
PET/MRI, Part 4: Clinical Applications

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PET/MRI as a hybrid modality provides novel imaging opportunities. Although there is a very broad array of diseases that could benefit from PET/MRI, there is only a narrow range of applications for which the benefit over standard care justifies the higher resource use and, in particular, offers a net positive trade-off over PET/CT. This benefit is generally associated with the omission of CT and the associated radiation dose from the patient workup. This article summarizes the generally accepted clinical applications of PET/MRI in both adult and pediatric populations. Although there are several potential applications and certainly exciting research that may expand applications in the future, the purpose of this paper was to focus on current, mainstream applications. This is the final article in a 4-part integrated series sponsored by the PET/MR and Publication Committees of the Society of Nuclear Medicine and Molecular Imaging–Technologist Section.

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Having learned how to establish a PET/MRI facility (1), acquired an understanding of the science and technology (2), and gained insight into protocols and sequences in PET/MRI (3) in the previous articles in this 4-part series, the reader now needs to ascertain how to integrate this knowledge with an understanding of the clinical applications of PET/MRI. For some diseases, MRI offers several advantages over CT, including lack of ionizing radiation, achievement of high soft-tissue contrast, and generation of physiologic images. The promise of multiparametric imaging remains a research rather than clinical tool (4). Consequently, when those advantages

are important, use of PET/MRI instead of PET/CT could improve detection, localization, staging, and response to therapy surveillance. Indeed, the common clinical applications of PET/MRI encompass those in which improved soft-tissue contrast results in improved diagnostic accuracy (most notably in oncology) and in which radiation dose reduction is a priority (pediatrics). Site-specific pediatric PET/MRI was shown to maintain tumor detection compared with PET/CT but reduce the radiation dose to the patient from 19.6 to 4.7 mSv, with a goal of using digital PET and low-dose protocols to achieve a dose of 1.7 mSv (Ken Herrmann, MD, RAINS Webinar, July 1, 2020). PET/MRI can be undertaken sequentially and coregistered; however, this article (and indeed the series) refers specifically to simultaneous PET/MRI on hybrid systems.

Like the emergence of other technologies, PET/MRI has followed the typical cycle of initial hype, a period of reflection or disillusionment in some cases, and then a more realistic adoption. This cycle is reflected in the journal paper numbers on PubMed, with PET/MRI papers showing exponential growth from 2010, when simultaneous PET/MRI emerged, until 2015 before a flattening of the curve (Fig. 1). The more linear yearly publication rates for PET/CT can be used as a reference, although there is an entire order of magnitude difference from PET/MRI (Fig. 1). The principal clinical applications of PET/MRI appear to relate to oncology and pediatric imaging, although a PubMed search indicates that neurologic applications are of significant interest (Fig. 2). Figure 2 represents all publications in 2020 related to PET/MRI, including research, not just clinical applications. The trend is consistent with previously published survey data (5), although the proportion of oncology studies was lower in 2020 (46%) than in the 2016 survey (76%–88%), a finding that may reflect a bias in the literature or an evolution into more nononcology applications. Among oncology applications, the greatest interest in the literature has been attracted by prostate, brain, and neuroendocrine tumor applications (Fig. 3). Outside oncology, neurology, and cardiology, there are several other clinical applications of

