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^{18}F-Fluoride PET Used for Treatment Monitoring of Systemic Cancer Therapy: Results from the National Oncologic PET Registry

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ABSTRACT

Background: In a national prospective registry, we previously studied the impact of ^{18}F-sodium fluoride positron emission tomography (NaF-PET) on intended management of cancer patients with osseous metastases. The clinical impact of NaF-PET for monitoring the response to systemic therapies in such patients is unknown.

Objective: Assess the impact of NaF-PET results performed for treatment monitoring of systemic cancer therapy.

Methods: Before and after NaF-PET, we collected prospective data from referring and interpreting physicians for cancer patients age ≥65 years receiving systemic therapy (use of one or more categories including hormonal, chemotherapy, bisphosphonates or immunotherapy). The analysis set consisted of 2,217 patients who had a total of 2,839 scans (68% prostate, 17% breast, 6% lung and 8% other cancers) ordered for treatment monitoring. Two or more categories of systemic therapy were planned in 56% of prostate and 43% of breast cancer patients.

Results: The overall rates of prior radionuclide bone imaging were 78%, 76% and 66% for prostate, breast and other cancers, respectively. 57% of patients had prior NaF-PET. Overall change in management associated with NaF-PET was 40%. In patients with prior NaF-PET scans for comparison, continuing current therapy was planned in 79% when scans showed no change or a decrease or absence of osseous metastasis. Treating physicians planned to switch therapy in 59% of patients after scans showed evidence of new or progressive metastasis. When an additional parameter, estimated prognosis, was worse, switching therapy was even more common (76%).

Conclusion: The impact of NaF-PET used for treatment monitoring was high in patients with evidence of progressive osseous metastasis. Most such patients had plans to switch to a new cancer-directed therapy.

INTRODUCTION

Oncologists have many options for tracking a patient's response to cancer therapy, including various imaging modalities and tumor markers.(*1-3*) Although there are multiple treatments for osseous metastatic disease, assessing treatment response is challenging because of the complex morphology of skeletal lesions and the difficulty in quantifying lesion volume. For patients with prostate and breast cancer, bone is often the dominant or only site of metastatic disease, and planar bone scintigraphy (BS) with ^{99m}Tc-phosphonates is a common imaging modality. Bone scintigraphy provides a total skeletal survey at relatively low cost and has high sensitivity for detecting osteoblastic activity.(*4-6*) However, BS has well-known limitations including being less sensitive for predominantly osteolytic lesions and limited specificity, with positive findings caused by benign lesions, prior trauma, and arthritis.(*4, 7*) The performance of conventional BS is improved by use of SPECT and SPECT/CT,*(4)* but whole-body imaging with these methods is not currently standard practice.

A promising alternative to conventional BS is positron emission tomography (PET) or integrated PET/computed tomography (PET/CT) with ^{18}F-sodium fluoride (hereinafter collectively referred to as NaF-PET). Advantages of NaF-PET include superior image quality with improved sensitivity, lower radiation dose, higher bone uptake, and superior pharmacokinetics (a shorter time from injection to imaging and faster blood clearance).(*8, 9*) When NaF-PET is performed with PET/CT, as is now common, the direct correlation of PET and CT findings allows improved specificity, because many benign processes have characteristic CT appearances.(*10, 11*) Although the excellent performance of NaF-PET for

detection of osseous metastasis is well documented, including in comparison to conventional BS,(*12-17*) its clinical impact when used to monitor treatment response is uncertain.

Since 2011, NaF-PET has been available in the United States, under a Coverage with Evidence Development (CED) program, for Medicare beneficiaries with suspected or known osseous metastasis. For each scan, prospective data to assess the referring physician's intended management were collected with a questionnaire-based approach and submitted to the National Oncologic PET Registry (NOPR).(*18*) We have previously reported the impact of diagnostic NaF-PET on intended management in men with prostate cancer and in patients with other types of cancer.(*19, 20*) We now report the impact of NaF-PET in NOPR patients when used to assess response to systemic therapy for osseous metastatic disease.

