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An international expert opinion statement on the utility of PET/MR for imaging of skeletal metastases

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Abstract

Background MR is an important imaging modality for evaluating musculoskeletal malignancies owing to its high soft tissue contrast and its ability to acquire multiparametric information. PET provides quantitative molecular and physiologic information and is a critical tool in the diagnosis and staging of several malignancies. PET/MR, which can take advantage of its constituent modalities, is uniquely suited for evaluating skeletal metastases. We reviewed the current evidence of PET/MR in assessing for skeletal metastases and provided recommendations for its use.

Methods We searched for the peer reviewed literature related to the usage of PET/MR in the settings of osseous metastases. In addition, expert opinions, practices, and protocols of major research institutions performing research on PET/MR of skeletal metastases were considered.

Results Peer-reviewed published literature was included. Nuclear medicine and radiology experts, including those from 13 major PET/MR centers, shared the gained expertise on PET/MR use for evaluating skeletal metastases and contributed to a consensus expert opinion statement. [18F]-FDG and non [18F]-FDG PET/MR may provide key advantages over PET/CT in the evaluation for osseous metastases in several primary malignancies.

Conclusion PET/MR should be considered for staging of malignancies where there is a high likelihood of osseous metastatic disease based on the characteristics of the primary malignancy, high clinical suspicion and in case, where the presence of osseous metastases will have an impact on patient management. Appropriate choice of tumor-specific radiopharmaceuticals, as well as stringent adherence to PET and MR protocols, should be employed.

Keywords Skeletal · Osseous · Metastases · PET/MR · PET/MRI · PET · MR

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Introduction

Positron emission tomography (PET) is a quantitative diagnostic imaging modality that investigates molecular processes in vivo. However, PET provides limited anatomic information. Magnetic resonance imaging (MRI) is a modality with high spatial resolution and soft tissue contrast that allows for the identification and characterization of bone and soft tissue abnormalities. Integrated PET/MR is a hybrid technology that allows the simultaneous acquisition of both metabolic and anatomic information. There are currently no clinical guidelines regarding the role of PET/MR in the evaluation of

skeletal metastases. We will discuss technical and clinical considerations relevant to the usage of PET/MR in the evaluation of skeletal metastases, both with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) and with non ^{18}F -FDG radiopharmaceuticals. We will also review current evidence and provide recommendations for the use of PET/MR in patients with suspected skeletal metastases.

Technical considerations

Simultaneous acquisition of PET and MR data using a single device required overcoming several technical challenges not present in combined PET/CT imaging. One such challenge was adapting PET detectors to operate within a magnetic field. The development of solid-state photodetectors (i.e., avalanche photodiodes, silicon photomultipliers), which are unaffected by the magnetic field, allowed for simultaneous acquisition of PET data and, in the case of silicon photomultipliers, provides time-of-flight information [1]. Three equipment manufacturers are currently commercializing fully integrated PET/MR scanners for clinical use.

On the methodological side, the major obstacle slowing the widespread clinical adoption of PET/MR has been the challenge of generating accurate attenuation correction (AC) maps [2, 3]. A correction must be applied to PET data to account for attenuation of the emitted photons prior to reaching the PET detectors [4, 5]. AC issues are particularly important for lesions in or adjacent to cortical bone for which incorrect AC might lead to erroneous PET quantification. Unlike PET/CT, where the CT images can be used to measure the linear photon attenuation coefficients of tissues, albeit at a lower energy, PET/MR generally relies on MR-derived image parameters to calculate an attenuation map. Bone heavily attenuates emitted photons and, if not appropriately accounted for, can result in considerable inaccuracy in the quantitative analysis of PET radiotracer distribution [6–8].

Early MR-based AC techniques used conventional T1-weighted or Dixon sequences to segment classes of tissues and create attenuation maps [9–11]. Cortical bone, despite having a high linear attenuation coefficient, has a low signal intensity on T1-weighted images and was misclassified as air using standard MR-based AC methods. Although this resulted in substantial bias in anatomic areas surrounded by bone, such as the head and pelvis, the reduction in standardized uptake values (SUVs) compared to PET/CT was shown to have minimal impact on the clinical evaluation of malignant bone lesions [12–14]. The impact of remaining bone-tissue misclassification has also been shown to be reduced when incorporating the time-of-flight information [15]. Application of model-based approaches in which bony structures are incorporated into the Dixon-based AC maps was shown to substantially reduce the bias caused by bony structures [16]. Additionally, techniques using specialized MR sequences

(i.e., ultrashort or zero echo time sequences) have been implemented to generate even more accurate AC maps, particularly in skull attenuation in brain PET/MR [17–22]. Recently, deep learning-based AC techniques have emerged to exploit information acquired either as part of diagnostic MR images or from separately acquired AC MR sequences to construct attenuation maps [23–26].

