Journal of Nuclear Medicine, published on May 10, 2018 as doi:10.2967/jnumed.118.211102

Prospective study of serial ^{18}F-FDG PET and ^{18}F-fluoride (^{18}F-NaF) PET to predict time to skeletal related events, time-to-progression, and survival in patients with bone-dominant metastatic breast cancer

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Running Title: FDG-PET and NaF-PET in bone dominant MBC

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This study was sponsored by R01CA124573, Komen SAC130060,

P30CA015704, and SFI 11/PI/1027. No potential conflicts of interest relevant to

this article exist.

Word Count: Total 5911

ABSTRACT

Assessing therapy response of breast cancer bone metastases is challenging. In retrospective studies, serial ^{18}F-FDG PET was predictive of time to skeletal related events (tSRE) and time-to-progression (TTP). ^{18}F-NaF PET improves bone metastasis detection compared to bone scans. We prospectively tested ^{18}F-FDG PET and ^{18}F-NaF PET to predict tSRE, TTP, and overall survival (OS) in patients with bone-dominant metastatic breast cancer (BD MBC).

***Methods*:** Patients with BD MBC were imaged with ^{18}F-FDG PET and ^{18}F-NaF PET prior to starting new therapy (scan1) and again at a range of times centered around approximately 4 months later (scan2). SUVmax and SULpeak were recorded for a single index lesion and up to 5 most dominant lesions for each scan. tSRE, TTP, and OS were assessed exclusive of the PET images. Univariate Cox regression was performed to test the association between clinical endpoints and ^{18}F-FDG PET and ^{18}F-NaF PET measures. mPERCIST (Modified PET Response Criteria in Solid Tumors) criteria were also applied. Survival curves for mPERCIST compared response categories of Complete Response+Partial Response+Stable Disease versus Progressive Disease (CR+PR+SD vs PD) for tSRE, TTP, and OS.

***Results*:** Twenty-eight patients were evaluated. Higher FDG SULpeak at scan2 predicted shorter time to tSRE ($p = <0.001$) and TTP ($p = 0.044$). Higher FDG SUVmax at scan2 predicted a shorter time to tSRE ($p = <0.001$). A multivariable model using FDG SUVmax of the index lesion at scan1 plus the difference in SUVmax of up to 5 lesions between scans was predictive for tSRE and TTP.

Among 24 patients evaluable by ^{18}F-FDG PET mPERCIST, tSRE and TTP were longer in responders (CR, PR, or stable) compared to non-responders (PD) (p= 0.007, 0.028 respectively), with a trend toward improved survival (p= 0.1). An increase in the uptake between scans of up to 5 lesions by ^{18}F-NaF PET was associated with longer OS (p=0.027).

***Conclusions*:** Changes in ^{18}F-FDG PET parameters during therapy are predictive of tSRE and TTP, but not OS. mPERCIST evaluation in bone lesions may be useful in assessing response to therapy and is worthy of evaluation in multicenter, prospective trials. Serial ^{18}F-NaF PET was associated with OS, but was not useful for predicting TTP or tSRE in BD MBC.

Key words: ^{18}F-FDG PET, ^{18}F-NaF PET, bone dominant breast cancer, response to therapy

INTRODUCTION

Bone is the most common site of breast cancer metastases (*1-3*) and is associated with significant morbidity (*4*). Patients with bone-dominant (BD) disease (involving exclusively bone or bone and soft tissue without visceral organ involvement) experience longer survival than those patients with predominantly visceral metastases (*5-10*). Bone metastases are detected using a variety of imaging modalities (*11*). However, assessing response to therapy in patients with BD metastatic breast cancer (MBC) remains challenging. Bone scans visualize the response of surrounding bone to cancer and may be slow to show response, and may even show a "flare" related to bone healing with effective therapy. Similar findings may occur with other modalities including CT (*12-15*). RECIST 1.1 criteria specifically exclude bone metastasis as a measurable site for response, and BD MBC patients are often excluded from clinical trials that measure response (*4,16-19*). This represents a large patient population that could benefit from improved use of systemic therapy, making accurate assessment of BD MBC response an imperative need.

