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Miscellaneous Cancers (Lung, Thyroid, Renal Cancer, Myeloma, and Neuroendocrine Tumors): Role of SPECT and PET in Imaging Bone Metastases

Sue Chua, MBBS, BSc, MRCPCH, FRCR,* Gopinath Gnanasegaran, MD,† and Gary J.R. Cook, MD, FRCR*

In this review, we assess the current role of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in the imaging of skeletal metastatic disease from a miscellaneous group of malignancies, including lung, thyroid, and renal carcinomas; multiple myeloma; and neuroendocrine tumors, and consider how recent advances may enhance their effectiveness in this area. Bone scintigraphy using technetium-labeled diphosphonates has long been the mainstay of functional imaging of bony metastases, but is of limited value in myeloma and aggressive osteolytic metastases, and has the limitation of relatively poor specificity. SPECT, as a tomographic imaging technique, produces three-dimensional images of tracer distribution from multiplanar images. Its application to bone scintigrams greatly aids accurate anatomic localization and sensitivity in detection of foci of tracer uptake. SPECT can equally be applied to scintigrams using radiotracers, which are specific for particular groups of tumors, such as somatostatin analogs for neuroendocrine tumors. The advent of combined SPECT/computed tomography (CT) systems has further enhanced the accuracy of SPECT in all these malignancies. PET uses positron-emitting radiotracers and achieves a higher spatial resolution than single-photon imaging. Its high resolution and coverage of the entire body have made it a highly effective technique for the evaluation of skeletal metastatic disease, particularly when combined with CT. ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT now forms part of routine staging for many carcinomas, such as non–small-cell lung carcinomas, and may obviate the need for routine staging scintigraphy in these patients. As uptake of the most common PET radiotracer, ^{18}F-FDG, is dependent on the increased cellular metabolism of most tumors, it may enable earlier detection of metastatic foci than bone scintigraphy, which relies on detecting an osteoblastic response. Another significant advantage of ^{18}F-FDG-PET is that it can detect soft-tissue components of metastases, which is particularly important in aggressive osteolytic metastases. The effectiveness of ^{18}F-FDG-PET is limited in slow-growing tumor types, but ^{18}F-sodium fluoride, a bone radiotracer that can detect early osteoblastic changes, shows promise in this area. Bony metastases from many neuroendocrine tumors can be detected with a high degree of specificity by PET using somatostatin analogs. Other novel and often highly specific radiotracers are under evaluation, which will further enhance the diagnostic capability of PET. The true potential of PET in this group of malignancies is gradually unfolding, although studied series of patients remain generally small and much further evaluation of its role is required.
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*Department of Nuclear Medicine and PET, The Royal Marsden Hospital NHS Foundation Trust, Surrey, United Kingdom.
†Department of Nuclear Medicine and PET, Guy's and St. Thomas Hospital NHS Foundation Trust, London, United Kingdom.
Address reprint requests to Sue Chua, MBBS, BSc, MRCPCH, FRCR, Department of Nuclear Medicine, PET, and Radiology, The Royal Marsden NHS Foundation Trust, Downs Rd, Sutton, Surrey SM2 5PT, United Kingdom. E-mail: sue.chua@rmh.nhs.uk

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This review looks at the application of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) to the evaluation of the skeletal metastases of a miscellaneous group of tumors (lung, renal, and thyroid carcinomas and neuroendocrine tumors), which frequently metastasize to bone, and multiple myeloma. Metastatic bony disease from these cancers often poses significant problems for the oncologist, usually mandating a radical change to the therapeutic approach, and in myeloma the accurate assessment of bony lesions is particularly important for minimizing the of risk of pathologic fracture. From a clinical point of view, both SPECT and PET can be valuable adjuncts to routine pretreatment staging, especially in the further investigation of patients with suspicious findings on bone scan or skeletal survey, and can also play a role in routine follow-up after therapy, the assessment of response and the detection of recurrence.

SPECT

Assessing metastatic skeletal involvement is frequently beyond the scope of plain-film radiography, and nuclear imaging in the form of bone scintigraphy has proved the mainstay of detection and characterization of skeletal metastases for over 40 years. The technique uses technetium-labeled diphosphonates and relies on detection of abnormal osteoblastic response elicited by the malignant cells. Bone scintigraphy offers the advantage of total body examination, low cost, and a high degree of sensitivity (the exception to this has been, in general, multiple myeloma, in which bone scintigraphs typically underestimate the amount of disease as myelomatous deposits are usually purely osteolytic). The major limitation of scintigraphy is its lack of specificity; many benign bone pathologies produce a hot spot on scintigraphy, which may not be distinguishable from a metastasis. Degree of avidity of uptake is of little help here, and the interpreter is reliant on the number of lesions and their location and distribution as a guide to making this judgment. An experienced interpreter can be quite specific for the presence of metastatic disease using these criteria but solitary skeletal lesions often remain indeterminate. SPECT has been shown to significantly improve the predictive value of bone scintigraphy, and can also be applied to scans with radiopharmaceuticals specific for particular tumors, such as iodine-131 (^{131}I) for differentiated thyroid carcinoma (DTC) metastases and ^{131}I or ^{123}I metaiodobenzylguanidine (MIBG) for neuroendocrine tumors. In one study, the addition of SPECT to bone scintigraphy improved diagnostic accuracy from 70.4% to 92%, and produced results almost comparable to magnetic resonance imaging (MRI) (97.7%).[1] One large study of bone SPECT used as an adjunct to planar bone scintigraphy showed an overall performance as follows: sensitivity 90.5%, specificity 92.8%, positive predictive value 73%, negative predictive value of 97.8%, and accuracy 92.4%.[2] In expert hands, the technique can approach the performance of whole-body MRI, which is generally considered the best imaging modality for studying metastasis to the vertebrae in particular.[3]

SPECT, as a tomographic imaging technique with computer-generated 3-dimensional images of tracer distribution, is particularly useful in evaluating the vertebral column, which is the most frequent site of bony metastasis.[2] Most metastases affect the posterior part of the vertebral body, particularly the posterolateral corner adjacent to the pedicle, whereas degenerative processes are more often associated with increased uptake in either the facet joints, laminae and transverse processes, or end plate. Localization of the exact site of a vertebral hot spot is therefore essential to its accurate characterization. Although SPECT accuracy is significantly higher than that of planar scintigraphy, there is still room for improvement of anatomic localization and characterization, a limitation that has now been addressed with the advent of combined SPECT/computed tomography (CT) systems that perform both functions on a single gantry and produce fused functional and anatomic data in a single imaging session.[4]

PET

PET can achieve a higher spatial resolution than that of single photon imaging, a factor that can be particularly helpful in interpreting subtle bony lesions. A drawback is that the uptake of the main tracer used, namely, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), is dependent on the higher glycolytic rates of most tumors compared with normal tissues.[5] This reduces the sensitivity of PET in the detection of metastases of slow-growing tumors, such as carcinoid tumors. It does, however, mean that uptake is directly dependent on the presence of tumor cells rather than the osteoblastic bone reaction as in the case of bone scanning, so that unlike the latter it can play a valuable role in myeloma.[5] It is especially effective in examining the pattern and position of subtle vertebral abnormalities. The addition of CT has significantly augmented the diagnostic accuracy of PET, such that PET/CT is now regarded as a highly effective technique for the evaluation of bony metastases. The only modality showing superior results in this scenario is whole-body MRI, which is still not widely available.[3] Bone scintigraphy and ^{18}F-FDG-PET should probably be considered as complementary investigations for the present, as some osteoblastic metastases may be more readily visualized on scintigraphy than by PET, although the clinical significance of PET negative metastatic deposits is unclear. Finally, ^{18}F-FDG-PET has proved valuable in the localization of equivocal skeletal lesions for biopsy.[6]