Radiation dose

In current practice, radiation dose from PET/MR can be up to 80% lower than the vast majority of PET/CT [27]. This is primarily due to the elimination of radiation exposure from CT used for AC and, if required, from a separately acquired diagnostic CT. Radiation exposure with PET/MR occurs only from the injected radiopharmaceutical [28–31]. Radiation exposure can be further reduced by decreasing radiopharmaceutical activity given for PET/MR. This can be achieved by taking advantage of features of current PET/MR scanners, including the longer axial field of view, and reduced diameter compared to PET/CT devices, as well as the longer acquisition times needed for acquiring multiparametric MR information. The end result is a reduction of injected radioactivity by up to 50–65% [32, 33].

The newest generation of PET/CT scanners, equipped with higher performance detectors (e.g., temporal resolution approaching 200 ps), allow for additional reductions in radiation dose. This class of detectors will likely be introduced in the next generations of PET/MR systems, with further expected decrease in radiation dose and acquisition time [34].

MR component of PET/MR and protocol considerations

A fundamental advantage of PET/MR over PET/CT is the superior diagnostic performance of MR compared to CT in the identification and, in many cases, the characterization of osseous lesions [35]. Detection of metastases by CT requires destruction of cortical or trabecular bone, adjacent sclerotic changes, or identification of soft tissue attenuation within the normal fat-attenuation marrow. In contrast, skeletal metastases on MR can be characterized by signal abnormality of the bone marrow on T1, STIR, and diffusion-weighted sequences [36–40]. Numerous studies have shown that MR is more sensitive than CT alone in the detection of focal marrow replacing lesions and that the higher soft tissue contrast provided by MR allows for better delineation of extra-osseous tumor spread and spinal cord compression (Fig. 1) [41–47]. Furthermore, MR can be a useful tool for distinguishing benign osteoporotic vertebral body fractures from pathologic fractures [48–50].

In addition to the superior performance of MR over CT in evaluating bone abnormalities, PET/MR benefits from the

Fig. 1 ^{18}F -FDG-PET/MR in a 74-year-old female with a history of endometrial cancer. **a** Axial 3D gradient echo T1 post-contrast, **b** ^{18}F -FDG-PET, **c** axial fused PET/MR, and **d** same-day contrast-enhanced CT images of the humerus. These images demonstrate a metastatic lesion (arrow) in the right humeral head which enhances after gadolinium administration and demonstrates associated increased ^{18}F -FDG uptake. No corresponding abnormality is seen on same day CT image, **d**

simultaneous acquisition of diagnostic anatomic images and PET data. This allows for more accurate co-registration and fusion of the MR and PET images. The combination of high-quality anatomic imaging and improved co-registration may facilitate lesion detection and characterization. It may help guide percutaneous or surgical intervention. Although most PET/MR protocols involve long acquisition times, which is sub-optimal for clinical situations where rapid scanning is needed, they can be streamlined to ensure the whole body is acquired within 20–25 min, depending on body habitus [27].

Based on the clinical experience of the co-authors of this study and on the published literature, PET/MR acquisition protocols should be tailored to the selected radiopharmaceutical with a focus on its effective half-life. For example, while most radiotracers do not require rapid MR image acquisition and can permit scan times of up to 1 h, the short biologic half-life of ^{18}F -fluciclovine necessitates MR image acquisition in under 20 min from tracer injection. For most studies of adult patients, image acquisition should start from the mid-thighs and end at the vertex of the skull to ensure the pelvis is imaged before the bladder fills, in case of urinary excreted radiopharmaceuticals. Radiopharmaceuticals within the distended bladder can result in halo artifacts due to overestimation of scatter contribution in PET reconstruction, which can obscure abnormal uptake in regional structures. PET/MR protocols of children and teenagers typically require head-to-toe acquisition [27].