^{18}F-FDG PET depicts aspects of breast cancer bone metastases distinct from bone scans, ^{18}F-NaF PET, and other modalities and may therefore offer a superior approach for assessing response for BD MBC patients (*11*). ^{18}F-FDG PET is hypothesized to visualize tumor metabolism (*11*). Compared to bone scans and ^{18}F-NaF PET, FDG has higher uptake in more lytic bone metastases, making ^{18}F-FDG PET more sensitive for these lesions, while bone scans and ^{18}F-

NaF PET perform better in identifying more blastic metastases (*20-22*). Although cases of “flare” in response to therapy have been reported on ^{18}F-FDG PET (*23*), this appears to be a rare event (*24*), and largely related to the known impact of agonist endocrine agents (*25*). Previously reported retrospective data show that serial ^{18}F-FDG PET can be used to measure bone metastasis response to therapy and to predict outcome (*26-29*). Higher FDG uptake predicted the time to skeletal-related event (tSRE) and changes in FDG uptake with treatment predicted time-to-progression (TTP). Alternatively, ^{18}F-NaF PET offers improved resolution and quantitative capability compared to bone scan and bone SPECT (*22,30-33*) and might therefore offer benefit for assessing response and progresson, as reported for prostate cancer (*34*). We therefore evaluated both serial ^{18}F-NaF PET and ^{18}F-FDG PET to predict tSRE, TTP, and OS in a prospective study of patients with BD MBC starting new systemic therapy.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients had histologically confirmed breast cancer, imaging findings of bone metastases, and no contraindications to PET imaging. The institutional review board (IRB) approved this study, and all patients signed a written informed consent and agreed to undergo four PET scans (two ^{18}F-FDG PET and two ^{18}F-NaF PET), as well as standard pre-therapy and clinical follow-up to determine response to therapy. Baseline ^{18}F-FDG PET and ^{18}F-NaF PET scans (scan1) were completed prior to initiation of new systemic therapy. Follow up ^{18}F-FDG PET and ^{18}F-NaF PET scans (scan2) were completed at the

discretion of the treating physician. The date of the ^{18}F-NaF PET scan1 was used to indicate the date of study entry. Full selection criteria are provided in **Supplemental Table 1.**

PET Imaging

^{18}F-FDG and ^{18}F-NaF were produced at the University of Washington Cyclotron facility or purchased from commercial suppliers (Cardinal Health, Seattle WA) in accord with manufacturing requirements for both tracer (*35,36*). FDG imaging was performed according to routine clinical protocol (*37*) on one of three institutional tomographs (Advance PET and two DSTE PET/CT scanners GE Healthcare, Waukesha, WI). Fasting was not required for ^{18}F-NaF PET studies and patients underwent a 60-minute dynamic scan prior to the torso survey. Scanners were calibrated using the manufacture's recommended procedures and cross-calibrated regularly for quantitative comparisons (*38,39*). Most patients were imaged on the same scanner in serial studies for each tracer; however, due to the addition of a second GE Discovery STE PET/CT at our center, some patients underwent scan2 on the alternate scanner. We have shown that our calibration and cross-calibration procedures and identical acquisition and reconstruction protocols provide test-retest accuracy comparable to a well-calibrated single scanner (*40*).

Image Analysis

Experienced nuclear medicine physicians reviewed the ^{18}F-FDG PET and ^{18}F-NaF PET scans (as well as corresponding CTs) to identify the same bone lesions on both scans (up to 10 lesions), including the 5 most dominant, not

previously irradiated, for each scan. Dominant lesions were selected on the basis of tracer uptake, not lesion size. The index lesion was defined as the lesion with the largest amount of tracer uptake in each scan, and was not necessarily the same lesion in both scans. In the ^{18}F-NaF PET scan, for each identified lesion and corresponding normal bone, square (3x3 pixel, approximately 1 cm) regions-of-interest (ROIs) were drawn on 3 adjacent planes where the pixel of maximum value was included in each lesion ROI. For the ^{18}F-FDG PET scans, ROIs for tumor and liver were drawn according to PERCIST criteria (*41,42*).

Cancer Therapy and Determination of the Response Endpoints

Systemic therapy for MBC was selected by the treating physician prior to baseline scans. Outcome data were ascertained from prospectively collected clinical data. tSRE was defined as time from study entry to pathologic fracture, need for radiation to stabilize bone lesion or hypercalcemia of malignancy. TTP and OS were defined as time from study entry to disease progression or death. tSRE and TTP were adjudicated by medical oncology review of clinical data independent of PET scan results obtained during trial participation.
Supplemental Table 2 details the PET imaging metrics, including SUV and SUL, and their formulation.

mPERCIST Evaluation

Based on our preliminary analysis, bone lesions have lower average SULpeak values than soft-tissue lesions previously studied using PERCIST (*41,42*). Thus, our mPERCIST lesion inclusion criteria included bone lesions with

SULpeak greater than 1.5x mean liver SUL, instead of 1.5x mean liver SUL + 2SD of the mean liver SUL. For the patients meeting this requirement, we followed the published PERCIST metabolic response criteria and classified patients as mPERCIST responders (CR, PR or SD) or non-responders (PD).

