Follow-up after radical therapy:

Why we should not postpone salvage RT until a positive PSMA-PET/CT

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10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	
Receipt of honoraria or consultation fees	Bayer, Ferring, Janssen
Stock shareholder	
Other support (please specify):	

The main management question for Joe:

Should Joe have salvage radiotherapy now or wait?

Now - level 1 evidence

Wait – absence of evidence demonstrating impact on improved patient outcomes

- Balance the risk of overtreatment / 'target' doubt versus undertreatment and possibly 'missing the boat'

- Joe's disease characteristics:
  - pT3b
  - PSA 0.35ng/ml
  - PSA doubling time 3.9 months

What data do we have to treat Joe now….

- RADICALS (PSA 0.1ng/ml / 3 consecutive rises)
- RAVES (PSA 0.2ng/ml) RT alone
- GETUG-AFU17 (PSA 0.2ng/ml and rising) RT + ADT

} ARTISTIC

- RTOG0534 SPPORT – rising PSA of between 0.1 and 2.0ng/ml

What data do we have to treat Joe now....

Trial characteristics: Summary

	RADICALS-RT	GETUG-AFU 17	RAVES
Accrual period	11/2007 – 12/2016	04/2008 – 06/2016	03/2009 – 12/2015
Key eligibility criteria	Positive margins pT3a / pT3b / **pT4** **Gleason 7-10**	Positive margins pT3a / pT3b	Positive margins **pT2** / pT3a / pT3b
RT schedule	66/33# OR **52.2/20#**	66/33#	64/32#
ART timing	≤ 6m of RP	≤ 6m of RP	≤ 6m of RP
Trigger for eSRT	**PSA > 0.1 ng/ml** and rising *OR* 3 consecutive rising PSA levels	PSA ≥ 0.20 ng/ml and rising	PSA ≥ 0.20 ng/ml
eSRT timing	**≤ 2m of trigger PSA**	**As soon as possible after PSA relapse and before PSA=1ng/ml**	**≤ 4m of trigger PSA**
Primary outcome	**FFDM**	**EFS**	**FfBF**
Trial design	Superiority	Superiority	**Non-inferiority**

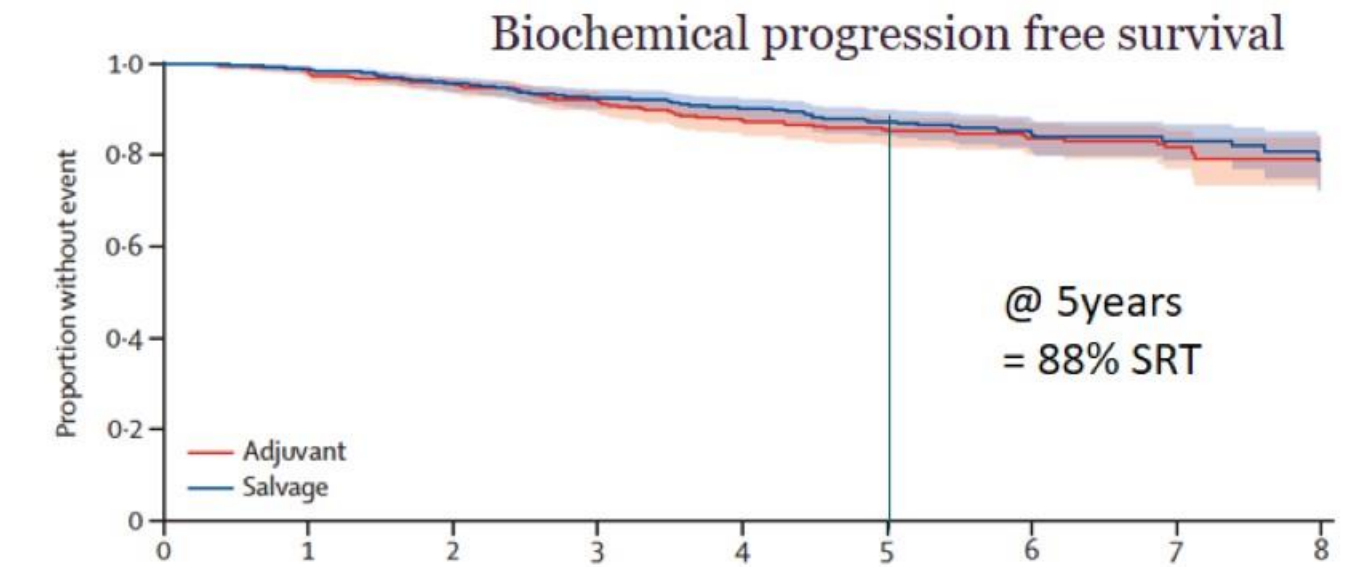
What data do we have to treat Joe now....