MATERIALS AND METHODS

NOPR Design. NOPR was initially designed to assess the impact of PET with ^{18}F-FDG on intended cancer management. We have previously reported the impact of ^{18}F-FDG-PET by cancer type and testing indication, including its use for monitoring cancer therapy.(*21-24*) The NaF-PET registry follows the basic design of the ^{18}F-FDG-PET registry in that data were prospectively collected from the requesting physician before and after imaging. The interpreting physician, using a structured case report form, also recorded the NaF-PET result. Our prior reports on ^{18}F-FDG-PET and NaF-PET include details on NOPR operations, human subject protections, and how data were collected. The research conducted using

NOPR data is registered at ClinicalTrials.gov #NCT00868582 and data forms are available on the NOPR web site (http://www.cancerpetregistry.org/).

Treatment Monitoring. The NOPR case report forms for NaF-PET included additional questions when the imaging indication was to "monitor tumor response to treatment during the planned course of therapy (i.e., when a change in therapy is anticipated)." Treatment was categorized by the category of systemic therapy (including chemotherapy, hormonal therapy, bisphosphonates, biologic response modifiers or immunotherapy). We also collected results on those receiving radiotherapy, but did not include those in this analysis since fewer than 10% received such treatment. The specific drugs or combinations of systemic therapies were not collected nor was a history of prior cancer-directed therapies. Before NaF-PET, the plan for treatment was recorded in response to the following question:

> If you were to continue your patient's management without doing any other testing first (e.g., PET, CT, MRI, biopsy), what would be your treatment plan today?
>
> ☐ Continue and complete currently ongoing therapy
>
> ☐ Modify dose or schedule of currently ongoing therapy
>
> ☐ Switch to another therapy or add another mode of therapy
>
> ☐ Stop therapy and switch to supportive care

After the PET results were available, the referring physician recorded the post-PET plan for treatment using the same four options. Additionally, before and after NaF-PET, the referring physician recorded his/her impression of the patient's therapy response and prognosis.

The interpreting physician recorded whether prior radionuclide bone imaging (BS or NaF-PET) was available for comparison, along with the date of the prior study. NaF-PET findings were categorized as normal/benign versus equivocal, probable, or definite osseous metastasis. Osseous metastatic disease was further characterized as unifocal, multifocal, or diffuse. If prior BS or NaF-PET were available, the comparison was categorized as showing no evidence, resolution, or reduction of metastasis; no change; or progression and/or new sites of osseous metastasis.

Analysis Plan and Cohort. The endpoint of greatest interest was the modification of the treatment.(*22*) Changes were defined as a binary variable at the scan level and multiple scans collected from the same patient were assumed to be independent observations. In addition to the routine descriptive statistics (e.g., mean, frequency, etc.), Pearson's chi-squared tests were used to assess the association between each pre-PET profile characteristic and the cancer type, as shown in Table 1. For the significance of the associated pre-PET profile characteristics, a *post-hoc* analysis with a Bonferroni correction for multiple comparisons was conducted to identify which category of that characteristic performed differently across various cancer types.

An *a priori* statistical plan for all registry indications of NaF-PET was based on an anticipated rate of change in intended management of 15% and a sample size of 13,040 cases for all imaging indications (see our prior reports for the impact of NaF-PET on initial staging, suspected first osseous metastasis and suspected progression of osseous metastasis).*(19,20)* To compare the pre- and post-PET therapeutic plans, a logistic regression model was fit to assess differences of change in management across different

cancer types. All tests were two-sided and a p-value threshold of 0.05 (or the Bonferroni-adjusted threshold for tests needing correction for multiple comparisons) was used to declare statistical significance. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) or R v2.15.3 (R project, http://www.r-project.org/) as previously reported.*(19,20)*

Final protocol revisions were implemented on January 27, 2012, and we report on the patient cohort from that date through June 30, 2014. The analysis was conducted at this time to coincide with submission, by the NOPR investigators, of data through this date to the Center for Medicare & Medicaid Services as part of a reconsideration request to modify the National Coverage Decision to end the prospective data collection requirements and provide Medicare coverage of NaF-PET.

In this report, we excluded patients less than 65 years of age (7.6%), thus limiting our analyses to the traditional Medicare age range.

