^{18}F-NaF PET/CT of Bone

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1. Introduction

Bone scintigraphy using ^{99m}Technetium labelled bisphosphonates is one of the standard nuclear medicine investigations for the detection of all kinds of lesions in which the bone turn-over is changed, preferably increased. Most commonly it is used for the detection of bone metastasis, primary bone tumours, metabolic bone disease or benign skeletal lesions especially in orthopaedics. This technique has been in use for decades and there is a large body of evidence supporting its use in the diagnosis and treatment monitoring of many different diseases. For this reason it is integrated in many protocols and guidelines. This technique has a high sensitivity for the detection of skeletal disease but there are some drawbacks. Most often planar scintigraphy is used which can lead to over projection of different skeletal structures, attenuation of deeper structures and a relatively poor spatial resolution. Also foci of high uptake lack specificity due to the fact that planar scintigraphy does not offer reference to anatomical structures. When additional imaging is added such as different views, or better SPECT (-CT), sensitivity is slightly improved and specificity is clearly improved. Due to the cost and time restrictions this can be done only for a small area of interest. After initial trials in the 50's and 60's ^{18}Fluoride in the form of a Na^{18}F solution is now available as a tracer in humans. Fluoride has the same uptake mechanism as bisphosphonates: it is incorporated into young bone by the osteocytes thus it shows increased bone turnover. Fluoride can have certain advantages compared to ^{99m}Tc labelled tracers. The incorporation or binding is faster so the scan can be performed after a shorter incubation period and generally the PET (-CT) scanner has a higher sensitivity and spatial resolution compared to planar gamma cameras or even SPECT (-CT). The dose used, and with that the absorbed dose to the patient, is lower than with ^{99m}Tc labelled tracers. Imaging is always 3D and often the accompanying CT will offer attenuation correction and anatomical information. Also the signal is (semi-) quantitative. In the recent past many departments in the Netherlands had a PET-CT scanner but not a SPECT-CT scanner. Last but not least: in times of molybdenum generator crisis it offers an alternative to the regular bone scan. Therefore it was suggested in the past that bone scintigraphy using ^{18}F would replace the regular ^{99m}Tc bone scintigraphy. However, due to the higher costs and the availability of SPECT-CT systems this change has not (yet) taken place. ^{18}F PET (-CT) has been proven (cost-) effective and accurate in the diagnosis of bone metastasis of lung cancer, prostate cancer and breast cancer. Compared to ^{99m}Tc based bone scintigraphy there is increased visualization of lytic metastasis although still not 100%. Sodium ^{18}Fluoride (NaF) can also be used in the assessment of degenerative bone disease, the evaluation of traumatic disease such as non-union and stress fractures, the evaluation of backache, visualization of osteonecrosis or the quantification of disease activity in metabolic bone disease e.g. Paget's disease. It can also be used in the evaluation of prosthetic joint disease although differentiation between loosening and infection is difficult. The vitality of bone grafts is easily assessed with NaF. There are

some disadvantages. NaF is still not registered for human use but can be administered under compassionate use. It is available under GMP production. When commercially bought the tracer is about 20 times more expensive than a ^{99m}Tc labelled tracer. Normally the perfusion and diffusion images are not acquired on a PET system because of the costs. This could limit the detectability of accompanying soft tissue disease e.g. enthesopathy, tendinitis, synovitis or bursitis. Taking all things into consideration:

a. ^{99m}Tc bone scintigraphy remains the first choice for all indications. In a few (more academic) situations such as metabolic bone disease or primary bone tumours NaF can be considered if there is local expertise available.
b. although there is no large body of evidence it is reasonable to assume that NaF PET (-CT) is at least as good (sensitivity and specificity) as ^{99m}Tc based bone scintigraphy for the detection of metastatic bone disease and probably also for benign bone lesions.
c. NaF PET (-CT) can be used as a substitute for ^{99m}Tc based bone scintigraphy when ^{99m}Tc is unavailable or when, after careful consideration, a NaF PET (-CT) will benefit the patient because of its higher accuracy.
d. Local patient population, experience and the availability of modalities such as PET-CT or SPECT-CT cab guide the choice for the tracer used.
e. The clinical value of NaF PET (-CT) should be subject of further clinical evaluation and trials.

