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Title: The Role of 18F-Sodium Fluoride PET/CT Bone Scans in the Diagnosis of Metastatic Bone Disease from Breast and Prostate Cancer

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The Role of 18F-Sodium Fluoride PET/CT Bone Scans in the Diagnosis of Metastatic Bone Disease from Breast and Prostate Cancer

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Abstract:

This article shall describe the role of ^{18}F-Sodium Fluoride (^{18}F-NaF) PET/CT bone scanning in the staging of breast and prostate cancer. ^{18}F-NaF PET was initially utilised as a bone scanning agent in the 1960s and early 1970s, however its usage was restricted by the then available gamma cameras. The advent of hybrid PET/CT cameras in the late 1990s has shown a resurgence of interest in its usage and role. After a brief introduction, this paper will describe the radiopharmaceutical properties, dosimetry, pharmacokinetics, and mechanism of uptake of ^{18}F-NaF. The performance of ^{18}F-NaF PET/CT is then compared with conventional bone scintigraphy utilizing current evidence from the literature. Strengths and weaknesses of ^{18}F-NaF PET/CT imaging shall be highlighted. Clinical examples of improved accuracy of diagnosis and impact on patient management shall be illustrated. Limitations of ^{18}F-NaF PET/CT imaging will be outlined.

Introduction

Many people with cancer will develop bone metastases during the course of their disease. The American Cancer Society estimated that of the 569,490 people who died of cancer in 2010, approximately 350,000 had bone metastases *(1)*.

There are two main types of bone metastasis: osteoblastic and osteolytic. Osteoblastic disease occurs when the cancer cells cause an increase in bone formation resulting in more dense or sclerotic features. This is often associated with prostate cancer tumour types. Osteolytic disease occurs when the cancer cells cause increased bone mineral turnover or resorption resulting in a decrease in bone density. This can cause weakening of the bone structures which can result in bone fractures with minimal trauma. Osteolytic disease is more commonly associated with lung or renal cancer tumour types. Some bone metastases including those originating from breast cancer will include a mixture of both osteoblastic and osteolytic types as a bone metastasis of solely one type is rare in breast cancer.

Primary cancers in the body can metastasise to bone, especially in patients with late stage or recurrent disease, but also earlier in the course of the disease. This is especially true in patients with breast and prostate cancer, but bone metastases can also be seen in lung, thyroid, and renal malignancies, as well as many other cancers.

Staging of a primary malignancy is essential to categorise the malignancy as either locally based, or with further spread to either lymph nodes, local or distant, or spread to distant organs or tissues such as the lungs, liver, brain, adrenal glands, bony skeleton or peritoneum.

Several staging classifications have been created to stage different types of cancers, the most commonly used being the TNM classification *(2)*, which describes the main tumour size and extent (T), the degree of involvement of lymph nodes (N) and the presence or absence of distant metastatic spread (M). If only locally based, after having had treatment for spread to the liver for example, then the cancer is “down-staged”. If the cancer is found to have confirmed spread to lymph nodes or distant organs, after initially being locally based in the primary organ, then the cancer is said to be “up-staged”.

Accurate delineation of bone metastases is important because the patients are either up-staged or down-staged according to whether the bone metastases are present or absent. This has a clear impact on patient management, according to whether there is curative surgery or palliative care.

Accurate location of bone metastases also allows response of bone metastases to therapy to be monitored, and acts occasionally as a guide to an appropriate bone biopsy site, should definitive histological confirmation be required, such as in solitary bony lesions.

Although the incidence of bone metastases at initial diagnosis is 1-2%, this increases significantly to approximately one third in patients diagnosed at an advanced stage or who have disease recurrence *(3)*.

Imaging of bone metastases has for several decades been undertaken via planar isotope bone scintigraphy utilising technetium 99m labelled with diphosphanate (e.g. methylene diphosphanate (^{99m}Tc-MDP)). A more bone specific PET tracer, sodium fluoride labelled with fluorine 18 (^{18}F-NaF) was first proposed as a bone scanning agent back in 1962 by Blau et al using animal models *(4)* and was approved by the US Food and Drug Administration in 1972. Its properties included a rapid and high uptake in the bony skeleton, yet the clinical use was restricted by gamma camera technology available at that time. Conventional gamma cameras can optimally image the 140-keV photons from ^{99m}Tc-MDP but are insensitive in detecting the high energy 511-KeV photons emitted by ^{18}F-NaF, resulting in the dominance of ^{99m}Tc-MDP imaging from the mid to late 1970s.

An example of an early ^{18}F-NaF image performed on a rectilinear bone scanner is demonstrated in Figure 1. Figure 2 shows an example of a rectilinear bone scanner.