RESULTS

Cohort Profile. Table 1 shows the cohort profile. The final dataset included 2,839 scans done in 2,217 patients; of these, 1,779 had a single scan for treatment monitoring, 320 had two, 76 had three and 42 had four or more. Of the 1,779 patients having a single NaF-PET for treatment monitoring during the study interval (January 2012-June 2014), 779 (n=44%)% had a prior NaF-PET scan and 427 (n=24%) had a prior conventional BS. Of the total 2,839 scans, 1,940 were performed for prostate (68.3%), 476 for breast (16.8%), 185 for lung (6.5%), and 238 for other cancer types (8.4%). The median patient

age was 75 years (25%-75% quartiles 70-80 years). 94.6% of scans were PET-CT and 5.4% PET only.

The clinical evidence prompting imaging was often an elevated or rising tumor marker, occurring as the sole indication in 38.2% and in conjunction with bone pain in 22.7%. Approximately 45% of patients had bone pain with similar rates across cancer types. About 5% had evidence of metastases on other imaging studies.

The vast majority of patients had metastatic disease. Patient summary stage was judged by referring physicians before NaF-PET to be multifocal metastatic disease in 59% overall, slightly lower in prostate and slightly higher in the other cancers. About 4% were in remission with no evidence of disease and about 10% had local or regional disease, but we did not ask whether patients had been receiving adjuvant therapy. Referring physicians did not commit to a specific stage in 18% of patients.

For patients with plans to continue current therapy, the category of systemic therapy was inferred. In prostate cancer patients, 75% of plans included hormonal therapy, 49% chemotherapy, 42% bisphosphonates and 19% immunotherapy. Combinations of two or more categories were predominant. Hormonal or chemotherapy as the sole systemic therapy was planned in 21% and 14% of patients, respectively. Among breast cancer patients, plans included chemotherapy in 77% and hormonal therapy in 47%.

For all patients combined, the pre-PET plans were to continue therapy in 67.3%, switch to another therapy in 24.8%, modify dose or therapy schedule in 7.0% and stop systemic therapy and switch to supportive care in 0.8%. Differences were noted across cancer types. Among patients with prostate cancer, continuing current treatment was less

often planned before PET (62.4% vs. 76-82%, chi-square p<0.0001) and progressive osseous metastatic disease was suspected more often (33.6% vs. 14-19%, chi-square p<0.0001) than for patients with other cancer types. Similarly, pre-PET plans to switch therapy were much more common in patients with prostate cancer (29.4%) than for other cancers (10%-17%, p=<0.0001). For all cancer types, plans to modify dose or schedule were infrequent (7%) and plans for stopping therapy and instituting supportive care were rare (1%).

Management Changes in Light of NaF-PET findings. Table 2 shows the cross-tabulation of pre-PET plans as columns with the post-PET plans as rows by cancer type (with lung cancer combined with other cancers). Concordant pre- and post-PET plans are shown in boldface. The frequency of a change in plan following NaF-PET (the sum of the discordances) was 40.3% overall. The frequencies of change in patients with prostate cancer (41.8%) and breast cancer (39.3%) were not significantly different (p=0.14), but the frequency of change was slightly lower in all other cancer types, including lung cancer (34.5%, p=0.006). Initial plans for continuing therapy were changed in about one-third of patients, plans of switching therapy changed in about half of patients, and less than 20% of the infrequent plans to modify dose or schedule or stop treatment were continued as the intended post-PET plan.

Comparison with Prior Scans. Prior bone radionuclide imaging was available for comparison in 76.1% of patients (bottom, Table 1). Prior NaF-PET was the comparator study in 75% of those with comparators (57% of all patients), with minimal differences across the cancer types. Prior conventional BS was the comparator study in 19% of all

patients, predominantly in prostate cancer patients.

Table 3 (top) shows the association between the change from prior scans, when available, and impact on post-PET plans. The findings were similar when either conventional BS or NaF-PET was the comparison scan; therefore, we report only the impact when the comparison scan was NaF-PET. The prior scan was performed a median of 5.6 months earlier (the interquartile range was 3.9 to 9.0 months).

