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3 year freedom from progression following ^{68}GaPSMA PET CT triaged management in men with biochemical recurrence post radical prostatectomy. Results of a prospective multi-center trial.

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Running title: 3-year FFP from PSMA triaged sRT post RP

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ABSTRACT

Background

^{68}Ga PSMA PET CT (PSMA) is increasingly used in men with biochemical recurrence (BCR) post radical prostatectomy (RP), but its longer term prognostic / predictive potential in these men is unknown. The aim of this study was to evaluate the predictive value of PSMA PET for 3 year freedom from progression (FFP) in men with BCR post RP undergoing salvage radiotherapy (sRT).

Methods

This prospective multi-center study enrolled 260 men between 2015 and 2017. Eligible patients were referred for PSMA with rising PSA following RP. Management following PSMA was recorded but not mandated. PSMA protocols were standardised across sites and reported prospectively. Clinical, pathological and surgical information, sRT, timing and duration of androgen deprivation (ADT), 3 year PSA results and clinical events were documented. FFP was defined as a PSA rise ≤ 0.2ng/mL above nadir post sRT, with no additional treatment.

Results

The median PSA was 0.26ng/mL (IQR 0.15 - 0.59) and follow-up 38 months (IQR 31-43). PSMA was negative in 34.6% (90/260), confined to prostate fossa 21.5% (56/260), pelvic nodes 26.2% (68/260), and distant disease 17.7% (46/260). 71.5% (186/260) received sRT, 38.2% (71/186) to the fossa only, 49.4% (92/186) fossa + pelvic nodes and 12.4% (23/186) nodes alone/SBRT. PSMA was highly predictive of FFP at 3 years following sRT. Overall, FFP was achieved in 64.5% (120/186) of those who received sRT, 81% (81/100) with negative/fossa confined vs. 45% (39/86) for extra fossa disease ($p<0.0001$). On logistic regression PSMA was more independently predictive of FFP than established clinical predictors, including PSA, T-stage, surgical margin status or Gleason score ($p < 0.002$). 32% of men with a negative PSMA PET did not receive treatment. Of these, 66% (19/29) progressed, with a mean rise in PSA of 1.59ng/mL over the 3 years.

Conclusion:

PSMA PET result is highly predictive of FFP at 3 years in men undergoing sRT for BCR following RP. In particular, men with negative PSMA PET or disease identified as still confined to the prostate fossa demonstrate high FFP, despite receiving less extensive radiotherapy and lower rates of additional ADT than those with extra fossa disease.

INTRODUCTION

Radical prostatectomy (RP) is the most widely used treatment for men with localized prostate cancer (PC). However, up to 20-50% of the PC patients managed with RP will experience biochemical recurrence (BCR), especially those with poorly differentiated disease and positive surgical margins (*1,2*). Currently, in these men salvage radiotherapy (sRT), with or without androgen deprivation therapy (ADT) is the only remaining potentially curative treatment option. Overall, the 5 year progression-free survival rate in patients undergoing sRT is strongly related to serum PSA at start of sRT and varies from 71% in men with a pre-sRT PSA < 0.2ng/ml to only 18% in men with a pre sRT PSA value > 1.5ng/ml(*1,3-5*). The addition of more extensive radiotherapy fields and short term ADT has further improved FFP (*4,6*). Prostate specific membrane antigen (PSMA) is a cell surface glycoprotein highly expressed on the cell surface of prostate cancers that has recently been effectively targeted using small molecule peptides labelled with PET radioisotopes(*7-10*). Prospective evaluation of PSMA PET in men with a rising PSA post RP has demonstrated a very high sensitivity for disease detection even in men with very low PSA values (*10,11*). Further, PSMA PET identifies disease outside the prostate fossa in up to 43% of men with a rising PSA post RP (*11,12*), and consequently has shown high impact on the management impact and early treatment responses in these men (*13,14*). However, what is not yet known is whether PSMA PET findings impact longer term outcomes, and if the PSMA PET results should indeed dictate subsequent treatment. The aim of this study was to prospectively observe how PSMA results impacted management, and subsequent treatment outcomes.