For ^{18}F -FDG/PET- and other non ^{18}F -fluciclovine-based studies, we recommend the following MR sequences: axial or/and coronal T1-weighted dual point Dixon gradient echo sequences (20–25 s per bed position), axial diffusion-weighted images with b -values of 50–400–800 s/mm^2 (3 min per bed position) and axial unenhanced or gadolinium-enhanced T1-weighted fat-suppressed gradient echo images (20–25 s per bed position) with simultaneous PET data acquisition (4 min per bed position). Some authors, despite the longer acquisition time, prefer whole-body coronal and spine sagittal T1-weighted fast spin echo sequences instead of axial or/and coronal T1-weighted dual point Dixon gradient echo sequences. Gadolinium administration may be advantageous but not strictly necessary for evaluation of skeletal lesions on PET/MR [51]. ^{18}F -FDG-PET images can be color-coded to reflect radiotracer uptake and superimposed on high-resolution gradient echo images. These fused images can be reconstructed in the coronal and sagittal planes. This protocol, depending on available PET/MR scanner hardware, takes approximately 20–25 min. If necessary, the primary tumor and any other areas of interest might be further interrogated with additional dedicated protocols as clinically appropriate [27].

For ^{18}F -fluciclovine-PET/MR, given its short relative half-life, we recommend acquisition of coronal T1-weighted high-resolution dual point Dixon gradient echo sequences or T1-weighted FSE simultaneously with PET from mid-thighs to vertex, and ensure completion within 20 min from injection.

Subsequently, the following sequences can be acquired: coronal STIR sequences and/or axial simultaneous multislice diffusion-weighted images with suggested b -values 50–400–800 s/mm² and axial and coronal contrast-enhanced T1-weighted fat-suppressed gradient echo images. Coronal T1-weighted high-resolution dual point Dixon gradient echo sequences can be secondarily reconstructed in the sagittal plane for evaluation of the spine. Additional imaging parameters may vary, given technical differences in currently available PET/MR scanner hardware.

Additional pre-contrast coronal STIR images can be obtained as deemed necessary.

In the authors' experience, single-shot fast spin echo T2-weighted images are less useful in the evaluation of bony metastases. Although acquisition time is short and the sequence is relatively resistant to respiratory and other types of motion artifact, the contrast between tumor lesions and the bone marrow is less conspicuous, as compared with DWI, STIR, and Gd-enhanced T1-weighted scans.

Suggested MRI sequences with descriptions of their roles in assessment of osseous metastases are described in Table 1.

¹⁸F-FDG PET/CT vs ¹⁸F-FDG-PET/MR

¹⁸F-FDG PET/CT is currently used to image a variety of cancers, including lymphoma, small-cell and non-small-cell lung cancers, head and neck squamous cell cancer, melanoma, colorectal cancer, breast cancer, esophageal cancer, gastric

cancer, pancreatic adenocarcinoma, cervical cancer as well as bone and soft tissue sarcomas. In general, these tumors show avid ¹⁸F-FDG uptake and can therefore be easily detected. Malignancies such as prostate cancer, hepatocellular carcinoma, renal cell carcinoma, and well-differentiated gastroenteropancreatic neuroendocrine tumors have generally low ¹⁸F-FDG uptake, underscoring the limited utility of ¹⁸F-FDG PET/CT in assessment of these diseases.

Although PET/MR has been approved for clinical use for the last 10 years, rigorous comparison with PET/CT is still underway. Studies that have compared ¹⁸F-FDG PET images from PET/CT to PET/MR in a variety of malignancies have generally shown similar diagnostic performance despite differences in quantitative and semi-quantitative assessment of ¹⁸F-FDG uptake [58–62]. A single study of two sequential PET/MR exams following a PET/CT exam showed comparable diagnostic performance of PET from PET/MR versus PET/CT and acceptable reproducibility between sequential PET/MR exams [63].

Currently, few dedicated studies have explored the performance of PET/MR compared to PET/CT for assessment of malignancies involving the musculoskeletal system. Available studies focus primarily on multiple myeloma, extra-nodal osseous involvement of lymphoma, and osseous metastases from breast and lung cancer. PET/MR offers higher diagnostic confidence and improved conspicuity than PET/CT for detection of bone lesions, especially in the case of early osseous metastatic disease (Fig. 2) [64].

