Do we postpone salvage RT until a positive PSMA-PET/CT?

10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

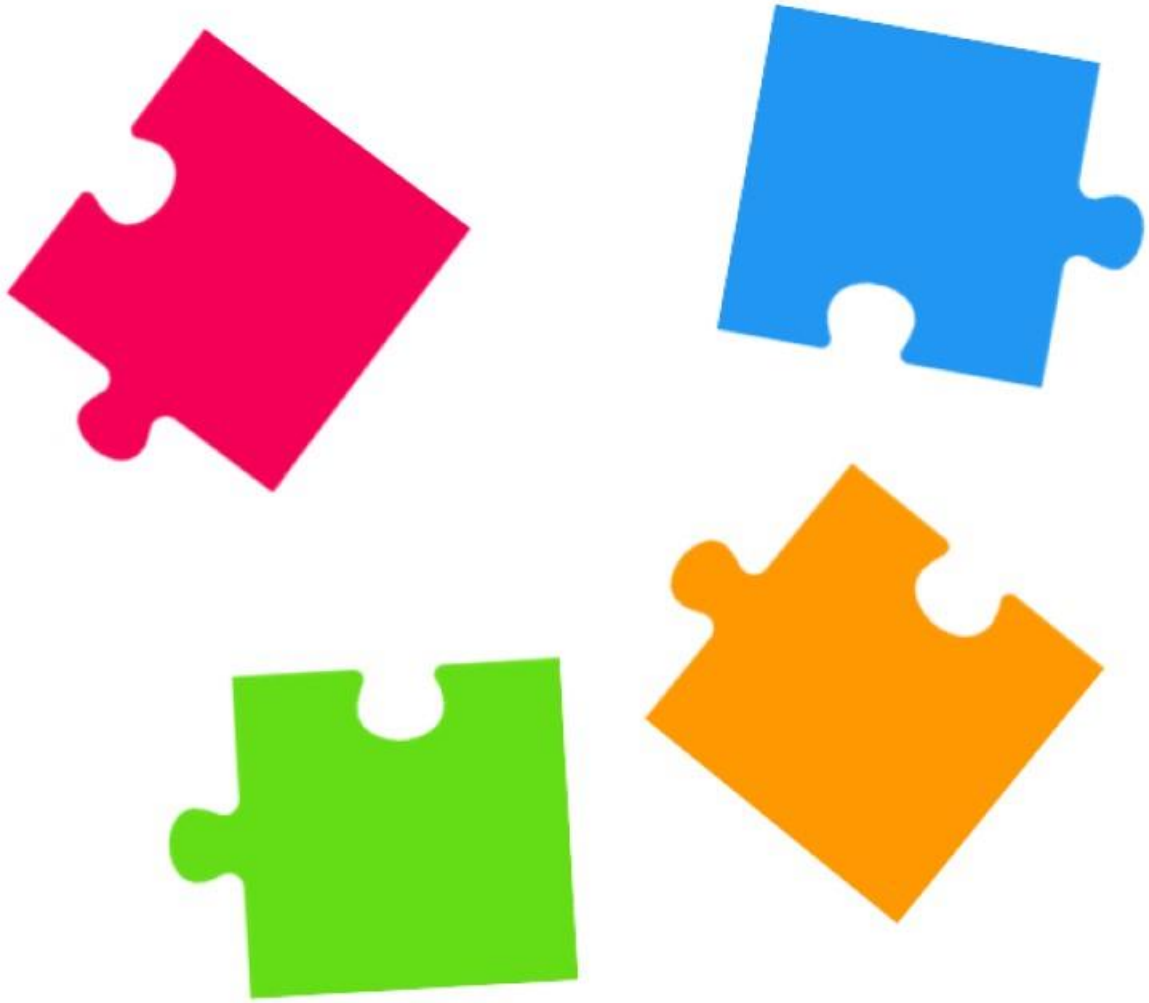
Yes!

Roderick van den Bergh

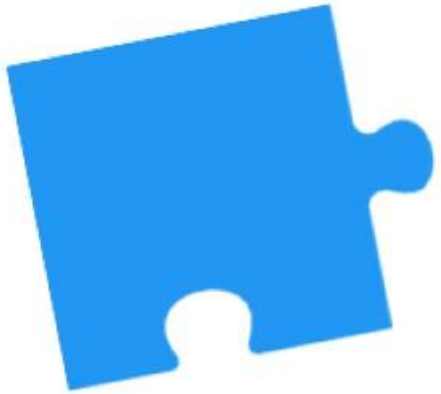
@roodvdb

Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Astellas, Janssen
Receipt of honoraria or consultation fees	Astellas
Receipt of speaker fees	Amgen, Astellas, Ipsen, Janssen, MSD
Stock shareholder	None
Other support (please specify):	None



1 - We overtreat with risk-based early salvage RT



BCR after surgery - scenarios

St Antonius
een santeon ziekenhuis

Imaging **neg**  Imaging **pos**

Imaging **neg**  Imaging **pos**

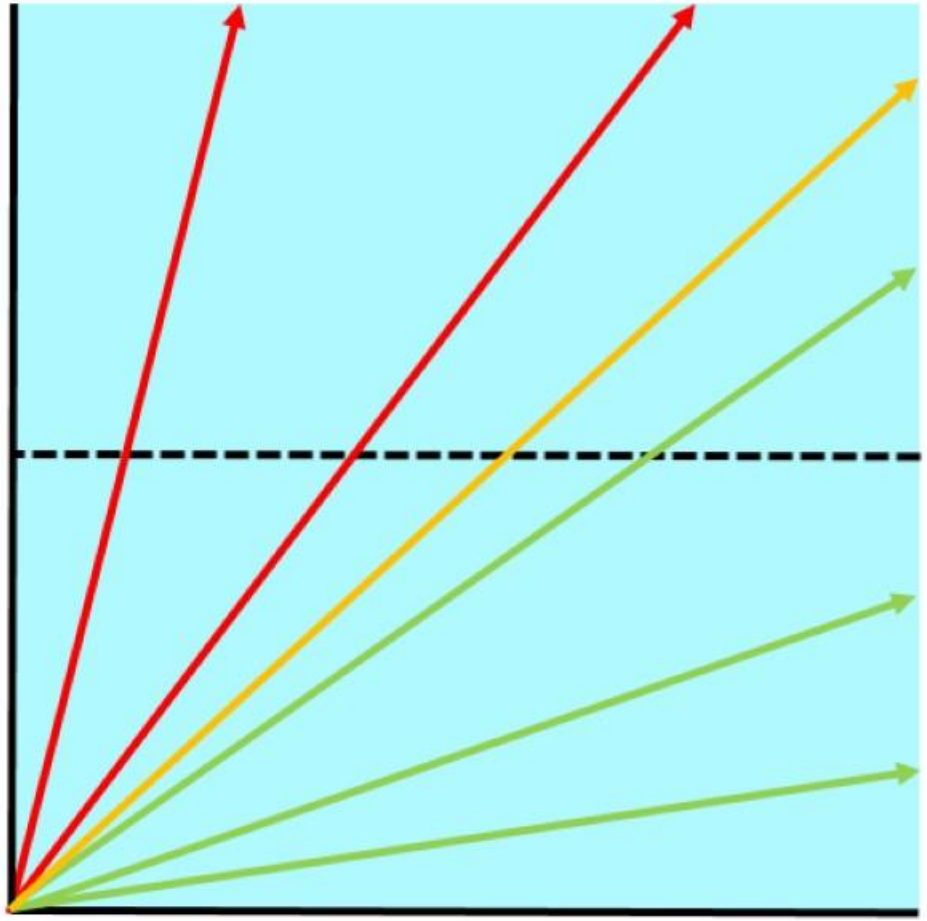
Metastasis,
visualized early,
no benefit local radiation

N M

Metastasis,
visualized later,
no benefit local radiation

N M

St Antonius
een santeon ziekenhuis



Local recurrence, CHANGING TO N/M
visualized at higher PSA,
benefits local radiation

