Clinical PET/MRI: 2018 Update

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OBJECTIVE. The purpose of this article is to provide an update on clinical PET/MRI, including current and developing clinical indications and technical developments.

CONCLUSION. PET/MRI is evolving rapidly, transitioning from a predominant research focus to exciting clinical practice. Key technical obstacles have been overcome, and further technical advances promise to herald significant advancements in image quality. Further optimization of protocols to address challenges posed by this hybrid modality will ensure the long-term success of PET/MRI.

PET/MRI has steadily transitioned from a predominant research focus to exciting clinical practice at a number of medical centers [1]. Here, we review recent changes in the field of PET/MRI, including indications and protocols where PET/MRI appears to have a clear foothold in clinical practice. This article will focus primarily on clinical PET/MRI and adult diseases. We review some key recent technical advances and clinical data that support these areas of growth. Finally, we touch on indications that show potential for success in the very near future.

PET/MRI has undergone rapid evolution in recent years. An article in 2016 by Spick and colleagues [2] combining data from multiple studies and over 2300 patients showed the equivalency of 18F-FDG PET/CT and PET/MRI in oncologic evaluation. A prior fixation on finding a single best application to justify investing in PET/MRI has given way to a multitude of clinically useful applications. The initial enormous hurdle of developing a PET detector system that could function in an MRI magnetic field was overcome with avalanche photodiode solid-state PET detectors. More recently, faster silicon photomultiplier detectors have been introduced, advancing PET performance to a new state of the art. The field is also addressing and overcoming core issues with MRI-based attenuation correction. Long scan times required for body PET/MRI result in patient dissatisfaction; however, more-rapid and robust MRI sequences promise to improve the patient experience and open new opportunities. Recent developments have offered an exciting glimpse into the potential of simultaneous PET/MRI to characterize tumor heterogeneity, perform complex motion correction, leverage advanced data mining and bioinformatics, and integrate biomarkers to better evaluate disease processes, cancer evolution, and therapy response [3].

Instrumentation Update

The core basic design of clinical and commercially available PET/MRI systems has remained unchanged for several years. Currently, there are two vendors producing PET/MRI systems: Siemens Healthcare and GE Healthcare. Both the Siemens Healthcare Biograph mMR [4] and the GE Healthcare Signa [5] are fully integrated PET/MRI systems in which solid-state PET detectors reside within a 3-T MRI gantry, allowing simultaneous PET and MRI acquisition. The important characteristics of both PET/MRI systems are listed in Table 1.

Attenuation Correction

Once a major challenge to the field, MRI-based attenuation correction is no longer viewed as a significant impediment to clinical adoption of PET/MRI. However, attenuation correction must be taken into account when reading PET/MRI in a similar manner to the many other factors that are known to affect standardized uptake value (SUV) in PET data. A detailed review of the numerous MRI-based attenuation correction techniques is beyond the scope of this article (see [6] for
an excellent summary). As opposed to the straightforward attenuation correction used with CT, MRI-based attenuation correction involves various components: patient attenuation correction, bed and coil hardware attenuation correction, and truncation correction [3]. To identify artifacts, it remains important that MRI-based attenuation correction maps and non–attenuation-corrected images be displayed and reviewed during interpretation [7].

For body MRI-based attenuation correction, vendors use a segmentation-based technique in which in-phase, out-of-phase, water, and fat images obtained using Dixon sequences [8] are separated into soft tissue, fat, and bone images obtained using zero-TE images of the pelvis into a quantitatively accurate attenuation map [23].

TABLE 1: Design and Performance Characteristics of the Biograph mMR (Siemens Healthcare) and Signa (GE Healthcare) PET/MRI Systems

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biograph mMR</th>
<th>Signa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnet component</td>
<td>3-T superconductor</td>
<td>3-T superconductor</td>
</tr>
<tr>
<td>Bore diameter (cm)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Gradient coil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (mT/m)</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Slew rate (T/m/s)</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Transaxial FOV (cm)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Axial FOV (cm)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>PET component</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystal material</td>
<td>Lutetium oxyorthosilicate</td>
<td>Lutetium-based scintillator</td>
</tr>
<tr>
<td>Crystal size (mm³)</td>
<td>4.0 × 4.0 × 20</td>
<td>4.0 × 5.3 × 25</td>
</tr>
<tr>
<td>Transaxial FOV (cm)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Axial FOV (cm)</td>
<td>25.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Detector type</td>
<td>Avalanche photodiode</td>
<td>Silicon photomultiplier</td>
</tr>
<tr>
<td>Timing resolution (ps)</td>
<td>2930</td>
<td>386</td>
</tr>
<tr>
<td>PET performance specifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET sensitivity (cps/kBq)</td>
<td>15.0</td>
<td>23.3</td>
</tr>
<tr>
<td>PET spatial resolution at 1 cm (mm)</td>
<td>4.3</td>
<td>4.4</td>
</tr>
<tr>
<td>PET peak noise equivalent count rate (kcps) at kBq/mL</td>
<td>184 at 23.1</td>
<td>218 at 17.8</td>
</tr>
</tbody>
</table>

Note—The system design characteristics have been described elsewhere [4, 5]. The National Electrical Manufacturers’ Association PET performance specifications have been described elsewhere [4, 16].