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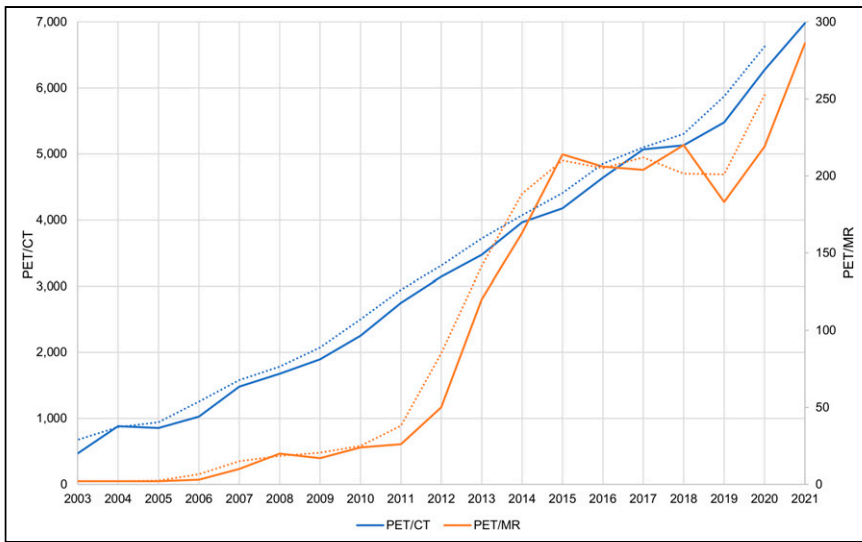


FIGURE 1. Yearly publication numbers from PubMed for PET/MRI (orange) compared with PET/CT (blue). Dashed lines are corresponding moving averages. PET/MRI showed almost exponential growth until 2015 before flattening of curve. Adjustment of 2021 data is based on projection from data collection point 80% through year.

PET/MRI. The most notable is ^{18}F -FDG PET/MRI for the differentiation of fibrotic from inflammatory tissue and for evaluation of systemic Crohn disease and ulcerative colitis (6).

CARDIOLOGY APPLICATIONS OF PET/MRI

It is not uncommon for patients to undergo both PET and MRI investigations for cardiac disease, and a role for simultaneous PET/MRI therefore seems logical. Nonetheless,

enhanced ^{18}F -FDG PET/MRI when sarcoidosis is suspected. The inflammatory nature of myocarditis might benefit from the same ^{18}F -FDG PET/MRI approach (9). Nonetheless, the principal application of cardiac PET/MRI lies in the evaluation of patients with known or suspected coronary artery disease.

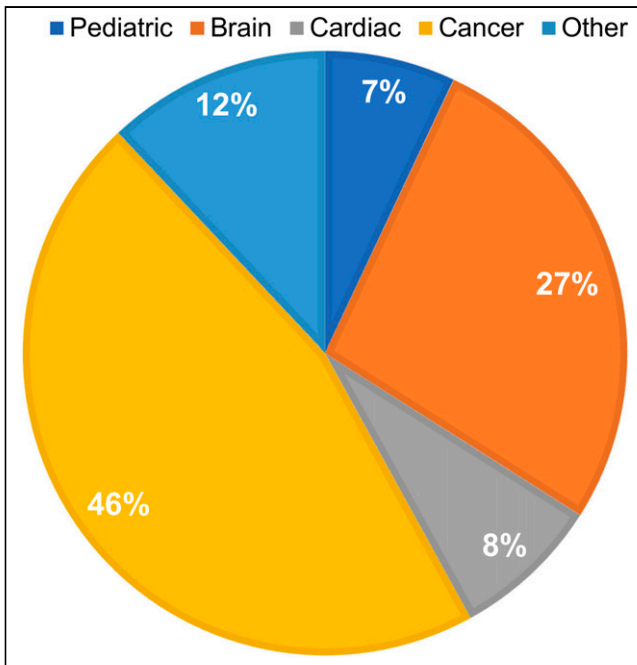


FIGURE 2. Yearly publication numbers for 2020 from PubMed for PET/MRI show that cancer has greatest engagement, followed by brain, other (unlisted applications), cardiac, and pediatric.

