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Non-FDG PET studies in oncology: bone PET with fluoride (^{18}F)

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Abstract

Various imaging modalities are currently available to diagnose and monitor bone malignancies. The two main functional modalities are scintigraphy and PET. PET has superior diagnostic performance over scintigraphy or SPECT in all indications, with the exception of some rare studies in mandibular invasion by squamous cell carcinoma or osteosarcoma. In oncology, it is not yet clear whether there is an added value of bone PET with fluoride (^{18}F) to information brought by the detection of cancer tissue itself by metabolic tracers such as FDG, fluorocholine (^{18}F), iodine-124, FDOPA (^{18}F) or somatostatin analogues labelled with gallium-68. This article reviews the results of the available studies on this topic.

Key words: bone PET, bone scintigraphy, fluoride (^{18}F), FDG, fluorocholine (^{18}F), bone metastasis, primary bone tumour, comparative study

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Introduction: bone PET vs. bone scintigraphy

Bone PET

Bone PET with sodium fluoride (^{18}F) (NaF) reflects incorporation of the fluoride ion into the forming cortical bone, associated with the concentration of bone-forming minerals, a metabolic process that is also traced by bisphosphonates used for bone scintigraphy (BS) [1]. F Na has been proposed for diagnostic imaging and metabolic quantitative measurements as early as 1962 by Blau et al. [2]. It was then approved by the Food and Drug Administration for clinical use and became the standard agent for bone functional imaging until the development of the technetium-99m labelled bisphosphonates in the 1970's. Its potential interest has been re-discovered with the development of clinical PET including whole-body imaging, at the beginning of the past decade. When a PET-only machine was used, Tayama et al. [3] showed that there was no need for attenuation correction in NaF PET images. Attenuation correction reduces the bone/muscle ratio for normal and abnormal bone.

The hybrid imaging technique, PET/CT, which has been available in routine practice for around 8 years, provides a better anatomic localisation of hypermetabolic foci and improves the diagnostic accuracy of PET in detecting malignant bone involvement. In patients with bone metastaesis, the lesions with sclerotic or mixed changes or located in bone cortex alone or bone cortex and medulla tend to show high SUV max on NaF PET/CT [4].

Our personal experience and data from literature [5] lead to conclude that PET/CT is definitely needed for a better interpretation of routine NaF bone PET. Bone PET/CT has even better diagnostic performance than those of the new multidetector CT (MDCT) with contrast enhancement. Overall, 662 bone lesions were detected in 39 breast cancer patients by Piccardo et al. [6]. Of these, 542 were malignant and 120 were benign according to the standard of reference. NaF PET/CT detected 491 bone metastases, 114 (23%) of which displayed no clear morphological changes on MDCT, whereas MDCT detected 416 bone metastases, 39 (9.3%) of which showed no NaF-PET uptake. Overall sensitivity and specificity were: 91% and 91%, respectively, NaF PET/CT, and 77% and 93% for MDCT. The integrated assessment of NaF-PET/MDCT yielded sensitivity and specificity values of 98% and 93%, respectively.

Bone scintigraphy

Bone scintigraphy, using a bisphosphonate labelled with 99mTc, reflects the metabolic turn-over of cortical bone [7]. The well-known Achilles' heel of BS is its lack of specificity. Bisphosphonates accumulate wherever bone remodeling and/or bone blood flow are increased. They concentrate not only in bone reacting to a malignant processes but also in cases of infection, fractures, arthritis and osteomyelitis as well as benign pseudo-tumours such as Paget's disease or benign bone tumours such as osteoid osteoma.

There is a clear need for improvement of diagnostic performance of planar BS. A more frequently used approach to further increase the sensitivity of BS is performing SPECT, which al-

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lows three-dimensional representation of the skeletal system and comparison or fusion of images with those of other cross sectional modalities. Except with regard to the negative predictive value, SPECT performs statistically better than planar imaging [8]. Hybrid cameras combining SPECT and spiral CT offer the opportunity to clarify around 90% findings classified as indeterminate on planar BS [9] or even SPECT [10, 11].

Comparison: bone PET vs. BS

Several studies have compared diagnostic performance of bone PET and BS, i.e. the efficacy of NaF. They will be summarised and discussed in the next chapters, according to the indication: detection of bone metastases, treatment monitoring of bone metastases, and malignant primitive bone tumours.

