

REVIEW

PET and PET/CT imaging of skeletal metastases

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Abstract

Bone scintigraphy augmented with radiographs or cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), has remained the commonest method to diagnose and follow up skeletal metastases. However, bone scintigraphy is associated with relatively poor spatial resolution, limited diagnostic specificity and reduced sensitivity for bone marrow disease. It also shows limited diagnostic accuracy in assessing response to therapy in a clinically useful time period. With the advent of hybrid positron emission tomography (PET)/CT scanners there has been an increasing interest in using various PET tracers to evaluate skeletal disease including [¹⁸F]fluoride (NaF) as a bone-specific tracer and [¹⁸F]fluorodeoxyglucose and [¹⁸F]choline as tumour-specific tracers. There is also early work exploring the receptor status of skeletal metastases with somatostatin receptor analogues. This review describes the potential utility of these tracers in the assessment of skeletal metastases.

Keywords: [¹⁸F]Fluoride; [¹⁸F]FDG; [¹⁸F]choline; [⁶⁸Ga]DOTATOC; positron emission tomography; skeletal metastases.

Introduction

Skeletal metastases are common in many cancers and 70% of patients with breast and prostate cancer have evidence of skeletal involvement at post mortem^[1]. Significant morbidity may result from skeletal metastases including pain, pathological fracture, spinal cord compression, bone marrow suppression and hypercalcaemia. In some patients with metastatic skeletal disease, survival may be relatively long (e.g. 24 and 20 months median survival in breast and prostate cancer, respectively)^[2]. Metastatic skeletal disease therefore has a significant effect on health care resources. Clinical management is highly dependent on the diagnosis and follow-up of patients with skeletal metastases and imaging techniques have traditionally played a major role in skeletal evaluation.

Historically, conventional bone scintigraphy, using technetium-99m-labelled diphosphonates, (e.g. [^{99m}Tc]methylene diphosphonate (MDP)) has been most commonly used. However, more recent improvements and development of other modalities including multidetector computed tomography (CT), whole-body magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT, has led to their greater use in skeletal disease. There has been particular interest in PET techniques as it is possible to use bone-specific tracers such as

[¹⁸F]sodium fluoride (NaF) or tumour-specific tracers such as [¹⁸F]fluorodeoxyglucose (FDG) and [¹⁸F]fluorocholine (FC) to evaluate different aspects of the biology of skeletal metastases and there is some early work investigating the receptor status of bone metastases with labelled somatostatin analogues such as [⁶⁸Ga]DOTA-D-Phe¹-Tyr³-octreotide (DOTATOC).

[¹⁸F]Fluoride (NaF) PET

Although the ^{99m}Tc-labelled diphosphonates were developed in the 1970s and 1980s, the positron emitter, NaF, was first described in 1962^[3]. As a result of the improvement in image quality following the development of clinical PET scanners in the 1990s and subsequently PET/CT scanners in the 2000s, there has been renewed interest in using NaF to assess the skeleton.

It is likely that the skeletal clearance of NaF is similar to the ^{99m}Tc-labelled diphosphonates, depending on blood flow and osteoblastic activity^[4]. Evidence suggests that NaF undergoes high first pass extraction approaching 100% in bone at physiological blood flow rates, therefore allowing the estimation of bone blood flow^[5]. There is subsequent chemisorption into bone crystals with the formation of fluoroapatite and this process occurs preferentially at sites of actively mineralising bone^[6,7]. Unlike

