Published in final edited form as:

J Nucl Med. 2016 July ; 57(7): 1058–1064. doi:10.2967/jnumed.115.169177.

Prediction of PSA progression in castrate-resistant prostate cancer based on treatment-associated change in tumor burden quantified by ^{18}F-fluorocholine PET/CT

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Abstract

Metabolically active tumor volume (MATV) measurements can be applied to ^{18}F-fluorocholine positron emission tomography/computed tomography (PET/CT) to quantify whole-body tumor burden. This study evaluates the serial application of these measurements as systemic treatment response markers and predictors of disease progression in patients with castrate-resistant prostate cancer (CRPC).

Methods—Forty-two patients completed sequential ^{18}F-fluorocholine PET/CT scans before and 1 to 3 months after starting treatment for CRPC. Whole-body tumor segmentation was applied to determine net MATV from each scan. Changes in net MATV were evaluated as predictors of time to PSA progression by Kaplan-Meier and proportional hazards regression analysis.

Results—Treatments consisted of chemotherapy in 16 patients, anti-androgens in 19 patients, ^{223}Ra-dichloride in 5 patients, and sipuleucel-T in 2 patients. A significant MATV response (defined as a 30% or greater decrease in net MATV) was observed in 20 patients based on in-treatment PET/CT performed an average (median) of 51 (49) days into treatment. Significantly longer times to PSA progression were observed in patients that exhibited a MATV response (418 days vs. 116 days, $p = 0.0067$). MATV response was associated with a hazard ratio of 0.246 ($p = 0.0113$) for PSA progression, which remained significant when adjusted for treatment type.

Conclusion—Significant changes in whole-body tumor burden can be measured on ^{18}F-fluorocholine PET/CT over the course of contemporary treatments for CRPC. In this study, these changes were found to be predictive of PSA progression as a potential surrogate marker of

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treatment outcome. Because ^{18}F-fluorocholine PET/CT can also be used for localizing resistant tumors, this modality can potentially complement other measures of response in the precision management of advanced prostate cancer.

Keywords

fluorocholine; PET/CT; castrate resistant prostate cancer; treatment response; tumor volume

INTRODUCTION

Prostate cancer accounts for over 300,000 deaths annually worldwide, and mortality from this disease is increasing in some regions, including Eastern Europe, Russia, China, and Korea (1). Over two-thirds of prostate cancer cases are now diagnosed in developed countries, where patients are typically identified at an early stage and treated first with prostatectomy or radiation therapy (1,2). For those patients presenting with metastatic disease or for those in whom the disease recurs after these primary treatments, hormonal therapy is readily available, delaying disease progression until the development of CRPC (2).

Effective agents for treating CRPC have fortunately expanded over the past decade to include chemotherapy, as well as advanced anti-androgens, immunotherapy, and recently, radiopharmaceuticals (2). However, these agents may only improve survival by weeks or months, and precision management of CRPC remains difficult because of the scarcity of tools for ascertaining tumor response in real-time (3,4). Although post-treatment declines in the level of PSA have been used in some prostate cancer clinical trials as surrogate markers of response (5), these “PSA response” measures have accounted for only a limited amount of the variation in treatment outcome in CRPC clinical trials (3,6). Because treatments for CRPC can also lead to clonal selection of tumors with down-regulated PSA expression (7), biomarkers that can complement PSA will be needed to not only advance drug development but also support the evolution of precision medicine in prostate cancer.

While conventional imaging modalities (eg. CT, magnetic resonance imaging, and bone scintigraphy) are useful for oncologic staging in prostate cancer, they are imperfect as treatment response biomarkers for CRPC because of their inherent limitations in quantifying therapeutic effects along two dominant metastatic routes in CRPC: the skeletal system and the lymphatic system (8). Molecular imaging, despite being more cumbersome than conventional imaging or serology, can reproducibly assess the skeletal system and other clinically relevant sites of disease activity in CRPC (4), allowing it to potentially complement other biomarkers while also helping to direct sequential treatments towards pockets of resistant disease.

