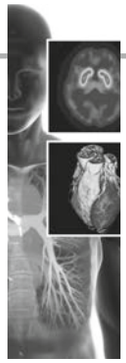

$Na^{18}F$ PET in oncology

Primary tumors of the skeleton are rare, but metastatic involvement from solid neoplasms, such as prostate, breast and lung, are unfortunately frequent. Skeletal metastases are clinically significant because of associated symptoms and complications (refractory pain, pathological fractures, spinal cord compression, hypercalcemia). Early detection and accurate evaluation of the extent of skeletal involvement is pivotal for treatment planning and prognosis. $Na^{18}F$ resurgence as an osteotropic agent for whole-body imaging of the skeleton has been made possible by the fast and wide diffusion of PET and PET/CT, which offer higher spatial resolution and sensitivity than conventional γ-cameras used in planar scintigraphy or SPECT. The article reviews the published literature reporting on $Na^{18}F$ PET and PET/CT diagnostic accuracy in the evaluation of osteosarcoma and bone metastases from different nonosseous solid tumors. A brief overview on current recommendations for bone metastasis imaging, $Na^{18}F$ general aspects and kinetics, PET scanning technical aspects, and radiation dosimetry are included.

KEYWORDS: bone metastases ■ breast cancer ■ fluoride ■ lung cancer ■ $Na^{18}F$ ■ primary bone tumors ■ prostate cancer ■ skeletal PET ■ skeletal PET/CT

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The rationale for diagnostic imaging in primary and metastatic bone malignancies is to identify bone involvement early, to determine its full extent in order to appropriately guide patient therapy and prevent skeletal-related events (e.g., fractures, cord compression), reason for severe morbidity and mortality in oncologic population.

For over four decades ^{99m}technetium diphosphonates (^{99m}Tc-DP) bone scintigraphy (BS) has served this purpose, imaging areas of increased osteogenic activity throughout the whole skeleton with high diagnostic accuracy (sensitivity 62–100%; specificity 78–100%; evidence level II–III) [1] and at reasonable costs. Nevertheless, the nontumor-specific nature of ^{99m}Tc-DP uptake limits BS specificity, whereas planar imaging combined with a relatively low spatial resolution reduces sensitivity. The availability of SPECT and SPECT/CT studies significantly increases ^{99m}Tc-DP BS accuracy in differentiating malignant from benign lesions in the axial skeleton [2], the most affected area for both solitary and multiple metastases due to its abundant vascularity and red marrow microenvironment (SPECT sensitivity for the diagnosis of bone metastases [BM] 87–92%; specificity 91–93%; evidence level II–III) [1]. Spinal SPECT has proven particularly accurate in detecting transcortical and subcortical metastases. However, this time-consuming technique is limited to suspicious conditions encountered at planar BS and it can fail to image small, predominantly lytic, metastases, especially when they are located in the bone marrow [3].

As a consequence the diagnostic strategy for imaging BM often relies on a multimodality approach where scintigraphic equivocal findings or negative feedback of a clinical suspicion advocate morphological confirmation by means of planar x-ray and, if that is not diagnostic, high-resolution CT, targeted MRI, or even biopsy [4]. High-resolution CT provides high-quality morphological detail of bone and bone marrow densities (high-resolution CT sensitivity for the diagnosis of BM 71–100%; evidence level II–III) [1]. It is recommended in the confirmation of suspected lesions at BS, the assessment of BM-related incipient fractures or collapses, surgical planning, and guiding bone biopsies [5]. MRI is suggested if scintigraphically doubtful findings are located in bones with large marrow cavities (e.g., vertebrae) [6]. Furthermore, MRI is advocated in case BS and planar x-ray are negative but vertebral involvement is clinically suspected; it is also the method of choice for the study of spinal cord compression (diagnostic sensitivity of skeletal MRI 82–100%; specificity 73–100%; evidence level II–III) [1]. Conversely, MRI is inadequate in assessing cortical involvement and the thoracic cage owing to respiratory artifacts.

The use of such a composite approach in the diagnosis of BM can result in an expensive and

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time-consuming process. With this regard a recent literature review by Talbot *et al.* summarized and commented on results from more than 140 comparative studies casting light on the strengths and limitations of each available diagnostic technique in staging and restaging a broad spectrum of neoplasms [7].

In this elaborate scenario a promising contribution could result from PET and especially from hybrid PET/CT imaging. Indeed both nonspecific ([^{18}F]FDG, [^{18}F]/[^{11}C]-choline) and specific ([^{68}Ga]-DOTATOC) oncotropic tracers (radiopharmaceuticals tracing tumor metabolic features) have proven highly accurate in detecting both skeletal and extraskeletal localizations in several clinical conditions, and the advent of hybrid PET/CT systems has provided tomographic metabolic maps with a morphological characterization and an anatomic localization resulting in an increased specificity and diagnostic accuracy.

With regard to skeletal metastases [^{18}F]FDG PET imaging, increasingly used in staging and restaging of multiple solid tumors, has proven more accurate than ^{99m}Tc-DP BS in detecting early bone marrow-based and lytic metastases, obviating in such cases the need for BS (sensitivity of [^{18}F]FDG PET for detecting bone metastasis 62–100%; specificity 96–100%; evidence level II–III) [1,8].

In spite of a relatively higher specificity compared with ^{99m}Tc-DP BS, [^{18}F]FDG PET/CT has proven less sensitive in detecting sclerotic metastases [9]. Indeed, as a positive tracer of glycolytic metabolism [^{18}F]FDG may fail to image sclerotic BM that are often characterized by poor and less aggressive cellularity, not prone to hypoxia. Pertaining to [^{18}F]FDG PET/CT other insidious conditions include on the one hand tumors with high mucin content, low proliferation rates and necrosis, which are likely to show low [^{18}F]FDG avidity.

Thus, favored by the wider availability of PET and especially hybrid PET/CT systems and the recent worldwide ^{99}Molybdenum/^{99m}Tc supply shortage, the interest directed towards Na^{18}F, a PET radiopharmaceutical able to define with high sensitivity areas of increased osteogenic activity. Its translation into clinical practice aims to replace ^{99m}Tc-DP BS in its staging and restaging indications. First published experiences and comparative studies with Na^{18}F PET claim a higher diagnostic accuracy than ^{99m}Technetium medronate (^{99m}Tc-MDP) BS (including SPECT) and suggest Na^{18}F PET as a complementary survey to oncotropic PET in the skeletal assessment of several solid malignancies [10–15]. The same papers, however, considered heterogeneous oncological populations, and had different study designs and statistical analyses of effectiveness and non-negligible methodological flaws, hence our aim is not to provide the reader with a meta-analysis or a systematic review on Na^{18}F PET imaging diagnostic accuracy, but rather we aim to convey a descriptive overview of these preliminary experiences (hematological malignancies are beyond the scope of this review). A table with essential information and major methodological issues from each included study is also provided (Table 1).

General aspects

First introduced by Blau *et al.* in 1962 as the standard bone-seeking agent for conventional BS, Na^{18}F was approved by the US FDA in 1972 but soon abandoned for market reasons in 1975 when the wide availability of ^{99}Molybdenum/^{99m}Tc generators allowed for more suitable solutions for γ-based bone imaging (i.e., ^{99m}Tc-DP) [16].

With the dramatic development of PET imaging technology and the consequent improvement of logistics for the delivery of [^{18}F]-radiopharmaceuticals, Na^{18}F has been reconsidered for bone imaging so much that in December 2008 the US National Cancer Institute (NCI, MD, USA) filed a new drug application for a different potency and dose from the Na^{18}F original new drug application. On 1 February 2011, as the new drug application for Na^{18}F was declared acceptable from a clinical pharmacological perspective, the FDA finally approved Na^{18}F use in PET bone scans. As far as the EU situation is concerned, Na^{18}F has an established monograph in the European Pharmacopoeia [17], which defines its standards for production, radioisotopic and radiochemical purity. Despite this, its clinical use is also subjected to national regulatory authorities, which are variable across the EU countries, therefore its use is not extensively accepted. Where accepted, clinical use of Na^{18}F must comply with Good Manufacturing Practice guidelines; Na^{18}F can also be purchased through nationally approved industrial suppliers that comply with national directives and Good Manufacturing Practice guidelines.

The revived interest towards Na^{18}F in PET imaging rely on its short half-life ($t_{1/2}$ = 109.7 min) positron-emission combined with the desirable characteristics of a rapid and high accumulation in bone and fast

Table 1. Design, limitations and impact on patient outcome of cited studies.