Patient characteristics

	RAVES	GETUG-AFU 17	RADICALS
Patients randomised	333	424	1396
Median follow up	73 months	47 months	60 months
Median Age (range)	64 (44-76)	64 (37-77)	65 (39-79)
Pre-operative PSA (median)	7.4	Not collected	7.9
pT 2 pT stage 3a/b pT4	76 (23%) 257 (77%) 0	0 411 (97%) 8 (2%)	339 (24%) 1047 (75%) 9 (1%)
Gleason score ≤6 7 ≥8	16 (5%) 266 (80%) 51 (15%)	43 (10%) 337 (79%) 40 (9%)	96 (7%) 1065 (76%) 235 (17%)
Positive margins	224 (67%)	418 (99%)	882 (63%)
Seminal vesicle involvement	43 (19%)	90 (21%)	259 (19%)
Extracapsular extension	257 (77%)	422 (100%)	954 (68%)

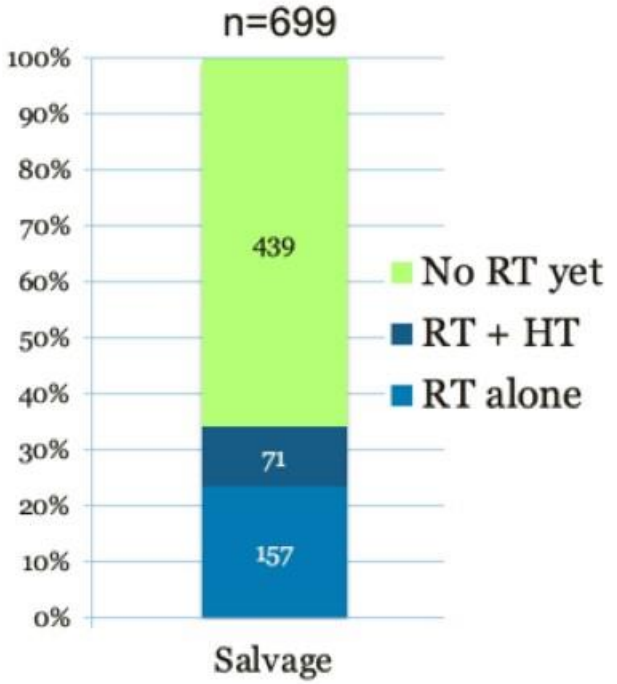
BARCELONA 2019 ESMO congress

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial



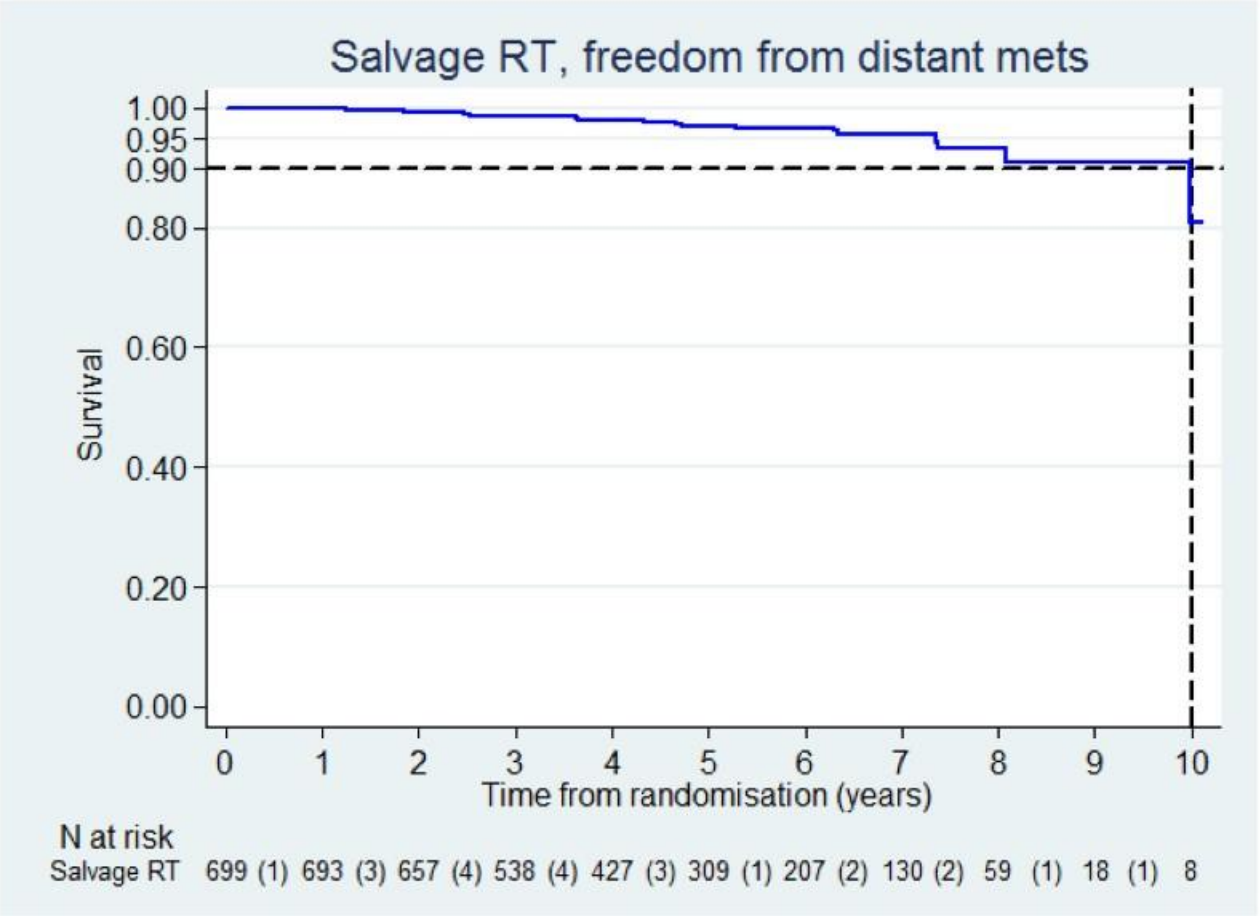
Adjuvant									
At risk	697	650	596	470	361	239	154	82	36
Censored	0	35	73	176	266	380	462	531	575
Event	0	12	28	51	70	78	81	84	86
Salvage									
At risk	699	665	601	477	378	263	165	95	42
Censored	0	26	69	175	263	368	459	527	577
Event	0	8	29	47	58	68	75	77	80

Median PSA at SRT = 0.2ng/ml (IQR 0.1-0.3)