Table 1 Suggested MRI sequences and role in assessment of osseous metastatic disease

Sequence	Plane of acquisition (axial/sagittal/coronal)	Interpretation criteria/limitations/pitfalls
T1-weighted Dixon gradient echo (GRE) and/or T1 weighted fast spin echo	Coronal and/or axial	<ul style="list-style-type: none"> • May be used for attenuation correction. • Identification of replacement of T1 hyperintense fatty marrow signal with T1 hypointense metastases [40]. • Differentiation of metastases from benign processes. • Identifying fractures or pathologic fractures. • Signal drop out on out of phase images can indicate intralesional fat, distinguishing focal red marrow from marrow replacing lesions [52].
Simultaneous multislice diffusion-weighted imaging (b -values 50, 400, 800 s/mm ²)	Axial	<ul style="list-style-type: none"> • High sensitivity for skeletal metastases [53]. • Distinguishing benign osteoporotic compression fractures from pathologic fractures of the spine [54]. • Evaluation of ADC maps can be helpful in distinguishing red marrow from metastases and may have a role in assessment of treatment response in some malignancies [38, 55–57].
High-resolution post-contrast T1-weighted fat-suppressed GRE	Axial (optional in sagittal or coronal planes)	<ul style="list-style-type: none"> • Identification of enhancing marrow replacing lesions as well as associated extra-osseous soft tissue extension.
Short tau inversion recovery (STIR) (optional, since time intensive)	Coronal	<ul style="list-style-type: none"> • Identification of hyperintense marrow replacing lesions in the background of low marrow signal due to fat suppression [40]. • Identification of extra-osseous tumor extension. • Improved identification of pathologic fracture and assessment of fracture acuity based on the presence of surrounding bone marrow edema. • Identification of degenerative disc disease and osteoarthritis.

Fig. 2 ^{18}F -FDG-PET/MR in a 16-year-old female with rhabdomyosarcoma of the pelvis. **a** Axial T2-weighted HASTE, **b** 3D gradient echo T1-weighted post-contrast, **c** ^{18}F -FDG-PET, **d** axial fused PET/MR. No definite signal abnormality of the T7 vertebral body is seen in **a**. Heterogeneous enhancement in the T7 vertebral body (arrow), in **b**, could reflect marrow replacement or normal erythropoietic bone marrow. However, focally increased ^{18}F -FDG-PET accumulation in the T7 vertebral body, consistent with osseous metastasis, is shown in **c** and **d**. Avid ^{18}F -FDG uptake helped increase the conspicuity of the metastasis in a background of hyperplastic red marrow

^{18}F -FDG PET/MR

Breast cancer

A recent meta-analysis that explored the overall performance of PET/MR for whole-body staging of breast cancer reported high whole-body patient-based pooled sensitivity (0.98) and specificity (0.87) and high lesion-based sensitivity (0.91) and specificity (0.95) [65]. In a study focused specifically on the performance of PET/MR in evaluating osseous metastases in breast cancer, 109 patients underwent same-day contrast-enhanced PET/CT and PET/MR, demonstrating a sensitivity of PET/CT and PET/MR of 0.85 and 0.96, respectively. More importantly, PET/MR was positive for osseous metastases in 12% of the patients who did not have osseous metastases detected by PET/CT [66].

A study of whole-body staging by PET/MR and PET/CT showed similar accuracy when evaluated using a patient-based analysis [67]. However, PET/MR was superior to PET/CT in identifying bone metastases (sensitivity of 0.92 vs 0.69, respectively). Another study of 50 patients showed improved sensitivity of ^{18}F -FDG PET/MR in the detection of bone and liver metastases versus PET/CT [30]. The superior performance of PET/MR in detecting osseous metastatic disease is in large part due to the conspicuity of marrow replacing lesions on the MR portion of the study. Such a finding, in conjunction with even faintly increased ^{18}F -FDG uptake on the PET images, allows for identification of metastases. On PET/CT, if an osseous metastasis is CT occult, faint ^{18}F -FDG uptake without a corresponding CT abnormality might be misinterpreted as normal marrow heterogeneity. The addition of MR can help improve detection of focal osseous lesions

(Fig. 3) and may also help in distinguishing metastases from ^{18}F -FDG-avid benign bone lesions [68].

Lung cancer

^{18}F -FDG PET/CT is an important tool in the initial staging and restaging of both small-cell (SCLC) and non-small-cell lung cancer (NSCLC). This is reflected in NCCN guidelines [69, 70]. There are very few studies assessing the performance ^{18}F -FDG PET/MR in the evaluation of NSCLC, none of which have specifically investigated differences in PET/MR versus PET/CT in the detection of bone metastases [71]. Current literature, however, points to a comparable diagnostic accuracy for identification of M1 disease overall, regardless of the site of origin, with potential incremental value of MR over CT for detection of brain, bone, and liver metastases. [72–75].