There has been a resurgence of interest in using ^{18}F-NaF for bone metastasis imaging since the first clinical hybrid PET/CT scanner was introduced in 1998 at the University of Pittsburgh Medical Centre. The high energy 511-KeV photons produced by ^{18}F-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 compared with conventional planar bone scintigraphy *(5,6)*. The low dose CT component also provides a unique platform with which to differentiate between benign and malignant bone lesions, which can both take up the PET tracer. The low dose CT component also allows for more accurate anatomical localisation within the bony skeleton. It should however be noted that the low dose CT does not provide a “gold standard” diagnosis.

In the UK, a recent publication *(7)* from the Royal College of Physicians (RCP), Royal College of Radiologists (RCR) and British Nuclear Medicine Society (BNMS) has stated that ^{18}F-NaF is recommended for assessment of benign and malignant diseases of the bone in selected patients and produces high quality images.

The European Association of Nuclear Medicine (EANM) has also produced procedure guidelines specifically for the use of ^{18}F-NaF PET/CT, outlining minimum standards for the performance and interpretation of ^{18}F-NaF PET/CT scans *(8)*. Both the UK and European publications refer to the SNMMI Guidance from the USA, published back in 2009 *(9)*.

It is therefore apparent that there is an international recognition of the need to replace conventional bone scintigraphy with ^{18}F-NaF PET-CT to detect bone metastases. This process is currently restricted by a lack of funding and availability of PET/CT scanners. No national form of

funding (e.g. UK) or reimbursement (e.g. USA, Canada, Australia) for these scans is set-up as is seen in Oncology and ^{18}F-fluorodeoxyglucose (^{18}F-FDG).

This article explores the resurging role of ^{18}F-NaF PET/CT in the detection of bone metastases, with an emphasis on production, pharmacokinetics, mechanism of uptake, comparisons with conventional imaging such as planar bone scintigraphy, CT, SPECT and SPECT/CT, clinical protocol, radiation dosimetry, clinical performance of ^{18}F-NaF PET/CT compared with conventional bone scintigraphy, and strengths and weaknesses.

Production and Pharmacokinetics

^{18}F-Na F is produced within a cyclotron by particle acceleration from water enriched ^{18}O. ^{18}F ions are trapped in an aqueous solution in a cation exchange column. The eluent from the cation exchange cartridge is passed through an anion exchange ($HCO3^-$ form) cartridge to trap the ^{18}F-NaF.

The anion exchange cartridge is then flushed with 10mls of sterile water, and the ^{18}F-NaF is then eluted with 10 ml of sterile normal saline and is passed through a sterile filter into a sterile multidose vial *(10)*.

F-18 decays by positron emission. After colliding with an electron, two 511-keV annihilation photons are produced 180^0 opposed: these are detected by a circular array of PET detectors.

The half life of ^{18}F-NaF is110 minutes, and hence it is widely available from the same facilities that produce ^{18}F-FDG for oncological diagnosis, with no further additional special facilities required.

Mechanism of Uptake

Once injected intravenously, after only a single pass of blood, most of the ^{18}F-Na F is deposited within the bony skeleton; the first pass uptake is considerably higher than ^{99m}Tc phosphates *(11)*.

There is twice the uptake in the bones seen with ^{18}F-NaF compared with ^{99m}Tc-MDP. The reason for this is that ^{18}F-NaF has only minimal binding with serum proteins, which allows for a rapid single pass extraction and fast clearance from the soft tissues. Conversely, 30% of Tc-MDP is protein bound after injection and hence this protein bound Tc-MDP is cleared slowly *(11)*. ^{18}F-NaF equilibrates with plasma and is then rapidly cleared after bone deposition and is excreted by the kidneys.

Patients can therefore be imaged at only one hour post injection of ^{18}F-NaF (compared with 3-4 hours with ^{99m}Tc-MDP). The higher bone uptake leads to a higher bone to background ratio and therefore better resolved images (See Figures 3a and 3b below).

The mechanism of uptake of ^{18}F-NaF specifically within bone is similar to ^{99m}Tc-MDP. ^{18}F ions exchange with hydroxyl ions (OH-) on the surface of hydroxyapatite of bone to form fluoroapatite. Uptake of ^{18}F-Na F reflects bone remodelling. Increased uptake occurs in processes which increase bone exposure with a higher number of binding sites (i.e. osteoblastic/lytic processes) or increased blood flow. The rate-limiting step is blood flow *(11)*.

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

Conventional bone scintigraphy utilising ^{99m}Tc MDP has reasonable sensitivity but does suffer from reduced specificity. The addition of Single Photon Emission Tomography (SPECT) significantly increases accuracy of metastatic bone detection and this is further increased with the usage of ^{18}F-NaF PET/CT, as the table below illustrates *(12)* (Table 1).

In addition, it should be noted that the reduced specificity of ^{18}F-NaF PET (62%) compared with ^{99m}Tc-MDP SPECT is because of the increased sensitivity of PET at detecting more bone lesions, which are more likely to be benign, but can lead to false positive results reducing the specificity, without the benefit of conventional CT.