^{18}F-sodium fluoride (^{18}F-NaF) has been recognized as a highly sensitive radiotracer for skeletal imaging since the early 1970s,[7] but it has since been largely superseded by technetium-labeled radiotracers because the high energy of the annihilation photons produced by the decay of ^{18}F necessitated special scanners.[8] There is currently a resurgence in use of this compound, as its clinical utility as a PET radiotracer has become better recognized. In contrast to ^{18}F-FDG-PET, which is believed to be less sensitive in detecting osteoblastic than osteolytic metastases, PET using ^{18}F-NaF appears to be equally sensitive in detecting both,[9] and can apparently identify extremely early osteoblastic changes in response to metastatic deposits. Little data has been published, which directly com-

pare ^{18}F-NaF and ^{18}F-FDG, although there is a suggestion that ^{18}F-NaF may be superior in detecting bony metastases from tumors with low FDG avidity, such as some thyroid carcinomas.[10] As with ^{18}F-FDG-PET/CT, ^{18}F-NaF PET/CT has shown higher specificity than PET alone when applied to a bony metastases from a variety of primary tumors.[11] Cost and reimbursement issues mean that ^{18}F-NaF PET and PET/CT are not yet widely used in clinical practice, usually being reserved for patients with a high clinical suspicion of skeletal metastases but a negative bone scan. Some experts suggest, however, that the technique may eventually replace bone scintigraphy in its current role.[12]

Role of SPECT and PET in Imaging Bone Metastases in Miscellaneous Cancers

Lung Cancer

Lung cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer deaths in both sexes. Skeletal metastatic disease is present in 20%-30% of patients at initial diagnosis[9] and usually excludes curative therapy as well as carrying the risk of pathologic fracture. Exclusion of bony metastases is particularly important in patients with non–small-cell lung cancer (NSCLC), which is potentially curable by surgery. Evaluation for metastases has conventionally been performed by planar bone scintigraphy using technetium-99m methylene diphosphonate (^{99m}Tc-MDP) or similar compounds. One study carried out in 2004 determined that without skeletal scintigraphy 14%-22% of a group of lung cancer patients would have undergone unnecessary surgery or neoadjuvant therapy.[13] New guidelines mandating ^{18}F-FDG-PET in NSCLC means that it has now largely replaced scintigraphy as a staging tool in this disease, where it is available.

SPECT

Planar bone scintigraphy alone has been shown to be of lower sensitivity than MRI and CT in detecting osteolytic and vertebral column metastases in particular.[14] In lung cancer, an advantage associated with its ability to image the entire skeleton is that it can demonstrate specific changes of hypertrophic pulmonary osteoarthropathy in patients with distal limb pain. SPECT allows for more accurate anatomic localization of areas of increased uptake, and tomographic reconstructions permit differentiation of structures that would otherwise overlap on planar images.[15] In a study of SPECT analysis of suspicious vertebral lesions, extension of an area of increased uptake from the vertebral body into the pedicle was found to be a useful sign in predicting malignancy.[2] Other pathologic conditions centered on the disc space and vertebral body, which may be confused with metastases include spondylodiscitis, vertebral body fracture, and degenerative disease. Fractures may be visualized on SPECT as horizontally orientated linear foci of increased uptake within the vertebral body, while in discitis tracer uptake is centered about the disc space and adjacent vertebral bodies and has a vertical orientation.[15] As noted above, metastases virtually always begin within the vertebral body, so that lesions confined to the pedicle without involvement of the vertebral body proper are seldom malignant (this appearance is more commonly produced by fractures or osteoid osteoma).[15] Routine SPECT scanning as an adjunct to scintigraphy has been recommended for newly diagnosed cases of lung cancer as it is cost-effective and improves the accuracy of scintigraphy, changing clinical management in around 9% of patients in a prospective study.[9] Although ^{18}F-FDG-PET may be more effective in absolute terms, the high initial setup costs mean that SPECT may be more practicable and cost-effective in some circumstances.[16] Integrated SPECT/CT systems are now available that can provide fused functional and anatomic data in a single imaging session. One study has assessed the additional diagnostic value of SPECT/CT in the evaluation of bony metastases from a number of cancers of which many cases were primary lung cancers.[17] It was found that fused images led to an improved ability of reviewers to differentiate benign lesions from metastases that were difficult to differentiate on scintigraphic and CT images viewed side by side. An additional benefit of fused images was that spatially registered SPECT and CT images could be used to generate attenuation maps to correct attenuation errors in SPECT images.

PET

^{18}F-FDG-PET/CT is now generally regarded as the most effective imaging tool for the whole-body evaluation of NSCLC (Fig. 1), and recent studies suggest it is equally effective in small cell carcinoma.[18] As it detects the presence of tumor by increased cellular metabolic activity, rather than, like scintigraphy, indirectly through increased osteoblastic activity, it may enable earlier detection of metastatic foci.[19] In a direct comparative study, accuracy of PET and scintigraphy in the detection of bony metastases in newly diagnosed lung cancer were 94% and 85%, respectively, with sensitivity values of 91% and 75%, and specificity of 96% and 95%, respectively.[20] This suggests that ^{18}F-FDG-PET could replace the staging role of bone scintigraphy. The vast majority of bony metastases from all types of lung carcinomas show a lytic pattern, usually making them readily detectable on both the CT and PET components of the study. It has been noted that CT-positive but PET-negative lesions are significantly more prevalent post-therapy.[5] These may appear osteoblastic, which presumably reflects a reparative effect after treatment.

The vertebral column is the most commonly affected region in patients with lung cancer metastases, lesions usually originating in the vertebral body.[21] Vertebral metastases are especially liable to be undetected by planar bone scintigraphy. One study focusing on this region showed PET to change clinical management over scintigraphy alone in 11% of patients with vertebral metastases.[9] MRI remains of particular value at this location in the detection of tumor extension to the intervertebral neural foramina and the spinal cord primarily because of its higher contrast resolution than CT.[22]