Statistical Analysis

Univariate Cox proportional hazard regression models for each of the clinical endpoints (tSRE, TTP, OS) were performed for each of the SUV measures of interest. ^{18}F-FDG PET variables showing promise in the univariate analysis were included in a multivariable Cox model (*43*). Hazard ratios, p-values for the regression coefficients, R^2 and index of concordance are reported. The primary objective (and pre-planned analysis) was to determine if SUVmax from bone metastases were useful prognostic indicators for progression and SREs. We considered multiple tests that included SUVmax at both scan1 and scan2, along with a mean of all available sites at scan1 and scan2. Other tests were considered for several other prognostic factors and secondary endpoints, as well as for other definitions of SUV. If this were a definitive clinical trial, the Bonferroni procedure (or other multiple testing procedure) should be applied in all instances where multiple testing occurs. However, the scope of this study is more limited. The results presented provide an indication of directions for future validation in a rigorously-conducted prospective clinical trial. We report standard p-values but include a clear caveat detailing limitations of the study and its exploratory nature.

To test the association between mPERCIST response criteria (discrete

variables) and clinical endpoints, Kaplan-Meier curves for patients in mPERCIST response profiles (CR+PR+SD vs PD) were evaluated for each endpoint and quantitatively assessed using the log-rank test.

RESULTS

Twenty-eight patients are included in this study. Twenty-four patients completed all scans (2 ^{18}F-NaF PET and 2 ^{18}F-FDG PET) and an additional four patients completed paired ^{18}F-FDG PET, but not paired ^{18}F-NaF PET scans. Trial accrual fell short of goal, but was stopped due to financial and logistical challenges, and not based on interim data analysis. Ten patients had their second scan done on a different scanner within the same institution (6 on the same model DSTE). **Table 1** summarizes the patient and tumor characteristics which were taken from metastatic biopsy (if available) or from breast primary. The majority of patients had hormone receptor positive, HER2 negative disease. The average number of prior therapies for MBC was 2.7 (range 0-8). The majority of patients (61%) started a new endocrine therapy after Scan1. Twenty patients received bisphosphonates and 2 patients received an anti-RANK ligand agent. No patient changed bone-stabilizing agents while on study. Although over 100 lesions were identified among the patients, the focus of this analysis was on the index lesion and 5 most dominant lesions in each scan. Disease burden assessed by number of lesions per patient is shown in **Table 1**.

Response measures for all patients are included in **Supplemental Table 3**. **Figure 1** illustrates an example of partial response by ^{18}F-FDG PET with

stable NaF uptake in bone metastases. Over half of the patients had a SRE, with the median time of 8.3 months (0.0–86.5 months). Median TTP was 5.8 months (2.2 – 29.5 months). All but 3 patients died with median survival of 35.0 months by Kaplan-Meier estimate, (6.06 – 87.29 months).

Supplemental Table 4 summarizes the interval between initial (scan1) and follow up (scan2) which was determined by the treating physician and therefore varied (mean of 4.3 months). Descriptive statistics for the index lesion and multiple lesion uptake measures are shown in **Table 2,** and univariate analysis of ^{18}F-FDG PET and ^{18}F-NaF PET measures to clinical endpoints (tSRE, TTP, and OS) are shown in **Table 3**. Persistence of FDG uptake (SUVmax) in the index lesion at scan2 was associated with shorter tSRE (HR 2.27, $p<0.001$). Persistence of FDG-avid disease at scan2 by SULpeak was associated with shorter time to SRE (HR 2.41, $p<0.001$) and shorter TTP (HR 1.58, $p=0.044$). SULpeak unit difference for up to 5 lesions between scan1 and 2 was also associated with shorter time to SRE (HR 2.21, $p=0.038$). FDG SUVmax at scan1 was not predictive of tSRE, TTP, or OS. Persistence of FDG at scan2 by SUVmax or SULpeak of index lesion or lesser change in mean SULpeak of up to 5 lesions were predictive of shorter time to SRE or TTP, but none was associated with OS.

