Impact of ^{18}F-Fluoride PET in Patients with Known Prostate Cancer: Initial Results from the National Oncologic PET Registry

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Under Medicare's Coverage with Evidence Development policy, PET using ^{18}F-sodium fluoride (NaF PET) to identify osseous metastasis became a covered service if prospective registry data were collected. The National Oncologic PET Registry (NOPR) developed a NaF PET registry built on the foundation of its prior registry for PET with ^{18}F-FDG. Men with prostate cancer represented 72% of the cases. **Methods:** Prospective data before and after NaF PET were collected from referring and interpreting physicians. The analysis set consisted of consenting men age 65 y or older with prostate cancer undergoing NaF PET for initial staging (IS, n = 1,024), suspected first osseous metastasis (FOM, n = 1,997), or suspected progression of osseous metastasis (POM, n = 510). **Results:** Referring physicians indicated that if NaF PET were not available, other advanced imaging (body CT, MR imaging, or ^{18}F-FDG PET) would be their plan in about half of the cases. After NaF PET, the postimaging plan was revised to treatment in 77%, 52%, and 71% for IS, FOM, and POM, respectively. When intended management was classified as either treatment or nontreatment, the overall change in intended management ranged from 44% to 52% and from 12% to 16% if no effect was assumed for those cases with pre-PET plans for other imaging (imaging-adjusted impact). Interpreting physicians recorded definite findings of bone metastasis in 14%, 29%, and 76% for IS, FOM, and POM, respectively. The intended care patterns varied widely across indication and scan abnormality category combinations. **Conclusion:** NaF PET has high overall impact, principally related to its effect on replacing intended use of other advanced imaging. Its imaging-adjusted impact was similar to that observed with ^{18}F-FDG PET for restaging or suspected recurrence in other cancer types.

Key Words: PET; prostate cancer; registry; bone scintigraphy; prospective studies

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Prostate cancer bone metastasis remains a frequent, feared event in terms of number of men affected, its impact on quality of life, and uncertainties in confirming the diagnosis (*1*). Tissue biopsy of suspected bone metastases is rarely used and is often risky and nondefinitive. Conventional ^{99m}Tc-methylene diphosphonate planar bone scintigraphy (BS) has long been the standard for first-line detection. The search for alternatives has been ongoing because of the limited sensitivity of BS, especially for low-volume metastases, and the limited specificity chiefly because of degenerative changes (*2*).

One alternative to BS is PET, with or without integrated CT, using ^{18}F-sodium fluoride (hereafter referred to as NaF PET) (*3,4*). The National Cancer Institute summarized the literature regarding NaF PET for detection of osseous metastasis as part of a 2009 Food and Drug Administration new drug application for NaF (*4,5*). This review heavily informed the 2010 Centers for Medicare and Medicaid Services (CMS) coverage decision on NaF PET use to identify bone metastasis in Medicare beneficiaries with cancer. CMS concluded that current evidence was inconsistent and that there was no evidence of NaF PET–based treatment strategies having a favorable impact on patient-centered outcomes (*6*). Thus, CMS applied coverage-with-evidence-development (CED) criteria (*7,8*)—namely, that coverage required participation in a suitable prospective registry or clinical trial—for its conditional approval.

In 2006, in response to the first PET CED policy by CMS, the National Oncologic PET Registry (NOPR) was created and began collecting data for PET studies with ^{18}F-FDG performed for previously noncovered cancer indications (*9*). NOPR's primary objective was to measure ^{18}F-FDG PET's impact on referring physicians' intended patient management by collecting prospective questionnaire data before and after the PET results were available. We have previously reported that ^{18}F-FDG PET was associated with a change in intended management in about one third of cases, with minimal clinically important differences across cancer types or indications (*10–13*).

In consultation with CMS, the NOPR investigators initiated a new, second registry for NaF PET that builds on the experience, infrastructure, and staffing of the ^{18}F-FDG PET registry (*9*). Consistent with CMS policy, the registry undertakes prospective data collection of the impact of NaF PET in patients with suspected or known osseous metastasis in any cancer type, using a questionnaire-based

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approach to assess referring physician–intended management; structured information on PET scan results is also collected from interpreting physicians.

In 2011, the NaF PET registry began accrual; 72% of patients have pathologically confirmed prostate cancer. Herein, we report NaF PET impact on intended management in prostate cancer for initial staging, suspected first development of osseous metastasis, and suspected progression of known osseous metastasis.

