Journal of Nuclear Medicine, published on June 25, 2015 as doi:10.2967/jnumed.115.160382

Title Page

Prospective comparison of the detection rate of ^{18}F-Fluoromethylcholine and ^{68}Ga-PSMA-HBED PET/CT in men with prostate cancer with rising PSA post curative treatment, being considered for targeted therapy.

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ABSTRACT:

In prostate cancer (PCa) and biochemical failure following therapy, current imaging techniques have a low detection rate at PSA levels at which targeted salvage therapy is effective. ^{11}C-Choline or ^{18}F-Fluoromethylcholine (FMC), though widely used, have poor sensitivity at low PSA levels. ^{68}Ga-PSMA-HBED (PSMA) has shown promising results in retrospective trials. Our aim is to prospectively compare detection rates of PSMA versus FMC PET/CT in men initially managed with either radical prostatectomy (RP), radiation treatment (RT) or both, being considered for targeted therapy.

Methods: A sample of men with rising PSA following treatment, eligible for targeted treatment, was prospectively included. Patients on systemic treatment were excluded. PSMA, FMC PET/CT and diagnostic CT were undertaken in all patients sequentially between January and April 2015, and assessed by blinded experienced readers. Scan results and management impact changes, together with histological follow-up when feasible, were documented.

Results: 38 patients (pts) were enrolled. 34/38 pts (89%) were post-RP, 4/38 pts (11%) were post-RT. 12/38 pts (32%) had salvage RT after primary RP. Mean PSA was 1.74 ± 2.54 ng/ml. 68% of pts (26/38) had a positive scan, 32% (12/38) were negative at both tracers. Of the 26 positive pts, 54% (14/26) were positive on PSMA alone, 42% (11/26) on both FMC and PSMA and only 4 % (1/26) on FMC alone.

With PSA <0.5ng/ml, PSMA detection rate (DR) was 50% vs. 12.5% for FMC. At PSA between 0.5-2.0 ng/ml, DR was 69% for PSMA vs. 31% for FMC, and at PSA >2.0, DR was 86% for PSMA vs. 57% for FMC. On lesion-based analysis, PSMA detected more lesions than FMC (59 vs. 29, $p < 0.001$). The TBR in positive scans was higher in PSMA than in FMC (28.6 for PSMA vs 9.4 for FMC, $p<0.001$). There was a 63% (24/38 pts) management impact, 54% (13/24 pts) due to PSMA imaging alone.

Histological follow-up was available for 9/38 pts (24%), and 9/9 PSMA positive lesions were consistent with Pca (PSMA True Positive). The one lesion positive on FMC and negative on PSMA resulted at biopsy as a false positive of FMC (PSMA true negative).

Conclusion: In patients with biochemical failure and low PSA, PSMA demonstrated a significantly higher detection rate with a high overall management impact.

Keywords: ^{18}F-fluoromethylcholine; ^{68}Ga-PSMA ; Molecular Imaging; PET/CT; Prostate Cancer; Prostate specific membrane antigen

Total word count: 4328

INTRODUCTION:

Despite advances in surgical technique and radio-therapeutic delivery, a significant proportion of men with prostate cancer will fail initial curative therapy [*1*]. In those men with biochemical failure following initial therapy, current available imaging techniques [*2,3*] have a low detection rate at the levels of PSA at which targeted salvage therapy has optimal effect. With regards to PET/CT, while ^{18}F-Fluoromethylcholine (FMC) [*4*] and ^{11}C-Choline [*5*] remain the best validated imaging tracer agents for the detection of recurrent Pca [*6,7*], they have significant limitations that preclude their effective use in patients with low PSA [*8*]. Recent retrospective data on the novel PET tracer agent Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)](PSMA) has demonstrated promising sensitivity and specificity for the detection of PCa in the biochemical recurrence setting [*9*], and suggest that it is likely to be more sensitive than FMC or ^{11}C Choline for the assessment of systemic spread in men with Pca [*10,11*]. This promising new PET tracer relies on the hyper-expression of Prostate specific Membrane Antigen (PSMA, a trans-membrane folate hydrolase) on the surface of PCa cells. This over-expression of PSMA has been demonstrated both locally and in metastatic lesions within bone, lymph nodes and soft tissue [*12,13*]. The aim of this imaging study is to prospectively compare detection rates and management impact of PSMA PET/CT and FMC PET/CT in patients with PCa and low detectable PSA relapse following curative therapy.

MATERIALS AND METHODS:

Study Design and Data Collection: Thirty-eight men diagnosed with PCa not yet on systemic therapy with rising PSA following radical prostatectomy (RP), radiotherapy (External beam or other) or both, being actively considered for further targeted therapy were enrolled into the trial. All patients enrolled in the trial were being considered for targeted treatment, and had had no target identified for treatment through clinical examination or imaging. All patients on hormonal or systemic treatment were excluded. Data on age, previous therapy, time since therapy, initial pathology (including T stage and Gleason), PSA double time (PSAdt), PSA at the time of scanning and prior imaging was collected at enrolment. The trial was approved from the Institutional Human Research and Ethics Committee and informed consent was obtained from all participating patients.

Scan Acquisition: Both the FMC and PSMA were produced on-site with a GLP compliant procedure using a TRASIS® automated radio-pharmacy cassette. Radio pharmacy quality control was undertaken using a high-pressure liquid chromatography method.