One molecular imaging agent, fluorine-18 fluorocholine (^{18}F-fluorocholine) enables in-vivo characterization of choline metabolism using PET/CT. It has shown greater tumor avidity than ^{18}F-fluorodeoxyglucose (FDG) in both androgen-dependent and independent prostate cancer (9). Tissue uptake of ^{18}F-fluorocholine mirrors the initial steps of tissue phosphatidylcholine synthesis, which is often high in CRPC tumors, but can diminish upon exposure to chemotherapeutic agents such as docetaxel and cabazitaxel (10), as well as

newer agents like abiraterone (11), and ^{223}Ra dichloride (12). Recently, estimates of tumor burden based on net metabolically active tumor volume (MATV) measurements from ^{18}F-fluorocholine PET/CT were shown to have prognostic value in patients with CRPC (13). The objective of the present study is to determine whether treatment-associated changes in these measurements on sequential ^{18}F-fluorocholine PET/CT scans are predictive of treatment outcome in CRPC.

MATERIALS AND METHODS

Patients

This institutional review board approved prospective clinical research study was conducted in accordance with the Declaration of Helsinki and its amendments. Forty-five patients (18 prescribed docetaxel-based chemotherapy, 19 prescribed anti-androgens, 6 prescribed ^{223}Ra dichloride, and 2 prescribed Sipuleucel-T) were enrolled after providing their written informed consent to participate in this study. Study eligibility was based on (a) age over 18 years, (b) an initial histopathology diagnosis of prostate cancer, (c) fulfillment of clinical criteria for CRPC as defined by 2 rising PSA measurements of 2.0 ng/mL or higher while on complete androgen blockade for longer than 3 months, (d) planned treatment for CRPC under the supervision of a medical oncologist or urologist, and (e) life expectancy of more than 12 weeks. Patients who could not tolerate PET/CT imaging, and those with other malignancies diagnosed in the past 3 years, except for basal cell carcinoma or superficial transitional cell carcinoma of bladder, were excluded.

Patients were treated in a community setting with all enrollment and clinical follow-up performed between August 2009 and August 2015. All patients underwent baseline ^{18}F-fluorocholine PET/CT before starting treatment for CRPC. A second in-treatment ^{18}F-fluorocholine PET/CT scan was scheduled before the mid-point of treatment, at approximately 1–3 months corresponding to clinic visits after the second chemotherapy treatment cycle, anti-androgen therapy follow-up, or the second dose of ^{223}Ra dichloride. All treatment decisions were made independently of the study by a medical oncologist or urologist.

Radiopharmaceutical Synthesis

An 11-MeV cyclotron (RDS 111; Siemens Medical Solutions) was used to produce fluorine-18. Radiotracer synthesis was performed by fluorination of ditosylmethane followed by alkylation of the intermediate with dimethylethanolamine using an automated chemical process control unit (CPCU; CTI/Siemens) (14). Each radiopharmaceutical batch passed standard assays for radiochemical purity, radionuclide identity, lack of pyrogenicity, and chemical purity prior to use. The final radiochemical purity was 99%.

PET/CT Imaging

All patients refrained from eating and drinking for at least 3 hours before undergoing PET/CT. Imaging was performed using a Gemini TF-64 PET/CT scanner (Philips Healthcare) beginning with CT scanning from the mid thigh to the skull with the patient in the supine position. The 64-channel helical CT scanning parameters were 120 kV, 50 mA/

slice, a rotation time of 0.75 s, and slice thickness and interval of 5.0 mm. No iodinated contrast agents were given. At approximately 10–15 minutes following the intravenous injection of a 2.6 MBq/kg (0.07 mCi/kg) dose of ^{18}F-fluorocholine, sequential static emission scans were obtained from the mid thigh to the skull at 2 minutes per section. Image reconstruction was completed using a vendor-supplied maximum-likelihood expectation maximization process using CT data for attenuation correction.