Study (year)	Study design	Participants	Selection bias	Method limitations	$Na^{18}F$ PET imaging impact on patients outcome	Ref.
Schirrmeister *et al.* (1999)	Prospective intrapatient comparison of $Na^{18}F$ PET and ^{99m}Tc-MDP BS diagnostic accuracy in identifying BM and its dependence on anatomical localization	44 patients with known prostate, lung and thyroid cancer	Only stage III and IV included Nine patients had known BM	Small sample size; multiple end points; composite SOR; although reading was blinded, discrepancies were resolved by consensus	$Na^{18}F$ PET correctly identified all 15 metastatic patients ^{99m}Tc-MDP BS overlooked metastatic bone disease in two out of 44 patients (4.5%) and underestimated it in eight patients (18.2%)	[12]
Even-Sapir *et al.* (2004)	Prospective intrapatient comparison of $Na^{18}F$ PET and $Na^{18}F$ PET/CT in assessing malignant osseous involvement and in differentiating malignant from benign bone lesions	44 patients with various oncologic diseases	It is not clear if inclusion criteria were prospectively determined	Small sample size; composite SOR (including [^{18}F]FDG and ^{99m}Tc-MDP BS) PET and PET/CT images were interpreted on consensus reading	On a patient basis sensitivity and specificity were 100 and 88% for $Na^{18}F$ PET/CT, respectively, and 88 and 58% for $Na^{18}F$ PET, respectively $Na^{18}F$ PET/CT assisted in identifying a potential cause for bone pain in oncologic patients among whom four had BM overlooked at ^{99m}Tc-MDP BS	[36]
Withofs *et al.* (2011)	Intrapatient prospective comparison of ^{99m}Tc-MDP BS + SPECT and $Na^{18}F$ PET/CT	34 patients with breast (n = 24) and prostate cancer (n = 10)	Only patients with high risk of metastatic disease included Five patients had known BM	Small sample size; reading protocol problematic	32 patients out of 33 (97%) were correctly diagnosed with $Na^{18}F$ PET/CT. All patients with BM were identified at $Na^{18}F$ PET/CT, but the extent of the disease was correctly estimated in seven patients, overestimated in three and underestimated in ten patients $Na^{18}F$ PET/CT erroneously characterized one patient as being metastatic	[25]
Beheshti *et al.* (2008)	Prospective intrapatient comparison of $Na^{18}F$ PET/CT and ^{18}F-FCH PET/CT	38 patients with prostate cancer	Only patients with high-risk of metastatic disease included Patients with an history of a second cancer were excluded	Small sample size; interpretation was not blinded; composite SOR; correlation between modalities ($Na^{18}F$ and ^{18}F-FCH PET/CT) not adequate for determination of efficacy Fifteen equivocal lesions without a final diagnosis were excluded from the study	$Na^{18}F$ PET/CT identified more lesions than did ^{18}F-FCH PET/CT but did not change patient management	[13]
Even-Sapir *et al.* (2006)	Prospective intrapatient comparison of diagnostic accuracy of ^{99m}Tc-MDP BS, SPECT, $Na^{18}F$ PET and $Na^{18}F$ PET/CT in detecting BM	44 patients with prostate cancer	Only patients with high risk of metastatic disease included	Small sample size; reading and interpretation protocol are problematic; composite SOR	$Na^{18}F$ PET imaging modified clinical management in seven out of 44 patients (15.9%)	[52]

^{99m}Tc-MDP: ^{99m}technetium medronate; BM: Bone metastases; BS: Bone scintigraphy; HCC: Hepatocellular carcinoma; NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer; SOR: Standard of reference.

Table 1. Design, limitations and impact on patient outcome of cited studies (cont.).

Study (year)	Study design	Participants	Selection bias	Method limitations	$Na^{18}F$ PET imaging impact on patients outcome	Ref.
Petrén-Mallmin *et al.* (1998)	Descriptive study correlating $Na^{18}F$ PET uptake with CT findings in the assessment of BM	Five patients with breast cancer	All patients had known BM	Small sample size; exploratory study, not prospective; primary end point not suitable for efficacy assessment; SOR not well defined; reading protocol incomplete	None	[64]
Schirrmeister *et al.* (1999)	Prospective intrapatient comparison of diagnostic accuracy of $Na^{18}F$ PET and ^{99m}Tc-MDP BS in the detection of BM	34 patients with breast cancer	Only patients with high-risk of metastatic disease included Six patients had known BM	Small sample size; composite SOR (missing rationale)	$Na^{18}F$ PET changed clinical management in four out of 34 (11.7%) and influenced in six out of 34 (17.6%)	[10]
Schirrmeister *et al.* (2001)	Intrapatient prospective comparison of $Na^{18}F$ PET and ^{99m}Tc-MDP BS and SPECT diagnostic accuracy in detecting BM	53 patients with lung cancer (NSCLC = 41) (SCLC = 12)	Only patients with newly diagnosed SCLC or locally advanced NSCLC were included; patients with extra-pulmonary cancer or known metastatic bone disease were excluded	Small sample size; composite SOR Radiologist reviewing MRI was not blinded to PET and BS results	Compared with ^{99m}Tc MDP BS, SPECT study changed the therapeutic strategy in five out of 53 patients (9%) whereas $Na^{18}F$ PET did in six out of 53 (11%)	[28]
Hetzel *et al.* (2003)	Intrapatient prospective comparison of ^{99m}Tc-MDP BS, SPECT and $Na^{18}F$ PET	103 patients with newly diagnosed lung cancer	Patients with extra-pulmonary cancer were excluded	Multiple end points; composite SOR; reading protocol is problematic	Compared with ^{99m}Tc-MDP BS, $Na^{18}F$ PET changed the therapeutic strategy in ten out of 103 patients (9.7%)	[15]
Krüger *et al.* (2009)	Intrapatient retrospective study comparing the diagnostic accuracy of [^{18}F]FDG PET/CT (index test) with $Na^{18}F$ PET and ^{99m}Tc-MDP BS for detection of BM	126 patients with NSCLC	Patients with extra-pulmonary cancer were excluded	Retrospective study; $Na^{18}F$ PET was available in 68 patients as part of the SOR	All BM were osteolytic. On a patient basis $Na^{18}F$ PET and [^{18}F]FDG PET/CT concordantly identified 13 out of the 18 patients with BM. Four patients with BM and an unremarkable [^{18}F]FDG PET/CT were correctly assessed by $Na^{18}F$ PET. A patient with one BM resulted a true positive at [^{18}F]FDG PET/CT and falsely negative on $Na^{18}F$ PET	[68]
Schirrmeister *et al.* (2001)	Prospective study evaluating the anatomical distribution and metabolic behavior of BM using a variety of imaging techniques	35 patients with well-differentiated thyroid cancer (follicular = 26; papillary = 9)	Patients with known BM were also included	Primary end point is not suitable for assessing $Na^{18}F$ PET diagnostic accuracy; small sample size; $Na^{18}F$ PET was used as the primary reference method	None	[28]

^{99m}Tc-MDP: ^{99m}technetium medronate; BM: Bone metastases; BS: Bone scintigraphy; HCC: Hepatocellular carcinoma; NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer; SOR: Standard of reference.

Table 1. Design, limitations and impact on patient outcome of cited studies (cont.).

Study (year)	Study design	Participants	Selection bias	Method limitations	Na^{18}F PET imaging impact on patients outcome	Ref.
Yen *et al.* (2010)	Prospective study evaluating diagnostic and prognostic usefulness Na^{18}F PET/CT compared with ^{99m}Tc-MDP BS for detection of BM	34 patients with HCC and suspicion of BM	Not specified	Small sample size	A significant correlation was reported between the presence of Na^{18}F PET/CT-positive BM and the survival time of HCC patients	[71]
Putzer *et al.* (2009)	Prospective intrapatient study testing diagnostic accuracy of [^{68}Ga]DOTATOC PET and CT in detecting BM	51 patients with neuroendocrine tumors	Only 19 patients underwent PET with all the three available tracers [^{68}Ga]DOTATOC, Na^{18}F and [^{18}F]FDG	Small sample size; Na^{18}F PET used as SOR in 34 patients	Despite the higher sensitivity of Na^{18}F, ^{68}Ga-DOTATOC was reported to be superior in the initial detection of still unknown BM thus having a greater impact on therapeutic management	[73]

^{99m}Tc-MDP: ^{99m}technetium medronate; BM: Bone metastases; BS: Bone scintigraphy; HCC: Hepatocellular carcinoma; NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer; SOR: Standard of reference.

clearance from the circulation allowing for a high bone:background ratio in a short time.

Its distribution and uptake are conditional on two limiting steps. Initial Na^{18}F distribution reflects blood perfusion that varies among different bones [18]. Around 30% of the injected Na^{18}F is present in erythrocytes, but this fact does not hamper ^{18}F$^-$ ions exchange in bone because Na^{18}F is freely diffusible across membranes [19]. Contrary to what happens with ^{99m}Tc-DP, ^{18}F$^-$ ions do not bind to plasma proteins either and clear out of the circulation twofold faster. Essentially all the Na^{18}F that is delivered to bone by the blood flow is retained in the bone (**Figure 1**) [20]. Tracer retention is a two-phase process [21]. In the first phase, ^{18}F$^-$ ions diffuse through capillaries into bone extracellular fluid and are chemisorbed onto bone surface by exchanging with hydroxyl groups in hydroxyapatite crystal of bone to form fluoroapatite [22]. In the second phase, the ^{18}F$^-$ ion migrates into the crystalline matrix of bone, where it is retained until the bone is remodeled. At 1 h after Na^{18}F administration approximately 10% of the injected dose remains in the blood [23].