All patients underwent an FMC and then a PSMA PET/CT plus a diagnostic contrast abdomen pelvis CT (CT) within 30 days. The diagnostic CT was embedded within the attenuation correction CT for the clinically indicated FMC scan, but was separately reconstructed by standard CT methods and separately read for the purposes of the study.

Routine clinical protocol was followed (3.5Mbq/kg dose, 10 minutes dynamic pelvic acquisition + 20 minutes static whole body acquisition for FMC and 2.0Mbq/Kg dose, with whole body scanning 45 minutes after injection for ^{68}Ga-PSMA). In all scans, whole body images were acquired from vertex to knees.

All PET CT imaging was undertaken using a Phillips® Ingenuity TOF – PET / 64 slice CT scanner. For the PSMA PT CT, a non-contrast-enhanced CT scan was performed 45 minutes post tracer injection using the following CT parameters: slice thickness of 2 mm, increment of 2 mm, 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. For FMC PET CT scans, a low-dose and modulated diagnostic CT with IV contrast was performed. The initial low-dose CT was acquired immediately prior to injection of F18-FMC using the following parameters: slice thickness of 2 mm, increment of 2 mm, soft tissue reconstruction kernel, 120 keV and 50 mAs, pitch of 0·828, 600 mm FOV and a 512 matrix. Injection of F18-FMC was performed simultaneously with the PET acquisition of 1 bed position for 10 minutes, acquired in list mode to obtain dynamic reconstruction. Immediately after, a modulated diagnostic CT with intravenous contrast whole body (vertex to mid-thighs) was performed with the following parameters: slice thickness of 2 mm, increment of 2 mm, soft tissue reconstruction kernel, 120 keV and 50-350 mAs, pitch of 0·828, 600 mm FOV and a 512 matrix. The whole body PET was then acquired for 2 minutes per bed position. For both PSMA and FMC Scans, the emission data were corrected for randoms, scatter and decay using Phillips® Body-dynamic.xml and Body.xml reconstruction protocol. All images were viewed and reported using Phillips® Fusion Viewer.

Image Interpretation: PET Images were interpreted by two experienced nuclear medicine physicians blinded to the subjects clinical and imaging results. Data for both the FMC and PSMA scans were analyzed visually and semi-quantitatively. Visual analysis included a four-point certainty scoring scale, as well as site and size of lesions. Semi-quantitative analysis was undertaken using an automated standardized maximum uptake value (SUV max) for both FMC and PSMA. No direct comparison was attempted. Instead, tumor to background ratio's (TBR) were determined for each lesion on both the PSMA and FMC images. The TBR was established by placing a two-dimensional region of interest (ROI) in the pelvic region and by measuring the SUV max of

background fat within the area. This value was then used as denominator for the SUV max of the lesion, resulting in the TBR. The diagnostic CT was interpreted separately by an experienced radiologist blinded to the PET results and the patient's clinical information.

Follow-up and Patient Management: Treating physicians were asked to report on the management plan prior and after each of the PET scans. Change of management after the FMC and PSMA results were classified as none, minor (change in delivery or site of the selected treatment) or major (change of selected treatment). Detailed questions addressing the type of management undertaken in each patient based on the imaging results and whether PSMA had a super-added management impact over FMC were posed. All clinical data, with the super-added value of imaging were considered by treating physicians in defining further treatment. Histopathology follow-up was gathered when available.

Statistical Analysis: A McNemar test was used to analyze scan positivity at different PSA intervals (0-0.5; 0.5-2.0; 2.0-12.0). Pearson Correlation and Stepwise Regression analysis were used to identify determinants of scan positivity, PSA at scan, PSAdt, Gleason Score, Age, initial treatment and years from treatment were included in the analysis. Wilcoxon signed-rank test was used for lesion-based analysis and management impact analysis. Two-tailed, paired t-test assuming unequal variance was used to analyze and compare (TBR) ratios between scans. PSAdt was calculated only in patients with PSA>0.2 according to standard formulas, based on ≥ two PSA values separated by ≥ 3 months within 1 year after recurrence and no adjuvant radiation or hormonal therapy before recurrence. Statistical analysis was carried out with SPSS v. 21 (SPSS INC., Chicago, Ill).

RESULTS:

A total of 38 patients (pts) with rising PSA post therapy were enrolled in the study (Table 1). Primary treatment was RP in 34/38 pts (89%) and radiotherapy in 4/38 pts (11%). 12/38 (39%) had undergone salvage radiotherapy following RP. Mean PSA was 1.72 ng/ml (range: 0.04-12ng/ml), and 29/38 (80.6%) pts had a PSA ≤ 2.0 ng/ml, at the time of imaging. Mean PSAdt was 15.6 months (range: 2.6-111.2months), calculated for 31 patients only due to insufficient data or low absolute values of PSA in the remaining patients.

Overall, 26/38 (68%) pts had a positive scan result. Of these positive results, 54% (14/26) were positive on PSMA alone, while 42% (11/26) were positive on both FMC and PSMA. Only 1/26 (4%) was positive on FMC

alone (subsequently confirmed as a false positive on biopsy). Overall, 12/38 scans (32%) were negative for both tracers.