MATERIALS AND METHODS

Study design

This prospective study was conducted at 4 Australian institutions (St Vincent's and Royal North Shore, Sydney and Sir Charles Gairdner and Fiona Stanley Hospitals, Perth). Eligible patients had a histological diagnosis of prostate cancer and were referred for PSMA PET/CT imaging for BCR with a rising PSA (PSA ≥0.05 and <5.0 ng/mL) following RP without contraindication for sRT. All PSMA PET CT were undertaken between January 2015 and March 2017. Informed written consent was

obtained from all patients and Institutional Human Research Committee Ethics approval was obtained for each site.

^{68}Ga-PMSA PET/CT

^{68}Ga-PSMA PET/CT scans were performed using a standardised protocol across institutions. Patients were injected with 1.8-2.2MBq/kg ^{68}Ga-PSMA (H-BED CC) 11 and imaged a minimum 60 minutes later, with no delayed imaging undertaken. Vertex to mid-thigh PET/CT imaging was performed on time-of-flight PET/CT scanners at all institutions (Siemens Biograph PET/ 64 slice CT, Phillips Ingenuity / 64 slice CT). For the PSMA PET CT, a non-contrast-enhanced CT scan was performed using the following CT parameters: slice thickness of 2 mm, with soft tissue reconstruction kernel, 120 keV and 50 mAs. Immediately after CT scanning, a whole-body PET scan was acquired for 2 minutes per bed position. All PET images were interpreted prospectively by credentialed nuclear medicine physicians with experience in reporting prostate PET images. Data for all PSMA scans was analyzed both visually and quantitatively. Visual analysis included a four-point certainty scoring scale (definitely negative, equivocal probably negative, equivocal probably positive, definitely positive), as well as anatomical site and size of lesions. Semi-quantitative analysis was undertaken using a standardized maximum uptake value (SUV max). For database purposes, each positive finding was coded according to anatomical site, SUV max, number of lesions and reporter certainty. The coded PSMA results were those available for treating investigators as a decision-making tool prior to undertaking salvage RT.

Data collection

Data collected at enrolment included age, time since RP, initial pathology including pathological T stage, Gleason Score (GS), surgical margin status, lymph node staging, and PSA at time of PSMA-PET. Following the PSMA PET, management impact questionnaires were documented, as were subsequent treatments. Importantly, PSMA PET results were made available to the treating clinician, however, treatments were monitored rather than mandated by the trial. Management plans following the PSMA PET were documented for each patient, including date and type of treatment initiated (observation, systemic and/or local therapy). The post treatment PSA was the most recent PSA recorded for each patient prior to analysis. As a part of the trial,

investigators undertook management impact questionnaires both before and after PSMA PET imaging, the results of which have been published previously (*13*).

Salvage Radiation Treatment

All sRT undertaken was based on the management decisions of the treating clinician after the PSMA PET result, using local institutional sRT treatment protocols. For the purposes of the trial, any site of targeted radiation treatment was documented. In the case of sRT fields delivered; patient's treatments were categorized as prostatic fossa only, prostatic fossa with pelvic lymph nodes, pelvic lymph nodes only, or stereotactic body radiotherapy to metastases within, or external to the pelvis. The use, timing and duration of ADT was also documented.

Outcome measures

The primary outcome measure was freedom from progression (FFP), defined as serum PSA remaining ≤ 0.2ng/ml above the post sRT nadir, without either the initiation of ADT or additional radiation therapy after completion of sRT (*5*).

Statistical Analysis

Time of follow-up was measured from the date of sRT to the last PSA undertaken prior to analysis, or date of either disease progression (PSA rise > 0.2ng/mL) or the addition of systemic treatment/radiation. The rates of FFP were estimated by Kaplan-Meier analysis. Multivariate Cox regression analyses were used to identify determinants for differences in FFP between the PSMA result, pathological T- and N-stage, radical prostatectomy surgical margins, Gleason score (sum), PSA level at the time of PSMA PET, and the time (months) to BCR after RP. Pearson Correlation were used to identify associations between FFP, PSMA result, pT-stage, pN-stage, GS, PSA level at the time of PSMA, PSA before surgery and time (months) to BCR after RP. For the purposes of analysis, all scans scored as either 'definitely positive' or 'probably positive' on the PSMA were considered a positive scan. *P* values <0.05 were considered statistical significance. Statistical analysis was carried out with IBM SPSS Statistics V25.0 (SPSS INC, Chicago, Ill).