Image Analysis

Lesion segmentation and MATV measurements were performed as described in a previous publication (13). Briefly, tumor lesions on ^{18}F-fluorocholine PET/CT images were classified by consensus of a reader with significant experience (SAK or MNC) and a reader with 3 weeks of training (JL) in ^{18}F-fluorocholine PET/CT interpretation. Lesions were classified according to their anatomical localization in the following categories: the prostate gland, a visceral organ, lymph node, or skeleton. Only lesions with a maximum standardized uptake value (SUV) of 3.0 or greater (exceeding 2 standard deviations above the normal-marrow SUV) were included for MATV measurement. SUV was calculated as measured voxel activity divided by injected radioactivity normalized to body weight. The MATV for each lesion was computed using a semi-automated segmentation algorithm. A volume of interest was generated around the voxel corresponding to the maximum SUV of the lesion, encompassing all contiguous voxels with SUV exceeding 40% of the lesion maximum SUV based on a previous study (13). A measure of activity distribution within the volume, termed total lesion activity (TLA), was also calculated by taking the product of lesion mean standardized uptake value and MATV. Measures reflecting the net tumor burden on each scan were defined as the sum of all MATVs (net MATV) and the sum of all TLAs (net TLA). Indexes of whole-body tumor response were then calculated as the percentage-change in these measures between baseline and in-treatment ^{18}F-fluorocholine PET/CT scans. A $MATV_{30\%}$ response was defined prospectively as a 30% or greater decline in net MATV from the pre-treatment net MATV, and a $TLA_{30\%}$ response was defined prospectively as a 30% or greater decline in net TLA from the pre-treatment net TLA.

PSA Measurements

Clinical PSA levels measured from the start of treatment over the period of follow-up were recorded. Time to PSA progression was calculated as the number of days from the start of treatment to the date of the first PSA test result that represented a 30% or greater increase from the PSA nadir, confirmed on the basis of repeated PSA measurements. To explore relationships between changes in PSA and changes in tumor indexes on ^{18}F-fluorocholine PET/CT, the percentage change in PSA levels within 15 weeks of starting treatment was calculated, using a 50% or greater decrease in the PSA level as a pre-defined definition of PSA response based on Prostate Cancer Working Group guidelines (5).

Statistical Analysis

Kaplan-Meier analysis was used to compare rates of PSA progression in patients stratified by $MATV_{30\%}$ response or $TLA_{30\%}$ response, with differences in progression curves assessed using the Wilcoxon and log-rank tests. Cox proportional hazards regression was used to evaluate the individual effects of age, baseline pre-treatment PSA, early changes in PSA, and

type of treatment on time to PSA progression. Multivariate analysis was used in a limited fashion to explore the interactions between indexes derived from PET/CT and another variable. Differences between serial measurements were assessed by Wilcoxon signed-rank test. Unpaired differences were assessed by the Mann-Whitney U test. Differences across categories were assessed by analysis of variance using the Kruskal-Wallis test. Correlations were assessed using Spearman's correlation. A probability of < 0.05 was considered statistically significant. All statistical tests were two-sided and performed using SAS 9.4 and JMP Pro 11 (SAS Institute Inc., Cary, NC).

RESULTS

Clinical Characteristics

Forty-five sequential patients were enrolled to the study. However, two patients experienced delays in treatment following the baseline PET/CT scan and were excluded, and one patient was found on the baseline PET/CT scan to have intracranial metastases leading to cancellation of planned treatment. Therefore, data from only 42 completed patients were included in the present analysis. The mean (median, range) duration of clinical follow-up was 784 (653, 180 to 2068) days. The clinical characteristics and treatments of the 42 completed patients are summarized in Table 1. There were no statistically significant differences in baseline patient characteristics across treatments (Table 2).

PSA measurements

Changes in PSA levels measured within 15-weeks of treatment initiation ranged from a 100% decrease to a 1648% increase (with a median 8% decrease). A PSA response based on the Prostate Cancer Working Group definition was noted in 20/42 patients. There was moderate correlation between percentage change in PSA level and percentage change in net MATV ($r = 0.71$, $p < 0.0001$), as well as percentage change in net TLA ($r = 0.73$, $p < 0.0001$). However, an increase in net MATV/TLA coincided with a decrease in PSA level in 5 patients, and a decrease in net MATV/TLA coincided with an increase in PSA level in 3 patients. On follow-up, PSA progression was identified in 17 patients with a mean (median, range) time to progression of 142 (116, 62 to 418) days. Early PSA progression was noted in 2 patients at 62 and 76 days in accordance with Prostate Cancer Working Group criteria for treatment discontinuation based on clinical progression (5).