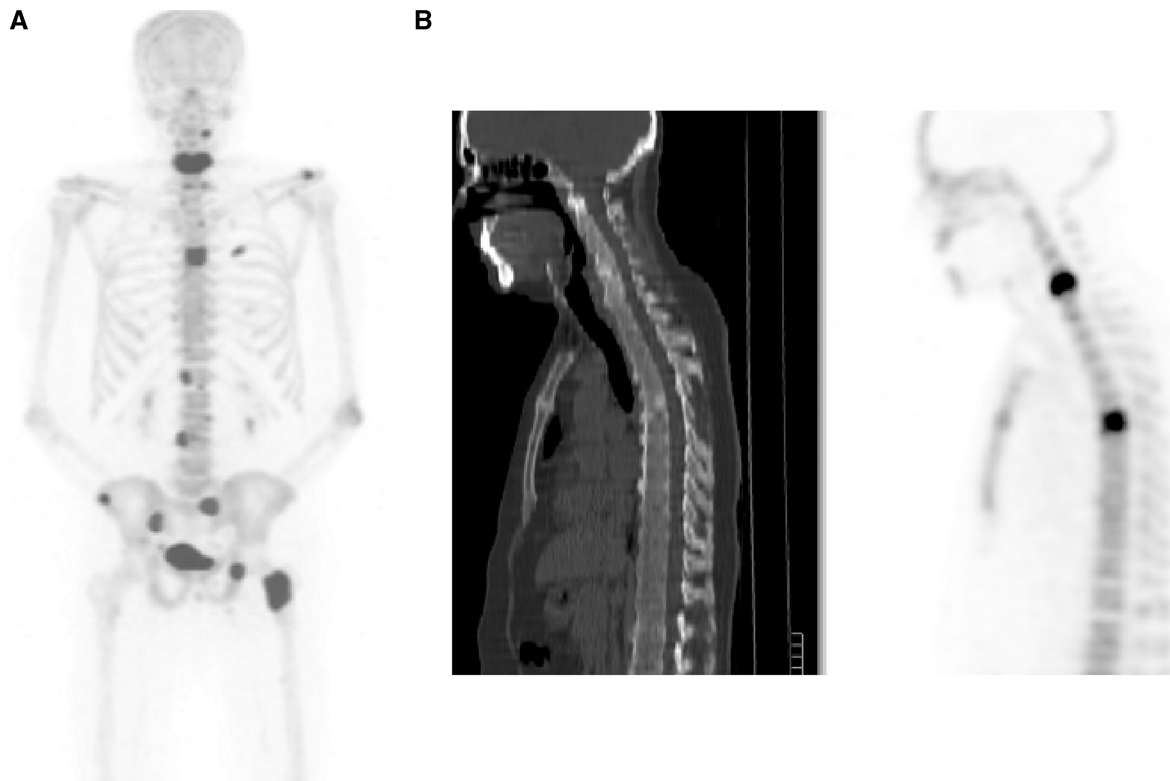


Figure 1 NaF-PET. (A) Maximum intensity projection (MIP) and (B) PET and CT sagittal images of a patient with metastatic prostate cancer with metastases in the cervical, thoracic and lumbar spine, left second rib, pelvis and left upper femur.

diphosphonates, NaF is not protein bound and as skeletal uptake is rapid, it is possible to obtain scans as soon as 1 h after injection^[8]. High lesion to background ratios are obtained with NaF at 1 h in both osteoblastic and osteolytic metastases^[9]. An injected activity of 250 MBq allows high quality skeletal images on modern PET imaging systems with a radiation dose to the patient of approximately 6 mSv^[10] (Fig. 1).

NaF-PET was prospectively investigated in 44 patients with prostate, thyroid and lung cancer, comparing it with [^{99m}Tc]MDP planar bone scintigraphy^[11]. Reference methods included radiographs, CT, MRI and iodine-131 scintigraphy. NaF-PET was more accurate in detecting skeletal metastases than bone scintigraphy (area under receiver operating curve (ROC) curves 0.99 and 0.64, respectively) on a lesion-by-lesion basis, but on a patient-by-patient basis the differences were smaller. Forty-four patients were correctly defined as positive for skeletal metastases by NaF-PET compared with 42 with planar bone scintigraphy. The improved accuracy for individual lesions appeared to depend on anatomical site with the greatest advantage for NaF seen in the spine and pelvis. The sensitivity of NaF-PET was the same for osteoblastic prostate cancer metastases as it was for osteolytic metastases from lung and thyroid carcinomas. NaF-PET was also more specific than bone scintigraphy, with the ability to correctly categorise a greater number

of benign and malignant lesions. Of 108 lesions present on NaF-PET and bone scintigraphy, NaF-PET correctly categorised 105 (45 metastases, 60 benign), whereas bone scintigraphy correctly categorised 87. The authors proposed that the superior spatial resolution and resultant anatomical localisation with NaF-PET was responsible for better specificity and no quantitative comparison was made.