T ▶ N M

Local recurrence,
visualized at higher PSA,
benefits local radiation

T

Local recurrence,
not visualized,
no benefit local radiation

T

Local recurrence,
not visualized,
no benefit local radiation

T

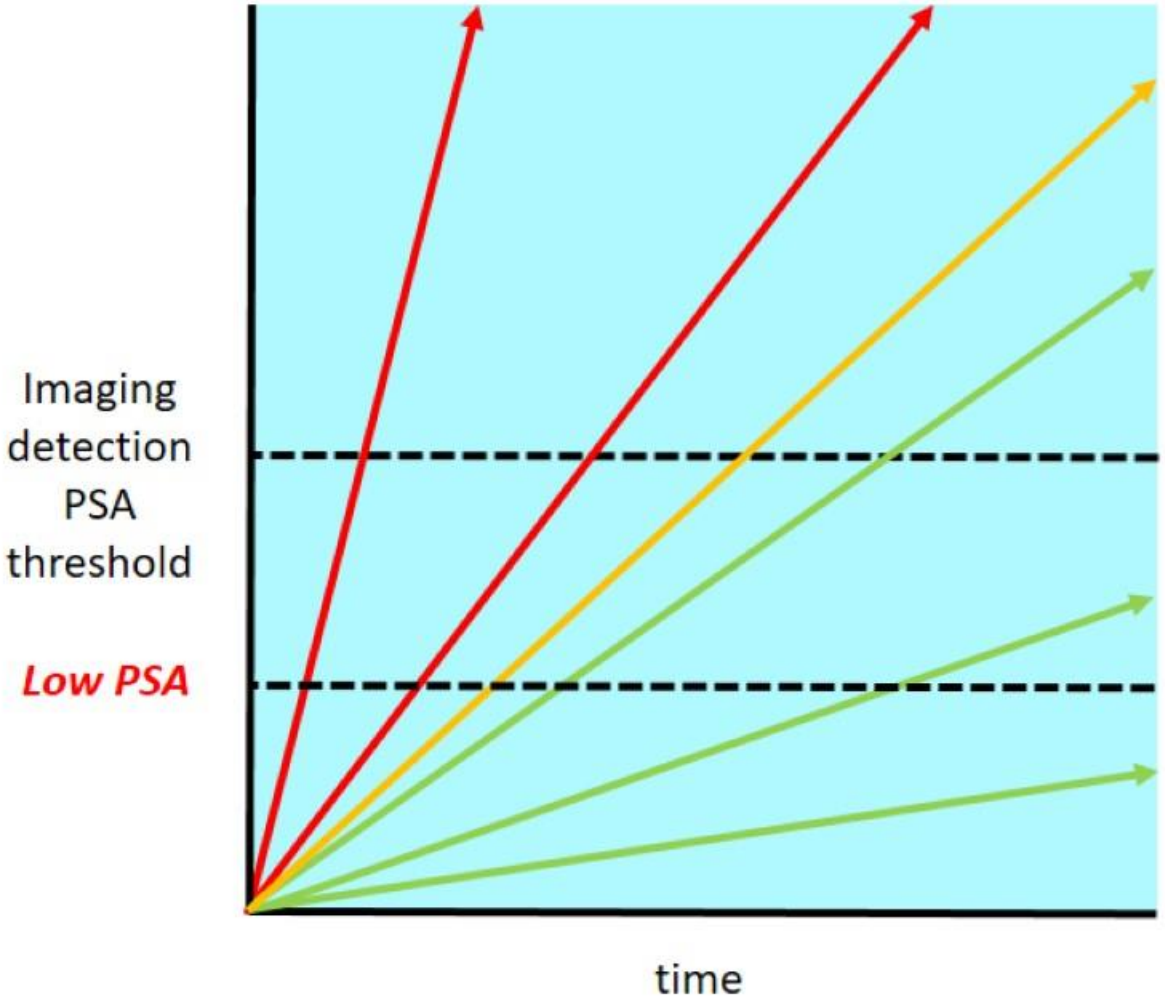
Metastasis,
visualized at low PSA,
no benefit local radiation

N M

Metastasis,
visualized only at higher PSA,
no benefit local radiation

N M

ST ANTONIUS
een santeon ziekenhuis



Local recurrence, CHANGING TO N/M
visualized at higher PSA,
benefits radiation

T ▶ N M

Local recurrence,
visualized at higher PSA,
benefits radiation

T

Local recurrence,
not visualized,
no benefit local radiation

T

Local recurrence,
not visualized,
no benefit local radiation

T

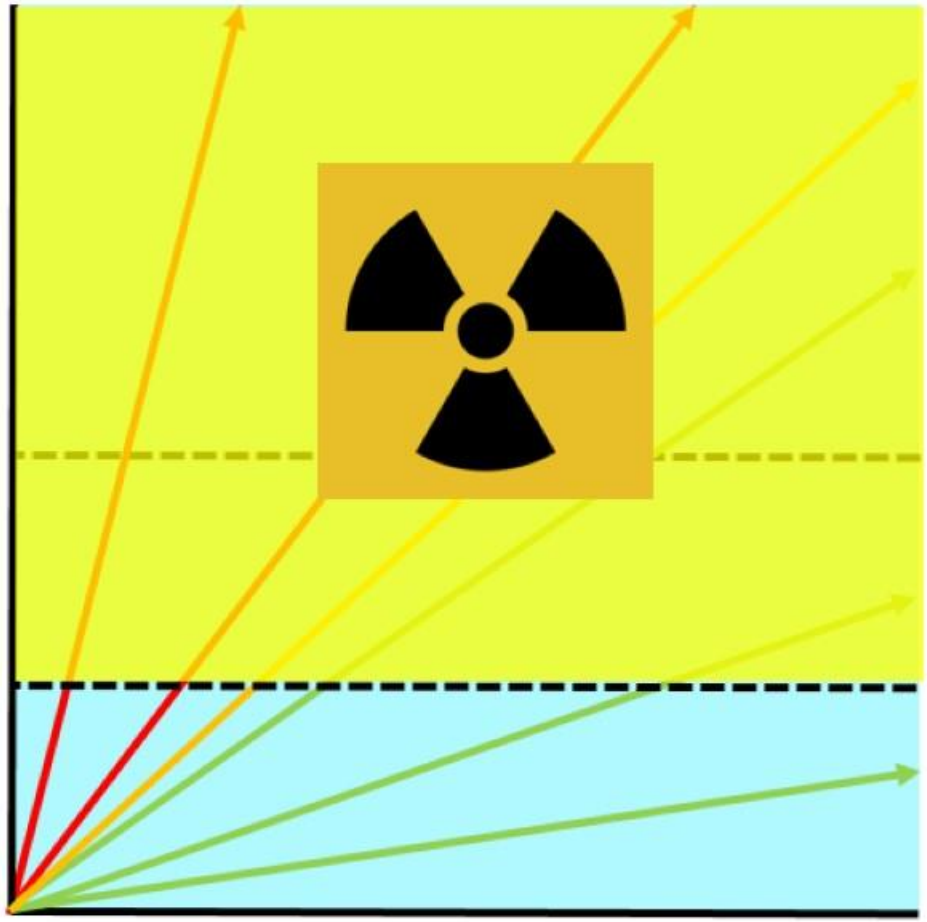
Metastasis,
visualized at low PSA,
no benefit local radiation

N M

Metastasis,
visualized only at higher PSA,
no benefit local radiation

N M

St Antonius
een santeon ziekenhuis



Local recurrence, CHANGING TO N/M
visualized at higher PSA,
benefits radiation

T ▶ N M

Local recurrence,
visualized at higher PSA,
benefits radiation

T

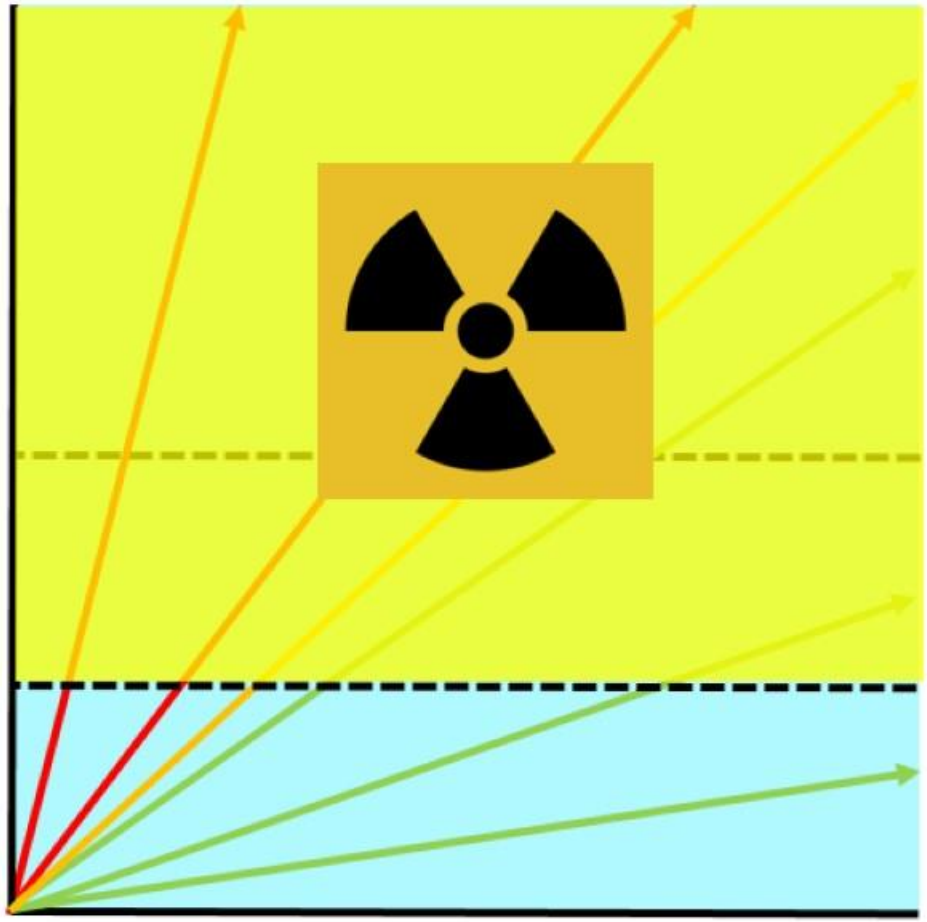
Local recurrence,
not visualized,
no benefit local radiation