Lancet 2020; 396: 1413–21

RADICALS – Freedom From Distant Metastases: Salvage RT Arm only



22 FFDM events

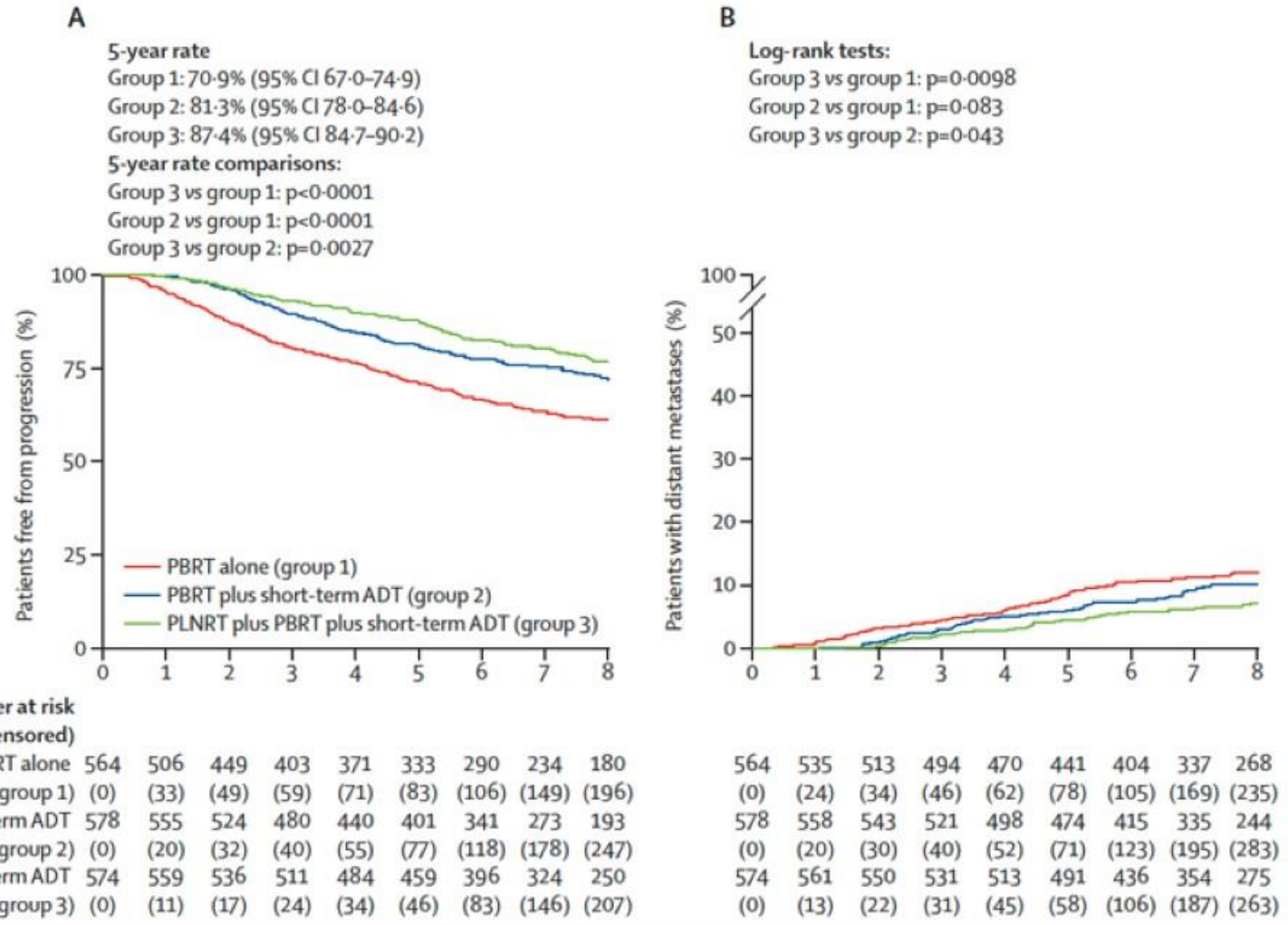
91% (95% CI 83–95)
FFDM at 9 years

'An observation policy with salvage radiotherapy for PSA biochemical progression should be the current standard after radical prostatectomy'

Lancet 2020; 396: 1413–21

The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial

What about the pelvic lymph nodes??



Number at risk (number censored)

PBRT alone (group 1)	564 (0)	506 (33)	449 (49)	403 (59)	371 (71)	333 (83)	290 (106)	234 (149)	180 (196)
PBRT plus short-term ADT (group 2)	578 (0)	555 (20)	524 (32)	480 (40)	440 (55)	401 (77)	341 (118)	273 (178)	193 (247)
PLNRT plus PBRT plus short-term ADT (group 3)	574 (0)	559 (11)	536 (17)	511 (24)	484 (34)	459 (46)	396 (83)	324 (146)	250 (207)

	564 (0)	535 (24)	513 (34)	494 (46)	470 (62)	441 (78)	404 (105)	337 (169)	268 (235)
	578 (0)	558 (20)	543 (30)	521 (40)	498 (52)	474 (71)	415 (123)	335 (195)	244 (283)
	574 (0)	561 (13)	550 (22)	531 (31)	513 (45)	491 (58)	436 (106)	354 (187)	275 (263)

