

Editorial.

Comparison Between ^{99m}Tc -MDP and ^{18}F -NaF in Diagnosis in Bone Metastases.

Abdelaziz, S¹ and Moustafa, H².

¹Nuclear medicine Unit, NCI and ²Kasr Al-Ainy Oncology and Nuclear Medicine Department, Cairo University, Egypt.

INTRODUCTION:

Imaging techniques such as CT and MRI as well as bone scan interrogate are common methods used for evaluation of metastatic bone lesions. However, the sensitivity of skeletal scanning in diagnosing bone metastases is remarkably high, exceeding 90 %. Also, it is used most commonly based on its effectiveness, low cost, widespread availability and favourable dosimetry. On the other hand, the specificity is rather low, however the specificity rates have improved since the introduction of hybrid cameras that make it possible to combine physiological and anatomical information together (SPECT/CT) ⁽¹⁾. Also, the spatial resolution of bone scintigraphy is poor measuring approximately 1 cm and can

result in difficulty determining the precise location of a lesion within a bone which can be of diagnostic significance ⁽²⁾.

^{18}F -labelled sodium fluoride (NaF) is an osteotropic compound used in positron emission tomography (PET) which has a higher first pass extraction rate than ^{99m}Tc -MDP which is on average approximately three times higher in metastatic lesions than in adjacent normal bone tissue. Consequently, ^{18}F -NaF has very high selectivity for bone metastases, however its relatively low specificity when not used in conjunction with morphological imaging techniques and the requirement of a cyclotron for production are limiting factors in its use ⁽²⁾.

Corresponding Author: Abdelaziz, S.

E-mail: dr.salmaabdelaziz@yahoo.com.

Bone Scintigraphy: Bone scintigraphy continues to be the most widely used radionuclide technique for investigation of skeletal metastasis primarily due to its widespread availability ⁽²⁾. Radiotracer uptake depends on local blood flow, osteoblastic activity and extraction efficiency. Once accumulated in bone diphosphonate are absorbed by hydroxyapatite crystals on mineralizing bone surfaces ⁽³⁾.

A major advantage of radionuclide bone scanning is that imaging of the whole skeleton can be performed this is important given that metastatic lesions can occur in regions of the appendicular skeleton that are not routinely included in a skeletal survey ⁽⁴⁾.

A further advantage relates the high sensitivity of scintigraphy which enables earlier detection of osseous metastases.

The sensitivity and specificity of bone scintigraphy for detection of bone metastasis is 78% and 48%, respectively. In particular, studies indicate that only a 5%-10% alteration in the ratio of lesion to normal bone is necessary to manifest abnormal tracer accumulation on a bone scan.

As a result, osteosclerotic bone metastases can be detected on bone scintigraphy up to 18 months earlier than on plain radiographs ⁽⁵⁾.

Limitations of skeletal scintigraphy:

Bone scintigraphy is non-specific and multiple benign osseous lesions, such as eosinophilic granuloma fibrous dysplasia and enchondroma, can lead to a false positive diagnosis with similar pattern as bone metastasis ⁽⁶⁾. Interpreting focal accumulation of radiotracer in the spine can be particularly problematic as degenerative disease may be indistinguishable from bone metastases. Consequently, other imaging modalities such as plain radiography, CT or MRI are often required for correlation to exclude benign causes. Secondly, the spatial resolution of scintigraphy is poor measuring approximately 1 cm and can result in difficulty determining the precise location of a lesion within a bone which can be of diagnostic significance ⁽²⁾. Thirdly, bone scintigraphy assesses osteoblastic processes rather than tumour proliferation and, consequently, false negative results can occur ⁽⁷⁾.

Furthermore, primarily osteolytic lesions with limited reactive osteoblastic reaction, such as renal cell carcinoma metastases, typically demonstrate low or absent tracer accumulation leading to a false negative result ⁽⁸⁾.

Finally, when bone metastases are extensive and diffuse, a bone scan on first inspection may appear normal due to the confluent nature of the lesions (referred to as a super scan because of the apparent good quality of the scan) and can be misinterpreted as a negative study. It is therefore needed to carefully assess the uptake in the kidneys on skeletal scintigraphy that indicative of renal excretion of radiotracer which is characteristically absent on a super scan ^(3, 4).

Follow-up scan that shows reducing activity at a vertebral fracture site suggests a benign etiology and a healing fracture. Secondly, lesions that extend from the vertebral body into the posterior vertebral elements or involve the pedicle are more likely to represent metastases. Finally, linear uptake of radiotracer in contiguous ribs is highly suggestive of trauma and not

metastasis ⁽³⁾.