Principe

A dose of radioactive fluoride in the form of sodium fluoride solution is administered to the patient. The fluoride is absorbed and incorporated into young bone tissue by osteocytes binding to the calcium phosphate. There is a linear relationship between osteoblastic activity and the deposition of NaF in the bone tissue and thus in the signal acquired by the PET scanner. Another factor influencing the uptake is the blood flow. Hyper vascularisation gives a higher tracer uptake in the bone tissue.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indication

Bone scintigraphy using NaF PET (-CT) is relatively new compared to the classical ^{99m}Tc based bone scintigraph. Indications largely coincide with the indications for classical ^{99m}Tc based bone scintigraphy.

a. Screening for metastatic bone disease in known malignant tumours
   In patients with a known solid tumour, to screen for bone metastasis, to evaluate the extent of metastatic bone disease or to evaluate treatment response. There should be a reasonable risk of having metastasis for instance PSA should be higher than 20 ng/ml or in breast cancer at least T2 or N1 disease.
b. Screening for metastatic bone disease in skeletal related events and known malignant tumours
   In lower stage solid tumours with skeletal pain or discomfort NaF PET (-CT) can be considered, especially when this could lead to a change of treatment. For instance

when considering partial liver resection as a metastasectomy in colon cancer even when there is a low risk of metastatic bone disease.

c. Metabolic bone disease
Primary diagnosis and treatment response monitoring of Paget's disease, fibrous dysplasia or osteoid osteoma.

d. Primary bone tumours (screening and staging)
The activity pattern of fluoride uptake or distribution combined with CT and MR imaging can help in differentiating between different types of primary tumours. This can help in evaluating the extent of disease and monitoring of treatment response. There is less evidence for the use of NaF than there is for the use of ^{99m}Tc labelled tracers.

e. Traumatic or orthopaedic disease
Enthesopathy, stress fractures, occult fractures, arthritis, prosthetic joint disease, osteomyelitis or the vitality of bone structures. All bone disease in small bones or joints (hand, feet or spine) in which the low spatial resolution of the regular bone scintigraph could miss disease.

For the diagnosis of inflammatory and infectious bone disease there is not enough evidence that NaF is sufficient to replace the classical ^{99m}Tc based bone scintigraph. Especially the lack of perfusion and diffusion imaging could impair the diagnostic accuracy of NaF PET (-CT) in these diseases.

4. Medical information necessary for planning

a. Symptoms such as pain or discomfort
b. Prior operations, radiation therapy, recent chemo therapy and trauma
c. Results of relevant prior radiological imaging (X-ray, CT, MRI)
d. Blood results such as Alk Phos (Alkaline Phosphatase), PSA (Prostate Specific Antigene), Ca^{2+}
e. Information about kidney function e.g. dialysis

5. Radiopharmaceutical

Preparation:	^{18}F sodium fluoride
Nuclide:	Fluorine-18
Dose used:	50-200 MBq
Route of administration:	Intravenous
Radiation safety:	0,027 mSv/MBq (ICRP-53) (2,7 mSv at 100 MBq, compare 2,3 mSv at 500 MBq ^{99m}Tc HDP)

Compared to ^{99m}Tc based tracers the dose can be considerably lower because of the efficiency of the PET (-CT) scanner used. Also, because of a more efficient distribution through the body (in a smaller sub compartment) and because of the fact that the incubation time is much shorter, the dose can be lower than with ^{18}FDG for comparable image quality. According to ICRP 106 there is no need to interrupt breastfeeding.

6. Patient preparation

Good hydration is important. Before administration and between administration and scanning the patient should drink enough fluids. Just before scanning the urinary bladder should be emptied. Administration of furosemide or bladder catheterisation is not

indicated. Total duration including waiting time: 1-2 h.

Utilities for acquisition

Fixation- and other means of patient support (head/neck cushion/armrest/knee support) so patient comfort is improved, reducing the risk of movement during acquisition.

Execution

a. *Timing:*
   As opposed to the classical ^{99m}Tc based bone scintigraph only the late phase is acquired in NaF PET (-CT). Perfusion and diffusion imaging is not part of the standard imaging protocol and at present there are no standardized procedures available for the acquisition of comparable data. Due to the faster uptake of the tracer, scanning can be started 20 min after administration but image quality improves in time. For standardisation purposes acquisitions 60 min after administration is recommended.
b. *Patient preparation:*
   Patients should empty their bladder prior to the acquisition.
c. *Field of view:*
   Most scanners acquire images from skull to toes in a continuous mode. If the maximum length of acquisition is insufficient a second acquisition may be needed, for instance from knees to toes. It is not always necessary to scan the entire skeleton. For metastatic bone disease, especially in breast cancer and prostate cancer, scanning till the knees is often sufficient. Sometimes scanning of just an area of interest such as the pelvic region in prosthetic joint disease can be enough.
d. *Body placement in the scanner during acquisition:*
   For optimal image quality it can be necessary to distribute the body mass evenly over the field of view. This means that it can be advisable to have the patient's arms resting above the head when imaging the spine, but placing the arms beside the torso for total body imaging. When imaging smaller body parts, especially hands and feet, fixation in an anatomical position is important.