For ^{18}F-NaF PET, an increase in the percent change of the mean SUVmax of up to 5 lesions was associated with longer OS ($P=0.027$). This association did not persist when SUV uptake was corrected for normal bone uptake ($P=0.237$) (**Supplemental Table 5).** No other associations between Na-F PET parameters

at scan1 or scan2 or change between scans and clinical outcomes were observed. Analyses of ^{18}F-FDG PET and ^{18}F-NaF PET measures by type of therapy (endocrine or chemotherapy), time between scans, and primary lesion type (lytic or sclerotic) are shown in **Supplemental Table 6**. We found no significant difference in performance of ^{18}F-FDG PET or ^{18}F-NaF PET in these subgroups.

Univariate analysis failed to support ^{18}F-NaF PET imaging as a useful predictor of tSRE and TTP; therefore, subsequent multivariable analysis included ^{18}F-FDG PET parameters (**Table 4**). A model incorporating SUVmax of the index lesion at scan1 and unit difference in SUVmax in up to 5 lesions led to stronger predictive capability for tSRE and TTP than single parameters or other multivariable models. Patients with greater reductions in uptake on scan2 vs scan1 were found to have improved prognosis. Specifically, patients in which the difference between scan2 and scan1 was 1 SD lower (greater decline wth therapy) saw a 75% decrease (HR 4.14) in risk of tSRE ($p<0.01$) and a decrease of 50% (HR 1.98) in risk of progression ($p=0.02$), suggesting that the combination of FDG uptake measures from both scans identifies patients at risk for skeletal related events or disease progression. Results were similar using SULpeak in this model. Kaplan-Meier curves for the multivariable analysis are shown in **Supplemental Figure 1**.

Table 5 and **Figure 2** show response by mPERCIST criteria. Eleven patients had PD by mPERCIST, while one patient had CR, 6 patients had PR

and 6 had SD. Four patients were unevaluable, either because none of the lesions were above the liver SULpeak threshold (n=3) or there was liver disease present and an alternative aorta ROI was not available. **Supplemental Table 7** details the tumor response parameters. Responding patients (mPERCIST CR+PR+SD) (n=13) had significant prolongation of tSRE, TTP, and a trend towards improved OS (not statistically significant) compared to non-responders (PD). The median tSRE of patients in the response group was 47.6 months (95% CI: 29.7 to NA months) compared to 4.6 months (95% CI: 4.1 to NA months) in patients with PD (p=0.007). The median TTP of patients in response group was 14.1 months (95% CI: 5.4 to NA months) compared to 3.8 months (95% CI: 3.5 to NA months) in patients with PD (p=0.028). Similarly, the median OS of patients in response group was 47.0 months (95% CI: 23.7 to NA months) compared to 25 months (95% CI: 18.5 to NA months) in patients with PD, but was not statistically significant (p=0.10).

PERCIST criteria have not be evaluated for ^{18}F-NaF PET, However, we note that in 8 patients that had both ^{18}F-FDG PET and ^{18}F-NaF PET scans with PD by ^{18}F-FDG PET mPERCIST, 5/8 (63%) were considered PD because of new FDG-avid lesions, but only 3/8 (38%) had new lesions noted in their ^{18}F-NaF PET scans. No scans that were not considered PD by ^{18}F-FDG PET were considered PD by ^{18}F-NaF PET.

DISCUSSION

The ability to accurately detect metastases in breast and prostate cancers has improved significantly in recent years with hybrid imaging methods. Nevertheless, no consensus has been reached on the best imaging modality for treatment response assessment of breast cancer bone metastases (*44*). We hypothesized that serial ^{18}F-FDG PET and ^{18}F-NaF PET would provide complementary measures of activity of breast cancer bone metastases and that each might predict response to therapy.