Dosimetry

Dosimetry is depending upon injected activity which is optimised according to the machine in use: SPECT/CT is usually demanding more activity than planar BS while modern PET/CT machines with 3D acquisition and time of flight capacity are demanding much less activity than the "conventional" 2D BGO machines which were used for most published studies, and are still reflected in the recommended activity for NaF in American guidelines that have been also adopted by EANM [12]. Thus there is currently a turning point and NaF PET/CT is becoming equally or less irradiating than bone SPECT/CT, its alternative. With a modern time-of-flight PET/CT machine the NaF activity is 2.5 MBq/kg i.e. 175 MBq for a 70kg adult. The effective dose recently re-evaluated is 0.017 mSv/MBq [13] which corresponds to somewhat less than 3 mSv for PET. Furthermore, the maximal recommended activity in the SmPC of HDP and HMDP, 700 MBq, is in practice frequently over-passed: in a recent study demonstrating that SPECT/CT significantly outperforms SPECT alone in 42 patients undergoing BS for metastases, the injected activity was 740-900 MBq [11]. Helyar et al. [9] recently injected 800 MBq to perform SPECT, "as specified by ARSAC", the British regulatory body for radiation protection. Effective doses greater than 5 mSv due to administration of 900 MBq methylene diphosphonate (99mTc) seem to be frequent, and the CT component adds to overall effective dose is of the same order of magnitude. Even recently, discrepant conclusions on this point have been reported in literature, e.g. Tateishi et al. [14] considered as a significant result of a meta-analysis that effective dose of NaF PET or PET/CT ranged (widely) from 2.7 to 28.0 mSv.

Technical performance, patient's convenience and medicines interaction

Apart from the disputed points of dosimetry, cost and availability of PET/CT machines, all the technical criteria favour bone PET vs. BS, even SPECT/CT: a more rapid uptake allowing imaging 45 min after injection instead of several hours, a more accurate quantification for follow-up of lesions, tomographic slices all over the field of view and no need to decide when the patient is present which region requires SPECT, and above all a better resolution of the functional component of hybrid imaging. This superior resolution of PET images, compared with that of BS and SPECT may lead to a better patient's management, in particular by revealing photopenic areas, which correspond to invasion of bone by the metastatic cancer itself and not to the osteoblastic reaction, and are of clinical significance [15].

Finaly, there is no interaction between NaF and bisphosphonates, event at therapeutic doses, whereas whether an interaction between bisphosphonates therapy and tracer bisphosphonate (99mTc) may lead to degradation of BS image quality is still a matter of controversy [16–26].

Detection of bone metastases

NaF has been registered in France in 2008, just before the beginning of the "technetium crisis", and then in several EU countries. Currently its only registered indication in oncology is "Detection and localisation of bone metastases in case of proven cancer in adults".

The skeleton is the third location of metastases after liver and lung. Bone metastases are diagnosed during follow-up in up to 70% of breast or prostate cancer patients and in about 15 to 30% in other cancer patients (thyroid, kidney, lung, stomach, uterus, bladder, colon, rectum). Autopsy studies disclose vertebral metastases among 30% of patients with a disseminated malignancy [27]. However, the primary cancer is unknown in 25% of cases [28–32]. Most of the metastases are located in the lumbar spine, less frequently in the thoracic spine, and rarely in the cervical spine (respectively 52%, 36% and 12% according to Pilge [27]). The metastasis involves primarily the hematopoetic medullar bone in the vertebrae, followed by the invasion of cortical bone [33], osteoclastic and osteoblastic activation with subsequent osteolysis (60%), osteosclerosis (20%) or mixed pattern (20%).

PET and PET/CT tracers for a direct detection of bone metastases

Bone PET and BS reveal bone metastases in an indirect way, through the reaction of cortical bone to the presence of metastatic cancer tissue; other functional imaging modalitites are able to detect the metabolic signal of the metastatic cancer tissue itself and constitute alternatives [15, 34].

Fluorodeoxyglucose (18FDG)

Other metabolic pathways allow direct detection of the cancer tissue with PET: tracing glucose intracellular transport and catabolism by means of the glucose analogue FDG is the most frequent approach in routine practice.

