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Comparison of ^{18}F-NaF Imaging, ^{99m}Tc-MDP Scintigraphy, and ^{18}F-FDG for Detecting Bone Metastases

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Abstract

Bone is a common metastasis site in several malignancies, most importantly prostate and breast cancers. Given the significance of the early and accurate diagnosis of bone metastases for preliminary staging, treatment planning and monitoring, restaging, and survival prediction in patients with malignancy, it is critical to compare and contrast the strengths and weaknesses of imaging modalities. Although technetium-99m-labeled diphosphonates [^{99m}Tc-MDP] scintigraphy has been used for assessing skeletal involvement, there is a renewed interest in fluorine-18-labeled sodium fluoride [^{18}F-NaF] bone imaging with positron emission tomography or positron emission tomography/computed tomography, since this approach provides essential advantages in bone metastases evaluation. This review study aimed to discuss the basic and technical aspects of ^{18}F-NaF imaging and its mechanism of action, and compare this modality with the ^{99m}Tc-MDP bone scan and 18F-fluorodeoxyglucose using current evidence from the pertinent literature and case examples of the center in the study.

Keywords
- skeletal metastases
- fluorodeoxyglucose (FDG)
- sodium fluoride (NaF)
- ^{99m}Tc-MDP

Introduction

Although the bone metastases frequency at initial cancer diagnosis is low, most patients with recurrence or those in advanced stages of malignancies experience metastases to the skeletal system.[1] Bone metastases are generally classified as lytic (with aggressive behavior and rapid growth), blastic (with an indolent course), or mixed. The vicious cycle of bone

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metastases theory proposed by Guise[2] predominantly describes the pathophysiology of bone metastases. Some complications of patients with osseous metastases include pathologic fractures, refractory pain, hypercalcemia, nerve root or cord compression, and myelosuppression. Therefore, it is necessary to initiate an appropriate bone management program to increase the patients' quality of life and decrease their morbidity.[3–5] Imaging tools are indispensable for accurate staging, evaluation of treatment response, restaging, and long-term oncologic management.

For decades, along with anatomical imaging tools, including conventional X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), technetium99m-labeled diphosphonates [^{99m}Tc-MDP], scintigraphy has been performed to evaluate bone metabolic activity.[6,7] However, another excellent bone-specific positron-emitting agent, sodium fluoride labeled with fluorine-18 [^{18}F-NaF], was introduced to clinical practice for bone imaging even before the initial use of ^{99m}Tc-MDP.[8] Although early studies demonstrated promising results of these imaging modalities, the need for high-energy 511-keV photons in conventional Anger-type gamma cameras limited the imaging performance of ^{18}F-NaF. Therefore, given the ideal imaging properties of gamma cameras with the 140-keV photons of ^{99m}Tc-MDP, ^{18}F-NaF imaging was ultimately replaced by whole-body scintigraphy with ^{99m}Tc-MDP in the 1970s.[9,10] The advent of positron emission tomography (PET) and hybrid PET/computed tomographic (PET/CT) systems has again focused on using ^{18}F-NaF for osseous imaging. The high resolution and sensitivity of PET/CT imaging compared with planar scintigraphy have helped improve the diagnostic accuracy of differentiation between benign and malignant bone lesions.

Various fluorodeoxyglucose (FDG) spectrum uptake has been observed in primary and metastatic heterogeneous bone lesions.[11,12] The sensitivity of ^{18}F-FDG in detecting osseous metastases is comparable to bone scintigraphy in most malignancies; nevertheless, it can change the clinical management course of the patients and evaluate the response to chemotherapy and hormonal therapy treatments.[13]

This review study provided a discussion of the basic and technical aspects of ^{18}F-NaF imaging and its mechanism of action and a comparison between this modality and ^{99m}Tc-MDP bone scan and ^{18}F-FDG using current evidence from relevant literature and case examples of the center in the study.