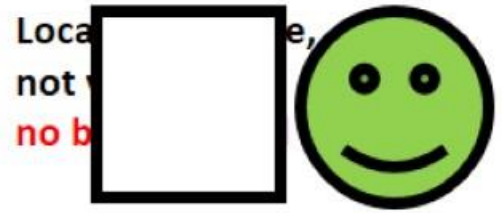
T

Local recurrence,
not visualized,
no benefit local radiation

T

ST ANTONIUS
een santeon ziekenhuis





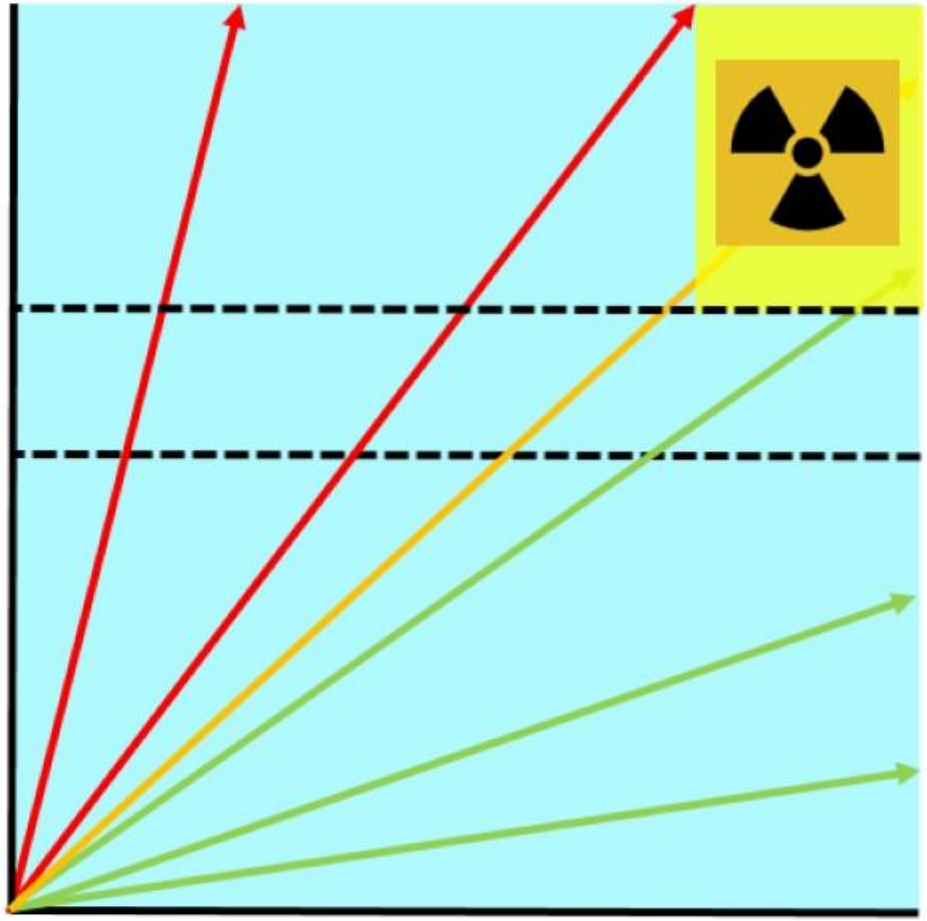
Metastasis,
visualized at low PSA,
no benefit local radiation

N M

Metastasis,
visualized only at higher PSA,
no benefit local radiation

N M

St Antonius
een santeon ziekenhuis



Local recurrence, CHANGING TO N/M
visualized at higher PSA,
benefits radiation

T ▶ N M

Local recurrence,
visualized at higher PSA,
benefits radiation

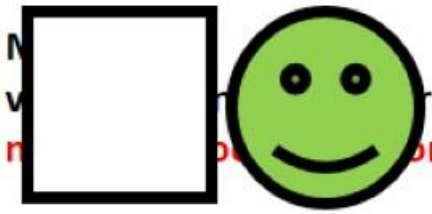
T

Local recurrence,
not visualized at higher PSA,
no benefit local radiation

T

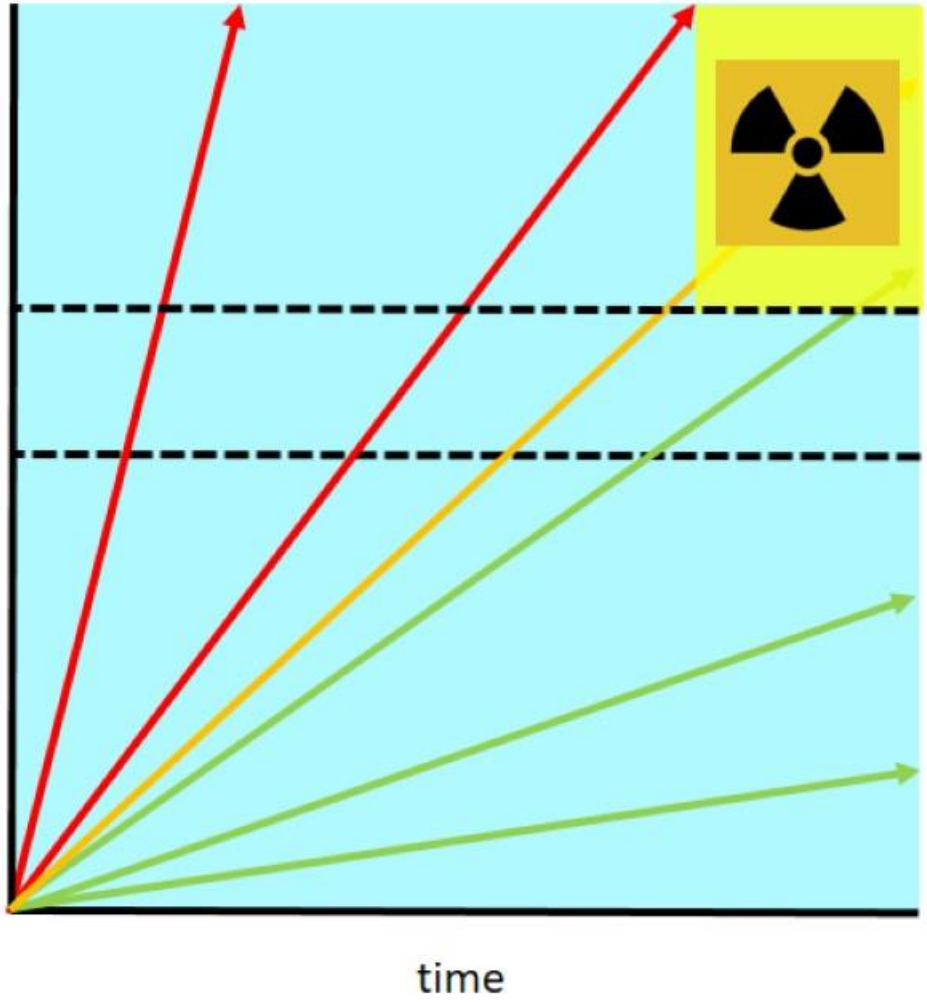
Local recurrence,
slowly progressing,
no benefit local radiation

T

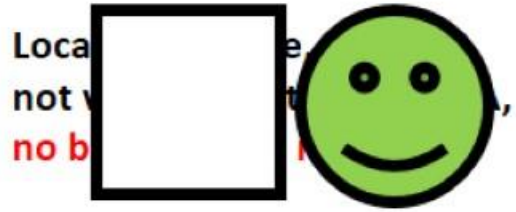


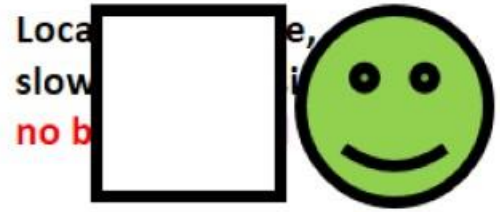
PSA,

ST ANTONIUS
een santeon ziekenhuis



NG TO N/M

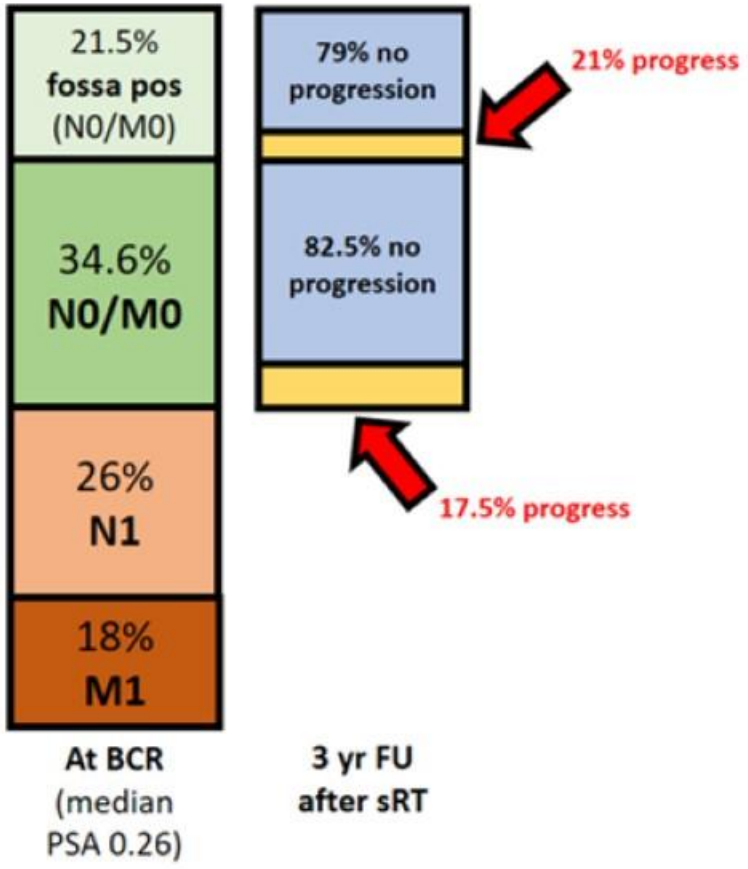




3-Year Freedom from Progression After ^{68}Ga-PSMA PET/CT–Triaged Management in Men with Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial

Louise Emmett[1,2], Reuben Tang[1,3], Rohan Nandurkar[2], George Hruby[4,5], Paul Roach[6,7], Jo Anne Watts[8,9], Thomas Cusick[3], Andrew Kneebone[4,7], Bao Ho[1], Lyn Chan[1], Pim J. van Leeuwen[10], Matthijs J. Scheltema[3,11], Andrew Nguyen[1], Charlotte Yin[6], Andrew Scott[12,13], Colin Tang[14], Michael McCarthy[15], Karen Fullard[1], Matthew Roberts[16,17], Roslyn Francis[9,15], and Phillip Stricker[2,7,18]

^{68}Ga-labeled prostate-specific membrane antigen (PSMA) PET/CT is increasingly used in men with biochemical recurrence (BCR) after radical prostatectomy (RP), but its longer-term prognostic or predictive potential in these men is unknown. The aim of this study was to evaluate the predictive value of PSMA PET for a 3-y freedom from progression (FFP) in men with BCR after RP undergoing salvage radiotherapy (sRT). **Methods:** This prospective multicenter study enrolled 260 men between 2015 and 2017. Eligible patients were referred for PSMA PET with a rising level of prostate-specific antigen (PSA) after RP. Management after PSMA PET was recorded but not mandated. PSMA PET protocols were standardized across sites and reported prospectively. Clinical, pathologic, and surgical information; sRT; timing and duration of androgen deprivation; 3-y PSA results; and clinical events were documented. FFP was defined as a PSA rise of no more than 0.2 ng/mL above nadir after sRT, with no additional treatment. **Results:** The median PSA was 0.26 ng/mL (interquartile range, 0.15–0.59 ng/mL), and follow-up was 38 mo (interquartile range, 31–43 mo). PSMA PET had negative results in 34.6% (90/260), showed disease confined to the prostatic fossa in 21.5% (56/260), showed disease in the pelvic nodes in 26.2% (68/260), and showed distant disease in 17.7% (46/260). Of the patients, 71.5% (186/260) received sRT: 38.2% (71/186) to the fossa only, 49.4% (92/186) to the fossa plus the pelvic nodes, and 12.4% (23/186) to the nodes alone or stereotactic body radiation therapy. PSMA PET was highly predictive of FFP at 3 y after sRT. Overall, FFP was achieved in 64.5% (120/186) of those who received sRT, 81% (81/100) with negative results or fossa-confined findings versus 45% (39/86) with extrafossa disease ($P < 0.0001$). On logistic regression, PSMA PET was more independently predictive of FFP than established clinical predictors, including PSA, T stage, surgical margin status, or Gleason score ($P < 0.002$). Thirty-two percent of men with a negative PSMA PET result did not receive treatment. Of these, 66% (19/29) progressed, with a mean rise in PSA of 1.59 ng/mL over the 3 y. **Conclusion:** PSMA PET results are highly predictive of FFP at 3 y in men undergoing sRT for BCR after RP. In particular, men with negative PSMA PET results or disease identified as still confined to the prostatic fossa demonstrate high FFP, despite receiving less extensive radiotherapy and lower rates of additional androgen deprivation therapy than those with extrafossa disease.



3-Year Freedom from Progression After ^{68}Ga-PSMA PET/CT–Triaged Management in Men with Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial

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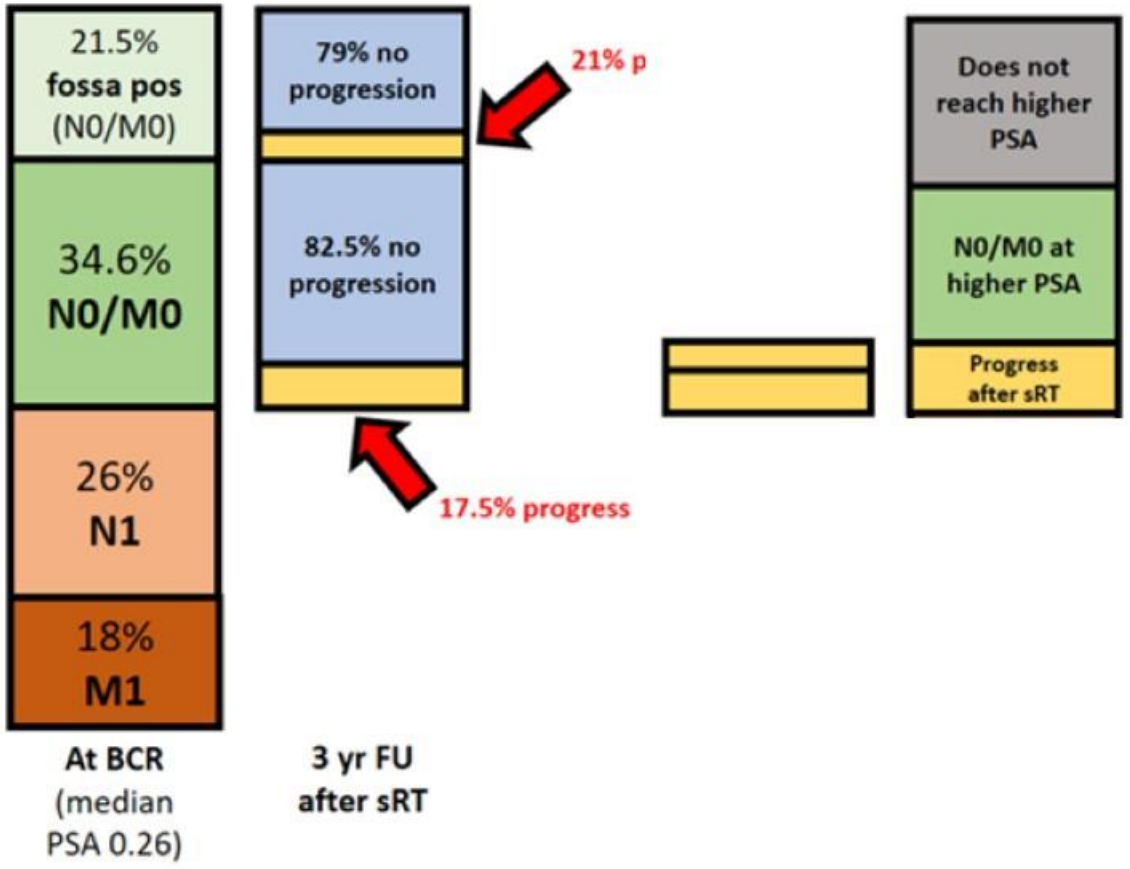
N=260

BCR after RALP

Median PSA 0.26

71.5% received sRT



2 – RT works better in PSMA selected cases

Background: Radiolabeled prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has shown superior diagnostic accuracy to conventional imaging for the detection of prostate cancer deposits . Consequently, clinical management changes have been reported in patients with biochemical recurrence (BCR) of disease after robot-assisted radical prostatectomy (RARP). We hypothesized that, due to the exclusion of patients with metastatic disease on PSMA-PET/CT, those who underwent local salvage radiation therapy (SRT) after restaging PSMA-PET/CT for BCR may have better oncological outcomes than patients who underwent "blind" SRT.

Objective: To compare the oncological outcome of a patient cohort that underwent PSMA-PET imaging prior to SRT with that of a patient cohort that did not have PSMA-PET imaging before SRT.

Design, setting, and participants: We included 610 patients who underwent SRT, of whom 298 underwent PSMA-PET/CT prior to SRT and 312 did not. No additional hormonal therapy was prescribed.

Outcome measurements and statistical analysis: To compare both cohorts, case-control matching was performed, using the prostate-specific antigen (PSA) value at the initiation of SRT, pathological grade group, pathological T stage, surgical margin status, and biochemical persistence after RARP as matching variables. The outcome variable was biochemical progression at 1 yr after SRT, defined as either a rise of PSA ≥0.2 ng/ml above the nadir after SRT or the start of additional treatment.