MATERIALS AND METHODS

NOPR Design and Workflow

The NOPR is a prospective data registry that collects information from the PET facility, from the physician requesting NaF PET, and from the interpreting physician's PET report. The NaF PET registry follows the same basic design as the ^{18}F-FDG PET registry. Detailed descriptions of NOPR operations, human subject protection procedures, and results for the impact of ^{18}F-FDG PET on physicians' intended management were previously reported (*10–13*). The American College of Radiology Institutional Review Board approved the protocol for data collection for this study. Patient, referring, and interpreting physician consent were required for the research use of the data for any given case. Each facility registers to participate and submits its data via the Internet at a secure Web site (https://www.cancerpetregistry.org). The research conducted using NOPR data is registered at ClinicalTrials.gov #NCT00868582.

The PET facility is responsible for collecting referring physician responses on pre-PET and post-PET forms and from the interpreting physician (http://www.cancerpetregistry.org/naf-petform.htm). The pre-PET form collects the specific testing indication, the patient's cancer type, symptoms or signs prompting the scan, working summary stage, and the referring physician's management plans if NaF PET were unavailable (with the added assumption that BS was not an option to avoid having this selected as the default response). The questions on the physician's intended management asked whether treatment, if planned, was to be directed against the primary tumor, local/regional disease, or systemic or osseous disease and whether it would include surgery, radiotherapy, chemotherapy, hormonal therapy, bisphosphonates, immunotherapy, or radiopharmaceutical therapy. Alternatives to treatment were other types of imaging if BS or NaF PET were unavailable, stopping current therapies, observation, or tissue biopsy. The interpreting physician recorded whether prior BS was available for comparison and its date. NaF PET findings were categorized as normal/benign versus equivocal, probable, or definite osseous metastases. Osseous metastases were further characterized as unifocal, multifocal, or diffuse. If prior BS was available, the comparison was categorized as showing no evidence of metastasis, resolution, or improvement of metastasis; no change; or progression or development of new sites of osseous metastasis. After PET completion, the PET facility uploaded the PET report and the interpreting physician data to the database. The final step was referring physician completion of the post-PET form recording the planned management in light of the PET findings (using the same options listed on the pre-PET form). In addition, the referring physician recorded an impression of the change in the extent of the cancer, the patient's summary stage, prognosis, and whether the NaF PET avoided additional noninvasive or invasive procedures.

NaF PET Accrual

Patient accrual began January 31, 2011. Preliminary analyses noted an unexpected more than 60% rate of pre-PET plans of other imaging if NaF PET or conventional BS were unavailable. Data form revisions were made to offer a menu of the specific type of alternative imaging that would be performed if NaF PET or BS were unavailable. Also, 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 analysis cohort extended from that date through December 31, 2012.

The initial period, which could be considered a learning phase for interpreting physicians unfamiliar with NaF PET, included 7,154 scans obtained at 633 facilities. In 2012, there was a modest increase in total scans (7,794) but not in the number of participating facilities. In both periods, about 50 facilities accounted for 50% of the patients and about 180 facilities performed 10 scans or more per year.

Analysis Cohort

Figure 1 is a tracking diagram indicating how the final analysis cohort was identified. The dataset consisted of cases with patient, referring physician, and interpreting physician consent for research use of the data, representing 85.2% of scans. For this report, we limited the analysis to patients with known prostate cancer (72% of patients) referred for NaF PET for 1 of 3 indications: initial staging (IS) that may or may not precede local therapy, suspected first osseous metastasis (FOM) of men with previously treated local disease, and suspected progression of osseous metastasis (POM) in men who have previously been or were being treated for osseous metastasis. We excluded men aged 65 y or younger, those without pathologically confirmed prostate cancer, and those with nonclassifiable pre-PET treatment plans. The final dataset included 3,531 scans in 3,396 patients, with 96.3% of men having a single scan and 3.7% having 2 scans or more. Most scans (95.3%) were obtained with PET/CT scanners.

Statistical Analysis

The 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 interval was calculated using the normal approximation for a binomial distribution. Multiple scans from the same patient were assumed to be independent observations.