Basic and Technical Aspect of ^{18}F-NaF Imaging

^{18}F-NaF was introduced and verified for clinical application by U.S. Food and Drug Administration in 1962 and 1972. ^{18}F-NaF has a high affinity for bones and is produced in a highly specific activity in a nuclear reactor. ^{18}F is generated by ^{18}O (p, n)^{18}F nuclear reaction on ^{18}O enriched water (water target).[14] ^{18}F emits positively charged positron when it decays into stable ^{18}O, which combines with an electron in an annihilation reaction, producing two 511-keV photons that allow PET imaging. The half-life of ^{18}F is 110 minutes, making it a necessary element in producing the radiotracer on the same day.[15] Another short-lived radionuclide in bone imaging, ^{99m}Tc ($t_{1/2} = 6$ hours, photon energy = 110 keV), is a generator-produced radionuclide produced by mixing ^{99m}Tc-sodium pertechnetate with commercially MDP kits.[16] Unlike 18F-FDG, a fasting state is not needed for ^{18}F-NaF scanning, and patients can take all their daily medications.[17]

NaF is an analog of the hydroxyl group in hydroxyapatite bone crystals that is well-localized within the bone. Nevertheless, even with early validation, this radiotracer was not extensively used due to some limitations, such as relatively high radiation exposure, technical restrictions of the gamma camera, and an insufficient number of PET scanners. The use of ^{18}F-NaF is growing due to the increased number of PET/CT scanners and the unavailability of optimal ^{m99}Tc tracers.[8,18] The rate of bone avidity for ^{18}F-NaF is twice higher than ^{99m}Tc-MDP.[19] Both of these radiotracers are nonspecific. Their local uptake can reflect the osteoblastic activity, which is not specific to primary and metastatic skeletal tumors and can also be seen in benign conditions as degenerative or infectious/inflammatory diseases and traumatic injuries.[17,20]

Newly designed PET scanners have axial fields of view ranging from 15 to 20 cm; hence, multiple bed positions will likely be necessary to achieve an appropriate image of the area of interest. Different factors affect PET imaging, such as the sensitivity or count rate of the PET scanner, the activity of the radiopharmaceutical, and two- or three-dimensional model of data acquisition resulting in spending 3 to 5 minutes per bed position.[21] ^{18}F-NaF PET/CT imaging should not be performed in pregnant patients like other radiopharmaceutical agents, except when the potential benefits surpass the radiation risk to the mother and fetus.[17] The typical activity ranges for ^{18}F-NaF and ^{99m}Tc-MDP are 185 to 370 MBq (5–10 mCi) 740–1, and 100 MBq (20–30 mCi).[22]

Mechanism of Action

Similar to ^{99m}Tc-MDP, the action mechanism of ^{18}F-NaF is based on ion exchange with hydroxyl ions on the outside of the hydroxyapatite that converts hydroxyapatite to fluorapatite.[23,24] However, the pharmacokinetics, osseous uptake, and blood clearance of ^{18}F-NaF are more favorable than ^{99m}Tc-MDP. These properties provide a high contrast mode, shorter ^{18}F-NaF imaging time, and high-quality imaging.[18,23,25] After administration of ^{18}F-NaF, the ^{18}F ions quickly equilibrate with plasma and are subsequently cleared rapidly as a consequence of bone deposition and excretion by the kidneys.[23] An additional value of ^{18}F-NaF is a low binding affinity toward serum proteins, leading to rapid first-pass extraction and rapid clearance from the soft tissues.[26] The uptake of ^{18}F-NaF is a function of the osseous blood flow, indicates osteoblastic activity by identifying reactive changes, and reflects bone remodeling.[17,23] Differentially, almost 30% of ^{99m}Tc-MDP is protein-bound instantly after injection. The non–protein-bound fraction clears

rapidly, while the protein-bound fraction of ^{99m}Tc-MDP clears slowly from the blood. Therefore, data recording can start 3 to 4 hours after intravenous injection of ^{99m}Tc-MDP. In comparison, ^{18}F-labeled NaF imaging can be performed within 1 hour after radiotracer administration.[19,27] This shorter examination time results in reduced patient motion artifact and better workflow productivity.[21]