Interpreting physicians were asked to record evidence on scan of "progression" while requesting physicians were asked to project "prognosis" based on scan results. Overall, 64% of scans showed interval non-progression (normal, benign changes, a decrease or no change in the scan findings of metastases), while 36% showed progression (worsening of previously seen metastatic disease in 31% and development of new osseous metastatic disease in 5%). Among patients whose scans showed non-progression, 79% had post-PET plans to continue current treatment versus only one-third of patients ($p<0.001$) with progression. Those with progression had plans to switch to another therapy in 59%.

The referring physicians rated patient prognosis, in light of the NaF-PET findings, as better in 28.0%, unchanged in 39.7% and worse in 32.2%. Whether the prognosis was rated better or unchanged, the rates of continuing current therapy were not different (80.8% vs. 79.1%, $p=0.36$). In contrast, when the prognosis was judged worse, current therapy was continued only 13.8% of the time (80.8% vs. 13.8% and 79.1% vs. 13.8%, both highly significant, $p<0.001$). If the prognosis was worse, a therapy switch was planned 76.2% of the time. This was uncommon if the prognosis was better (9.3% switch) or no change (15.7% switch). The differences were highly significant (9.3% vs. 15.7% vs. 76.2%,

$p < 0.001$).

DISCUSSION

The optimal type and frequency of imaging for assessing treatment response to systemic therapies in patients with metastatic cancer are uncertain; monitoring strategies in routine practice are frequently guided by those used in clinical trials.(*25*) Generally, the same method of assessment used to detect metastatic disease at a particular site (e.g., chest CT) should be used over time to evaluate response. Standards for functional imaging techniques, in contrast to anatomic ones, are still evolving, but functional imaging is appealing since changes in metabolic indicators often precede anatomic changes.(*26*) Assessing osseous metastasis is particularly challenging since bone lesions are generally considered to be non-measurable by anatomical imaging. Accordingly, functional imaging approaches may be more useful in patients with bone-dominant disease(*27, 28*) Standards for interpreting such studies are under development; for example, new guidelines for response assessment by conventional BS in patients with metastatic prostate cancer define progression as two or more new lesions on two subsequent treatment monitoring scans.(*2, 29, 30*) and the MD Anderson Cancer Center response criteria in bone-only metastatic breast cancer do not yet include ^{18}F-FDG-PET or NaF-PET.(*27, 31*)

NaF-PET is evolving as an important imaging method for detection of osseous metastatic disease and has both greater sensitivity and specificity than conventional BS, when imaging is performed with an integrated PET/CT scanner.(*11*) However, NaF-PET shares the same limitations as conventional BS—it is an indicator of reactive bone

formation in response to various insults and is not tumor specific and it is subject to the flare phenomenon associated with systemic therapy. Osseous changes from degenerative processes, trauma and infection can be misleading, although these often can be diagnosed accurately based on the CT findings when the study is performed by PET/CT, as is now the dominant approach throughout the United States. The CT component of conventional BS that includes SPECT/CT provides a similar improvement in specificity, but whole-body SPECT/CT is not yet a standard procedure in general nuclear medicine practice.*(4)*

To date, however, relatively little information is available about the impact of NaF-PET on clinical decision making when used to assess the biological response of osseous metastatic disease in order to guide continuing, switching or stopping systemic therapy.(*28, 32*) Since 2011, NaF-PET has been available for Medicare beneficiaries in the United States under Coverage with Evidence Development, thereby providing an opportunity to assess how NaF-PET is being used in clinical practice for patients with osseous metastases.

In this report from the NOPR, we compared the management plans before and after NaF-PET in patients receiving systemic therapy for metastatic cancer. In prostate and breast cancer patients, the most common plans included two or more types of systemic therapy. Details about the specific drugs/products, the extent and timing of the current and preceding therapies were not collected. Four treatment-related options—continue, modify, switch or stop all therapy—were considered. Overall, we found a 40% change in treatment plan after NaF-PET.