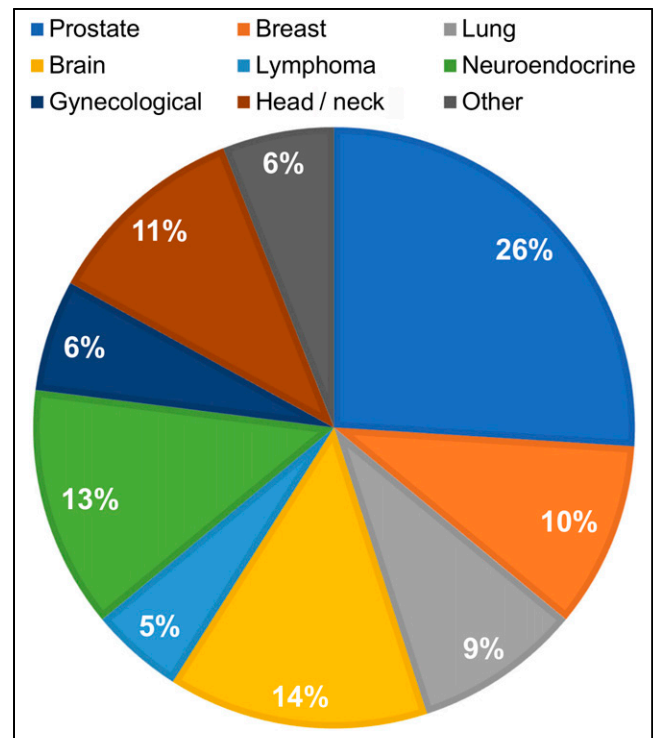


FIGURE 3. Yearly publication numbers for 2020 from PubMed for PET/MRI for various oncology applications suggest that prostate, brain, and neuroendocrine (including pancreatic) are most significant applications.

there is a paucity of firm evidence of the clinical utility of simultaneous cardiac PET/MRI (7). A key requirement for cardiac PET/MRI is the ability to perform cardiac gating and respiratory gating. Indeed, MRI-based gated motion correction of the cardiac PET scan has been shown to improve image quality over PET-based corrections (8). Simultaneous PET/MRI of the heart allows time-efficient imaging of anatomic, functional, and metabolic quantitative information about the heart with reduced coregistration and gated coregistration (4). PET/MRI could provide superior sensitivity and specificity associated with differentiating benign from malignant cardiac tumors with the potential to detect metastatic spread (4). Both MRI and PET play an important role in cardiac sarcoidosis and, thus, have a proposed benefit in contrast-

Atherosclerosis and Coronary Artery Disease

PET myocardial perfusion with ^{13}N -ammonia, ^{82}Rb , or ^{18}F -flurpide combined with the soft-tissue characterization of MRI provides a valuable application of PET/MRI (9). Late gadolinium enhancement is helpful in identifying even small areas of myocardial scarring, whereas T1-weighted sequences identify diffuse myocardial changes (Fig. 4). Furthermore, the MRI sequences can have the addition of MR angiography at both end diastole and end systole. Gated PET and gated MRI data can each provide insights into the functional status of the myocardium. A single 10- to 15-min imaging window provides rich information on the anatomic, morphologic, functional, and molecular status of the myocardium with simultaneous PET/MRI (9). ^{18}F -FDG and gadolinium-enhanced PET/MRI can also provide complementary insights in the evaluation of myocardial viability (9). Evaluation of myocardial viability and prediction of left ventricular wall motion recovery after revascularization are superior for ^{18}F -FDG PET/MRI over MRI or PET alone (10). Although MRI is useful in the assessment of myocardial infarction, combined PET/MRI in heart failure patients with myocardial infarction has some potential using more novel PET tracers such as ^{68}Ga fibroblast activation protein inhibitor (11).

