remember toxicity, cost, and long term natural history of BCR

THANK YOU