The most significant predictor of a positive PET scan for both FMC and PSMA was PSA at the time of imaging ($p < 0.001$). In men with PSA < 0.5ng/ml, PSMA detection rate was 50% vs. 12.5% for FMC ($p=0.03$). At PSA 0.5-2.0ng/ml, 71% were PSMA positive vs. 36% for FMC ($p=0.02$) and with PSA >2.0ng/ml 88% of PSMA scans were positive vs. 63% in the FMC group (Table 2). Additionally, PSMA identified a higher number of lesions at every PSA cohort when compared to FMC (Figure 1). PSMA detected a higher number of positive lesions than FMC (59 lesions vs. 29 lesions, $p < 0.001$). A higher percentage of lesions (Figure 2) were identified loco-regionally, in lymph nodes and in bone on PSMA. Local lesions occurred both in radiotherapy-treated (figure 3) and RP pts. Positive uptake in residual tissue of radiotreated prostate was detected in 1 FMC scan and 3 PSMA scans. For RP patients, Seminal vescicle uptake was detected in 3 scans on PSMA solely (FMC - , PSMA +). Finally, one RP patient was positive on PSMA and negative on FMC within the prostate bed. Qualitative evaluation of the PET scan and the 2mm thick contrast CT were used to differentiate between urinary activity and positive uptake within the pelvis. With lesion-based analysis, only PSA at time of scan was significantly correlated with total number of lesions on PSMA ($p<0.001$) or FMC ($p =0.002$). No significant statistical correlation was identified between PSAdt or Gleason score with either FMC or PSMA detection rate. On diagnostic contrast CT, no lesions were considered definitely positive.

Following imaging, there was an overall 63% (24/38), (Figure 4) major or moderate management impact, of which 54% (13/24) were attributable to the findings on PSMA imaging alone (Figure 5). In the 11/24 (46%) patients who had a management impact on both FMC and PSMA, the PSMA scan showed additional change in management in 4/11 cases (36%). There were no management changes based on the results from FMC alone. In summary, PSMA imaging accounted (either alone or in concordance with FMC) for all the management impact in our patient cohort (24/38 for PSMA vs. 11/38 for FMC, $p<0.001$). Higher TBR on PSMA in comparison to FMC was identified in positive scans (figure 6). The mean TBR for FMC was 9.4, while mean TBR for PSMA was 28.6 ($p<0.001$). Mean value of fat uptake was similar in the two scans (SUV max 0.3 for FMC and SUV max 0.26 for PSMA.)

Histopathologic confirmation was obtained in 9/38 (24%) patients with positive findings on PSMA or FMC. Confirmation of true positive lesions was obtained in 9/9 biopsied PSMA positive lesions, and in 2 FMC positive

lesions (1 lesion was true positive and the second lesion a false positive for FMC (and MRI) and true negative for PSMA) .

DISCUSSION:

Our key finding is that PSMA has a higher detection rate than FMC at all PSA levels in pts with a rising PSA post curative treatment. This was most evident at lower PSA values (<0.5 ng/ml), where 50% of pts had a positive scan result on PSMA. The high sensitivity of this novel tracer at low PSA levels has important implications for the management of patients with a rising PSA following therapy with curative intent (RP or RT)[*14*].To date, there is a paucity of published literature regarding PSMA in humans. Although three retrospective studies[*9,11,15*] demonstrate promising results, no prospective studies have been published. The diagnostic value of ^{11}C-Choline and FMC is well documented[*6,16*] and these agents are increasingly being used in the biochemical relapse setting[*17*]. However both tracers suffer from a lack of sensitivity at low PSA levels[*8*], and are not yet standardized[*18*].This study re-enforces the limited sensitivity of FMC at low PSA levels. However, our results suggest that Ga^{68} PSMA may more effectively detect recurrent disease at low PSA levels. The value of treating recurrent PCa at low PSA levels have been recently outlined in European[*14*] guidelines and is associated with a reduced incidence of biochemical failure[*19*].

Currently men with biochemical relapse following RP often undergo salvage radiotherapy to the prostatic bed at low PSA levels even without significant findings at imaging. Hence it is no surprise that, as per the Stephenson nomogram[*20*], only about half these men are currently cured. Furthermore, salvage RT may cause harm in a small proportion of men. Therefore, the high sensitivity of Ga^{68} PSMA at low PSA levels demonstrated in this trial may be beneficial in the management of patients with early rising PSA following initial treatment. Based on the findings from this study, in the group of patients who would be

eligible for salvage prostate bed radiotherapy (PSA<1.0ng/ml), up to 75% (6/8) of PSMA positive patients in this PSA cohort had disease identified outside the prostate bed on PSMA alone. These patients would have failed the current clinical paradigm of either FMC guided or image blind salvage prostate bed radiotherapy.

The superior sensitivity of PSMA compared to FMC has been previously demonstrated in a single retrospective study[*11*], although there are important differences in the study population. While 78% of patients in our study had a serum PSA < 2.0, the previous retrospective study included men with higher PSA values (mean 11.1) and was less able to demonstrate the additional benefit of PSMA compared to FMC at low PSA levels. However,

despite the different patient cohorts in the 2 studies, both demonstrated a statistically higher total number of lesions detected on PSMA compared to FMC in all positive patients.