Our current findings on the impact of NaF-PET are comparable to those we have

previously reported for ^{18}F-FDG-PET used for treatment monitoring of chemotherapy. Those results from data collected from 2009 through 2011 were based on 15,611 patients with similar frequencies of metastatic disease, but a somewhat different distribution of cancer types. Pancreas, small cell lung and kidney cancers were most common. Only 9% had prostate cancer and breast cancer patients were excluded since PET was covered by Medicare for treatment monitoring of breast cancer.(*24)* Overall, therapy was changed in 48.5% of the patients in the ^{18}F-FDG-PET cohort (switch 25.9%, modify 6.3% and stop 16.3%). The most notable difference was the greater frequency of stopping therapy based on the findings of ^{18}F-FDG-PET.

As expected, most of the patients (79%) in whom NaF-PET showed non-progression continued on their current therapy, whereas those with evidence of progression would have a change in treatment (which occurred in 59%). From the information collected we don't know why 41% with apparent progression continued on the same treatment, but this might have been the result of mixed responses or limited evidence of disease progression in patients with few treatment options. A worse prognosis was more likely to result in a change in treatment. In both the ^{18}F-FDG-PET and the NaF-PET NOPR cohorts, we assessed both disease extent and the clinical prognosis (better, unchanged, worse). ^{18}F-FDG-PET resulted in a "better" prognosis rating more commonly than did NaF-PET (41% vs. 28%). With both PET modalities, prognosis was rated "worse" with the same frequency (32%). Plans to continue therapy in patients with a better or unchanged prognosis were somewhat lower with ^{18}F-FDG-PET than with NaF-PET (66% vs. 79%). However, the impact of a "worse" prognosis on management was about the same with both ^{18}F-FDG-PET and NaF-

PET: plans to switch therapy or to stop all therapy were the result of a "worse" prognosis (81% in the FDG-PET cohort and 79% with NaF-PET). This may in part be a reflection of the greater uncertainty in the criteria used to define osseous metastasis response, while progression is usually clearer. The clinicians' estimation of prognosis was based on their impression and was not based on any defined parameters from the scan, such as lesion number, SUV or other criteria.

An inherent limitation of this observational registry is its non-comparative design. Therefore, we cannot claim that NaF-PET is superior to traditional BS, other bone imaging approaches, or FDG-PET. Given the relatively good prognosis of bone-only metastatic disease in patients with prostate and breast cancer, prospective studies will be necessary to define the optimal interval between tests. The NOPR data do not allow us to assess whether the clinical action plans were beneficial or appropriate or whether the interval between scans is optimal. Nonetheless, our results suggest that NaF-PET leads to alterations in planned treatment in a substantial fraction of patients with osseous metastatic disease. The impact of NaF-PET in this setting is greatest in patients who were found to have evidence of progressive disease. Most such patients had plans of switching to a new active cancer-directed therapy rather than to supportive care.

REFERENCES[BAS1]

1. Weber WA. Assessing tumor response to therapy. *J Nucl Med.* 2009;50:1S-10S.

2. Morris MJ, Autio KA, Basch EM, Danila DC, Larson S, Scher HI. Monitoring the clinical outcomes in advanced prostate cancer: what imaging modalities and other markers are reliable? *Semin Oncol.* 2013;40:375-392.

3. Gaeta CM, Vercher-Conejero JL, Sher AC, Kohan A, Rubbert C, Avril N. Recurrent and metastatic breast cancer PET, PET/CT, PET/MRI: FDG and new biomarkers. *Q J Nucl Med Mol Imaging.* 2013;57:352-366.

4. Brenner AI, Koshy J, Morey J, Lin C, DiPoce J. The bone scan. *Semin Nucl Med.* 2012;42:11-26.

5. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 2.2014. *J Natl Compr Canc Netw.* 2014;12:686-718.

6. Gralow JR, Biermann JS, Farooki A, et al. NCCN task force report: Bone health in cancer care. *J Natl Compr Canc Netw.* 2013;11:S1-S50.

7. Costelloe CM, Rohren EM, Madewell JE, et al. Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. *Lancet Oncol.* 2009;10:606-614.

8. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with ^{18}F-fluoride: applying new technology to an old tracer. *J Nucl Med.* 2008;49:68-78.