Bone attenuation in the head is much more significant than in most of the body and has required special attention. The Signa system uses an atlas-based approach (an average skull is inserted into the MRI-based attenuation correction map) to compensate for skull attenuation [14]. A zero-TE MRI sequence has recently been introduced to produce a patient-specific skull attenuation map [15, 16] (Fig. S1 can be viewed in the AJR electronic supplement to this article, available at www.ajronline.org). The Biograph mMR system uses an ultrashort-TE sequence, and an atlas-based approach (multipatient database of matched MR and CT images) has recently been introduced as well. In a comparison of MRI-based attenuation correction algorithms applied to a large cohort of patient studies acquired on the Biograph mMR, it was shown that methods that specifically account for bone achieved low global and local bias and variance [17].

Other MRI-based attenuation correction approaches under development, but not yet commercially available, include those using joint estimation and deep learning. In joint estimation, the PET emission data are used to provide an estimate of the attenuation information. This method is the maximum likelihood reconstruction of activity and attenuation algorithm [18]. By incorporating time-of-flight information, the activity and attenuation distributions can be determined up to a constant [19]. Deep convolutional neural networks have been developed for noise reduction and segmentation of medical images [20, 21]. A deep convolutional neural network has been developed to overcome some of the limitations of maximum likelihood reconstruction of activity and attenuation [22], and a deep convolutional neural network has been trained to transform Dixon MRI and zero-TE images of the pelvis into a quantitatively accurate attenuation map [23].

Motion Correction

Diaphragmatic motion correction on both body MRI and PET are routine practice in current clinical PET/MRI. More exciting is the developing practice of correcting PET images for multiple types of motion simultaneously. Simultaneous PET/MRI can be corrected for respiratory, cardiac, and bulk patient motion using simultaneously acquired MR images. As a result, the PET images have reduced motion artifacts, decreased blurring, improved colocalization of PET and MRI anatomy, and more accurate SUV measurements. These techniques may improve PET beyond what is currently available in PET/CT. There have been several publications showing the effectiveness of these promising techniques (see [24] for a good review), but to date there are no commercially available algorithms.

Oncologic Body Applications

General Considerations

Integrated PET/MRI has several technical advantages over PET/CT that are particularly relevant for body applications. With PET/CT, most protocols are performed with nongated CT followed by nongated PET, which introduces misregistration artifacts due to respiratory motion, particularly in the upper abdominal organs. In contrast, integrated PET/MRI protocols routinely use respiratory gating, and recently even the MRI-based attenuation correction can be gated. Therefore, there is a high degree of temporal and spatial coregistration, which results in superior image fusion. Another clear advantage of PET/MRI is the length of time PET data can be collected while simultaneously collecting MRI data, which generates PET images with decreased noise that are more sensitive for subtle lesions. Newer radiotracers targeting neuroendocrine tumors (NETs) (e.g., the recently U.S. Food and Drug Administration [FDA]–approved ⁶⁸Ga-DOTATATE)
**Update on Clinical PET/MRI**

**Hepatobiliary Cancer**

PET/MRI has been shown to be particularly helpful for assessment of liver metastases and, therefore, has utility in evaluating malignancies with a propensity for hepatic spread (Fig. 2). A recent study found that multiparametric FDG PET/MRI had comparatively higher accuracy for the detection of liver metastases from nonmucinous colorectal tumors when compared with the individual modalities (PET and MRI) [25]. Hepatobiliary phase liver imaging after administration of hepatocyte-specific contrast agent, such as gadoxetate, has critical advantages for the detection of hepatic metastases. Navigated hepatobiliary phase imaging using gadoxetate aligns well with respiratory-compensated list mode liver PET data [26]. PET/MRI overlay of metabolic information on the hepatobiliary phase images adds to the ability to detect active versus inactive cancer and improves reader diagnostic confidence [27]. The field still lacks standardized PET/MRI protocols [1], allowing some novel approaches to develop. For example, an adaptive PET/MRI protocol with whole-body PET/MRI followed by dedicated MRI of organs with positive PET findings has been applied to colorectal cancer, adding clinical value compared with contrast-enhanced CT, especially in lymph nodes and liver lesions [28]. The improved characterization of these lesions with PET/MRI was mainly the result of the information provided by MRI. In 21.6% (11/51) of patients, treatment strategy was changed because of additional information provided by PET/MRI. However, PET/MRI had inferior performance for detection of pulmonary metastases (detection rate of 52.9%).

The inferior performance of PET/MRI compared with CT for the detection of pulmonary metastases is primarily due to known limitations of the MRI component. However, a study examining pulmonary nodules missed at PET/MRI in a heterogeneous cohort of patients with cancer [29] found that most missed non–FDG-avid nodules either disappeared or remained stable at follow-up imaging. A free-breathing ultrashort-TE sequence (not yet clinically available) or incorporation of a 3D contrast-enhanced T1-weighted thoracic sequence in the PET/MRI protocol may improve the detection of solid pulmonary nodules at MRI down to 6 mm [30]. It is important to note that the nondiagnostic CT component of PET/CT is also inferior to diagnostic CT for the detection of pulmonary nodules. Therefore, additional diagnostic chest CT may be considered as part of cancer staging.