A similar subsequent study from the same group investigated NaF-PET in patients with breast cancer^[12]. NaF-PET showed a better diagnostic accuracy than planar bone scintigraphy on a lesion-by-lesion basis (area under ROC 0.99 and 0.74, respectively) and patient-by-patient basis (1.0 and 0.82, respectively). A change in management resulted from detection of metastases in 4 out of 34 patients with NaF-PET compared with the management strategy that would have been used with bone scintigraphy.

A limitation of these studies was that for bone scintigraphy, only planar images were acquired with no single photon emission-computed tomography (SPECT) and so there was an inherent advantage for the PET technique in which tomographic images are routine. This was addressed in a subsequent study of 53 patients with lung cancer where NaF-PET was compared with planar bone scintigraphy augmented with SPECT of the spine^[13]. Of 12 patients with bone metastases, there

were 6 false-negatives with planar scintigraphy, 1 with planar scintigraphy augmented with spinal SPECT and no false-negatives with NaF-PET. There was not a significant difference in the area under the ROC curve between SPECT and PET (0.944 and 0.993, respectively). Clinical management was changed in 5 patients as a result of the SPECT findings and in 6 as a result of the PET findings. These results suggested that the differences between [^{99m}Tc]MDP and NaF imaging were mainly technical rather than the result of pharmacokinetic differences in the tracers. A subsequent larger study of 103 patients with lung cancer compared NaF-PET with both planar bone scintigraphy and planar scintigraphy augmented with SPECT of the spine^[14]. Of 33 patients with bone metastases, there were 13 false-negatives with planar bone scintigraphy, 4 with SPECT and 2 with PET. A statistical difference was found in the areas under the ROC curves (0.771, 0.875 and 0.989, respectively). A change in management resulted in 8 patients due to SPECT and in 10 due to PET. A cost-effectiveness analysis was also undertaken that showed that the additional cost for each correctly diagnosed patient was 1272 euros for SPECT and 2861 euros for PET but with the potential to improve patient outcomes in the latter.

In a more recent study, NaF-PET was compared with FDG-PET/CT and planar bone scintigraphy in 126 patients with non-small cell lung cancer^[15]. In this group of patients more skeletal metastatic lesions were detected with FDG-PET/CT than with NaF-PET overall (53 vs 40) but there were 4 patients in whom metastases were only detected with NaF-PET. Although FDG-PET/CT was more accurate than bone scintigraphy, it remains uncertain whether it can also replace NaF-PET in staging the skeleton in lung cancer in this particular scenario.

In one of the first studies evaluating hybrid NaF-PET/CT in cancer patients with a variety of primary tumours, it was found that the additional morphological information from the CT component of the hybrid scans significantly improved specificity compared with NaF-PET alone^[16]. Ninety-four of the 111 metastases corresponded to lytic or sclerotic changes on the CT component and 16 out of the remaining 17 lesions showed normal CT appearances. In only one metastasis did PET/CT falsely suggest a benign lesion. It was also found that the low-dose CT component was of sufficient quality so that a full diagnostic CT was not required for correlative purposes in most lesions.

A subsequent study from the same group compared planar bone scintigraphy, SPECT, NaF-PET and NaF-PET/CT in 44 patients with prostate cancer^[17]. SPECT was more sensitive and specific than planar scintigraphy and in turn, NaF-PET was more sensitive than SPECT. NaF-PET/CT was also more sensitive and specific than planar and SPECT bone scintigraphy. As in the previous study, the additional morphological information from the CT component of PET/CT led to an increase in

specificity compared with NaF-PET alone and resulted in fewer equivocal interpretations. Three of the 25 patients with a new diagnosis of prostate cancer had bone metastases detected with NaF-PET/CT that were not detected with planar scintigraphy, leading to management with systemic rather than local therapy.

In view of the different mechanisms of uptake of NaF and FDG in skeletal metastases, some researchers have postulated combining the two tracers to optimise diagnostic information^[18,19]. In the earlier study, FDG and NaF were injected simultaneously (300 MBq and 100MBq, respectively) and compared with a control group who only had FDG administered. Correlation with other imaging findings occurred in 88% of the combined group and 78% of the control group. This was not a statistically significant difference but interobserver agreement in lesion localisation improved from 0.74 in the control group to 0.95 in the combined group. To some extent the better skeletal or soft tissue localisation that resulted from this study has been superseded by combined PET/CT. The later study compared FDG, NaF and combined FDG/NaF-PET/CT scans in patients with varied cancers. Development of an image-processing algorithm in a mouse model allowed images of only the combined tracer uptake in the skeleton to be produced. It was found that these corresponded well with the NaF-PET scans performed as a separate acquisition. This method allowed separate interpretation of the FDG and NaF distribution, even though the tracers were injected together.

