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Treatment outcomes from ^{68} GaPSMA PET CT informed salvage radiation treatment in men with rising PSA following radical prostatectomy: Prognostic value of a negative PSMA PET.

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ABSTRACT

Introduction: ^{68}Ga PSMA PET CT (PSMA) is increasingly used in men with PSA failure post radical prostatectomy (RP) to triage those who will benefit from salvage radiation treatment (SRT). This study examines the value of PSMA informed SRT in improving treatment outcomes in the context of biochemical failure post RP.

Methods: We analysed men with rising PSA post RP with PSA readings between 0.05 and 1.0 ng/ml, considered eligible for SRT at the time of PSMA. For each patient, clinical and pathological features as well as scan results, including site of PSMA positive disease, number of lesions, and a certainty score were documented. Using medical records, subsequent management, including SRT, and most recent PSA was recorded. Treatment response was defined as both PSA ≤ 0.1ng/ml and >50% reduction in PSA. Multivariate logistic regression analysis was performed for association of clinical variables and treatment response to SRT.

Results: 164 men were included. PSMA was positive in 61% (n=102/164): 38/102 in the prostatic fossa, 41/102 in pelvic nodes, and 23/102 distantly. 24 patients received ADT and were excluded for outcomes analysis. In total 99/146 received SRT with median follow up post RT of 10.5 (IQR 6-14) months. Overall treatment response after SRT was 72% (n=71/99). 44% (n=27/60) of patients with a negative PSMA underwent SRT while 56% (33/60) did not. Men with a negative PSMA who received SRT, 85% (n=23/27) demonstrated a treatment response, compared to further PSA increase in 65% (22/34) in those not treated. In the 36/99 with disease confined to the prostate fossa on PSMA, 83% (n=29/36) responded to SRT. In total 26/99 men had nodal disease on PSMA, of whom 61% (n=16/26) had treatment response following SRT. On multivariate logistic regression analysis, PSMA and serum PSA significantly correlated with treatment response, while pT stage, Gleason score and surgical margin status did not.

Conclusion: PSMA PET is independently predictive of treatment response to SRT, and stratifies men into a high treatment response to SRT (negative or fossa confined PSMA) versus men with poor response to SRT (nodes or distant disease PSMA). In particular, a negative PSMA PET predicts a high response to salvage fossa radiotherapy.

INTRODUCTION

Radical prostatectomy (RP) is the most widely used treatment for men with localized prostate cancer (PC). Following surgery, patients are monitored with serial prostate-specific antigen (PSA) measurements. Approximately 20-50% of pT2-3, node negative PC patients treated with RP will experience biochemical recurrence (BCR), particularly those with poorly differentiated disease and positive surgical margins. Salvage radiation treatment (SRT) to the prostatic fossa (or fossa + pelvic nodes in higher risk patients) is the only potentially curative treatment option for patients with biochemical failure following RP. The 5 year progression-free survival rate in patients undergoing salvage RT is 56%, varying from 71% in men with pre-RT PSA level of <0.01-0.2ng/ml, down to 18% in men with a PSA > 1.5ng/ml undergoing SRT without ADT[1-4]. This indicates that men with low volume recurrent PC benefit the most from SRT; and that there are a significant number of patients who do not show a lasting PSA response after salvage. Because SRT is only clinically useful in patients with local disease (disease confined to the fossa), and because SRT is related to significant disadvantages in treatment related quality of life, patients with tumour spread outside of the prostatic fossa should ideally be excluded when selecting patients for prostatic fossa only salvage RT. Postoperative conventional imaging techniques such as transrectal ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and bone scan, are neither sensitive nor specific enough to detect recurrent PC at an early stage where salvage RT may be curative. Recent publications have reported PSMA PET/CT identifying disease outside the prostate fossa in 28 - 43% in men with a rising PSA post RP [5-7]. These findings have led to significant changes in patient care, with many patients confirmed with metastatic disease on PSMA PET scan not proceeding to salvage fossa radiotherapy[8 9].

Currently, the treatment outcomes of the PSMA PET guided change in disease management in this patient cohort are unknown. The aim of this study is to evaluate treatment outcomes from PSMA PET informed SRT in men with rising PSA following radical prostatectomy.