Several other studies *(13-16)* show improved accuracy of bone lesion detection, as well as a very high negative predictive value of ^{18}F-NaF PET/CT compared with ^{99m}Tc-MDP SPECT *(13)* and planar ^{99m}Tc-MDP *(15,16)*. Some of these studies are summarized in the table below (Table 2).

The high negative predictive value of ^{18}F-NaF PET/CT thus rules out metastatic spread to the bony skeleton with a very high degree of confidence. This is important for example in high risk prostate cancer patients with rising PSA and adverse clinical features.

No skeletal spread renders radiotherapy or radical prostatectomy with a curative approach feasible in these patients, who might otherwise had been managed with a more conservative or palliative approach.

Procedure and patient preparation (Adapted from Segall G et al *(9)* and EANM Gudelines 2015 *(8)*):

Patients are provided with an information leaflet prior to the test. The procedure is explained on the patient arrival in the department by a member of the PET/CT team. 370 MBq of 18F-Na F radiotracer is injected into the patient intravenously. There is usually a one hour wait before the scan, although this can be shortened to 30-45 minutes if necessary. Any metal objects on the patient should be removed to prevent attenuation artefacts. There is no requirement to starve or avoid medications beforehand, and the patient can talk before procedure.

The patient should be well hydrated to enhance ^{18}F-NaF renal excretion *(17)*, which also reduces radiation exposure and helps to achieve optimal target to background ratio. The patient is required to void their bladder immediately prior to the PET/CT scan.

Regarding pregnant patients, this examination should be avoided, unless the potential benefits outweighs the radiation risk to the mother and fetus.

Arm position during scanning depends on the indications for the study. The arms may be by the sides for whole-body imaging or elevated when only the axial skeleton is imaged.

A low dose CT scan is performed first from the skull vertex to mid-thighs (< 30 seconds). The low dose CT is performed for attenuation correction and also for anatomical localization. The usual CT settings sufficient for attenuation correction and localization are a tube current of 30 mA, voltage of 120 kVp, rotation of 0.5 s, and a pitch of 1 *(8)*.

PET imaging can then be performed from the vertex of skull to the mid-thighs (approximately 20 minutes duration). PET images may be acquired in 2- or 3-dimensional mode. Three-dimensional mode is usually recommended for whole-body acquisition because the higher count rates compensate for the shorter acquisition times required for imaging a larger area. Acquisition time per bed position can vary but is usually 1-2 minutes per bed position in 3D mode.

Images can be acquired on either a 128x128 matrix or 256x256 matrix and reconstructed with a 3 dimensional Ordered Subset Expectation Maximization (OSEM) Time of Flight (TOF) algorithm, ideally with iterative reconstruction.
Co-registered fused PET/CT images are then sent to the workstation for further interpretation. Maximum intensity projection (MIP) images should also be generated to help facilitate lesion detection.

Dosimetry

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

tion correction up to 8 mSv for a diagnostic CT scan. A typical value is 3.2 mSv *(16)*, and consequently the total effective dose of ^{18}F-NaF PET/CT is 12.1 mSv (8.9 + 3.2 mSv) compared to 7.4 mSv (4.2 + 3.2 mSv) for a ^{99m}Tc-MDP bone SPECT/CT study.

The total effective dose administered does need to be considered when requesting repeat scans to monitor progress, especially in light of the fact that cancer patients in general could be having multiple CT scans, fluoroscopy and plain radiography which could further increase the radiation dose that the patient receives.

Advantages of ^{18}F-NaF PET/CT over ^{99m}Tc-MDP bone scintigraphy (planar and SPECT): *(11,19)*

^{18}F-NaF PET/CT has many advantages over ^{99m}Tc-MDP planar bone scintigraphy and ^{99m}Tc-MDP SPECT/CT.

^{18}F-NaF PET tracer emits higher energy photons, hence there is better penetration of tissues, after administration to the patient, with less scatter and more gamma 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 tomography greatly increases spatial resolution and sensitivity, and hence also image quality as a result.

The injection-to-scan-time is greatly reduced from 3-4 hours down to 30-60 minutes, and this significantly reduces the overall examination time for patients, which also increases throughput, meaning a greater number of patients can be scanned in one session (e.g. morning session can scan 6-7 patients on ^{18}F-NaF PET/CT compared with 3-4 with ^{99m}Tc-MDP).

In view of the faster uptake and clearance of ^{18}F-NaF, there is twice as much uptake in the bony skeleton, which also leads to better quality imaging compared with ^{99m}Tc-MDP.

The low dose CT scan reduces the need for plain radiographs, diagnostic CT or MRI scans in order to exclude metastatic disease in equivocal cases. This leads to reduced patient anxiety in terms of no extra waiting for investigations and also helps to make swifter and more definitive management decisions in the multi-disciplinary cancer meetings, which could significantly affect patient management.