Lymphoma

^{18}F -FDG PET/CT plays a critical role in staging and restaging of Hodgkin lymphoma and of certain subtypes of non-Hodgkin lymphoma [76, 77]. ^{18}F -FDG PET/MR has similar accuracy to PET/CT in the evaluation of lymphoma, particularly in identification of nodal disease [29, 78]. In selected cases, current National Comprehensive Cancer Network (NCCN) guidelines suggest the usage of MR and PET/MR for the initial workup of Hodgkin lymphoma [79].

Despite the paucity of literature specifically addressing the evaluation of lymphomatous involvement of bone marrow by PET/MR, there is substantial literature showing the superior sensitivity and specificity of MR compared to CT for the detection of marrow replacing lesions [43, 47]. CT may miss

Fig. 3 DOTATOC-PET/MR in a 57-year-old male with a history of gastric neuroendocrine tumor. **a** Axial 3D gradient echo T1 post-contrast, **b** DOTATOC-PET, and **c** axial fused PET/MR images through the neck show a focus of enhancement with corresponding

DOTATOC uptake in the spinous process of C4 (arrow), consistent with a bone metastasis. These findings are subtle and may be easily missed on stand-alone MR or stand-alone PET

sites of marrow involvement that can be detected by MR and considered suspicious if there is corresponding abnormal ^{18}F -FDG uptake. This was demonstrated in a study evaluating 28 consecutive lymphoma patients, where, although PET/MR and PET/CT were concordant in 96.4% of patients and demonstrated a similar sensitivity, lymphomatous bony involvement of bone was detected in one patient by PET/MR where it was missed by PET/CT. This patient was therefore correctly upstaged to stage IV by PET/MR, with potentially important treatment implications [80]. Based on our unpublished personal experience, integrated PET/MR can further improve the sensitivity of stand-alone ^{18}F -FDG PET and of stand-alone MR, detecting lesions which might be apparent on the MR or PET alone. The superior performance of the MR component of PET/MR over PET/CT may also help distinguish extra-nodal involvement of cortical bone from bone marrow involvement by lymphoma, a distinction that has important staging and treatment implications [81]. PET/MR may provide additional prognostic implications, given that chemotherapy first decreases glucose metabolism and then increases hydrogen proton diffusion [82]. Future investigation is needed to determine if tumors with concordant response on ^{18}F -FDG PET and DWI on interim scans show better outcomes compared to tumors with early ^{18}F -FDG PET response and delayed DWI response.

Non ^{18}F -FDG PET/MR

^{18}F -Sodium fluoride

^{18}F -Sodium fluoride (^{18}F -NaF) PET has proven clinically useful in the identification of both benign and malignant conditions. ^{18}F -NaF localizes to areas of elevated osseous blood flow and bone formation [83]. NCCN guidelines recommend bone scintigraphy or ^{18}F -NaF-PET/CT for evaluation of specific bone lesions in locally advanced or metastatic breast cancer [84]. Radiotracer uptake by osteoblasts is nonspecific

and may be elevated in benign conditions such as degenerative changes, osteonecrosis, fractures, inflammatory conditions, and benign bone neoplasms [85, 86]. This underscores the importance of careful interpretation of the radiotracer uptake pattern and correlation with anatomic imaging, where available. Although ^{18}F -NaF-PET/MR has been used in rat models, there are to date no published studies using ^{18}F -NaF-PET/MR to assess for bony metastases in humans [87]. In unpublished work, the authors have performed ^{18}F -NaF-PET/MR on humans showing radiotracer uptake corresponding to marrow signal abnormalities on MR at sites of bone metastases (Fig. 4).

^{18}F -Fluciclovine

^{18}F -Fluorocyclobutane-1-carboxylic acid (^{18}F -FACBC or ^{18}F -fluciclovine) is an amino acid analogue that localizes to areas of increased amino acid transport. Normal distribution of ^{18}F -fluciclovine uptake includes the pancreas, liver, salivary glands, pituitary glands, gastrointestinal tract, bone marrow, and muscle [88, 89]. Prostate cancer and glial brain lesions show uptake of ^{18}F -fluciclovine [90, 91].