Our ^{18}F-FDG PET results were consistent with previously reported retrospective data for breast cancer (*26-29*) and similar to studies in castrate resistant prostate cancer, which tends to have higher FDG uptake compared to hormone-sensitive disease (*45*). Neither ^{18}F-NaF PET measures at scan1 or scan2 nor change in NaF SUV uptake over course of treatment were predictive of tSRE or TTP. However, the percent difference (but not the unit difference) of the average SUVmax of up to 5 lesions was associated with OS. The direction of the hazard ratio suggests that an increase in uptake was predictive, but the association does not persist when SUV uptake is corrected for normal bone uptake. This may be related to the “flare” effect, artifactual, or related to effects not specific to the metastases, as seen in a similar study in prostate cancer (*46*). Additional analyses evaluating performance of serial NaF by lesion type (lytic vs. sclerotic vs. mixed) also failed to demonstrate predictive value of NaF (**Supplemental Table 6**). The difference between our results for ^{18}F-NaF PET and the promising results in prostate cancer (*46-49*), particularly when

quantitative assessment of NaF uptake is incorporated (*34*), may relate to biologic differences in breast cancer bone metastases. Breast cancer lesions, although phenotypically both blastic and lytic, tend to be more driven by primarily lytic molecular process compared to prostate cancer metastases (*50*). Our ^{18}F-NaF PET results are consistent with other studies showing confounding repsonses for breast cancer bone metastases by bone scan and ^{18}F-NaF PET (*14,51*). While useful as a mode of detection of osteoblastic bone lesions, our results do not support use of serial ^{18}F-NaF PET as a response measure or predictor of clinical outcomes in BD MBC.

There are several limitations to this study including small sample size (n=28). We found a wide range of SUV uptake values in bony lesions by both ^{18}F-FDG PET and ^{18}F-NaF PET, likely due to heterogeneity in lytic versus sclerotic lesions which may be related to both underlying tumor biologic differences and prior therapy (*20,22,52*). Treatment while on the study incorporated standard endocrine agents or chemotherapy prescribed at physician discretion and the timing of PET post-therapy scanning was not uniform, influenced by clinical practice. Results of the multivariable analysis should be considered exploratory and parameters from the model validated in larger studies.

Some patients were imaged on different scanners, all in same institution with similar patient preparation and where machine calibrations were done quarterly using the same calibration procedures and daily QC to keep them as closely aligned as possible. Recent work demonstrated that ^{18}F-FDG PET

scanner qualification and calibration can yield highly reproducible SUV measurements with percent test-retest difference in tumor SUVmax for bone of 7% and for soft tissue 10% (data not shown).

We found that mPERCIST criteria may be valuable to assess response to therapy and are associated with differences in clinical endpoints (*41,53*). Lower average FDG uptake in bone versus soft-tissue metatases prompted our modification to include bone lesions with SULpeak greater than 1.5X value of normal liver. We found that patients with metabolic response (CR, PR and SD) experienced significant prolongation in tSRE (47.6 vs. 4.6 months) and TTP (14.1 vs. 3.8 months). ^{18}F-FDG PET uptake changes assessed by mPERCIST were strongly associated with clinical outcomes of interest. Our results support the use of ^{18}F-FDG PET and a modified PERCIST approach to monitor response to therapy in BD MBC and indicate a need for validation in larger prospective, multicenter trials.

CONCLUSIONS

This prospective study of serial and ^{18}F-FDG PET and ^{18}F-NaF PET in patients with BD MBC, confirmed prior retrospective studies showing that FDG uptake measures predict key clinical outcomes (tSRE and TTP) and supported the use mPERCIST criteria. Our results do not support a clear role for serial ^{18}F-NaF PET in this patient population. These results endorse a larger prospective trial of ^{18}F-FDG PET/CT as a response endpoint for BD MBC, and suggest that ^{18}F-FDG PET/CT could be used as a response endpoint that would increase access of this patient population to clinical trials and promising new therapies.

ACKNOWLEDGEMENTS

This study was sponsored by R01CA124573, Komen SAC130060, P30CA015704 and SFI 11/PI/1027. The authors would like to thank the patients who participated in the study. The authors would also like to thank Finbarr O'Sullivan, Lisa Dunnwald, Erin Schubert, William Barlow, Robert Doot, and Larry MacDonald and all of the radiochemistry staff, technologists, physicists, and physicians who helped with this study.

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Figure 1. Image example. Sagittal images of a 43-year old female. Top panel (A) are scan1 images and bottom panel (B) are scan2 images. Index lesions (not the same lesions) decreased 58% by ^{18}F-FDG PET and 2% by ^{18}F-NaF PET. Response was considered partial by mPERCIST. Bone metastates were considered stableby ^{18}F-NaF PET.