Results and limitations: After case-control matching, 216 patients were matched in both cohorts (108 patients per cohort). In the patient cohort without PSMA-PET/CT prior to SRT, of 108 patients, 23 (21%) had biochemical progression of disease at 1 yr after SRT, compared with nine (8%) who underwent restaging PSMA-PET/CT prior to SRT ($p = 0.007$).

Conclusions: PSMA-PET/CT is found to be associated with an improved oncological outcome in patients who undergo SRT for BCR after RARP.

Patient summary: Performing prostate-specific membrane antigen positron emission tomography/computed tomography imaging in patients with biochemical recurrence of disease after robot-assisted radical prostatectomy, before initiating salvage radiation therapy, resulted in improved short-term oncological outcomes.

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European Association of Urology

EUO Priority Article – Prostate Cancer

Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Is Associated with Improved Oncological Outcome in Men Treated with Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer

Dennie Meijer[a,b,], Wietse S.C. Eppinga[c], Roos M. Mohede[a], Ben G.L. Vanneste[d], Philip Meijnen[e], Otto W.M. Meijer[e], Laurien A. Daniels[e], Roderick C.N. van den Bergh[f], Anne P. Lont[g], Rosemarijn H. Ettema[a], Frederik H.K. Oudshoorn[h], Pim J. van Leeuwen[i], Henk G. van der Poel[i], Maarten L. Donswijk[j], Daniela E. Oprea-Lager[b], Eva E. Schaake[k], André N. Vis[a,i]*

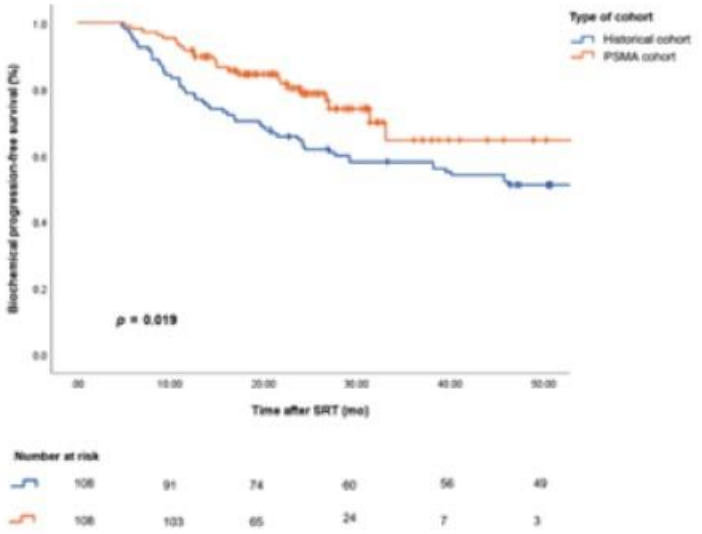

Fig. 1 – Kaplan-Meier curve of the case-control matched population (n = 216) assessing biochemical progression-free survival after salvage radiation therapy. PSMA = prostate-specific membrane antigen; SRT = salvage radiation therapy.

N= 610 sRT:

298 prior PSMA

312 NO prior PSMA

Case-matching:

PSA at sRT, GG, T, PSM, PSA persistence

216 matched cases

Outcome:

Biochemical progression 1 yr after sRT

21%

Vs

8%

(p=0.007)

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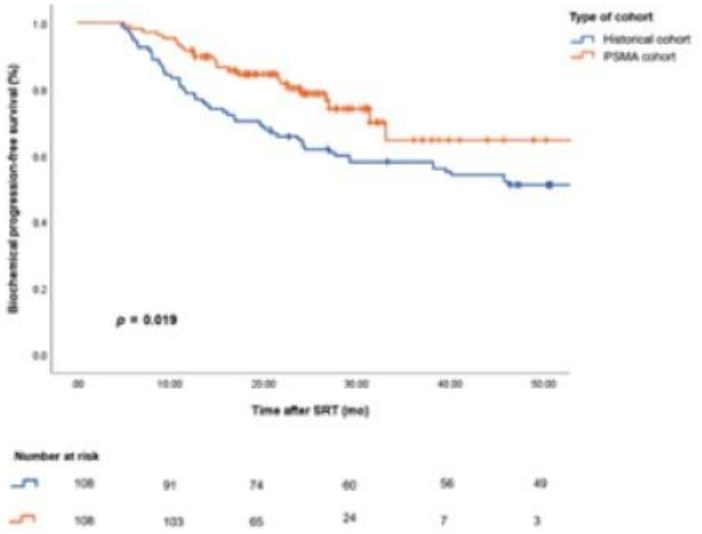

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Prostate Specific Membrane Antigen Positron Emission Tomography/Computerized Tomography in the Evaluation of Initial Response in Candidates Who Underwent Salvage Radiation Therapy after Radical Prostatectomy for Prostate Cancer

Dennie Meijer,*,† Henk B. Luiting,* Pim J. van Leeuwen, Sebastiaan Remmers, Bernard H. E. Jansen, Yves J. L. Bodar, Thelma Witteveen, Eva E. Schaake, Henk G. van der Poel, Maurits Wondergem, Martijn B. Busstra, Jakko A. Nieuwenhuijzen, Philip Meijnen, Tessa Brabander, R. Jeroen A. van Moorselaar, N. Harry Hendrikse, Daniela E. Oprea-Lager, Monique J. Roobol and André N. Vis

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Purpose: We assessed predictors of short-term oncologic outcomes of patients who underwent salvage radiation therapy for biochemical recurrence after robot-assisted laparoscopic radical prostatectomy without evidence of metastases on prostate specific membrane antigen positron emission tomography/computerized tomography.

Materials and Methods: We retrospectively analyzed 194 patients with biochemical recurrence after robot-assisted laparoscopic radical prostatectomy who underwent prostate specific membrane antigen positron emission tomography/computerized tomography prior to salvage radiation therapy. Patients with lymph node or distant metastases on restaging imaging or at the time of extended pelvic lymph node dissection during robot-assisted laparoscopic radical prostatectomy were excluded, as were patients who received androgen deprivation therapy during or prior to salvage radiation therapy. A multivariable logistic regression analysis was performed to assess predictors of treatment response, defined as prostate specific antigen value ≤0.1 ng/ml after salvage radiation therapy.

Results: Overall treatment response after salvage radiation therapy was 75% (146/194 patients). On multivariable analysis, prostate specific antigen value at initiation of salvage radiation therapy (OR 0.42, 95% CI 0.27–0.62, p <0.001), pathological T stage (pT3a vs pT2 OR 0.28, 95% CI 0.11–0.69, p=0.006; pT3b vs pT2 OR 0.26, 95% CI 0.09–0.71, p=0.009) and local recurrent disease on imaging (OR 5.53, 95% CI 1.96–18.52, p=0.003) were predictors of treatment response.

Table 4. *ORs using multivariable analysis for complete treatment response after SRT for predefined clinical variables*

	OR (95% CI)	p Value
PSMA PET/CT findings:		0.003
Neg (no evidence of disease)	Reference	
Local recurrence of disease	5.53 (1.96–18.52)	
Median log_2 PSA value at initiation of SRT (IQR)	0.42 (0.27–0.62)	<0.001
ISUP RARP grade group:		
1–2 (Gleason score 3+3=6, 3+4=7)	Reference	
3 (Gleason score 4+3=7)	0.49 (0.20–1.18)	0.11
≥4 (Gleason score ≥8)	0.45 (0.17–1.24)	0.12
Pathological T stage:		
pT2 (a,b,c)	Reference	
pT3a	0.28 (0.11–0.69)	0.006
pT3b	0.26 (0.09–0.71)	0.009
Surgical margin status:		0.08
Neg	Reference	
Pos	2.02 (0.93–4.55)	

Prostate Specific Membrane Antigen Positron Emission Tomography/Computerized Tomography in the Evaluation of Initial Response in Candidates Who Underwent Salvage Radiation Therapy after Radical Prostatectomy for Prostate Cancer

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Predictors for PSA ≤0.1 after sRT

N=194

All PSMA before sRT

miN0M0, pN0, no ADT

75% response

Predictors:

PSA at sRT, pT, local disease on PSMA

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pT3a	0.28 (0.11–0.69)	0.006
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Surgical margin status:		0.08
Neg	Reference	
Pos	2.02 (0.93–4.55)	

3 – Late salvage RT is safe

PSA (ng/mL)	^{68}Ga-PMSA PET positivity
< 0.2	33% (CI: 16–51)
02–0.49	45% (CI: 39–52)
0.5–0.99	59% (CI: 50–68)
1.0–1.99	75% (CI: 66–84)
2.0+	95% (CI: 92–97)

PSA = prostate-specific antigen; ^{68}Ga-PSMA PET = Gallium-68 prostate-specific membrane antigen positron emission tomography.

Abstract

Background: Recently, a new prognostic model for patients harboring biochemical recurrence(BCR) after radical prostatectomy(RP) has been proposed by the European Association of Urology(EAU).

Objective: To assess, if this risk stratification may help choosing patients for salvage radiotherapy(SRT).