Thus, similarly to ^{99m}Tc-DP, Na^{18}F distribution reflects blood perfusion and osteogenic activity; it is not tumor specific (**Figure 2**) [24], therefore it accumulates not only in malignant processes but also when nonmalignant causes for altered blood flow and increased deposition of osteoid matrix occur (e.g., fracture, arthrosis, arthritis, osteomyelitis and benign bone tumors).

Both primary bone tumors and metastatic bone lesions are often characterized by an increased regional blood flow and bone turnover. With respect to osteogenic activity not only sclerotic metastases are easily imaged by Na^{18}F PET but also predominantly lytic lesions, as they prompt, to some extent, a reactive new bone deposition (**Figure 3**). Na^{18}F uptake in BM is fast and it is threefold higher compared with that of normal bone resulting in an optimal tumor:normal-bone tissue ratio. Combined with the higher resolution of PET scanners and morphological and anatomical characterization provided by PET/CT hybrid systems Na^{18}F has proved accurate in detecting even small lesions with minimal osteoblastic activity and/or normal CT patterns [10,11,25–28].

To conclude, no safety issues concerning the clinical use of Na^{18}F have been reported so far. The impact of treatments, such as bisphosphonates, antihormonal therapy, chemotherapy and radiotherapy, on the uptake of ^{18}F$^-$ ions are yet to be determined.

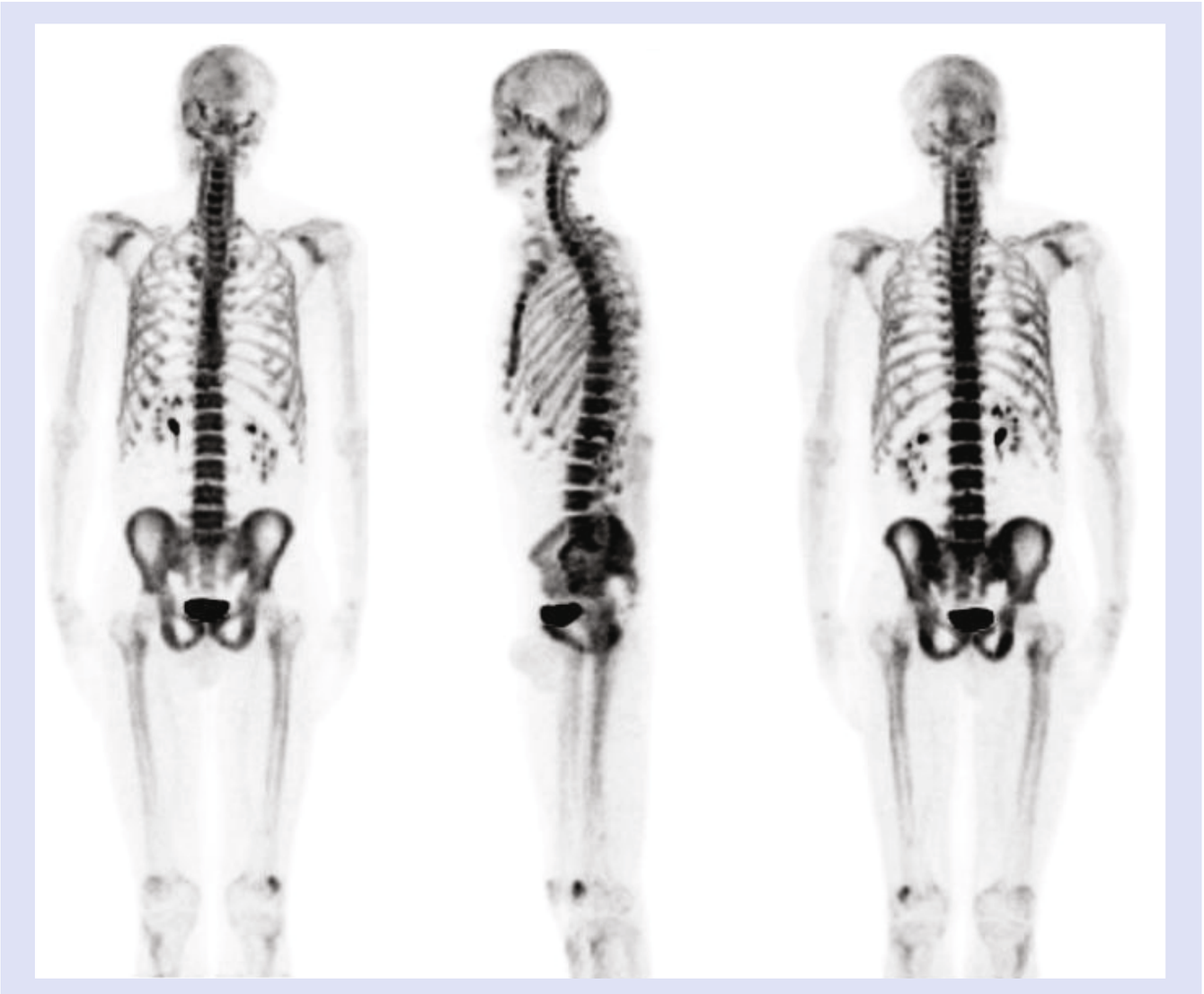

Figure 1. Maximum-intensity projection demonstrates normal Na^{18}F PET biodistribution in adults. Although the pattern of Na^{18}F uptake in the skeleton is similar to the more familiar ^{99m}Tc-diphosphonate bone scans, Na^{18}F bone PET provides higher quality images, better ratios of bone:soft tissue uptake and shorter studies. Blood perfusion and bone remodeling are the reasons for Na^{18}F biodistribution, with greater deposition in the axial skeleton (e.g., trabecular bone of vertebrae and pelvis) than in the appendicular skeleton (where compact bone shows a higher uptake compared with the cancellous bone). A greater deposition in the bones around joints than in the shafts of long bones is normally observed as well. The major route of excretion is via the urinary tract. The kidneys, ureter and bladder should be visible in the absence of renal insufficiency.

Technical aspects of Na^{18}F PET scanning

Patients undergoing Na^{18}F PET/CT scanning do not require specific preparation, however, they should be well hydrated. The Na^{18}F activity recommended for adults is 185–370 MBq, reserving a highest dose (444 MBq) for obese patients. Pediatric activity should be weight based (2.1 MBq/kg), using a range of 19–148 MBq [29]. In patients with a normal renal function whole-body images can be acquired 1 h after Na^{18}F administration, preferably in 3D mode because the higher count rates compensate for the shorter acquisition times required for imaging a large area.

With regard to tumors predominantly displaying a retrograde venous metastatic dissemination (e.g., prostate and breast cancers) and no clinical suspicion of acral involvement, the overall PET field of view can be limited between the cranial vault and the proximal tibiae epiphyses resulting in a reduced effective dose and time saving. Conversely, neoplasms likely to metastasize via arterial embolization (e.g., lung and kidney carcinomas) as well as clinical suspicion of peripheral skeletal involvement

prompt a complete scan to rule out peripheral localizations.

For a more comprehensive treatment of technical aspects of Na[18]F PET/CT scanning the reader is invited to consult Segall *et al.* [30].

Radiation dosimetry

In adults the effective dose for Na[18]F is 0.027 mSv/MBq. For a typical activity of 370 MBq, the effective dose is nearly 10 mSv. With regard to hybrid systems an additional dose from the low-dose CT portion should be considered. For a whole-body, low-dose CT scan the effective dose is at least 3.2 mSv (CT parameters: voltage of 120 keV, current of 30 mA, rotation of 0.5 s, pitch of 1).

Conversely the effective dose for ^{99m}Tc-MDP is 0.0057 mSv/MBq. Thus a typical adult activity of 740 MBq would result in an effective dose of 4.2 mSv. Compared with planar ^{99m}Tc-MDP BS the radiation dose to patients is approximately twofold higher using Na[18]F PET and threefold higher using Na[18]F PET/CT. The highest absorbed doses extrapolated to patients are in the bone surface, bone red marrow and bladder walls for both modalities.

The effective dose for children is significantly higher. Considering a 15-year-old patient weighing 55 kg, the extrapolated effective doses would be 0.034 mSv/MBq for Na[18]F (Na[18]F dose: 116 MBq; overall effective dose: 4 mSv) and 0.0070 mSv/MBq for ^{99m}Tc-MDP (^{99m}Tc activity: 407 MBq; overall effective dose: 2.9 mSv) [31,32].