MATERIALS AND METHODS

Between February 2015 and July 2016, PSMA PET/CT was performed in 657 consecutive patients at a single institution. Written informed consent was obtained from all patients included in the Prostate Cancer Imaging Database (ProCan-I). The Pro Can -I aims to prospectively collect clinical and imaging information on patients undergoing a PSMA PET scan for PC and to assess the impact of the imaging results on clinical management and patients outcomes. The trial was approved by the St Vincent's Institutional Human Research and Ethics Committee.

Patient Population

Men who had undergone RP and were diagnosed with a rising PSA (PSA ≥0.05 and <1.0 ng/mL) and suitable for SRT were selected for the present study (Figure 1). None of the patients had evidence of loco-regional recurrence or metastatic disease on conventional clinical work-up. Men who subsequently received any form of systemic treatment were excluded from analysis of treatment outcomes, but included in analysis on scan findings. Data to be collected at enrolment included age, previous therapy, time since RP, initial pathology (including T stage and Gleason Score (GS)), surgical margin involvement, PSA at time of PSMA-PET scanning and prior imaging.

Imaging Protocol

PSMA was produced on-site compliant to the Good Laboratory Practices procedure using a TRASIS® automated radio-pharmacy cassette. Radio pharmacy quality control was undertaken using a high-pressure liquid chromatography method. Patients were injected with 2.0MBq/kg ^{68}Ga-PSMA (H-BED CC). All PET CT imaging was undertaken using a Phillips® Ingenuity TOF – PET / 64 slice CT scanner. For the PSMA PET CT, a non-contrast-enhanced CT scan was performed 45 minutes post tracer injection using the following CT parameters: slice thickness of 2 mm, with 2 mm slices, soft tissue reconstruction kernel, 120 keV and 50 mAs, pitch of 0·828, 600 mm FOV and a 512 matrix. Immediately after CT scanning, a whole-body PET scan was acquired for 2 minutes per bed position. The emission data were corrected for randoms, scatter and decay using the Phillips® Body-dynamic.xml and Body.xml reconstruction protocol. All images were viewed and reported using the Phillips® Fusion Viewer.

Image Interpretation

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 an automated 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.

Follow-up and Treatment outcomes

Management following the PSMA PET was documented for each patient, including date and type of treatment initiated (surveillance, systemic or local therapy). Any site of targeted treatment was documented. In the case of RT treatment was divided into fossa only RT (FORT), fossa + pelvic nodes, or SBRT external to the pelvis. The post treatment PSA was the last PSA recorded for the patient prior to analysis of results. Based on previous literature demonstrating a post SRT PSA ≤0.10 ng/ml nadir as predictive of longer term outcome, treatment response was defined as both PSA ≤0.10 ng/ml and a > 50% reduction from pre-treatment level [10]. Follow-up time was defined as the interval (months) between salvage RT and last recorded PSA.

Statistical Analysis

Pearson's correlation and binary logistic regression analyses were used to identify determinants for differences between the patients with a positive scan and those with a negative scan considering pT stage, pLN stage, Gleason score, PSA level at the time of Ga-PSMA scan, and time (months) after RP. Uni - and multivariate binary logistic regression analyses were used to identify predictive determinants (PSMA PET results, serum PSA at PSMA PET, Gleason score at RP and surgical margins status at RP) for treatment response in men that received SRT without ADT. *P* values <0.05 were considered to indicate statistical significance. Statistical analysis was carried out with IBM SPSS Statistics V22.0 (SPSS INC., Chicago, Ill).

RESULTS

Baseline characteristics

Baseline characteristics are summarized in Table 1. 164 patients in total were included in this study. Median age at PSMA PET was 68 (IQR 62-71) years. Median time between RP and PSMA PET was 37 months (IQR 13-74), median PSA at PSMA PET 0.23 (IQR 0.14-0.35).