**Neuroendocrine Tumors**

A novel class of somatostatin analogs labeled with the positron-emitting radionuclide 68Ga have become part of standard evaluation of NETs. Of the available agents, 68Ga-DOTATATE is approved in the United States for this indication. Molecular imaging with 68Ga-DOTATATE PET allows accurate delineation of disease extent, identification of a primary tumor that may be occult on cross-sectional imaging, and noninvasive characterization of tumor receptor status and heterogeneity [31, 32]. On the other hand, MRI is considered a robust anatomic modality for liver imaging. In particular, DWI and the hepatobiliary-specific MRI contrast agent gadoxetate disodium have shown a very high sensitivity for the detection of hepatic metastases (Fig. 3) from gastroenteropancreatic (GEP) NETs [33–35]. Because many patients with GEP NETs undergo dedicated liver MRI and PET during routine staging and after therapy, a combined PET/MRI approach offers the promise to provide one comprehensive study for GEP NETs (Fig. 3). In a study that used a single-injection dual-imaging protocol, PET/MRI using 68Ga-DOTATOC (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–D-Phyl-Tyr3-octreotide) correctly identified more NET lesions than did 68Ga-DOTATOC PET/CT and provided superior lesion conspicuity. A strong correlation was observed in the maximum SUVs from the two modalities [36]. However, the MRI component of the imaging protocol was performed with gadoxetate, which is an extracellular contrast agent. Another single-injection dual-imaging protocol PET/MRI study that used a hepatobiliary-specific contrast agent, gadoxetate, found an increased detection rate for hepatic metastases on the hepatobiliary phase imaging [27]. Thus, a synergistic combination of 68Ga-peptide PET with optimized multiphase MRI, including a hepatobiliary-specific contrast agent, has the potential to affect management of patients with GEP NET, and this has rapidly gained traction in our own practice.

**Pancreatic Adenocarcinoma**

FDG PET/CT has not been widely adopted for the evaluation of pancreatic ductal adenocarcinoma (PDAC), likely in part because of the low level of FDG activity of these tumors [37]. However, the higher sensitivity of silicon photomultipliers combined with respiratory gating and longer PET acquisition that is possible with simultaneous PET/MRI may be particularly beneficial for the evaluation of PDAC. In a small study, PET/MRI has shown better performance than multiphase CT to detect liver metastases in patients with PDAC [38]. However, CT and PET/MRI are complementary to each other in PDAC evaluation: CT is the preferred imaging modality for locoregional assessment, whereas PET/MRI is mainly used to evaluate distant metastatic disease and response to neoadjuvant therapy in patients with borderline resectable PDAC [37]. Imaging biomarkers from integrated PET/MRI may also predict prognosis [38, 39]. In one study, the ratio of metabolic tumor volume to minimum apparent diffusion coefficient (ADC) was found to correlate with tumor aggressiveness, clinical stage, and progression-free survival in patients with PDAC or periampullary cancer [39].

**Prostate Cancer**

Multiparametric MRI has a well-established role in the evaluation of prostate cancer at the time of initial staging but can have variable results depending on the protocol, tumor grade, and tumor size. Integrated PET/MRI using prostate-specific PET probes has been evaluated to improve performance of the individual modalities for staging; however, this is an off-label indication in the United States but is a relatively common use of PET/MRI in Europe [1]. In one study, 68Ga-PSMA-11 PET/MRI showed incremental gain in diagnostic performance over the individual modalities (multiparametric MRI and PET) for localization of primary prostate cancer [40]. These results have the potential to improve the performance of targeted fusion image–guided biopsy. In theory, integrated PET/MRI also has the potential to improve detection of regional lymph node and distant metastases at the time of initial staging. However, there have been limited and contradictory preliminary data about the usefulness of 68Ga-PSMA PET for this indication [40–42], necessitating further research.
Another potential use of PET/MRI is in the investigation of biochemical recurrence of prostate cancer. In general, MRI is considered superior for the detection of local recurrence, compared with 11C-choline and 18F-fluciclovine PET/CT, whereas PET using these approved prostate-specific probes is considered the modality of choice for the detection of nodal and distant metastases [43]. Therefore, the combination of the two modalities can offer a one-stop shop for the evaluation of prostate cancer biochemical recurrence (Fig. 4). Initial studies using the single-injection dual-imaging protocol have shown equivalent performance of PET/MRI and PET/CT for the detection of nodal and osseous metastases from recurrent prostate cancer [44, 45].

Gynecologic Cancer

Both MRI and PET have well-defined and independent utility in the evaluation of gynecologic malignancies. The major gynecologic applications of PET/MRI have been in the primary staging of cervical and endometrial malignancies, planning of radiotherapy in cervical cancer, evaluation of response to therapy in ovarian cancer, and detection of recurrence in these malignancies [46–49]. In many of these studies, combined PET/MRI showed incremental benefits in accuracy compared with PET and MRI individually. However, it should be noted that Medicare in the United States limits the approved use of FDG PET in initial staging of cervical cancer to patients with evidence of distant metastases.

Nononcologic Body Applications: Inflammatory Bowel Disease

In patients with Crohn disease and ulcerative colitis, FDG PET/MRI may hold promise. There are two potential indications: differentiation of predominantly fibrotic from predominantly inflammatory strictures and assessment of systemic disease activity [50, 51]. Both CT enterography and MR enterography have shown inconsistent results for differentiation of fibrotic and inflammatory strictures because of their reliance on contrast enhancement for this distinction. In one PET/MRI study, the product of maximum SUV and ADC showed a trend toward better performance than did individual PET and MRI metrics for the identification of predominantly fibrotic enteric strictures [50]. Integrated PET/MRI has also shown higher accuracy for the detection of active inflammation in patients with Crohn disease than either MRI or PET alone [52]. Moreover, PET/MRI can be performed at a significantly lower radiation dose than can PET/CT, which is especially important in young patients needing serial imaging evaluation. In one prospective pilot study in patients with ulcerative colitis, hybrid PET/MRI metrics were more accurate than serum biomarkers for assessing subclinical inflammation, and the combination of serum biomarkers plus PET/MRI was even more accurate than either alone [53].