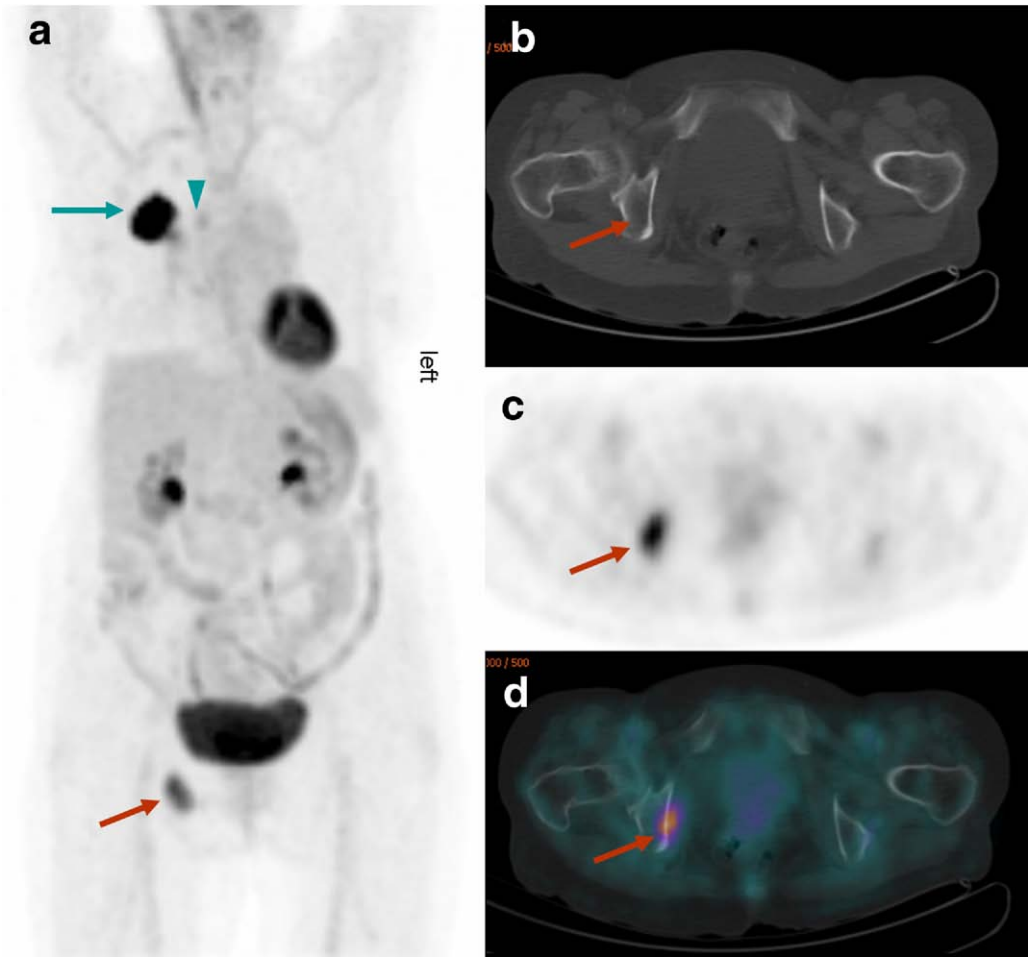

Figure 1 An 84-year-old woman with a T2N2M0 non-small-cell lung carcinoma on initial staging contrast-enhanced CT. Preoperative staging ^{18}F-FDG-PET/CT showed a solitary FDG-avid bony metastasis in the right ischium, extending to the inferior pubic ramus (red arrows). Structurally, this was occult on CT. The T2 (blue arrow) N2 (precarinal nodes, blue arrow head) tumor was metabolically active (a) maximum intensity projection (MIP), (b) transaxial CT image from the PET/CT, (c) transaxial PET image, (d) transaxial fused PET/CT image.

In selected lung cancer patients with one or a few metastases amenable to 3-dimensional conformal radiotherapy ^{18}F-FDG-PET/CT has been shown to be an effective tool in gross tumor volume delineation.[23] Few studies have addressed the role of ^{18}F-NaF PET in lung cancer. In a study of NSCLC patients assessing the technique (in combination with MRI for equivocal lesions) against planar scintigraphy, ^{18}F-NaF PET/MRI altered clinical management in 9% of all patients in the series and in 50% of those with bony metastases.[9] It was noted that 2 SPECT acquisitions were necessary for assessment of the entire vertebral column so the total acquisition time was 120-150 minutes for scintigraphy/SPECT, as compared with 72-84 minutes for PET. ^{18}F-NaF-PET was shown in another study to be significantly more accurate in the evaluation of bone metastases in lung cancer than either planar bone scintigraphy alone or scintigraphy combined with SPECT, changing management over the latter techniques in 9.7% of patients, albeit at a higher cost.[24]

Because of its high degree of accuracy and convenience as a "one-stop" whole-body imaging tool, ^{18}F-FDG-PET/CT is likely to dominate the evaluation of skeletal metastases from lung carcinoma in the near future. ^{18}F-NaF PET/CT is likely also to find a niche role, especially in the setting of a high clinical suspicion of skeletal disease but ^{18}F-FDG-PET/CT negativity, but planar scintigraphy may in future be relegated to a much more minor role in centers in which PET is available.

Thyroid

Bone metastases from DTC (papillary and follicular carcinomas) occur in 2%-13% of patients.[25] They are more frequent in follicular carcinoma (7%-28% incidence) compared with papillary carcinoma (1.4%-7%).[26] When bone metastases are present, the overall 10 years survival rate is around 13%-21%,[25] which compares with an overall 10-year survival of over 80% in these cancers. The amount of metastatic bony disease and its responsiveness to radioactive iodine correlate directly with survival.[27-29] Metastatic lesions from these cancers are typically osteolytic and may significantly impact on patient quality of life through bone pain, fractures, and, occasionally, spinal cord impingement.

SPECT

As bone scintigraphy is reliant on the presence of detection of a perimetastatic osteoblastic reaction, which is often absent in osteolytic metastases, a relatively high proportion of false-negative results occur in differentiated thyroid cancer.[30]

Tumor cell imaging by ^{131}I or ^{123}I whole-body scan (WBS) is a more specific and sensitive technique than ^{99m}Tc-MDP but is only effective for well-differentiated, sodium/iodide symporter-positive thyroid tumors.[31,32] Despite its high diagnostic specificity, interpretation of the whole body iodine scintigram can be hindered by the lack of good anatomical localization and false-positive results due to physiological uptake or secretion in a number of organs. These may include ectopic foci of normal thyroid tissue, physiological uptake by salivary glands or stomach, by a variety of inflammatory and infectious processes in various organs and sometimes unexplained uptake by the liver, breast, or thymus.[33] The use of SPECT/CT can significantly increase both the sensitivity and specificity of radioiodine scintigraphy. A study by Ruf et al[34] analyzed the added value of performing SPECT/CT in equivocal foci of ^{131}I uptake on planar whole-body radioiodine imaging. SPECT/CT achieved accurate diagnosis of 95% of these foci and improved their anatomic localization in 44%. SPECT/CT was deemed to have contributed to clinical management in 25% of patients. Zanotti-Fregonara et al[35] also showed early diagnosis of iodine-avid bone foci to be significantly improved by the appropriate use of SPECT/CT, which may be followed by aggressive, case-tailored ^{131}I therapy.

In another study of the value of ^{131}I-SPECT/CT in DTC, Tharp et al[36] demonstrated that SPECT/CT improved diagnostic accuracy in 57% of patients through the identification of additional sites of disease, confirming that foci of pathologic uptake were skeletal in nature, accurately characterizing of physiological tracer uptake, and differentiating uptake in remnant tissue in the thyroid bed from local nodal disease. All these results suggest that SPECT/CT is a valuable adjunct in the whole-body radioiodine imaging of thyroid carcinoma.

PET

Involvement of multiple skeletal sites often correlates with less differentiated histology. In these circumstances, ^{18}F-FDG-PET is likely to be a valuable investigation due to the high proliferative rates of these tumors, especially in cases of elevated thyroglobulin and negative diagnostic or post-therapy radioiodine WBS[37-39] (Figs. 2A and B). A multicenter series by Grünwald et al[38,40] found ^{18}F-FDG-PET achieved higher sensitivity (75%) than ^{131}I WBS (50%) and ^{99m}Tc-sestamibi/^{201}Tl WBS (53%), with comparable specificities. The sensitivity of ^{18}F-FDG-PET increased to 85% in the subgroup of patients with negative ^{131}I WBS. Robbins et al[41] showed an inverse relationship between survival time and both the degree of ^{18}F-FDG avidity of the most active lesion and also the number of ^{18}F-FDG-avid lesions. As well as achieving higher sensitivity, ^{18}F-FDG-PET appears to allow for earlier assessment of treatment response in less differentiated cancers compared with bone scintigraphy.[42] Thyrotropin (TSH) stimulates thyroid metabolism, glucose transport, and glycolysis. Several studies have demonstrated TSH stimulation to improve detection of occult thyroid metastases with ^{18}F-FDG-PET, compared with scans performed on TSH suppression.

