Impact of ^{18}F-Fluoride PET on Intended Management of Patients with Cancers Other Than Prostate Cancer: Results from the National Oncologic PET Registry

Bruce E. Hillner[1], Barry A. Siegel[2], Lucy Hanna[3], Fenghai Duan[3], Anthony F. Shields[4], Bruce Quinn[5], and R. Edward Coleman[†6]

[1]*Department of Internal Medicine and the Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia;* [2]*Division of Nuclear Medicine, Mallinckrodt Institute of Radiology and the Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri;* [3]*Departments of Biostatistics and Center for Statistical Sciences, Brown University, Providence, Rhode Island;* [4]*Karmanos Cancer Institute, Wayne State University, Detroit, Michigan;* [5]*Foley Hoag LLC, Boston, Massachusetts; and* [6]*Department of Radiology, Duke University School of Medicine, Durham, North Carolina*

The National Oncologic PET Registry prospectively assessed the impact of PET with ^{18}F-sodium fluoride (NaF PET) on intended management of Medicare patients with suspected or known osseous metastasis. We report our findings for cancers other than prostate and make selected comparisons to our previously reported prostate cancer cohort. **Methods:** Data were collected from both referring and interpreting physicians before and after NaF PET in patients (age ≥ 65 y) stratified for initial staging (IS; $n = 570$), for suspected first osseous metastasis (FOM; $n = 1{,}814$; breast, 781 [43%]; lung, 380 [21%]; and all other cancers, 653 [36%]), and for suspected progression of osseous metastasis (POM; $n = 435$). **Results:** The dominant indication was bone pain. If NaF PET were unavailable, conventional bone scintigraphy would have been ordered in 85% of patients. In IS, 28% of patients had suspected or confirmed nonosseous metastasis. If neither conventional bone scintigraphy nor NaF PET were available, referring physicians would have ordered other advanced imaging more than 70% of the time rather than initiate treatment for suspected FOM (11%–16%) or POM (18%–22%). When intended management was classified as either treatment or nontreatment, the intended management change for each cancer type was highest in POM, lower in IS, and lowest in FOM. For suspected FOM, intended management change was lower in breast (24%), lung (36%), or other cancers (31%), compared with prostate cancer (44%) ($P < 0.0001$), but the NaF PET finding (normal/benign/equivocal, probable, or definite metastases) frequencies were similar across cancer types. After normal/benign/equivocal PET results, 15% of breast, 30% lung, and 38% prostate cancer patients had treatment, likely reflecting differences in management of nonosseous disease. For patients with definite metastasis on NaF PET, nonprostate, compared with prostate, cancer patients had post-PET plans for more frequent biopsy, alternative imaging, chemotherapy, and radiotherapy. In the smaller IS and POM cohorts, differences among cancer types were not significant. **Conclusion:** Overall, NaF PET led to change in intended management in a substantial fraction of nonprostate cancer patients. In the setting of suspected FOM, NaF PET had a lower immediate impact on the treat/nontreat decision in nonprostate versus prostate cancer patients, which is consistent with current practice guidelines.

Key Words: positron emission tomography; sodium fluoride/diagnostic use; patient registry; bone scintigraphy; lung cancer; breast cancer; prostate cancer

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The skeleton is the most common site of distant metastasis in men with prostate cancer and women with breast cancer (*1*). Osseous metastasis also occurs in other cancers (lung, bladder, kidney, thyroid, and other solid tumors), usually together with evidence of extraosseous metastasis (*2*). Osseous metastatic disease accounts for substantial morbidity, ranging from pain to debilitating complications such as pathologic fractures and spinal cord compression (*3*). In addition to local radiotherapy, bisphosphonates and denosumab have modest efficacy in reducing skeletal complications across cancer types, although these therapies have not to date been shown to prolong survival (*4,5*).

There are numerous imaging techniques available to assess osseous metastasis (*5–7*) including conventional radiography; CT; MR imaging; conventional bone scintigraphy (BS) with ^{99m}Tc-diphosphonates, conducted via either planar imaging or SPECT; and PET with ^{18}F-FDG or ^{18}F-sodium fluoride (NaF).

Optimal imaging strategies for identifying osseous metastasis differ between prostate cancer and other solid tumors. For many years, the dominant effective method for whole-body imaging has been conventional BS. This modality has variable sensitivity by cancer type, reflecting differences in the dominant osseous pathobiology—predominant osteoblastic disease in prostate cancer versus predominant osteolytic disease in breast, lung, and most other solid tumors (*2,5,8*). One alternative to conventional BS is NaF PET, with or without integrated CT. It has been reported that NaF PET offers many advantages in comparison to BS including superior pharmacokinetics with a shorter time from injection to imaging, higher bone uptake, faster blood clearance, lower radiation dose, immediate CT evaluation, and superior image quality (*9,10*). Additionally, a number of studies that have directly compared the relative accuracy of NaF PET and conventional BS have documented its superior performance (*11–17*).