Comparison of ^{18}F-NaF and Tc-MDP Bone Scan

^{18}F-NaF PET/CT has many advantages: early detection, providing accurate information about the extent of metastatic bone lesions, and excellent image quality (4–5 mm spatial resolution), compared with ^{99m}Tc-MDP planar bone scintigraphy and ^{99m}Tc-MDP single-photon emission computed tomography/computed tomography (SPECT/CT).[21,28,29] ^{18}F-NaF PET tracer emits high-energy 511-keV photons that provide better penetration into tissues with minimum scatter. These characteristics also increase the number of gamma rays detected by the scanner.[30] Nevertheless, the accumulation of ^{18}F-NaF in lesions is not tumor-specific, and thus, has a lower specificity for ruling out metastatic skeletal involvement. This property limits the potential of ^{18}F-NaF PET imaging to distinguish metastatic lesions from benign lesions such as degenerative changes, which typically occur in elderly cancer patients. In this regard, the possibility of false-positive results is higher due to the similar uptake pattern of bone pathogenesis using ^{18}F-NaF PET.[30,31] Therefore, the PET/CT technology, that is, the incorporation of low-dose CT in PET technology, was developed to partially overcome this problem and improve its specificity.[28,32] Even-Sapir et al compared the diagnostic accuracy of ^{18}F-NaF PET/CT and ^{18}F-NaF PET in 44 oncologic patients and found a superior specificity for ^{18}F-NaF PET/CT (97%) versus ^{18}F-NaF PET (72%) for detecting lytic and sclerotic malignant lesions.[33]

Conventional whole-body bone scintigraphy has limited applications due to low specificity. Moreover, anatomic correlation is essential for specificity improvement. The combination of SPECT/CT with conventional planar bone scintigraphy significantly improves the diagnostic accuracy and provides anatomic localization in addition to morphological information.[34] Although conventional planar ^{99m}Tc-MDP scintigraphy is time tested, easily accessible, and widely available thanks to using gamma cameras,[35] different studies have shown that ^{18}F-NaF PET can be positive before planar and SPECT using ^{99m}Tc-MDP scintigraphy in small bone lesions in various malignancies, such as breast, prostate, and lung cancers.[19,31,36,37]

Several studies have evaluated major diagnostic applications of ^{18}F-NaF PET and PET/CT compared with ^{99m}Tc-MDP bone imaging using a gamma camera, SPECT, and SPECT/CT in detecting skeletal lesions for patients with prostate, breast, lung, hepatocellular carcinoma, urinary bladder, and thyroid cancers.[38–42] ►**Table 1** summarizes the results of several studies investigating metastasis detection that calculated the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ^{18}F-NaF PET or PET/CT, ^{18}F-FDG PET, and ^{99m}Tc-MDP bone scintigraphy using planar and SPECT imaging.

Assessment of 12 patients with newly diagnosed lung cancer demonstrated planar bone scintigraphy and ^{99m}Tc-MDP SPECT imaging, and ^{18}F-NaF PET produced six, one, and no false-negative result for detecting bone lesions.[41] In a multidimensional prospective study including 44 patients with high-risk prostate cancer, the diagnostic efficiencies of ^{99m}Tc-MDP planar scintigraphy, ^{99m}Tc-MDP SPECT, ^{18}F-NaF PET, and ^{18}F-NaF PET/CT were compared. The results showed that ^{18}F-NaFPET/CT was a significantly sensitive and specific modality compared with ^{18}F-NaF PET alone and planar and SPECT bone scan to detect metastatic osseous lesions in these patients. The authors reported that ^{18}F-NaF PET/CT might positively impact treatment decisions and clinical management of patients with high-risk prostate cancer.[42] A meta-analysis found that the sensitivity and specificity of ^{18}F-NaF PET/CT for detecting bone lesions were 96 and 98%, respectively, compared with 57 and 98% sensitivity and specificity for the ^{99m}Tc-MDP bone scans in prostate cancer patients with metastatic bone lesions.[43]

Additionally, ^{18}F-NaF PET/CT has been more sensitive and specific than planar ^{99m}Tc-MDP and ^{99m}Tc-MDP SPECT/CT to identify bone metastases in urinary bladder carcinoma.[40] Another meta-analysis of 507 patients revealed that ^{18}F-NaF PET/CT had an outstanding diagnostic efficiency for detecting osseous metastases in staging and restaging patients with high-risk prostate cancer. The performance of ^{18}F-NaF-PET/CT was superior to ^{99m}Tc bone scintigraphy and SPECT and comparable to diffusion-weighted magnetic resonance imaging.[44] Yen et al reported that the diagnostic result of ^{18}F-NaF PET/CT in hepatocellular carcinoma showed that this modality could be considered a prognostic indicator in these patients due to a significant correlation between the number of ^{18}F-NaF PET/CT–positive bone lesions and the overall survival.[45]

In conclusion, these results indicate the advantages of ^{18}F-NaF PET/CT and its potential to be considered a gold standard for identifying malignant bone involvement (►**Figs. 1** and **2**). However, this indication needs to be validated in extensive retrospective studies.