Median pre-treatment PSA level = 0.35ng/ml

Lancet 2022

What about the side effects?

	PBRT alone	PBRT + 6/12 ADT	PB + pelvic RT + 6/12 ADT	
Acute adverse events§				
All				
Grade ≥2	98 (18%)	201 (36%)	246 (44%)	<0·0001
Grade ≥3	18 (3%)	41 (7%)	63 (11%)	<0·0001
Blood or bone marrow				
Grade ≥2	12 (2%)	10 (2%)	29 (5%)	0·0016
Grade ≥3	3 (1%)	1 (<1%)	15 (3%)	0·0012
Gastrointestinal				
Grade ≥2	11 (2%)	22 (4%)	38 (7%)	0·00041
Grade ≥3	1 (<1%)	5 (1%)	4 (1%)	0·286
Renal or genitourinary				
Grade ≥2	49 (9%)	68 (12%)	67 (12%)	0·177
Grade ≥3	5 (1%)	5 (1%)	8 (1%)	0·622
Late adverse events‖				
All				
Grade ≥2	308 (57%)	322 (58%)	350 (62%)	0·116
Grade ≥3	65 (12%)	87 (16%)	96 (17%)	0·047
Blood or bone marrow				
Grade ≥2	20 (4%)	10 (2%)	25 (4%)	0·038
Grade ≥3	3 (1%)	2 (<1%)	7 (1%)	0·181
Gastrointestinal				
Grade ≥2	56 (10%)	57 (10%)	51 (9%)	0·753
Grade ≥3	4 (1%)	5 (1%)	8 (1%)	0·488
Renal or genitourinary				
Grade ≥2	202 (37%)	194 (35%)	223 (40%)	0·226
Grade ≥3	29 (5%)	37 (7%)	45 (8%)	0·201

lymphopenia

diarrhoea

Lancet 2022

EAU BCR Risk Classification as decision tool for salvage RT (2019)