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For correspondence or reprints contact: Bruce E. Hillner, Virginia Commonwealth University, 1101 East Marshall St., Rm. 7013 (Sanger Hall), Richmond, VA 23298-0170.
E-mail: Hillner@vcu.edu
†Deceased.
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Limited data exist on how physicians use NaF PET in clinical practice. 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 our findings of NaF PET's impact on intended management in men with prostate cancer (*19*). We now report the impact of NaF PET on intended management for patients with other cancer types and compare these results with those in prostate cancer patients.

MATERIALS AND METHODS

NOPR Design and Workflow

NOPR was initially designed to assess the impact of ^{18}F-FDG PET on intended cancer management (*20*). The NaF PET registry follows the same basic design as the ^{18}F-FDG PET registry in that data are collected prospectively for each case from the physician requesting NaF PET, from the PET facility, and from the interpreting physician. Detailed descriptions of NOPR operations, human subject protection procedures, and results for ^{18}F-FDG PET's impact on physicians' intended management were previously reported (*21–24*). Patient registration and data are submitted at https://www.cancerpetregistry.org. Research use of the data for any given case required patient and both referring and interpreting physician consent. This study is registered at ClinicalTrials.gov (#NCT00868582).

The pre-PET form collects the indication; cancer type; symptoms, signs, or other findings prompting the scan; working summary stage; and the referring physician's management plans, including treatment details, if NaF PET were unavailable (with the added assumption that BS also would not be an option to avoid having this selected as the default response). Alternatives to treatment were other types of imaging if both BS and NaF PET were unavailable, tissue biopsy, stopping current therapies, and observation. NaF PET findings were categorized as normal or benign disease only versus equivocal, probable, or definite evidence of osseous metastatic disease. Osseous metastatic disease was further characterized as unifocal, multifocal, or diffuse. The referring physician completed the post-PET form by recording the planned management in light of the PET findings (using the same options listed on the pre-PET form) as well as recording the impression of the change in the extent of the cancer, the patient's summary stage, prognosis, and whether the NaF PET allowed additional noninvasive or invasive procedures to be avoided.

NaF PET Accrual

Patient accrual began January 31, 2011. Preliminary analysis revealed a more than 60% rate of pre-PET plans of other imaging if neither NaF PET nor conventional BS were available. To better understand this decision strategy, data collection was revised to ask what the alternative imaging method would be. If prior BS was available to the interpreting physician, the revised form requested the date of that study. These revisions were implemented on January 27, 2012, and the present report uses data from that date through December 31, 2013. Our prior report analyzing NaF PET in men with prostate cancer used cases accrued from January 27, 2012, through December 31, 2012 (*19*). The extended prostate cancer cohort in this report includes both the previously reported cases (through December 31, 2012) and the 4,753 further cases accrued through December 31, 2013.

In this report, we focus on NaF PET performed for 1 of 3 indications: initial staging (IS) that may or may not precede local therapy of the primary cancer, suspected first osseous metastasis (FOM) of patients with previously treated local disease, and suspected progression of osseous metastasis (POM) in patients previously treated or now being treated for osseous metastasis. We excluded patients younger than 65 y and those without pathologically confirmed cancer. The fully consented research dataset included 11,103 scans; 13.6% of patients underwent two or more scans. The research dataset accounted for 84.7% of the total registry scans during this interval.

Statistical Analysis

We used the same statistical approach as in our prior analyses. Intended management was classified as either treatment or nontreatment and its change was reported as the proportion of scans with different pre- and post-PET plans relative to the total scan number. The 95% confidence intervals of these proportions were calculated using the normal approximation for a binomial distribution. Multiple scans from the same patient were assumed to be independent observations. As we have previously reported (*19,22,24*), to address overestimation of PET's impact by inclusion of cases for which the pre-PET plan was imaging, we computed an imaging-adjusted impact by assuming no change in intended management for all cases for which the initial management plan was alternative imaging. Differences between nonprostate and prostate cancer groups for specific comparisons were assessed for statistical significance with χ^2 analyses. All statistical analyses were performed using SAS (version 9.3; SAS Institute).

RESULTS

Patient Characteristics

The analysis cohort consisted of 2,819 (25.4%) nonprostate, compared with 8,284 (74.6%) prostate, cancer scans. The indications for the nonprostate cancer scans were IS (n = 570 scans), FOM (n = 1,814), and POM (n = 435). The most common cancer was breast cancer (44% of patients assessed for FOM and POM; supplemental material [available at http://jnm.snmjournals.org]). About one quarter of patients in the IS and FOM subgroups had lung cancer. Bladder, kidney and colorectal cancer, myeloma, and lymphoma each represented from 3% to 5% of the cohort. Stratified by IS, FOM, and POM, each other cancer type accounted for fewer than 25 patients (cumulatively, 18% of the nonprostate cancer cohort).