Comparison of 18F-NaF and FDG Imaging

FDG is a glucose analog that is rapidly transported through the cell membrane and phosphorylated within cells. FDG uptake increases in metabolically active cells with a high glucose demand, such as tumor cells.[46] ^{18}F-FDG PET/CT provides the opportunity for simultaneous detection of malignant skeletal and extraskeletal involvement in addition to its usefulness for the general assessment of cancer patients.[47] Researchers have found that FDG PET/CT is more beneficial for detecting lytic metastases than ^{99m}Tc-MDP scintigraphy. It is also more accurate for detecting purely marrow metastases, particularly fast-growing lesions[37,48] (►**Fig. 3**). Moreover, ^{18}F-NaF PET/CT is more suitable for identifying skeletal metastases with low FDG

Table 1 Some of the important studies comparing ^{18}F-NaF imaging with other bone imaging modalities

Authors	Year[ref]	Target group	Index tests	Sensitivity (%)	Specificity (%)	PPV(%)	NPV (%)	Accuracy (%)
Even-Sapir et al	2006[42]	Patients with prostate cancer	Planar BS	70	57	64	55	
			Tc-MDP SPECT	92	82	86	90	
			^{18}F-NaF PET	100	62	74	100	
			^{18}F-NaF PET/CT	100	100	100	100	
Chakraborty et al	2013[40]	Patients with urinary bladder carcinoma	Planar BS	82.35	64.51%	56	86.95	70.83
			Tc-MDP SPECT/CT	88.23	74.19	65.2	92	79.16
			^{18}F-NaF PET/CT	100%	87.09%	80.9	100	91.66
Yen et al	2010[45]	Patients with hepatocellular carcinoma	Tc-MDP BS	NA	NA	NA	NA	74.5
			^{18}F-NaF PET/CT					95.7
Broos et al	2018[56]	Patients with breast cancer	^{18}F-NaF PET/CT	96	91	89	97	93
Lagraue et al	2011[31]	Patients with skeletal metastases in sarcoma	Tc-MDP BS	66.7	100	–	–	–
			^{18}F-NaF PET/CT	83.3	100			
			^{18}F FDG PET/CT	60	92.9			
Withofs et al	2011[57]	Patients with prostate cancer	^{18}F-NaF PET/CT	100	94.7	85.7	100	96
			Tc-MDP SPECT	66.7	84.2	57.1	88.9	80
Withofs et al	2011[57]	Patients with breast cancer	^{18}F-NaF PET/CT	73.9	79.3	86.1	63.7	76
			Tc-MDP SPECT	43	76.8	76.3	43.8	55
Damle et al	2007[50]	Patients with breast cancer patients	^{18}F-NaF PET/CT	100	75	88.9	100	91.67
			Tc-MDP BS	81.25	62.5	81.25	62.5	75
			^{18}F FDG PET/CT	43.7	100	100	47.06	62.5
Zacho et al	2018[58]	Patients with nasopharyngeal carcinoma	^{18}F-NaF PET/CT	08.3	65.7	–	–	–
			^{18}F-FDG PET/CT	42.9	97.1	–	–	–
Chan et al	2012[59]	Patients with head and neck cancer	^{18}F-NaF PET	72.2	93.5	76.5	92.1	88.8
			^{18}F-NaF PET/CT	72.2	96.8	86.7	92.3	91.3
			^{18}F-FDG PET	72.2	100	100	92.5	93.8
			^{18}F FDG PET/CT	77.8	100	100	93.9	95

Abbreviations: BS, bone scanning; ^{18}F FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-NaF, fluorine-18-labeled sodium fluoride; ^{99m}Tc-MDP, technetium-99m-labeled diphosphonates; NA, not available; NPV, negative predictive value; PET/CT; positron emission tomography/computed tomography; PPV, positive predictive value; SPECT, single-photon emission computed tomography.

uptakes, such as thyroid and renal malignancies.[13] ^{18}F-FDG PET/CT is not recommended for detecting blastic bone metastases.[49]