The weaknesses are that there are more false positive results as ^{18}F-NaF PET/CT has a tendency to pick up more benign pathology (e.g. degenerative joints) as well as 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 seen. There is an increased total effective radiation dose to the patients, and it takes longer to report ^{18}F-NaF PET/CT bone scans, in view of more pathology picked up by the more sensitive scans, and having to view the CT in detail.

Clinical Examples

An example of a F-NaF PET/CT true positive bone scan is shown below (Figures 4 and 5). This patient has primary breast cancer, with multiple bone metastases, at several sites including the skull, ribcage, right pedicle of T12 vertebra, the right hemipelvis and also the right inferior pubic ramus. The prior bone scintigraphy study utilising ^{99m}Tc phosphate, failed to show the full extent of these bone metastases.

An example of a false positive ^{18}F-NaF PET/CT study, a MIP image is shown below, with the low dose CT showing benign pathology (Figures 6 and 7). This patient also suffers from primary breast cancer with a lesion in the right sacro-iliac joint (SIJ) identified as a potential metastasis on ^{18}F-NaF PET/CT. The right SIJ lesion was found to be a benign sclerotic fibro-osseous lesion on further diagnostic CT and MR scanning.

Conclusions

The history and main usage of ^{18}F-NaF has been described in detecting bone metastases primarily in breast but also prostate cancer patients. ^{18}F-NaF PET/CT is more accurate than traditional planar bone scintigraphy and SPECT/CT. ^{18}F-NaF PET/CT produces images of superior quality, with a greater throughput of patients. The low dose CT is good at excluding benign disease. Greater accuracy results in fewer anxious waits for patients for extra tests (e.g. plain film radiography, diagnostic CT or MRI scanning). It is also important to be aware of limitations including a small number of false positives and the increase in radiation dose.

The main challenges concerning its more widespread usage are related to the high cost and lack of reimbursement, which is worldwide, as well as a lack of awareness of the procedure from the referring clinicians. It is hoped that the latter issues shall be addressed in the coming years as the procedure becomes more available to hospitals and more acceptable by the clinicians.

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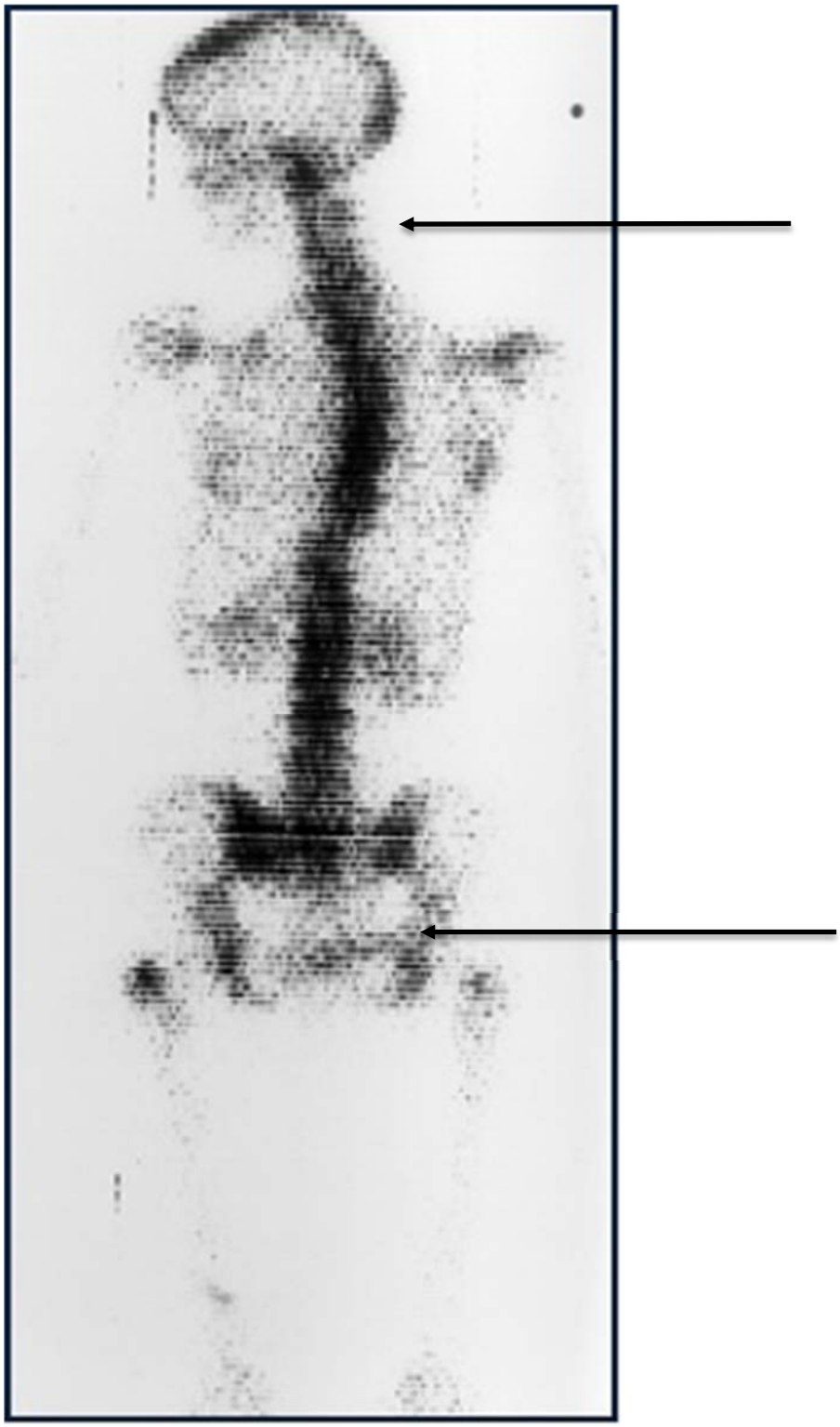