The numbers of breast, lung, and all other cancer patients (range, 166–223) scanned for IS were each less than one tenth of those with prostate cancer (n = 2,301). Symptoms, signs, and other findings prompting NaF PET were quite different for nonprostate versus prostate cancer patients (Table 1). For nonprostate cancer patients, only 30%–46% of patients had no symptoms or evidence of suspected metastases. Bone pain was the dominant and only sign in 36%–46% of patients depending on indication. Evidence of metastasis using other imaging was noted in about 10% of patients. In contrast, for prostate cancer patients, elevated or rising prostate-specific antigen was the dominant indication, and 59% of patients had no specific symptoms or other indications.

When NaF PET was requested for IS, the referring physicians' pre-PET estimates of summary stage differed for nonprostate and prostate cancer patients, with 43% lung, 30% other, 15% breast, and 8% prostate cancer, respectively, already judged to have some type of distant metastasis.

Referring physicians recorded the prescan summary stage as unknown in more than one third of patients with all cancer types referred for suspected FOM. Before the scan, breast and prostate cancer patients had higher frequencies of no evidence of disease

TABLE 1
Profile of Patients Undergoing NaF PET Stratified by Indication

Profile	IS				FOM				POM		
	Breast	NSCLC	Other	Prostate	Breast	NSCLC	Other	Prostate	Breast	Other	Prostate
Scans by indication (*n*)	181	166	223	2,301	781	380	653	4,686	199	236	1,297
Symptoms, signs, or test results (%)											
None	45.9	30.1	38.1	58.9	10.0	18.9	19.9	16.2	8.5	12.7	10.7
Pain only	36.5	45.8	37.7	5.0	57.0	56.6	49.3	14.6	47.2	52.5	25.9
Elevated or rising tumor marker*	1.7	3.6	1.8	27.2	7.2	2.1	3.8	49.5	10.6	3.8	36.5
Evidence from other imaging	10.5	11.4	9.4	4.5	9.6	10.3	10.1	6.2	6.5	11.9	5.9
Other	5.5	9.0	13.0	4.4	16.3	12.1	16.8	13.6	27.1	19.1	20.9
Pre–NaF PET summary stage (%)											
Local/no evidence of disease	39.8	12.0	22.0	57.8	28.2	19.5	21.7	24.8	4.5	6.4	5.2
Regional (direct extension or nodal)	14.9	12.7	9.0	5.0	1.9	7.6	3.4	5.0	0.5	1.3	0.8
Single metastasis	5.0	13.3	5.8	3.3	11.1	12.6	10.6	11.2	13.6	12.7	15.2
Multiple metastases	10.5	29.5	24.2	4.6	19.6	30.0	30.5	21.1	74.9	68.2	67.3
Unknown	29.8	32.5	39.0	29.5	39.2	30.3	33.8	37.8	6.5	11.4	11.5
Conventional BS would have been ordered if NaF PET had been unavailable (%)	88.4	78.9	84.3	91.7	82.7	77.6	74.9	85.9	74.9	68.6	87.4

*Abnormal tumor markers including elevated alkaline phosphatase.
NSCLC = non–small cell lung cancer.

(25%–28%) and lower frequencies of multiple metastases (20%). In FOM, bone pain was again the dominant nonprostate cancer indication and elevated or rising prostate-specific antigen the dominant indication in prostate cancer patients.

Conventional BS would have been performed slightly less often in nonprostate, compared with prostate, cancer patients for all indications yet would have been performed in more than 75% if NaF PET were unavailable.

Pre-PET Plans in Lieu of NaF PET or BS

Table 2 shows the results of the thought experiment in which referring physician were asked to define their pre-PET plan if both NaF PET and conventional BS were unavailable. In patients with previously treated nonprostate cancers (FOM and POM), referring physicians were rarely prepared to make a treatment plan (11%–22%) and would predominantly undertake other imaging studies (66%–77%). In this group, the most frequent pre-PET plan if NaF PET were unavailable would be ^{18}F-FDG PET (25%–30%), followed by body CT or MR imaging (12%–21%). In prostate cancer patients, the skew between treatment and alternative imaging was less extreme, and body CT was more likely to be the alternative imaging modality. In FOM, in nonprostate cancer patients, conventional radiographs were planned in 10%–13%. For other groups (IS, POM, or prostate cancer patients), radiographs were even less likely (<4% of patients).