Comparisons have also been made in prostate cancer between NaF and the tumour-specific agent reflecting cell membrane metabolism, FC. An initial study of 38 men (17 preoperative and 21 postoperative, with suspected recurrence)^[20] was performed. Sensitivity, specificity and accuracy for NaF for the diagnosis of bone metastases was 81%, 93% and 86%, respectively and for FC, 74%, 99% and 85%. The differences in specificity were statistically significant in keeping with the tumour-specific nature of FC uptake compared with relatively non-specific bone uptake of NaF. FC-PET led to a change in management in 2 patients with bone metastases not detected by NaF. This was assumed to be due to detection of metastases in the bone marrow before an osteoblastic response was visible. Although more metastases were detected with NaF in other patients, this did not change management. It was also noted that sclerotic lesions with higher density as measured by CT Hounsfield units (HU), tended to be negative with both tracers and there was a negative correlation between standardised uptake value (SUV) and HU measurements. A subsequent study explored the relationship of FC with CT density further^[21]. It was found that an HU level >825 was associated with absence of uptake and that most of these patients were receiving hormone therapy. This suggested that the lesions may have been rendered metabolically inactive by the hormone therapy and

that a healing sclerotic response was responsible for the high density on CT. A longitudinal study would obviously be of interest in exploring this relationship further.

At the time of writing, a multicentre study is underway in the United States to assess the use of NaF-PET in routine use of skeletal staging in cancer^[22]. This study proposes to compare NaF-PET/CT with [^{99m}Tc]MDP bone scintigraphy in 500 patients with breast, prostate and non-small cell lung cancer. This large collaborative project will be of great interest in answering any remaining questions regarding skeletal staging with NaF.

In addition to using NaF-PET for skeletal staging, there are some early data suggesting that NaF can be used to assess treatment response in metastatic prostate cancer. A small pilot study of patients with metastatic prostate cancer confined to the skeleton, being treated with [²²³Ra]chloride, used NaF-PET at 6 and 12 weeks^[23]. Although serial NaF-PET scans showed no subjective difference in uptake, it was possible to differentiate responders from non-responders, as determined by prostate-specific antigen response, by measurement of serial SUVs. It remains to be seen whether this quantitative approach works as well in other cancers and with different types of therapy.

[¹⁸F]Fluorodeoxyglucose

The mechanism of uptake of FDG into bone metastases differs from NaF and accumulation is assumed to be into viable, metabolically active tumour cells rather than reactive bone. As uptake of FDG is not restricted to tumour involving the skeleton, it has the advantage of demonstrating both skeletal and soft tissue metastases in patients with cancer.

A few reports specifically describe the use of FDG-PET in the investigation of bone metastases and compare with conventional [^{99m}Tc]MDP scintigraphy. When comparing FDG-PET with [^{99m}Tc]MDP scintigraphy in 110 patients with small cell lung cancer, Bury *et al.*^[24] found a similar sensitivity on a patient-by-patient basis (19 out of 21 with bone metastases). However, FDG-PET correctly confirmed the absence of skeletal involvement in a much larger proportion of cases (87 out of 89 compared with 54 out of 89). This is probably because FDG activity is more specific for metastatic involvement compared with [^{99m}Tc]MDP, where coincidental benign skeletal lesions may cause false-positive interpretation of metastases.

A similar study compared FDG-PET and bone scintigraphy and FDG-PET demonstrated a higher sensitivity and specificity on a lesion-by-lesion basis^[25]. Although the apparent improvement in sensitivity with FDG may be partly due to the routine acquisition of tomographic images that were not available for [^{99m}Tc]MDP, it is also likely that the observed differences are due to the fact that by imaging tumour metabolism directly with FDG, detection may occur at an earlier stage when only the



Figure 2 FDG-PET MIP image of a patient with stage IV Hodgkin disease shows nodal disease above and below the diaphragm (arrows), spleen (curved arrow) and bone and bone marrow involvement (arrowheads).

bone marrow is involved and before an identifiable bone reaction, required for abnormal [^{99m}Tc]MDP accumulation, has taken place.