9. Li Y, Schiepers C, Lake R, Dadparvar S, Berenji GR. Clinical utility of ^{18}F-fluoride PET/CT in benign and malignant bone diseases. *Bone.* 2012;50:128-139.

10. Segall G, Delbeke D, Stabin MG, et al. SNM practice guideline for sodium ^{18}F-fluoride

PET/CT bone scans 1.0. *J Nucl Med.* 2010;51:1813-1820.

11. Mick CG, James T, Hill JD, Williams P, Perry M. Molecular imaging in oncology: (18)F-sodium fluoride PET imaging of osseous metastatic disease. *AJR Am J Roentgenol.* 2014;203:263-271.

12. Damle NA, Bal C, Bandopadhyaya GP, et al. The role of ^{18}F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and ^{99}mTc-MDP bone scan. *Jpn J Radiol.* 2013;31:262-269.

13. Chakraborty D, Bhattacharya A, Mete UK, Mittal BR. Comparison of ^{18}F fluoride PET/CT and ^{99}mTc-MDP bone scan in the detection of skeletal metastases in urinary bladder carcinoma. *Clin Nucl Med.* 2013;38:616-621.

14. Bortot DC, Amorim BJ, Oki GC, et al. ^{18}F-fluoride PET/CT is highly effective for excluding bone metastases even in patients with equivocal bone scintigraphy. *Eur J Nucl Med Mol Imaging.* 2012;39:1730-1736.

15. Iagaru A, Mittra E, Dick DW, Gambhir SS. Prospective evaluation of (99m)Tc MDP scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT for detection of skeletal metastases. *Mol Imaging Biol.* 2012;14:252-259.

16. Yen RF, Chen CY, Cheng MF, et al. The diagnostic and prognostic effectiveness of F-18 sodium fluoride PET-CT in detecting bone metastases for hepatocellular carcinoma patients. *Nucl Med Commun.* 2010;31:637-645.

17. Withofs N, Grayet B, Tancredi T, et al. ^{18}F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. *Nucl Med Commun.* 2011;32:168-176.

18. Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer. Pub 100-03 Medicare National Coverage Determinations - Transmittal 119. http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/2010-Transmittals-Items/CMS1234261.html (accessed November 11, 2013).

19. Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF, Coleman RE. Impact of ^{18}F-fluoride PET in patients with known prostate cancer: initial results from the National Oncologic PET Registry. *J Nucl Med.* 2014;55:574-581.

20. Hillner BE, Siegel BA, Hanna L, et al. Impact of ^{18}F-Fluoride PET on intended management of patients with cancers other than prostate cancer: Results from the National Oncologic PET Registry. *J Nucl Med.* 2014;55:1054-1061.

21. Hillner BE, Siegel BA, Liu D, et al. Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. *J Clin Oncol.* 2008;26:2155-2161.

22. Hillner BE, Siegel BA, Shields AF, et al. The impact of positron emission tomography (PET) on expected management during cancer treatment: findings of the National Oncologic PET Registry. *Cancer.* 2009;115:410-418.

23. Hillner BE, Siegel BA, Shields AF, et al. Relationship between cancer type and impact of PET and PET/CT on intended management: findings of the National Oncologic PET Registry. *J Nucl Med.* 2008;49:1928-1935.

24. Hillner BE, Siegel BA, Hanna L, et al. Impact of ^{18}F-FDG PET used after initial treatment of cancer: comparison of the National Oncologic PET Registry 2006 and 2009 cohorts.

J Nucl Med. 2012;53:831-837.

25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.

26. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50 Suppl 1:122S-150S.

27. Hayashi N, Costelloe CM, Hamaoka T, et al. A prospective study of bone tumor response assessment in metastatic breast cancer. *Clin Breast Cancer.* 2013;13:24-30.

28. Lecouvet FE, Talbot JN, Messiou C, Bourguet P, Liu Y, de Souza NM. Monitoring the response of bone metastases to treatment with magnetic resonance imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer.* 2014;50:2519-2531.

29. Dennis ER, Jia X, Mezheritskiy IS, et al. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. *J Clin Oncol.* 2012;30:519-524.

30. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26:1148-1159.