Although ^{18}F-FDG-PET is in itself a valuable tool in the follow-up of patients with thyroid cancer, accurate anatomical localization of ^{18}F-FDG positive lesions is often crucial to

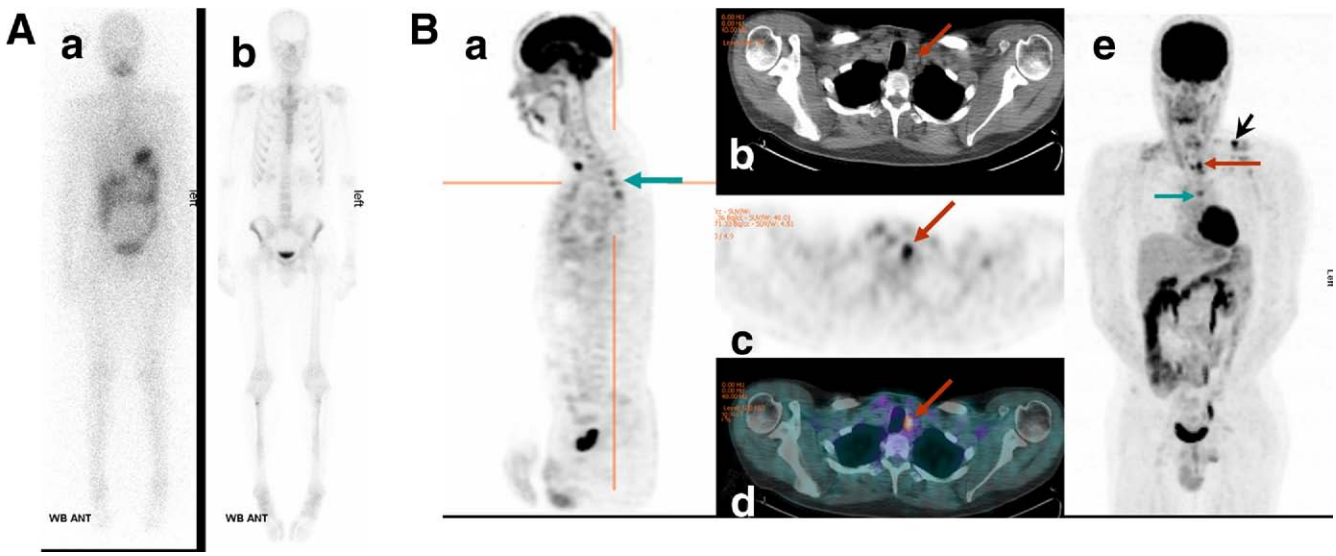

Figure 2 (A) A 27-year-old man had a total thyroidectomy and left-sided neck dissection for a pT4aN1aM0 papillary thyroid carcinoma. A few years later he presented with an abnormally increased thyroglobulin level, but negative WB planar imaging I-131 (image a) and WB ^{99m}Tc-MDP bone (image b) scintigrams. (B) ^{18}F-FDG-PET/CT revealed FDG-avid recurrent disease within the thyroid surgical bed (red arrows), metastatic infiltration within an FDG-avid left supraclavicular node (black arrow) and bony metastases within the upper thoracic vertebrae (blue arrows) (a, whole-body PET sagittal projection; b, transaxial CT image from the PET/CT; c, transaxial PET image; d, transaxial fused PET/CT image; e, MIP).

their correct interpretation. As with SPECT/CT, the use of PET/CT has markedly improved sensitivity and specificity over PET or CT alone. A number of recent studies have confirmed the value of ^{18}F-FDG-PET/CT in follicular and papillary thyroid cancer, especially in thyroglobulin-positive but iodine-negative cases, with alteration in clinical management made in 23%-51% of cases because of this technique. With the development of new and more specific molecular probes, the potential scope of PET/CT in thyroid carcinoma is likely to continue to expand. The positron-emitting radioisotope ^{124}I, for instance, has shown promising results in one study in which PET using this tracer detected more small bone metastases compared with ^{131}I-WBS.[43]

Renal Cancer

Up to 20% of patients with renal cell carcinoma (RCC) have metastatic disease at presentation, of which 30%-40% of cases involve the skeleton,[44] and up to 35% of all patients will develop bone metastases at some point during the course of their disease.[45] Bone metastases of RCC are typically expansile, osteolytic, often highly vascular, lesions that may give rise to severe bone pain and debilitating complications, such as pathologic fractures and spinal cord compression. They frequently necessitate orthopedic fixation and/or radiotherapy to treat or prevent fractures or for palliation of symptoms. Bone metastases from RCC are often particularly poorly responsive to standard radio- and chemotherapy.[46,47] The natural history of RCC bone metastases was evaluated recently in a 5-year review of 103 patients with metastatic disease on standard therapy protocols.[45] About 30% of patients developed bone lesions, which were associated with substantial morbidity, over 40% of patients experienced long-bone fractures and over 80% required palliative radiotherapy to bone.

SPECT

Most bone metastases from RCC are symptomatic, so that bone scintigraphy is usually undertaken only when patients show suggestive symptoms.[48-50] Performing routine scintigraphy in newly diagnosed patients has demonstrated a low yield of skeletal metastatic involvement (7.5% in one series).[51] Bone metastases of RCC show a variable, often low, degree of uptake on bone scintigraphy owing to their osteolytic nature. Scintigraphy is also not capable of detecting accompanying soft-tissue extension, which is relatively common in this disease and often neurologically significant. Correlation with plain radiography is therefore helpful in interpretation. A study of bone scintigraphy in RCC metastases showed its sensitivity to be relatively low, varying from 10% to 60%, even among patients with a high probability of skeletal involvement.[52] In the same series, bone scintigraphy also underestimated the extent of metastatic involvement in all cases.[52] A review of the natural history of RCC skeletal metastases showed the most commonly affected sites to be the pelvis and ribs (48% of patients in each case) and the vertebral column (42% of patients).[45] Evaluation of scintigraphic hot spots can be particularly challenging in these areas, and the additional structural delineation provided by SPECT would be expected to significantly improve the diagnostic capability of scintigraphy, but no study to date has specifically examined this.

PET

^{18}F-FDG-PET appears to offer improved accuracy in the detection of bone metastases compared with bone scintigraphy. Wu et al[53] showed that ^{18}F-FDG-PET had both a sensitivity and accuracy of 100% compared with 77.5% and 59.6%, respectively, for scintigraphy. In another study, ^{18}F-FDG-PET had a sensitivity and specificity of 77.3% and 100.0% for bone metastases, respectively, compared with 93.8% and 87.2%, respectively, for combined CT and bone scan.[54] Although till date, there appear to have been no studies of ^{18}F-FDG-PET/CT investigating specifically bone metastases, its addition of accurate anatomic localization to the PET data would be expected to significantly improve detection rates, as demonstrated in other cancers. Given the high incidence of clinically significant pathologies associated with skeletal metastases in RCC, the ability to detect spinal cord compression would be particularly useful. Bone metastases of RCC are also noted to have a higher frequency of associated soft-tissue masses than most other cancers, and this is a scenario where PET/CT has proven to be of particular value. Although little published data are available, combined ^{18}F-NaF-PET/CT may well be an excellent means of evaluating bony metastases of RCC. A case report showed it to be highly sensitive, demonstrating predominantly peripheral uptake within the lytic metastases, at the interphase of bone and an associated soft-tissue component in which new bone formation was noted.[55]

Multiple Myeloma

Radiographic imaging in multiple myeloma is used for initial staging of the disease, the identification of potential complications, especially pathologic fractures, and the assessment of response to therapy. Conventionally, staging has relied on a whole-body radiographic survey (Durie and salmon system), but this may significantly underestimate skeletal involvement, especially in newly diagnosed patients.[56] Bone scintigraphy has proved largely unhelpful in the evaluation of myeloma owing to its reliance on the presence of osteoblastic activity, which is usually lacking in the lytic lesions of myeloma.[57] MIBI imaging and ^{18}F-FDG-PET have both shown considerable promise in this area and although they remain under evaluation, both techniques are recommended within certain clinical scenarios in guidelines for the use of imaging in myeloma published by the British Committee for Standards in Hematology.[58]