FDG PET directly depicts the increased glucose metabolism of neoplastic cells, in the bone marrow as well as invading cortical bone. The normal red marrow usually demonstrates low-intensity FDG uptake, thereby assisting in detecting increased uptake in early marrow involvement before an identifiable bone reaction. These early metastases are missed on BS and CT.

Accumulating data suggest that FDG is more sensitive in detecting lytic metastases than sclerotic metastases [35]. The latter type may show uptake of lower intensity compared with lytic lesions or even a normal uptake. It is assumed that the greater avidity of FDG in lytic metastases reflects the high glycolytic rate and the relative hypoxia characterising this type of lesion, in contrast to sclerotic metastases, which are relatively of a poor cellularity, less aggressive, and not prone to hypoxia.

In children and younger adults, special diagnostic problems occur with the differentiation of highly cellular hematopoietic marrow and neoplasia, requiring knowledge of age-dependent conversion patterns from hematopoietic to fatty bone marrow [36].

Cancer tissue detection with FDG PET is highly susceptible to recent chemotherapy and radiotherapy. The use of granulocyte colony-stimulating factors in patients receiving myelosuppressive chemotherapy may induce an increased FDG uptake in red marrow, which can either mask or simulate malignant infiltration [37, 38].

Concerning specificity, FDG PET is less hampered, compared with BS, by non-specific benign bone lesions which are incidentally found. However, focal non-degenerative and more diffuse degenerative arthritis [39], spondylodiscitis [40] or sarcoidosis [41] may generate false-positive results, as well as benign tumours, especially histiocytic or giant cell-containing lesions, including osteoblastoma, brown tumour (osteoclastoma), aneurysmal bone cyst [42]. Tissue histiocytic and giant cells are the in monocytes–macrophage lineage and play a central role in the host response to injury and infection. Their energy is predominately supplied by means of intracellular glucose metabolism.

The hybrid modality PET/CT not only provides a better anatomical localisation of lesions but it also helps to reduce those false-positive findings. In the study of Metser et al. [43], 242 spinal lesions in 51 patients detected on FDG PET/CT were interpreted separately on PET, CT, and fused PET/CT images. PET alone identified 220 lesions and CT alone identified 159; 217 (90%) were malignant and 25 benign. The specificity was 56% for both PET alone and CT alone. PET alone was incorrect in determining the level of abnormality within the vertebral column in 33 (15%) lesions and in determining the part of the vertebra involved in 40 (18%) lesions. On a patient-based analysis, the sensitivity of PET and of CT for the detection of spinal metastasis was 98% and 74%, respectively.

In 150 consecutive patients, referred for whole-body FDG PET/CT for evaluation of known or suspected malignancy, Rosen et al. [44] determined the prevalence of abnormal spinal FDG uptake and assessed the relationship between the severity of findings on FDG PET and the severity of degenerative spinal disease on CT. Only 42% of the patients had no abnormal findings in the spine on PET, and 22% of patients with FDG foci had probable or definite degenerative disease, while 2 patients (1.3%) had apparent spinal metastases with no degenerative changes and 5 patients (3.3%) had metastases and degenerative disease. This study sends a warning that incidental findings on FDG PET related to degenerative spinal disease are common, most common in the lumbosacral spine, and can be recognized on CT. Although the SUV of FDG in malignant bone lesions is generally higher compared with benign bone lesions, there is overlap.

However, FDG foci are not matching abnormal aspects on CT in all cases. Of 133 FDG-positive lesions in 33 patients which were clinically confirmed to be bone metastases at follow-up and/or histopathologic examination, CT revealed osteolytic changes in 31% and osteoblastic changes 16%, but only non-specific changes in 17% or no anomaly in 37% [45]. Taira et al. [46] retrospectively evaluated, in 59 patients with 113 bone lesions, the positive predictive value (PPV) of FDG PET/CT in the identification of malignant bone lesions, depending on whether findings on PET and CT were concordant or discordant. PET and CT were concordant in 42% of cases with a very high PPV of 98%. However, 58% of lesions displayed discordant PET and CT findings. In such discrepant combinations, PPV was 17% for CT vs. 61% for FDG PET.