In a study including 126 patients with nonsmall cell lung cancer, the authors compared the diagnostic accuracy of ^{18}F-FDG PET/CT with standard planar bone scintigraphy and ^{18}F-NaF PET for detecting bone metastases. Only 13 out of 18 patients with bone metastases had concordant ^{18}F-FDG PET/CT and ^{18}F-NaF PET findings. They concluded that hybrid ^{18}F-FDG PET/CT modality was superior to bone scintigraphy to detect osteolytic lesions in patients with nonsmall cell lung cancer. Hence, PET/CT can eliminate the need for extra bone scintigraphy or ^{18}F-NaF PET for staging of these patients, which reduces the expenditures significantly.[37] In 2018, a retrospective study was conducted to compare ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT to detect skull base invasion and bony metastases in 45 patients with pathologically proven nasopharyngeal carcinoma. A significant discrepancy was found in sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for diagnosing skull-base invasion between ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT. Moreover, the sensitivity, specificity, and agreement rate of ^{18}F-NaF PET/CT for detecting metastatic bone lesions were higher than the values for ^{18}F-FDG PET/CT.[48]

A comparative study showed that ^{18}F-NaF PET/CT had a very high sensitivity, negative predictive value, and accuracy than SPECT bone scan to detect bone metastases in breast cancer patients. Moreover, ^{18}F-FDG PET/CT had a higher positive predictive value and specificity than ^{18}F-NaF PET/CT and ^{99m}Tc-MDP SPECT in these patients. Therefore,

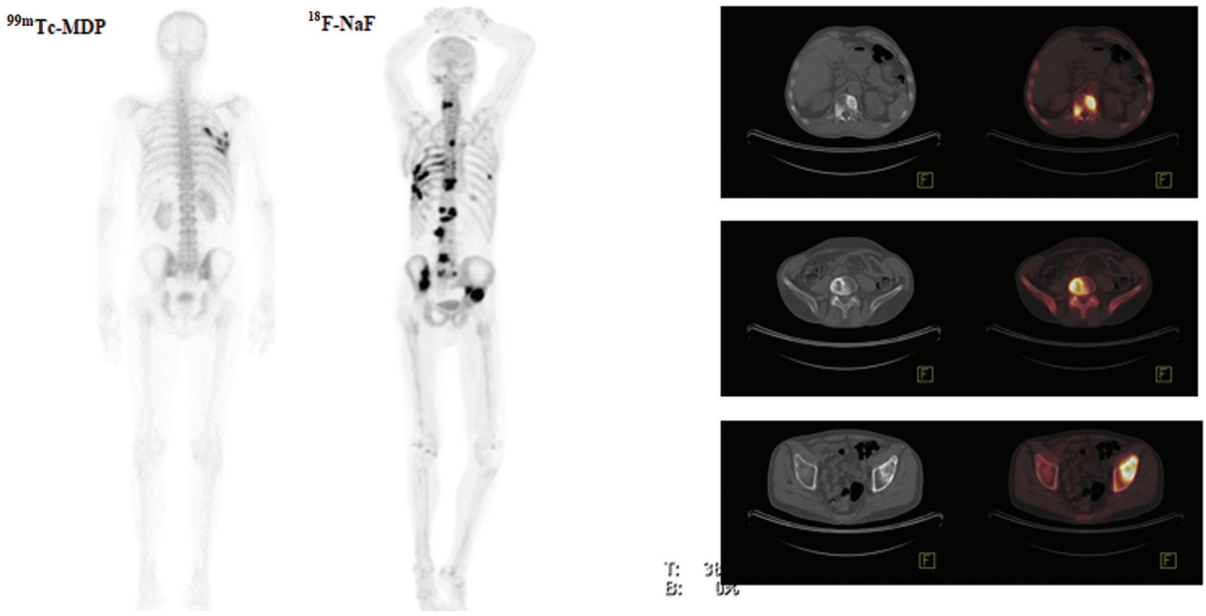

Fig. 1 A 60-year-old man with a history of lung cancer that performed surgery, chemotherapy, and radiation therapy was referred to our department. After administration of 20 mCi technetium-99m-labeled diphosphonates (^{99m}Tc-MDP), the whole body and static images of the skeleton were obtained. The scan shows foci of increased radiotracer uptake in the spine in several levels, ribs, sternum, pelvis, and distal right femur. Subsequently, 7.67 mCi of fluorine-18-labeled sodium fluoride (^{18}F-NaF) was injected intravenously. Images were obtained with six-slice SIEMENS Biograph 6 True-v device from the top of the head to the toes. There is a different region of increased uptake in the right frontal, C4, T4, multiple ribs on the right side, T7, T9, T12, L1, L3, L4, seventh left rib, pelvic bones, and right side of the sacroiliac joint.