Bone metastases responding to treatment will demonstrate reduced or absent radiotracer uptake when compared with the pre-treatment scan ⁽⁸⁾. It is important to recognize, however, that early in the course of treatment a flare response can occur, which is characterized by a transient elevation in radiotracer accumulation secondary to the stimulation of osteoblasts during the repair process which can be misinterpreted as treatment failure, as it can have an imaging appearance indistinguishable from disease progression ⁽⁵⁾.

The flare response is most commonly associated with hormone based therapies and may last for up to 6 months after therapy ⁽³⁾. Progression of disease is suggested when new deposits develop or there is an interval increase in the activity or size of existing deposits ⁽⁹⁾.

SPECT imaging of the skeleton uses ^{99m}Tc-MDP, the same radionuclide used in conventional skeletal scintigraphy; however images are acquired in a cross-sectional rather than a planar fashion.

Whereas planar imaging is limited by superimposition of structures, SPECT can show axial slices through the body, providing better localization of abnormal radionuclide uptake ^(5,10).

The sensitivity and specificity of SPECT for detection of bone metastasis is 87% and 91%, respectively ⁽⁹⁾. A limitation of SPECT when compared with other available nuclear medicine technique is an inability to generate absolute quantification values ⁽⁸⁾.

PET Radiopharmaceuticals

PET has two major advantages in comparison to SPECT. First of all, the better spatial resolution (4 mm compared to 8 mm), which allows the investigators to see smaller structures. Secondly, PET offers the possibility of absolute quantification, leading to an improved sensitivity of the follow-up of metastatic lesions. PET imaging allows us to diagnose and monitor not only the number and size of pathological lesions, but also the amount of uptake per lesion. This uptake intensity is calculated by using the Standardized Uptake Value (SUV). It represents the tissue activity within a region of interest corrected for the injected

activity and for patient's weight or lean body mass ⁽¹¹⁾. This quality makes PET imaging useful to monitor response to therapy and/or disease progression ⁽¹²⁾.

¹⁸F-Sodium Fluoride:

There has been a resurgence of interest in using ¹⁸F-NaF for bone metastasis imaging since the first clinical hybrid PET/CT scanner was introduced in 1998. The high-energy 511-keV photons produced by ¹⁸F-NaF can be detected accurately by the hybrid PET/CT scanner. PET/CT allows high-resolution functional imaging of bone metastases with significantly greater sensitivity, specificity, and accuracy than conventional planar bone scintigraphy. The low-dose CT component also allows for more accurate anatomic localization within the bony skeleton ^(13,14).

The European Association of Nuclear Medicine produced procedure guidelines specifically for the use of ¹⁸F-NaF PET/CT, outlining minimum standards for the performance and interpretation of ¹⁸F-NaF PET/CT scans ⁽¹⁵⁾. It is therefore apparent that there is an international recognition of the need to replace conventional bone scintigraphy with ¹⁸F-NaF PET/CT to detect bone metastases ⁽¹⁶⁾.

Uptake of ^{18}F -NaF in the bones is twice that of $^{99\text{m}}\text{Tc}$ -MDP because ^{18}F -NaF has only minimal binding with serum proteins, allowing for a rapid single-pass extraction and fast clearance from the soft tissues. Conversely, 30% of $^{99\text{m}}\text{Tc}$ -MDP is protein-bound after injection, and hence this protein-bound $^{99\text{m}}\text{Tc}$ -MDP is cleared slowly. ^{18}F -NaF equilibrates with plasma and is then rapidly cleared after bone deposition and excreted by the kidneys ⁽¹⁷⁾.

^{18}F -fluoride is a positron emitter specific for bones since it images any form of calcification. The “normal” bone scan (labeled diphosphonate) became the standard in nuclear bone imaging. However, the introduction of high resolution PET cameras in the early 1990s, ^{18}F -fluoride is reintroduced into nuclear medicine imaging. Patients can therefore be imaged at only 1 h after injection of ^{18}F -NaF (compared with 3–4 h with $^{99\text{m}}\text{Tc}$ -MDP). The higher bone uptake leads to a higher bone-to-background ratio and therefore better-resolved images.