Consequent to our findings, when undertaken at low absolute PSA levels, the management impact of PSMA was exceptionally high. This is for several reasons. Firstly, in those found to have tumour bed recurrence, potentially curative and directed salvage RT was delivered. Secondly, in those with oligo-metastatic disease, targeted treatments such as SBRT or LND were administered. Finally those with metastatic disease on PSMA (or less likely, FMC) were commenced on systemic treatment and spared salvage RT to the prostatic fossa.

This study demonstrates a significantly higher TBR for PSMA compared to FMC. Lesions identified on PSMA were more than twice as intense compared to background tissue than FMC. The significantly higher TBR in PSMA allows easier identification of lesions even at very small sizes.

The major limitation of this trial is the lack of histopathological confirmation of all positive findings. Confirmation of diagnostic accuracy is impaired in the trial due to the small volume of individual lesions, and the high incidence of lymph node and bone recurrence inaccessible to biopsy. We were able to confirm true positive PSMA findings in all patients undergoing successful biopsy, and a false positive biopsy in an FMC positive (MRI positive) lymph node (PSMA negative). The aim of this trial was to assess the detection rate of these tracer agents at low PSA levels, rather than a diagnostic accuracy trial. Many of these patients with disease identified on PET/CT imaging will be undergoing targeted therapy as part of their routine clinical care. It is the intention of the investigators to continue long-term follow-up of this cohort of patients to document response to therapy and gain proxy diagnostic accuracy.

Histopathologic confirmation was obtained in only 24% of the pts. However, it is remarkable that 100% of the biopsied PSMA positive lesions were True positives, and that the single lesion positive to FMC and negative to PSMA was of reactive nature. While this study confirms a high detection rate for PSMA in men with low PSA, further prospective trials addressing sensitivity and specificity are urgently needed.

A further limitation of this trial is the small cohort of men enrolled. Despite this, it is impressive that, with such a small trial cohort there was a statistically significant difference in detection rates of PSMA compared to FMC at both a patient based and lesion based level. However, large, adequately powered prospective trials are needed to better evaluate PSMA.

Though previously reported in ^{11}C-Choline[*8,21*] and more recently in ^{68}Ga-PSMA [*22*]publications, our study did not find any statistically significant correlation between PSAdt, Gleason Score and positivity of FMC or PSMA

scans. This is probably related to the low mean PSA value of this patient cohort (<2.0 ng/ml), and the small number of men enrolled, that allowed calculation of the PSAdt for only 31 patients therefore limiting statistical analysis for this variable.

Development of Ga68 PSMA is at an early stage. Currently there are a number of different PSMA ligands in clinical use and research development [*23*]. This makes extrapolation of this data across all clinical sites problematic. Further product development, comparative trials, and harmonization of tracer utilization are urgently needed.

CONCLUSIONS:

In patients with rising PSA being evaluated for curative intent therapy with low PSA levels, ^{68}Ga-PSMA-HBED PET/CT demonstrated a significantly higher detection rate for recurrent disease than ^{18}F-Fluoromethylcholine, and impacted on management in a high proportion of subjects imaged. While confirmation is required in larger trials, this prospective trial suggests ^{68}Ga-PSMA-HBED PET/CT will be an effective imaging tool for the early detection of PCa recurrence.

AKNOWLEDGMENTS:

St Vincent's Prostate Cancer Centre and the Australian Department of Health and Ageing through the Australian Prostate Cancer Research Centre – New South Wales (APCRC-NSW) for funding.

Bibliography

1. Schwarz R, Graefen M, Krüll A. Therapy of treatment failure after curative treatment of prostate cancer. *EAU-EBU Updat Ser*. 2006;4:228-240.

2. Ménard C, Iupati D, Publicover J, et al. MR-guided prostate biopsy for planning of focal salvage after radiation therapy. *Radiology*. 2015;274:181-191.

3. Cochet A, Kanoun S, Humbert O, et al. [Multimodality MRI and PET for restaging prostate cancer after biochemical failure of the treatment]. *Cancer Radiother*. 2014;18:509-516.

4. Bauman G, Belhocine T, Kovacs M, Ward A, Beheshti M, Rachinsky I. 18F-fluorocholine for prostate cancer imaging: a systematic review of the literature. *Prostate Cancer Prostatic Dis*. 2011;15:45-55.

5. Fuccio C, Rubello D, Castellucci P, Marzola MC, Fanti S. Choline PET/CT for prostate cancer: main clinical applications. *Eur J Radiol*. 2011;80:e50-6.

6. Beheshti M, Haim S, Zakavi R, et al. Impact of 18F-choline PET/CT in prostate cancer patients with biochemical recurrence: influence of androgen deprivation therapy and correlation with PSA kinetics. *J Nucl Med*. 2013;54:833-840.

7. Castellucci P, Fanti S. Prostate cancer: Identifying sites of recurrence with choline-PET-CT imaging. *Nat Rev Urol*. 2015 Mar;12:134-5.

8. Mamede M, Ceci F, Castellucci P, et al. The role of 11C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level <0.5 ng/mL. *Clin Nucl Med*. 2013;38:e342-e345.

9. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the 68Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2014;42:197-209.

10. Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH. *Eur J Nucl Med Mol Imaging*. 2012;39:1085-1086.