Intended plans involving treatment were noted in only 14% of patients imaged for suspected FOM and 20% for suspected POM. The higher treatment rates in prostate cancer patients were predominantly attributable to planned hormone therapy. Plans for radiotherapy and chemotherapy were minimally different across all cancer types. In nonprostate cancer patients referred for IS scans, their physicians were already planning chemotherapy in about one quarter.

Patterns of NaF PET Findings

Table 3 (top) shows the distribution of summary categories of recorded PET findings. Within each imaging indication, there were minimal differences between nonprostate and prostate cancer patients. Scan findings were interpreted as definitely positive for osseous metastasis in 13%–24% of IS, 25%–28% of FOM, and 63%–76% of POM scans, respectively.

Summary of Impact on Further Testing

Referring physicians indicated that the NaF PET findings reduced the need for additional diagnostic tests in 78%–90%.

Impact on Treatment Versus Nontreatment Plans

Table 3 (center) summarizes the impact of NaF PET on intended management, classified as either treatment or nontreatment, before and after PET.

There was a common pattern among all patients scanned for IS or POM. For these indications, patients with nontreatment (watch, biopsy, and image) pre-PET plans had post-PET plans for treatment (range, 36%–47% in IS, and 47%–55% in POM) that were always greater than plans for nontreatment (range, 15%–28% in IS, and 23%–35% in POM). In contrast, among the smaller groups for all indications with pre-PET treatment plans, few patients switched from treatment to nontreatment (4%–7%).

Given the relatively small numbers of scans for each cancer type by scan indication, the confidence intervals around the point estimates were wide. However, the overall rates of change in intended management (classified as treatment to nontreatment or vice versa) were similar for these indications and across cancer types (range, 43%–60%). The imaging-adjusted rates, for which those cases with initial plans of alternative imaging were not

TABLE 2
Pre-PET Plans of Patients Undergoing NaF PET Stratified by Indication

Profile	IS				FOM				POM		
	Breast	NSCLC	Other	Prostate	Breast	NSCLC	Other	Prostate	Breast	Other	Prostate
Scans by indication (*n*)	181	166	223	2,301	781	380	653	4,686	199	236	1,297
Pre-PET plan (%)											
Image	50.3	52.4	66.4	52.6	73.2	77.4	70.8	57.1	66.3	72.0	59.5
Body CT	9.4	11.4	16.1	23.6	16.9	18.2	16.5	22.6	17.6	19.9	21.4
Body MR imaging	9.9	10.2	11.7	12.0	13.6	15.0	11.9	16.8	15.6	20.8	18.3
^{18}F-FDG PET	25.4	27.1	32.7	14.0	26.4	29.2	29.9	13.0	25.1	24.6	15.8
Plain films	3.3	2.4	3.1	1.4	12.8	9.2	8.6	2.9	3.5	3.0	1.3
Other imaging	2.2	1.2	2.7	1.7	3.6	5.8	3.8	1.9	4.5	3.8	2.7
Treatment (overall)	39.8	38.0	24.7	39.6	11.0	10.8	15.6	25.6	21.6	17.8	29.6
Radiotherapy	26.0	22.3	9.9	33.1	6.8	5.3	7.7	12.2	10.1	5.9	8.6
Hormone	23.2	1.2	0.4	20.2	4.1	0.3	1.4	16.6	8.0	0.4	18.4
Surgery	27.6	11.4	7.6	12.6	1.4	1.1	2.0	1.8	0.5	0.0	0.3
Chemotherapy	25.4	33.7	20.6	5.1	6.1	8.7	11.3	8.5	14.6	14.4	13.5
Bisphosphonates	1.7	1.2	3.6	3.3	2.8	2.1	2.8	7.1	4.5	5.9	11.5
Biopsy	3.9	3.6	4.0	1.5	4.4	3.7	4.6	3.4	4.0	2.5	1.9
Watch/no additional therapy	6.1	6.0	4.9	6.2	11.4	8.2	9.0	13.8	8.0	7.6	8.9

*Referring physicians could select more than one treatment modality. Percentages do not sum to 100.
NSCLC = non–small cell lung cancer.

counted as having a management change, were also similar in IS and POM across cancer types (9%–14%).

Impact of Imaging for Suspected FOM

The impact of NaF PET on intended management for suspected FOM was different in nonprostate and prostate cancer patients (Tables 3 and 4; Fig. 1). For breast cancer patients with initial plans of nontreatment, the post-PET plan remained nontreatment in 78%. A similar but less marked trend was seen with lung cancer (67%) and all other cancers (69%). In contrast, a smaller fraction of prostate cancer patients (53%) continued to have nontreatment plans after PET.