In lymphoma, where skeletal involvement is often predominantly marrow-based, it has been found that FDG-PET is more sensitive than conventional bone scintigraphy^[26] and it has been suggested that it might be possible to replace bone marrow biopsy as a staging procedure in these patients^[27,28] (Fig. 2). There are obvious potential advantages in sensitivity with FDG-PET in this respect when marrow involvement spares the iliac crest, but it is unlikely that FDG-PET could completely replace bone marrow biopsy, particularly where there is microscopic involvement or in cases with low-grade lymphomas that accumulate FDG less avidly. After chemotherapy or granulocyte colony stimulating factors, it is not uncommon for the bone marrow to show a diffuse increase in activity that is reactive, a factor that may limit the use of this method in assessing disease response in bone marrow^[29].

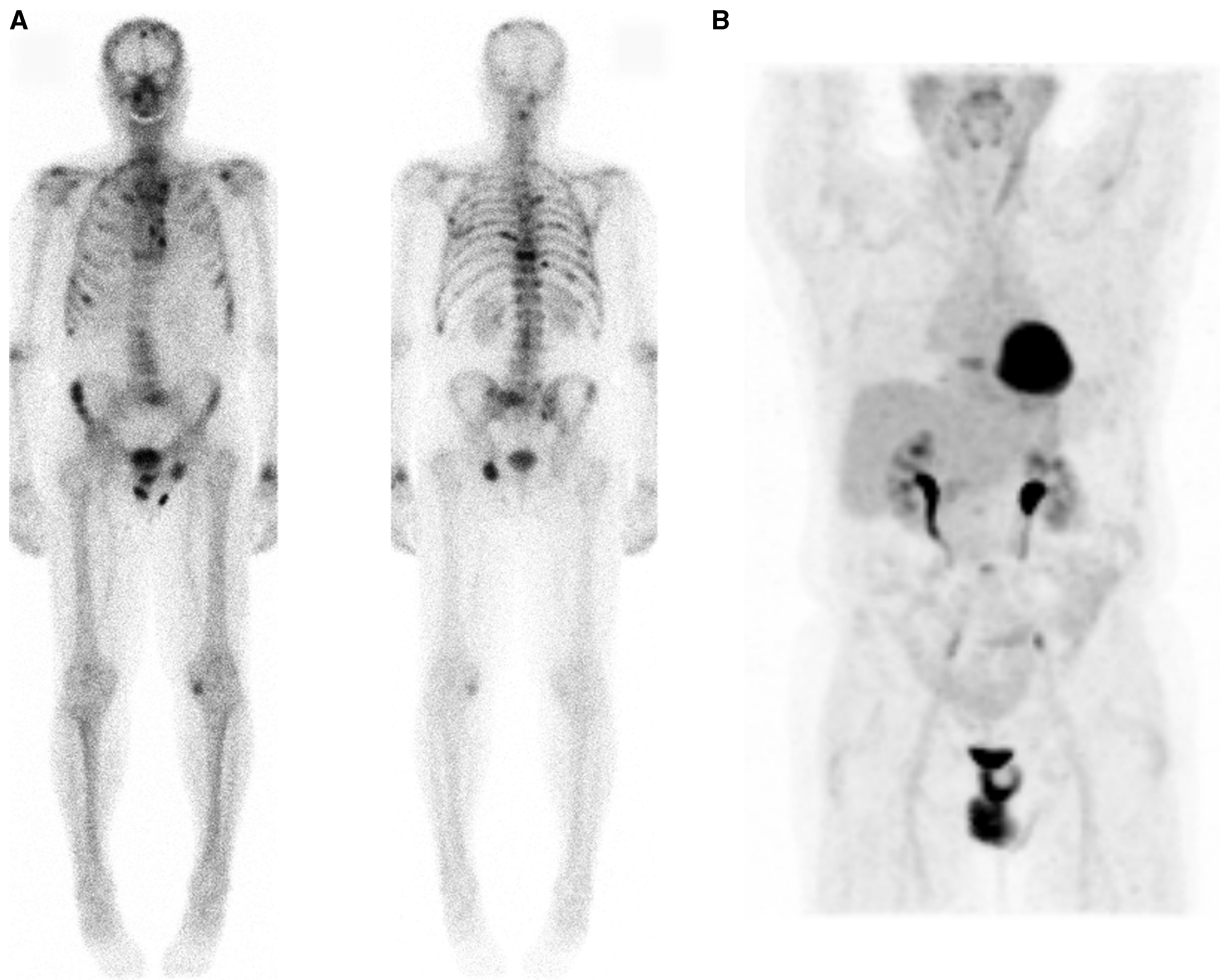


Figure 3 (A) [^{99m}Tc]MDP bone scan and (B) FDG-PET MIP image of a patient with metastatic prostate cancer with osteoblastic skeletal disease. The bone scan shows a greater number of metastases and a greater lesion to background ratio than that seen on the FDG-PET scan.

Much of the literature describing PET and skeletal metastases compares bone scintigraphy with FDG-PET in patients with breast cancer^[30–32]. Most of the studies indicate that FDG-PET is more accurate, although some show this is predominantly because of improved specificity rather than sensitivity^[30,31]. It would appear that the sensitivity for lytic metastases is better with FDG-PET but that osteoblastic metastases are less FDG avid and may even be less sensitive compared with bone scintigraphy in this subgroup^[32–39]. Although