RESULTS

Demographics

Baseline characteristics are summarized in Table 1. 260 patients met the inclusion criteria for this study and were prospectively enrolled. Only 2.3% (6/260) men were lost to long-term follow-up. Median age at time of PSMA PET scanning was 68 (IQR 63-72) years. Median time between RP and PSMA PET was 37.8 months (IQR 8.6 – 87.0). Median PSA value at PSMA PET was 0.26ng/mL (IQR 0.15- 0.59), and median follow-up after PSMA PET 38 months (IQR 31- 43).

PSMA PET

PSMA PET was positive in 65.4% (170/260) of enrolled patients. Sites of disease included prostatic fossa only 21.5% (56/260), pelvic nodal involvement 26.2% (68/260), distant lymph nodes 6.2% (16/260), bone 9.6% (25/260) or visceral disease 1.9% (5/260) (Table 2). In total 46% of men had positive PSMA PET findings beyond the prostate fossa and 18% had extra-pelvic metastatic disease. PSMA PET positivity increased with higher PSA values, with 50.6% (42/84) positive at PSA <0.2ng/mL compared to 90.2% positive (37/41) in men with PSA > 1.0ng/mL ($p < 0.001$) (Table 3). 34.6% (90/260) of patients had a negative PSMA PET. A negative PSMA PET was strongly associated with lower PSA levels ($p<0.001$), pT stage ($p = 0.03$) and surgical margins ($p = 0.03$), but not with GS, pN stage or extra capsular extension.

Salvage Radiation Treatment

186 men underwent salvage RT, of whom 38% (71/186) received treatment to the prostatic fossa alone, 50% (92/186) the prostatic fossa and pelvic lymph nodes, 5% (9/186) to pelvic lymph nodes only, and 7% (14/186) received stereotactic body radiotherapy to either pelvic lymph nodes or distant sites. Finally, 25% (46/186) received adjuvant ADT with sRT (median 10.25 months (IQR 6.33-9.18)). Overall, PSMA PET positivity conferred a higher likelihood of treatment with sRT (Table 4). The use of more extensive sRT fields was significantly more likely in those with PSMA positive disease compared to men with negative PSMA PET scans [42% (71/170) vs 23% (21/90) respectively, $p< 0.03$]. The use of ADT was also significantly higher in men with positive PSMA PET [31% (40/129), compared to negative PSMA scans, 11% (6/56) $p < 0.001$]. 75 men did not receive sRT, of whom 45% (34/75) had negative

PSMA scans. 32% (26/75) of these men received either ADT or other forms of systemic treatment. 4% (3/75) were managed with surgical lymph node dissection, and 65% (49/75) were observed with no documented treatment in the follow-up period.

3 Year Freedom From Progression

Overall 64.5% of men who underwent sRT enjoyed FFP at 3 years. PSMA PET findings prior to salvage treatment were highly predictive of FFP in those men who underwent sRT. Three-year FFP dropped from 81% (81/100) in those with negative/fossa confined findings, to 45% (39/86) where PSMA positive disease was identified outside the prostate fossa ($p < 0.0001$) (Fig. 1). A negative PSMA PET in men receiving sRT was most predictive of 3 year FFP at 82.5% (47/57) followed closely by PSMA avid disease confined to the prostate fossa at 79% (34/43), pelvic nodal involvement 55% (33/59), distant lymph nodes 25% (2/8) and visceral or bone metastatic disease 21% (4/19; $p<0.0001$) (Table 5). On univariate Cox regression analysis, PSMA PET findings, PSA at the time of sRT and surgical margin status were all predictive of FFP. Following multivariate Cox regression analysis, PSMA PET positivity was the only independently predictive factor for FFP in men who underwent sRT (Table 6). Despite a strong association between PSA levels and PSMA findings, Kaplan Meier curves demonstrate the stronger predictive value of PSMA for FFP (Fig. 2).