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Nononcologic Body Applications: Primary Brain Tumors

Neurooncologic PET/MRI uses targeted radiotracers to evaluate different aspects of tumor function and behavior, including glucose metabolism (FDG), amino acid transport, protein synthesis (1C-methionine, 18F-fluoroethyl-L-tyrosine [FET], and 18F-fluoro-L-3, 4-dihydroxyphenylalanine [DOPA]), DNA synthesis (18F-fluorothymidine), and hypoxia (18F-fluoromisonidazole). In the United States, the use of these agents, with the exception of FDG, is mainly in the research domain.

FDG PET has proven utility in differentiating radiation necrosis from recurrent tumor [54], correlates with tumor grade [55], and may show transformation from low- to high-grade glioma [55, 56]. However, FDG interpretation is hampered by high intrinsic uptake of FDG in normal brain parenchyma, resulting in inferior differentiation of tumor margins compared with amino acid tracers such as 11F-FET PET [57] and 18F-DOPA [58]. These tracers have greater signal-to-background noise ratio and specificity for tumoral tissue compared with FDG and have been shown to be the PET agents of choice for glioma assessment [59, 60].

Advanced MRI techniques, including DWI, perfusion-weighted imaging (PWI), diffusion-tensor imaging, and MR spectroscopy (MRS), have now become an integral part of brain tumor management [61]. For example, the combination of functional MRI and diffusion-tensor imaging can show the spatial relationship between intracranial lesions and white matter tracts, which is highly useful for preoperative planning and risk assessment [62].

The unprecedented multiparametric functional, anatomic, and metabolic capability of integrated PET/MRI seems well suited for primary CNS lesion evaluation, but initial reports have been conflicting. A recent retrospective study of 60 gliomas evaluated with FDG PET and multiparametric MRI showed that PET delineated between high- and low-grade gliomas with accuracy similar to that of MRI but did not improve accuracy when considered in addition to multiparametric MRI (which included contrast-enhanced imaging, DWI, ADC, PWI, and MRS) [63]. A recent prospective study examining integrated FDG PET/MRI showed a better overall performance of PWI compared with PET in differentiating low- from high-grade gliomas and also recurrent tumor from treatment effect. Interestingly, there was poor correlation between perfusion measures and SUVs, which the authors attributed to these parameters showing different aspects of tumor biology [64]. Similarly, a recent study examining integrated 18F-FET PET/MRI in predicting glioma grade showed that 18F-FET PET and PWI differentiated low- from high-grade gliomas with similar accuracy, but that regional abnormalities were often incongruent between PET and PWI, likely indicating different pathophysiologic phenomena [65]. Simultaneous PET/MRI has been shown to be useful in evaluation of patients with suspected recurrent glioma [66], including differentiation of recurrence from radiation necrosis [67]. Integrated 18F-DOPA PET/MRI has been shown to have excellent accuracy for assessing striatal involvement in pediatric glioma [68]. Given these results, amino acid PET/MRI is expected to have a significant effect for patients with glioma in the United States once it is clinically available.

Primary CNS lymphoma (PCNSL) and glioblastoma multiforme (GBM) can have overlapping imaging features at MRI, including corpus callosum involvement. Several studies have shown the utility of FDG PET to differentiate PCNSL (which typically is more FDG avid) from GBM (which typically is less FDG avid) [63, 69] (Fig. 5). FDG PET has also shown benefit in PCNSL treatment response evaluation [70] and offers prognostic information for these patients [71]. Makino and colleagues [72] examined the added benefit of FDG uptake and quantitative ADCs to conventional MRI to differentiate between PCNSL and GBM and found increased accuracy by inclusion of metabolic data (95% vs 75%) but no diagnostic effect from the inclusion of ADC data. In contrast, larger and more recent studies have shown the utility of both PWI and DWI in differentiating PCNSL and GBM [73, 74]. There have yet to be any studies detailing the performance of integrated PET/MRI for this purpose.

Intracranial Metastases

Although there has been tremendous research into the roles of PET and MRI in evaluation of primary CNS tumors, intracranial metastatic disease occurs up to 10 times more
commonly than does primary CNS tumor [75]. Simultaneous brain PET/MRI may be acquired to assess the presence of intracranial metastatic disease from sources outside the CNS, including advanced lung cancer [76] (Fig. 6) and high-risk melanoma [77]. Complete staging in a single examination increases patient convenience and is a key advantage of integrated PET/MRI compared with separate PET/CT and brain MRI in patients at risk for brain metastases.

Head-and-Neck Cancer

Head-and-neck cancer represents another exciting avenue for PET/MRI use given the widespread use of PET/CT and MRI for radiation and preoperative planning. FDG PET/CT has a well-established role in head and neck squamous cell carcinoma, including staging, detection of occult primary malignancies, assessment of chemoradiotherapeutic response, and differentiation of local recurrence from treatment effect [78].