Given that prostate cancer has a predilection for osseous metastases, it is conceivable that ^{18}F -fluciclovine PET/MR would be helpful for evaluation of metastatic prostate cancer. However, most research has focused on identification of lymph node or soft tissue disease involvement [18, 92]. Evaluation of bone metastases using ^{18}F -fluciclovine has largely been performed with PET/CT [93]. Densely sclerotic bony lesions might not take up enough ^{18}F -fluciclovine to be easily detected by PET. Moreover, the background marrow tracer uptake may further obscure small subtle areas of increased tracer accumulation. Only one study to date has evaluated the diagnostic performance of ^{18}F -fluciclovine PET/MR for the evaluation of bone metastases from prostate cancer, demonstrating detection rates of 0.68 for stand-alone PET and of 1.00 for PET/MR. In this study, the lesions most

Fig. 4 ^{18}F -NaF-PET/MR in a 56-year-old female with metastatic breast cancer. **a** Axial T1 in phase Dixon images, **b** fused PET/MR. A low signal lesion in the left hemisacrum (arrows in **a**) exhibits increased ^{18}F -NaF uptake (arrows in **b**). These findings are compatible with an osseous metastasis

commonly missed on stand-alone PET belonged to the densely sclerotic category. These were identified readily on T1-weighted MR sequences [94].

^{68}Ga and ^{18}F -PSMA

Prostate-specific membrane antigen (PSMA) radiopharmaceuticals labeled with ^{68}Ga and ^{18}F target cell surface

receptors and have shown clinical utility in investigating prostate cancer. Since ^{68}Ga -PSMA-11 was first developed, most of the available studies have employed this radiopharmaceutical. The normal distribution of ^{68}Ga -PSMA-11 in the body is in the lacrimal and salivary glands, liver, spleen, kidneys, gastrointestinal tract, and neural ganglia [88]. Other PSMA based imaging agents labeled with ^{68}Ga have a very similar biodistribution. A critical limitation of PSMA imaging is that

Fig. 5 PSMA-PET/MR in a 73-year-old male with elevated prostate specific antigen. **a** Coronal T2-weighted and **b** coronal PSMA-PET images through the prostate and left medial acetabulum. **c** Axial 3D gradient echo T1 post-contrast and **d** fused axial PET/MR images through the left acetabulum. These show a T2w hypointense lesion in the right peripheral zone of the prostate at the level of the mid-gland (arrow) consistent with a primary prostate adenocarcinoma. A T2w hypointense, enhancing lesion in the left medial acetabulum (arrowhead) with associated PSMA uptake is consistent with a prostate adenocarcinoma metastasis

renal excretion results in accumulation of radiotracer in the bladder and renal collecting system. The resultant halo phenomenon can obscure abnormal uptake in the prostate or prostatectomy bed as well as regional metastatic disease in the pelvis [95]. Strategies for reducing the halo phenomenon include late imaging with or without administration of diuretics or early imaging prior to substantial accumulation of radiotracer in the urinary tract [96–99]. Development of PSMA imaging agents with hepatobiliary excretion, such as ^{18}F -PSMA-1007, has shown progress in mitigating this problem [100].

Much like ^{18}F -fluciclovine, most research on PSMA labeled with ^{68}Ga has focused on PET/CT rather than PET/MR [101]. In limited studies of ^{68}Ga -PSMA PET/MR, bone metastases were detected following definitive treatment with early biochemical recurrence even at low serum prostate-specific antigen levels (PSA < 0.2 ng/mL) [102]. One recent study demonstrated similar performance of ^{68}Ga -PSMA PET/MR and PET/CT for the evaluation of bone metastases from prostate cancer. However, the MR of the PET/MR was able to detect two bone metastases which were not visible on CT and may have been otherwise missed [103]. Furthermore, in another study, four lesions, including one bone lesion, were indeterminate on ^{68}Ga -PSMA PET/CT but were definitively characterized as metastases on ^{68}Ga -PSMA PET/MR [104]. Given that benign osseous lesions such as fibro-osseous lesions can demonstrate radiotracer uptake and therefore be misinterpreted as metastases, it is important to assess the characteristics of osseous lesions on anatomic imaging [105]. This is a clear point of strength of PET/MR versus

PET/CT. Another recent study comparing the performance of ^{68}Ga -PSMA PET/CT and PET/MR showed agreement on sites of pelvic and distant metastatic disease, including osseous metastatic disease. However, ^{68}Ga -PSMA PET/MR was superior in detection of localized disease such as extracapsular tumor extension and seminal vesicle involvement, primarily owing to the high soft tissue contrast and multiparametric nature of MR [106]. Quantitative metrics incorporating ^{68}Ga -PSMA uptake and multiple MR imaging parameters have also been shown to distinguish normal prostatic tissue from clinically significant prostate cancer [107]. Therefore, given the benefits of MR in detection and characterization of bone lesions as well as the superior performance in evaluation of prostatic and local extra-prostatic disease, it is expected that PET/MR might be advantageous over PET/CT (Figs. 5, 6, 7).