Negative PSMA PET

Men with negative PSMA PET scans (34.6% (90/260)) were the most likely group to achieve 3-year FFP if they received sRT (82.5%), despite receiving less extensive radiotherapy fields or ADT (Table 3). Paradoxically, this group was also the least likely to receive sRT, with a higher chance of observation only in men with a negative compared to a positive PSMA PET: 32% (29/90) vs. 12.3% (21/170) $p < 0.001$). In those men with negative scans who were observed without treatment 66% (19/29) had ongoing rise (> 0.2ng/ml) in PSA over the 3 years of follow-up (mean increase from baseline PSA 1.59 ng/mL) (Fig. 3). Subgroup analysis of those men with negative scans who were observed demonstrated that the PSA at the time of PSMA was lower in those men who did not have a significant rise in PSA during follow-up (0.15ng/mL vs 0.56 ng/mL (p = ns). There was no significant difference in risk grouping (surgical

margin, GS or surgical T stage) between men with negative scans who were treated with sRT versus those who were observed.

DISCUSSION

Salvage prostate fossa RT for men with BCR following RP is the last potentially curative treatment, with up to 56% of these men enjoying long-term treatment control or 'cure' (*5*). However, sRT is not without toxicity, and a significant proportion of these men will fail treatment, with the added burden of treatment-induced toxicity. More recently reported studies have improved disease control rates by escalating treatment regimens, expanding radiotherapy fields, which modern sRT techniques such as intensity modulated radiotherapy safely permit, and/or adding adjuvant androgen deprivation (ADT)(*4*). However, while beneficial in improving FFP rates, treatment intensification increases the possibility of toxicity from both larger sRT fields and the metabolic effects of ADT. Identifying those men who would best benefit from escalated treatment regimens, versus those likely to be cured with fossa sRT alone (or safely observed) is a current need. PSMA PET has been thrown into the mix as a powerful diagnostic tool that is capable of identifying biochemically recurrent prostate cancer at low PSA levels that are still potentially curable (*10,11,15,16*). This study reports the first longer term FFP results from PSMA triaged treatments in a prospective study of men with BCR following RP.

This multisite prospective study has previously demonstrated a high management impact (62%) for pre-treatment PSMA PET CT in men with biochemical failure following radical prostatectomy (*13*). Ongoing follow-up at 3 years in this cohort has now highlighted the valuable predictive potential of PSMA PET in men with biochemical recurrence managed with sRT. Men with either a negative scan or PSMA positive disease confined to the fossa who underwent sRT had significantly higher 3 year FFP rates compared to those men with either pelvic nodal or distant metastatic disease on PSMA. Furthermore, PSMA-PET was found to be a significantly more powerful predictive indicator of 3 year FFP than established clinical predictors such as GS, pathological stage, surgical margin status, extra-capsular extension or PSA level at time of sRT.

PSMA PET CT is a sensitive technique for identifying sites of recurrence in the post RP biochemical failure setting at low PSA levels (*11,12,17,18*). The majority of

men with a PSA < 1.0ng/ml will have a positive PSMA PET scan, with the detection rate of the scan dependent on PSA level at the time of imaging (*12,17,19-22*). Around half the men with a positive scan will have disease beyond the fossa, a finding confirmed in this report. However, a significant proportion of men with PSA in the curative range for salvage radiotherapy will have a negative scan (35% of our cohort). This study suggests that these men are excellent candidates for sRT with the negative finding on PSMA being a more important predictor of long-term sRT control than risk factors such as PSA level, high Gleason score, higher T-stage and positive surgical margin status. Further, this excellent treatment control in men with negative PSMA is achieved despite the fact that treatment intensification via the use of more extensive sRT fields and/or adjuvant ADT was lower in this group, compared to men with positive PSMA PET findings.

Negative scans in men who respond to fossa sRT are likely to represent a combination of low PSMA expression and low volume of disease at the time of imaging. That men with low PSMA expression do well with targeted therapy fits with our knowledge of the pathophysiology of the PSMA receptor in prostate cancer (*23*). The receptor plays a key role in glutamate cleavage and activation of growth pathways (Pi3K and AkT) in the cancer cell. High PSMA expression is known to equate to poor outcomes (*24*). It is likely that men with PSMA positive disease occupy a biologically poorer prognostic category to those with negative scan results, with higher growth rates and metastatic potential in those demonstrating significant PSMA expression. It has previously been shown that men with a negative PSMA PET do well with sRT, even in the presence of other high risk indicators on the Stephenson nomogram (*25*) While men in this study with negative scans who did not undergo sRT had a significant rise in PSA in the majority of men, 34% of these men had PSA levels that rose < 0.2ng/mL over the 3 years, suggesting it may be possible to safely monitor a subgroup men with negative scans. The predictive potential of PSMA in personalizing treatment regimens in BCR warrants further evaluation.