Huang et al. [79] found that fused PET/MR images had a higher coefficient of correlation with pathologic tumor size than did contrast-enhanced CT, MRI, or PET/CT. Combined gadolinium-enhanced PET/MRI has been shown to yield similar radiation treatment gross tumor volumes compared with CT in patients with primary oropharyngeal cancer [80], although the authors noted cases in which PET/MRI substantially altered the gross tumor volume and, therefore, radiation plan. Researchers from Zurich have found improved performance of contrast-enhanced PET/MRI versus contrast-enhanced PET/CT in 85 patients with head-and-neck cancer undergoing sequential PET/CT and PET/MRI on a trimo-dality system, noting increased diagnostic confidence for accurate lesion detection (especially in the nasopharynx or larynx), infiltration of adjacent structures, and perineural spread of tumor [81]. This is especially critical given the higher risk of local recurrence, metastatic disease, and decreased survival in patients with perineural metastasis [82]. An additional study examining integrated PET/MRI evaluation of 16 patients with pathologically proven laryngeal cancer reported on the usefulness of PET/MRI for staging, noting a significant correlation between PET/MRI findings and endoscopic or histologic evaluation and also a significant effect on patient management [83].

Nononcologic Neurology Applications

Dementia

MRI plays an important role in dementia evaluation. It is useful to exclude treatable structural lesions and to show specific atrophy patterns, such as atrophy of the medial temporal lobes in patients with Alzheimer disease (AD) [84], one of the best-established neuroimaging biomarkers of AD. Moreover, MRI can detect specific patterns of atrophy and signal abnormality in less-common neurodegenerative processes, such as selective midbrain atrophy in progressive supranuclear palsy and pontocerebellar atrophy with cruciform T2 hyperintensity in multiple system atrophy [85, 86].

PET has a well-proven ability to detect pathologic abnormalities at a molecular level, long before the structural and signal changes occur at MRI. There are several available radiotracers in clinical use for imaging of patients with dementia, including FDG and several amyloid PET agents, including [18F-florbetapir, [18F-florbetaben, and [18F-flutemetamol. FDG PET has high accuracy in distinguishing AD from other neurodegenerative disorders, such as frontotemporal dementia [87]. Although FDG PET is FDA approved only for distinguishing AD from frontotemporal dementia, distinctive patterns of cerebral hypometabolism have been described in many other neurodegenerative conditions [85, 86, 88]. The typical pattern of AD hypometabolism is considered an imaging biomarker [89]. Amyloid PET has emerged as an invaluable tool for noninvasive evaluation of amyloid burden [90]. Patients with amyloid-positive findings at PET tend to experience faster cognitive decline, greater likelihood of mild cognitive impairment progression to AD, and faster rates of brain atrophy than do control subjects with amyloid-negative findings [91]. As such, positive cortical amyloid binding is also considered a biomarker of AD pathology and has been implemented into the diagnostic criteria of mild cognitive impairment and AD-related dementia [92].

Given the ability of PET/MRI to depict biomarkers of β-amyloid plaque deposition (cortical amyloid PET binding) and neuronal degeneration and injury (MRI temporal lobe atrophy and FDG PET hypometabolism), integrated PET/MRI offers the possibility of a complete neuroimaging assessment in one convenient session. A recent study of simultaneous amyloid PET/MRI in 100 subjects with suspected mild cognitive impairment, AD, or frontotemporal dementia who underwent simultaneous PET/MRI with [18F-florbetaben or [11C-labeled Pittsburgh compound B found feasibility and high patient or caregiver and referrer acceptance of this new one-stop imaging test [92]. Other studies have detailed early success with both FDG and amyloid PET/MRI in patients with AD, dementia with Lewy bodies, vascular dementia, frontotemporal dementia, and logopenic aphasia [93–95].

Epilepsy

FDG PET/MRI has been successful in helping to bring more patients with intractable epilepsy to surgery for cure. FDG is the most commonly applied PET radiotracer for these patients, because epileptogenic foci typically show hypometabolism on interictal imaging [96]. Focal FDG hypometabolism may correspond to subtle abnormalities identified at MRI, thus increasing confidence, or when the MRI appears normal, FDG PET can independently suggest a target for surgical resection [58] (Fig. 7). For example, a significant portion of patients with focal cortical dysplasia and negative MRI have positive PET findings [97, 98].

Studies have shown that fusion of FDG PET with separately acquired MRI improves the diagnosis of focal cortical dysplasia compared with each modality on its own. It has been found to be especially helpful in patients with normal MRI scans and subtle cases of cortical dysplasia [99] and allows more limited cortical resection in select patients [100]. A study of 29 patients with refractory epilepsy undergoing PET/MRI showed that PET/MRI increased the diagnostic accuracy of localizing an epileptogenic focus compared with separate MRI and PET/CT [101]. Additional pilot data have indicated a clear role for PET/MRI in patients with refractory epilepsy [102]. Combination high-sensitivity electroencephalography and PET with functional MRI evaluation has been shown to achieve reliable interictal data with better efficiency, reduced bias, and decreased cost [103].