^{68}Ga -DOTATATE, ^{68}Ga -DOTATOC, and ^{68}Ga -DOTANOC

^{68}Ga -DOTATATE is one of several radiopharmaceuticals targeting the somatostatin receptor (SSTRA) for PET imaging. ^{68}Ga -DOTATATE, unlike other somatostatin analogs ^{68}Ga -DOTANOC and ^{68}Ga -DOTATOC, binds with highest affinity to the surface somatostatin receptor subtype 2, which tends to be overexpressed in well-differentiated neuroendocrine tumors (Fig. 8) [108].

^{68}Ga -DOTATATE PET/CT has proven to have a significant impact on the management of neuroendocrine tumor patients when compared to conventional anatomic and nuclear

Fig. 6 PSMA PET/MR in a 78-year-old male with metastatic prostate cancer. **a** Axial 3D gradient echo T1 post-contrast **b** PET, and **c** fused PET images through the lower chest from PSMA PET/MR show an enhancing lesion in the left 11th rib near the costovertebral junction with corresponding increased radiotracer uptake (arrow). This is consistent with an osseous metastasis. **d** Axial 3D gradient echo T1

post-contrast **e** PET, and **f** fused PET images through the lower chest from PSMA PET/MR following radiotherapy to the medial 11th rib show near complete resolution of enhancement of the left 11th rib near the costovertebral junction with corresponding resolution of increased radiotracer uptake (arrow) suggesting treatment effect

Fig. 7 PSMA PET/MR in an 82-year-old male with untreated metastatic prostate cancer. **a** Axial 3D gradient echo T1 **b** PET, and **c** fused PET/MR images through the sacrum show T1 weighted hypointense signal involving the right hemisacrum in keeping with metastasis. Mild

corresponding radiotracer uptake may reflect relatively low overexpression of PSMA by the prostate cancer in this patient and underscores the value of the MR component for the detection of marrow signal abnormalities

Fig. 8 DOTATOC-PET/MR in a 61-year-old female with a history of pancreatic neuroendocrine tumor presenting with bone and nodal metastatic disease. **a** Axial diffusion-weighted **b** ADC map, **c** DOTATOC-PET, and **d** fused PET/MR images show a lesion in the left aspect of the L1 vertebral body which demonstrates restricted diffusion with corresponding DOTATOC uptake (arrow). Retroperitoneal lymph nodes at this level show similar restricted diffusion with DOTATOC uptake (arrowheads). This example demonstrates correlation between somatostatin receptor expression, as assessed by DOTATOC-PET, and increased cellular density, as demonstrated on DWI

Table 2 PET/MR radiopharmaceuticals and role in assessment of osseous metastatic disease

PET radiopharmaceutical	Principal indications	Interpretation criteria	Limitations/pitfalls
FDG	Breast cancer, lung cancer, lymphoma (Ly), multiple myeloma (MM), sarcoma	Focal areas of increased uptake in the bones; diffuse and intense uptake in bone marrow (BM) can occur in Ly and MM	<ul style="list-style-type: none"> • Diffuse increased uptake in BM in Ly after treatment, especially after colony-stimulating factors, reflects BM hyperplasia rather than infiltration [122]. • False positive results can occur with degenerative change, fractures, or benign tumors. MR can be helpful for differentiation.
PSMA	Prostate cancer	Focal areas of uptake in the bones	<ul style="list-style-type: none"> • False positive results can occur with benign osseous tumors. MR can be helpful for differentiation [35, 105].
Fluciclovine	Prostate cancer	Focal accumulation above background	<ul style="list-style-type: none"> • Limited sensitivity in detecting sclerotic bone lesions which can have low radiotracer uptake [94]. • Physiological BM uptake, typically heterogeneous or patchy, can be seen, particularly in the setting of previous systemic therapy [89, 123].
NaF	Breast cancer, prostate cancer	Focal areas of increased uptake higher than in normal bone	<ul style="list-style-type: none"> • Tracer specifically localizes to skeletal metastases, limiting PET assessment of nonosseous structures. • False positive results can occur with degenerative changes, fractures, benign tumors [85, 86].
SSTRA	Neuroendocrine tumors	Focal areas of increased uptake	<ul style="list-style-type: none"> • False positive results can occur in degenerative changes, fractures, benign tumors [120, 121].