^{18}F-fluorocholine PET/CT findings

The mean (median, range) interval from the baseline ^{18}F-fluorocholine PET/CT to the start of treatment was 4 (1, 0 to 26) days. The mean (median, range) time interval between the start of treatment and the in-treatment ^{18}F-fluorocholine PET/CT was 51 (49, 21 to 98) days. Twenty patients met the study criteria for a $MATV_{30\%}$ response. The same 20 patients also met study criteria for a $TLA_{30\%}$ response. Because the distribution of patients with $MATV_{30\%}$ responses is the same as the distribution of patients with $TLA_{30\%}$ responses, the predictive power of either index will be the same, and thus "MATV response" will generically refer to $MATV_{30\%}$ response or $TLA_{30\%}$ response in discussing these results. The anatomical distributions of lesions detected on the baseline and in-treatment ^{18}F-fluorocholine PET/CT scans are summarized in Table 1. Examples of the changes in tumor

activity and MATV that can be quantified on ^{18}F-fluorocholine PET/CT are shown in Figures 1, 2, and 3.

Analysis of PSA Progression

Time to PSA progression differed significantly between patients with and without a MATV response (median 418 days vs. 116 days, respectively, log-rank p = 0.0067, Wilcoxon p = 0.0138). On univariate analysis, MATV response was associated with a significantly lower risk of PSA progression (hazard ratio of 0.246, p = 0.0113) (Figure 4), while age, baseline PSA level, PSA response, and the distribution of lesions on PET/CT were not significantly associated with PSA progression (Table 3). However, chemotherapy treatment was associated with a relatively lower risk (hazard ratio 0.309, p = 0.0333) of PSA progression, while anti-androgen treatment was associated with a relatively higher risk (hazard ratio 5.650, p = 0.0236). MATV response remained significant as a predictor of PSA progression on multivariate analysis adjusted for treatment type (Table 3).

DISCUSSION

Over the past decade, a variety treatments directed toward different cellular targets and mechanisms have emerged to improve the survival of men with CRPC (2). However, assessing treatment efficacy in CRPC remains a significant clinical challenge to the present day (3–5,8). In the present study, whole-body indexes of tumor response derived from ^{18}F-fluorocholine PET/CT were evaluated as therapeutic predictors in patients undergoing contemporary management of CRPC. This study found that decreases in net MATV observed early in the course of treatments for CRPC were associated with significantly longer times to PSA progression independent of other clinical characteristics including the type of treatment that was given. This observation supports ^{8}F-fluorocholine PET/CT as a potential independent predictor of treatment outcome in CRPC. ^{18}F-fluorocholine has been extensively studied for prostate cancer, and this study contributes to data supporting its usefulness across a variety of clinical applications that require accurate determination of metastatic spread (15). Because the changes that can be seen on ^{18}F-fluorocholine PET/CT in response to anti-androgens and ^{223}Ra have been previously documented (12,16), this report presents images from patients treated with docetaxel and sipuleucel-T as further examples of significant changes in disease pattern that can be seen in the course of treatment for CRPC.

Time to PSA progression was the main endpoint of this study for evaluating MATV response since increases in the PSA level after the post-treatment nadir (ie. PSA progression) have proven more reliable in predicting clinical outcomes in CRPC than acute changes in the PSA level following treatment initiation (ie. PSA response) (6,17–19). Nonetheless, tumor metabolism depicted by^{18}F-fluorocholine PET/CT was also evaluated in relation to early changes in PSA level. Early changes in PSA level were found to be moderately correlated with changes in tumor activity quantified on ^{18}F-fluorocholine PET/CT. These results were comparable to those of a previous study evaluating ^{11}C-choline for measuring therapeutic response to docetaxel in CRPC (20). Like this previous study, decreases in tumor activity on ^{18}F-fluorocholine PET/CT did not necessarily coincide with decreases in PSA level, and

in fact coincided with increasing PSA levels in some cases (example in Figure 1). The limitations of acute PSA changes as response measures in CRPC are well described (3,6). For example, acute rises in the PSA level ("PSA flares") may occur in over 10% of CRPC patients receiving docetaxel, and while they are not predictive of treatment outcome, they can confound decisions to continue treatment (17). Conversely, declines in PSA level may also be misleading, since some treatments can inhibit PSA production independent of their tumoricidal effects (7). Although a case where PET/CT and PSA measurements proved discordant despite being performed within 24-hours of each other is shown in Figure 1, the average interval between in-treatment follow-up PET/CT and follow-up PSA measurements in the present study was 8 days. Therefore, additional studies will be needed to further investigate treatment-associated changes in tumor metabolic activity underlying fluctuations in PSA production in CRPC.