The inclusion of cases in which the pre-PET plan was imaging may overestimate PET's impact. Specifically, it is possible that, if these patients had undergone CT, MR imaging, or ^{18}F-FDG PET, the same postimaging management plan would have been selected as was reported after NaF PET. As previously reported (*11*), to address overestimation of impact by inclusion of cases in which the pre-PET plan was imaging, we computed an imaging-adjusted impact by assuming no change in intended management for all cases in which the initial management plan was alternative imaging. We believe this represents a lower boundary estimate of the impact of PET on intended management with respect to our primary endpoint.

The Cochran–Armitage test for trend was used to test for an increasing or decreasing trend in proportion of cases having single or multiple signs, symptoms, or other abnormal imaging increased when compared with cases referred with no signs or symptoms. All analyses were generated using SAS software (SAS Institute) (*14*).

RESULTS

Cohort and Patient Characteristics

In the analysis cohort, 1,024 scans were requested for IS, 1,997 for FOM, and 510 for POM. Table 1 shows the patients' clinical characteristics stratified by indication. The median age was 73–76 y—2–3 y older than the NOPR ^{18}F-FDG PET cohort (*10,11*). No symptoms or other abnormalities were noted before NaF PET in 61.9% of men referred for IS versus only 13%–15% of those referred for FOM or POM. An elevated or rising prostate-specific antigen (PSA) was the sole indication in 47.0% of men with FOM and 36.7% of those with POM. Bone pain alone was noted in 17.0% of those with FOM and 23.5% of those with POM.

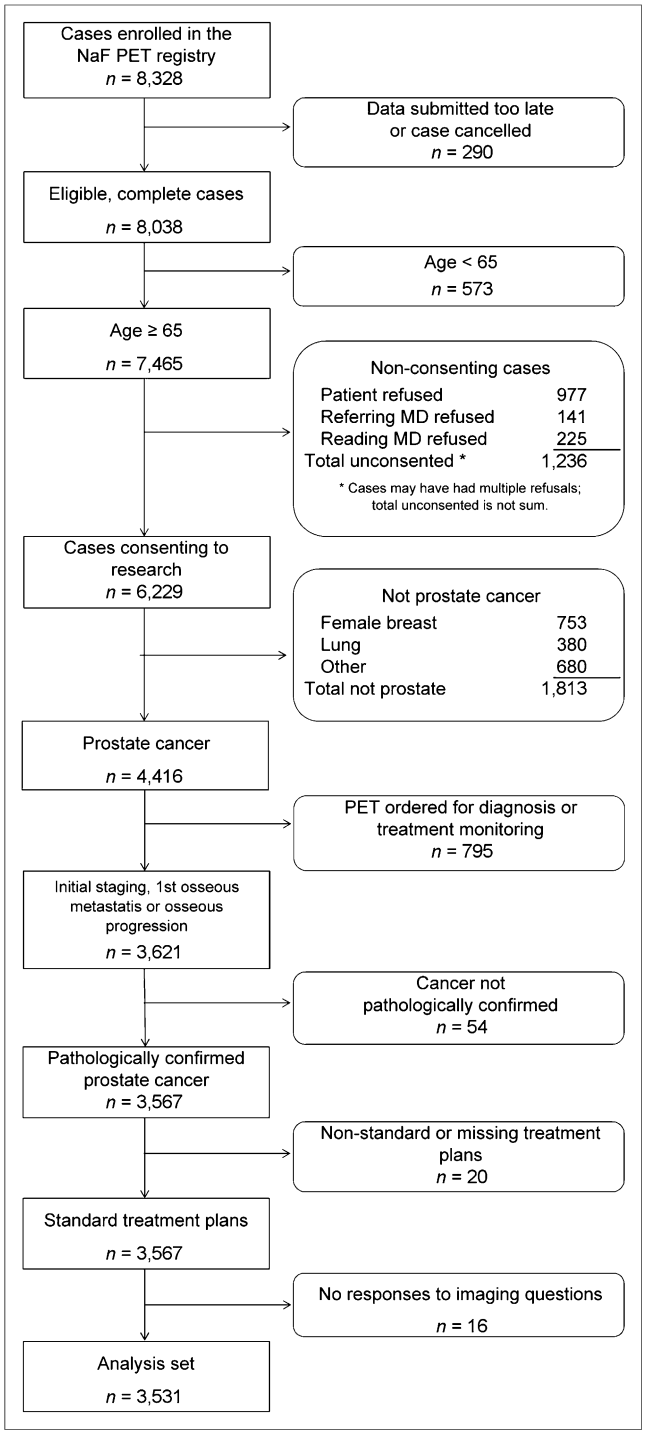

FIGURE 1. NaF PET prostate cancer cohort delineation.