Plaque Vulnerability

Imaging plaque vulnerability remains a challenge in this important pathologic condition. PET/MRI potentially combines the inflammatory imaging of macrophages in plaque development using ^{18}F -FDG PET with the high-contrast imaging of luminal stenosis using MRI without the limitation that CT confronts with calcification (7). This ability would benefit coronary and carotid plaque vulnerability assessment and could be further developed with novel PET tracers demonstrating increased accumulation associated with plaque vulnerability, such as ^{68}Ga -DOTATATE. Importantly, the

MRI coregistration through simultaneous PET/MRI allows clear delineation of plaque morphology from the vascular pool. Both ^{18}F -FDG and ^{18}F -sodium fluoride PET have been used for imaging of inflammation and calcification, respectively, in coronary artery atherosclerosis. PET/MRI in these cases can reduce motion artifacts, add the angiographic phase, and significantly reduce the radiation dose over PET/CT approaches (12,13).

Other Cardiac Pathologic Conditions

For cardiac sarcoidosis, MRI provides insight into myocardial structure, function, and the pattern of injury (late gadolinium enhancement)—insight that can be combined with the ^{18}F -FDG PET, which maps myocardial and extracardiac inflammation. In both cases, the changes can be subtle, and combining PET and MRI therefore increases disease detection (14). In a direct comparison of PET/CT and PET/MRI using ^{18}F -FDG in cardiac sarcoidosis, PET was considered equivalent whereas MRI provided additional pathologic insights not afforded by CT (15).

Myocarditis is another inflammatory condition in which the addition of ^{18}F -FDG PET to MRI may provide additional insight into inflammation or myocyte necrosis not evident on MRI alone, but PET/MRI is not a commonly performed procedure in this condition (16). Although MRI is used for the evaluation of cardiac masses, the addition of ^{18}F -FDG for PET/MRI allows differentiation of cardiac masses as malignant or benign with 100% sensitivity and specificity, as reported in 1 study (17).

There is an emerging role of PET/MRI with ^{18}F -labeled β -amyloid tracers in assessing cardiac and systemic amyloidosis (4). A combination of late gadolinium-enhanced MRI and ^{18}F -sodium fluoride PET can be used to show the characteristic diffuse myocardial enhancement on MRI and differentiation of acquired monoclonal immunoglobulin light-chain and transthyretin-related (familial and wild-type/senile) amyloid subtypes on PET (18).

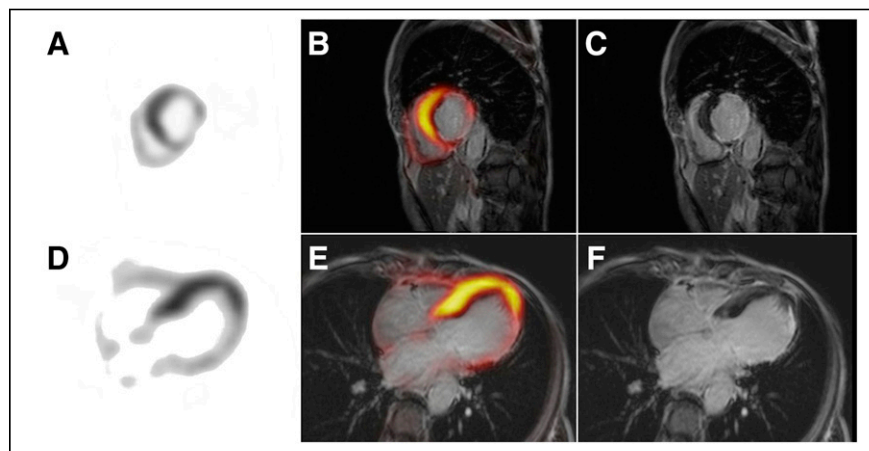


FIGURE 4. Patient with left ventricular ejection fraction of 30% and inferior-to-posterolateral akinesia on echocardiography. ^{18}F -FDG PET/MRI shows decreased metabolic activity of posterolateral wall (A and D), corresponding to late gadolinium enhancement on MR images (C and F) and confirmed on fused images (B and E). (Reprinted from (31).)

Protocol Considerations

Attenuation correction on PET/MRI remains a challenge, with a risk of artifacts, especially when imaging smaller structures (e.g., coronary arteries or valves). Given that MRI attenuation correction methods remain confounded by cortical bone and air, the proximity of the heart to both bone and lung means that even recently developed solutions remain imperfect. This limitation is compounded by potential respiratory misalignment and cardiac motion.