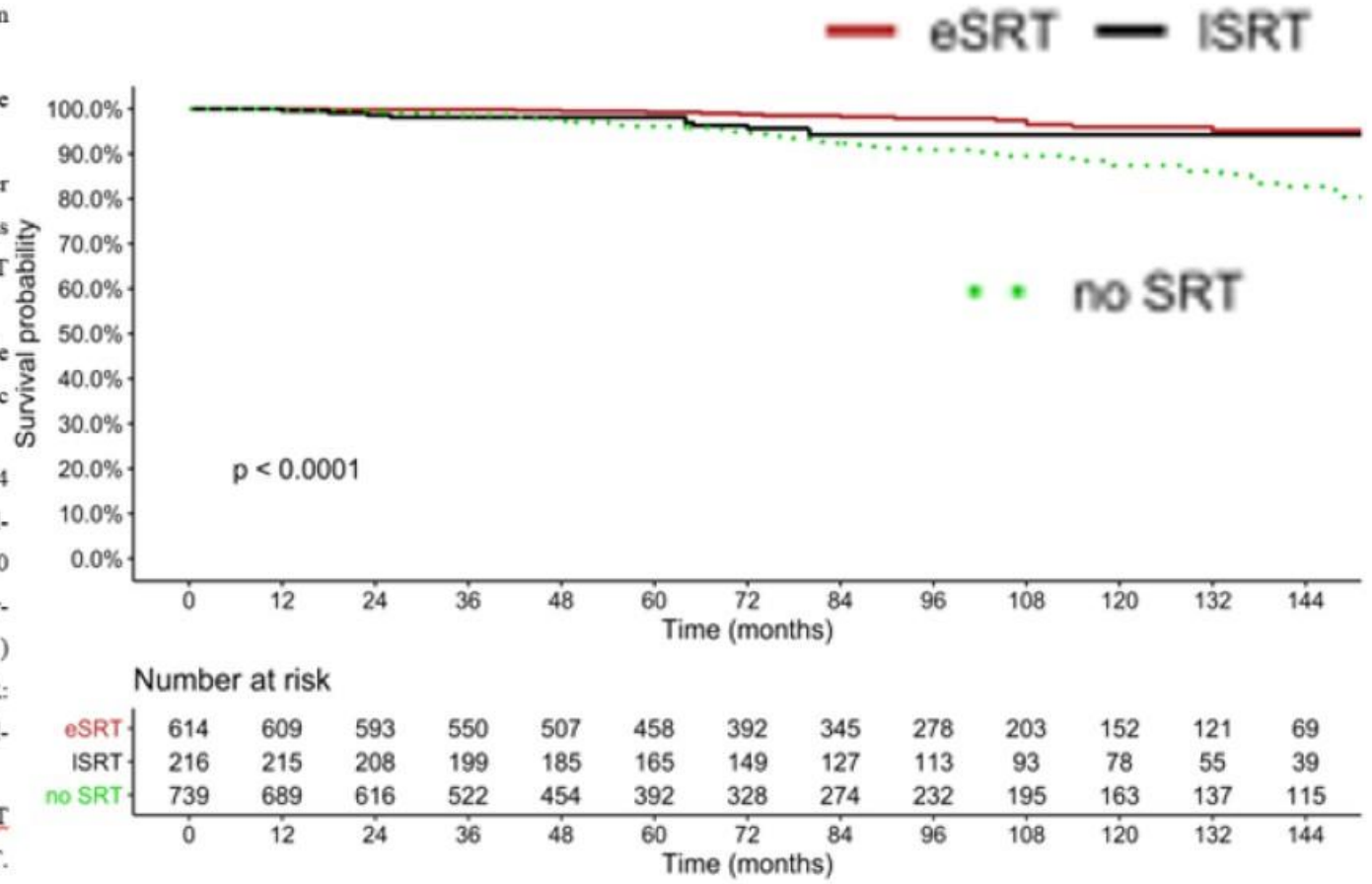
Design, setting and participants: Analyses of 2379 patients who developed BCR after RP(1989-2020), within ten European institutional high-volume centers. Early SRT(eSRT) was defined as SRT delivered at PSA-values <0.5ng/ml, late SRT(lSRT) was defined as SRT delivered at PSA-values ≥0.5ng/ml.

Outcome measurements and statistical analysis: Kaplan-Meier curves and multivariable Cox models tested the effect of eSRT vs. lSRT vs. noSRT on death and cancer-specific mortality(CSM) within each risk group.

Results and limitations: Overall, 805 patients were classified as EAU low-(l-BCR) and 1574 patients EAU high-risk BCR(h-BCR), respectively. Median follow-up was 84.4 months. For l-BCR, 12-yr overall and cancer-specific survival were 92.0 vs. 92.6 vs. 89.0% (p=0.1) and 100.0 vs. 100.0 vs. 97.6%(p=0.1) for eSRT vs. lSRT vs. noSRT. For h-BCR, 12-yr overall and cancer-specific survival were 84.7 vs. 81.8 vs. 76.0%(p<0.01) and 95.1 vs. 94.2 vs. 82.7%(p<0.001) for eSRT vs. lSRT vs. noSRT. In multivariable analyses, eSRT decreased the risk for death(HR: 0.67, p=0.04) and CSM(HR: 0.27, p<0.001) only within the h-BCR group. Conversely, for l-BCR, SRT was no predictor of death or CSM.

Conclusions: An improved survival within the h-BCR group for patients treated with eSRT compared to observation was recorded. In contrast, men with l-BCR had no benefit from SRT. Our results suggest recommending eSRT in men with h-BCR. Conversely, surveillance only might be suitable for men with l-BCR.

Patient summary: In this manuscript, we assessed the impact of eSRT on cancer-specific outcomes stratified according to the new EAU BCR risk classification. While men with h-BCR should be offered eSRT, surveillance only might be a suitable option for men classified as l-BCR.



Cancer-specific survival – EAU high risk BCR

Preisser et al, submitted. vdBroeck et al, Eur Urol 2019.

EAU risk stratification BCR after RALP

Low risk (GG <4 and slow PSA-DT)

vs

High risk (GS ≥4 or fast PSA-DT)

N=2379 (European centres)

No sRT

vs

Early sRT (PSA <0.5)

vs

Late sRT (PSA ≥0.5)

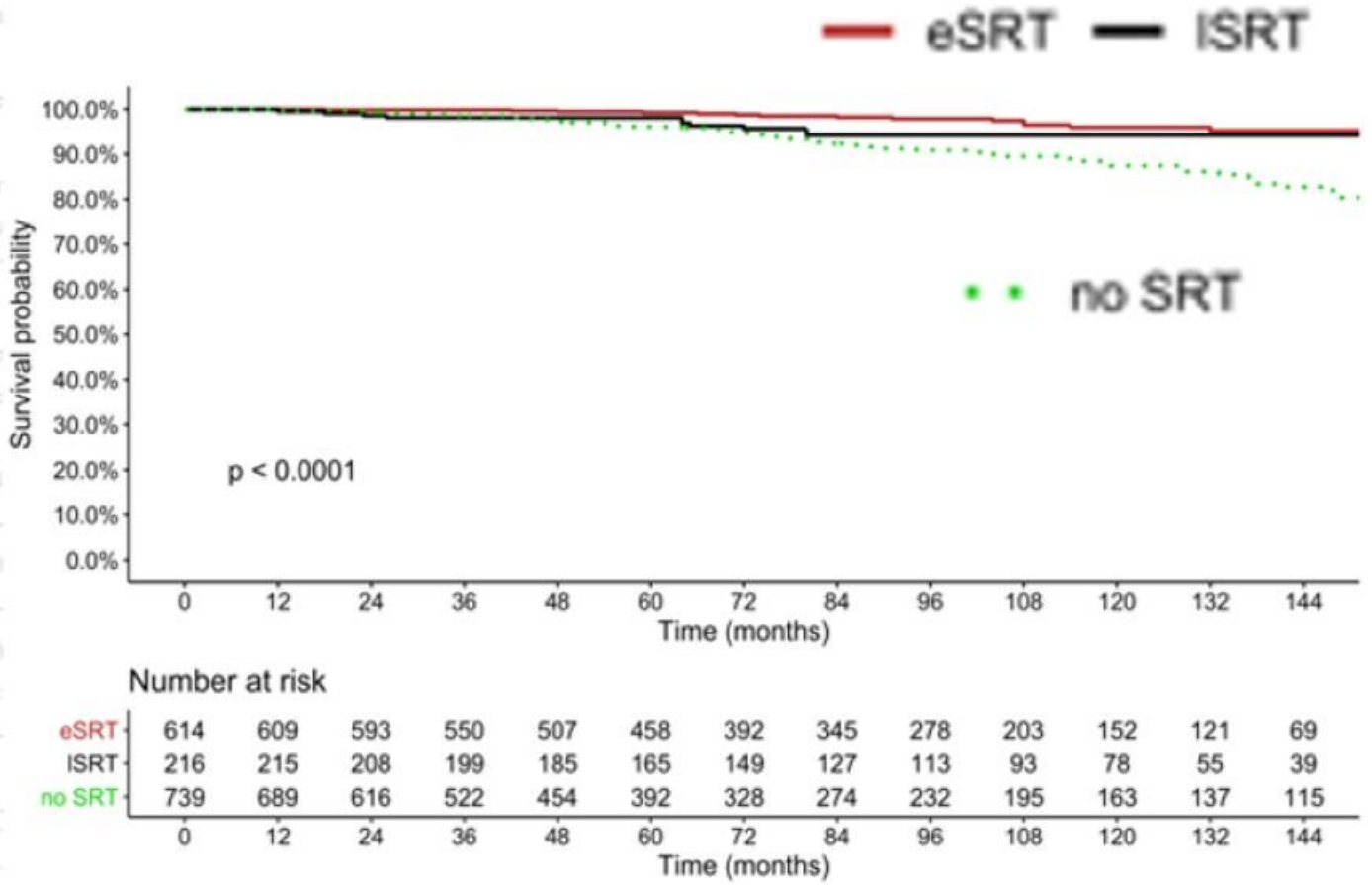
Low risk:

No benefit sRT

High risk:

Early and late comparable

Better than no sRT



Cancer-specific survival – EAU high risk BCR

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4 – But isn’t earlier always better?