PSMA PET results

In 61% (n=102/164) of the patients, PSMA PET/CT identified recurrent disease. The distribution of positive PSMA PET/ stratified by PSA levels is displayed in Figure 2. A positive PSMA PET/CT scan was reported in 50.0% (32/64) of the patients with a PSA 0.01-0.19 ng/ml, 64.4% (29/45) in PSA 0.20-0.29 ng/ml, 66.7% (16/24) in PSA 0.30-0.39 ng/ml, 83.3% (10/12) in PSA 0.40-0.49 ng/ml and 79.2% (19/24) in PSA 0.50-1.00 ng/ml.

Of 102 men with a positive scan, 38 /102 were positive in the prostatic fossa, 41/102 in pelvic nodes and 23/102 had distant metastasis on the PSMA PET/CT (Table 1).

PSMA PET/CT-directed treatments and outcomes

A total of 24/164 (13.6%) patients received ADT after PSMA PET/CT and were excluded from outcome analysis. Of the 140 remaining men, 60/140 (43%) had a negative and 80/140 (57%) a positive PSMA PET/CT scan. The median follow-up for these patients was 10.5 months (IQR 6-14). Scan positivity and the site(s) of recurrence had an important impact on choice of subsequent management. Overall, the SRT treatment rate was 70% (n=99/140); this ranged from 100% (n=36/36) for disease confined to the fossa, to 88% (n=26/30) for nodes, 71% (n=10/14) for distant disease and 44% (n=27/60) for a negative PSMA PET.

Among the 99 patients receiving SRT, the overall treatment response rate was 72% (n=71/99). This rose to 82.5% (52/63) in those with either a negative scan or a scan that was positive solely in the fossa, compared to 53% (19/36) response rate in men with PSMA PET positivity for lymph nodes or distant disease ($p < 0.002$).
Compared to clinical predictors of response to SRT, PSMA result was independently more predictive of a treatment response than PSA at imaging, GS, pT stage or surgical margins (Table 2). Results of the salvage treatments, stratified by PSMA PET findings and clinical parameters, are presented below and in Table 3.

Negative PSMA PET: 60/140 men had a negative PSMA PET result. Of these, 45% (n=27/60) of patients with a negative PSMA PET underwent SRT, while the remaining 55% (33/60) did not undergo treatment. There was no statistical difference in Gleason score, serum PSA, T stage or surgical margins in those who underwent SRT compared to those who did not.
Of those with a negative scan who underwent SRT, 86% (n=23/27) demonstrated a treatment response. 10% (3/29) had PSA failure with progressive rise in PSA despite fossa RT. In contrast, in men with a negative scan and no treatment, 65% (n=22/34) demonstrated a further rise in PSA, and 35% (12/34) a stable or declining PSA. In this cohort of men with a negative scan who underwent SRT, 20/27(74%) received standard fossa RT, and 7/27(26%) both fossa + pelvic node field RT.

Disease confined to the prostate fossa: In the 36/99 men with disease confined to the prostate fossa on PSMA PET who underwent SRT and did not receive ADT, 83% (n=29/36) had a significant treatment response. 17% (n=7/36) demonstrated biochemical progression in spite of RT. In this cohort, 19/36 (53%) received standard fossa RT and 17/36 (47%) received fossa + pelvic node field RT.

Nodal involvement on PSMA PET: 26/99 men with nodal disease (+/- involving the prostate fossa) on PSMA PET received SRT without ADT. Of these, 61.5% (n=16/26) had a significant treatment response following SRT. In this cohort, 38.5% (n=10/26) demonstrated biochemical progression in spite of SRT. Men in this cohort all received SRT targeting PSMA identified nodal disease (fossa + nodes SRT).

Distant disease: In the 15 men with distant metastasis on PSMA PET that did not receive ADT or systemic treatment, 10/15 (60%) received RT, of which 30% (n=3/10) had a significant treatment response following RT while 70% (n=7/10) demonstrated biochemical progression in spite of RT.