Oncologic Musculoskeletal PET/MRI

Bone and Soft-Tissue Sarcomas

MRI is the reference standard for assessing the T stage of bone sarcomas and soft-tissue sarcomas (STSs), given its ability to show the tumor’s relationship to neurovascular structures, joints, and muscular compartments [77, 104–106]. The addition of novel MRI techniques, such as DWI, ADC, dynamic contrast enhancement, and MRS, may improve diagnostic accuracy compared with conventional MRI [105, 107, 108]. Combining these techniques with metabolic measures, such as SUV, total lesion glycolysis, and metabolic tumor volume, provides powerful multiparametric
evaluation. Combined metabolic and MRS evaluation on FDG PET/MRI has already been explored in STS [109], and a radiomics model examining FDG PET/MRI texture features has been used to predict the presence of pulmonary metastases in 51 patients with extremity STS [110].

The addition of focused PET assessment of primary bone sarcoma and STS provides prognostic information and can help guide biopsy. Baseline FDG activity in STS and bone sarcoma has been correlated with survival in several studies [111, 112]. Dedicated PET evaluation of sarcomas may also allow sampling of the most FDG-avid high-grade areas of tumor [113, 114]. This can be especially important in large or large-grade sarcomas, which may be prone to non-diagnostic biopsy or undersampling given significant heterogeneity (Fig. 8).

In 2017, Platzek et al. [115] assessed the role of FDG PET/MRI in staging 29 patients with bone sarcoma and STS. They found identical T, M, and N staging for PET/MRI and conventional imaging in 28 of 29 patients. PET/MRI had a slightly increased sensitivity for detecting distant metastases (97.8% vs 94.4% for conventional imaging), but this was insignificant (p = 0.51). A number of small case series and pilot studies have also shown potential benefit of PET/MRI in STS staging [116–118].

The utility of FDG PET for response assessment after chemotherapy has been shown for patients with STS [119, 120] and bone sarcoma [121, 122]. Quantitative ADC maps have been used to assess STS response at MRI [107, 108]. Combined PET and MRI evaluation would therefore seem synergistic in evaluating chemotherapeutic response, but several studies have shown discordant results between PET and MRI measures [123, 124] after neoadjuvant therapy. However, a recent study found superior diagnostic accuracy of integrated FDG PET/MRI compared with stand-alone MRI for identification of locally recurrent STSs, and PET/MRI also conferred higher confidence levels for delineating malignant lesions [125]. Future prospective studies are expected to define the role of integrated PET/MRI in the posttherapy setting.

**Multiple Myeloma**

The diagnosis of multiple myeloma can be made on the basis of clinical and laboratory measures alone [126]. However, advanced imaging can play a key role in better diagnosing active versus inactive disease, prognosticating, and assessing early response to therapy. MRI can detect marrow signal changes of myelomatous lesions before osseous destruction is seen at CT. MRI also has proven superiority in detecting diffuse bone marrow involvement compared with whole-body low-dose CT or PET/CT [127–129]. Incorporation of DWI results in greater lesion conspicuity compared with conventional MRI [130, 131], and ADC values have excellent accuracy to differentiate diseased from normal marrow [132, 133]. FDG PET/CT performs equally well to MRI in detecting focal lesions but, again, is inferior for detecting diffuse disease [127–129, 134, 135].

Both MRI and PET are beneficial in evaluating treatment response. Giles and colleagues [136] showed that increased ADC has excellent accuracy in determining positive treatment response, which has also been supported by other studies [137]. The role of FDG PET/CT in assessing treatment response was well seen in a recent meta-analysis including 690 patients with myeloma from 10 studies [138]. PET/CT may show disease response earlier than MRI, because resolution of FDG activity is typically seen before MRI signal normalization.

Shott and colleagues [141] found that, although whole-body MRI outperformed FDG PET/CT in assessment of active multiple myeloma, adding FDG PET information to MRI improved the results of MRI alone. Sachpekidis et al. [142] showed the equivalency of PET/CT and PET/MRI for the detection of myeloma lesions in 30 patients using a single-injection PET/CT and PET/MRI protocol. PET/MRI missed rib lesions identified at PET/CT evaluation, which is unsurprising given that MRI has known limitations in evaluation of the ribs, skull, and clavicles [143].

In our experience, PET/MRI has been helpful in cases of diffuse myelomatous disease, which is better seen with MRI than PET (Fig. 9), and also in depicting resolution of FDG activity in responding lesions before normalization of signal abnormality at MRI (Fig. 10). There are conflicting data on the importance of osteosclerosis at PET/CT, but despite this, the updated International Myeloma Working Group guidelines necessitate the presence of osteosclerosis to make the diagnosis of active disease at PET/CT [126]. This is an additional advantage of integrated FDG PET/MRI, to depict intramedullary lesions at MRI that are occult at CT, thereby increasing sensitivity for active disease (Fig. 10).

**Cardiac Applications**

Cardiac PET/MRI has been advancing into clinical practice for the evaluation of coronary, infiltrative, and inflammatory diseases [1, 146, 147]. Coronary ischemia represents the most common indication for cardiac PET/MRI. Recent work has shown benefit in combining complementary coregistered coronary blood flow and myocardial flow reserve as assessed by PET, with simultaneous functional imaging and infarct- or scar-related delayed enhancement as assessed by MRI [147]. Improvements in complex respiratory and cardiac motion correction take advantage of simultaneous PET/MRI acquisition to improve image resolution, colocalization, and diagnostic confidence, thus making PET/MRI superior to PET/CT plus MRI for evaluating these cardiac conditions [148–151].