the authors proposed that a combination of ^{18}F-NaF and FDG PET/CT could markedly modify patient management.[50] Some studies have proposed combining ^{18}F-NaF and FDG by simultaneous injection of these radiotracers. This combination increases the sensitivity for detecting skeletal metastases compared with stand-alone ^{18}F-NaF and improves the patient's convenience.[51–53] Fifteen women with breast cancer and fifteen men with prostate cancer were prospectively analyzed to evaluate the extent of skeletal disease using combined ^{18}F-NaF/^{18}F-FDG PET/CT. There were no statistically significant differences in the diagnostic ability between ^{18}F-NaF/^{18}F-FDG PET/CT and a combination of whole-body MRI and bone scintigraphy in these patients. However, ^{18}F-NaF/^{18}F-FDG PET/CT showed a significantly higher imaging sensitivity and accuracy for detecting skeletal lesions than whole-body MRI and ^{99m}Tc-MDP scintigraphy.

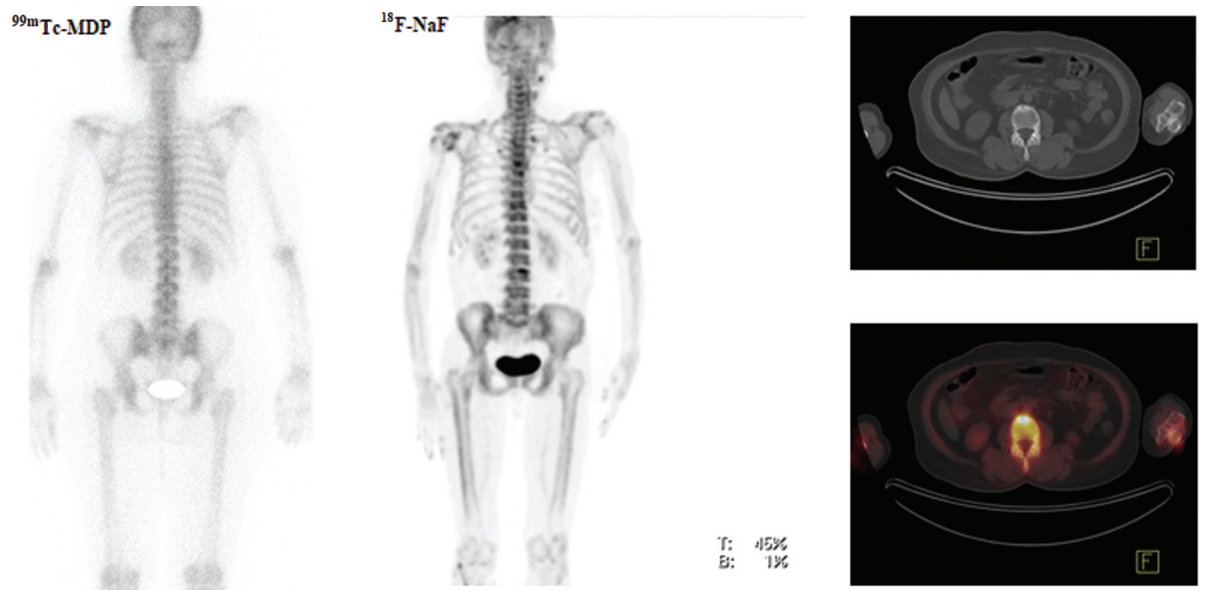

Fig. 2 A 54-year-old woman with a history of breast cancer was referred to our department. 20 mCi technetium-99m-labeled diphosphonates (^{99m}Tc-MDP) were injected intravenously, and whole-body images of the skeleton were obtained. The scan showed homogenous tracer uptake throughout the skeleton. No abnormal increased tracer uptake was seen. Subsequently, 7.67 mCi of fluorine-18-labeled sodium fluoride (^{18}F-NaF) was injected intravenously. There was a different region of increased uptake in the vertebral.