SPECT

As noted above, bone scintigraphy using ^{99m}Tc-labeled diphosphonates shows poor accuracy in the staging of myeloma. ^{99m}Tc-MIBI is a lipophilic radiotracer whose uptake appears to parallel cellular mitochondrial activity[59] so that it is increased in neoplastic cells, including those of myeloma. The degree of ^{99m}Tc-MIBI uptake correlates with extent of myelomatous involvement as well as serologic markers of disease activity, such as lactate dehydrogenase, C-reactive protein, and beta-2 microglobulin.[60] A negative ^{99m}Tc-MIBI scan has a high neg-

ative predictive value in excluding myeloma in patients with monoclonal gammopathy of unknown significance (MGUS). A recent study of ^{99m}Tc-MIBI, ^{18}F-FDG-PET/CT, and MRI in the evaluation of myeloma concluded that both ^{18}F-FDG-PET/CT and MRI performed better in detecting focal lesions than ^{99m}Tc-MIBI, whereas both ^{99m}Tc-MIBI and MRI were more effective at visualizing diffuse areas of disease. ^{99m}Tc-MIBI is less effective in detecting extraosseous lesions in particular than ^{18}F-FDG-PET/CT.[61] The resolution and therefore overall accuracy of the technique could however be improved by performing SPECT. The British Committee for Standards in Haematology recommends the technique in selected cases that warrant clarification of previous imaging findings, ideally within the context of a clinical trial.[58]

PET

Clinical experience of ^{18}F-FDG-PET and PET/CT in the evaluation of myeloma remains at a relatively early stage. Its value has however been recognized by the Scientific Advisory Group of the International Myeloma Foundation, who recently proposed a staging system called "Durie and Salmon PLUS," which integrates ^{18}F-FDG-PET or MRI findings into conventional plain-film staging.[62] From the diagnostic point of view, ^{18}F-FDG-PET may detect active foci of marrow involvement in patients with plasmacytoma, enabling a correct diagnosis of myeloma.[63] One prospective study demonstrated a positive predictive value for active disease of 100% in patients with focal or mixed focal/diffuse skeletal ^{18}F-FDG uptake and 75% in patients with diffuse bone marrow uptake. For varying types of lesion, the sensitivity ranged from 83.8% to 91.9% and the specificity from 83.3% to 100%.[64] In the same study, ^{18}F-FDG-PET revealed a greater extent of disease than routine radiographs in 60.9% of patients with osteolytic bone lesions, and overall management was altered in 14% of patients. ^{18}F-FDG-PET can also be used to support a diagnosis of MGUS with a negative scan.[62]

An important limitation of PET scanning is its limited spatial resolution. Lesions of size <1 cm in maximum dimension may be undetectable, resulting in a false-negative result.[65] ^{18}F-FDG-PET/CT has been demonstrated to be of significant help in overcoming this, and the ability of the combined technique to show simultaneously both metabolically active disease (PET component) and bone destruction (CT) should be especially useful in myeloma. As always with ^{18}F-FDG-PET, it must be borne in mind that increased cellular turnover produced by inflammation or recent chemo- or radiotherapy may result in false-positive results.[66] It is therefore advisable to avoid ^{18}F-FDG-PET within 4 weeks of chemotherapy or 3 months of radiotherapy.[58]

A recent study compared the relative merits of ^{18}F-FDG-PET/CT and MRI in the assessment of myeloma.[56] ^{18}F-FDG-PET/CT performed better than MRI in detecting focal lesions throughout the body as a whole. MRI outperformed ^{18}F-FDG-PET/CT in detecting more diffuse lesions. This probably relates to the high uptake of ^{18}F-FDG within focal myelomatous deposits composed entirely of neoplastic plasma cells relative to diffuse lesions where the plasma cells form an interstitial infiltrate among normal hemopoietic elements of a lower proliferative index, and hence lower ^{18}F-FDG avidity. ^{18}F-FDG-PET/CT and MRI were comparable in terms of visualizing pelvic and spinal foci of involvement. A significant limitation of MRI is that whole-body studies are not yet widely performed due to poorer resolution than focused MRI and long imaging times. For the present, therefore, ^{18}F-FDG-PET/CT is likely to be most helpful in the further evaluation of ambiguous lytic lesions detected on skeletal survey, especially in the appendicular skeleton, and also for the investigation of suspected extramedullary disease (Fig. 3A).

As with MIBI scanning the British Committee for Standards in Haematology recommends ^{18}F-FDG-PET in selected cases requiring clarification of previous imaging findings, particularly in which other imaging techniques have failed to accurately determine the extent of extramedullary disease.[58] These guidelines also suggest considering PET for the follow-up of selected patients, such as those with predominantly extramedullary disease or nonsecretory myelomas where paraprotein assay cannot be used for disease surveillance. A consensus report from the Scientific Advisors of the International Myeloma Foundation suggests that whole-body ^{18}F-FDG-PET imaging may be helpful in clarification of disease classification (eg, consistent with MGUS if negative) or prognostic categorization (eg, demonstration of extramedullary disease). The report states that ^{18}F-FDG-PET imaging can substitute for MRI if this is not done or not available for staging, restaging, and/or serial monitoring[67] (Fig. 3B). Early studies suggest that the radiotracer ^{11}C-methionine may be of value in the PET imaging of myeloma.[68] This tracer reflects amino acid metabolism, transport, and protein synthesis, which may be a more useful biomarker than ^{18}F-FDG for neoplasms with low proliferative rates. Individual cases of myeloma show highly variable proliferative indexes,[69] which may explain the false negativity of ^{18}F-FDG-PET in some instances. This technique, however, remains experimental for the present.

Neuroendocrine Tumors

Neuroendocrine tumors (NET) are a group of rare neoplasms, which share the ability to produce biogenic amines and polypeptide hormones but differ widely in biology and clinical behavior. NETs may be functioning or nonfunctioning, and although most are well-differentiated slow-growing tumors, a proportion are highly aggressive.[70-72] The principal categories of NETs, which will be considered here are gastroenteropancreatic neuroendocrine tumors (which includes carcinoids and pancreatic endocrine tumors), neuroblastoma, pheochromocytoma, and medullary thyroid carcinoma (MTC). About 70% originate from endocrine islets or dispersed endocrine cells in the pancreas and the gastrointestinal tract,[71] with other tumors originating either from endocrine glands, such as the adrenal medulla, pituitary and parathyroids, and the C cells of the thyroid or scattered endocrine cells in the respiratory tract.[73] Tumors with endocrine activity may manifest early with symptoms relating to inappropriate hormone production, while nonsecreting NETs may only come to clinical attention through a local mass effect or the presence of disseminated disease.[70,72,74] The incidence of