ONCOLOGY APPLICATIONS OF PET/MRI

The widest application of simultaneous PET/MRI is in oncology. The

bulk of the literature suggests that PET/MRI is superior to MRI alone for a variety of indications; however, much of the data do not reflect direct comparison of PET/CT and PET/MRI or provide any insight into potential loss from decoupling of PET/CT that would be offset by a PET/MRI gain not seen with an independent PET/CT and MRI scan. Simultaneous PET/MRI combines the enhanced soft-tissue contrast, improved assessment of anatomy, and functional information of diffusion-weighted MRI with the established molecular and metabolic insights of PET to enhance lesion characterization. As discussed previously (3), PET/CT is not simultaneous but sequential, and when combined with the rapid acquisition for CT compared with the prolonged PET bed position, this sequential nature can result in inaccuracy associated with small lesions or misregistration associated with physiologic motion (respiratory or cardiac). Indeed, in whole-body PET acquisitions in which the CT is performed before or after the PET acquisition, it is possible for physiologic movement or altered biodistribution to impact registration or attenuation correction (e.g., bladder filling or movement in the gastrointestinal tract). This limitation is largely overcome by simultaneous acquisition at each bed position of the PET and MRI data and the use of motion detection, respiratory gating, and cardiac gating. An important application of PET/MRI in oncology is in the evaluation of the liver, for which MRI is superior to CT (19).

Breast Cancer

Since MRI plays an integral role in the diagnosis, staging, and restaging of breast cancer, the role of ^{18}F -FDG PET/MRI in breast cancer is important (20). PET can also be performed with tracers that target hypoxia (^{18}F -fluoromisonidazole), estrogen receptors (^{18}F -fluoro-17 β -estradiol), and human epidermal growth factor receptor 2 (^{89}Zr trastuzumab, ^{68}Ga -human epidermal growth factor receptor 2-single-domain antibody, or ^{64}Cu -NOTA-trastuzumab). The multiparametric radiomic data associated with PET/MRI are likely to drive improved management. Breast MRI provides excellent contrast and spatial resolution, assessment of vascular permeability, and evaluation of neoangiogenesis, which allow high sensitivity in detection of malignancy (21). The combination with ^{18}F -FDG PET produces the metabolic insights that improve specificity, as shown in 1 study that reported an improvement in specificity from 53% to 97% (22). Breast-focused PET/MRI is useful in preoperative staging of breast cancer, although there is less value than for ^{18}F -FDG PET/CT in whole-body surveillance. There is significant future potential for whole-body PET/MRI using targeting of estrogen receptors or human epidermal growth factor receptor 2.

Prostate Cancer

PET/MRI can be useful for the initial staging of prostate cancer before therapy and for detecting patients at intermediate or high risk (14). PET/MRI can be performed with ^{18}F -choline, ^{18}F -fluciclovine, ^{18}F -DCFPyL, or ^{68}Ga -PSMA. The value of PET/CT in biochemical recurrence will limit

the usefulness of PET/MRI (14). Diffusion-weighted MRI combined with PET may have value in assessing response to treatment (14). The bulk of the literature suggests that ^{68}Ga -PSMA PET/MRI is superior to MRI alone for initial staging of prostate cancer, detection of recurrence, and therapy surveillance (4); however, the data do not reflect direct comparison of PET/CT and PET/MRI or provide any insight into potential loss from decoupling of PET/CT that would be offset by a PET/MRI gain not seen with an independent PET/CT and MRI scan.

Lung Cancer

In non-small cell lung cancer, although there was no difference in patient management between PET/MRI and PET/CT, PET/MRI had poorer sensitivity for small lesions in the lung because of respiratory motion (20). Furthermore, the limitations of MRI associated with bone and air can cause attenuation correction artifacts. Generally, a free-breathing radial volumetric interpolated breath-hold technique is adopted for assessment of pulmonary nodules.