Na[18]F PET imaging in oncology

■ Na[18]F PET in osteosarcoma

A heterogeneous mesenchymal malignancy osteosarcoma is one of the most common pediatric cancers. Frequently affecting long bones, such as the femur, tibia and humerus, it is associated with the production of extracellular osteoid

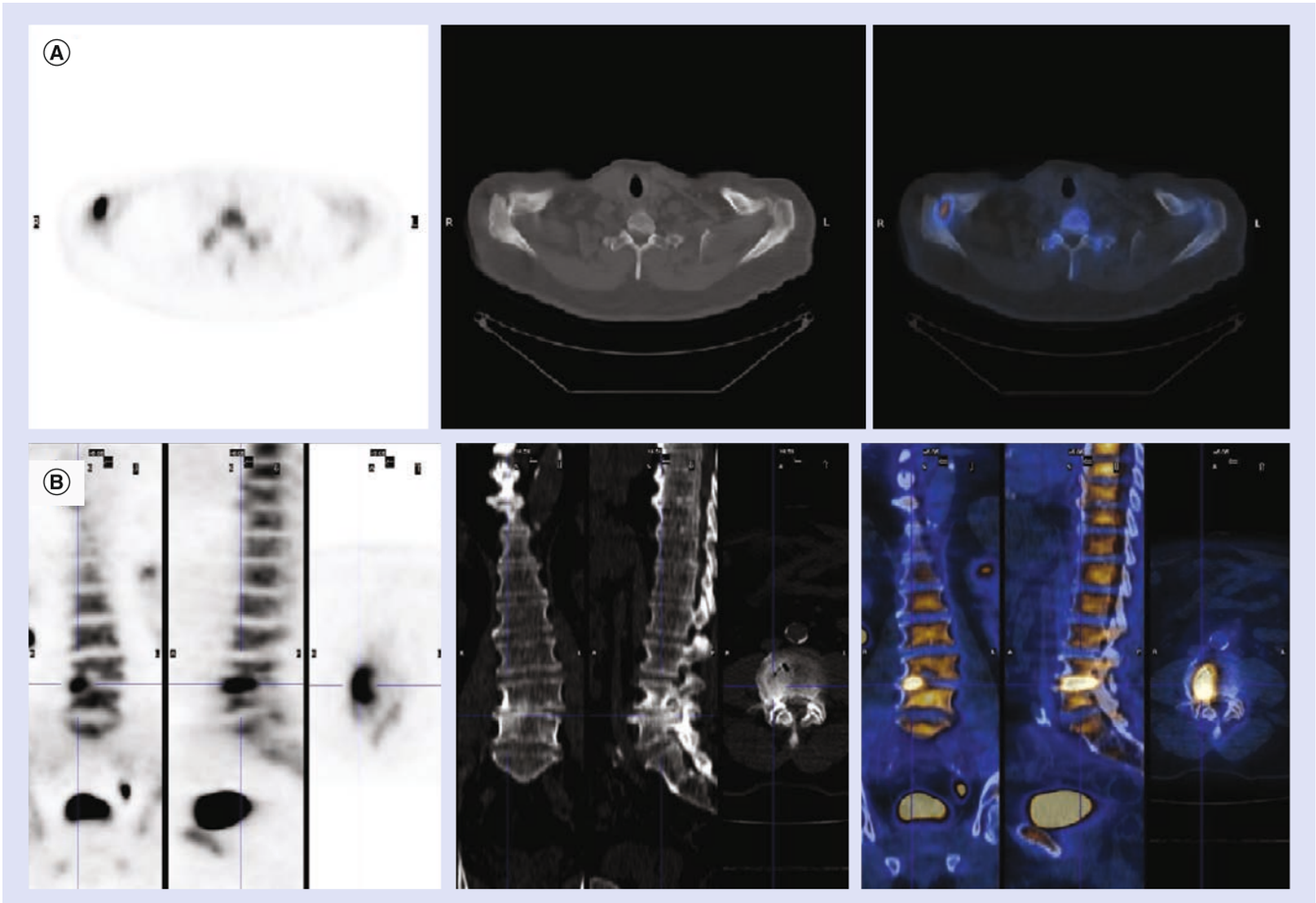

Figure 2. Na[18]F PET/CT in a 69-year-old male recently diagnosed with clear cell renal cell cancer and referred for skeletal staging. (A) Axial views of Na[18]F PET, low-dose CT and fused Na[18]F PET/CT show focally increased Na[18]F uptake at right acromioclavicular joint corresponding to arthrosic changes on CT. **(B)** Coronal, sagittal and axial views of Na[18]F PET, low-dose CT and fused Na[18]F PET/CT, show abnormal Na[18]F uptake at L4–L5 level on the right side, corresponding on low-dose CT to degenerative changes, including joint-space narrowing, an intradiscal fissure, retrolisthesis and anterior osteophytes.

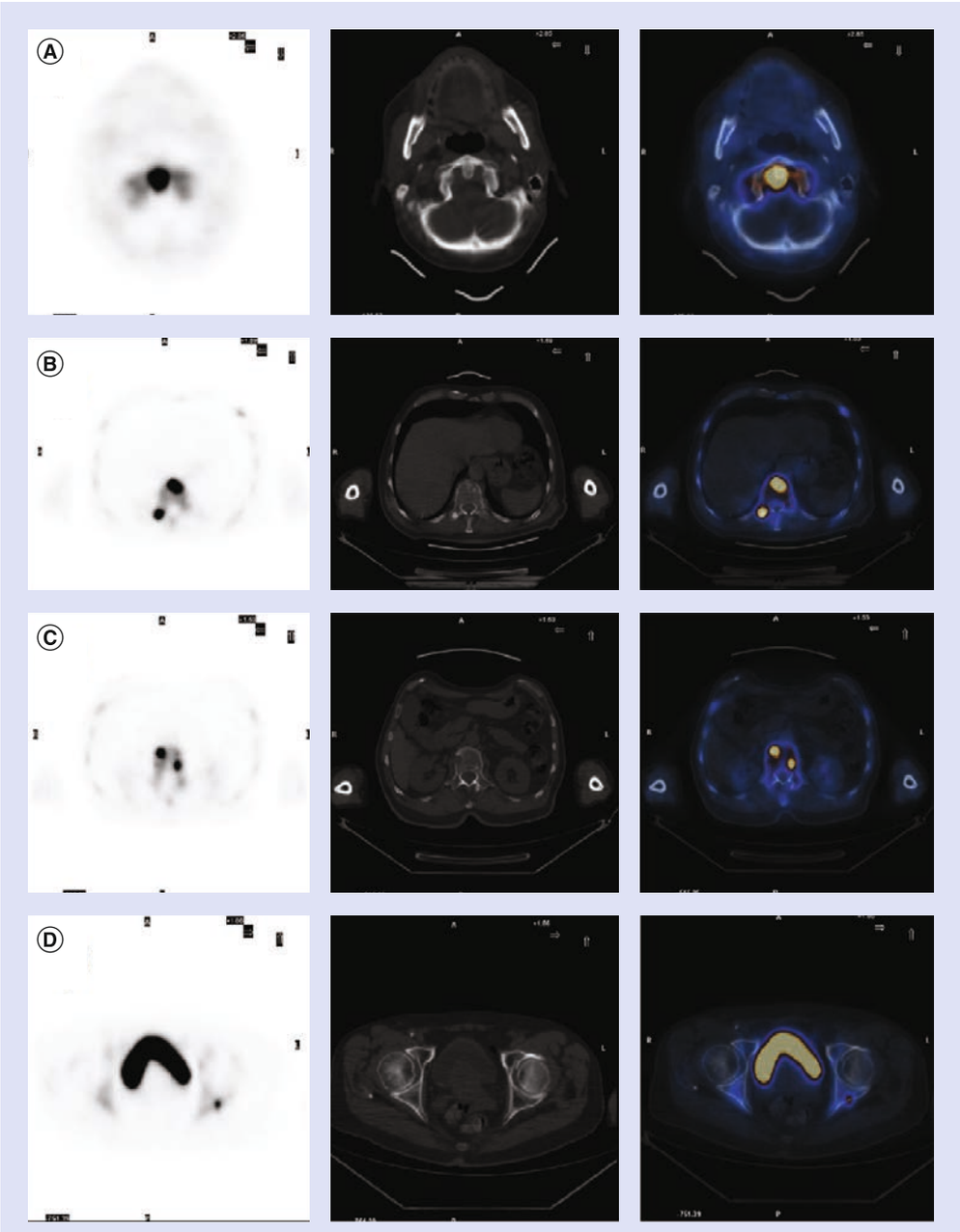

Figure 3. Na^{18}F PET/CT performed in a 75-year-old male with newly diagnosed non-small-cell lung carcinoma. Transaxial Na^{18}F PET, low-dose CT and fused images are presented in rows. **(A)** Blastic lesion involving the dens of epistropheum. **(B)** Osteolytic (anterior part of the vertebral body) and blastic (right transverse process) metastases are seen in T8. **(C)** Osteolytic metastasis on the right side of T12 vertebral body. Initial bone sclerotic metastasis with high Na^{18}F uptake is seen contralaterally. **(D)** Small periosteal lytic metastasis in the left acetabulum.

matrix and early hematogenous spread, mainly to the lungs and bone. Currently, staging of primary tumors and synchronous regional metastases (skip metastases) mainly relies on planar x-ray, CT and MRI, whereas lung metastases and distant bone localizations are screened by means of CT and ^{99m}Tc-MDP BS, respectively. Despite all these diagnostic measures, only 15% of patients harboring metastases will be correctly assessed. An accurate evaluation of both regional and distant metastases is, however, crucial for surgical planning and prognostic stratification. In the first published report on the use of Na^{18}F for skeletal PET, Hoh *et al.* enrolled 13 patients with primary and metastatic bone lesions including four cases with osteosarcoma [33]. All of them showed increased Na^{18}F uptake in the primary tumor site and in one case Na^{18}F PET

also imaged CT-proven lung metastases. Three patients with untreated osteosarcoma at the time of Na^{18}F PET scan, showed the highest tumor:normal-bone uptake ratios compared with other malignant bone lesions, whereas one patient, referred for Na^{18}F PET imaging after treatment with chemotherapy and immunotherapy, had a tumor uptake ratio clearly reduced when compared with untreated cases, therefore suggesting a Na^{18}F PET semiquantitative approach for monitoring therapy response. A case report by Tse *et al.* on a patient with a history of congenital polyostotic fibrous dysplasia, metastatic osteosarcoma and a breast mass described abnormal Na^{18}F uptake in lung nodules supporting the diagnosis of osteosarcoma metastases [34].