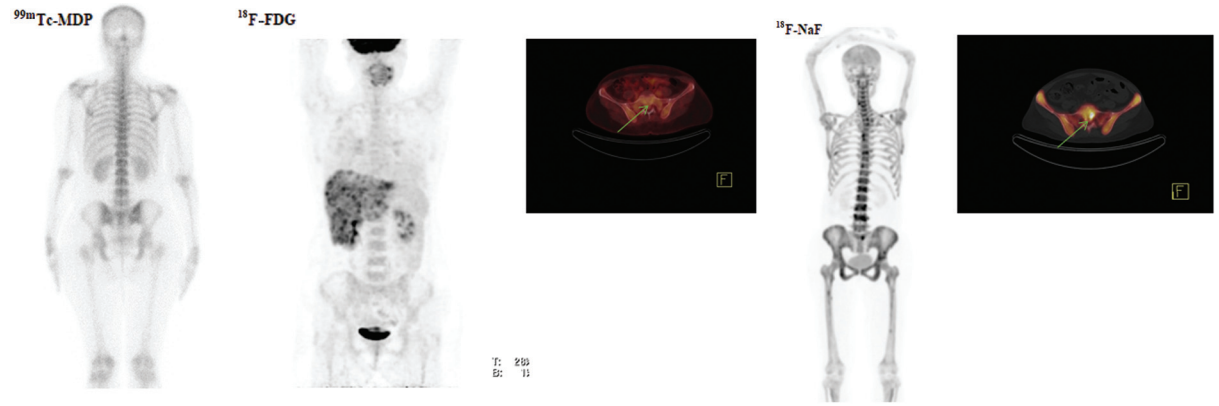

Fig. 3 A 50-year-old woman with a history of right breast cancer, total mastectomy, and chemotherapy was referred to our department. 6.26 mCi 18F-fluorodeoxyglucose (^{18}F-FDG) was administered intravenously. Imaging was performed on an integrated six-slice positron emission tomography/computed tomography scanner. Numerous hypermetabolic mass lesions throughout the liver more compatible with liver metastasis. Other regions were negative for the active hypermetabolic disease. However, some suspicious lesions were found. Subsequently, 20mCi technetium-99m-labeled diphosphonates (^{99m}Tc-MDP) whole-body scan in the anterior and posterior projections was obtained. The scan showed almost homogeneous radiotracer uptake throughout the skeleton, and there was no abnormal radiotracer uptake in any part of the skeletal system. However, bone metastases were confirmed with fluorine-18-labeled sodium fluoride (^{18}F-NaF) imaging.

Furthermore, Yang et al conducted a meta-analysis of 67 studies, including 145 patients published from January 1995 to January 2010, to compare ^{18}F-FDG PET, CT, MRI, and bone scintigraphy to detect bone metastases.[54] On a per-patient basis, the sensitivity of ^{18}F-FDG PET, CT, MRI, and bone scintigraphy was 89.7, 72.9, 90.6, and 86.0%, and the specificity of ^{18}F-FDG PET, CT, MRI, and bone scintigraphy was 96.8, 94.8, 95.4, and 81.4%, respectively. The results showed that ^{18}F-FDG PET and MRI were comparable, while both were more accurate than CT and bone scintigraphy to detect metastatic bone lesions. ^{18}F-FDG PET/CT is independently associated with overall survival in breast cancer patients with bone metastases. The prognostic impact of ^{18}F-FDG PET/CT is more than common clinical and biological prognostic factors. However, ^{18}F-NaF PET/CT demonstrates a better diagnostic sensitivity than ^{18}F-FDG PET/CT, but it is not independently associated with overall survival.[55]

Limitations

However, ^{18}F-NaF PET/CT has been demonstrated as the most suitable imaging modality with high diagnostic performance in assessing bone metastases. Note that ^{18}F-NaF has yielded inconclusive results for sclerotic lesions in bone metastases of prostate cancer patients.[56] Either malignant or benign lesions often have sclerotic lesions. In this regard, the potential of gallium-68-labeled prostate-specific membrane antigen [^{68}Ga-PSMA] should be evaluated to estimate bone metastases as a complementary modality when ^{18}F-NaF PET/CT is inconclusive.[57,58] One of the limitations of this research is that it lacks the benefit of an additional ^{68}Ga-PSMA to assess prostate cancer patients with bone metastases. A more comprehensive systematic or meta-analyzed review is recommended.

Conclusion

The differences in the physical and technical aspects of imaging procedures result in discrepancies in their diagnostic performances. ^{18}F-NaF has a great diagnostic performance for identifying and describing the extent of osseous metastases. However, there are still several challenges: high costs, lack of widespread availability of ^{18}F-NaF, false-positive results, and a high radiation dose. With the increase in the efficiency of ^{18}F-NaF PET/CT imaging scanners and the development of new scanners and reconstruction methods, this modality is expected to slowly replace bone scintigraphy in clinical practice for cancer patients and those with benign skeletal lesions.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

The Institutional Review Board of Razavi Hospital approved all case reports.

Conflict of Interest

None declared.

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