VOLUME 34 · NUMBER 32 · NOVEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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Improved Metastasis-Free and Survival Outcomes With Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer

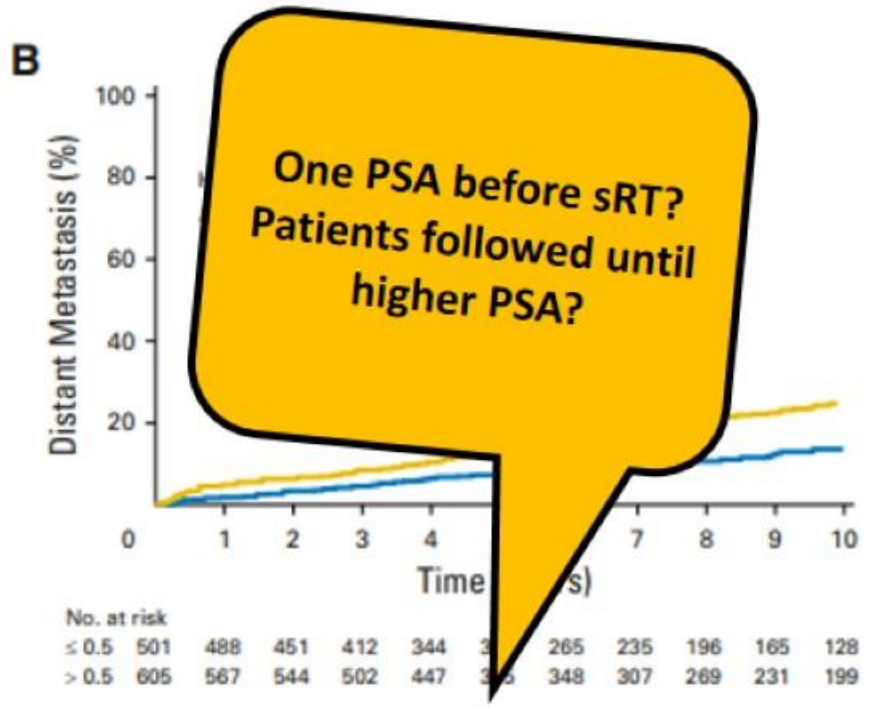
Bradley J. Stish, Thomas M. Pisansky, William S. Harmsen, Brian J. Davis, Katherine S. Tzou, Richard Choo, and Steven J. Buskirk

Purpose
To describe outcomes of salvage radiotherapy (SRT) for men with detectable prostate-specific antigen (PSA) after radical prostatectomy for prostate cancer and identify associations with outcomes.

Patients and Methods
A total of 1,106 patients received SRT between January 1987 and July 2013, with median follow-up 8.9 years. Outcomes were estimated using Kaplan-Meier for overall survival (OS) and cumulative incidence for biochemical recurrence (BcR), distant metastases (DM), and cause-specific mortality (CSM). Variable associations with outcomes used Cox or Fine-Gray methods, as appropriate. Multiple variable analyses used backward selection with $P < .05$ for retention.

Results
In multiple variable analyses, pathologic tumor stage, Gleason score, and pre-SRT PSA were associated with BcR, DM, CSM, and OS; androgen suppression and SRT doses > 68 Gy were associated with BcR; and age was associated with OS. Each pre-SRT PSA doubling increased significantly the relative risk of BcR (hazard ratio [HR], 1.30; $P < .001$), DM (HR, 1.32; $P < .001$), CSM (HR, 1.40; $P < .001$), and all-cause mortality (HR, 1.12; $P = .02$). Using a pre-SRT PSA cutoff ≤ 0.5 versus > 0.5 ng/mL, 5-year and 10-year cumulative incidences for BcR were 42% versus 56% and 60% versus 68% ($P < .001$), DM 7% versus 14% and 13% versus 25% ($P < .001$), CSM 1% versus 4% and 6% versus 13% ($P < .001$), and OS of 94% versus 92% and 83% versus 73% ($P > .05$).

Conclusion
SRT outcomes are in part affected by factors associated with prostatectomy findings but may be positively affected by using SRT at lower PSA levels, including reductions in BcR, DM, CSM, and all-cause mortality. These findings argue against prolonged monitoring of detectable postprostatectomy PSA levels that delay initiation of SRT.



VOLUME 34 · NUMBER 32 · NOVEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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ST ANTONIUS
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In multiple variable analyses, pathologic T stage, Gleason score, and pre-SRT PSA were associated with BcR, DM, CSM, and OS; androgen suppression and SRT doses > 68 Gy were associated with BcR; and age was associated with OS. Every 2-fold pre-SRT PSA doubling increased significantly the relative risk of BcR (hazard ratio [HR], 1.39; $P < .001$), DM (HR, 1.32; $P < .001$), CSM (HR, 1.40; $P < .001$), and all-cause mortality (HR, 1.12; $P = .02$). Using a pre-SRT PSA cutoff ≤ 0.5 versus > 0.5 ng/mL, 5-year and 10-year cumulative incidences for BcR were 42% versus 56% and 60% versus 68% (P [illegible]). CSM 1% versus 4% and 6% versus 13% ($P < .001$), and OS of 94% versus 92% and 83% versus 73% ($P > .05$).

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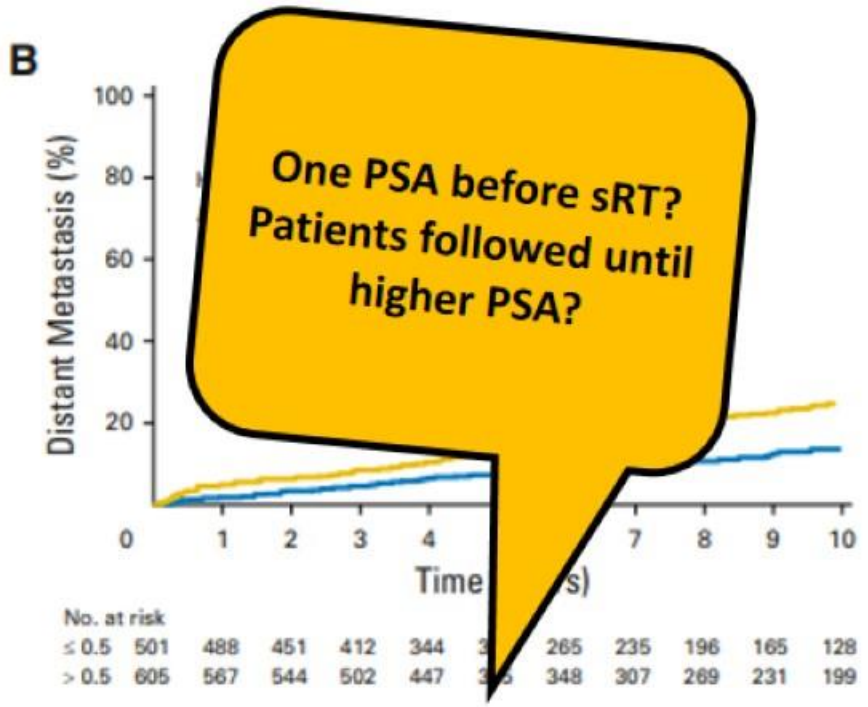
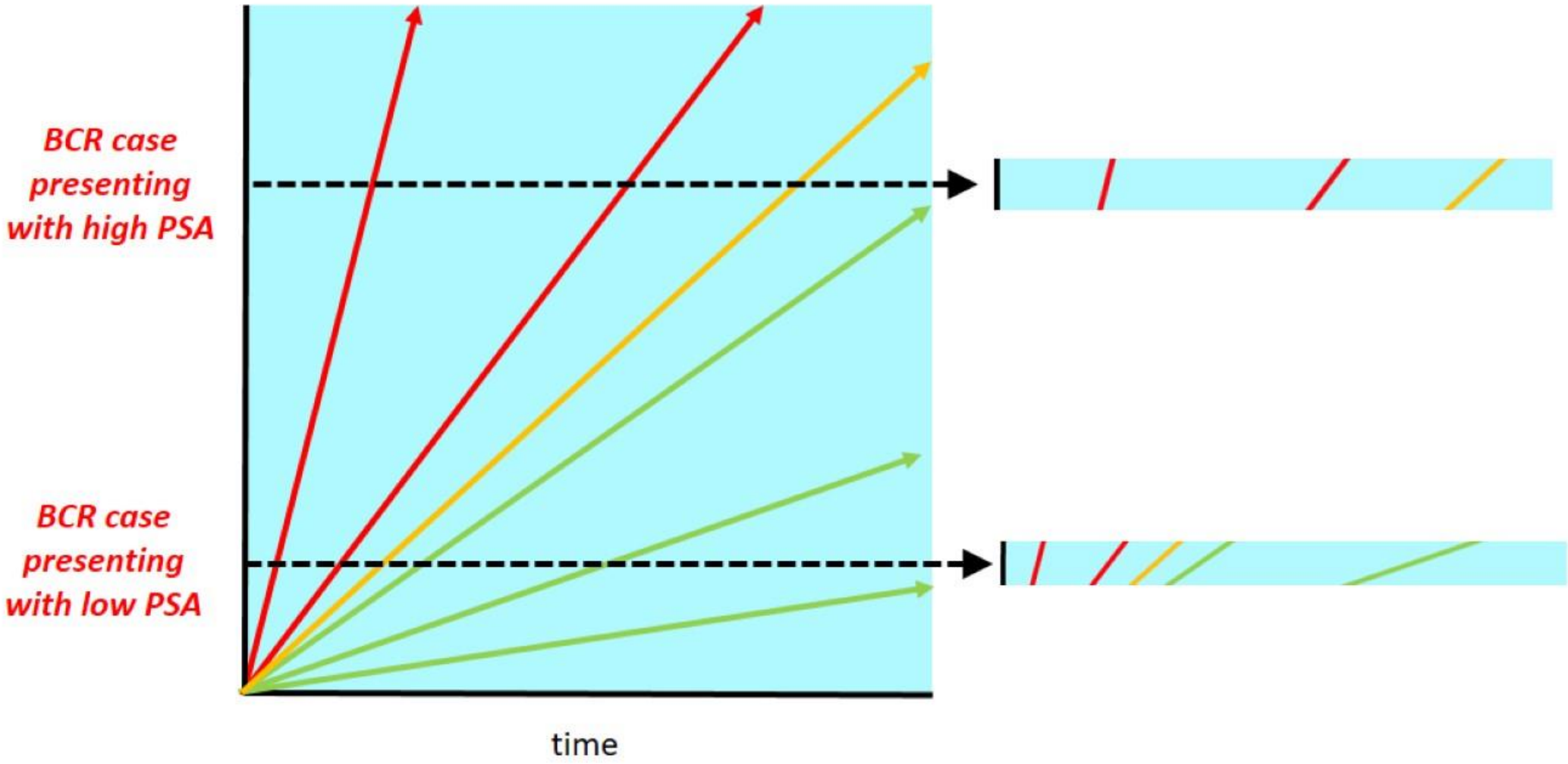
N=1106 sRT