31. Hamaoka T, Costelloe CM, Madewell JE, et al. Tumour response interpretation with new tumour response criteria vs the World Health Organisation criteria in patients

with bone-only metastatic breast cancer. *Br J Cancer.* 2010;102:651-657.

32. Vassiliou V, Andreopoulos D, Frangos S, Tselis N, Giannopoulou E, Lutz S. Bone metastases: assessment of therapeutic response through radiological and nuclear medicine imaging modalities. *Clin Oncol (R Coll Radiol).* 2011;23:632-645.

Table 1: Pre-PET profile of treatment monitoring of systemic therapy

	Prostate	Breast	Lung	Others	Combined	Difference between cancer types Chi-square,p-value†
Total scans (% of cohort)	1,940 (68.3)	476(16.8)	185(6.5)	238(8.4)	2,839 (100)	
Clinical manifestations at the time of NaF-PET						P <.0001
Elevated or rising tumor marker(s)*	709 (36.5)	181 (38.0)	94 (50.8)	101 (42.4)	1,085 (38.2)	
Bone pain	583 (30.1)	45 (9.5)	3 (1.6)	13 (5.5)	644 (22.7)	
Bone pain & rising tumor marker(s)*	314 (16.2)	164 (34.5)	57 (30.8)	92 (38.7)	627 (22.1)	
Other imaging findings	109 (5.6)	27 (5.7)	10 (5.4)	11 (4.6)	157 (5.5)	
Other evidence	170 (8.8)	39 (8.2)	8 (4.3)	12 (5.0)	229 (8.1)	
None	55 (2.8)	20 (4.2)	13 (7.0)	9 (3.8)	97 (3.4)	
Pre-PET summary stage (%)						P <.0001
No evidence of disease	73(3.8)	38 (8.0)	7 (3.8)	10 (4.2)	128 (4.5)	
Local	160 (8.2)	8 (1.7)	15 (8.1)	15 (6.3)	198 (7.0)	
Regional	53 (2.7)	6 (1.3)	16 (8.6)	1 (0.4)	76 (2.7)	
Single distant metastases	168 (8.7)	54 (11.3)	20 (10.8)	26 (10.9)	268 (9.4)	
Multiple distant metastases	1,082 (55.8)	311 (65.3)	118 (63.8)	159 (66.8)	1,670 (58.8)	
Unknown	404 (20.8)	59 (12.4)	9 (4.9)	27 (11.3)	499 (17.6)	
Pre-PET Suspected Response (%)						P <.0001
Probable complete response	105 (5.4)	56(11.8)	14 (7.6)	22 (9.2)	197 (6.9)	
Possible partial response	972(50.1)	252 (52.9)	103 (55.7)	134 (56.3)	1,461 (51.5)	
Suspect no response	212 (10.9)	79 (16.6)	34 (18.4)	49 (20.6)	374 (13.2)	
Suspect progression	651 (33.6)	89 (18.7)	34 (18.4)	33 (13.9)	807 (28.4)	
Pre-PET Treatment plan (%)						P <.0001
Continue current treatment	1,211 (62.4)	365 (76.7)	141 (76.2)	194(81.5)	1,911 (67.3)	
Modify dose or schedule	145 (7.5)	26 (5.5)	14 (7.6)	15 (6.3)	200 (7.0)	
Switch to another treatment	571 (29.4)	81 (17.0)	28 (15.1)	25 (10.5)	705 (24.8)	
Stop treatment and switch to supportive care	13 (0.7)	4 (0.8)	2 (1.1)	4 (1.7)	23 (0.8)	
Comparison with prior bone imaging?						P <.0001
Comparison made (%)	1,520 (78.4)	362 (76.1)	120 (64.9)	158(66.4)	2,160 (76.1)	
Conventional BS (%)	423 (21.8)	71 (14.9)	11 (5.9)	25 (10.5)	530 (18.7)	
NaF-PET Scan (%)	1,097 (56.5)	291 (61.1)	109 (58.9)	133(55.9)	1,630 (57.4)	
No comparison made (%)	420 (21.6)	114 (23.9)	65 (35.1)	80 (33.6)	679 (23.9)	

*Abnormal tumor markers including elevated alkaline phosphatase.