There is growing excitement about the role of cardiac PET/MRI, particularly in the evaluation of inflammatory and infiltrative cardiomyopathies, such as sarcoidosis and amyloidosis [1, 152]. MRI has long been a mainstay in the evaluation of patients with infiltrative cardiomyopathies. In cardiac sarcoidosis, MRI allows accurate diagnosis and assessment of cardiac injury and function, whereas PET adds the ability to detect active inflammation and assess whether further antinfammatory treatment is needed [153]. PET/MRI allows simultaneous assessment of all of these cardiac factors, making it a potential modality of choice for imaging [154]. A recent joint Society of Nuclear Medicine and Molecular Imaging and American Society of Nuclear Cardiology expert consensus statement suggests that PET/DE/CT can be used for follow-up of patients with cardiac sarcoidosis to assess for treatment response and that specialized coronary blood flow imaging with 82Rb or 13N-ammonia plus FDG cardiac and body imaging should be used [155]. When appropriate, this same method has been applied to PET/MRI. Recent data suggest that radiotracers such as Ga-DOTATOC (not FDA approved) or Ga-DOTATATE (FDA approved, but off-label for cardiac imaging), which target somatostatin receptors, could also be used to image cardiac and systemic sarcoidosis without the need for hard-to-follow special dietary preparations [156].

PET/MRI has great potential in evaluating myocardial deposition of light-chain and amyloidogenic transthyretin (ATTR) amyloid. In the right clinical setting, bone radiotracer imaging, such as pyrophosphate planar and SPECT/CT, is specific enough as to have been suggested to potentially remove the need for more invasive diagnostic procedures, such as endomyocardial biopsy, for diagnosing ATTR in some patients [157]. More recently, the use of 18F-NaF (FDA
approved, but off-label for use in the heart) PET for the detection of ATTR using PET/MRI has been proposed [157]. The use of SPECT-based bone scan agents is already becoming the standard of care to diagnose ATTR cardiomyopathy [156], and 18F-NaF allows this strategy to move to PET and PET/MRI. Another exciting option is to use FDA-approved radiotracers designed to target \( \beta \)-amyloid in the brain (FDA approved, but off-label for use in the heart), including florbetapir, flutemetamol, and florbetaben for targeting either amyloidosis or ATTR in the heart [158]. These techniques promise to directly bind to amyloidosis in the heart and, when used in combination with blood-flow analysis, may be able to quantify amyloid burden. Given these promising new therapies, there is excitement that this imaging method may allow therapy assessment at follow-up.

**Conclusion**

Clinical PET/MRI is in a dynamic period, and the future appears bright. Critical issues have been overcome, and the unique advantages of simultaneous PET/MRI are being harnessed to better diagnose disease. Comparison with PET/CT is generally no longer needed. MRI-based attenuation correction is adequate for clinical use and is rapidly advancing. Complex motion correction and advances in silicon photomultipliers and image reconstruction promise to bring significant improvements in image quality. Imaging of certain diseases, such as liver metastases, uniquely benefits from PET/MRI. Several new radiotracers are and will be used to better advantage on PET/MRI compared with PET/CT. Faster and more robust MRI protocols allow more-complete scans with improved patient satisfaction. Continued efforts to standardize protocols across institutions and develop innovative solutions for the challenges posed by this hybrid modality will be critical to the long-term success of PET/MRI.

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**Fig. 1**—Patient undergoing FDG PET/MRI study. **A–F,** Coronal in-phase (**A**), water (**B**), and fat (**C**) images are used to generate attenuation correction map (**D**), which is then used in attenuation correction of PET data (**FDG PET image**, **E**; fused PET/MR image, **F**). Regions containing head, lung, abdomen, and pelvis are identified during acquisition setup to prescribe head versus body attenuation correction modes and to assist segmentation of Dixon sequence images into various tissue classes. Note that there is no bone component in body and that head portion of attenuation correction map (**D**) consists of atlas and head and neck coil.
Fig. 3—41-year-old woman with metastatic pancreatic neuroendocrine tumor undergoing staging $^{68}$Ga-DOTATATE PET/MRI.

A–E, PET maximum intensity projection image (A) shows multiple hepatic metastases (circle) and right second rib metastasis (arrowhead). Axial T2-weighted fat-saturated MRI (B) of liver shows no T2-hyperintense hepatic metastases. However, DW image shows focus of restricted diffusion in right hepatic lobe (arrow, C), with corresponding hypointensity on hepatobiliary phase contrast-enhanced image (arrow, D) and DOTATATE uptake on fused PET/MR image (arrow, E), consistent with neuroendocrine hepatic metastasis. Neuroendocrine tumor in pancreatic tail also shows intense DOTATATE uptake (solid arrowhead, E), and there were DOTATATE-avid locoregional lymph node metastases (dashed arrowhead, E).

(Fig. 3 continues on next page)
Fig. 3 (continued)—41-year-old woman with metastatic pancreatic neuroendocrine tumor undergoing staging 18F-DOTATATE PET/MRI. A–E, PET maximum intensity projection image (A) shows multiple hepatic metastases (circle) and right second rib metastasis (arrowhead). Axial T2-weighted fat-saturated MRI (B) of liver shows no T2-hyperintense hepatic metastases. However, DW image shows focus of restricted diffusion in right hepatic lobe (arrow, C), with corresponding hypointensity on hepatobiliary phase contrast-enhanced image (arrow, D) and DOTATATE uptake on fused PET/MR image (arrow, E), consistent with neuroendocrine hepatic metastasis. Neuroendocrine tumor in pancreatic tail also shows intense DOTATATE uptake (solid arrowhead, E), and there were DOTATATE-avid locoregional lymph node metastases (dashed arrowhead, E).