Neuroendocrine Tumor

Since both MRI and PET are widely used in neuroendocrine tumors, there is some value in simultaneous PET/MRI using ^{68}Ga -DOTATATE for improved delineation and detection of liver metastases (23). Diffusion-weighted MRI may combine with the PET imaging to provide richer insights into predicting progression-free survival in advanced disease (23). PET/MRI could be particularly useful in assessment of the liver in these patients. ^{68}Ga -DOTATATE PET/MRI with contrast medium was shown to detect more lesions and with improved contrast over PET/CT (24), but the addition of a biliary contrast agent will yield more liver lesions (25).

Head and Neck Cancer

Recent studies suggest there is no difference between the overall performance of PET/MRI and PET/CT in head and neck cancers; given the complexity and cost, this suggestion could be an argument against PET/MRI (20). PET/MRI may improve lymph node metastasis detection (20). Compared with PET/CT, PET/MRI in head and neck cancer provides generally similar results, but PET/MRI provides superiority when there is intracranial tumor invasion (4). Nonetheless, the role of PET/MRI in head and neck cancer includes TNM staging, radiation therapy planning, and treatment response surveillance, predominantly using ^{18}F -FDG (26). In the head and neck, PET/MRI presents challenges associated with bone, air, and soft-tissue interfaces, which undermine the accuracy of attenuation correction and quantitation.

Other Malignancies

PET/MRI is particularly useful in the evaluation of liver metastases, with hybrid techniques providing higher accuracy than PET or MRI individually (27). Key protocol requirements include use of a biliary contrast agent for MRI and respiration-gated list-mode PET data (23). In 1 study, the management of 22% of colorectal carcinoma patients

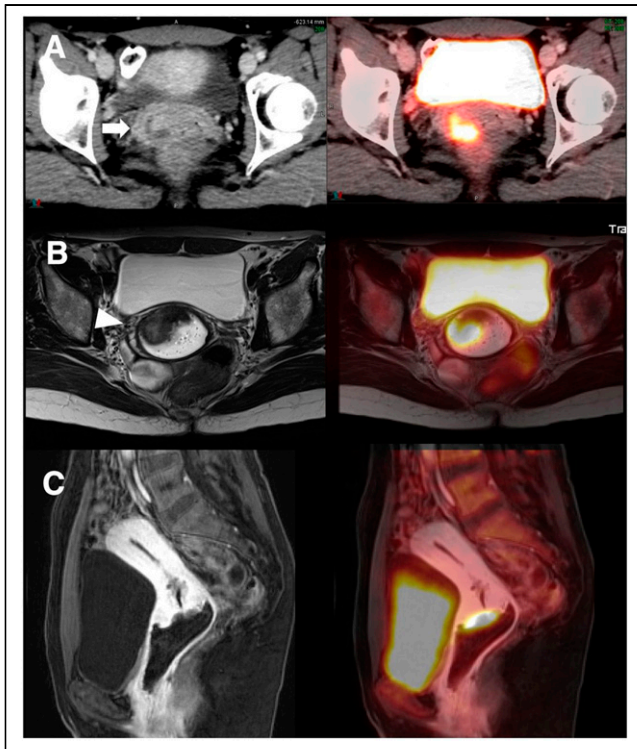


FIGURE 5. Poorly differentiated squamous cell carcinoma of cervix on CT (A, left) and PET/CT (A, right), with corresponding unenhanced T2-weighted turbo spin-echo CT (B, left) and T2-weighted turbo spin-echo PET/MRI (B, right) and contrast-enhanced sagittal MRI T1-weighted MRI (Dixon-visual background extractor sequence) (C, left) and PET/MRI (C, right). (Reprinted from (32).)

was changed as a result of PET/MRI, but PET/MRI was noted to be problematic (inferior to PET/CT) in pulmonary lesion detection (28). ^{18}F -FDG PET/MRI has also been used in ovarian and cervical malignancies for staging, therapy planning, evaluation of response to therapy, and detection of recurrence (Fig. 5). There has been some discussion of the clinical role of PET/MRI in sarcoma and multiple myeloma. In multiple myeloma, PET/MRI has the advantage of differentiating active from inactive disease and monitoring response to therapy (6).