there seems little doubt that lytic and sclerotic metastases behave differently with regard to FDG uptake and that osteoblastic breast cancer lesions may be associated with a better prognosis^[33], prior treatment probably influences this relationship^[36,40]. Other tumours for which FDG-PET or PET/CT have shown superior diagnostic accuracy compared with bone scintigraphy include thyroid cancer^[41], nasopharyngeal carcinoma^[42] and oesophageal carcinoma^[43]. However, one study found no advantage of FDG-PET over bone scintigraphy in a variety of tumour types^[44] and another found bone scintigraphy with SPECT more

sensitive in breast cancer because of the poor sensitivity of FDG-PET for osteoblastic lesions^[39].

Although FDG-PET often detects more skeletal disease than conventional bone scintigraphy, this is not a universal finding in all cancers. There have been a number of reports on the use of FDG in prostate cancer, a tumour in which skeletal metastases are usually osteoblastic in nature, in which a lower sensitivity has been found in the skeleton compared with conventional bone scintigraphy^[45,46] (Fig. 3).

The reason for a greater avidity for FDG in lytic metastases is unknown but may reflect increased glycolysis or expression of glucose membrane transporters. It might also be expected for these more aggressive metastases to become hypoxic, another factor that is known to increase FDG accumulation^[47]. In contrast, the relative acellularity that may occur in sclerotic metastases, with comparatively smaller volumes of tumour tissue in individual lesions, may influence the degree of FDG uptake whilst; the predominant sclerotic process leads to high uptake of bone-specific tracers such as NaF or MDP.