Brenner *et al.* reviewed the potential applications of PET imaging in osteosarcoma and suggested that Na^{18}F PET could be useful in staging and restaging of distant lung and BM thus replacing conventional ^{99m}Tc-MDP BS and assisting thoracic CT assessment and prognostic stratification [35]. Given the exceptional dual nature of Na^{18}F in osteosarcoma (oncotropic and osteotropic agent at once) its application in therapy response monitoring has been suggested but it is still speculative and beyond the scope of this review.

■ Skeletal Na^{18}F PET & PET/CT in heterogeneous oncologic populations

In the attempt to select a population with a similar prevalence of lytic and sclerotic BM Schirrmeister *et al.* [12] prospectively included 44 patients affected by prostate (n = 20), thyroid (n = 19) and lung cancer (n = 5). Their aim was to estimate the sensitivity of ^{99m}Tc-MDP BS in detecting both BM patterns and describe how their anatomic localization influenced ^{99m}Tc-MDP BS detection rate by direct intrapatient comparison with Na^{18}F PET. Reference standard included a composite panel of imaging techniques and clinical follow-up. On a lesion-based analysis the receiver operating characteristic (ROC) curve was 0.99 for Na^{18}F PET and 0.64 for ^{99m}Tc-MDP BS. Indeed, Na^{18}F PET yielded a significantly higher detection rate regardless of BM pattern and localization, whereas ^{99m}Tc-MDP scan detected half of osteoblastic and osteolytic lesions. Furthermore, ^{99m}Tc-MDP BS sensitivity varied according to the anatomic location of the lesion, confirming a lower sensitivity in the spine and pelvis. Na^{18}F PET had a limited number of equivocal findings and was found to be more accurate than ^{99m}Tc-MDP BS in discriminating benign from malignant findings. In a patient-based analysis, two patients (4.5%) with undetectable BM on ^{99m}Tc-MDP BS (positive at Na^{18}F PET) were later proven false negative, and the extent of BM was underestimated in eight patients (18.2%). Conversely, Na^{18}F PET accurately assessed the extent of disease in all 15 true positive patients.

Considering the downside of aspecific Na^{18}F uptake, Even-Sapir *et al.* evaluated the added value of low-dose CT morphological characterization offered by hybrid PET/CT systems compared to PET alone in assessing malignant osseous involvement and in differentiating malignant from benign findings in an heterogeneous oncologic population [36]. Reference methods for final diagnosis were histopathology, imaging and clinical follow-up. In a lesion-based analysis, the sensitivity of PET alone in differentiating benign from malignant bone lesions ranged from 72 to 90%, whether inconclusive lesions (Na^{18}F positive, no CT abnormalities) were considered false negative or true positive. On the other hand, PET/CT yielded an overall sensitivity of 99% for tumor detection when inconclusive findings were considered as true positive. Furthermore, PET/CT specificity was significantly higher than that of PET alone (97 vs 72%; $p < 0.001$). Noteworthy among the 12 patients referred for Na^{18}F assessment because of bone pain despite negative findings on ^{99m}Tc-MDP BS, Na^{18}F PET/CT suggested malignant bone involvement in all four patients with proven skeletal metastases.

Recently Withofs *et al.* have prospectively studied 34 patients with breast (n = 24) and prostate cancer (n = 10) at high risk of BM to evaluate Na^{18}F PET/CT diagnostic accuracy compared with ^{99m}Tc-MDP BS completed with SPECT/CT [25]. Both examinations were obtained for all 34 patients and the results were compared with a radiological gold standard (MRI or thin-slice CT). The overall sensitivity, specificity and accuracy of Na^{18}F PET/CT were 76.0, 84.2 and 80.0%, respectively. For BS, they were 44.8, 79.2 and 60.0%, respectively (sensitivity significantly decreased for lytic lesions). They also reported that low-dose CT scanning did not improve specificity of PET compared with BS, but greatly improved lesion localization. PET/CT imaging with Na^{18}F correctly modified the BS results in 12.1% (four patients). On the basis of their results Na^{18}F PET/CT was suggested as an alternative for staging high-risk patients.

A meta-analysis performed by Tateishi on 11 eligible studies (overall including

425 patients) aimed to evaluate the diagnostic accuracy of $Na^{18}F$ PET, $Na^{18}F$ PET/CT, ^{99m}Tc-MDP BS and ^{99m}Tc-MDP SPECT in detecting bone metastatic involvement [37]. The patient-based sensitivity and specificity obtained for $Na^{18}F$ PET or $Na^{18}F$ PET/CT were 96 and 99%, respectively. Conversely ^{99m}Tc-MDP BS, even when completed with a SPECT study, showed a sensitivity of 81 and a specificity of 99%. On a lesion-based analysis, sensitivity and specificity were 97 and 98%, respectively, for $Na^{18}F$ PET or PET/CT, and 56 and 96% for ^{99m}Tc-MDP BS or SPECT, respectively.

■ $Na^{18}F$ PET in BM from prostate cancer

Prostate cancer is the most common neoplasm in men in the western world [26,38], and, although it is not always lethal, it accounts for approximately 27,000 deaths per year in the USA, making it the second leading cause of cancer-related deaths in men [39,40]. Prostate cancer is a heterogeneous disease; it ranges from asymptomatic slow-growing forms to rapidly progressive systemic malignancy, the skeleton being the most affected distant organ. As the major cause of morbidity and mortality the presence of BM is related to a poor prognosis. Indeed prostate BM are predominantly sclerotic but are associated with an increased osteolysis as well, causing destruction of normal bone and formation of abnormally woven bone generated by osteoblastic hyperstimulation [41]. Consequently patients are at risk of vertebral deformity or collapse, spinal cord compression and fractures. Approximately 20% of patients with BM will develop pathologic fractures typically in load-bearing sites, and approximately 30% will have bone pain requiring palliative radiation therapy [42]. Economically, the lack of an early detection method for these complications will understandably imply increased healthcare costs. Therefore, a thorough evaluation of BM is pivotal both in staging as it will lead to the choice of the optimal therapeutic strategy, and restaging when evocative symptoms or biochemical recurrence occur after radical prostatectomy or radiotherapy to assess the true extent of skeletal disease at an earlier stage and prevent skeletal-related events. With this regard ^{99m}Tc-DP BS is currently indicated in the asymptomatic patient staging if the risk of metastatic disease is deemed high [43,44] (i.e., prostate-specific antigen [PSA] higher than 10 ng/ml; Gleason score >7; stage T3 or higher); after radical prostatectomy or radiation therapy in case of clinical or biochemical recurrence (suggested by a PSA at least higher than 10 ng/dl or by a PSA doubling time shorter than 6 months). Nevertheless several studies comparing the sensitivity of planar BS with that of MRI have shown that planar BS is less sensitive than previously accepted [45–47]. Current clinical indications for oncotropic PET agents such as ^{18}F-choline and ^{11}C-choline in prostate cancer include preoperative lymph nodal staging for intermediate and high-risk selected patients as they perform better than clinical nomograms [48]. ^{18}F/^{11}C-choline is also indicated for the early detection of locoregional and/or distant recurrence after radical prostatectomy and radiation therapy [49–51] even with small increases of serum PSA levels. Considering skeletal metastases, a comparative study by Beheshti *et al.* examined 38 patients with prostate cancer by means of ^{18}F-choline and $Na^{18}F$ PET/CT [13]. Inclusion criteria comprised preoperative high-risk (high Gleason score and/or elevated PSA) and a post-operative clinical or radiological suspect of bone recurrence. Their results documented a sensitivity, specificity and accuracy for detection of BM respectively of 74, 99 and 85% for ^{18}F-choline PET/CT, respectively, and 81, 93 and 86% for $Na^{18}F$ PET/CT, respectively. Lytic lesions showed more intense uptake than sclerotic lesions using both imaging modalities. Although on a patient basis both procedures had a close concordance ($\kappa = 0.76$), on a lesion basis they coincided in 80% of lesions ($\kappa = 0.57$). $Na^{18}F$ PET/CT documented a higher number of BM in some patients, with these findings not affecting their clinical management. ^{18}F-choline PET/CT on the other hand led to a change in management in two of 38 patients in preoperative evaluation owing to early detection of BM; in both patients, CT and $Na^{18}F$ PET scans were negative, but malignancy was confirmed in follow-up examinations. These findings were interpreted as bone marrow metastases without significant bone remodeling, suggesting that ^{18}F-choline PET/CT has an advantage in the early detection of BM. Conversely, for discordant $Na^{18}F$ positive/^{18}F-choline negative findings observed exclusively in patients under hormone therapy, the hypothesis of reactive bone replacing a no longer metabolically active lesion was put forward. This assumption was supported by the evidence of increasing bone mineralization observed on CT in view of a progressive decrease in ^{18}F-choline uptake expressing positive response to therapy. Indeed, what is known under the name of 'flare phenomenon' in conventional BS, was also reported by Wade *et al.* using $Na^{18}F$ PET/CT [14]. The same trend, metabolically negative and sclerotic at CT, was also