The specialty distribution of referring physicians varied by indication. For IS, urologists accounted for 62% of referrals, urologists and medical oncologists were approximately equal contributors in FOM at about 38% each, and medical oncologists accounted for 61% in POM. Radiation oncologists accounted for 16%–22% across the 3 indications.

We were not surprised that, for 31% of men undergoing NaF PET for IS, referring physicians were unwilling to estimate their stage, given that bone imaging was needed to complete the evaluation. However, we did not anticipate that 38% of men imaged for FOM would have their stage listed as unknown. We also suspect that many of the 7% of men imaged for POM, with stage listed as no evidence of disease or as only local/regional disease, were misclassified instances of imaging for FOM. Before NaF PET, metastatic disease was estimated to be present in about 8%, 34%, and 81% of patients across the 3 indications.

In 87%–92% by indication, BS would have been performed if NaF PET were unavailable.

The pre-PET form explicitly stated that for the purposes of the intended management question, the physician should assume that neither NaF PET nor BS would be available. Overall, 49.8%–57.1% of patients for each indication had a pre-PET management plan of other imaging. The distribution of other imaging types varied modestly by the indication. Body CT was most common at 20.6%–24.0%, body MR imaging ranged from 9.0% to 16.9%, and ^{18}F-FDG PET ranged from 12.0% to 16.1% of men across the 3 indications. Tissue biopsy was rarely planned—1.9%–3.3% of patients. A plan of watching (including no additional therapy) was uncommon but occurred most often in FOM (15.1%) versus 7.6% undergoing IS or 11.2% of those with POM ($P < 0.0001$). A pre-PET intended treatment plan occurred in 40.7% of IS patients versus only 25.9%–29.2% of patients with FOM or POM.

Impact on Treatment Versus Nontreatment Plans

Table 2 summarizes the impact of NaF PET on intended management classified as either treatment or nontreatment. The difference between the pre- and post-PET plans (rows) is compared with the indication for the scan (columns).

Changes from an intended nontreatment plan (predominantly imaging) to a treatment plan varied by indication—41.4% in IS, 35.2% in FOM, and 46.9% in POM. In contrast, the change from intended treatment to nontreatment was 3.9- to 9.2-fold less frequent (occurring in only 5.3%–8.9% of cases). Overall, the frequency of change from nontreatment to treatment or vice versa was 46.7% for IS, 44.1% for FOM, and 52.0% for POM. The imaging-adjusted impact was highest for cases of FOM at 15.8% versus 12.4% for POM and 12.0% for IS.

Action-Type Changes

Table 3 summarizes the frequencies of the pre- and post-PET management plans stratified by NaF PET indication (more detailed information is provided in the supplemental data [available at http://jnm.snmjournals.org]).

Pre-PET plans for imaging were revised to either treatment or watching in more than 85% of patients. After NaF PET, action plans to obtain additional data (e.g., biopsy or imaging) were reported in only 7.5%–12.8% of any cohort. Post-PET plans of watching or no additional therapy were much more common after scans done for FOM than either suspected POM or IS (35.0% vs. 21.6% or 14.2%, $P < 0.0001$). Pre-PET plans of watching or no additional therapy were revised to treatment after PET in about two thirds of patients undergoing PET for FOM and more than 80% for suspected POM or IS.

NaF PET Findings

Table 4 summarizes the NaF PET findings recorded by the interpreting physicians. As anticipated, the frequency of scans categorized as benign disease versus definite metastasis was related to the imaging indication. Benign changes were reported in 71.0%, 52.0%, and 16.1% of IS, FOM, and POM scans, respectively.