The mechanism of uptake of ^{18}F -NaF specifically within bone is similar to that of $^{99\text{m}}\text{Tc}$ -MDP. ^{18}F ions exchange with hydroxyl ions (OH^-) on the surface of hydroxyapatite of bone to form

fluoroapatite. Uptake of ^{18}F -NaF reflects bone remodelling. Increased uptake occurs through processes that increase bone exposure by increasing the number of binding sites (i.e., osteoblastic or lytic processes) or the blood flow ⁽¹⁷⁾.

The characteristics of ^{18}F -fluoride are in general identical to the diphosphonate complexes. It is normally symmetrically distributed throughout the entire skeleton. ^{18}F -fluoride depositions favour the axial over the appendicular skeleton and is greater for joints than for shafts of long bones. The route of excretion is through the urinary tract.

In accordance with the $^{99\text{m}}\text{Tc}$ -diphosphonate bone scan, the degree of uptake does not differentiate benign from malignant lesions. However, the pattern may be suggestive for a specific diagnosis. Still, physiological uptake may be more variable in ^{18}F -fluoride due to higher resolution of the PET/CT imaging ⁽¹⁸⁾.

Limitation of ^{18}F -Fluoride:

This technique is the high costs (five times higher compared to the bone scan with diphosphonate) and the non-possibility to perform flow and blood pool imaging.

A study performed by *Even-Sapir et al.*, reported sensitivity for bone metastases of 100 %, a specificity of 62 %, a positive predictive value of 74 %, and a negative predictive value of 100 %. By applying CT to the PET scan all afore mentioned parameters were improved to 100 % ⁽¹⁹⁾.

The bone scan with diphosphonate is still the standard imaging for the detection of bone metastases. However, ¹⁸F-fluoride PET is more sensitive and should be considered for the individual patient although most bone metastases can also be detected with ¹⁸F-FDG.

Comparison of ^{99m}Tc-MDP, ^{99m}Tc -MDP SPECT, and ¹⁸F-NaF PET/CT:

¹⁸F-NaF PET/CT has many advantages over ^{99m}Tc- MDP planar bone scintigraphy and ^{99m}Tc-MDP SPECT/ CT. ¹⁸F-NaF PET tracer emits higher-energy photons; hence, there is better penetration of tissues after administration to the patient, with less scatter and more rays able to reach the scanner detector. Attenuation correction corrects for photons having to travel through dense objects to reach the scanner, and this is provided in all PET/CT scans by means of the CT component. Full-body CT greatly increases spatial resolution and sensitivity and consequently also image quality ^(17, 20).

In view of the faster uptake and clearance of ¹⁸F-NaF, there is twice as much uptake in the bony skeleton, which also leads to better-quality imaging than with ^{99m}Tc-MDP. The low-dose CT scan reduces the need for plain radiographs or diagnostic CT or MRI scans to exclude metastatic disease in equivocal cases.

By not requiring patients to wait for extra scans, this reduces their anxiety. A reduced need for additional scans also helps radiologists make swifter and more definitive management decisions in multidisciplinary cancer meetings, which could significantly affect patient management ⁽²¹⁾.

A weakness of ¹⁸F-NaF PET/CT is that there are more false-positive results because there is more of a tendency to pick up benign pathology (e.g., degenerative joints) instead of just malignant. There are occasional false-negative scans, seen particularly if there is a solitary small lytic metastasis in the bone marrow with little associated osteoblastic activity. There is an increased total effective radiation dose to the patients, and interpretation of the scans requires more time because their greater sensitivity picks up more findings and the CT portion must be viewed in detail ⁽²²⁾.

Conventional bone scintigraphy using ^{99m}Tc -MDP has reasonable sensitivity but suffers from reduced specificity.

The addition of SPECT significantly increases the accuracy of metastatic bone detection, and accuracy is further increased with the use of ^{18}F -NaF PET/CT.

Although these are more likely to be benign, their detection can lead to false-positive results and reduced specificity, without the benefit of conventional CT. Several other studies showed improved accuracy in bone lesion detection, as well as a high negative predictive value, for ^{18}F -NaF PET/CT compared with ^{99m}Tc -MDP SPECT or planar ^{99m}Tc -MDP (23).

The high negative predictive value of ^{18}F -NaF PET/CT thus rules out metastatic spread to the bony skeleton with a high degree of confidence. This is important in such cases as high-risk prostate cancer patients with rising prostate specific antigen and adverse clinical features. Determination that there is no skeletal spread renders radiotherapy or radical prostatectomy with a curative approach feasible in these patients, who might otherwise have been managed with a more conservative or palliative approach (17).