The present study evaluated indexes of treatment response that incorporated every tumor lesion identified on ^{18}F-fluorocholine PET/CT. In contrast, other studies have evaluated predictive indexes derived from a fixed number of "target" lesions (11,21). This latter approach may be simpler and quicker to perform than whole-body tumor assessments. However, because metastases can vary in morphology, immune-phenotype, and genotype within the same patient (22), assessments of treatment response reflecting only a limited number of lesions could possibly be misleading. The feasibility and reproducibility of whole-body and target-lesion based approaches for assessing treatment response deserve further comparisons in a clinical trial setting.

There are several promising investigational fluorine-18 labeled tracers for prostate cancer imaging on the horizon, such as the prostate-specific membrane antigen ligands and fluorocyclobutanecarboxylic (anti-^{18}F-FACBC) (4,23,24), as well as sodium ^{18}F-fluoride which is commercially available in many areas (25). Since these tracers are associated with very high lesion-to-background uptake ratios, whole-body quantification of tumor burden based on MATV measurements should also work with these tracers. However, each tracer warrants its own evaluation as a treatment biomarker since the expression of some imaging targets may not necessarily change in response to treatment in a manner consistent with other targets (7). Since ^{18}F-fluorocholine PET/CT is one of the most extensively studied PET techniques for prostate cancer imaging (15), it was a good platform for developing methods for assessing tumor response in CRPC using whole-body MATV measurements.

This study has certain limitations as a single-institution study conducted in a limited number of patients. MATV calculations are based on voxel SUV measurements and thus depend on the PET scanner calibration, imaging protocol, and image reconstruction method used by the institution. Additional efforts are required to validate not only the concept of quantifying whole-body tumor response with ^{18}F-fluorocholine PET/CT, but also to generalize the methods supporting this approach. Furthermore, patients were enrolled to the present study with no control over the selection of treatments, introducing potential treatment-related bias into the study. However, no significant associations between treatment type and clinical parameters were noted (Table 2).

Previously, tumor burden measured on ^{18}F-fluorocholine PET/CT was found significantly associated with overall survival in CRPC even after adjusting for treatments rendered after patients were imaged (13). This implies that survival in CRPC is either largely influenced by the extant quantity of disease confronting treatment or that individual treatments have a relatively small impact on survival. However, because there are now multiple dissimilar treatments for CRPC that could impact specific manifestations of disease differently, it may be possible to judiciously select treatments based on an individual patient's pattern of disease to compound the survival benefits of sequential treatments. Based on the findings of the present study across the current spectrum of treatments for CRPC, ^{18}F-fluorocholine PET/CT may be able to support such a strategy.

CONCLUSION

In this study, significant changes in whole-body tumor burden measured on ^{18}F-fluorocholine PET/CT early in the course of contemporary treatments for CRPC were found to be predictive of PSA progression. The growing selection of treatments for CRPC and feasibility of applying ^{18}F-fluorocholine PET/CT for measuring changes in tumor burden following those treatments support further clinical evaluation of this imaging approach in the management of advanced prostate cancer.

Acknowledgments

The United States National Institutes of Health supported this work under National Cancer Institute grant R21CA139687-02. Patients receiving anti-androgen treatments were enrolled under clinicaltrials.gov study ID NCT00928174, and all other subsequent patients were enrolled under study ID NCT00928252. Additional funding was provided by Bayer Healthcare to support the enrollment of ^{223}Ra treated patients through an Investigator-Initiated Studies Program.