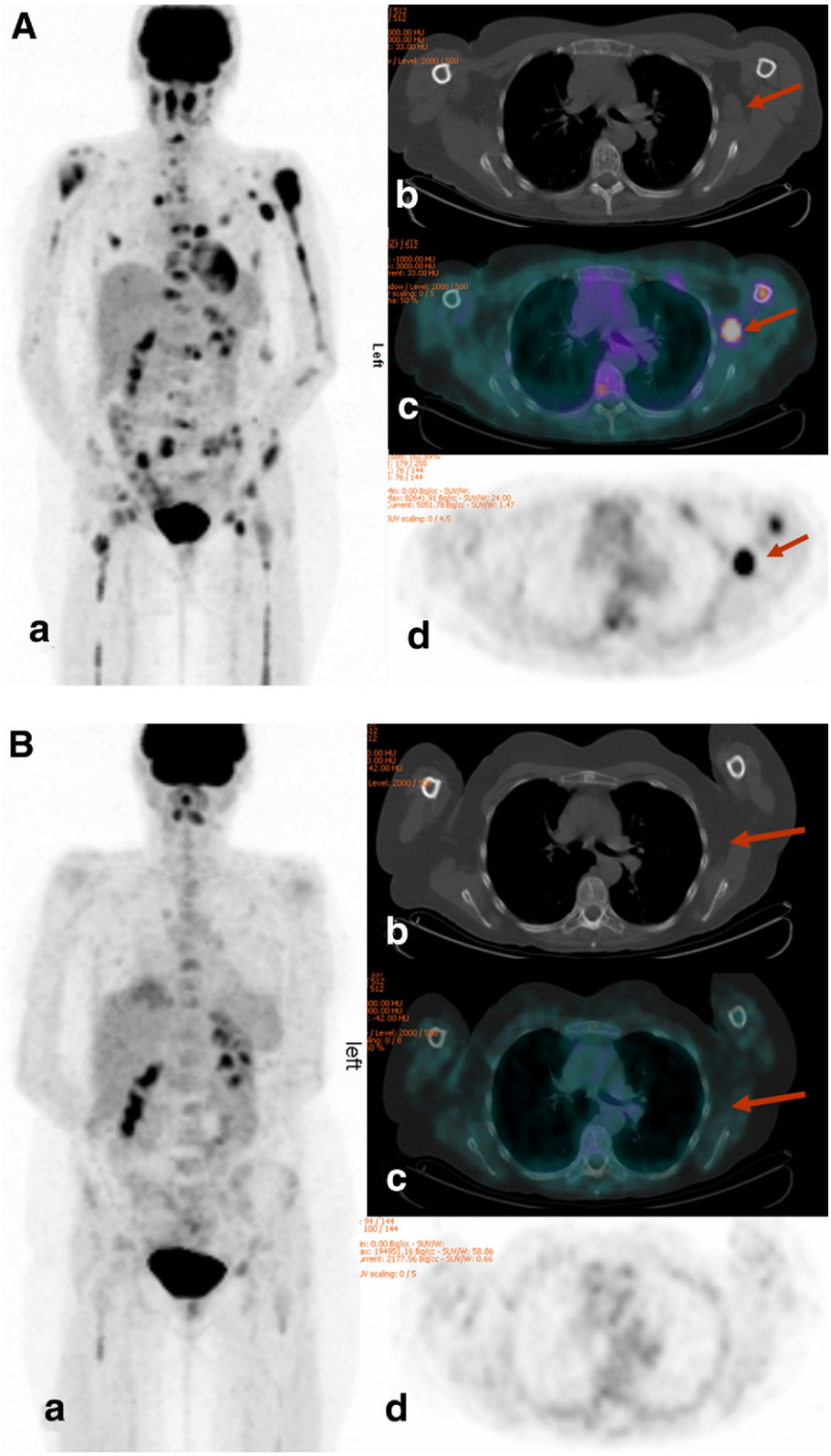

Figure 3 (A) A 43-year-old woman with multiple myeloma had a normal initial skeletal survey and unremarkable CT (not shown). Staging ^{18}F-FDG-PET/CT was performed, which showed multifocal areas of FDG-avid bony uptake in the axial and most of the visualized appendicular skeleton (a, MIP). In addition, there was an FDG-avid right axillary nodal lesion, consistent with an extramedullary myeloma (red arrows) (b, transaxial CT from the PET/CT; c, transaxial fused PET/CT image; d, transaxial PET image). (B) Post-treatment ^{18}F-FDG-PET/CT demonstrated foci of low-grade FDG uptake in the preexisting bony abnormalities with a complete resolution of the right axillary nodal lesion (red arrows) (a, MIP; b, transaxial CT from the PET/CT; c, transaxial fused PET/CT image; d, transaxial PET image), demonstrating a favorable partial treatment response to treatment.

skeletal metastases in NET as a group has been reported to be approximately 10%.[75,76] Functional imaging has become standard in the diagnostic/staging algorithm of patients with NET, as well as in follow-up after surgery and the diagnosis of recurrence in the setting of increasing tumor markers. Nuclear imaging techniques are increasingly used for the evaluation of therapy response in neuroendocrine tumors, as their often low-grade nature and the cytostatic rather than cytotoxic therapies often employed against them mean that functional rather than morphologic response is often the most effective indicator of therapeutic success.

SPECT and PET Imaging of Carcinoid/Pancreatic Endocrine Tumors

Bone metastases occur in approximately 8%-13% of patients with carcinoid tumors, although many are clinically undetected, and an autopsy study revealed a higher rate (42%) in patients with advanced disease.[77] Although it has been suggested that bone metastases arise more often from bronchial or foregut primaries than from other carcinoid tumors, recent studies have failed to demonstrate any preferential primary site.[75] The axial skeleton is the most commonly affected region.

Only a limited number of studies have analyzed the imaging of bone metastases in patients with carcinoids and related neuroendocrine tumors. Radiographic signs may be subtle. Most metastases are sclerotic in nature and give rise to bone pain clinically. They may be demonstrable on CT but MRI is a more sensitive method of detecting them (up to 100% sensitivity in the series of Meijer et al)[75] and particularly in identifying bone marrow and spinal involvement, with the usual drawback that only a restricted part of the skeleton is normally visualized in one MRI scan. Bone scintigraphy also shows a sensitivity of around 90% in detecting metastases from carcinoids, but suffers from poor specificity.[78] The presence of somatostatin receptors on the cell membranes of most carcinoid tumors has meant that somatostatin receptor scintigraphy (SRS) has become a sensitive whole-body imaging technique for metastatic disease, including skeletal disease. This employs a radiolabeled analog of somatostatin, such as ^{111}In-pentetreotide, which is accumulated in most carcinoid tumors. SRS shows a sensitivity of around 81% in detecting carcinoid bone metastases,[79] but this technique is somewhat limited in cases in which metastases are small and it may also be difficult to precisely localize lesions. The role of bone scans and SRS is complementary owing to their different mechanisms (detection of osteoblastic response vs somatostatin receptor density) and they should ideally be used together in disease assessment.[75] SRS can also provide an assessment of patients' suitability for therapy with radiolabeled analogs of somatostatin and be used to monitor the effect of this therapy.

Significantly improved image interpretation, in particular, increased specificity when evaluating equivocal lesions, has been obtained by SPECT/CT imaging.[80-82] One study concluded that SPECT/CT significantly improved tumor localization and characterization in patients with NET and indicated that SPECT/CT was better than SPECT or CT alone[82] (Fig. 4). The authors suggested that use of a higher resolution CT component than that available to them could have improved accuracy of SPECT/CT, as they found CT to miss bone involvement in several cases. Surgical and chemotherapeutic treatment was altered in 28% of patients due to the image fusion results.[82]

The sensitivity of PET is inherently greater than gamma camera (SPECT) imaging, so that tumors as amenable to targeted imaging as neuroendocrine tumors should be an ideal application for PET. Most oncological PET, using ^{18}F-FDG, relies on the increased glucose metabolism of most neoplasms over normal tissues. However, because most carcinoid tumors are well-differentiated and slow-growing tumors, they have a low metabolic rate and cannot be effectively visualized with this tracer. Increased ^{18}F-FDG uptake may however be seen in less differentiated cases, which often lack somatostatin receptors; in such cases, the sensitivity of ^{18}F-FDG-PET is clearly higher than that of scintigraphy with ^{111}In-pentetreotide.[83]

A number of compounds that are intermediates in the hormone production process are being evaluated for PET to assess the metabolism and functionality of NET. These include ^{11}C-5-hydroxytryptophan, ^{11}C-/^{18}F-dihydroxyphenylalanine, 6-^{18}F-fluorodopamine, and ^{68}Ga-labeled tracers.[84] Several of these have shown promising preliminary results. ^{11}C-5-HTP is preferentially taken up by serotonin-producing tumors and this uptake may be enhanced if it is coadministered with carbidopa. PET imaging with ^{11}C-5-HTP has demonstrated superior results to CT scanning in diagnosing gastroenteropancreatic neuroendocrine tumors and monitoring their response to therapy, but specific data on bone metastases is lacking. A recent study concluded that PET/CT using 6-^{18}F-fluorodopa (^{18}F-DOPA) now represents the optimal imaging modality for staging in carcinoid patients and ^{11}C-5-HTP PET/CT in islet cell tumor patients.[85] These techniques showed sensitivities of 89% and 100%, respectively, compared with 78% for SRS and 87% for CT in the staging of islet cell tumors.[85] In all cases the CT component of the scan was found to increase sensitivity.