Figure 1. A breast cancer patient with bone metastases (black arrows). The examination was undertaken on a rectilinear scanner at Guy's Hospital, London, 1973. (Reproduced with permission from Professor Gary Cook, Clinical Nuclear Medicine, 4th Edition, Hodder and Arnold)

Figure 2. Rectilinear Bone scanner

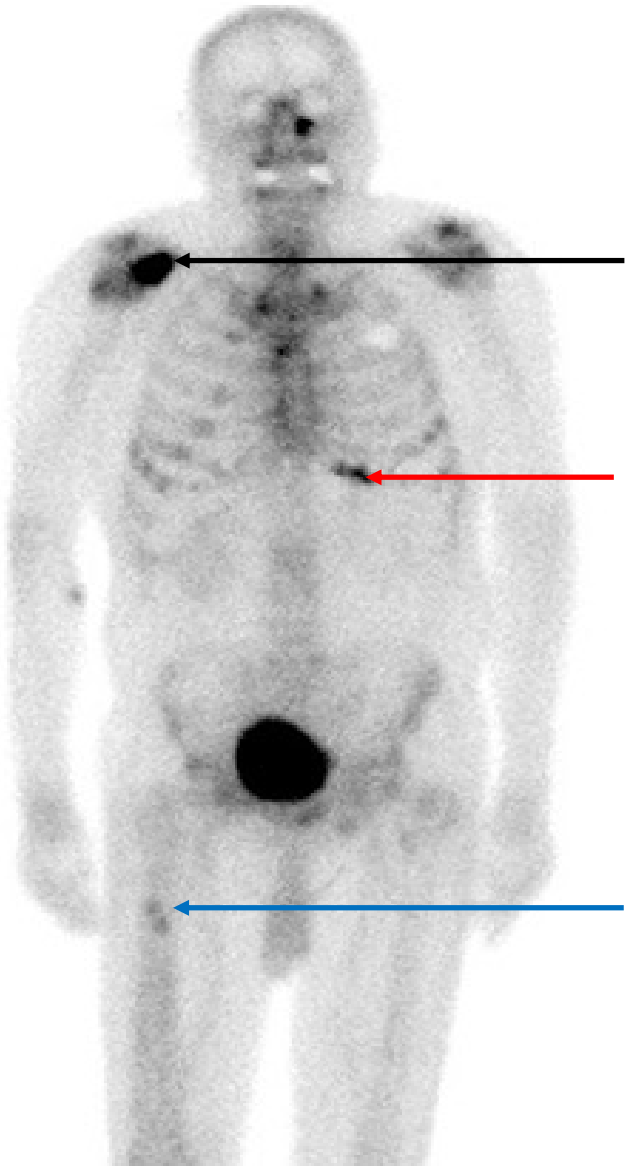
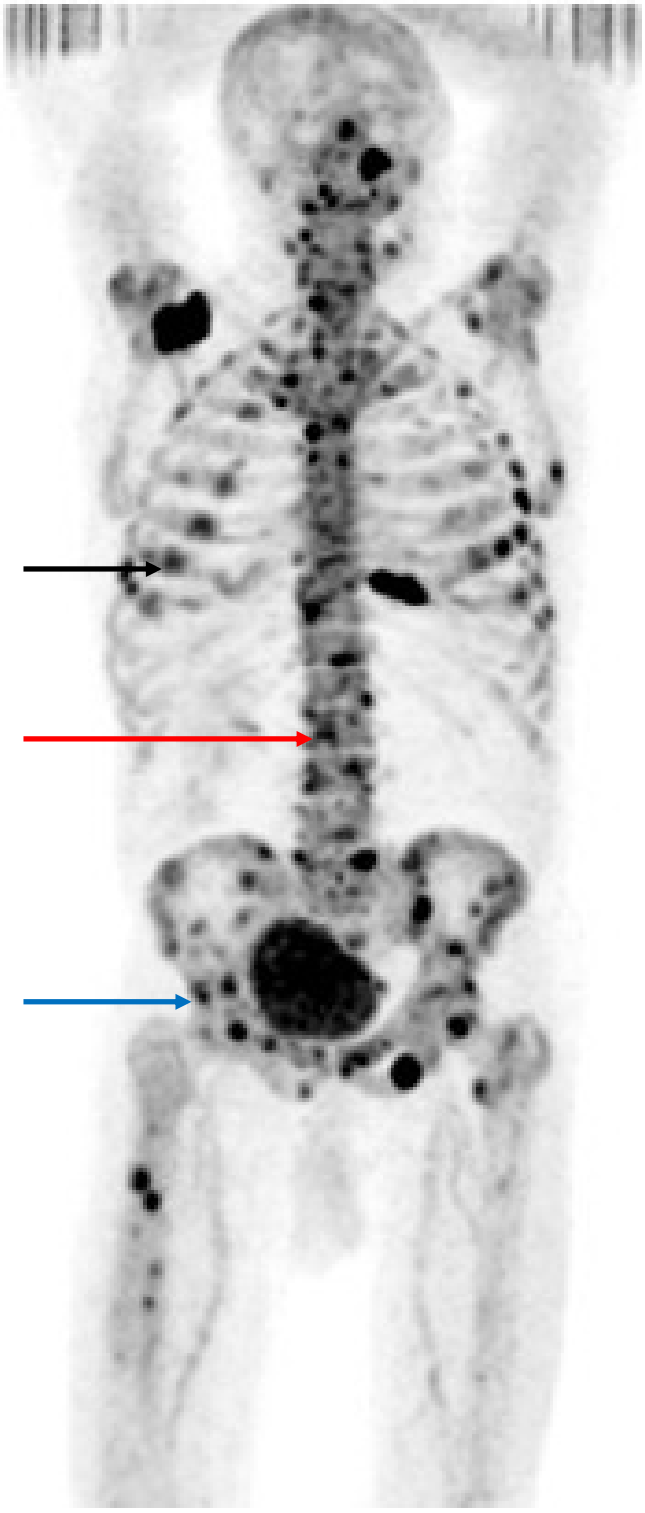