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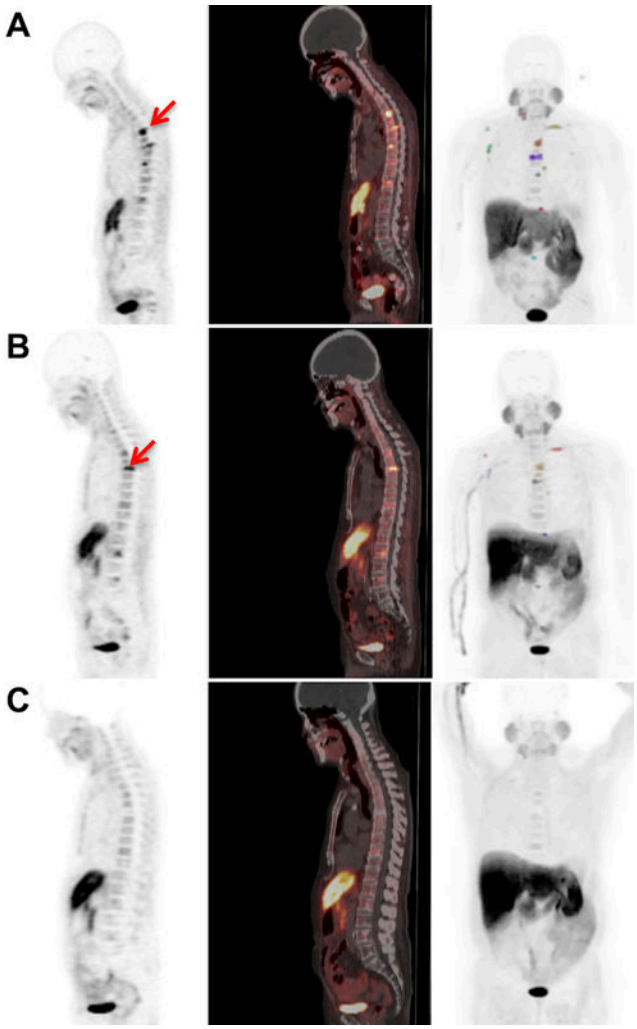

Figure 1. Early MATV response discordant with PSA response

^{18}F-fluorocholine PET (left column), PET/CT (middle column), and maximum intensity projection (MIP) (right column) images from a 74 year old patient receiving docetaxel. Color indicates MATV contours on the MIP images. Multiple bone metastases are evident on the pre-treatment PET/CT (arrow, row A; net MATV = 42.7 cm^3, PSA = 39.3 ng/mL). Net MATV decreased after the second chemotherapy cycle to 21.6 cm^3 (row B), while PSA increased to 41.7 ng/mL. After the 6th chemotherapy cycle, PET/CT (row C) demonstrated resolution of abnormal activity (net MATV = 0.0 cm^3) and PSA level decreased to 8.1 ng/mL.