Two randomized trials have examined the role of treatment intensification in men with rising PSA post RP (*4*). Both studies pre-date PSMA-PET imaging. The first randomized 743 men to either sRT alone or fossa sRT combined with 6 months of ADT. This trial reported a 20% benefit in FFP (from 62 to 80%) at 5 years with the addition of ADT (GETUG16)(*4*). In the second study, a 3-arm multicenter randomized trial of 1736 eligible men with rising PSA post RP, the 5 year FFP increased from 71%

to 89% for fossa alone RT compared to Fossa + pelvic nodes + 6 months ADT. That trial defined PSA progression as nadir + 2 ng/mL, likely explaining the higher FFP rates compared to the current trial (*26*). Clearly, further prospective work is required to determine if PSMA PET can help identify those men who will benefit from treatment intensification, and those in whom it can be safely avoided.

Overall treatment response rate to sRT in this study is lower than some reported studies. This is likely due to 2 reasons. Firstly, the definition of FFP with a rise in PSA > 0.2ng/mL is lower than in the recently reported studies which used a PSA rise of > 2ng/mL. Pisansky et al. used a PSA > 0.2ng/mL with similar FFP rates (63.5% FFP at 5 years) to those documented in this current study in over 1000 men (*5,27*). Secondly, a number of patients with negative or fossa confined disease did not receive sRT over the 3 years of the study, with a significant rise in PSA in the majority of these men (mean PSA rise 1.59ng/mL). If these men had received sRT, we estimate the overall response rate to sRT would be >70%.

At the time this prospective trial was commenced, the value of PSMA PET in the setting of biochemical failure post RP was poorly understood. Hence it was appropriate for this trial, that treatment decisions were documented, but not dictated based on the PSMA PET findings. Although treatment was not mandated and left to the discretion of the treating radiation oncologist, men with positive pelvic nodes more frequently received pelvic nodal sRT and ADT compared to those with negative scan results. This clearly reinforces our findings, as the predictive power of negative/ fossa confined PSMA result for FFP was not impacted by treatment intensification. Men with negative /fossa confined PSMA PET were more likely to received standard radiotherapy fields without including pelvic nodes, and less likely to receive ADT.

This study prospectively recorded PSMA PET results using a standardised method across sites, with experienced prostate imagers. However, it did not implement a double read assessment to derive kappa scores or assess biopsies undertaken. These results have been documented for PSMA PET in other trials (*11,28,29*). We have previously undertaken a prospective trial where histopathology was directly compared to PSMA PET result in men undergoing extended pelvic lymph node dissection. This study demonstrated a 62% sensitivity and 95% specificity for lymph nodal involvement on PSMA PET(*29*). Similarly, Fendler et al recently reported an excellent PPV (84%) for PSMA PET based on histopathology gold standard, giving good evidence for the diagnostic accuracy of the modality(*11*). The focus of this

trial was to evaluate the outcomes of PSMA triaged management based on the PET results conveyed to the treating clinician prior to treatment, which we believe is a more generalizable (and clinically relevant) scenario.

CONCLUSION

PSMA PET result is highly predictive of FFP at 3 years in men undergoing sRT for BCR following RP. In particular, men with negative PSMA PET or disease identified as still confined to the prostate fossa demonstrate high FFP, despite receiving less extensive radiotherapy and lower rates of additional ADT than those with extra fossa disease.

KEY POINTS:

Question: PSMA PET frequently changes management in men with BCR post RP, but we do not know if it improves longer term outcomes, or if PSMA PET results should dictate subsequent treatment choices.

Pertinent Findings: This prospective observational multicenter study found that PSMA PET results in 260 men with BCR post RP was highly predictive of freedom from failure at 3 years following salvage radiotherapy treatment

Implications for Patient Care: The study demonstrates the predictive value of PSMA PET in dictating which patients will best benefit from targeted radiation therapy, and those who need further treatment intensification to control their disease.