observed with $Na^{18}F$ PET/CT, but in a later phase of hormonal therapy and with an even higher level of density at CT (mean HU, 1148 ± 364), likely to express the completion of reparative bone deposition. A prospective study by Even-Sapir *et al.* compared the diagnostic accuracy of planar ^{99m}Tc-DP BS, SPECT, $Na^{18}F$ PET and $Na^{18}F$ PET/CT in patients with either newly diagnosed, localized, high-risk prostate cancer or suspected recurrence/disease progression [52]. The sensitivity and specificity for detection of BM was 70 and 57% for planar BS, respectively, and 92 and 82% for bone SPECT, respectively. As far as PET imaging was concerned, sensitivity and specificity, when equivocal lesions were characterized as malignant, yielded 100 and 62% for $Na^{18}F$ PET, respectively, and 100 and 100% for $Na^{18}F$ PET/CT, respectively. Of the 23 patients with proven BM (on biopsy or follow-up) $Na^{18}F$ PET/CT correctly identified 20 patients with corresponding sclerotic pattern on CT, whereas findings in three patients were classified as equivocal given the radiologically normal bone appearance. Overall $Na^{18}F$ imaging caused a change of treatment in seven patients (15.9%): in three of the 11 newly diagnosed cases with bone metastatic spread $Na^{18}F$ PET/CT detected early bone involvement, otherwise overlooked on ^{99m}Tc-DP BS, leading to the choice of a systemic therapy. Among the 19 patients with suspected recurrence or disease progression $Na^{18}F$ PET/CT made two patients shift to chemotherapy and two others modify their androgen withdrawal therapy.

■ $Na^{18}F$ PET in BM from breast cancer

Breast carcinoma is the most prevalent cancer in women. BM affect approximately 5–10% of breast cancer patients at early stages and are found in up to 70% of advanced stages. The skeleton represents the most common site of distant recurrence; the first site of recurrence in 25–50% of relapsed patients. At diagnosis, risk factors for skeletal involvement are a primary tumor size greater than 2 cm (T2 or more) and/or more than three axillary nodes and/or an estrogen receptor-positive status [53–55].

However, a skeletal-confined breast carcinoma is associated with a more indolent clinical course compared with visceral involvement. Its distribution has proven a prognostic factor itself. Yamashita *et al.* [27] found that patients who had BM exclusively located superiorly to the lumbosacral junction had a significantly longer survival than patients with BM in the pelvis and the lower limbs [56].

BM from breast cancer are predominantly lytic (50%) or mixed (40%), being sclerotic in approximately 10% of cases. Nevertheless in a retrospective analysis of patients presenting with neoplastic bone involvement from breast cancer Quattrocchi *et al.* described an increased prevalence of sclerotic lesions in patients under zoledronic acid treatment, suggesting diphosphonates as a possible cause for this change [57]. No significant correlation between the histotype of breast cancer and radiological appearance of BM have been found.

^{99m}Tc-DP BS has a low diagnostic yield in early stages and it is currently recommended in staging patients with positive axillary nodes (N+), large tumors (T3) or clinical signs, symptoms, or laboratory values that suggest a metastatic involvement. It is also indicated to rule out a bone involvement if a neoadjuvant therapy is planned [58]. During follow-up ^{99m}Tc-DP BS is indicated if patients are clinically symptomatic, with negative planar x-ray and/or show elevated bone or tumor markers (alkaline phosphatase, carcinoembryonic antigen, CA 15.3) [59,60].

Currently [^{18}F]FDG PET is complementary to BS in surveying the skeleton for metastatic involvement as it has proven superior in detecting lytic and intramedullary metastases, but unable to demonstrate sclerotic lesions [61].

Indeed, a recent meta-analysis comparing diagnostic accuracies of [^{18}F]FDG PET, MRI and ^{99m}Tc-DP BS in detecting BM in patients with breast cancer pointed out the superiority of MRI, but also described a significantly higher lesion-based sensitivity for ^{99m}Tc-DP BS compared with [^{18}F]FDG PET, the latter resulting more specific (^{99m}Tc-DP BS sensitivity and specificity of 87.8 and 96.1%, respectively; [^{18}F]FDG PET sensitivity and specificity of 52.7 and 99.6%, respectively) [62].

As specificity is the main limitation of ^{99m}Tc-DP BS an additional potential pitfall must be taken into account when restaging breast cancer patients who also underwent local-regional radiotherapy. Park *et al.* reviewed bone scans from 294 such patients and described hot spots inside the irradiated field of the bony thoracic cage in 30 patients (cumulative incidence at 5 years = 12.9%) [63]. These findings, benign in nature but misleading at interpretation, were more common in postmenopausal patients who weighed less than 60 kg and whose field of irradiation included the supraclavicular area.

Currently, only a few studies have evaluated the ability of $Na^{18}F$ PET to detect BM in breast cancer patients. In a case series including five

patients with multiple skeletal metastases from breast cancer, Pétren-Mallmin *et al.* reported a high tracer uptake in both sclerotic and lytic BM [64]. Schirrmeister *et al.* compared $Na^{18}F$ PET with BS in 34 patients with high-risk breast cancer and clinical or biological suspect of skeletal involvement [10]. The gold standard was represented by MRI, CT and planar x-ray. On a lesion-based analysis $Na^{18}F$ PET detected 64 metastatic lesions in 17 patients, whereas BS only detected 29 metastases in 11 patients. The reported ROC area was 0.99 for $Na^{18}F$ PET and 0.74 for BS. Overall $Na^{18}F$ skeletal PET changed the clinical management of four patients (11.8%).

■ $Na^{18}F$ PET in BM from lung cancer

Unlike prostate and breast cancer, lung neoplasms are often diagnosed at advanced stages and 30–50% have distant metastases at the time of presentation, the skeleton being one of the most common sites of distant metastases [11,65]. The extent of disease is the most important prognostic factor, suffice it to say that non-small-cell lung cancer (NSCLC) without distant metastases is potentially curable, whereas small-cell lung cancer, which accounts for approximately 25% of lung cancers, has a high propensity for the early systemic spread so that 70% patients already have distant metastases at the time of diagnosis [66]. Lung cancer metastases normally appear purely lytic, with poor margination, no matrix and cortical destruction. Regarding the limited survival prospect after diagnosis of BM and the high costs of thoracic surgery, preoperative exclusion of BM is crucial. As a consequence current protocols include the routine use of [^{18}F]FDG PET for assessing both lymphonodal and distant metastatic involvement. With respect to skeletal disease [^{18}F]FDG PET showed a sensitivity similar to BS, but a higher specificity (98 vs 61%) proving very useful in staging patients eligible for radical surgery, even where there is a lack of symptoms and signs of BM. As Cook *et al.* suggested, [^{18}F]FDG might be generally less sensitive in detecting osteoblastic metastases but more sensitive in detecting osteolytic lesions [66]. Conversely, $Na^{18}F$ PET has been shown to be highly sensitive in detecting both osteolytic and osteoblastic lesions (**Figure 3**). Schirrmeister *et al.* prospectively studied 53 patients affected by small-cell lung cancer and locally advanced NSCLC in order to evaluate the clinical impact of BS, SPECT and $Na^{18}F$ PET [67]. MRI, FDG PET, spiral CT and follow-up were used as reference methods. All 12 patients who harbored BM were correctly identified by $Na^{18}F$ PET, whereas one was missed at SPECT. BS failed to prove BM in six patients. The area under the ROC curve was then 0.779 for BS, 0.944 for SPECT and 0.993 for $Na^{18}F$ PET. As a result of $Na^{18}F$ PET imaging, clinical management was changed in six patients (11%). Another study by the group from Ulm, primarily designed to assess $Na^{18}F$ PET accuracy and cost–effectiveness compared with BS and SPECT in skeletal staging of NSCLC, evaluated 103 patients, of whom 33 had BM [15]. $Na^{18}F$ PET correctly staged 31 BM patients, proving to be more accurate with a significantly superior area under the ROC curve ($Na^{18}F$ PET = 0.989 vs BS = 0.771; BS and SPECT = 0.875). Thirteen patients were falsely negative at BS, four at SPECT and one at ^{18}F PET. Owing to the superior diagnostic accuracy of $Na^{18}F$ PET imaging, clinical management was changed in 9.7% of cases either because curative surgery was cancelled or because radiation therapy was omitted. Of note, in the same study [^{18}F]FDG PET/CT was carried out in 41 patients, correctly indicating BM in eight out of ten patients and strongly underestimating the extent of skeletal spread in four patients. To conclude, in a series of 126 NSCLC patients studied by means of [^{18}F]FDG PET/CT Krüger *et al.* assessed its diagnostic accuracy compared with BS (in 58 patients) and to $Na^{18}F$ PET (in 68 patients) [68]. $Na^{18}F$ PET proved to be at least as sensitive as [^{18}F]FDG PET/CT. Krüger *et al.* concordantly diagnosed BM in 13 out of 18 patients. On a patient-based analysis $Na^{18}F$ PET correctly identified four patients with BM and a negative [^{18}F]FDG PET/CT. Noteworthy a patient with one osteolytic BM resulted positively true at [^{18}F]FDG PET/CT but falsely negative at $Na^{18}F$ PET. On a lesion basis [^{18}F]FDG PET/CT identified a higher number of BM compared with $Na^{18}F$ PET (53 malignant lesions vs 40).