The table below shows certain scan parameters such as dose and time per bed position for different types of PET (-CT) scanners. For the imaging of hand and feet, longer times are recommended. For children one can use the EANM dose reduction schemes.

	Time per bed position		
Scanner	1 min	2 min	4 min
Standard full-ring dedicated PET-scanner (for instance Siemens ECAT Exact, Philips Allegro, GE)		2 MBq/kg Min 100 MBq Max 200 MBq	1 MBq/kg Min 50 MBq Max 100 MBq

High sensitivity full-ring PET scanner (for instance Philips Gemini TOF, Siemens Biograph True-V)	2 MBq/kg Min 100 MBq Max 200 MBq	1 MBq/kg Min 50 MBq Max 100 MBq

e. *Acquisition mode:*
Preferably 3D because of the higher sensitivity. The 2D acquisition mode is not recommended. Due to the optimal bio-distribution and reduced scatter there is no need for 2D acquisition.

f. *Acquisition time:*
Depends on scanner used and the tracer dose. See table for recommend times and dose combinations.

g. *Attenuation correction:*
Is not necessary for the diagnosis. The impact on the reliability of treatment monitoring of metabolic bone disease is unknown. For comparing the bio distribution with other known tracers such as FDG, standard attenuation correction is often used.

h. *Use of CT in a PET-CT scanner:*
When using a PET-CT scanner the standard vendor protocol should be applied. This will most often mean starting with a scanogram for planning purposes, followed by a CT acquisition and then the PET acquisition. Consider the use of a CT with optimised parameters e.g. mAs, kV, filtering and slice thickness for bone imaging. In these indications, there is no role for oral or intravenous contrast agents. Even a low dose CT often has very good diagnostic value especially when co-read with radiologist. Consider making one report for both PET and CT taking into account all the available imaging data.

7. Camera

See separate chapter "PET/CT Scanner", page 637

8. Reporting

a. *Scan parameters:*
Mention the scan parameters and other settings used e.g.dose, interval between administration and scanning, scan protocol, use of attenuation correction and CT protocol used. Mention which other relevant imaging is used for comparison.

b. *Global image quality:*
Describe the bio-distribution, especially the uptake in the bones compared to soft tissue activity. Clinical relevance is not straightforward. See interpretation and pitfalls.

c. *Soft tissue distribution:*
Mention abnormal distribution/accumulation or anatomical anomalies of kidney and bladder as seen on the PET scan.

d. *Bone uptake:*
Describe normal and abnormal distribution in the bones using anatomical landmarks, focal or diffuse sites of uptake, intensity etcetera. Correlate the findings with abnormalities seen in prior imaging and with the (low dose) CT.

e. *Unexpected findings:*
Inform the referring physician of threatening findings e.g. spinal metastasis with the risk of spinal cord impairment.

9. Interpretation and pitfalls

For interpretation of NaF PET (-CT) the guidelines for bone scintigraphy using ^{99m}Tc labelled agents can be used. In essence the findings are comparable:

a. *Bisphosphonates:*
When using bisphosphonates the uptake of NaF can be significantly lower, especially in the hands and feet. If there is a diffuse increase in bone turnover it is often also visible as increased uptake in hands and feet.

b. *Flare phenomenon after radiation or chemotherapy:*
With NaF the same flare phenomenon can be seen as with ^{99m}Tc labelled agents after radiation or chemotherapy. This is a temporary increase in bone metabolism because of inflammation. Because of the higher sensitivity of NaF PET (-CT) the flare is often more clearly visible than with traditional bone scintigraphy using ^{99m}Tc labelled agents.

10. Relation to other diagnostic procedures

Information about active bone deposition and activity of bone forming osteoblasts can give valuable additional information in the interpretation of radiological findings or abnormalities. In physiological terms the increased bone formation precedes radiological abnormalities by many months. MRI can be more sensitive in the detection of metastasis in the bone marrow and in osteonecrosis. FDG PET (-CT) is often more useful in the detection of lytic bone metastasis as seen in NSCLC and gastric tract carcinomas.

11. Literature

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