Figure 3a showing conventional ^{99m}Tc-MDP planar scintigraphy showing several bone metastases in the right scapula (black arrow), left lower anterior ribcage (red arrow) and in the right proximal femoral shaft (blue arrow), in a patient with prostate cancer metastases,



Same patient as in Figure 3a (Figure 3b), having a ^{18}F-NaF PET/CT bone scan (shortly after bone scan), clearly showing a greater burden of bone metastases, especially in the ribcage (black arrow), spine (red

arrow) and pelvis (blue arrow).(Images adapted from Even-Sapir, Metser U, Mishani E, Lievshitz G, Lerman H, Liebovitch I. The detection of bone metastases in patients with high risk prostate cancer: 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(2):287-297 *(12)*)

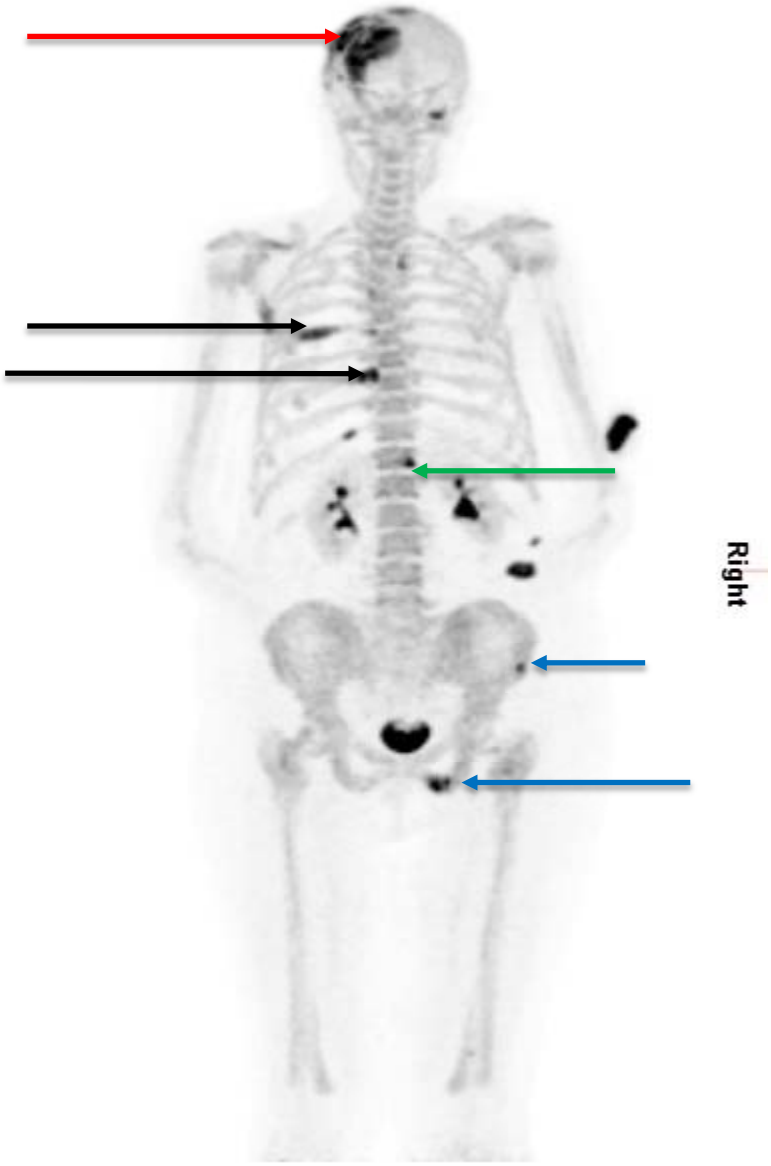


Fig. 4: MIP 18-F NaF PET/CT bone scan (posterior view) showing bone metastases in the left fronto-parietal skull near the vertex (red arrow), left posterior ribs (black arrows), right pedicle of T12 (green arrow), and right hemipelvis (blue arrows), not shown clearly on a previous planar bone scan. Courtesy of Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK, 2016.

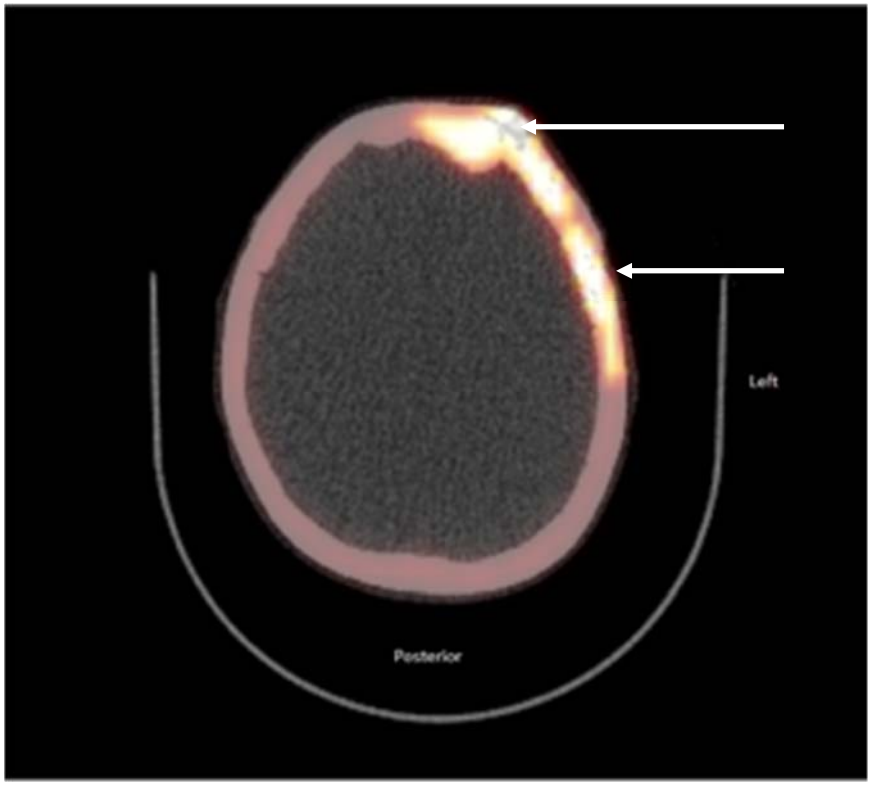


Fig. 5: Axial fused 18F-NaF PET/CT bone scan of previous case from Figure 4 showing left fronto-parietal skull bone metastasis, clearly showing bony involvement on the CT component (white arrows). Courtesy of Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK, 2015.