■ $Na^{18}F$ PET in BM from other cancers

Well-differentiated thyroid cancer

BM is a frequent complication of well-differentiated thyroid carcinoma that severely reduces a patient's quality of life and decreases their 10-year survival by 50% [69]. Indeed, it has been demonstrated that patients with BM have a worse prognosis than those with iodine-avid lung lesions. The skeletal distribution of thyroid metastases presents a lower percentage of vertebral localizations as compared with other malignancies and the number of patients with one single metastasis is higher [28]. The onset of bone

pain or an increasing trend of thyroglobulin serum levels in thyroidectomized patients justifies a whole-body imaging assessment in order to localize and evaluate the extent of skeletal involvement. Since thyroid BM often maintain the ability to concentrate iodine and have a predominantly lytic pattern with a poor osteosclerotic reaction whole-body iodine scintigraphy (^{131}I WBS) proved to be more accurate in identifying bone (and soft tissue) lesions than conventional ^{99m}Tc-DP BS. ^{131}I WBS proved more accurate when performed after the administration of therapeutic doses. On the other hand ^{131}I WBS carried out with diagnostic doses yields lower sensitivity, and is burdened with a stunning effect. Experience with Na^{18}F PET is limited. In a prospective study carried out on 35 patients with suspected thyroid BM, Schirrmeister *et al.* used Na^{18}F PET as a gold standard procedure to evaluate results of visual interpretation of planar ^{99m}Tc-MDP BS with and without ^{131}I WBS [28]. At this juncture Na^{18}F PET could detect 21 previously unknown BM, 13 of which had very low sclerotic activity that was undetectable on BS, confirming the high sensitivity and resolution of the PET procedure.

Hepatocellular carcinoma

The prognosis for patients with extrahepatic metastases of hepatocellular carcinoma (HCC) is poor with a 1-year survival rate of approximately 21.7%. The skeleton is the third most frequent target-organ, after the lungs and lymph nodes. Although most HCC patients with extrahepatic metastases should undergo treatment for the intrahepatic HCC mainly, treatment of extrahepatic metastases in selected HCC patients who have good hepatic reserve, low intrahepatic tumor stage and are free of portal venous invasion may improve survival [70]. Yen *et al.* compared the diagnostic accuracy of Na^{18}F PET/CT and BS in 34 HCC patients with a suspect skeletal involvement. Both procedures were performed within 1 month for each patient. Pathology and clinical follow-up were the standard of reference [71]. Once again Na^{18}F PET/CT demonstrated significantly higher accuracy than BS (95.7 vs 75.4%; p = 0.0001). They also reported a significant correlation between the presence of Na^{18}F PET/CT positive bone lesions and the survival time of HCC patients, which was not observed with BS.

Neuroendocrine tumors

The incidence of BM in neuroendocrine patients, typically sclerotic or mixed, varies between 7 and 17% [72]. As a predictor of poor prognosis and a contraindication to extended surgical resection skeletal involvement must be accurately evaluated. Putzer *et al.* compared the diagnostic accuracy of CT and ^{68}Ga-DOTATOC PET in the detection of BM in a cohort of 51 patients affected by NET tumors, and included Na^{18}F PET among the standards of reference [73]. A subset of 19 patients were evaluated by means of ^{68}Ga-DOTATOC, [^{18}F]FDG and Na^{18}F PET. In this subset Na^{18}F revealed 245 secondary lesions versus 218 disclosed by ^{68}Ga-DOTATOC and 80 observed with [^{18}F]FDG. Despite the higher sensitivity of Na^{18}F, ^{68}Ga-DOTATOC was reported superior in the initial detection of still unknown BM, thus having a greater impact on therapeutic management [73].

Renal clear cell carcinoma

Renal clear cell carcinoma accounts for 80–90% of all renal malignancies and the overall 5-year survival rate is approximately 45%. BM present in 20–25% of renal clear cell carcinoma cases, and are highly osteolytic and are particularly destructive. Their number and localization are established prognostic factors. Szendroi *et al.* reported that in case of solitary resectable metastasis 1-year-survival was 75.0% whereas at 5 years only 35.5% of patients survived. [74]. If multiple metastases were present, no patient survived at 5 years. Palliative treatments include surgery to prevent or stabilize pathological fractures, antiresorptive drugs, painkillers, radionuclide therapy and local irradiation to relieve pain, thus impacting on patients' quality of life [74]. Na^{18}F PET experience in this contest is limited. Bhargava *et al.* reported the case of a symptomatic 59-year-old patient with metastatic renal clear cell carcinoma and documented a higher sensitivity of Na^{18}F PET/CT compared with CT [75].

Conclusion & future perspective

Imaging BM often results in a complex and multimodal process primarily influenced by the patient's underlying tumor, clinical situation and expected change in clinical management. Nevertheless when a whole-body skeletal assessment is specifically advocated ^{99m}Tc-DP BS is still the recommended modality for the majority of primary solid tumors and for osteosarcoma. However, with the advent of high-resolution modalities such as CT, PET and MRI, ^{99m}Tc-DP BS sensitivity is no longer perceived as highly as it was in the past decades. On the one hand, given the low specificity of ^{99m}Tc-DP uptake, BS

can result in equivocal or falsely positive findings. On the other hand ^{99m}Tc-DP BS can fail to image purely lytic and early intramedullary BM as well as lesions whose dimensions are below BS spatial resolution. Although ^{99m}Tc-DP BS completed with a SPECT or SPECT/CT study may partially obviate these limitations, resulting at once as the most cost-effective approach in the assessment of BM, its routine use in clinical practice is strongly hampered by the prolonged examination time. On the contrary the favorable biochemical kinetics of $Na^{18}F$ allows for a faster whole-body acquisition resulting in a more efficient workflow and improved patient compliance. $Na^{18}F$ PET reproducibility is not an issue either, since recent official guidelines are available to recommend doses and scanning protocols. As far as skeletal staging and restaging indications are concerned, $Na^{18}F$ PET and PET/CT have proven undisputedly more sensitive and accurate than ^{99m}Tc-DP BS and SPECT in a variety of malignancies. Indeed $Na^{18}F$ can image sclerotic, mixed and lytic lesions with poor and/or radiologically undetectable margination. Besides, PET spatial resolution allows for the detection of a higher number of small metastases when compared with ^{99m}Tc-DP BS and SPECT. Conversely, a dramatic limitation seems to emerge from the few comparative studies testing diagnostic accuracy of $Na^{18}F$ and oncotropic PET agents, as the former displays a low sensitivity in imaging bone marrow-based BM that is the early phase of metastatic dissemination. Since $Na^{18}F$ is not tumor specific, the reviewer should also be aware of the different causes for benign $Na^{18}F$ uptake and seek them out in patient's anamnesis (Box 1). In general, distinction between malignant and benign lesions of the skeleton is not insidious owing to new hybrid PET/low-dose CT systems that provide anatomical and morphological characterization of PET findings, further improving the specificity and overall accuracy of this imaging modality (Figure 2). If intermodality discrepancies are encountered (i.e., PET positive/CT negative or PET negative/CT positive or other multimodality fusion imaging when available), their interpretation, as suggested by Paycha *et al.,* should prompt an integrative reading aimed at maximizing the chances to correctly classify benign and malignant skeletal lesions [76]. In fact, such discrepant combinations should convey clues to achieve the highest possible levels of expertise. In spite of the increasing availability of PET scanners and the improved logistics for the delivery of ^{18}F-derived radiopharmaceuticals, $Na^{18}F$ PET imaging has not widely entered clinical practice yet. This delay is mainly due to the higher costs and lack of insurance coverage with $Na^{18}F$ PET, as its cost–effectiveness has not been systematically demonstrated yet. Indeed most of the cited studies had heterogeneous inclusion criteria and designs, and primary outcomes mostly addressed diagnostic accuracy rather than $Na^{18}F$ PET impact on therapeutic management. For this purpose, starting from 2010, the US Centers for Medicare and Medicaid Services (CMS) initiated an Evidence Development Program under whose aegis prospective, well-controlled clinical trials are being financially covered. Their aim is to produce sufficient evidence on the real cost–effectiveness of $Na^{18}F$ PET and PET/CT, especially in assisting the primary therapeutic strategy or guide subsequent therapies by the identification, location and quantification of BM in patients in whom metastases are strongly suspected, based on clinical symptoms or the results of other diagnostic studies. Compared with ^{99m}Tc-DP BS and oncotropic PET/CT the greatest diagnostic gain by means of $Na^{18}F$ PET/CT would be reasonably expected for specific subsets of patients. With regards to prostate cancer, $Na^{18}F$ PET imaging could complement radiolabeled-choline PET/CT in staging high-risk patients (PSA >10 ng/ml; T3; Gleason score >7; N+) with no evidence of skeletal involvement or when equivocal findings are encountered (typically sclerotic, noncholine-avid lesions) to better characterize them. $Na^{18}F$ PET/CT could

Box 1. Potential pitfalls: non-malignant conditions for increased $Na^{18}F$ uptake.