Figure 1 provides additional explanation. It shows the post-PET management plans in patients with pre-PET plans of alternative imaging. By comparison with the prostate cancer cohort, patients with breast, lung, or all other nonprostate cancers had more frequent post-PET plans of watching (36% prostate vs. 56% breast [$P < 0.0001$], 48% other cancers [$P < 0.0001$], and 46% lung [$P < 0.018$]) or plans for additional imaging (11% in prostate vs. 17% in nonprostate cancer patients [$P < 0.001$]) but less frequent plans for treatment (50% prostate vs. 23% breast, 35% lung, or 33% other cancers [all $P < 0.0001$]).

Table 4 summarizes the overall frequency of change in intended management by cancer type and indication. As suggested by Figure 1, the lowest impact on intended management was in suspected FOM of breast cancer patients (24.3%), followed by all other cancers (31.1%), lung (36.0%), and prostate (43.3%) ($P < 0.0001$). The impact of scans done for IS was slightly greater, with change in intended management ranging from 42% in breast cancer to 54% in lung cancer, but was not significantly ($P = 0.059$) different by cancer type given the wide confidence intervals. For POM, even higher rates of change in intended management were found—52% all other cancers, 53% prostate, and 60% in breast cancer with similarly broad confidence intervals ($P = 0.14$). For each cancer type, the relative magnitude of change in intended management was lowest in FOM, intermediate in IS, and greatest in POM. The imaging-adjusted rates, for which cases with initial plans of alternative imaging were not counted as having a management change, were higher for prostate cancer than for nonprostate cancers (15% vs. 8%, $P < 0.0001$).

Plans Stratified by NaF PET Findings

Table 5 shows the relationship between NaF PET findings and post-PET plans by cancer types for FOM, the largest grouping. If the interpreting physician's classification of the NaF PET study was normal, benign disease, or equivocal evidence of osseous metastasis, treatment plans were lowest in breast (15%), 25% other cancers, 30% lung, and 39% prostate. About two thirds of the prostate cancer treatment plans in such cases included hormone therapy, likely a continuation of prescan care.

Findings of probable osseous metastases were uncommon (8%–11%). Twice as many nonprostate cancer patients had biopsy planned than prostate cancer patients (15% vs. 6%).

When NaF PET findings were recorded as definite osseous metastasis, 23% of breast and 19% of lung cancer patients had plans for additional, presumably confirmatory, imaging and 4%–8% for biopsy; both of these were planned more often than in prostate cancer patients (Table 4). Given definite evidence of osseous metastasis, plans for post-PET chemotherapy and radiotherapy were more common in nonprostate cancer cases than in prostate cancer cancers. This finding is consistent with treatment guidelines—that is, in prostate cancer osseous symptoms may

TABLE 3
Findings and Change in Management Associated with NaF PET by Indication

Indication	IS				FOM				POM		
	Breast	NSCLC	Other	Prostate	Breast	NSCLC	Other	Prostate	Breast	Other	Prostate
Scans by indication (*n*)	181	166	223	2,301	781	380	653	4,686	199	236	1,297
NaF PET findings (%)											
Benign	72.4	59.6	70.9	71.9	62.1	54.2	57.1	53.3	14.6	18.2	15.0
Equivocal	4.4	7.8	4.9	8.7	7.2	8.9	7.4	7.8	3.0	4.2	2.9
Probable	4.4	9.0	7.6	6.6	6.3	10.3	9.2	10.8	6.5	14.8	6.6
Definite	18.8	23.5	16.6	12.8	24.5	26.6	26.3	28.1	75.9	62.7	75.6
Unifocal	1.1	5.4	3.6	1.7	2.7	3.7	5.4	3.5	4.5	8.5	4.0
Multifocal	9.4	16.3	9.4	8.3	15.4	19.7	16.2	18.8	42.7	44.9	44.7
Diffuse	8.3	1.8	3.6	2.9	6.4	3.2	4.7	5.9	28.6	9.3	26.8
Pre-PET vs. post-PET plans (%)											
Nontreatment to treatment	66 (36.5)	78 (47.0)	105 (47.1)	956 (41.5)	162 (20.7)	119 (31.3)	171 (26.2)	1,656 (35.3)	110 (55.3)	112 (47.5)	624 (48.1)
Nontreatment to nontreatment	43 (23.8)	25 (15.1)	63 (28.3)	433 (18.8)	533 (68.2)	220 (57.9)	380 (58.2)	1,829 (39.0)	46 (23.1)	82 (34.7)	289 (22.3)
Treatment to treatment	61 (33.7)	51 (30.7)	44 (19.7)	800 (34.8)	58 (7.4)	23 (6.1)	70 (10.7)	814 (17.4)	33 (16.6)	31 (13.1)	321 (24.7)
Treatment to nontreatment	11 (6.1)	12 (7.2)	11 (4.9)	112 (4.9)	28 (3.6)	18 (4.7)	32 (4.9)	387 (8.3)	10 (5.0)	11 (4.7)	63 (4.9)
Impact on future actions											
Avoid future diagnostic tests (%)	81.2	89.8	77.6	72.0	84.4	88.4	84.5	76.5	85.9	89.4	80.9

NSCLC = non–small cell lung cancer.
Data in parentheses are percentages.