Combined FDG and Na F PET/CT

Hoegerle et al. [47] proposed the combined application of FDG and NaF PET for the simultaneous evaluation of soft tissue and of the skeleton. Interobserver agreement was 0.95 with FDG and NaF vs. 0.74 in patients who were injected FDG alone, due to better skeletal landmarks. This procedure has not been further reported for a decade, probably because PET/CT fusion provides better landmarks for localisation of FDG foci than just the visualisation of the skeleton with NaF. Ten years later, the use of combined FDG and NaF PET/CT imaging in oncology has been reported by Iagaru et al. [48]. Fourteen patients referred for staging of various malignancies underwent 3 PET/CTs each, with FDG, with NaF and with a combination of FDG and NaF. The main potential advantage is a reduction in health care costs if both PET/CTs are scheduled, as two PET/CT examinations are performed at the same time. In a recent study, the same team tested two approaches for combined imaging, in a total of 47 patients with suspicious foci [49]: the simultaneous imaging after injection of both tracers and a sequential imaging starting with FDG and then NaF after ca. two hours. In 16 cases (34%) a greater number of foci was detected with the combined imaging; in 29 cases, the number was identical, but in 2 cases (4%) foci in mediastinal lymph nodes visible on FDG PET/CT were no longer visible on the combined imaging. No focus of uptake was characterised histologicaly.

The advantage is not to miss any osteoblastic metastases which may be FDG-negative. A disadvantage is a possible reduction of the diagnostic performance. Reduction in specificity by showing many non-malignant fluoride-positive bone lesions usually not seen on FDG PET/CT and also in sensitivity, as the uptake of Na F in the normal skeleton may obscure an abnormal FDG-avid focus in the bone marrow [50, 51].

PET and PET/CT with lipids, aminoacids or receptor ligands

In case of malignancies which do not usually accumulate FDG, tracers of pathways of the lipid metabolism such as acetate (^{11}C) or fluorocholine (^{18}F) (FCH) or aminoacids analogues such as fluorodihydroxyphenylalanin (^{18}F) (FDOPA) are now registered and routinely used to detect bone metastases among other distant metastases [52]. Interesting results have also been reported with radioligands of receptors overexpressed in some tumours, such as fluoroestradiol (FES) in breast and gynaecological cancers, fluorotestosterone in prostate cancer, or the somatostatin analogues labelled with ^{68}Ga in neuroendocrine tumours. All those functional tracers of the tumour tissue allow early detection of metastatic sites in the cortical bone, but also in bone marrow and soft tissues. At the moment, only FCH has been compared with bone PET in a prospective study [53].

Comparative studies

Bone PET vs. BS

Schirrmeister et al. pointed out that the sensitivity gap between BS and NaF PET depends on anatomical localisation. Compared

with Na F PET, bisphosphonates (^{99m}Tc) BS had a detection rate for benign or malignant lesions of 72–89% in the skull, ribs, sternum and extremities but only of 20–43% in the spine and pelvis [54].

More recently Withofs et al. [55] obtained concordant result by comparing whole body NaF PET/CT and bone SPECT in 34 patients with breast or prostate cancer, the SOT being contrast-enhanced CT or MRI. In a site-based analysis (274 lesions), Na F was more accurate than bone SPECT (sensitivity 75% vs. 45%, specificity 84% vs. 79%), with a marked difference in the detection of pelvic or lumbar lesions. On a per-patient level, a correct diagnosis was obtained with NaF in 32 of 33 patients (97%), compared with 28 of 33 (85%) with bone SPECT.

A population of 103 patients with initial diagnosis of non-small cell lung cancer (NSCLC) was prospectively examined with planar BS, SPECT of the vertebral column and PET using NaF [56]. Thirteen of 33 patients with bone metastases were false-negative on BS, 4 on SPECT, and 2 on NaF PET. The area under the ROC curve was 0.77 for BS, 0.88 for SPECT, and 0.99 for NaF PET ($p < 0.05$). As a result of SPECT and NaF PET imaging, clinical management was changed in 8 (8%) and 10 (10%) patients. Authors conclude that NaF PET is more effective than bisphosphonates (^{99m}Tc) SPECT but is associated with higher incremental costs.