- EAU low-risk BCR: PSA-DT > 1year and pGS<8 for RP
- EAU high-risk BCR: PSA-DT ≤1 year or pGS 8-10 for RP

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

5 year metastatic progression free and PCSM-free survival rates were significantly higher among patients with low BCR risk

Salvage RT, especially when delivered at PSA <0.5ng/ml was highly protective

European Urology 2019

Imaging in patients with BCR after RP

- Imaging is of value if it leads to a treatment change which results in an **improved outcome**
- PET/CT has proven its accuracy in restaging and several studies have proven that implementation of PET/CT resulted in a significant management change rate in the post-op setting

HOWEVER

- Does improved staging and resultant change in management improve clinical outcomes??

Imaging in patients with BCR after RP

EAU guidelines:

- perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.

What does this negative PMSA PET-CT mean for Joe?

Joe is EAU high-risk

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

Radiotherapy and Oncology xxx (2018) xxx–xxx

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Radiotherapy for recurrent prostate cancer: 2018 Recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group

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increased sensitivity of PSMA-PET after administration of ADT [44,45]. As with the introduction of any new imaging modality, there is a learning curve for nuclear medicine physicians and treating clinicians in the interpretation of results and we recommend that PET scans be reviewed in a multidisciplinary team meeting and management plans discussed. It is suggested that confirmation of a corresponding anatomic lesion on CT or MRI, histological verification, or evidence of progression on serial imaging should be obtained where possible, if PET findings are used to alter treatment recommendations.

In patients in whom SRT would otherwise be recommended, SRT should not be withheld due to a negative PET scan, as microscopic locoregional disease may be below the sensitivity of detection. With evidence demonstrating improved efficacy of early SRT [1,46–48], delaying radiotherapy until gross disease is seen may compromise treatment outcomes. One study of PSMA-PET for biochemical recurrence post-prostatectomy found that a negative PSMA-PET was independently predictive of treatment response to SRT, and that these patients had a more favourable treatment response to SRT than those with a positive PSMA-PET [49].

In men with a negative PSMA who received SRT – 85% demonstrated a treatment response.

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In men with a negative PSMA who received SRT – 85% demonstrated a treatment response.

How good is PSMA PET- CT as an imaging tool in the recurrent setting?

- Most studies are retrospective

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)

Sensitivity, Specificity, and Predictors of Positive ^{68}Ga–Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis

Marlon Perera[a], Nathan Papa[a], Daniel Christidis[a], David Wetherell[a], Michael S. Hofman[b], Declan G. Murphy[c,e], Damien Bolton[a,d], Nathan Lawrentschuk[a,c,d,]*