11. Afshar-Oromieh A, Zechmann CM, Malcher A, et al. Comparison of PET imaging with a 68Ga-labelled PSMA ligand and 18F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2013;41:11-20.

12. Ross JS, Sheehan CE, Fisher H a G, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res*. 2003;9:6357-6362.

13. Rajasekaran A. Is prostate-specific membrane antigen a multifunctional protein? Am J Physiol Cell Physiol. 2005 May;288:C975-81.

14. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65:467-479.

15. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668-74.

16. Ceci F, Herrmann K, Castellucci P, et al. Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. *Eur J Nucl Med Mol Imaging*. 2014;41:2222-2231.

17. Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol. 2011;59:51-60.

18. Mottet N, Bellmunt J, Bolla M, et al. Reply to Stefano Fanti, Bernd Krause, Wolfgang Weber, et al's Letter to the Editor re: Nicolas Mottet, Joaquim Bellmunt, Michel Bolla, et al. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate C. *Eur Urol*. 2011;60:e39-e41.

19. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol*. 2007;25:2225-2229.

20. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol*. 2007;25:2035-2041.

21. Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [11C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2010;37:1106-1116.

22. Ceci F, Uprimny C, Nilica B, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging*. 2015. [Epub ahead of print]

23. Haberkorn U, Afshar-Oromieh A, Giesel F, et al. P8.01PSMA ligands for diagnosis and therapy of prostate cancer. *Ann Oncol*. 2015;26 Suppl 2:ii33.

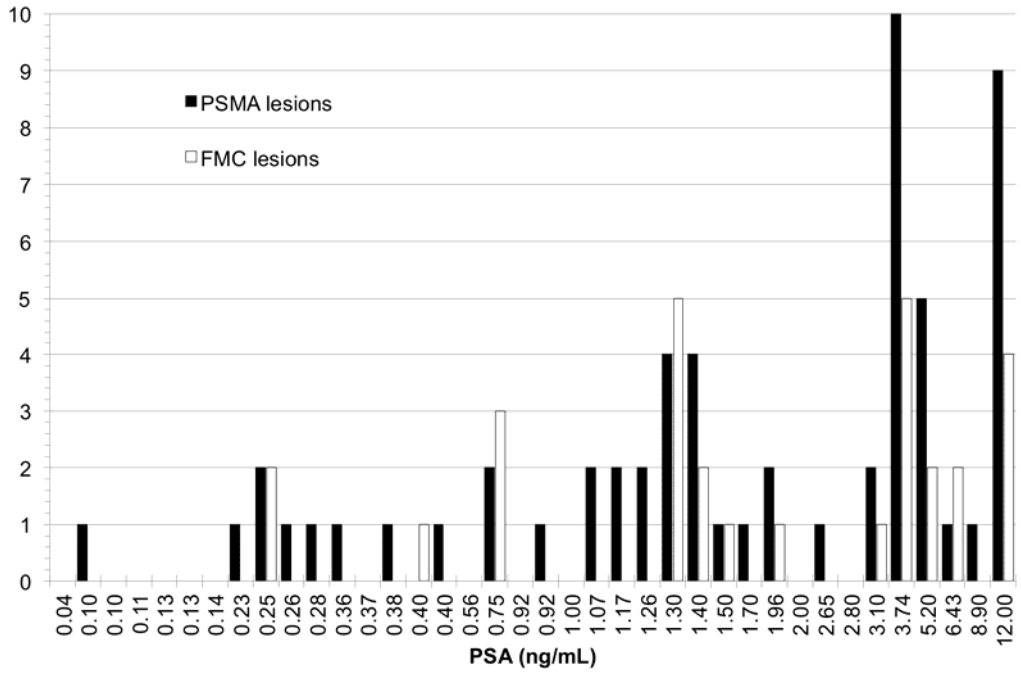

Figure 1

Total number of lesions detected for each patient with both FMC and PSMA, ranked by ascending PSA value.