Schirrmeister's group [57] compared NaF PET with BS in 34 breast cancer patients with known (6 cases) or clinically or biologically suspected (28 cases) metastatic bone disease. SOT consisted in a panel of methods, including MRI (28 patients), planar X-ray (17 patients), and spiral CT (4 patients). With Na F PET, 64 bone metastases were detected in 17 patients, while only 29 metastases were detected in 11 patients with BS. On a per-lesion basis, the area under the ROC curve corresponding to Na F PET was 0.99, vs. 0.74 for the ROC curve corresponding to BS; $p < .05$). On a per-patient basis, the corresponding areas were 1.00 for Na F PET vs. 0.82 for BS ($p < .05$). As a result of Na F PET imaging, clinical management was changed in 4 patients (12%).

In a prospective study, BS and NaF PET/CT were performed on the same day in 44 patients with high-risk prostate cancer [58]. Lesions were interpreted separately as normal, benign, equivocal, or malignant. In patient-based analysis, 23 patients had skeletal metastatic spread (52%). Categorising equivocal and malignant interpretation as suggestive for malignancy, the sensitivity was 70% for planar BS, 92% for bone SPECT, 100% for NaF PET and 100% for NaF PET/CT. Specificity was then 57% for planar BS, 82% for bone SPECT, 62% for NaF PET, and 100% for NaF PET/CT. NaF PET/CT was statistically more sensitive and more specific than planar or SPECT BS ($p < 0.05$) and more specific than NaF PET ($p < 0.001$). Detection of bone metastases is improved by SPECT compared with planar BS, and by NaF PET compared with SPECT.

In the study by Schirrmeister et al. [59] on 35 patients with known or suspected bone metastases of thyroid cancer, NaF PET was part of the SOT and cannot be compared to other modalities. However, it detected 21 previously unknown bone metastases, 13 of which had very low sclerotic activity. Those findings of a missing or only slight osteosclerotic bone reaction explain the limited sensitivity of planar BS alone. Interesting results could be expected from comparative PET studies with FDG and iodine-124 in suspicion of metastatic spread of thyroid cancer.

Yen et al. [60] prospectively evaluated the diagnostic and prognostic usefulness of NaF PET/CT relative to planar BS in 34 consecutive patients with hepatocellular carcinoma (HCC) patients suspicious for bone metastasis. Patient-based sensitivity was 94% for NaF vs. 77% for BS, and specificity 100% for NaF vs. 70% for BS. The area under ROC curve was 1 for NaF vs. 0.75 for BS ($p < 0.004$). Furthermore, there was a significant correlation between the presence of NaF PET/CT bone lesions that are predominantly osteolytic and the survival of HCC patients.

This is an interesting feature of NaF PET/CT already underlined by Even-Sapir in 2007 [61]: "Although (^{18})F-fluoride uptake mechanism corresponds to osteoblastic activity, it is also sensitive for detection of lytic and early marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal". This is in our experience particularly usefull in renal cell cancer, an indication illustrated for the moment only by few figures in articles or case reports [15, 62].

In the assessment of mandibular bone invasion by squamous cell carcinoma, 10 patients underwent bone SPECT and NaF PET; SPECT had a high sensitivity (100%) and specificity (92%); NaF PET showed a sensitivity of 100%, but its specificity only reached 50% [63]. This is the only study reporting better results with BS than NaF PET, probably because of a lack of fusion with CT: NaF shows a lot of degenerative non-malignant foci invisible on BS due to its poor resolution, which require experienced reading and fusion with CT to avoid false-positives.

Tatehishi et al. [64] performed a meta-analysis of all available studies addressing the diagnostic accuracy of NaF PET or PET/CT, planar BS, and planar BS & SPECT for detecting the metastatic bone cancer; 11 articles were available for analyses, which represented a total of 425 patients. On a per patient basis, sensitivity value of PET or PET/CT was 96%, and specificity 99%. Corresponding lesion-based values were 97% and 98%. The areas under the SROC curve of NaF PET or PET/CT were 0.99 for the patient basis and 0.91 for the lesion basis, whereas those of planar BS or planar BS & SPECT were 0.87 for the patient basis and 0.85 for the lesion basis. Authors concluded that NaF PET or PET/CT has excellent diagnostic performance for the detection of bone metastases.