TABLE 4
Change in Intended Management by Indication and Cancer Type with Comparison to Prostate Cancer

Indication	Breast	NSCLC†	Others	Prostate‡	*P*‡
IS					
Participants (*n*)	181	166	223	2,301	
Change in intended management (%)	42.5 (35.3–49.7)	54.2 (46.6–61.8)	52.0 (45.5–58.6)	46.4 (44.4–48.5)	0.059
Imaging-adjusted frequency of change (%)	11.0 (6.5–15.6)	13.9 (8.6–19.1)	11.2 (7.1–15.4)	10.3 (9.0–11.5)	0.52
Suspected FOM					
Participants (*n*)	781	380	653	4686	
Change in intended management (%)	24.3*** (21.3–27.3)	36.0** (31.2–40.9)	31.1*** (27.5–34.6)	43.6 (42.2–45.0)	<0.0001
Imaging-adjusted frequency of change (%)	7.7*** (5.8–9.5)	8.7** (5.8–11.5)	8.0*** (5.9–10.0)	15.0 (13.9–16.0)	<0.0001
Suspected POM					
Participants (*n*)	199	–	236	1297	
Change in intended management (%)	60.3 (53.5–67.1)	–	52.1 (45.7–58.5)	53.0 (50.2–55.7)	0.14
Imaging-adjusted frequency of change (%)	11.6 (7.1–16.0)	–	9.3 (5.6–13.0)	10.9 (9.2–12.6)	0.72

†For suspected POM stratum, NSCLC participants were grouped into other cancer type.

‡For each comparison, logistic regression was performed to test difference of rates across specified cancer types on change (or imaging adjusted) in intended management, respectively. Prostate cancer group was used as reference level in regression. *P* value was calculated using global Wald test.

If global Wald test from logistic regression was significant ($P < 0.05$), individual tests were performed to find out which cancer types were different from prostate cancer (reference) in terms of change rates. Multiple comparisons were corrected for within this analysis, such that cutoff value for significance level was 0.0167 (0.05/3).

**P* value of individual test was smaller than 0.0167.

***P* value was smaller than 0.01.

****P* value was smaller than 0.001.

Data in parentheses are 95% confidence intervals, computed using normal approximation for binomial proportion.

respond adequately to hormone therapy whereas pain from osseous metastases may require more aggressive palliation in other cancers (*5,25,26*).

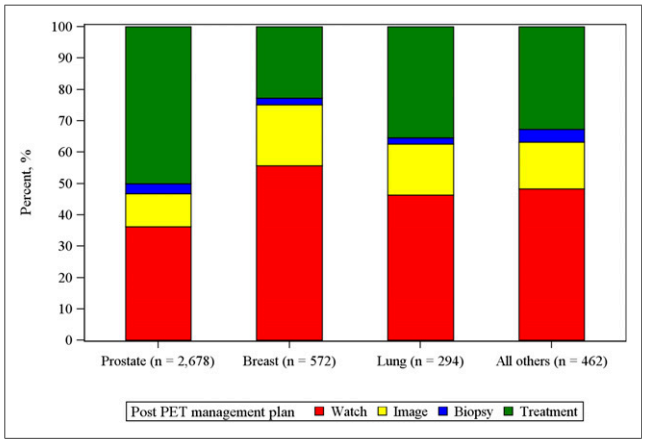

FIGURE 1. Frequency distribution of post-PET intended management plans among patients scanned for suspected FOM with pre-PET plans of alternative imaging, stratified by cancer type. Seventy-three percent of nonprostate cancer patients and 57% of prostate cancer patients scanned for suspected FOM had pre-PET plans of alternative imaging.

DISCUSSION

Suspected skeletal metastasis may be evaluated by bone-specific radionuclide imaging (with either ^{99m}Tc-diphosphonates or NaF) or by other imaging methods. For many nonprostate cancer patients, evidence from other types of advanced imaging (CT, MR imaging, or ^{18}F-FDG PET) (*26,27*) is routinely available from staging evaluations, and those studies may provide the first evidence of osseous metastasis. However, the tendency of different cancer types to produce osteoblastic versus osteolytic metastases affects the relative cancer-specific sensitivity of these different modalities (*2,8*). Generally, when the primary clinical motivation for an imaging study is to assess osseous metastasis, bone-specific methods are preferred. NaF PET has several advantages over BS, including increased sensitivity, lower radiation dose, and a less time-consuming imaging procedure.