In a recent study by Gabriel M et al,[86] somatostatin receptor PET with ^{68}Ga-dota-TOC showed a significantly higher detection rate compared with conventional SRS and diagnostic CT, but a combination of the PET and CT findings achieved even higher overall accuracy. The difference in detection rates was most marked in skeletal metastases, in which 72.5% of lesions demonstrated by PET were visible using SPECT and only 50% using CT. Of particular interest is that uptake was not influenced by whether the tumor was functional or not. The additional information provided by PET prompted changes in therapeutic regimens in a number of patients and had a significant clinical impact overall. Baum et al[87] reported a higher diagnostic accuracy of 68-Ga-dota-NOC PET/CT than SRS SPECT in detecting all known tumor lesions and in addition very small lymph node and bone metastases (<5 mm) were easily visualized. This same group has recently shown PET/CT with this tracer to be an effective marker of early response to peptide receptor radionuclide therapy. The sensitivity and specificity of ^{68}Ga-dota-NOC PET to predict response to radio peptide therapy were calcu-

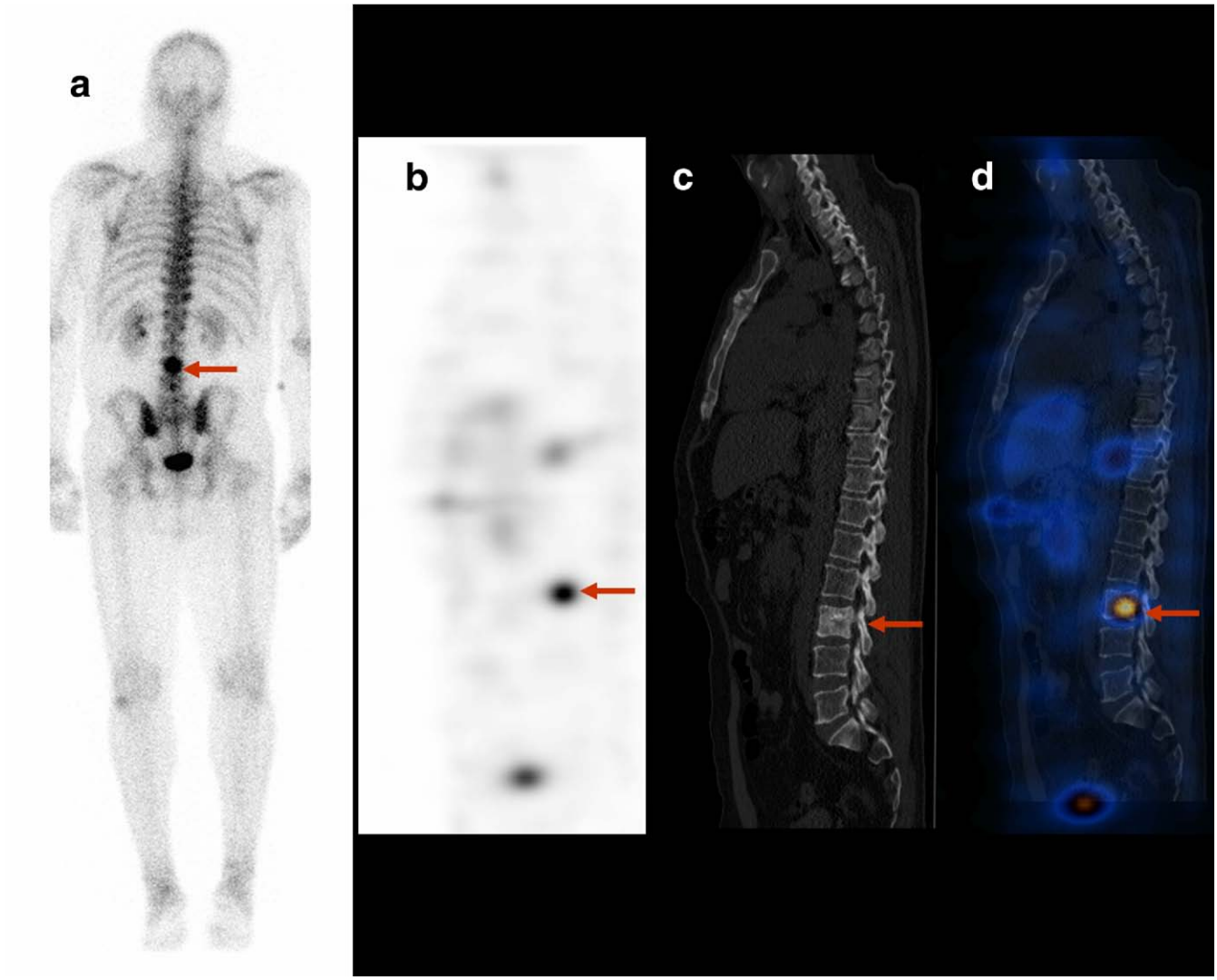

Figure 4 WB ^{99m}Tc-MDP bone planar imaging of an adult patient with a neuroendocrine tumor shows focal intense increased uptake approximately within the L3 vertebral body (a), suspicious of a solitary bone metastasis. On ^{111}In-Octreotide SPECT/CT images, the focus of increased uptake corresponds to an osteosclerotic bony metastasis (arrows) on the CT component of the study. SPECT/CT provides precise anatomical localization, enabling accurate characterization of the suspicious lesion (b, sagittal SPECT projection; c, sagittal CT component of SPECT/CT; d, sagittal SPECT/CT fused image).

lated as 89% and 71%, respectively. ^{68}Ga-dota-TOC PET may also aid in radionuclide therapy dosimetry through its ability to make quantitative assessments of radioactivity in different tissues over time. ^{68}Ga-labeled tracers have a particular practical advantage over octreotide in that they are generator produced, and therefore do not require a cyclotron. Therefore, it has been suggested that they may eventually replace octreotide in its current roles.

SPECT and PET Imaging of Pheochromocytoma

The prevalence of malignancy in pheochromocytoma is around 10%, with a high incidence of metastatic disease, and bone is the most common site of metastatic spread. Pathologic fractures are a significant cause of morbidity in patients with metastatic disease. Bone scintigraphy remains the most sensitive modality for detecting bone metastasis, with 74% of all suspected lesions being identified with the technique in one series.[88] The addition of ^{131}I-MIBG scanning, which offers excellent specificity (95%-100%) but less good sensitivity (approximately 77%)[89] is nevertheless recommended for maximum accuracy, with the addition of CT in which findings remain equivocal. The use of SPECT in these cases can significantly reduce the number of false-positive findings due to unilateral, asymmetric, low-intensity MIBG uptake, which occur in around 10%-33% of cases.[90] Scintigraphy using the somatostatin analog ^{111}In-pentetreotide can demonstrate pheochromocytoma metastases not avid to scintigraphy with MIBG.[91,92] To date, there is as yet only scanty data on the role or impact of hybrid imaging in the imaging of skeletal involvement in pheochromocytoma.

Although a number of specific PET radiotracers for pheo-

chromocytoma have been evaluated, none are yet in widespread clinical use. ^{18}F-fluorodopamine (^{18}F-DA) and ^{18}F-DOPA can detect metastatic pheochromocytomas at rates higher than ^{131}I-MIBG.[93] ^{11}C-hydroxyephedrine and ^{11}C-adrenaline[94] are highly specific but possess very short half-lives, making imaging difficult.[95] ^{18}F-FDG-PET can accurately identify metastatic lesions,[96] particularly if they are negative for ^{131}I-MIBG or ^{123}I-MIBG.[97]

SPECT and PET Imaging of Neuroblastoma

Neuroblastoma has a strong propensity to metastasize to cortical bone and bone marrow, and accurate detection of skeletal involvement is essential for accurate staging and selecting the most appropriate treatment strategy. Although any bone may be affected, the skull, periorbital bones, vertebral column, pelvis, and long bone metaphyses are most commonly involved.