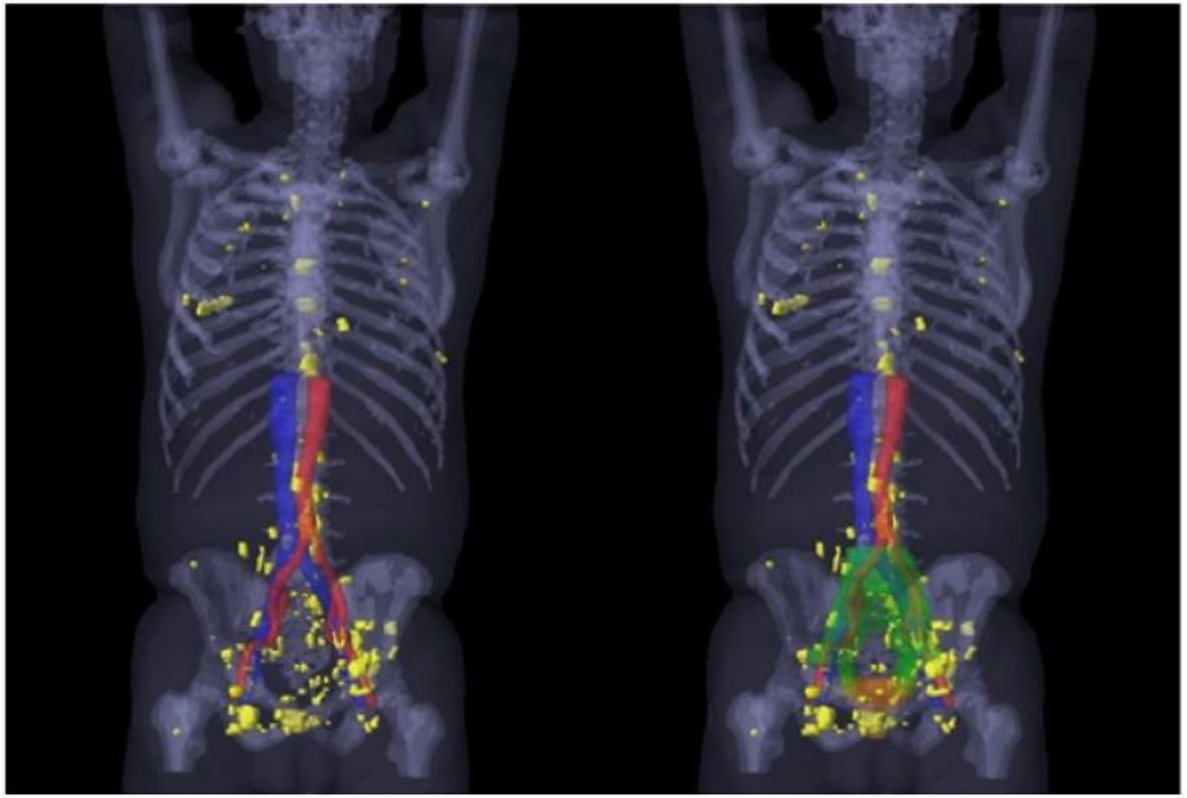
16 articles – 1309 patients

Pre-PET PSA predicts the risk of positive PET scan

Eur Urol 2016

^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning

Jeremie Calais[1], Johannes Czernin[1], Minsong Cao[2], Amar U. Kishan[2], John V. Hegde[2], Narek Shaverdian[2], Kiri Sandler[2], Fang-I Chu[2], Chris R. King[2], Michael L. Steinberg[2], Isabel Rauscher[3], Nina-Sophie Schmidt-Hegemann[4], Thorsten Poeppel[5], Philipp Hetkamp[5], Francesco Ceci[1], Ken Herrmann[1,5], Wolfgang P. Fendler[1,6], Matthias Eiber[1,3], and Nicholas G. Nickols[2,7]



Median PSA – 0.48ng/ml (range 0.03-1ng/ml)

^{68}Ga-PSMA-11 PET/CT Patterns of Relapse

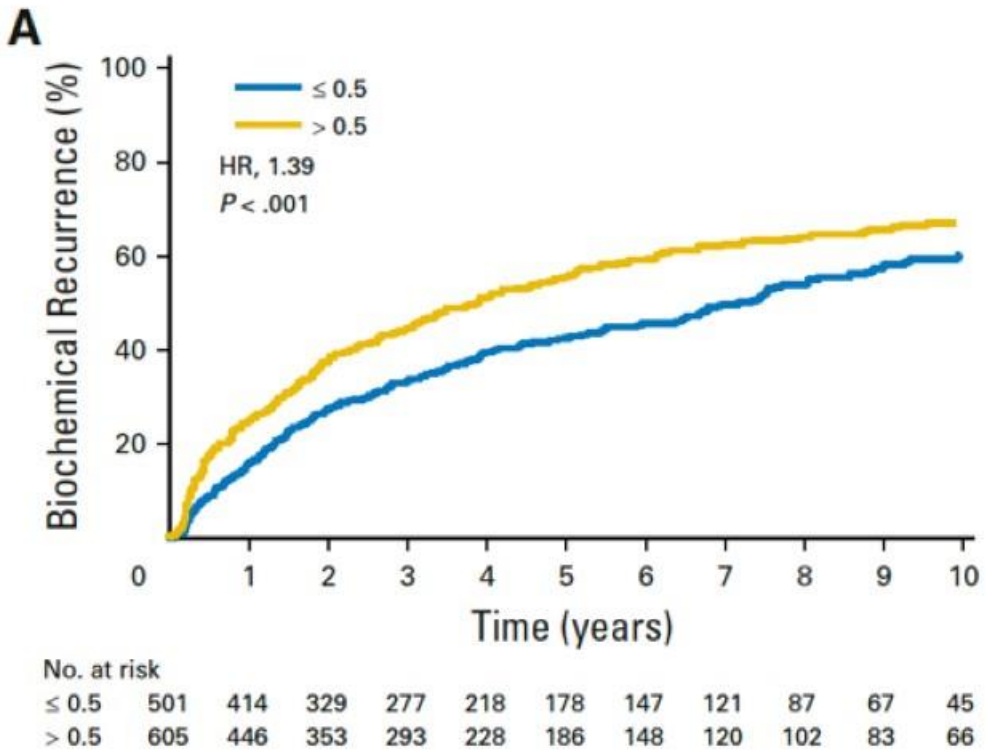
Pattern	Number of patients
PSMA-11 PET/CT+	132 (49%)
Prostate bed (T+)	47 (17.5%)
Pelvic LN (N1)	83 (30.5%)
Extrapelvic LN (M1a)	9 (3.5%)
Bone (M1b)	23 (8.5%)
Visceral (M1c)	3 (1%)