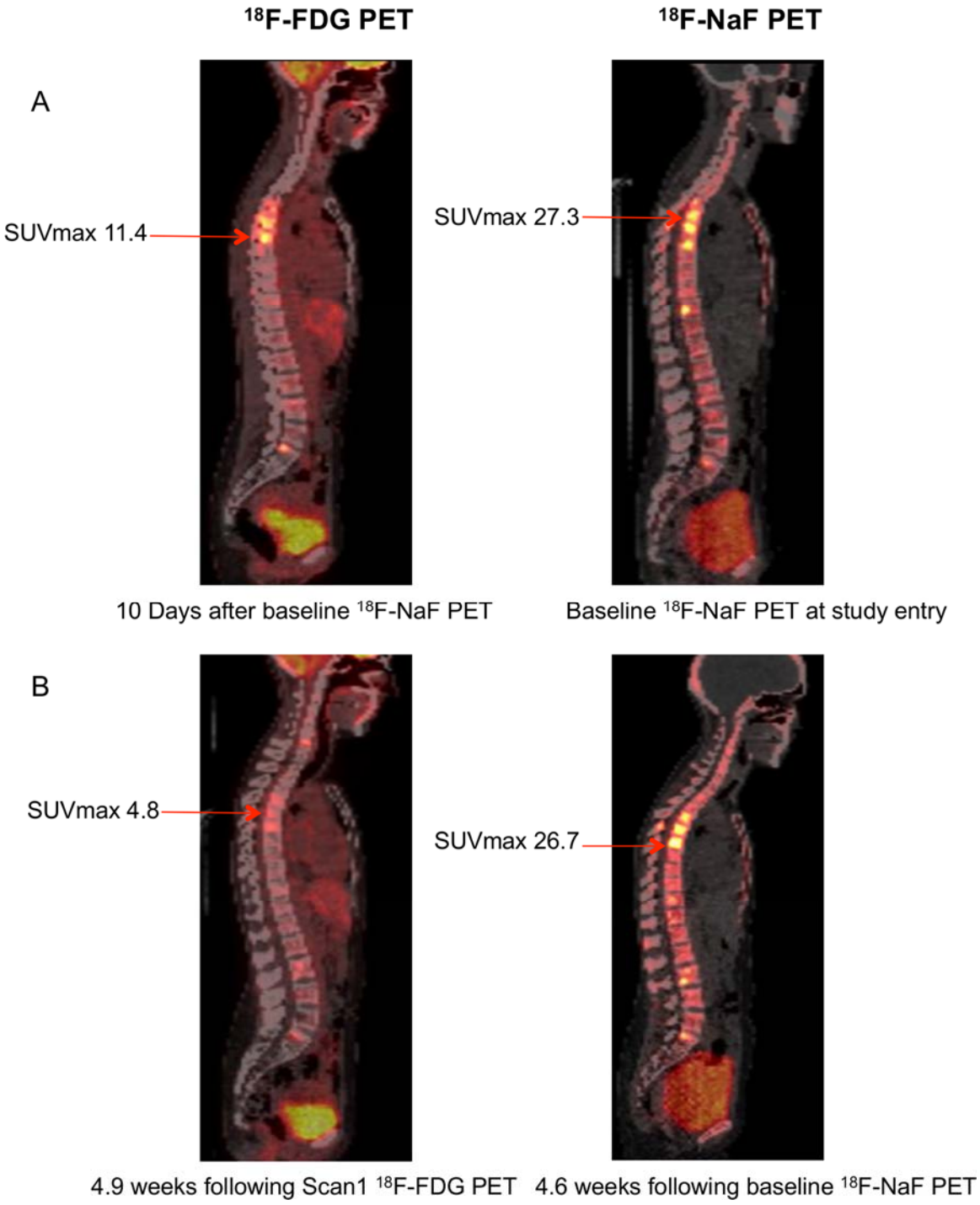

Figure 2. Kaplan-Meier plots for FDG mPERCIST response criteria. Responders by mPERCIST (CR, PR or SD) (n=13) and non-responders (n=11). **A** tSRE, **B** TTP and **C** OS.