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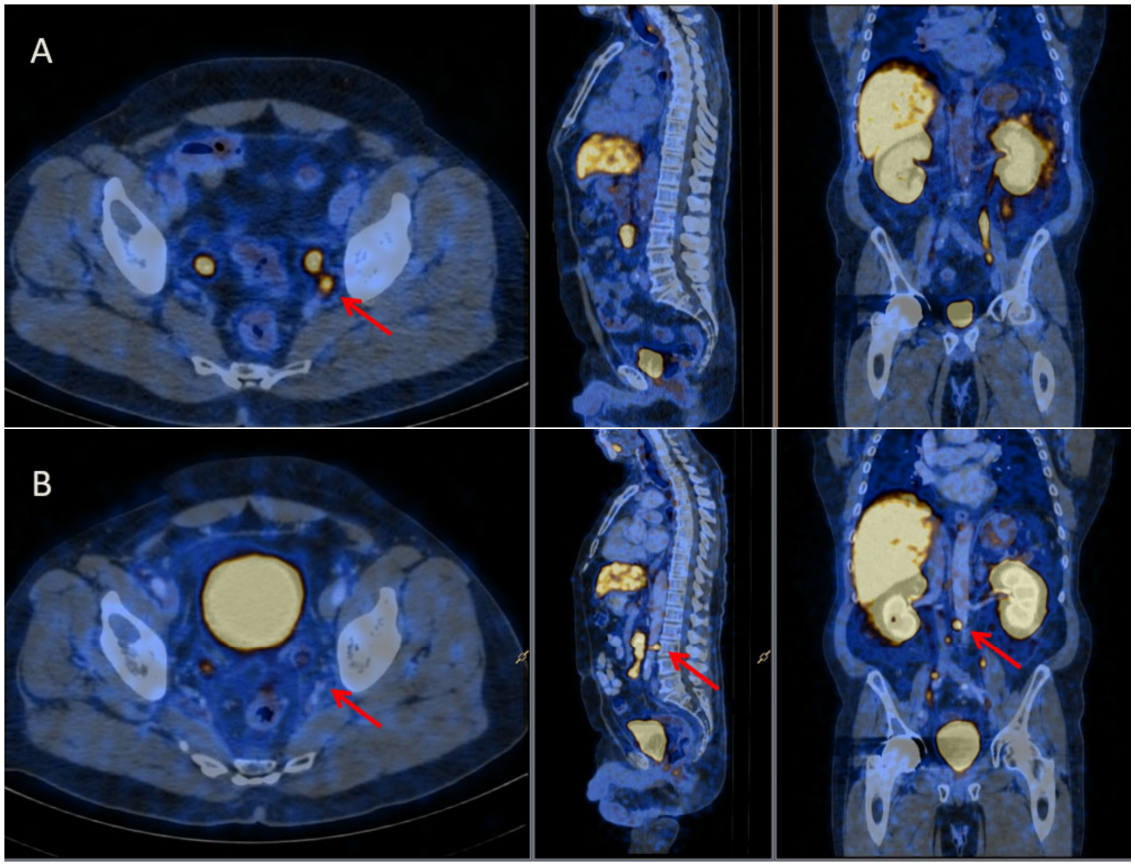

Fig 1. A PSMA PET (A) in this man with Gleason score 9 PC, PSA 0.23ng/mL, treated with initial RP 12 months prior demonstrates a PSMA positive left obturator node (red arrow). The patient subsequently underwent sRT to the prostate fossa and pelvic nodes. However, the PSA did not respond and repeat PSMA PET 10 months later (B) demonstrates treatment response in the left obturator lymph node, but multiple new PSMA avid lymph nodes (red arrow) immediately above the sRT treatment field, extending superiorly to the para-aortic region.