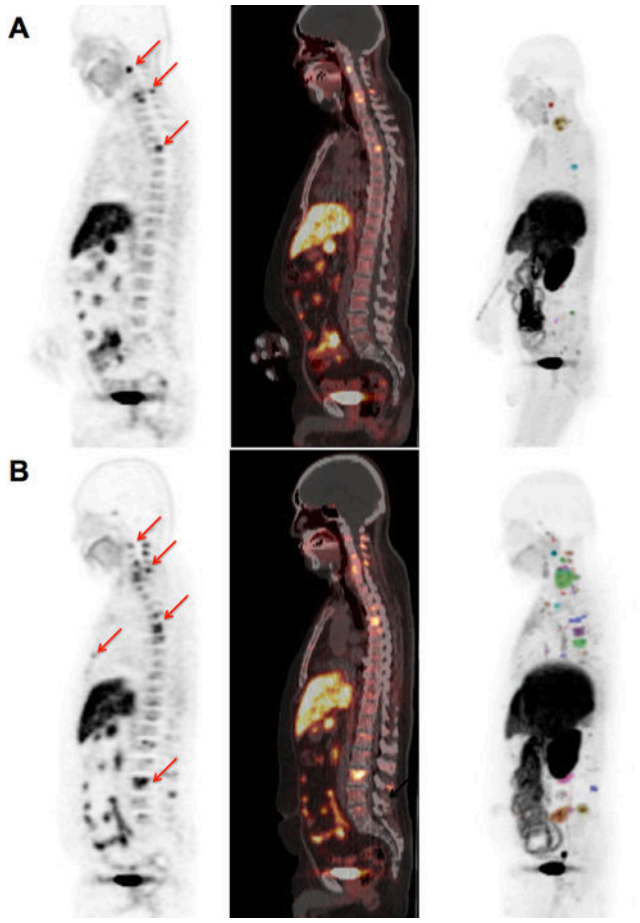

Figure 2. Cancer progression reflected by increasing net MATV

^{18}F-fluorocholine PET (left column), PET/CT (middle column), and maximum intensity projection (MIP) (right column) images from a 65 year old patient receiving sipuleucel-T. Color indicates MATV contours on the MIP images. Pre-treatment PET/CT (row A) shows hyperactive vertebral metastases (arrows; net MATV = 42.9 cm^3, PSA = 38.0 ng/mL). PET/CT obtained 36 days after initiating treatment (row B) demonstrates increasing activity and new lesions in the sternum and lumbar spine (arrows; net MATV = 338.4 cm^3, PSA = 46.7 ng/mL). The PSA level after 4 months increased to 241.4 ng/mL.

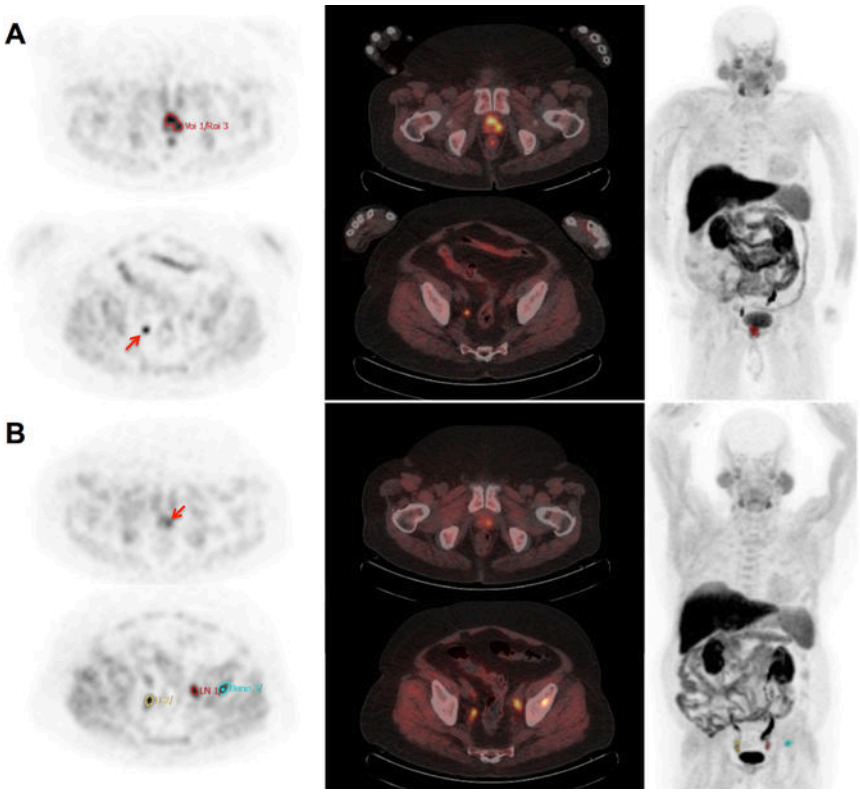

Figure 3. Heterogeneous response on serial ^{18}F-fluorocholine PET/CT

PET (left column), PET/CT (middle column), and maximum intensity projection (MIP) (right column) images from a 64 year old patient receiving sipuleucel-T. Pre-treatment images show abnormal activity in the prostate gland (red contour, top row A). PET/CT obtained 60 days after starting treatment shows significant decline in prostatic activity (arrow, top row B) but new abnormal activity in a left iliac lymph node and the ilium (red and blue contour, bottom row B). Net MATV increased from 32.5 to 34.0 cm^3 and PSA increased from 35.0 to 47.9 ng/mL. PSA progression was confirmed 3 months later (PSA = 65.1 ng/mL). Excreted tracer in the right ureter was not confused as a lesion (arrow in bottom row A and yellow contour in bottom row B).