Outcomes:
BCR, metastases, CSS, OS

PSA <0.5 better for all outcomes



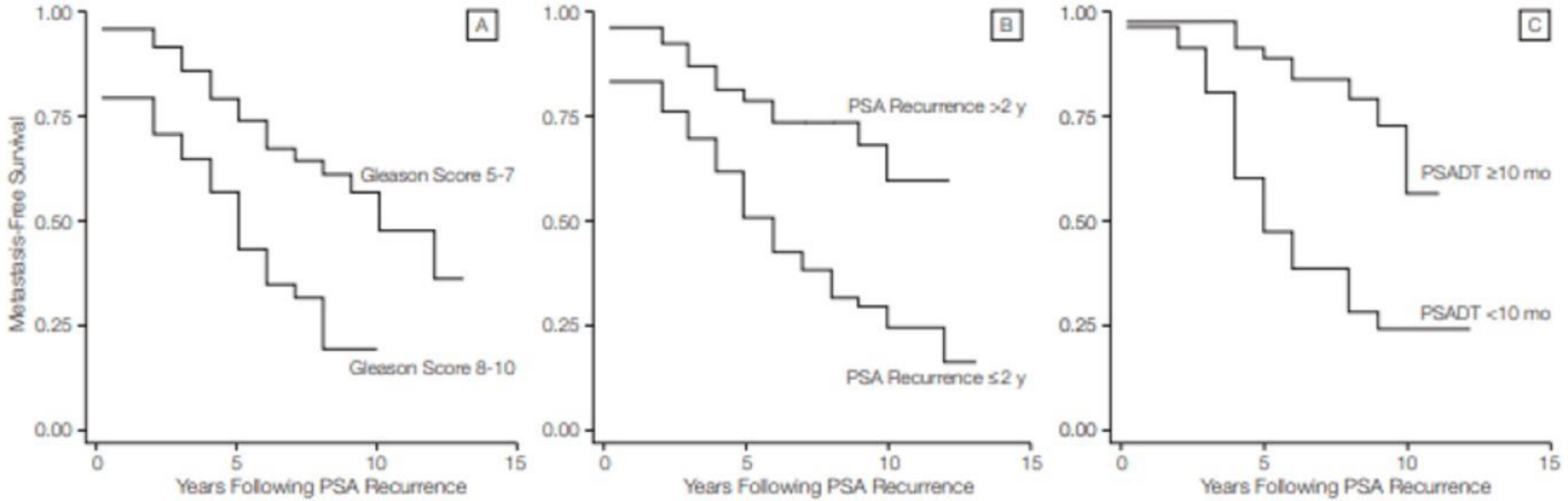
PSA at first BCR presentation



Natural History of Progression After PSA Elevation Following Radical Prostatectomy

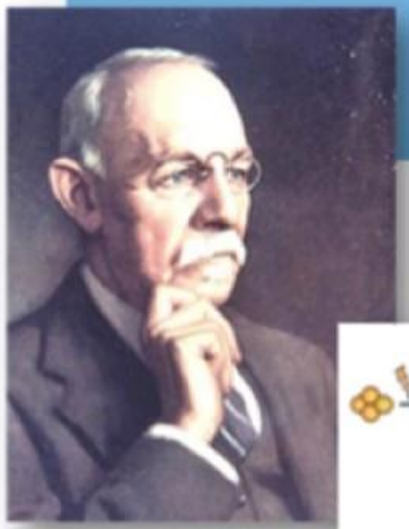
JAMA®
The Journal of the American Medical Association

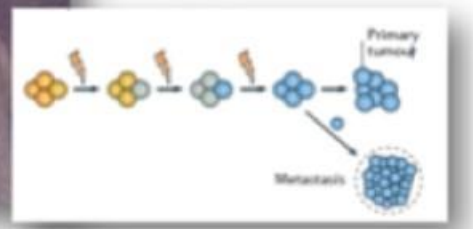
Pound et al 1999

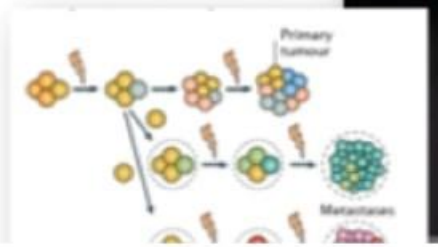


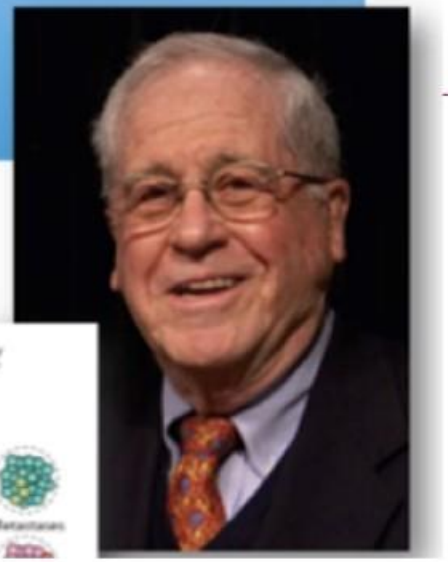
PSA-DT very important!

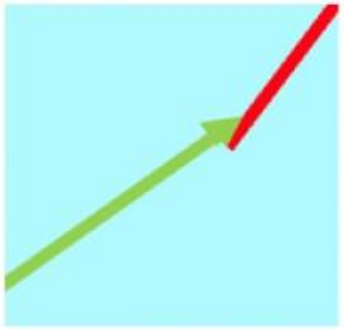
Contiguous vs Systemic
Halsted vs Fisher

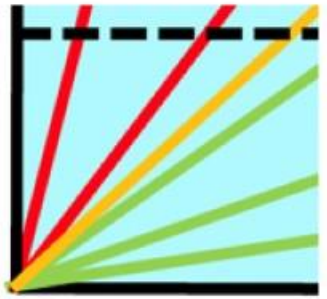












Conclusions

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- BCR = many scenarios
- Sweet spot salvage RT prostate fossa somewhere in between:
  - High risk cases in whom salvage RT does not alter disease course
  - Low risk cases not needing salvage RT
- PSMA-selected RT has more favorable outcomes
- Initial expectant management is:
  - Unlikely to miss the window of curability
  - Providing opportunity to exploit the diagnostic accuracy of imaging

EAU guidelines

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Local salvage treatment	Strength rating
Recommendations for biochemical recurrence (BCR) after radical prostatectomy	
Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong

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Let's use our eyes!

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Before PSMA

After PSMA