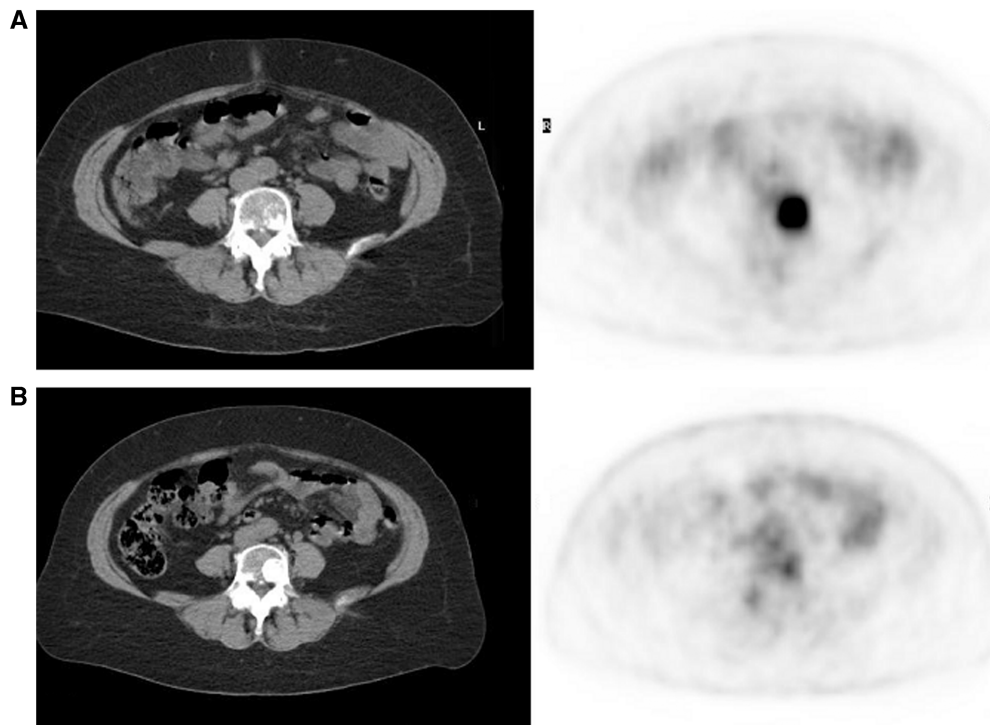


Figure 4 FDG-PET/CT scans before (A) and after (B) 2 cycles of chemotherapy in a woman with metastatic breast cancer. A mixed lytic/sclerotic metastasis at baseline shows increased sclerosis and reduced FDG uptake after treatment indicating a good metabolic response.

There are as yet little data available to determine the value of combined FDG-PET/CT, compared with FDG-PET alone, in bone metastases but at least one study suggests a complementary role for the PET and CT components of the examination by finding a much higher positive predictive value (PPV) when PET and CT findings are concordant (98%) compared with PET positive/CT negative discordant cases (PPV=61%) and PET negative/CT positive cases (PPV=17%)^[48]. A further study showed an improved specificity in the spine of patients with different types of primary tumour when using FDG-PET/CT compared with FDG-PET alone^[49].

By reflecting tumour cell viability in bone metastases directly, FDG-PET has the potential to monitor therapy response more accurately than bone-specific tracers that reflect the osteoblastic bone reaction. In a study of 24 women with bone-predominant, advanced breast cancer it was shown that quantitative changes in FDG-PET correlated with overall clinical assessment of response and changes in tumour markers^[50] (Fig. 4). It is possible that changes in FDG activity to therapy may also be prognostic. A retrospective study of breast cancer patients with bone-predominant disease showed that a high baseline SUV was associated with a shorter time to a skeletal-related event and that non-responders had a shorter time to progression^[51].

Somatostatin receptor PET imaging

Because there is some evidence of therapeutic efficacy of somatostatin analogues in the treatment of androgen-independent prostate cancer^[52], there is a requirement for a non-invasive imaging technique to measure somatostatin receptor density in metastatic disease and to monitor response to treatment. A preliminary study of 20 patients with advanced prostate cancer compared conventional bone scintigraphy with [⁶⁸Ga]DOTATOC PET/CT^[53]. Only 30% of metastases in the 13 patients with multifocal disease showed uptake of [⁶⁸Ga] DOTATOC with only 2 patients showing the same number of metastases. Of the 6 patients with a scintigraphic superscan, 1 showed diffuse abnormality, 3 showed some focal abnormalities and 2 showed no correlation with [⁶⁸Ga]DOTATOC PET/CT. One patient with a neuroendocrine prostate tumour showed no PET abnormality. As this somatostatin analogue predominantly targets receptor subtypes 2 and 5, the authors suggested that future research should concentrate on prostate cancer specific somatostatin receptor subtypes 1 and 4.

Conclusion

A number of PET radiopharmaceuticals are available or are being developed that have the potential to improve

diagnostic accuracy and ability to monitor treatment response in skeletal metastases. Different aspects of tumour biology can be assessed, including osteoblastic activity (NaF), tumour cell metabolism (FDG and FC) and tumour cell receptors (labelled somatostatin receptor analogues). The improvement in imaging skeletal metastases is further enhanced with hybrid imaging. PET/CT has already shown some advantages over PET and with the future development of PET/MRI, there is potential for further advances in non-invasive assessment of the skeleton and bone marrow.

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