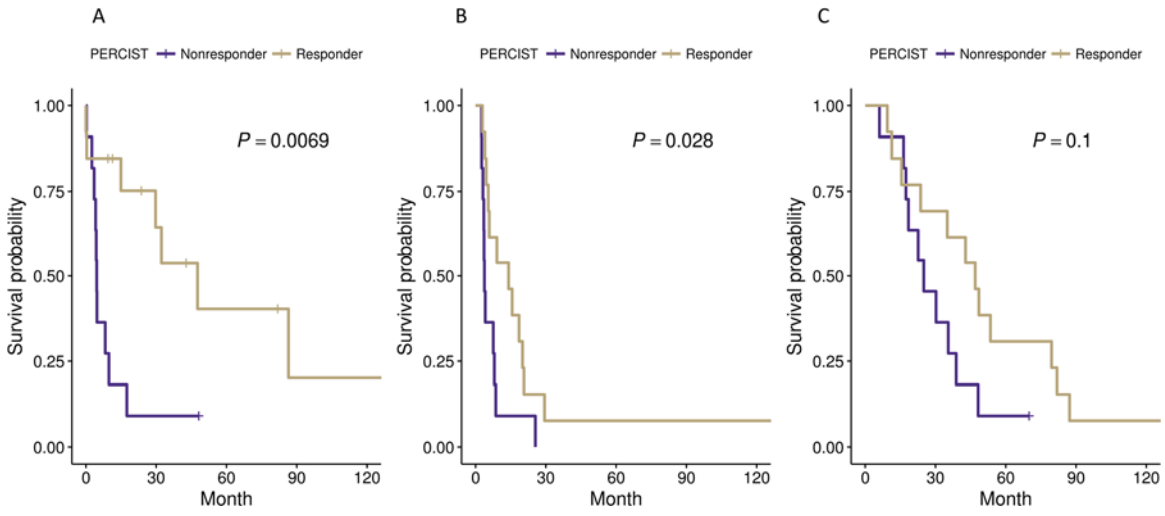

Table 1: Selected patient and tumor characteristics

	N=28 (%)	Mean (range)
Age, years		56 (33-90)
Histology		
Ductal	18 (64%)	
Lobular	4 (14%)	
Mixed or Unknown	6 (21%)	
Receptor status		
Estrogen receptor positive	24 (86%)	
Progesterone receptor positive	21 (75%)	
HER2 negative	20 (70%)	
Dominant lesion type		
Lytic	11 (39%)	
Sclerotic	7 (25%)	
Mixed	8 (29%)	
Unknown	2 (7%)	
Bone lesions per patient		
1-5	11 (39%)	
6-10	3 (11%)	
>10	14 (50%)	
Prior therapy		
Chemotherapy	15 (54%)	
Endocrine therapy	17 (61%)	
Radiation	13 (46%)	
No. prior therapies prior to enrollment		2.7 (0-8)
On study therapy*		
Chemotherapy	11 (39%)	
Endocrine therapy	17 (61%)	
Time from diagnosis to metastatic diagnosis		71.8 mos (0-440.3)
Time from metastatic diagnosis to enrollment		18.3 mos (0-71.4)

* biologic therapy (trastuzumab) was given with chemotherapy or endocrine therapy for patients with HER2+ disease

Table 2: Uptake characteristics. A and **B** are the mean (range) for FDG SUVmax and SULpeak uptake values and the change in uptake for the 28 patients completing 2 ^{18}F-FDG PET scans. **C** is the mean (range) for NaF SUVmax uptake values and the change in uptake for the 24 completing 2 ^{18}F-NaF PET and 2 ^{18}F-FDG PET scans.

	Scan1	**Scan2**	**Unit change (scan2 – scan1)**	**% change (scan2 – scan1)**
A-FDG SUVmax (N=28)				
Index lesion	10.0 (3.0-31.3)	6.9 (2.4-16.9)	-2.87 (-20.7-4.1)	-16 (-83-117)
up to 5 lesions	7.6 (2.7-20.2)	5.7 (2.1-13)	-1.7 (-16.9 - 3.0)	-14 (-84 - 65)
B-FDG SULpeak (N=28)				
Index lesion	5.1 (1.2-14.3)	4.1 (1.2-12.3)	-1.0 (-11.8-7.0)	-3 (-83-133)
up to 5 lesions	3.9 (1.0-11.5)	3.3 (1.0-10.7)	-0.58 (-9.6-6.4)	-2 (-85-147)
C-NaF SUVmax (N=24)				
Index lesion	34.37 (12.0-73.7)	31.11 (12.7- 68.8)	-3.26 (-44.0 - 16.6)	-2.52 (-59.6 - 46.8)
up to 5 lesions	27.77 (12.0-60.2)	24.47 (12.7 - 61.1)	-3.30 (-34.2 – 16.6)	-7.58 (-56.7 – 39.3)