TABLE 1
Profile of Men with Prostate Cancer Undergoing NaF PET by Indication

Characteristic	Initial staging (n = 1,024)	Suspected FOM (n = 1,997)	Suspected POM (n = 510)
Age (y)			
Median	73	75	76
25%–75% quartile	69–78	70–81	70–81
Symptoms, signs, or test results (%)			
None	61.9	15.3	13.5
Elevated or rising PSA only	22.8	47.0	36.7
Pain only	6.1	17.0	23.5
Evidence from other imaging	5.0	6.1	5.5
Multiple signs/abnormal imaging	3.4	11.7	18.0
Specialty of requesting provider (%)			
Urologist	61.7	38.2	16.9
Radiation oncologist	22.4	17.7	15.7
Medical oncologist	14.5	37.5	61.0
Other	1.4	6.6	6.4
Pre-PET summary stage (%)			
No evidence of disease or local only	56.6	22.3	6.3
Regional or nodal	4.3	5.3	0.8
Single metastasis	3.8	11.1	13.7
Multiple metastases	4.2	22.9	67.1
Unknown	31.1	38.5	12.2
Conventional bone scan would be ordered if NaF PET were unavailable (%)	91.9	87.0	87.3
Pre-PET plan (%)			
Imaging	49.8	55.7	57.1
Body CT	24.0	22.2	20.6
Body MR imaging	9.0	16.0	16.9
^{18}F-FDG PET	13.2	12.0	16.1
Other imaging	3.6	5.5	3.5
Treatment*	40.7	25.9	29.2
Radiotherapy	34.1	13.9	8.4
Hormonal therapy	18.6	15.4	18.0
Surgery	11.8	1.9	0.2
Chemotherapy	4.9†	8.5	16.1
Radiopharmaceutical therapy	0.3†	0.9	1.4
Immunotherapy	1.6†	5.0‡	4.1‡
Bisphosphonates	3.2	7.0	11.6
Biopsy	1.9	3.3	2.5
Watch/no additional therapy	7.6	15.1	11.2

*Treatment types are not mutually exclusive.
†Suspected inappropriate therapies within this indication in hormone-naïve disease.
‡Immunotherapy should be limited to men with castrate-resistant disease.

Conversely, definite changes of osseous metastasis, most commonly in a multifocal distribution, were reported in 13.9% of IS scans, 29.0% of FOM, and 76.5% of POM. Unifocal abnormalities rated as definite metastatic disease were reported in only 2.0%–3.4% of scans.

About one third of men scanned for FOM or POM had prior conventional BS. However, about 70% of these were done more than 1 y earlier. When the interval between BS and NaF PET was less than 90 d, 35% (26/75) of NaF PET scans showed more evidence of bone metastasis than did BS. For FOM or POM NaF PET scans with an interval from BS less than 180 d, 40% (67/167) and 76% (56/73), respectively, showed more extensive disease.

Referring physicians reported that NaF PET allowed them to avoid additional diagnostic tests in about three quarters of patients and to avoid invasive procedures in about one-half.

Post-PET Treatment Plans by Type

The post-PET treatment plans by indication are summarized at the bottom of Table 4. As anticipated, local therapies for the primary prostate cancer predominated in IS and were rarely used in more advanced disease. In the IS setting, there was a large impact on intended surgery. For example, NaF PET findings of probable or definite osseous metastasis should lead to a change from pre-PET plans of prostatectomy to alternative therapies. Such changes were noted: 52.1% of patients with a pre-PET plan for surgery (n = 121) were revised to nonsurgery. Almost half (46.8%) of post-PET surgery plans (n = 190) were in patients with pre-PET plans of imaging. In the IS setting, the overall cohort had post-PET plans of local radiotherapy alone in 23.4%, surgery with or without additional therapies in 18.5%, and combined radiotherapy and hormonal therapy in 18.1%.

TABLE 2
Change in Management Associated with NaF PET Categorized as Treatment Versus Nontreatment and Stratified by Indication

Treatment plan		Initial staging (n = 1,024)	Suspected FOM (n = 1,997)	Suspected POM (n = 510)
Before PET	After PET			
Nontreatment	Nontreatment	183 (17.9)	777 (38.9)	122 (23.9)
Treatment	Treatment	363 (35.4)	339 (17.0)	123 (24.1)
Nontreatment	Treatment	424 (41.4)	703 (35.2)	239 (46.9)
Treatment	Nontreatment	54 (5.3)	178 (8.9)	26 (5.1)
Rate of change in management		46.7% (95% CI, 43.6–49.7)	44.1 (95% CI, 41.9–46.3)	52.0 (95% CI, 47.6–56.3)
Imaging-adjusted rate*		12.2% (95% CI, 10.2–14.2)	15.8 (95% CI, 14.2–17.4)	12.4 (95% CI, 9.5–15.2)

*Adjusted to assume no effect of NaF PET for cases with pre-PET plan of imaging.