DOSIMETRY:

After an injection of 370 MBq of ^{18}F -NaF, the total effective dose of ^{18}F -NaF PET is 8.9 mSv compared with a total effective dose of 4.2 mSv for ^{99m}Tc -MDP SPECT. These values vary according to the injected dose (24).

The radiation exposure associated with the CT component of the PET/CT and SPECT/CT studies is highly variable and ranges from less than 1 mSv for CT attenuation correction up to 8 mSv for a diagnostic CT scan. A typical value is 3.2 mSv, and consequently the total effective dose of a ^{18}F -NaF PET/CT study is 12.1 mSv (8.9 + 3.2 mSv) compared with 7.4 mSv (4.2 + 3.2 mSv) for a ^{99m}Tc -MDP bone SPECT/CT study (25).

Clinical Application of ^{18}F NaF:

One of the earliest studies was reported by *Schirrmeister et al.*, comparing ^{99m}Tc -MDP (planar and SPECT) with sodium ^{18}F -fluoride PET in 53 men with lung cancer. Sodium ^{18}F -fluoride PET was more sensitive (100%) than planar ^{99m}Tc bone scanning (54%) and SPECT (92%) in 12 patients with bone metastases (26).

Even-Sapir in 2006, studied 44 men with high-risk prostate cancer using ^{18}F -sodium fluoride PET/CT and $^{99\text{m}}\text{Tc}$ -diphosphonate with multi-field-of-view SPECT.

In a patient-based analysis of 23 patients with bone metastases, the sensitivity and specificity of PET/CT were 100% and 92% versus bone SPECT 100% and 82%, respectively.

Furthermore *Krüger*, compared the diagnostic accuracy of ^{18}F -fluorodeoxyglucose (FDG) PET/CT versus planar bone scintigraphy (BS) and ^{18}F -labelled NaF (^{18}F) PET for the detection of bone metastases in 126 patients with in non-small cell lung cancer (NSCLC). Lesions were graded on a scale from 1 (definite bone metastasis) to 5 (degenerative lesion), and equivocal lesions were determined as indifferent (grade 3). A total of 92 patients showed degenerative lesions (grade 4/5) on PET/CT, BS or ^{18}F PET. In 34 patients (27%) bone metastasis lesions were diagnosed (grades 1 and 2). In 13 of 18 patients bone metastasis were concordantly diagnosed with PET/CT and ^{18}F PET.

Naf PET/CT showed more bone metastasis compared to ^{18}F PET (53 vs 40 ⁽²⁷⁾).

A meta-analysis comparing sodium ^{18}F -fluoride with $^{99\text{m}}\text{Tc}$ -diphosphonate was

published in 2010 by *Tateishi*, In a patient-based analysis, the pooled sensitivity and specificity of sodium ^{18}F -fluoride in 10 studies were 96% and 98%, respectively, whereas the pooled sensitivity and specificity of $^{99\text{m}}\text{Tc}$ -diphosphonate planar, or planar plus SPECT, bone scanning in 8 studies were 57% and 98%, respectively ⁽²⁸⁾.

Also, the National Oncologic PET Registry (NOPR) created a new registry to evaluate sodium ^{18}F -fluoride for the detection of metastatic disease in the skeleton. The registry was performed on 20238 patients. The most common cancer types were prostate, breast, cancer. The study shows that sodium ^{18}F -fluoride PET/CT substantially affected intended management across 3 groups of patients: initial staging, suspected first skeletal metastasis, and suspected progression of known skeletal metastatic disease.

PET/CT had a high overall impact, primarily related to replacing intended use of other advanced imaging in about half of the cases. More significantly, when intended management was classified either as treatment or as non-treatment, the intended management after sodium ^{18}F -fluoride was changed in 44%–52% of patients.

After adjustment for those cases for which the pre-PET plan—including other advanced imaging—may have led to the same changes in intended management. Prior ^{99m}Tc bone scanning results were available only for a few patients (9.3%).

Understanding the value of sodium ^{18}F -fluoride as a first imaging study is important because access to PET/CT is more limited than access to ^{99m}Tc -diphosphonate bone scanning, but the cost is higher ⁽²⁹⁾.