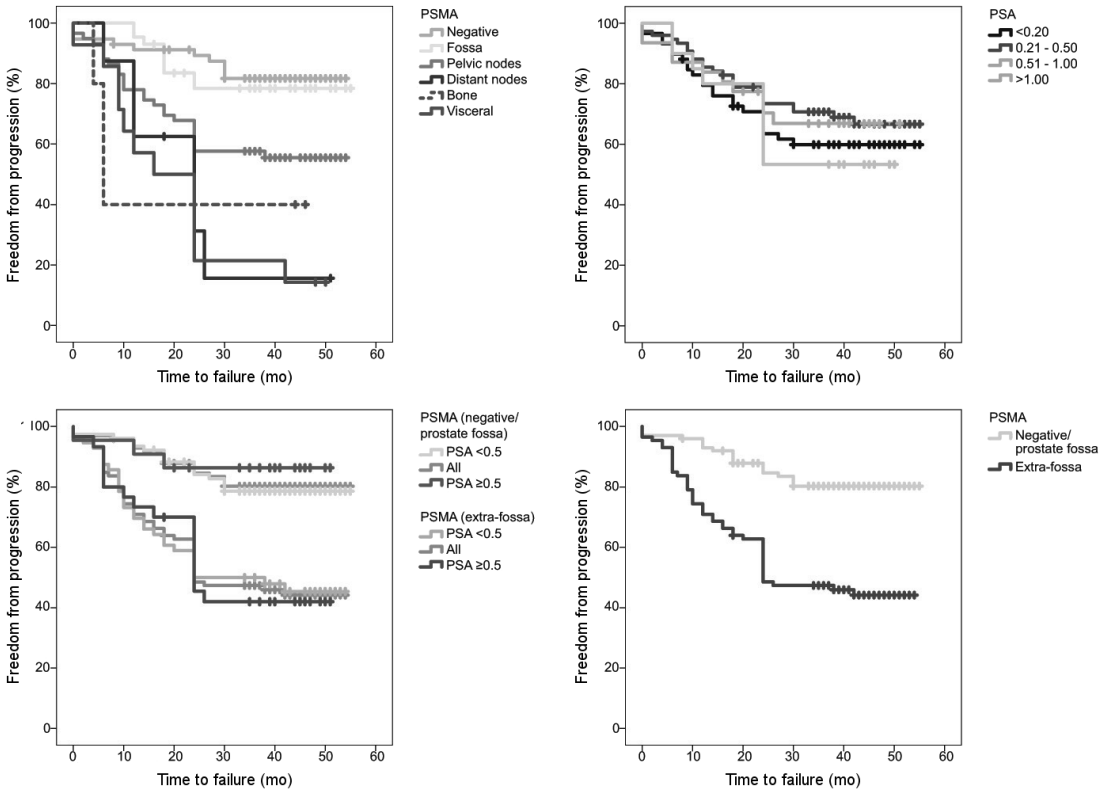

Fig 2. Kaplan Meier curves for FFP based on PSMA result (A), PSA at PSMA PET (B), PSMA (neg/fossa confined vs extra fossa) (C) and (D) – stratified for both PSA and PSMA (neg/fossa confined vs extra fossa).

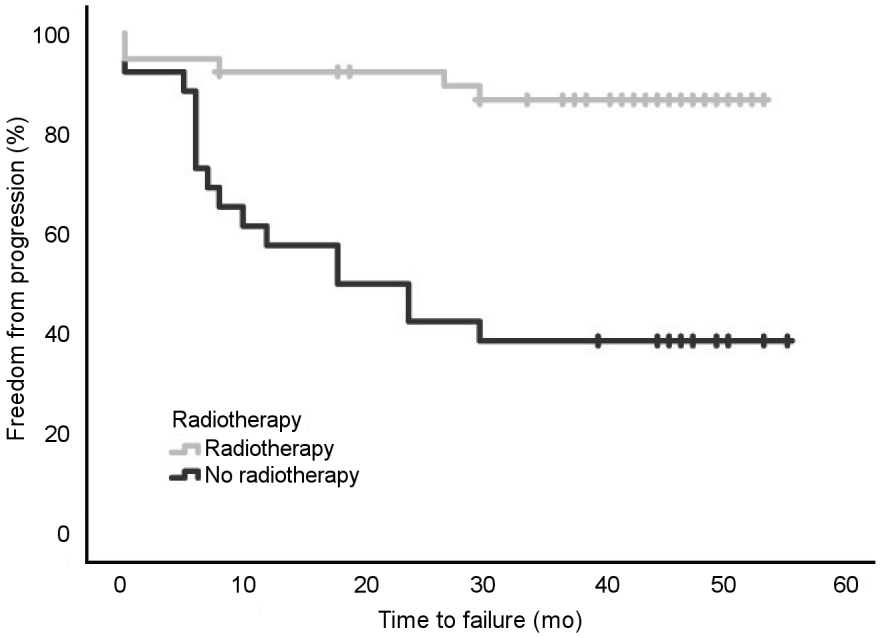

Fig 3. FFP in men with negative scans who underwent sRT versus men who were observed over the 3 years ($p < 0.0001$)

Table 1: Patient Characteristics.