Difference between pre- and post-PET plans (rows) is compared with indication for scan (columns). Data in parentheses are percentages.

CI = confidence interval.

Bone-targeted therapies were planned in about 11% of men after PET for IS, 19% for FOM, and 39% for POM. In all indications, the most frequent bone-targeted therapy was bisphosphonates. Radiotherapy directed at osseous disease was planned for about 5% of subjects scanned for IS, 8% for FOM, and 15% for POM.

As also anticipated, planned systemic therapy and the intended use of multiple systemic therapies increased by indication. Post-PET hormonal therapy modestly differed between indications ranging from 32.3% to 40.8%. Hormonal therapy was used predominantly concurrently with local radiotherapy after IS, as monotherapy after FOM, and concurrently with chemotherapy after POM.

For patients having had prior prostate cancer therapies, post-PET revised plans included chemotherapy in 13.5% of FOM and 29.0% POM. For both indications, chemotherapy was predominantly planned in combination with either radiation or hormonal therapy.

Incorrect recording of testing indication may explain some of the chemotherapy and immunotherapy plans. These systemic treatments are not appropriate as initial therapy in hormone-naïve disease. Plans for immunotherapy were infrequent in men having had prior therapy (6%–8% overall), but many were likely inappropriate because the recorded intended plans also included concurrent chemotherapy in one-third and hormonal therapy in one-half.

Because one half of registry patients had other imaging as their pre-PET plan, post-PET plan conversion to systemic therapies contributed substantially to the post-PET management profiles. Of those patients with post-PET plans for systemic therapy, 72%–82% were new (compared with pre-PET plans of treatment), with a marked rise in chemotherapy or immunotherapy plans ($P < 0.0001$), although these remained less frequent than hormonal therapy. Pre-PET–planned systemic therapies also substantially declined after PET—hormonal therapy declined by 42%, chemotherapy by 62%, and immunotherapy by 74%.

Analyses Stratified by NaF PET Findings

Given the high frequency of pre-PET plans for other advanced imaging, we assessed whether there was a different distribution of abnormal NaF PET studies in such patients (in relation to the type of advanced imaging selected) when compared with patients with any plan for treatment. A modest, but clinically relevant, difference was found only for FOM; patients with alternative plans of ^{18}F-FDG PET had an 8%–12% greater frequency of definite metastasis than those with plans for CT, MR imaging, or treatment (Table 5, $P < 0.001$).

Although we did not collect data on PSA levels, the distribution of abnormal NaF PET findings in patients in whom the only indication was an elevated (IS) or rising PSA (FOM) was compared with that in patients with no signs or symptoms, bone pain alone, or multiple findings. The pattern of NaF PET findings in patients referred for testing based on abnormal PSA alone did not differ from those for patients having no signs or symptoms for IS or FOM (data not shown). In each indication, definite changes of osseous metastasis were twice as frequent in patients with bone pain alone or with multiple factors ($P < 0.0001$) than in men with abnormal PSA alone as the indication.

TABLE 3
Intended Management Plan Associated with NaF PET Stratified by Indication for Scan

	Initial staging		Suspected FOM		Suspected POM	
Intended management (%)	Pre-PET	Post-PET	Pre-PET	Post-PET	Pre-PET	Post-PET
Watch	7.6	14.2	15.1	35.0	11.2	21.6
Image	49.8	5.9	55.7	8.6	57.1	5.5
Biopsy	1.9	3.1	3.3	4.2	2.5	2.0
Treatment	40.7	76.9	25.9	52.2	29.2	71.0

TABLE 4
NaF PET Findings, Post-PET Extent of Disease, and Treatments Planned

Characteristic	Initial staging (n = 1,024)	Suspected FOM (n = 1,997)	Suspected POM (n = 510)
NaF PET findings (%)			
Benign	71.0	52.0	16.1
Equivocal	8.5	8.0	1.6
Probable	6.3	11.0	5.9
Definite	13.9	29.0	76.5
Unifocal	2.0	3.4	3.3
Multifocal	8.7	19.0	47.8
Diffuse	3.2	6.7	25.3
Avoid diagnostic tests (%)	69.3	75.2	79.6
Avoid invasive procedures (%)	51.3	58.7	55.9
Treatment*	76.9	52.2	71.0
Local therapies	58.6	10.5	2.4
Surgery	18.5	1.8†	0.4§
Radiotherapy	52.2	10.5	3.7
Directed at bone	10.8	19.3	39.2
Radiotherapy	5.3	7.8	15.3
Radiopharmaceutical therapy	0.1‡	1.1	2.4
Bisphosphonates	6.7	11.5	27.8
Systemic therapies	38.0	41.6	61.4
Hormonal	35.4	32.3	40.8
Chemotherapy	7.9‡	13.5	29.0
Immunotherapy	2.4‡	6.2§	7.6§