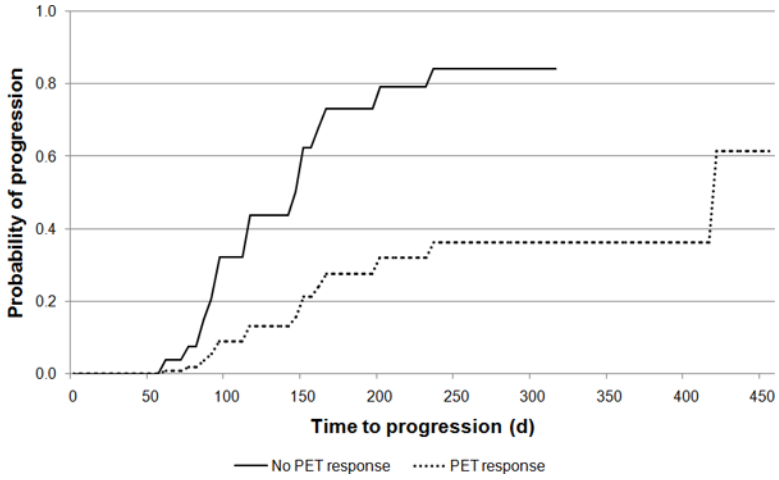

Figure 4. Probability of PSA progression over time based on MATV response

Median time to PSA progression was 418 days in MATV responders and 116 days in MATV non-responders. Both early and late differences in time to PSA progression were statistically significant on Kaplan-Meier analysis (Wilcoxon p = 0.0138 and Log-Rank p = 0.0067, respectively).

TABLE 1

Patient Characteristics (n=42).

Characteristic	Values
Age (years)	73 (70.0–75.2)
Baseline PSA (ng/mL)	329.4 (12.2–646.7)
Treatment Type	**# of patients**
Chemotherapy	16
Anti-androgen	19
^{223}Ra-dichloride	5
Sipuleucel-T	2
PET Tumor Burden Measurements	
Baseline net TLA (g)	2380.8 (706.9–4054.6)
Follow-up net TLA (g)	1438.9 (555.0–2322.8)
Baseline net MATV (cm^3)	516.0 (151.9–880.1)
Follow-up net MATV (cm^3)	356.1 (135.7–576.4)
Sites of Disease	**# (%) on 1st PET / # (%) on 2nd PET**
Bone	32 (76%) / 30 (71%)
Lymphatics	19 (45%) / 15 (36%)
Prostate	13 (31%) / 12 (29%)
Visceral *	3 (7%) / 3 (7%)

Continuous values expressed as mean (95% interval). PSA, prostate-specific antigen; MATV, metabolically active tumor volume; TLA, total lesion activity

*lung and adrenal glands

TABLE 2

Baseline clinical parameters according to treatment type.

Variable	Treatment Type				*P*
	Anti-androgen (n = 19)	Docetaxel (n =16)	^{223}Ra (n = 5)	Sipuleucel-T (n = 2)	
Age (years)	75.1	69.9	75.0	64.5	0.0789
Baseline PSA (ng/mL)	293.7	331.0	577.1	36.5	0.3460
Baseline net MATV (cm^3)	591.2	582.5	208.7	37.8	0.8010
Baseline net TLA (g)	2691.5	2768.3	837.3	186.5	0.8224

P values are by Kruskal-Wallis Test.

TABLE 3

Proportional hazards regression analysis of time to PSA progression.

Variable	Hazard Ratio	95% Confidence Limits	*P*
Clinical Parameters:			
Age > 70 years	0.756	0.274–2.078	0.5882
PSA level (pre-treatment)	1.050	0.778–1.422	0.7424
PSA response at ≤ 15 weeks	0.383	0.125–1.173	0.0944
PET Parameters:			
PET ($MATV_{30\%}$) Response	0.246	0.083–0.728	0.0113
PET ($TLA_{30\%}$) Response	0.246	0.083–0.728	0.0113
Lesion pattern on PET:			
Bone Involvement	1.773	0.617–5.092	0.2902
Lymph Node Involvement	0.967	0.368–2.538	0.9452
Prostate Involvement	0.870	0.321–2.357	0.7857
Visceral Involvement	2.219	0.273–18.05	0.4584
Treatment type:			
Chemotherapy vs. other	0.309	0.105–0.906	0.0333
Anti-androgen vs. other	5.650	1.2715–25.1	0.0236
Multivariate Analysis:			
Age-adjusted PET Response	0.227	0.074–0.698	0.0100
Treatment (Chemotherapy)- adjusted PET Response	0.298	0.097–0.922	0.0366
Treatment (Anti-androgen)- adjusted PET Response	0.298	0.096–0.930	0.0380