Variable	**Number**	**IQR / %**
Median age (years)	68	63-72
Median PSA at PSMA PET (ng/mL)	0.26	0.15-0.59
Tumor stage		
T2	58 / 260	22.4%
T3a	111 / 260	42.7%
T3b	41/ 260	15.7%
Missing	50 / 260	19.2%
Positive surgical margins	55 / 219	25%
Gleason score		
6 -7	161/260	58%
8 -10	72/260	42%
Missing	27/260	10%
Months to BCR from RP	37.8	8.6-87.0
Months follow-up since sRT	38	31-43

Table 2: Sites of disease recurrence on PSMA PET.

PSMA PET: Site of recurrence	Number	Percent
Negative scan	90/260	34.6%
Fossa recurrence	56/260	21.5%
Pelvic lymph nodes	68/260	26.2%
Distant lymph nodes	16/260	6.2%
Bone metastases	25/260	9.6%
Visceral metastases	5/260	1.9%

Table 3:PSMA PET result stratified by increasing PSA level.

PSA (ng/mL)	PSMA PET -	PSMA PET+	Overall
<0.2	41 (49.4%)	42 (50.6%)	83
0.2-0.5	36 (34.9%)	67 (65.1%)	103
0.51-0.99	9 (27.3%)	24 (72.7%)	33
1.0 -5.0	4 (9.8%))	37 (90.2%)	41
Total	90 (34.6%)	170 (65.4%)	260

Table 4: Treatment administered based on the PSMA PET result.

Treatment	PSMA result: Negative scan	Fossa positive	Pelvic node positive	Distant Disease
sRT to fossa only	35/90 (39%)	19/56 (43%)	12/68 (21%)	5/46 (11%)
sRT to fossa + pelvic nodes	21/90 (23%)	23/56 (41%)	38/68 (64%)	10/46 (22%)
SBRT to pelvic nodes only	0/90 (0%)	0/56 (0%)	9/68 (13%)	14/46 (30%)
Adjuvant ADT + sRT	6/56 (11%)	8/42(19%)	20/59 (34%)	12/28 (43%)
ADT alone	5/90(5%)	2/56 (4%)	5/68 (7%)	13/46 (28%)
No treatment over 3 years	29/90 (32%)	12/56 (26%)	4/68 (6%)	5/46 (11%)

Table 5: Incidence of FFP or progressive disease based on the PSMA PET findings in men treated with sRT.

PSMA PET result	FFP at 3 years	Progressive disease	Overall
Negative	47 (82.5%)	10 (17.5%)	57/186 (31%)
Fossa positive	34 (79%)	9 (21%)	43/186 (23%)
Pelvic LN positive	33 (55%)	26 (45%)	59/186 (32%)
Distant LN positive	2 (25%)	6 (75%)	8/186 (4%)
Bone or viscera	4 (21%)	15 (79%)	19/186 (10%)
Total	120 (64.5%)	66 (35.4%)	186 (100%)

Table 6: Cox logistic regression analysis of clinical and imaging variables for the prediction of FFP in men who underwent sRT.

		95.0% CI for Exp(B)		
	Hazard Ratio	**Lower**	**Higher**	**Significance**
Extra-capsular extension	.73	0.25	2.13	0.57
RP surgical margin	1.1	0.19	6.18	0.94
T-stage at RP	.71	0.11	4.45	0.71
Lymph node stage at RP	0.54	0.11	2.69	0.45
Gleason Score	.69	0.23	2.06	0.50
PSA at PSMA	1.17	0.82	1.68	0.38
PSMA neg/fossa vs extra fossa	2.73	1.45	5.14	0.002