*Treatment types are not mutually exclusive.
†Surgery for presumed impending or pathologic fracture.
‡Suspected incorrect indication since these therapies are inappropriate in hormone-therapy naïve disease.
§Immunotherapy should not be used in combination with other systemic therapies.

DISCUSSION

NaF PET has many advantageous technical features over conventional BS: superior pharmacokinetics with a shorter time from injection to imaging, higher bone uptake, faster blood clearance, lower radiation dose, and superior image quality (*4,15*). The addition of concurrent CT improves the specificity of NaF PET (*16*). In 2010, the Society of Nuclear Medicine and Molecular Imaging published a practice guideline for NaF PET that should facilitate-minimal protocol variation and dosage in general practice (*17*). Whether these technical advantages lead to improved test performance and clinical outcomes is uncertain. Since 2010, 2 small single-center series (*18,19*) and a meta-analysis of 425 patients (*20*) found superior diagnostic accuracy of NaF PET, compared with BS. CMS in its CED decision stated particular interest in changes to more appropriate (palliative or curative) care, improved quality of life, or survival (*6*).

The NaF PET registry is the second national registry of cancer-related imaging under the auspices of NOPR in consultation with CMS to assess the impact of PET on intended management. In this report, we have limited our analysis to the most frequent imaging indications in men with prostate cancer. Although NaF PET in this patient population specifically targets detection of bone metastasis, characterizing the subsequent clinical impact of NaF PET is complex given the various local, hormonal, and increasing systemic treatment options for metastatic prostate cancer.

Our results show that, in about one half of patients, physicians would defer making the treatment versus observation decision if NaF PET were not available and instead would obtain alternative advanced imaging. In patients in whom the alternative would have been body CT or body MR imaging, within each indication, there was no difference in the frequency of NaF PET

TABLE 5
Distribution of NaF PET Findings for Suspected FOM Based on Pre-PET Plan

Plan	Benign or equivocal	Probable	Definite			P value
			Unifocal	Multifocal	Diffuse	
Any treatment (n = 517)	317 (61.3)	58 (11.2)	17 (3.3)	97 (18.8)	28 (5.4)	–
Body CT (n = 443)	292 (65.9)	36 (8.1)	17 (3.8)	71 (16.0)	27 (6.1)	0.3992
Body MR imaging (n = 320)	177 (55.3)	42 (13.1)	13 (4.1)	65 (20.3)	23 (7.2)	0.1260
^{18}F-FDG PET (n-240)	116 (48.3)	30 (12.5)	3 (1.3)	59 (24.6)	32 (13.3)	<0.0001

Data in parentheses are percentages.

findings considered definitive for osseous metastasis than if the pre-PET plans were treatment. The NaF PET interpretation was equivocal or probable metastasis in just 8%–19% of patients. In patients studied for IS and FOM, the estimated disease extent after NaF PET was more or less than anticipated in approximately equal fractions. After NaF PET, referring physicians reported that 70%–80% of patients would avoid additional noninvasive imaging and that plans to gather additional information (biopsy or more imaging) would be necessary in only 7%–12%. These data reflect referring physicians' confidence (or overconfidence) in NaF PET's value in stratifying risk and their willingness to make definitive plans immediately. In contrast, the National Comprehensive Cancer Network (NCCN) Task Force Report on Bone Health in Cancer Care (*21*) suggests confirmatory CT or MR imaging, depending on the site and number of bone scan abnormalities noted.

Within each indication, we have some concerns regarding data accuracy. Scans supposedly done for initial staging appear to be misclassified in at least 14% based on inappropriate intended plans of systemic chemotherapy or immunotherapy in men who have not yet received any hormone therapy. At least 7% of men scanned for POM likely had FOM as the correct indication, because the pre-PET stage was no evidence of disease or local/regional disease. Also, a random sample quality audit of 100 FOM reports found 10% of these scans were clearly for either IS or POM.