DISCUSSION

Salvage prostate fossa radiation treatment (RT) is current standard of care in men with biochemical failure following radical prostatectomy. It remains the last chance for cure in these men, with around 56% of men achieving complete biochemical response at 5 years following RT ([2 3 11]). Studies have shown that low serum PSA values post RP are correlated to significantly better treatment outcomes, supporting early SRT at a serum PSA < 0.2 ng/ml or < 0.5 ng/ml[3]. Treatment response drops off dramatically once the PSA rises above 1.0ng/ml[4]. However, a significant number of men, even with low PSA levels, do not respond to this treatment, presumably due to disease beyond the prostatic bed at the time of salvage. In a previous study, we demonstrated that up to 29% of men in this patient cohort have disease outside the prostate fossa at the time of imaging with PSMA PET CT[5]. We know that there is a high management impact with the use of PSMA PET CT in this patient population [7-9 12 13]. However, what has not yet been evaluated, is whether a

finding of disease outside the prostate fossa on PSMA PET impacts treatment outcomes.

This study shows that, in the cohort of men for whom salvage fossa radiotherapy remains standard of care, PSMA PET effectively stratifies men into those with a high (82.5%) versus low response (53%) to salvage radiation treatment. High treatment responders being men with negative PSMA PET or with disease confined to the fossa, while low responders had PSMA avidity in nodes or distantly. Furthermore, this difference in treatment response was evident despite the fact that the RT fields were predominately limited in the high treatment response cohort, and involved more extensive radiotherapy fields in the low treatment response group. PSMA PET result proved to be more predictive of treatment response to SRT than established clinical predictors, such as PSA level, Gleason score, pT stage and surgical margin status.

PSMA PET CT is a sensitive technique for identifying sites of recurrence in the post RP biochemical failure setting at low PSA levels[6]. A significant proportion 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 at the time of imaging[5 7 14-17] . Men imaged with a PSA of between 0.05 – 0.5ng/ml can expect to have a positive scan approximately 60% of the time, rising to 80% in the PSA range 0.5-1.0ng/ml. By contrast, we also know that PSMA PET underestimates the extent of disease. PSMA PET does not detect small volume nodal deposits, with sensitivity of the technique dropping off sharply at sizes below 4mm due to the inherent physical limitations of PET imaging [16 18]. Sensitivity is further reduced in the region of the prostate fossa due to adjacent excreted activity in the bladder [19 20]. The results of this study confirm that the extent of local recurrence may be underestimated by PSMA PET, and that, this must be taken into consideration in interpretation of scan results.

We have demonstrated that the group with the highest treatment response to salvage fossa radiotherapy is in those men with a negative PSMA PET scan. This may reflect the ability of PSMA PET to differentiate between disease phenotypes. Negative scans may identify patients with less aggressive disease that will benefit from local salvage and targeted treatment. Of the more than 56% of men with a negative PSMA PET who did not proceed to salvage RT, with the clinician electing to watch the PSA, up to 67% progressed biochemically. There was no significant differences in risk factors found between the men treated or not treated(Gleason score, T stage, surgical margins, PSA) with the decision to treat likely influenced by the negative finding on the PET scan. This high treatment response to salvage RT in men with a negative scan confirms that PSMA PET is not sufficiently sensitive to exclude microscopic disease recurrence around the prostate fossa. More significantly, it demonstrates that a high proportion of men with a negative scan respond to local (potentially curative) treatment, with low volume recurrent disease amenable to RT. This has important implications for the clinical management of men with prostate cancer and biochemical failure.

The study also confirms that a negative or fossa confined pre-treatment PSMA PET was the strongest independent determinant of treatment response after salvage RT, even when PSA level at time of scan, pTstage, GS or surgical margins were included in the analysis, reinforcing the paradigm that clinicians should recommend salvage RT even in men with a negative PSMA PET/CT. While median PSA was lower in the men with negative PSMA PET, there was no difference in PSA at imaging between men with disease confined to the fossa, and those with positive nodes or distant disease. The question as to what PSA level is optimum for PSMA PET imaging of men with biochemical failure has not been addressed by this study and requires well designed prospective trials.