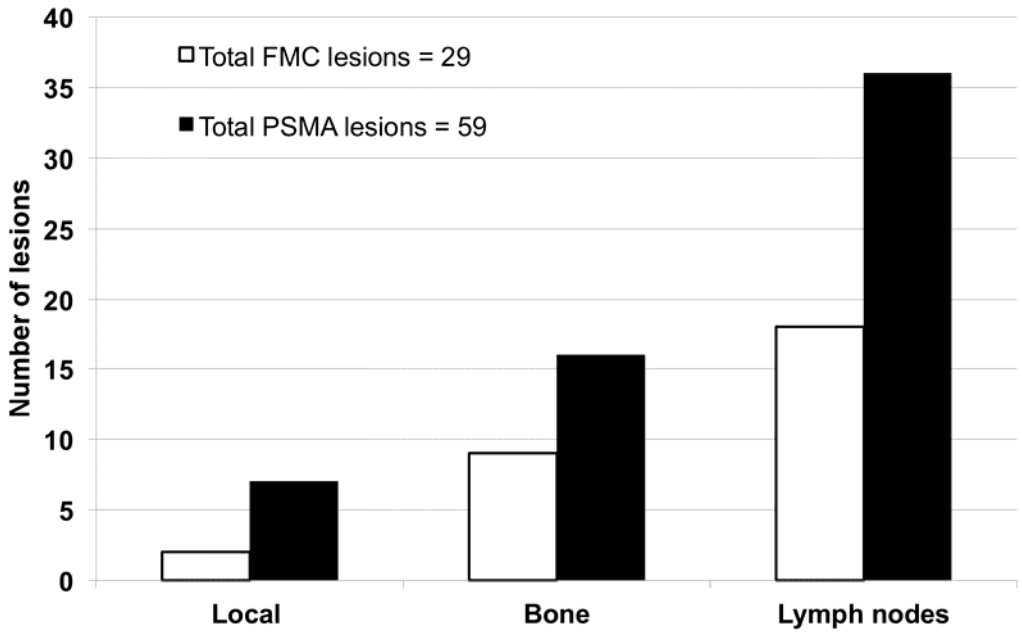

Figure 2

Total number of FMC and PSMA positive lesions per anatomical site, including prostate bed or seminal vesicles (local), bone or lymph nodes.

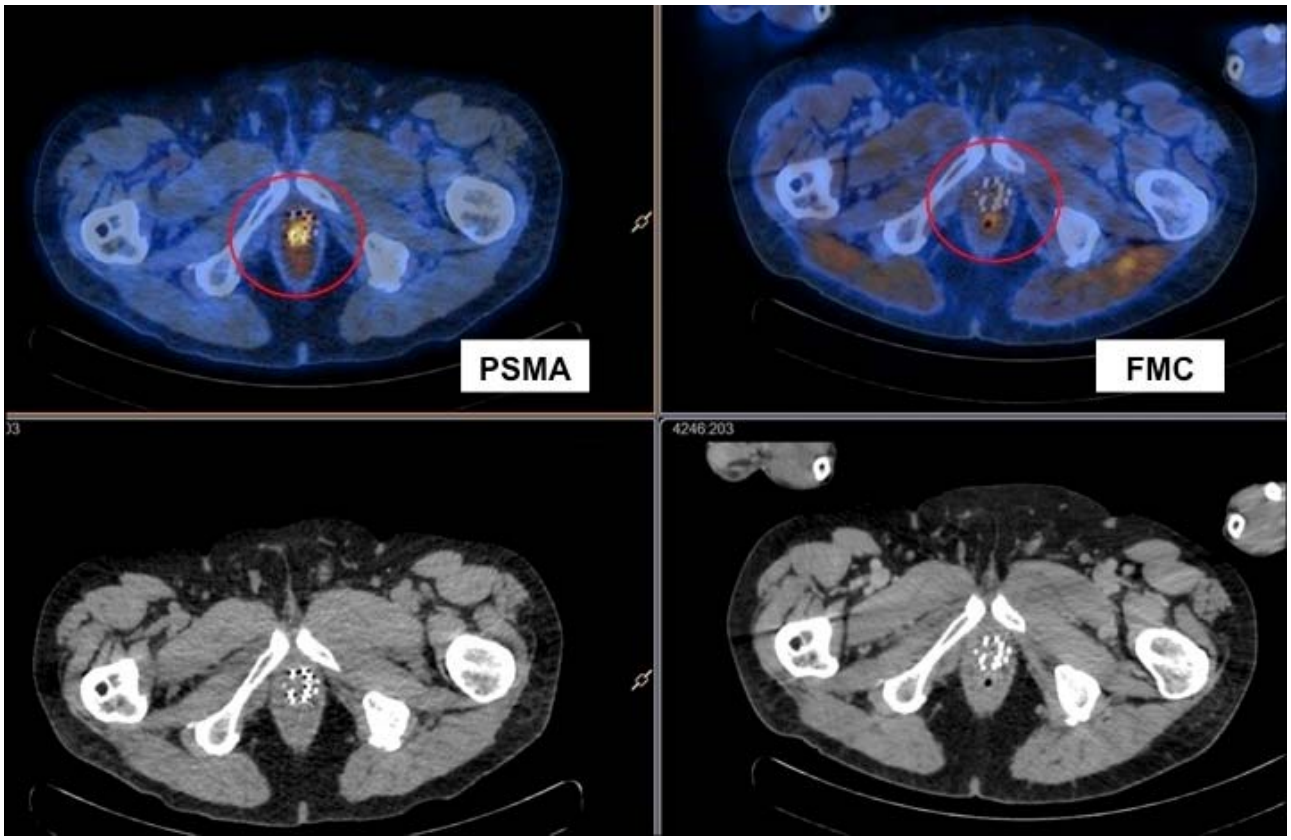

Figure 3: 70 y.o male with Gleason 7 prostate cancer treated with Rtx. Presents with a rising PSA (8.9) and a PSAdt of 9.5 months. The FMC scan was negative, while the PSMA scan demonstrated intense uptake in the prostate (SUVmax=4.5). Subsequent biopsy confirmed local recurrence.