medicine imaging. Additional information gleaned from ^{68}Ga -DOTATATE PET/CT compared to conventional nuclear medicine studies may result in a change in management in up to 75% of patients [109]. A meta-analysis showed a sensitivity and specificity of ^{68}Ga -DOTATATE PET/CT for neuroendocrine tumors of 0.93 and 0.96, respectively [110]. However, poorly differentiated neuroendocrine tumors (WHO G3) typically show decreased ^{68}Ga -DOTATATE uptake and greater ^{18}F -FDG uptake, likely in part owing to decreased expression of somatostatin surface receptors [111]. As a result, greater ^{18}F -FDG uptake in neuroendocrine tumors is associated with a poorer prognosis mostly due to a greater tumor heterogeneity and presence of hepatic metastatic disease at presentation [112]. Beyond gastrointestinal neuroendocrine tumors, somatostatin analogs have shown early promise with pheochromocytomas, paragangliomas, neuroblastomas, and meningiomas [113–118].

Osteoblasts express subtype 2 somatostatin surface receptor [119]. Although osteoblastic activity is associated with sclerotic osseous lesions including metastases, it can be seen in response to a wide variety of non-malignant processes in bone, including osteoarthritis and fractures. ^{68}Ga -DOTATATE uptake can also be seen with benign osseous lesions such as fibrous dysplasia and hemangiomas [120, 121]. MR is more accurate in distinguishing these benign processes from malignant-appearing marrow replacing lesions than CT. Although there are currently no studies comparing the performance of ^{68}Ga -DOTATATE PET/CT and PET/

MR for skeletal or other metastatic disease, we believe that the benefits of superior anatomic imaging gained by simultaneous MR will better help assess the burden of skeletal metastatic disease.

PET/MR radiopharmaceuticals with indications, interpretation criteria, and limitations/pitfalls for assessment for skeletal metastases are described in Table 2.

Recommendations

^{18}F -FDG avid malignancies

For staging of ^{18}F -FDG avid malignancies including lymphoma, small-cell and non-small-cell lung cancers, head and neck squamous cell cancer, melanoma, colorectal cancer, breast cancer, esophageal cancer, gastric cancer, pancreatic adenocarcinoma, and sarcoma, consider ^{18}F -FDG PET/MR if there are suspected skeletal metastases or if the presence of skeletal metastases will change management.

Prostate adenocarcinoma

PSMA and ^{18}F -Fluciclovine imaging with PET/CT and PET/MR show similar promise in identifying sites of metastatic disease in the setting of biochemical recurrence. Given the propensity of prostate adenocarcinoma to result in osseous metastases, anatomic imaging of the MR portion of the PET/

MR may permit for more definitive characterization of osseous lesions.

Well-differentiated neuroendocrine tumors

For staging of well-differentiated neuroendocrine tumors, consider ^{68}Ga -DOTATATE or ^{68}Ga -DOTANOC or ^{68}Ga -DOTATOC PET/MR. PET/MR may be particularly helpful for evaluating skeletal metastatic disease, both in the identification of neoplastic focal marrow replacing lesions and in distinguishing them from benign osteoblastic activity. In poorly differentiated neuroendocrine tumors, ^{18}F -FDG PET/MR should be considered.

Conclusions

Technical advances in PET/MR have made it well suited for the evaluation of skeletal involvement of malignancies. To date, relatively few studies specifically explore the performance of PET/MR for identifying bone metastases. Despite their heterogeneity and small numbers, these studies suggest that PET/MR detects more bone metastases than PET/CT both on a per-lesion analysis and, more importantly, on a per-patient analysis. Moreover, PET/MR may also improve specificity owing to superior lesion characterization by the MR component [124].

In our opinion, based on experience imaging thousands of patients at 13 major PET/MR centers on 3 continents, when a hybrid PET study is indicated, PET/MR should be considered for staging of malignancies where there is a high likelihood of osseous metastatic disease based on the characteristics of the primary malignancy, high clinical suspicion, or where the presence of osseous metastases will have an impact on patient management. Tumor-specific tracers continue to emerge and should be considered, when available. However, to do so, both the MR and PET components must be used optimally, which means dedicated and accurate MR protocols, choice of the proper radiopharmaceuticals, and stringent up-to-date PET acquisition protocols.

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Declarations

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