PSMA PET is being increasingly utilized in men with rising PSA post RP. A positive scan may significantly alter RT intent, doses and volume. This study describes a significantly reduced treatment response in men with nodal involvement on PET or distant disease compared to either a negative scan or disease confined to the fossa, despite the more complex radiation treatment plans in those with disease beyond the fossa on PSMA PET. This highlights two points. Firstly, it demonstrates the ability of PSMA PET to stratify patients into those who will respond well to standard fossa RT, compared to those who may require more extensive treatment. Secondly it raises questions regarding optimum treatment for those men with PSMA PET positive findings outside the prostate fossa, targeted or systemic. This study has insufficient patient numbers to analyse the treatment response based on variations in radiation treatment. Further, the short follow up interval would make this type of analysis futile.

This study had an overall 75% early response rate to salvage RT in men with rising PSA (0.05-1.0ng/ml) post RP. This is lower than expected from the literature for biochemical response at this median PSA level [3]. There are several possible reasons for this. Firstly, all those who were treated with concurrent ADT were excluded from analysis. Further, the PSA decline following SRT continues for more than 12 months, and median time in this study between salvage RT and follow-up PSA was just 10.5 months. Our definition of treatment response involves low PSA levels not previously measurable prior to the widespread use of supersensitive PSA assays. The criteria we used for defining early treatment response (PSA <0.1ng/ml and >50% decline in PSA) to SRT was based on recent data demonstrating that a PSA nadir post SRT <0.1ng/ml has prognostic implications [10], and attempted to define men who had a significant decline in PSA (>50% reduction) due to accurate targeting of disease. Finally, more than half the men with a negative PSMA scan, which we have shown in this study as predictive of treatment response, did not in fact receive RT.

This may well have reduced our overall treatment response, and raises questions regarding optimal current practice for men undergoing PSMA informed management.

A major limitation of this study is the short follow up post treatment. With a median of 10.5 months in the treated cohort of patients, it is difficult to compare treatment response to larger studies of salvage RT (measuring biochemical failure) in this population. While it is not possible to extrapolate long term findings from early treatment responses, it is most likely that the non-responders (those with PSA rise despite salvage RT) will not be cured, and further follow-up is not required.While the ability of PSMA PET to stratify treatment responses, and characterize men with early biochemical failure has been demonstrated in this interim study, further follow-up will be undertaken to determine if the stratification in biochemical failure persists up to 5 years following therapy, and whether PSMA targeted treatment is appropriate.

A further limitation of the study is the relatively low numbers of patients enrolled. This limits the studies ability to evaluate appropriate PSA levels for imaging. Larger prospective studies with longer follow-up are needed to confirm that the prognostic value of a PSMA PET adds additional value to the predictive clinical findings included in the Stephenson nomogram and other predictors of salvage radiation treatment failure.

CONCLUSION

PSMA PET is independently predictive of a treatment response to SRT, and stratifies men into a high treatment response to SRT (negative or fossa confined PSMA PET) versus men with a poor response to SRT (nodes or distant disease on PSMA PET). A negative PSMA PET predicts a high response to salvage fossa radiotherapy.

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Figure 1. Flow chart for patient selection.

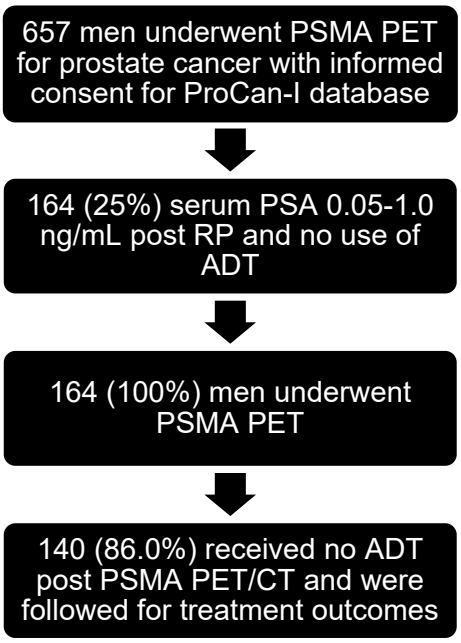

Figure 2. PSMA PET positivity at incremental PSA levels in men with rising PSA post radical prostatectomy.