NaF PET vs.FDG PET/CT (Figure 1)

In the study of Krüger et al. [65], FDG PET/CT was compared to Na F PET, which was performed instead of BS in 68 patients with NSCLC, 18 patients being diagnosed with bone metastases. In 13 of them, bone metastases were concordantly diagnosed with FDG PET/CT and NaF PET. FDG PET/CT showed more bone lesions suspected to be metastases compared to NaF PET, but on per-patient basis Na F was more sensitive: 94% vs. 78% for FDG. No false-positive result was observed with both radiopharmaceuticals, which at least shows the experience of readers, since it is easier to avoid false-positive results with NaF on PET/CT fused images. In one patient, one osteolytic metastasis was false-negative on NaF PET. However, NaF PET identified 4 patients with bone metastases compared to negative findings on FDG PET/CT.

Bone PET/CT vs. FDG PET/CT vs. BS

In a recent prospective pilot-phase trial including 52 patients with proven malignancy referred for evaluation of skeletal

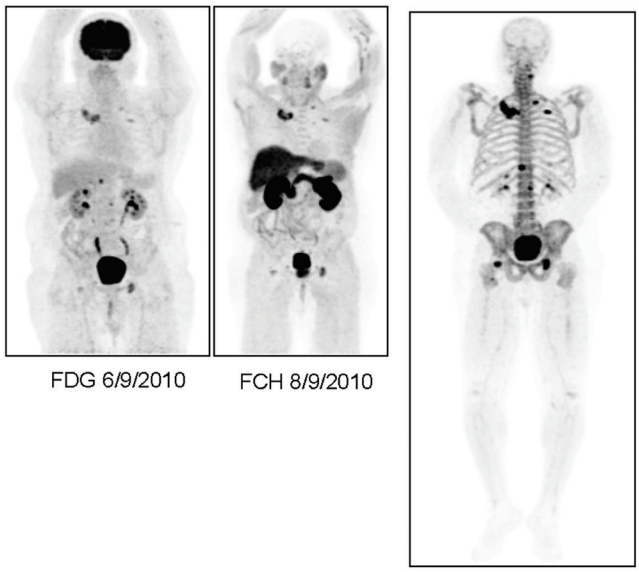

Figure 1. MIP of FDG, FCH and NaF PET/CTs performed in a patient with metastatic castration-resistant prostate cancer before chemotherapy. In this patient, there was a remarkable match between the bone foci on the 3 different PET/CTs, while in less advanced stage of prostate cancer FDG usually shows fewer foci than NaF or FCH

metastases [66], skeletal lesions were detected by BS in 22 of 52 patients, by NaF PET/CT in 24 of 52 patients, and by FDG PET/CT in 16 of 52 patients. The image quality and evaluation of extent of disease were superior by NaF PET/CT over BS in all 22 patients with skeletal lesions on both scans and over FDG PET/CT in 11 of 16 patients with skeletal metastases on FDG PET/CT. In two patients, NaF PET/CT showed skeletal metastases not seen on either of the other two scans.

NaF PET vs. Fluorocholine (18F) PET (Figure 1)

Fluorocholine (18F) or FCH is an analogue of choline, a lipidic component of cell membrane. Choline is accumulated in several cancer tissues, as demonstrated with MR spectroscopy. Due to the low sensitivity of FDG to detect bone metastases in non-aggressive forms of prostate cancer [67], lipid PET tracers labelled with 11C or 18F have been tested during the past decade [68, 69].

The team in Linz performed NaF and FCH PET/CT for the detection of bone metastases in prostate cancer [70]. No significant difference was found in detection rate, whether or not the patient received hormonal therapy. Furthermore, FCH PET/CT is able to detect local recurrence or soft tissue metastases. Osteolytic lesions demonstrated higher FCH uptake than osteoblastic lesions. The authors identified 3 correlative FCH PET/CT patterns for bone metastases: lesions with FCH uptake without morphologic changes on CT, probably representing bone marrow infiltration; lesions with FCH uptake and CT morphologic changes corresponding to extension a viable metastasis into the cortical bone; lesions with no FCH uptake but displaying dense sclerosis on CT (Hounsfield units > 825), it seems probable that these sclerotic bone metastases might no longer be metabolically viable. A prospective study was performed in cooperation with our team in 40 evaluable patients [53]. Bone extension was present in 22 patients and absent in 18. Patient-based performance for FCH vs. NaF was 91% vs. 91% for sensitivity, 89% vs. 83% for specificity and 90% vs. 88% for accuracy (no significant difference). Of 360 skeletal sites, 68 were malignant and 292 non-invaded. There was no significant difference in site-based performance in the group of patients referred at initial staging, but in the group of patients referred for suspicion of recurrence, FCH was significantly more specific than NaF (96% vs. 91%, $p = 0.02$) while sensitivity was the same, 89%. In conclusion both radiopharmaceuticals, based on a very different metabolic approach, showed a good diagnostic performance. If FCH is available, it should be preferred in patients after initial treatment.