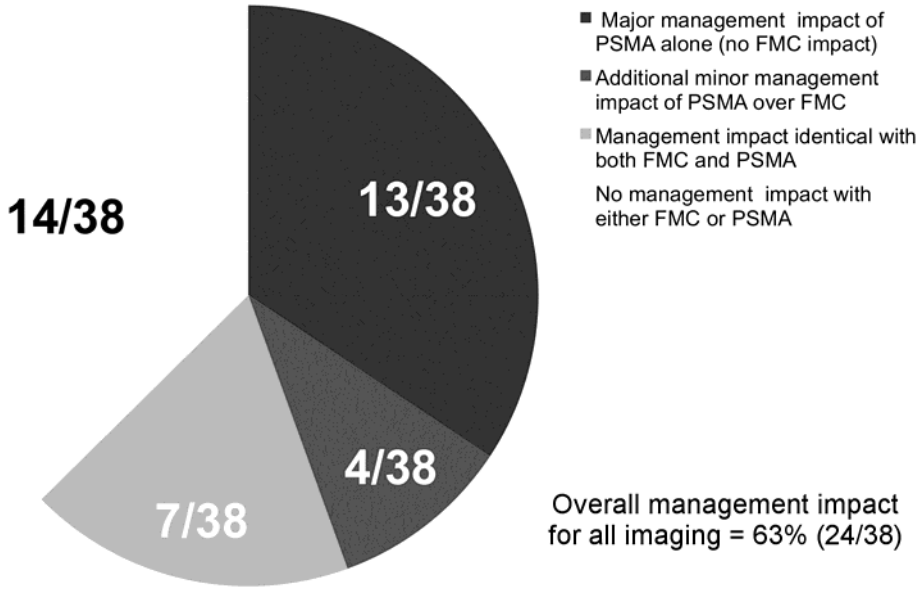

Figure 4

Management Impact Chart

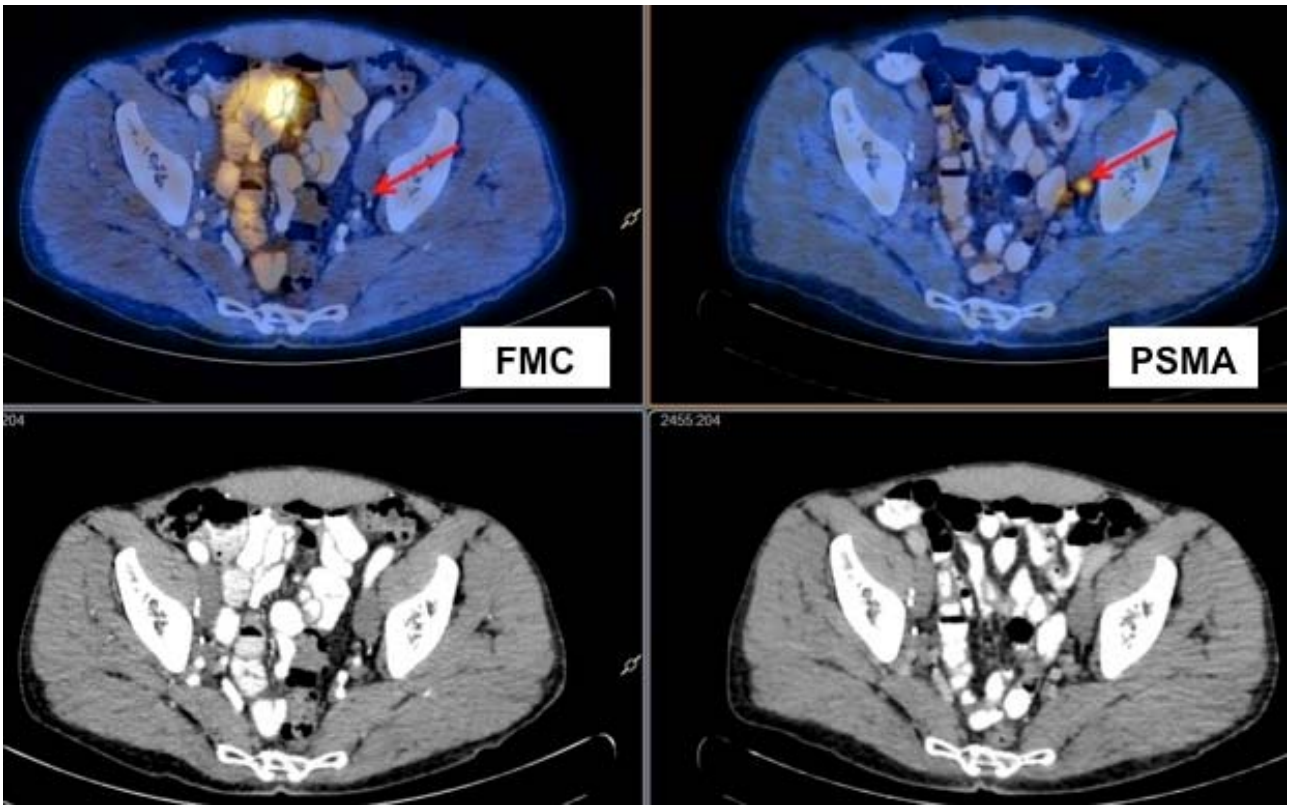

Figure 5: 62 y.o male with Gleason score 7 prostate cancer treated with RP and salvage RTx presenting with a rising PSA (0.4) and a PSAdt of 8 months. The FMC PET/ CT scan resulted negative, while the PSMA PET/CT scan demonstrated a single positive left obturator lymph node (SUVmax=3.7). Subsequent biopsy confirmed prostate cancer recurrence.