† Pearson's chi-squared tests were used to assess the association between each pre-PET profile characteristic and cancer type. If significant, certain contrasts were constructed for the comparisons of interest.

Table 2: Comparison of pre-PET and post-PET therapeutic plans

	Pre-PET therapeutic plan				
	Continue current treatment	**Modify dose or schedule**	**Switch to another treatment**	**Stop treatment and switch to supportive care**	**Overall Change, %**
Scans, (%)	1,911 (67.3)	200 (7.0)	705 (24.8)	23 (0.8)	
Post-PET plans (rows)					
All cancers					40.3
Continue current therapy	1,286 (67.3)	106 (53.0)	258 (36.6)	11 (47.8)	
Modify dose or schedule	82 (4.3)	22 (11.0)	43 (6.1)	2 (8.7)	
Switch to another therapy	497 (26.0)	64 (32.0)	382 (54.2	5 (21.7)	
Stop therapy and switch to supportive care	46 (2.4)	8 (4.0)	22 (3.1)	5 (21.7)	
Prostate					41.8*
Continue current therapy	790 (65.2)	76 (52.4)	203 (35.6)	5 (38.5)	
Modify dose or schedule	46 (3.8)	16 (11.0)	35 (6.1)	1 (7.7)	
Switch to another therapy	351 (29.0)	46 (31.7)	320 (56.0)	4 (30.8)	
Stop therapy and switch to supportive care	24 (2.0)	7 (4.8)	13 (2.3)	3 (23.1)	
Breast					39.3†
Continue current therapy	2,534 (69.3)	16 (61.5)	38 (46.9)	4 (100.0)	
Modify dose or schedule	17 (4.7)	1 (3.8)	5 (6.2)	0 (0)	
Switch to another therapy	91 (24.9)	9 (34.6)	35 (43.2)	0 (0)	
Stop therapy and switch to supportive care	4 (1.1)	0	3 (3.7)	0 (0)	
Other cancers ∫					34.5
Continue current therapy	243 (72.5)	14 (48.3)	17 (32.1)	2 (33.3)	
Modify dose or schedule	19 (5.7)	5 (17.2)	3 (5.7)	1 (16.7)	
Switch to another therapy	55 (16.4)	9 (31.0)	27 (50.9)	1 (16.7)	
Stop therapy and switch to supportive care	18 (5.4)	1 (3.4)	6 (11.3)	2 (33.3)	

Agreement shown in shaded cells.

∫ Other cancers include lung cancer

† Difference between breast cancer and other cancer patients, p=0.20.

* Difference between prostate and other cancer patients, p=0.018.

Table 3: Impact of change since comparison scan and estimated prognosis on post-PET plans

			Post-PET plans			
	N*		**Continue current treatment**	**Modify dose or schedule**	**Switch to another treatment**	**Stop treatment and switch to supportive care**
All scans	2,839		1,661(58.5)	149 (5.2)	948 (33.4)	81 (2.9)
Comparison made to prior NaF-PET	1,630					
No change, normal	290 (17.8)		218 (75.2)	10 (3.4)	50 (17.2)	12 (4.1)
Resolution of previously seen metastatic disease	30 (1.8)		24 (80.0)	1 (3.3)	1 (3.3)	4 (13.3)
Decrease in metastases	275 (16.9)		238 (86.5)	10 (3.6)	22 (8.0)	5 (1.8)
No change in metastases	443 (27.2)		345 (77.9)	23 (5.2)	64 (14.4)	11 (2.5)
Progression of metastases	506 (31.0)		166 (32.8)	30 (5.9)	300 (59.3)	10 (2.0)
New metastases	86 (5.3)		30 (34.9)	5 (5.8)	50 (58.1)	1 (1.2)
Prognosis in light of PET (all scans)						
Better	796 (28.0)		643 (80.8)	37 (4.6)	74 (9.3)	42 (5.3)
No change	1,128(39.7)		892 (79.1)	42 (3.7)	177 (15.7)	17 (1.5)
Worse	915 (32.2)		126 (13.8)	70 (7.7)	697 (76.2)	22 (2.4)

* The relative percentage of the column