Treatment monitoring of bone metastases

With the development of new therapies that may be active even in advanced stages of cancer, the evaluation of response of bone metastases has become more and more important. This is particularly important in breast or in prostate cancer. According to RECIST 1.1 criteria, osteoclastic bone metastases are target lesions providing that soft tissue masses measure ≥ 10 mm [71], but such large lytic bone metastases are infrequent, in particular in prostate cancer. Furthermore some of those new treatments are only ment to stabilize the disease and the lack of metabolic progression or even metablic regression without significant change in size is meaningful. Functional imaging has thus a role to play in this setting.

To the best of our knowledge, the use of NaF PET (not PET/CT) to assess reponse in bone metastases was reported in only one study of 5 castration-resistant prostate cancer patients treated with radium-223 [72].

Two pitfalls of the metabolic approach should be avoided: misinterpretation of flare reaction or of bone marrow activation.

Flare reaction

This increase in the number or intensity of visible foci on-treatment has already been reported in 1984 [73]. This drawback of BS has been confirmed in a large number of articles since then [74]: "The flare response is the rule rather than the exception after successful systemic therapy for bone metastases. The appearance of new lesions or increasing activity in known lesions during the first 3 mo is as likely to herald radiological response as disease progression". More than two decades later, this phenomenon is still confusing for the evaluation of response of bone metastases, e.g. in monitoring treatment of castration-resistant prostate cancer [75].

Even after the flare reaction or when is did not occure, the persistence of uptake at the site of bone metastases responding to treatment is a limitation to monitoring with BS [76]. To circumvent these metabolic drawbacks, the prostate cancer working group-2 (PCWG2) required the emergence of two or more unequivocal metastatic lesions, beyond the flare period, to declare progression. Hence, contemporarily the PCWG2 defines bone scintigraphy progression as either 2 new lesions noted on the first on-treatment scan followed by 2 additional lesions on the next scan, or 2 new lesions seen on any scan after the first on-treatment scan that are confirmed on a subsequent scan [76]. This procedure delays the diagnosis of progression and is a burden to the patient.

^{18}F-fluoride PET suffers from the same metabolic drawbacks as bone scintigraphy; in particular flare response was reported in one case of breast cancer [77].

As with BS, though by a different mechanism, the flare phenomenon can also be seen on FDG PET. Dehdashti et al reported an increase in FDG uptake after the initiation of tamoxifen in responsive patients, opposed to no change in FDG uptake in non-responders [78]. It has been proposed that this reaction is due to temporary agonist effects of the hormone on the tumour.

To the best of our knowledge, no flare has been reported using FCH or "specialised" PET tracers such as FDOPA or somatostatin analogues.

Activation of bone marrow

Most cytotoxic agents of chemotherapy are myelotoxic and stimulating factors of hematopoeisis are administred to the patient at the end of a cycle of chemotherapy. The use of granulocyte colony-stimulating factors in patients receiving myelosuppressive chemotherapy may induce an increased FDG uptake in red marrow [79], which can mask malignant foci by reducing the contrast or will hamper the diagnosis of diffuse malignant infiltration. As recently observed by our team, this is also true when using FCH in patients with advanced prostate cancer [80, 81]. In contrast, it has not been reported with fluoride (^{18}F) since the cortical bone is not involved.

Malignant primitive bone tumours

Osteosarcoma is a malignant mesenchymal sarcoma characterised by the direct formation of bone or osteoid by malignant tumour cells. Osteosarcoma represents the second most common primary malignancy of bone after myeloma. The incidence is estimated to be about 2 or 3 per million. Although osteosarcoma is a heterogeneous disease covering a large range of pathologic types and subtypes, at the time of primary diagnosis, as many as 75% of all patients are classified as clinical stage IIIB. Primary high-grade, intramedullary accounts for 75% of all lesions. Introduction of multiagent chemotherapy in combination with surgery has improved survival rates. However, in 80% of these patients, occult metastases, presumed on the basis of the experience in the prechemotherapy era, will develop in overt metastases within months. If these metastases are predominantly located in the lungs, they occur too in second bone sites in 10% to 20% of patients.