NEUROLOGIC APPLICATIONS OF PET/MRI

There are several potential applications of simultaneous PET/MRI in neurologic conditions, including neurodegenerative and oncologic conditions and epilepsy. Although it is convenient to perform brain PET/MRI as part of a wider whole-body PET/MRI protocol, the ease with which PET, MRI, and CT of the brain are accurately coregistered without hybrid systems is perhaps the

biggest barrier to more widespread use of neurologic simultaneous PET/MRI. For clinical sites without hybrid PET/MRI for neurologic use, there is no strong independent justification for investment, despite the advantages of PET/MRI. Nonetheless, the convenience in simultaneous PET/MRI should not be discounted and is especially beneficial when CT is not part of the imaging request. Brain PET can also forgo use of the CT component for attenuation correction, as the calculated methods used before hybrid systems were developed offer an accurate option independent of MRI-based methods. Given that brain imaging is performed at a single bed position, protocols are significantly more convenient than oncology protocols.

Alzheimer Disease and Dementias

Perhaps the greatest challenge in PET/MRI for neurodegenerative disease is the sensitivity and early detection of PET, many years before MRI changes are evident. Nonetheless, MRI offers a valuable anatomic map of physiologic and molecular changes in brain function associated with neurodegenerative disorders and, thus, has potential to improve patient care when simultaneous PET/MRI is performed using ^{18}F -FDG, ^{18}F -labeled β -amyloid (Fig. 6), or ^{18}F -tau radiopharmaceuticals (29). MRI could add blood flow information by extending the imaging sequence timings. PET/MRI offers simultaneous imaging of β -amyloid plaque deposition and neuronal injury or degeneration (6). Likewise, there is a theoretic benefit for performing simultaneous PET/MRI in Parkinson disease using ^{18}F -6-fluoro-L-dopa or other dopamine radiopharmaceuticals.

Neurologic Malignancy

The independent value of MRI and novel PET radiopharmaceuticals (beyond ^{18}F -FDG) in characterizing brain tumors leaves PET/MRI in a position to have a significant benefit in neurologic malignancy. Clinically, the most important opportunity for PET/MRI in neurologic malignancy is differentiating tumor recurrence from treatment effects (surgery or radiation) (14). MRI is the gold standard in brain tumor imaging;

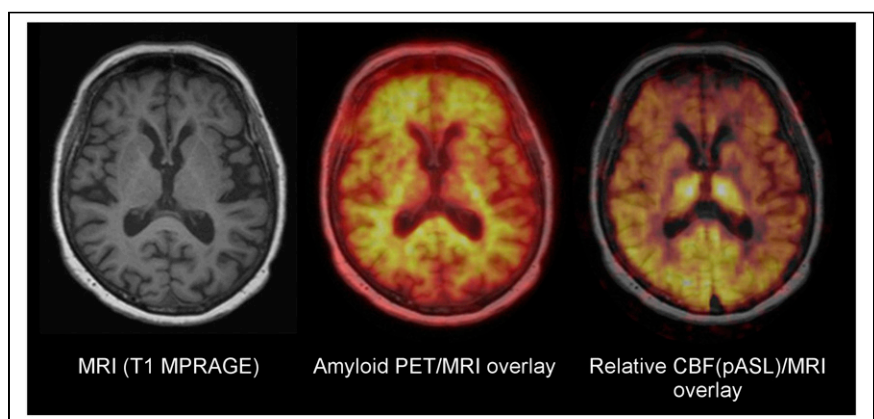


FIGURE 6. Simultaneous PET/MRI in dementia using ^{18}F -florbetaben PET and pulsed arterial spin labeling (pASL) MRI. MPRAGE = magnetization-prepared rapid gradient echo. (Reprinted from (33).)