Despite these potential advantages, until a recent CED decision allowing coverage within the NOPR of NaF PET for Medicare patients, limited data were available to determine whether and when clinicians nationwide would actually order NaF PET for older cancer patients and how such scans might affect clinical decision making. Overall, the impact of NaF PET on patient management was similar to the impact we have reported on management after ^{18}F-FDG PET (*21,22,24*).

TABLE 5
Post-PET Intended Management Stratified by NaF PET Findings in Patients with FOM

Finding	Benign				Probable				Definitive			
	Breast	NSCLC	Other	Prostate	Breast	NSCLC	Other	Prostate	Breast	NSCLC	Other	Prostate
Scans (*n*)	485	206	373	2,498	105	73	108	870	191	101	172	1,318
Scans (%)	13.6	5.8	10.5	70.1	9.1	6.3	9.3	75.3	10.7	5.7	9.7	74.0
Post-PET intended management (%)												
Watch	71.3	58.7	63.0	52.3	30.5	39.7	37.0	23.1	15.2	19.8	16.3	12.1
Biopsy	0.8	0.0	2.7	3.5	12.4	11.0	7.4	4.9	4.2	6.9	7.6	2.4
Image	12.4	11.7	9.1	6.4	23.8	13.7	22.2	15.5	23.0	18.8	11.6	7.0
Any treatment	15.5	29.6	25.2	37.8	33.3	35.6	33.3	56.4	57.6	54.5	64.5	78.5
Treatment modalities*												
Hormones	8.2	1.9	1.1	24.0	11.4	1.4	0.9	36.6	27.7	0.0	5.8	49.7
Chemotherapy	6.8	24.8	20.6	5.8	13.3	21.9	25.9	12.0	28.3	33.7	39.0	24.7
Radiotherapy	2.7	4.4	3.8	15.0	12.4	15.1	13.0	15.9	19.9	33.7	28.5	19.9
Bisphosphonate	1.2	2.9	1.3	4.3	16.2	12.3	9.3	16.7	27.2	10.9	20.9	29.3

*Referring physicians could select more than one treatment modality.
NSCLC = non–small cell lung cancer.

About one quarter of the 11,103 total scans reported here are from nonprostate cancer patients. In some cases, the new data are confirmatory. For example, prior reports indicate that the dominant clinical problem leading to bone imaging in such patients is focal bone pain (*5*). We confirmed that when NaF PET is ordered for Medicare-age patients, bone pain is the main trigger in nonprostate cancer patients, followed by findings of prior imaging studies. In contrast, in prostate cancer patients, rising prostate-specific antigen exceeded bone pain as the reported trigger for NaF PET.

The scale of the NaF PET registry provides enough nonprostate cancer patients to allow analysis by indication and by cancer type, at least for the more common cancers. The most common scan indication was FOM, where sample sizes were 3-fold larger than for IS or POM. In FOM, the NaF PET study (as categorized by the interpreting physician) was normal/benign/equivocal (60%–70%), probable metastasis (6%–11%), or definite metastasis (25%–30%). These differed minimally by cancer type. However, cancer type did affect the post-PET intended management changes (i.e., shift between treatment and nontreatment categories).

For the IS and suspected POM indications, comparing the results for breast and lung cancer with those for all other cancer types is limited by sample sizes of the latter—on average fewer than 10 consenting patients per cancer type were scanned per month for these indication. IS patients with lung and other cancers had slightly higher rates of scans scored as definite metastasis than did breast cancer patients, consistent with the fact that their pre-PET evidence for nonosseous metastasis was also greater.

In patients scanned for suspected FOM and having normal/benign or equivocal NaF PET findings, there were meaningful differences in the subsequent treatment frequency and in the treatment types planned. For example, after a negative NaF PET finding, patients with breast cancer were planned for observation more frequently (70%) than those with lung (56%) or prostate (50%) cancers. This finding likely reflects differences in the prescan care—hormone therapy was a continuation treatment for men with biochemical recurrences, many lung cancer patients were receiving chemotherapy for nonosseous metastasis, and most breast cancer patients were receiving no therapy and had no nonosseous metastases. When NaF PET findings were categorized as definite metastasis, about one quarter of breast and lung cancer patients had post-PET plans for biopsy or other imaging rather than proceeding directly to treatment. This finding likely reflects physician assessment of a lower post-PET probability of true osseous metastasis for these cancer types, compared with prostate cancer, and is fully consistent with current practice guidelines (*5,26,27*). In these cases, NaF PET findings likely direct the optimal biopsy site, rather than obviating the biopsy entirely.