Table 3: Univariate analysis of ^{18}F-FDG PET and ^{18}F-NaF PET parameters and clinical endpoints. A and **B** are the FDG SUVmax and SULpeak uptake values and the change in uptake for the 28 patients with 2 ^{18}F-FDG PET scans. **C** is the NaF SUVmax uptake values and the percent change in uptake for the 24 patients with 2 ^{18}F-NaF PET and 2 ^{18}F-FDG PET scans.

	tSRE				TTP				OS			
A-FDG SUVmax (N=28)	*HR*	*P*	R^2	*C*	*HR*	*P*	R^2	*C*	*HR*	*P*	R^2	*C*
Index Lesion												
$SUV_{max}1$	1.38	0.159	0.060	0.631	1.09	0.679	0.006	0.507	1.28	0.196	0.052	0.580
$SUV_{max}2$	2.27	<.001	0.304	0.787	1.36	0.130	0.072	0.584	1.12	0.642	0.008	0.528
Unit Difference	1.18	0.576	0.012	0.653	1.07	0.710	0.005	0.578	0.81	0.290	0.036	0.528
% difference	1.12	0.579	0.010	0.688	0.94	0.682	0.006	0.403	0.71	0.112	0.098	0.547
Up to 5 lesions												
Unit difference	1.52	0.246	0.061	0.670	1.23	0.302	0.042	0.629	0.88	0.525	0.013	0.512
% difference	1.35	0.191	0.058	0.677	1.10	0.568	0.012	0.613	0.82	0.320	0.035	0.536
B-FDG SULpeak (N=28)												
Index Lesion												
$SUL_{peak}1$	1.18	0.447	0.019	0.589	1.03	0.855	0.001	0.496	1.26	0.215	0.049	0.566
$SUL_{peak}2$	2.41	<.001	0.308	0.755	1.58	0.044	0.122	0.589	1.33	0.290	0.037	0.534
Up to 5 lesions												
Unit difference	2.21	0.038	0.165	0.684	1.40	0.155	0.080	0.626	0.999	0.999	0	0.493
C-NaF SUVmax (N=24)												
Index Lesion												
$SUV_{max}1$	1.22	0.381	0.030	0.571	1.15	0.426	0.025	0.564	1.21	0.334	0.037	0.532
$SUV_{max}2$	1.16	0.440	0.023	0.528	1.38	0.138	0.077	0.582	1.00	0.986	0.000	0.424
Unit Difference	0.943	0.827	0.002	0.547	1.01	0.946	0.0	0.48	0.77	0.212	0.056	0.587
% difference	0.874	0.647	0.008	0.547	0.94	0.8	0.003	0.538	0.70	0.169	0.072	0.591
Up to 5 lesions												
Unit Difference	0.854	0.630	0.010	0.504	0.83	0.443	0.023	0.564	0.71	0.109	0.090	0.665
% difference	0.861	0.623	0.010	0.528	0.81	0.321	0.040	0.567	0.58	0.027	0.191	0.669

Table 4: Multivariable analysis (FDG only). A shows multivariable analysis using FDG SUVmax uptake at scan1 plus the unit difference in SUVmax for up to 5 lesions. **B** includes the same variables, but for SULpeak.

	tSRE				TTP				OS			
A-SUVmax (N=28)	*HR*	*P*	R^2	*C*	*HR*	*P*	R^2	*C*	*HR*	*P*	R^2	*C*
$SUV_{max}1$ (index lesion)	3.66	4.0E-4	0.379	0.805	2.00	0.021	0.187	0.658	1.38	0.236	0.057	0.563
Unit difference (up to 5 lesions)	4.14	0.006			1.98	0.021			1.11	0.712		
B-SULpeak (N=28)												
$SUL_{peak}1$ (index lesion)	2.93	0.004	0.385	0.794	1.98	0.022	0.234	0.650	1.69	0.070	0.106	0.582
Unit difference (up to 5 lesions)	4.14	0.006			2.34	0.004			1.56	0.183		

Table 5: Response by mPERCIST. Median and 95% confidence intervals (CI) for each response measure for 24 patients.

	N=24 (%)	tSRE (95% CI)	TTP (95% CI)	OS (95% CI)
Responders (CR+PR+SD)	13 (54%)	47.6 mos (29.7-NA)	14.1 mos (5.4-NA)	47 mos (23.7-NA)
Non-responders (PD)	11 (45%)	4.6 mos (4.1-NA)	3.8 mos (3.5-NA)	25 mos (18.5-NA)