however, molecular imaging provides crucial insights not captured by anatomic imaging. Several PET radiotracers are currently used to evaluate brain tumors, including ^{18}F -FDG, ^{18}F -fluoroethyltyrosine, ^{18}F -6-fluoro-L-dopa, ^{18}F -fluorothymidine, ^{18}F -choline, and ^{18}F -fluoromisonidazole (30). PET/MRI using the amino acid metabolism radiopharmaceutical ^{18}F -fluorothymidine enhances MRI evaluation of recurrence in glioma and metastatic brain lesions (14). PET/MRI using ^{18}F -fluorothymidine or ^{18}F -FDG may also have a role in differentiating low-grade from high-grade gliomas, especially with respect to aggressiveness and timing of repeat biopsies (6,14).

Epilepsy

For patients who have epilepsy with the potential for curable surgery, accurate localization of the seizure foci is essential for surgical planning (14). ^{18}F -FDG PET/MRI provides accurate detection to enhance surgical outcomes, and patients have the added benefit of a reduced radiation dose associated with not using CT. Indeed, ^{18}F -FDG PET/MRI provides improved seizure focus detection over either MRI or PET alone (29). As with all PET/MRI applications, there is also the convenience to the patient, who may undergo both PET and MRI in a single visit, as opposed to traditionally coming in for 2 separate appointments. This is one of the biggest benefits for patients who experience frequent seizures and may have difficulty making it to 2 appointments, resulting in a delay in receiving care while the patients are waiting to undergo the separate imaging procedures.

PEDIATRIC APPLICATIONS OF PET/MRI

An important application of simultaneous PET/MRI is in the assessment of cancer in pediatric patients. PET/MRI is particularly useful in solid tumors. The advantage of PET/MRI over PET/CT in this population relates to the absence of the radiation dose associated with CT. This advantage could be extended in pediatric patients (and adult patients) by adopting deep-learning approaches for low-dose PET scanning (14). The main applications of PET/MRI in pediatric patients include staging, restaging, and response to therapy, predominantly for lymphoma but also leukemia; neuroblastoma, neurofibromatosis type I, and sarcoma; seizure focus localization using ^{18}F -FDG and fused interictal MRI to guide surgical intervention; and infection (e.g., pyrexia of unknown origin) and inflammation (e.g., inflammatory bowel disease).

Although these applications relate to ^{18}F -FDG PET, newer developments may see the emergence of broader applications of PET/MRI in the pediatric population. For example, ^{18}F -meta-fluorobenzylguanidine is a PET alternative to ^{123}I -meta-iodobenzylguanidine for neuroblastoma, and ^{18}F -fluorothymidine could be a better agent for lymphoma and sarcoma.

CONCLUSION

PET/MRI is a relatively new imaging modality still establishing its place in clinical medicine. Although the potential

applications of PET/MRI are broad, the applications in which cost, time, and benefit over standard care, especially when standard care includes PET/CT and MRI, are more limited. Omitting the radiation dose associated with CT remains the primary benefit, although exquisite MRI soft-tissue contrast fused with molecular information from PET provides improved sensitivity and specificity in some diseases. Nonetheless, the time and cost impost, and limitations associated with the interface between bone, air, and soft tissue, continue to plague attenuation correction algorithms. Among the range of clinical applications of PET/MRI discussed, the most significant to clinical practice include neurooncology, neurodegeneration, epilepsy, prostate cancer, neuroendocrine or pancreatic tumors, pediatric malignancy, cardiac inflammation associated with sarcoidosis, myocarditis and plaque vulnerability, and cardiac amyloidosis.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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