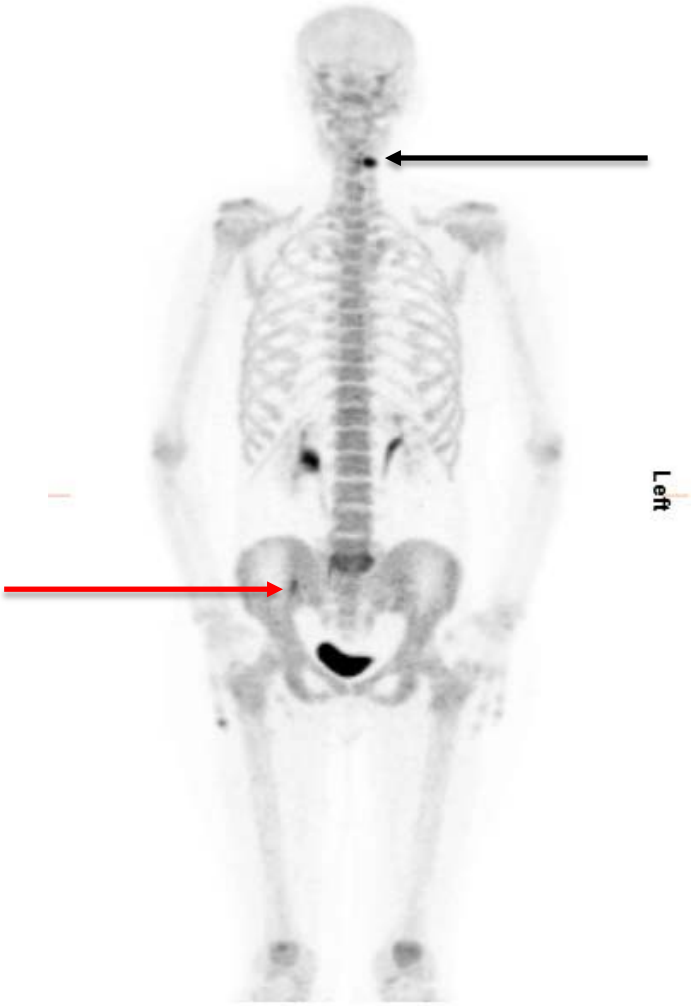


Fig. 6: False Positive. MIP 18-F NaF PET/CT showing lesions in left upper cervical region (black arrow) and right iliac bone region close to the right SIJ (red arrow). Courtesy of Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK, 2015.

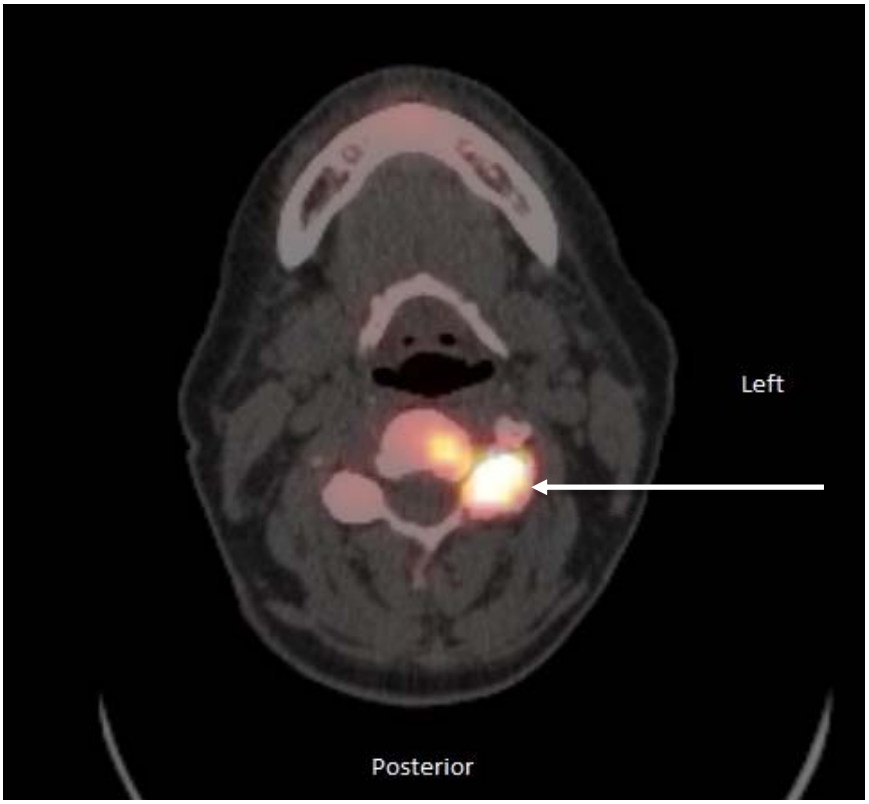


Fig. 7: Axial fused 18F-NaF PET/CT bone scan showing degenerative change in upper left cervical facet joint (white arrow), corresponding to previous MIP image lesion in this area. Courtesy of Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK, 2015.

	^{99m}Tc-MDP	^{99m}Tc-MDP SPECT	^{18}F-NaF PET	^{18}F-NaF PET/CT
Sensitivity (%)	70	92	100	100
Specificity (%)	57	82	62	100

Table 1. Comparison with ^{99m}Tc-MDP, ^{99m}Tc-MDP SPECT, and ^{18}F-Fluoride PET (44 patients high risk prostate cancer patients, Even-Sapir et al*(12)*)

Paper	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Withofs et al*(14)*/^{99m}Tc MDP bone scintigraphy (prostate)	66.7	84.2	57.1	88.9
Withofs et al*(14)*/ ^{18}F NaF PET/CT (prostate)	100	94.7	85.7	100
Bortot et al*(16)*/ ^{18}F NaF PET/CT (all tumour subtypes)	100	88	84	100

Table 2. Other studies showing improved accuracy of bone lesion detection using ^{18}F NaF PET/CT over planar bone scintigraphy.