Bone scintigraphy using ^{99m}Tc-MDP is an effective technique in assessing skeletal involvement in neuroblastoma, with a sensitivity of 87.5% in one series.[98] Bone scan cannot, however, accurately differentiate between metastases involving the cortex and the bone marrow, which limits its usefulness, particularly in differentiating stage 4 from stage 4 s.[99] MIBG is taken up by most neuroblastomas. As well as being a useful imaging tracer, with a sensitivity of around 90% in the detection of bony metastases,[100] high-dose therapy with ^{131}I-MIBG is an effective treatment for neuroblastoma.[101] A positive MIBG scan, either at time of diagnosis or postinduction chemotherapy is of prognostic significance, suggesting a poor outcome. MIBG is, however, best performed as a complementary technique to ^{99m}Tc-MDP scintigraphy for maximum accuracy.[102] For optimal staging, it is recommended that all patients should undergo both MIBG scanning and bone scintigraphy, as well as CT. MRI should also be performed in case of suspicion of intraspinal or epidural tumor spread or when bone scintigraphy yields an equivocal finding in a distant site.[103] Application of SPECT to bone scan imaging improves both detection rate and anatomic localization. SPECT/CT has also been shown to be useful in determining the clinical significance of equivocal sites of MIBG uptake. It can be especially helpful in the clarification of physiological uptake in the heart, which may mimic vertebral involvement, and activity in cervical brown fat/skeletal muscle, which may mimic scapular or costal metastases. Use of combination SPECT/CT to determine CT-defined volume of interest may be valuable in quantifying radiation doses delivered during ^{131}I-MIBG therapy.

PET using a variety of radiotracers has been performed in neuroblastoma. ^{18}F-FDG-PET is taken up by most neuroblastomas and may be particularly useful in monitoring the effects of therapy in the 10%-20% of cases, which are negative for MIBG.[104] One practical advantage of PET is that the imaging can commence 60 minutes after ^{18}F-FDG administration compared with 1-2 days after injection of ^{123}I or ^{131}I-MIBG. Published studies of ^{18}F-FDG-PET/CT remain extremely scanty, but the technique has been used effectively for follow-up of metastatic neuroblastoma, which became MIBG-negative at the time of relapse.[105] ^{11}C-Hydroxyephedrine is the first available positron-emitting tracer specifically taken up by cells of the sympathetic nervous systems, and hence neuroblastomas. PET imaging with ^{11}C-hydroxyephedrine produces high-quality images and overall tumor detection rates comparable to MIBG and possibly higher in soft tissues and the extracranial skeleton.[106] Other related tracers, such as ^{18}F-fluorodopamine and ^{68}Ga-labeled peptides, are expected to also show uptake in neuroblastomas but more studies are needed to assess their potential roles.

SPECT and PET Imaging of MTC

MTC accounts for 3%-12% of all thyroid tumors.[107] It originates from the parafollicular or C cells of the thyroid, which derive from the neural crest and secrete calcitonin. Surgical excision forms the sole curative therapeutic approach, and requires accurate tumor staging. Bone metastases may be either osteolytic or osteoblastic. The latter uniquely occur in medullary but no other thyroid carcinomas, and are assumed to be caused by biologically active tumor–secreted calcitonin. Functional imaging with bone scintigraphy and ^{111}In-pentetreotide are sometimes used preoperatively, but are especially important for postoperative follow-up. A number of novel specific radiotracers have been proposed for imaging of MTC, including ^{111}In-pentetreotide,^{123}I/^{131}I-MIBG, pentavalent ^{99m}Tc-dimercaptosuccinic acid, ^{99m}Tc-Edda/HYNIC-TOC, ^{111}In-minigastrin, and radiolabeled anti-staphylococcal enterotoxin A antibodies.

Coregistration of anatomic and functional imaging data has been used in a small number of patients with MTC, as part of a larger series of neuroendocrine tumors. Perault et al[108] employed fusion of ^{111}In-pentetreotide SPECT with CT data in 3 patients to enable accurate localization of 5 tumor sites; of these 5 tumor sites, 3 were not visualized on CT, which led to refinement of the surgical procedure. This protocol, however, required injection of an additional radionuclide so that it would be impractical on a routine basis. SRS SPECT/CT, without the necessity of additional tracer injection, allowed the detection of clavicular tumor invasion in 1 patient with uptake in the lower neck and superior mediastinum, with resultant alteration in treatment plan.

^{18}F-FDG-PET has shown itself as a promising imaging tool in MTC staging with a higher lesion detection efficacy when compared with scintigraphic studies.[109,110] A multicenter study of 85 MTC patients compared ^{18}F-FDG-PET, ^{111}In-pentetreotide, ^{99m}Tc-sestamibi, CT, and MRI as staging modalities. Sensitivity and specificity were 78% and 79% for ^{18}F-FDG-PET, 25% and 92% for SRS, 25% and 100% for sestamibi, 50% and 20% for CT, and 82% and 67% for MRI, respectively.[110] De Groot et al[109] in a prospective study of ^{18}F-FDG-PET in 26 MTC patients, demonstrated a sensitivity of 96%, compared with 41% sensitivity for ^{111}In-pentetreotide imaging. This suggests that somatostatin receptor expression may be downregulated in metastatic tumors, many of which nevertheless show high ^{18}F-FDG uptake. Although ^{111}In-pentetreotide imaging is generally recommended as the most effective functional staging scan for MTC, ^{18}F-FDG-PET may be useful if the former is either negative or shows findings inconsistent with those of structural scans. To date, there is very scanty published data on the role of ^{18}F-FDG-PET in detecting metastatic bone disease of MTC, with no subanaly-

ses for bony metastases in most of the published studies. Giraudet et al[111] prospectively studied 55 consecutive MTC patients with persistent elevated calcitonin levels. Bone metastases were demonstrated in 35% of patients by ^{18}F-FDG-PET, in 40% by bone scintigraphy, and in 40% by MRI; effectiveness of bone scintigraphy was comparable with that of MRI for axial lesions but superior for the detection of peripheral lesions. The combination of scintigraphy and WB-MRI detected all patients with bone metastases and 94% of bone lesions.[111] It was concluded that ^{18}F-FDG-PET cannot be used alone for imaging MTC patients because of its low sensitivity. This is likely to reflect the low-grade histology and low proliferative index of many MTCs, and perhaps also the fact that many metastases are paucicellular and sclerotic/calcified.[112-115] ^{18}F-NaF PET has shown high sensitivity in the postsurgical follow-up of patients, detecting all bone metastases in a small series of patients with elevated calcitonin levels or residual masses,[116] but remains little studied in this tumor. Several new PET tracers have been proposed for use in assessment of MTC, including ^{18}F-DOPA, ^{18}F-FDA, and ^{68}Ga-labeled somatostatin analogs.

Conclusion

Bone scintigraphy is a well-accepted functional imaging method for the detection of bone metastases from a variety of primary tumors, which is highly sensitive and cost-effective. Its main drawback is its lack of specificity, especially in the setting of vertebral lesions. SPECT imaging provides valuable additional information, which is often crucial in differentiating between bone metastasis and benign lesions, and significantly improves the predictive value of scintigraphy. It is equally applicable to scintigraphy with a variety of tumor-specific radioisotopes. The accuracy of SPECT can be further improved by new combined SPECT/CT systems with fused scintigraphic and CT images.

PET has only been in widespread use for a few years, and its cost has meant that it has often been funded only for specific malignancies; thus, relatively little data have accrued in relation to its role in skeletal assessment. The high-quality tomographic images produced with ^{18}F-FDG-PET have shown significantly improved sensitivity and specificity over conventional bone scintigraphy in a number of studies thus far, which is likely to relate to the technique's direct detection of the increased metabolic rate of malignant cells rather than osteoblastic response. ^{18}F-NaF PET may also have an important role in detecting bony metastases from tumors with low ^{18}F-FDG avidity. There is emerging evidence to suggest that PET/CT together with whole-body MRI may represent the most powerful imaging technique yet for the detection and characterization of bony metastases. Additional analysis of the role of these techniques in this setting and that of the evaluation of myeloma needs to be performed. Further evolution of this field also holds the exciting prospect of the introduction of new and more specific radiotracers for individual malignancies.

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