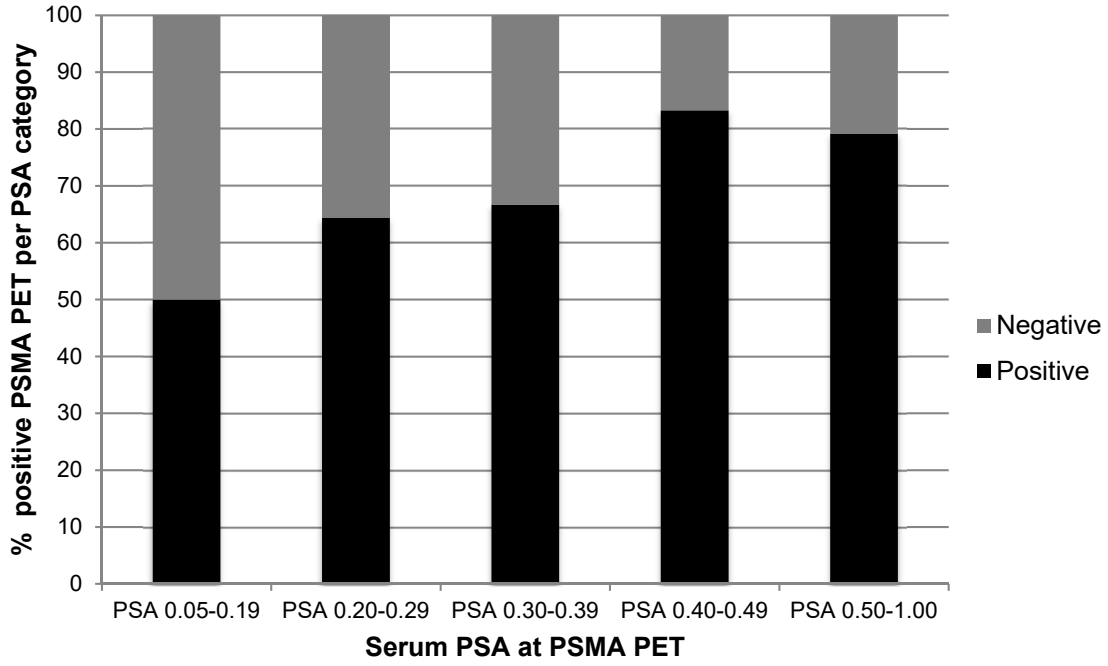

Table 1: Patient Characteristics.

Median age	65 (57-67)
Median PSA at PSMA PET	0.23 (0.14-0.35)
Tumour stage	
T2	43 (24.8%)
T3a	78 (44.4%)
T3b	29 (16.6%)
Missing	14 (14.2%)
Positive surgical margins	55 (32.5%)
Gleason score	
6 -7	118 (84%)
8 -10	46 (26%)
Months since RP	48 ± 43
PSMA PET Result	
Negative	62/164 (38%)
Fossa recurrence only	38/164 (23%)
Lymph node positive	41/164 (25%)
Distant disease	23/164 (14%)

Table 2. Logistic regression analysis of clinical variables for the prediction of treatment response to salvage radiation treatment.

	Odds Ratio	**Significance (p value)**
PSMA PET Negative/ Local Lymph nodes Distant disease	0.15	0.001
PSA at PSMA PET	0.026	0.02
p T stage	0.98	0.98
Gleason Score	0.91	0.91
Surgical margins	0.80	0.80

Table 3. Comparison of clinical variables between men with a treatment response to SRT and men who did not have a PSA response to SRT.

	All patients	Treatment response to SRT	No Treatment response to SRT	p value
PSA at PSMA PET	0.28 ± 0.19	0.24 ± 0.15	0.35 ± 0.25	0.01
PSMA PET result				
Negative/ Local	63/99	52/63	11/63	0.002
Lymph nodes/ distant	36/99	19/36	17/36	
pT stage at RP				
T2	27	19/27	8/27	ns
T3	65	47/65	18/65	
Gleason Score				
6-7	72	53/72	19/72	ns
8-9	27	18/27	9/27	
Surgical Margins				
Positive	35	25/35	10/35	ns
Negative	58	42/58	16/58	
Radiation Therapy				
Fossa alone	49	38/49	11/49	0.007
Fossa + Nodes	44	32/44	12/44	
Distant SBRT	6	1/6	5/6	