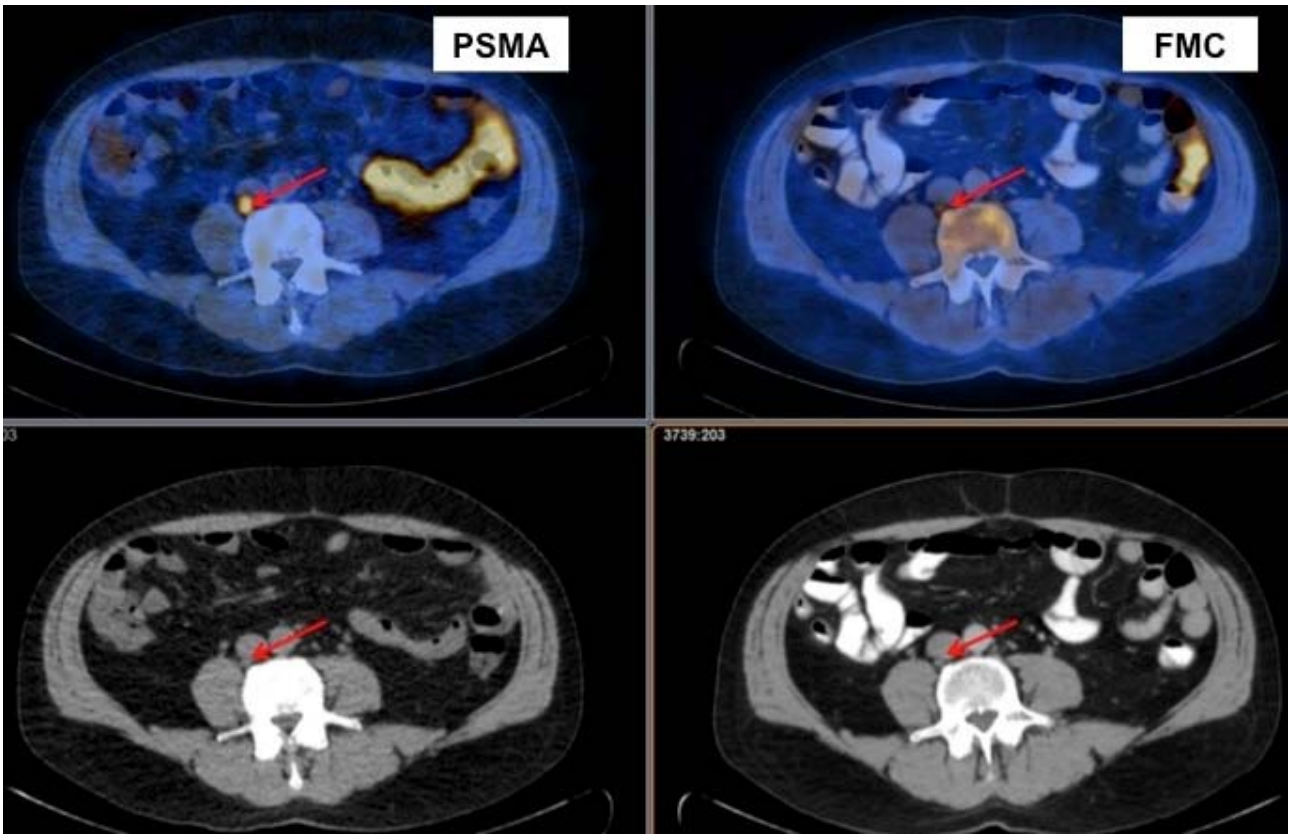

Figure 6: 70 y.o male with Gleason 7 prostate cancer treated with RP, presents with a rising PSA (12.0) and a PSAdt of 5.8 months. Both FCH and PSMA are positive for nodal disease (4 positive lesions on FMC and 9 on PSMA). However PSMA shows a higher TBR than FMC (25.0 vs 7.0 in this image of a positive para-caval lymph node). Biopsy confirmed nodal recurrence of prostate cancer.

Table 1

Patients characteristics and pre-imaging data.

Patients Characteristics	**Mean** ± CI (min-max)
Age (years)	68 (54-81)
PSA at time of scan (ng/dl)	1.72 ± 2.54 (0.04-12.0)
PSAdt (months)	15.6 ± 22.1 (2.6-111.2)
Initial treatment	***n* (%)**
Surgery (Radical Prostatectomy)	34/38 (89%)
Radiotherapy (EBRT, Brachytherapy)	4/38 (11%)
Surgery + Salvage Radiotherapy	12/38 (32%)
PSA at diagnosis (ng/dl)	9.7 ± 4.9 (2.8-20.2)
Years since diagnosis	7 (1-18)
Gleason Score	***n* (%)**
6-7	23/38 (61%)
8-9	15/38 (39%)
Risk group (EAU guidelines)	***n* (%)**
Intermediate	11/38 (24%)
High	27/38 (76%)

Table 2

Detection rates of FMC and PSMA at different PSA intervals

PSA group	Positive FCH scan	Positive PSMA scan	pValue
<0.5 ng/ml	12.5% (2/16)	50% (8/16)	0.03
0.5-2.0 ng/ml	36% (5/14)	71% (10/14)	0.02
>2.0 ng/ml	63% (5/8)	88% (7/8)	0.18
Tot.	**32% (12/38)**	**66%(25/38)**	<0.001