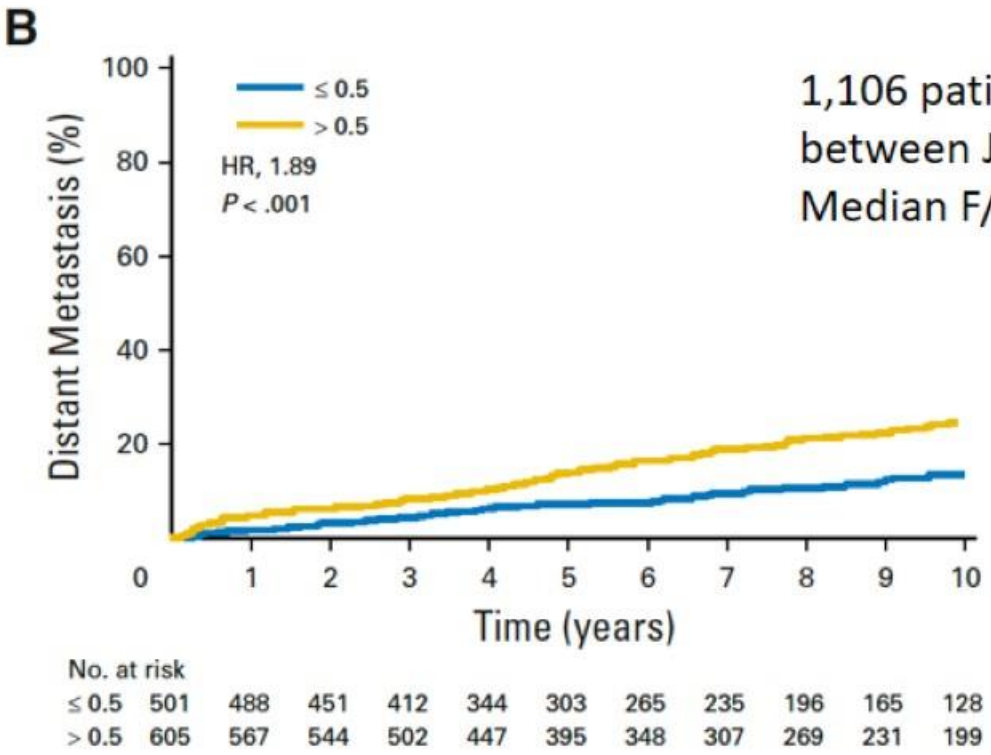
J Nucl Med. 2018;59(2):230-237

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

JCO, 2016





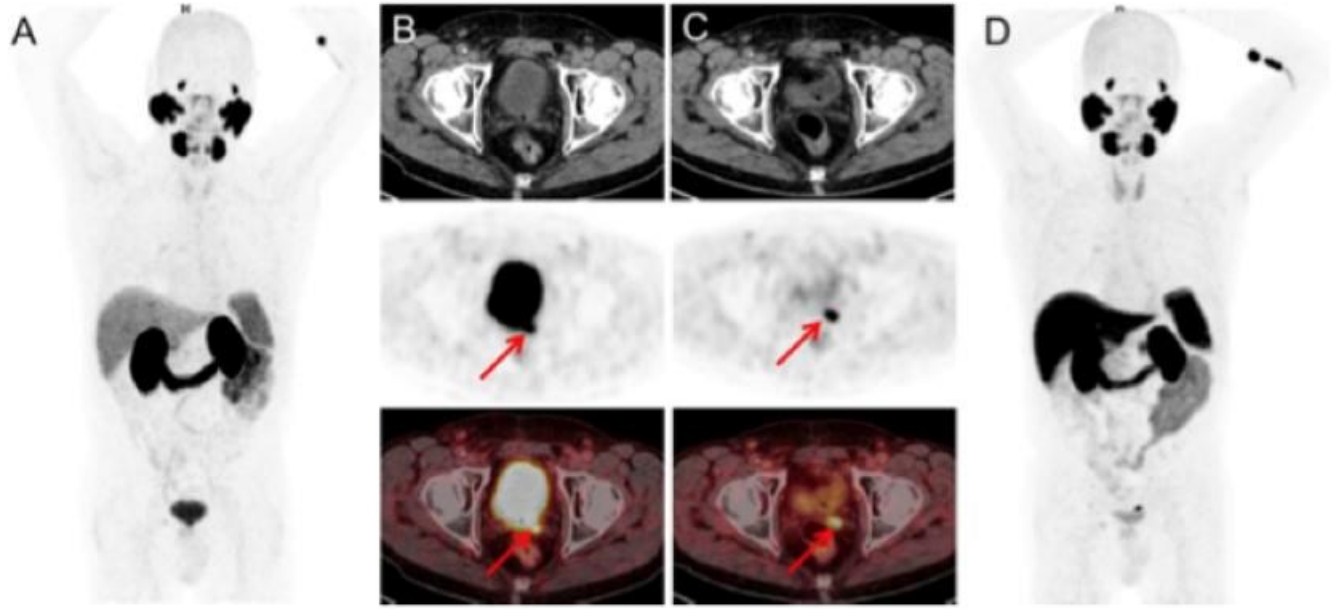
1,106 patients received SRT between Jan 1987 and July 2013
Median F/U – 8.9 years

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.

Other challenges of PSMA PET-CT imaging

- Detection of cancer recurrence at the prostate bed – complicated by the accumulation of tracer in the bladder and urethra and can obscure evaluation at the VUA



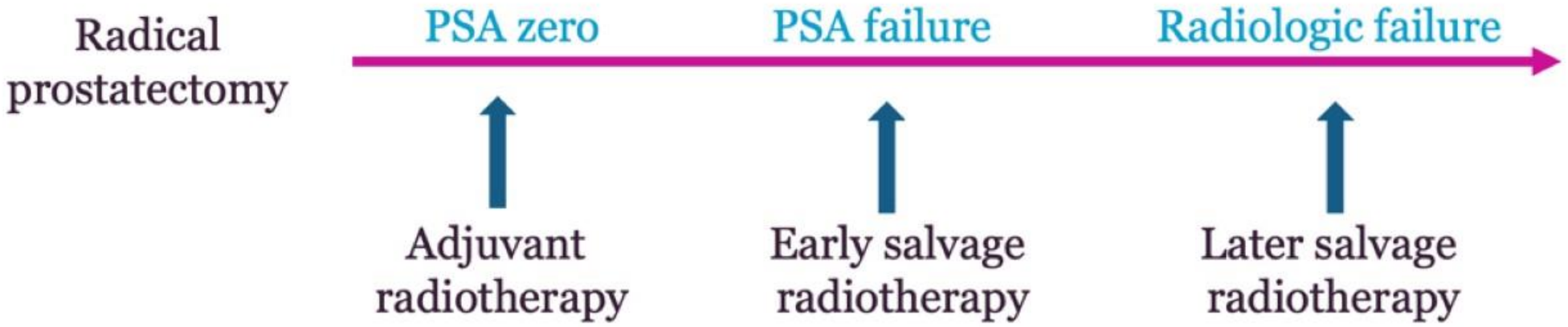
Detection efficacy of [^{18}F]PSMA-1007 PET/CT in 251 Patients with biochemical recurrence after radical prostatectomy

Giesel FL (1,8,9), Knorr K (2), Spohn F (1,8), Will L (1), Maurer T (3), Flechsig P (1), Neels O (5,8), Schiller K (4), Amaral H (6), Weber WA (2), Haberkorn U (1,9), Schwaiger M (2), Kratochwil C (1), Choyke P (7), Kramer V (6), Kopka K (5,8), Eiber M (2,8)

2018

- Detection of LN metastases is moderate – inherent limitation in spatial resolution to detect small (<3mm) nodal metastases

Timing of radiotherapy post RP



Our mission is to reduce the risk of Joe missing the boat for curative treatment

- *The use of PSMA PET-CT is to personalise the radiotherapy field not to omit radiotherapy*