Osteosarcoma is well known for the capacity to produce skip metastases, a second smaller focus of histopathologically proven tumour occurring in the same bone, remote from the primary tumour, or a second focus of tumour on the opposite side of the joint. They have been observed in up to 25% of osteosarcomas in one series. Patients with skip lesions demonstrate a higher local recurrence rate and a lower disease-free interval and have a shorter survival compared with those without such lesions.

Ewing's tumour is thought to represent the most undifferentiated form of peripheral primitive neuroectodermal tumours family. Ewing's tumours are primarily located in bony sites, and represent the second most common primary osseous sarcoma in childhood and adolescence. About 50% of patients with localised disease can be cured, whereas the 5-year survival rate is 35% in patients presenting with lung metastases, and less than 20% in patients presenting with osseous metastases or bone marrow infiltration. Primary osseous metastasis is the main adverse prognostic factor in patients with Ewing's tumours.

NaF PET preliminary clinical cases

Almost three decades ago, Reiman [82] emphasised that whole-body PET imaging with NaF generates tomographic images that are useful in mapping patterns of bone metabolism, as well as identifying extraosseous sites of bone formation or calcification, especially in malignant primitive bone tumours.

In the first report on the use of NaF for skeletal PET in cancer patients published by Hoh et al. in 1993 [83], among 13 patients with documented malignant bone lesions, 4 had osteosarcoma. The 3 highest tumour-to-normal bone activity ratios of all the patients investigated were observed in untreated osteosarcoma as compared with other malignant bone lesions. In a patient with proven lung metastases of osteogenic sarcoma, Hoh et al. also found an increased NaF uptake in these metastases. Interestingly, in 1 patient with osteosarcoma after treatment with chemo- and immunotherapy, the tumour activity ratio was clearly reduced to about one third of those observed in untreated osteosarcoma, suggesting quantitative PET with NaF as a useful tool for monitoring therapy response.

Tse reported the case of a patient with polyostotic fibrous dysplasia complicated by sarcomatous degeneration of left upper extremity, initially treated by amputation [84]. The patient experienced a respiratory distress. A chest CT revealed multiple contrast-enhancing masses in both lungs and mediastinum. A CT-guided fine-needle aspiration of a lung lesion disclosed material compatible with metastatic osteogenic sarcoma. A NaF PET study was performed and confirmed the nature of the pulmonary nodules by showing multiple areas of abnormal uptake. PET demonstrated also multiple heterogeneous increased uptakes involving the whole skeleton, matching precisely the fibrous dysplasia lesions documented on X-rays and CT.

The impact on clinical management of the association of NaF and FDG PET examinations has been illustrated in the case of a 15 year-old female who was undergoing high-dose EDMP-(153 Sm) internal radiotherapy: a more precise staging was obtained by combining those PET modalities and the primary curative intent had to be abandoned in favour of pain palliation only [85].

BS and FDG PET

BS is recommended by several European Guidelines in case of primary bone tumours, but FDG PET is being considered more and more frequently. In USA, the National Cancer Comprehensive Network (NCCN) recommends either FDG PET or BS at staging, but also recommends that the same modality will be used for staging and post-treatment restaging. Reecent studies showed that for the detection of osseous metastases of osteosarcoma FDG PET is not clearly superior to BS [86, 87]. In contrast FDG has a clear superiority over BS, in both sensitivity and specificity, in case of Ewing's sarcoma [86–88].

Conclusion

Bone scintigraphy is no longer the most sensitive modality and has a limited specificity to detect bone malignancies, even

though its performance is enhanced by using modern SPECT/CT machines. NaF bone PET/CT has a superior sensitivity as compared to bone scintigraphy, but it is not likely to be widely used in FDG-avid cancers, at least when osteoblastic metastases are not predominant. In prostate cancer, a competition for the first diagnosis of bone spread is open between NaF, FCH and whole-body MRI. The competition also includes FDG in case of monitoring treatment of castrate-resistant prostate cancer, whereas the currently recommended functional imaging modality is still bone scintigraphy. There is currently a lack of data in some oncologic settings in which NaF could compete with FDG, in particular osteosarcoma, renal cell cancer, urothelial cancers and myeloma.

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