Fig. 4—71-year-old man with prostate carcinoma who underwent radical prostatectomy and radiation therapy and later presented with slowly increasing prostate-specific antigen level, currently 0.8 ng/mL. A–E, Carbon-11-choline PET/MRI maximum intensity projection image (A), T2-weighted MR images (B and D), and fused PET/MR images (C and E) show choline-avid left seminal vesicle recurrence (circle, A; ovals, B and C) and metastatic left internal iliac node (arrows, A, D, and E).

(Fig. 4 continues on next page)
Fig. 4 (continued)—71-year-old man with prostate carcinoma who underwent radical prostatectomy and radiation therapy and later presented with slowly increasing prostate-specific antigen level, currently 0.8 ng/mL. A–E, Carbon-11-choline PET/MR maximum intensity projection image (A), T2-weighted MR images (B and D), and fused PET/MR images (C and E) show choline-avid left seminal vesicle recurrence (circle, A; ovals, B and C) and metastatic left internal iliac node (arrows, A, D, and E).
Fig. 5—67-year-old man with primary CNS lymphoma undergoing restaging after chemotherapy. 
A–F. FDG PET maximum intensity projection image (A) shows intense foci of intracranial activity, but no evidence of systemic disease. PET/MR images show infiltrative lesion involving splenium of corpus callosum with increased signal on T2-weighted FLAIR image (arrows, B), diffusion restriction with high signal on DW image (arrows, C), low signal on apparent diffusion coefficient image (arrows, D), and intense FDG activity on PET image (arrows, E) and fused PET/MR image (arrows, F). Fused PET/MRI examination enabled full diagnostic brain MRI and torso PET in single session.
Fig. 6—61-year-old woman with right perihilar pulmonary adenocarcinoma. A–D, FDG PET/MRI maximum intensity projection (A), PET (B), contrast-enhanced T1-weighted fatsaturated (C), and fused PET/MR (D) images show large FDG-avid pulmonary mass (arrowhead, A) and small enhancing metastases in left cerebellar hemisphere (arrows, B–D). Integrated PET/MRI allowed complete staging in single session.

Fig. 7—33-year-old man with 10 years of nocturnal general tonic-clonic seizures. A–D, Initial MRI (A) was interpreted as negative. Coronal 3D T1-weighted (B) and coronal FLAIR (C) images are also shown. Subsequent interictal FDG PET/MRI (D) shows hypometabolism throughout anterior left temporal lobe (ovals, C and D). Placement of left temporal grid confirmed seizure focus and patient has been seizure-free since left temporal resection.

(Fig. 7 continues on next page)
Fig. 7 (continued)—33-year-old man with 10 years of nocturnal general tonic-clonic seizures. A–D, Initial MRI (A) was interpreted as negative. Coronal 3D T1-weighted (B) and coronal FLAIR (C) images are also shown. Subsequent interictal FDG PET/MRI (D) shows hypometabolism throughout anterior left temporal lobe (ovals, C and D). Placement of left temporal grid confirmed seizure focus and patient has been seizure-free since left temporal resection.

Fig. 8—27-year-old woman undergoing staging FDG PET/MRI for pelvic sarcoma. A–E, FDG PET maximum intensity projection image shows increased uptake in right pelvis (arrow, A) and no evidence of regional or distant metastatic disease. Axial (B and C) and coronal (D and E) T2-weighted fat-saturated (B and D) and fused PET/MR images (C and E) show locally advanced T2-hyperintense mass involving right sacrum and ilium, with soft component. Note increased FDG activity in extraosseous component (arrows, B–E). FDG-avid extraosseous component was subsequently targeted for biopsy, with pathologic analysis showing chondroblastic osteosarcoma.
Fig. 9—54-year-old woman with multiple myeloma undergoing staging FDG PET/MRI. A–D, Coronal (top) and sagittal (bottom) PET (A), STIR (B), and fused PET/STIR (C) images of spine and pelvis show diffuse T2-hyperintense marrow infiltration, consistent with diffuse involvement by multiple myeloma, but no significantly increased FDG activity. PET maximum intensity projection image (D) shows relatively normal FDG biodistribution, with exception of healing right rib fracture (arrow). Subsequent bone marrow biopsy showed involvement by 80–90% clonal plasma cells.
Fig. 10—Two patients with myeloma. 
A and B, 43-year-old woman with myeloma undergoing restaging FDG PET/MRI after chemotherapy. Axial T1-weighted MR image (A) shows rounded T1-hypointense marrow-replacing lesion in posterior right iliac bone (arrow). Corresponding fused T1-weighted fused PET/MR image (B) shows no FDG activity within lesion (arrow), consistent with successfully treated lesion showing decreased FDG activity before normalized MRI signal.

C–F, 60-year-old man with history of multiple myeloma who underwent chemotherapy and had laboratory evidence of relapse. Restaging whole-body low-dose CT shows subtle area of soft-tissue density in proximal left femoral shaft (arrow, C), without corresponding osteolysis (arrow, D). Subsequent FDG PET/MRI shows T1-hypointense marrow-replacing lesion in same location (arrow, E) with increased FDG activity seen on fused PET/MR image (arrow, F), consistent with active disease.