Rao, in 2016 compared the diagnostic accuracy of ^{18}F -NaF PET-CT with ^{99m}Tc -MDP SPECT to detect bone metastases (BMs) in patients with preoperative lung cancer. 181 Patients with lung cancer were examined with ^{18}F -NaF PET-CT, and another 167 patients with lung cancer were examined with ^{99m}Tc -MDP SPECT. Lesions were graded on a scale of 0 (degenerative lesion) to 4 (definite BM), and equivocal lesions were determined as indifferent (grade 3). Based on patient-based analysis, there were only 4 equivocal patients in ^{18}F -NaF PET-CT detection. However, in ^{99m}Tc -MDP SPECT detection, there were 19 equivocal patients, which indicated a significant difference in terms of occurrence ratio. Sensitivity and specificity of PET-CT was significantly better than that of SPECT when equivocal reading was categorized as

malignant or benign ($P < 0.05$). Based on lesions-based analysis, SPECT produced 26 equivocal lesions of 333 lesions, but PET-CT produced only 5 equivocal lesions of 991 lesions. PET-CT was significantly better than SPECT in the aspect of producing equivocal patients. Sensitivity and specificity of PET-CT was significantly better than that of SPECT when equivocal reading was categorized as malignant or benign ($P < 0.05$). They concluded that ^{18}F -NaF PET-CT is a highly sensitive and specific modality for the detection of BM in patients with preoperative lung cancer. It is better than conventional ^{99m}Tc -MDP SPECT in detecting BM in patients with preoperative lung cancer ⁽³⁰⁾.

Fonager, prospectively compare planar, bone scan (BS) versus SPECT/CT and NaF PET/CT in detecting bone metastases in prostate cancer. Thirty-seven consecutive, newly diagnosed, prostate cancer patients with prostate specific antigen (PSA) levels ≥ 50 ng/mL and who were considered eligible for androgen-deprivation therapy (ADT) were included in this study. BS, SPECT/CT, and NaF PET/CT, were performed prior to treatment and were repeated after six months of ADT. Twenty-seven (73%) of the 37 patients had bone metastases according to the reference standard.

The sensitivities for BS, SPECT/CT and NaF PET/CT were 78%, 89%, and 89%, respectively, and the specificities were 90%, 100%, and 90%, respectively. The positive predictive values of BS, SPECT/CT and NaF PET/CT were 96%, 100%, and 96%, respectively, and the negative predictive values were 60%, 77% and 75%, respectively ⁽³¹⁾.

Broos et al., assessed the accuracy of ¹⁸F-NaF PET/CT in bone metastasis detection and its effect on patient management in patients with breast carcinoma. A total of 118 patients were included in the study. Bone metastases were found in 42%, whereas 53% of the scans were negative and 5% yielded equivocal results. Correlation with the reference standard yielded a sensitivity of 0.96, a specificity of 0.91, a positive predictive value of 0.89, a negative predictive value of 0.97, and an accuracy of 0.93. In 25% of the patients, the scan results led to alterations in patient management. ¹⁸F-NaF PET/CT for the evaluation of bone pain showed no explanation in 29%, benign pathology in 66%, and bone metastases in 5%. They concluded that ¹⁸F-NaF PET/CT detected bone metastases in 42% with an accuracy of 0.93. The scan results led to a change in patient management in 25%.

In the evaluation of bone pain, an explanation for pain was found in 71% of the scans ⁽³²⁾. Recent meta-analysis performed by **Liu** to assess the diagnostic performance of combined ¹⁸F-fluoride PET/CT in bone metastases (BM) and explore whether there is an added value when compared with ^{99m}Tc- MDP planar bone scintigraphy (BS). Studies evaluating the performance of ¹⁸F-fluoride PET/CT in BM detection and using histopathology or clinical/imaging follow-up for ≥ 6 months as the reference standard were included. Twenty articles comprising 1,349 patients were included. On the patient basis, the pooled sensitivity and specificity of ¹⁸F-fluoride PET/CT were 93% and 95% when equivocal results were considered as negative for BM; and 96% and 93% when equivocal results were considered as positive. On the lesion basis, the pooled sensitivity and specificity were 93% and 96% when equivocal results were considered as negative; and 94% and 95% when equivocal results were considered as positive. Seven articles reported the comparison between ¹⁸F-fluoride PET/CT and ^{99m}Tc-MDP BS. ¹⁸F-fluoride PET/CT showed both higher sensitivity ($p < 0.005$) and specificity ($p < 0.05$) when equivocal results were considered as positive.

When the equivocal results were considered as negative, ^{18}F -fluoride PET/CT showed higher sensitivity ($p < 0.005$), but no significant difference in specificity ($p = 0.08$).

He concluded that ^{18}F -fluoride PET/CT showed superior diagnostic performance in BM detection and had higher accuracy when compared with $^{99\text{m}}\text{Tc}$ -MDP BS⁽³³⁾.

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