At least 2 limitations of our study reflect initial design choices. First, the NaF PET registry was open to patients with all cancer types, but we anticipated that prostate, breast, lung, and other cancers, in descending order, would be studied. Therefore, in retrospect, the questionnaires were not as granular as would be desirable for an observational study limited to men with prostate cancer. In such a more focused study, it would have been useful to collect data on time from initial therapy, past versus current androgen-deprivation therapy, whether hormonal therapy was initial (leuprolide) or second-line (flutamide, bicalutamide), and the level or rate of change of PSA levels. Second, we limited the information requested from referring physicians because of concern about the burden on these referring physicians who were asked to provide relevant clinical information without financial compensation. Moreover, referring physicians were not required to complete any specific training about registry requirements; the pre- and post-PET form instructions were felt to be sufficient.

Several factors are associated with a high risk of metastasis—for men undergoing initial staging: Gleason score greater than 7, clinical stage greater than T3, PSA greater than 10 ng/mL, or bone pain (*22*). For men with biochemical failure after local treatment, important factors are the absolute PSA level and the PSA doubling time (*23*). We found that bone pain is a critical risk factor for osseous metastasis detected by NaF PET for IS or FOM, whereas a high PSA alone (even without specific levels) did not indicate risk greater than that for men with no signs or symptoms.

It is impossible to estimate how often the registry scans were appropriate based on practice guidelines (*24*). Determining this would require much greater individual disease-specific detail, of the type described above. We suspect that our impact results are inflated in advanced disease in which many pre-PET plans of alternative imaging are correct but incomplete because ongoing androgen-deprivation therapy was currently being given. We also suspect that many FOM scans done in the 15% of men with no signs or symptoms actually represented surveillance imaging, which is explicitly not covered by Medicare and not recommended by NCCN guidelines (*24*).

The imaging-adjusted impact assumes no change in management attributable to NaF PET for all cases in which the initial management plan was an alternative imaging modality. Nonetheless, under this framework, the NaF PET's impact was substantial at 12.2%–15.8% (i.e., the number needed to test per management change was 6–8). There was imaging-driven impact on high-cost plans, such as surgery for presumed local disease and chemotherapy or immunotherapy for FOM (inferred castrate-resistant disease), declining by more than 50% after NaF PET results were available. Some may find it disconcerting that clinicians were so often willing to make such decisions after 1 imaging study without additional evidence, contrary to NCCN guidance (*21*).

A major CMS goal of its CED program for NaF PET was in determining whether NaF PET is associated with appropriate changes in the goals of managing osseous metastatic disease and in the associated quality of life (*6*). Although these goals are clear, it was recognized from the inception of the NaF PET registry (the design of which was approved by CMS) that we would not be able to obtain definitive evidence of those outcomes given the limitations of a questionnaire-based registry. Also, because other imaging was so often the pre-PET plan, changes from curative to palliative intent in patients with pre-PET treatment plans occurred in 15.7% (only ~3% of all patients). However, at a November 2012 Medical Imaging and Technology Alliance meeting on types of evidence needed for coverage of PET, Dr. Louis Jacques of the CMS Coverage and Analysis Group noted that CMS remained willing to consider intermediate endpoints for diagnostic test results (such as change in intended management) for which the different management strategies are well defined (e.g., for locoregional vs. systemic disease) (*25*).

The NOPR NaF PET and ^{18}F-FDG PET registries share the same limitations—the lack of confirmation of actual initiation or cessation of treatments or changes in the use of relevant diagnostic studies, the uncertain effect of patient acceptance and patient preferences on postscan management intentions, and the lack of a comparator cohort (*26,27*). Pending the results of large direct randomized comparisons of NaF PET and other modalities (*28*), our findings indicate that NaF PET has a substantial impact across the common testing indications in prostate cancer.

CONCLUSION

NaF PET has high overall impact, principally related to its effect on replacing intended use of other advanced imaging. Its imaging-adjusted impact was similar to that observed with ^{18}F-FDG PET for restaging or suspected recurrence in other cancer types.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. NOPR is sponsored by the World Molecular Imaging Society, managed by the American College of Radiology Imaging Network, and 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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