- Degenerative disk disease
- Osteophytes
- Vertebral facet joint disease
- Hemisacralization of lumbar vertebrae
- Schmorl's node
- Radionecrosis
- Postoperative changes
- Arthritic changes
- Avulsion injury
- Paget's disease
- Osteomyelitis
- Sinusitis
- Mastoiditis
- Osteoma
- Enchondroma
- Subchondral cysts
- Trochanteric bursitis
- Tendonitis
- Stress fracture
- Hyperostosis
- Fibrous dysplasia

Executive summary

Background information

- Major drawbacks of ^{99m}technetium diphosphonates (^{99m}Tc-DP) bone scintigraphy (BS) influencing its diagnostic accuracy (i.e., low specificity, planar imaging, poor resolution images, impaired sensitivity in axial skeleton and lytic metastases) can be partially overcome by performing an additional SPECT or SPECT/CT study, however, in clinical practice this procedure is heavily hampered by the prolonged examination time. Besides, ^{99m}Tc-DP BS often advocates morphological confirmation resulting in incremental costs and, potentially, in a delayed diagnosis.
- [^{18}F]FDG PET, increasingly used in staging and restaging of a number of [^{18}F]FDG-avid tumors, has proven highly sensitive in detecting early bone marrow-based and lytic metastases, but it is burdened with a relatively low sensitivity for sclerotic lesions when compared with ^{99m}Tc-DP BS.
- Na^{18}F, an extremely effective bone-seeking agent recently applied to PET and PET/CT imaging, is emerging as a highly sensitive alternative to ^{99m}Tc-DP BS in staging and restaging skeletal metastatic disease.
- Na^{18}F PET/low-dose CT may potentially obviate the need for further morphological examinations, reducing incremental radiation exposure, costs and delay of diagnosis.

General aspects

- In the USA Na^{18}F has an US FDA-approved NDA (new drug application) for use in PET bone scans; in the EU Na^{18}F has established monograph in the European Pharmacopoeia but its clinical use is subjected to national regulatory authorities, which is therefore variable across the EU countries, so its use is not extensively accepted.
- Na^{18}F is a short half-life positron emitter and an aspecific probe for osteogenic activity, its uptake being dependent on regional blood supply and new bone formation. Its favorable biochemical kinetics allows for a whole-body acquisition of high-contrast images in a short time.
- Lytic, sclerotic and mixed BM can be imaged by Na^{18}F. Indeed, even predominantly lytic lesions prompt, to some extent, reactive bone formation detectable by means of Na^{18}F PET. Occasionally Na^{18}F also detected BM with nonevident CT changes.
- Benign conditions such as infections, fractures, arthrosis, arthritis, osteomyelitis or benign primary tumors can increase Na^{18}F uptake.

Technical aspects of Na^{18}F PET/CT scanning & radiation dosimetry

- The activity for adults ranges from 5 to 10 mCi. A higher activity is justified in obese patients. Pediatric activity should be weight-based.
- In patients with a normal renal function whole-body images can be acquired 1 h after Na^{18}F administration, preferably in 3D mode with typical acquisition times of 2–5 min per bed position. Global PET/CT field of view can be limited if a peripheral metastatic involvement is unlikely.
- Compared with planar ^{99m}Tc-MDP BS the radiation dose to patients is approximately twofold higher using Na^{18}F PET and threefold higher using Na^{18}F PET/CT.

Na^{18}F PET in osteosarcoma

- Na^{18}F in osteosarcoma has an exceptional dual nature being an oncotropic and osteotropic agent at once.
- According to preliminary experiences, Na^{18}F PET could be useful in staging and restaging of distant lung and bone metastases, thus replacing conventional ^{99m}Tc-MDP BS and assisting thoracic CT assessment and prognostic stratification.

Na^{18}F PET in bone metastases

- Na^{18}F PET and PET/CT accuracy is superior to BS and SPECT imaging, resulting in a higher number of detected lesions (both osteolytic and osteoblastic). Benign findings increase as well, but their recognition is generally not insidious.
- Hybrid systems allow better anatomical localization and morphological data about Na^{18}F findings.
- Conversely to ^{99m}Tc-MDP BS, Na^{18}F PET detection sensitivity seems to not be influenced by the anatomical location of the lesion.

Na^{18}F PET in bone metastases from prostate cancer

- Compared with BS and SPECT, Na^{18}F PET and PET/CT proved more accurate with significant changes in patients' therapeutic management.
- Preliminary results show that even if it detects numerically more lesions, Na^{18}F is less specific than ^{18}F-choline. Besides Na^{18}F can fail to image bone marrow-based metastases. With this regard ^{18}F-choline permits an earlier detection and assessment of response to hormonal therapy is also made possible, whereas a 'flare phenomenon' with Na^{18}F at the beginning of treatment could lead to misinterpretation.
- Na^{18}F PET imaging could be a complement to radiolabelled-choline PET/CT in staging high-risk patients (PSA higher than 10 ng/ml, T3, Gleason score >7, N+) with no evidence of skeletal involvement or when equivocal findings are encountered (typically sclerotic, noncholine-avid lesions) to better characterize them. It could be equally indicated in a restaging scenario if skeletal metastases are not detectable at radiolabelled-choline PET/CT and conventional imaging but signs of recurrence are present (i.e., PSA doubling time <6 months).

Na^{18}F PET in bone metastases from breast cancer

- A whole-body skeletal investigation by means of ^{99m}Tc-DP BS is clinically indicated in high-stage patients (III and IV), in symptomatic patients and/or with elevated bone or tumor markers (alkaline phosphatase, CEA, CA 15.3).
- In these scenarios Na^{18}F PET proved more accurate than ^{99m}Tc-DP BS in detecting both lytic and sclerotic BM, and impacting on patients' management by a preliminary 10%.
- [^{18}F]FDG PET is complementary to bone scintigraphy in surveying the skeleton for metastatic involvement as it has proven superior in detecting lytic and intramedullary metastases, but unable to demonstrate sclerotic lesions.

Executive summary (cont.)

Na^{18}F PET in bone metastases from breast cancer (cont.)

- Potential indications to Na^{18}F PET imaging could be preoperative staging of high-risk patients with a locally advanced tumor and a [^{18}F]FDG PET/CT negative for distant metastases. During follow-up Na^{18}F PET/CT might be equally indicated if patients are clinically symptomatic, with negative [^{18}F]FDG PET and conventional imaging and elevated bone remodeling or tumor markers.

Na^{18}F PET in bone metastases from lung cancer

- With respect to skeletal disease [^{18}F]FDG PET showed a sensitivity similar to BS, but a higher specificity (98% versus 61%). Its sensitivity decreases when osteoblastic metastases are present.
- Compared with Na^{18}F PET and reference methods (MRI and follow-up) the extent of metastatic bone disease is significantly underestimated with ^{99m}Tc-DP BS and SPECT. Furthermore, with regard to skeletal staging Na^{18}F PET proved a higher accuracy than [^{18}F]FDG PET/CT.
- In locally advanced non-small-cell lung cancer and small-cell lung cancer lung cancer a whole-body Na^{18}F PET/CT could assist [^{18}F]FDG PET imaging in preoperative staging if no BM have been detected but the risk is deemed high on a clinical basis.

be equally indicated in a restaging scenario if skeletal metastases are not detectable at radiolabeled-choline PET/CT and conventional imaging but signs of recurrence are present (i.e., PSA doubling time <6 months). In locally advanced NSCLC a whole-body Na^{18}F PET/CT could assist [^{18}F]FDG PET imaging in preoperative staging if no BM have been detected, but the risk is deemed high on a clinical or biochemical basis. Moreover, Na^{18}F PET/CT would be particularly useful in bronchioloalveolar carcinoma since it is often characterized by mild or no [^{18}F]FDG uptake. In small-cell lung cancer, Na^{18}F PET/CT could be indicated at staging for confirmation of limited disease.

As far as breast cancer is concerned potential indications to Na^{18}F PET imaging could be preoperative staging of high-risk patients with a locally advanced tumor and a [^{18}F]FDG PET/CT negative for distant metastases. During follow-up Na^{18}F PET/CT might be equally indicated if patients are clinically symptomatic, with negative [^{18}F]FDG PET and conventional imaging and elevated bone remodeling or tumor markers.

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- ▪▪ of considerable interest

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