Comparison of post-PET treatment plans for different cancer types after NaF PET showing definite metastasis illustrates differences between cancer types that seem logical. About one half of breast cancers are initially responsive to hormone therapy; thus, the observed 46% fraction of hormone therapy plans is consistent. In all cancer types, treatments plans predominantly included 2 different modalities. Chemotherapy (either new or continued) and radiotherapy were slightly more common in each of the nonprostate groups than in prostate cancer. The lower imaging-adjusted impact in FOM in nonprostate cancers (8%) than among prostate cancer and prior reports from our ^{18}F-FDG PET registry (*22,24*) are predominantly due to there being fewer eligible patients because about three quarters had pre-PET plans for other imaging.

Limitations of the NOPR and other decision-impact studies have been discussed in our previous publications (*19,21,22,24*). The reported intended management changes in this study were not confirmed by chart review. However, when we have conducted claims analyses of inferred care, actual clinical procedures or management were reasonably consistent with those reported on NOPR decision-impact questionnaires (*28,29*). There is no control group that was randomized to undergo BS rather than NaF PET, so the relative value of these 2 modalities on decision making or on

health outcomes cannot be assessed from the data presented here. A randomized, multicenter trial in suspected FOM in breast, lung, and prostate cancer patients with centralized masked interpretation is comparing BS and NaF PET. The trial has completed accrual, but the results have not yet been reported (*30*). The present study is specific to the Medicare population and enrolled a larger number of patients than any prior study of NaF PET.

CONCLUSION

In the current study, we have shown that referring physicians change their intended management after NaF PET (from nontreatment to treatment or vice versa) in about one quarter to more than half of patients with cancers other than prostate cancer, depending on cancer type and the indication for imaging. These results are similar to those we have previously reported for prostate cancer. Our results cannot directly address whether NaF PET is superior to conventional BS for detection of osseous metastasis generally or whether NaF PET should be differentially recommended based on cancer type. However, taken together with other studies that have directly compared the relative accuracy of these 2 forms of radionuclide bone imaging (*11–17*), the present data indicate that NaF PET has substantial impact on clinical decision making in patients with nonprostate cancers as well as in the larger number of patients with prostate cancer in whom this test is currently being used.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. NOPR is sponsored by the World Molecular Imaging Society and managed by the American College of Radiology. It is self-supported by the fees paid by participating PET facilities. No other potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer.* 2002;2:584–593.
2. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;350: 1655–1664.
3. Coleman RE. Bone cancer in 2011: prevention and treatment of bone metastases. *Nat Rev Clin Oncol.* 2012;9:76–78.
4. Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol.* 2011;29: 1221–1227.
5. Gralow JR, Biermann JS, Farooki A, et al. NCCN task force report: bone health in cancer care. *J Natl Compr Canc Netw.* 2013;11(suppl 3):S-1–S-50.
6. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: ^{99m}Tc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, ^{18}F-fluoride PET, and ^{18}F-fluoride PET/CT. *J Nucl Med.* 2006;47:287–297.
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. Nielsen OS, Munro A, Tannock I. Bone metastases: pathophysiology and management policy. *J Clin Oncol.* 1991;9:509–524.
9. 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.
10. 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.
11. 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.
12. 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.
13. Chakraborty D, Bhattacharya A, Mete UK, Mittal BR. Comparison of ^{18}F fluoride PET/CT and ^{99m}Tc-MDP bone scan in the detection of skeletal metastases in urinary bladder carcinoma. *Clin Nucl Med.* 2013;38:616–621.
14. Schirrmeister H, Glatting G, Hetzel J, et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and ^{18}F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med.* 2001;42:1800–1804.
15. Schirrmeister H, Guhlmann A, Elsner K, et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus ^{18}F PET. *J Nucl Med.* 1999;40:1623–1629.
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. 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.
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 April 22, 2014.
19. Hillner BE, Siegel BA, Hanna L, Fenghai D, 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, Liu D, Coleman RE, et al. The National Oncologic PET Registry (NOPR): design and analysis plan. *J Nucl Med.* 2007;48:1901–1908.
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. 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.
23. 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.
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. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 1.2014. *J Natl Compr Canc Netw.* 2013;11:1471–1479.
26. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5S):e211S-250S.
27. Theriault RL, Carlson RW, Allred C, et al. Breast cancer, version 3.2013. *J Natl Compr Canc Netw.* 2013;11:753–760.
28. Hillner BE, Tosteson AN, Tosteson TD, et al. Intended versus inferred care after PET performed for initial staging in the National Oncologic PET Registry. *J Nucl Med.* 2013;54:2024–2031.
29. Hillner BE, Tosteson TD, Tosteson AN, et al. Intended versus inferred management after PET for cancer restaging: analysis of Medicare claims linked to a coverage with evidence development registry. *Med Care.* 2013;51:361–367.
30. F18PET/CT Versus TC-MDP Scanning to Detect Bone Mets. NCT00882609. http://clinicaltrials.gov/show/NCT00882609. Accessed April 22, 2014.