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PET/MR Part 4: Clinical Applications of PET/MRI

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Learning objectives:

- demonstrate an understanding of clinical applications in PET/MRI
- demonstrate strong conceptual understanding of the applications in PET/MRI from the context of adult and pediatric procedures

Abstract

Position emission tomography (PET) and magnetic resonance imaging (MRI) as a hybrid modality provides novel imaging opportunities. While there are a very broad array of pathologies that could benefit from PET/MRI, there is only a narrow range of applications where benefit over standard care justifies the higher resource utilization 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 manuscript provides a summary of the generally accepted clinical applications of PET/MRI in both adult and pediatric populations. While there are a number of 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 manuscript in a four-part integrated series sponsored by the SNMMI-TS PET/MR Task Force in conjunction with the SNMMI-TS Publication Committee.

Introduction

Having established a PET/MRI facility (*1*), understood the science and technology (*2*), and gained insight into protocols and sequences in PET/MRI (*3*), this knowledge integrates with understanding of the clinical applications of PET/MRI. MRI offers a number of advantages over CT for some pathology including, but not limited to, no ionizing radiation, high soft tissue contrast and physiological imaging. The promise of multi-parametric imaging remains a research rather than clinical tool (*4*). Consequently, where those advantages are important, PET/MRI over PET/CT could improve detection, localization, staging and response to therapy surveillance. Indeed, the common clinical applications of PET/MRI lie in those areas where improved soft tissue contrast results in improved diagnostic accuracy (most notable in oncology) and where radiation dose reduction is a priority (pediatrics). In work presented by Ken Herrmann site specific pediatric PET/MRI was shown to maintain tumor detection compared to PET/CT but reduce radiation dose to the patient from 19.6 mSv to 4.7 mSv with a goal using digital PET and low dose protocols to 1.7 mSv. PET/MRI can be undertaken sequentially and co-registered, 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 is reflected in the journal paper numbers (pubmed.gov) with PET/MR papers showing exponential growth from 2010 when simultaneous PET/MRI emerged until 2015 before a flattening of the curve (figure 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 (figure 1). The principle clinical applications of PET/MRI appear to relate to oncology and pediatric imaging although a search amongst published literature (pubmed.org) indicates that neurological applications are of significant interest (figure 2). It should be recognized that 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 is lower in 2020 (46%) than the 2016 survey (76-88%) which may

reflect a bias in the literature or an evolution into more non-oncology applications. Among oncology applications, prostate, brain and neuroendocrine tumors have attracted the greatest interest in the literature (figure 3). Outside oncology, neurology and cardiology, there are a number of other clinical applications of PET/MRI. Most notably is ^{18}F-FDG PET/MRI for the differentiation of fibrotic from inflammatory tissue, and for evaluation of systemic disease in Crohn's 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 pathology and, therefore, a role for simultaneous PET/MRI seems logical. Nonetheless, 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 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 co-registration and gated co-registration (*4*). PET/MRI could provide superior sensitivity and specificity associated with differentiating benign and malignant cardiac tumors with the potential to detect metastatic spread (*4*). Both MRI and PET play an important role in cardiac sarcoidosis so a proposed benefit in contrast 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 (CAD).

Atherosclerosis and CAD

PET myocardial perfusion with ^{13}N-ammonia, ^{82}Rb or ^{18}F-fluropidez 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 scar while T1 sequences identify diffuse myocardial changes (figure 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

myocardial. A single 10-15 minute imaging window providing rich anatomical, morphological, 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 predicting left ventricular wall motion recovery after revascularization is superior for ^{18}F-FDG PET/MRI over MRI and PET alone (*10*). While MRI is useful in assessment of myocardial infarction, combined PET/MRI imaging in heart failure patients with myocardial infarction has some potential using more novel PET tracers like ^{68}Ga fibroblast activation protein inhibitor (FAPI) (*11*).

Plaque vulnerability

Imaging plaque vulnerability remains a challenge but important pathology. PET/MRI potentially combines the inflammatory imaging of macrophages in plaque development using ^{18}F-FDG with the MRI high contrast imaging of the luminal stenosis without the limitation CT confronts with calcification (*7*). This would benefit coronary and carotid plaque vulnerability assessment. This could be further developed with novel PET tracers demonstrating increased accumulation associated with plaque vulnerability like ^{68}Ga-DOATATATE. Importantly, the MRI co-registration 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 inflammation and calcification respectively in coronary artery atherosclerosis. PET/MRI in these cases can reduce motion artefact, add the angiographic phase (MRA) and significantly reduced radiation dose over PET/CT approaches (*12,13*).

Other pathology

For cardiac sarcoidosis MRI provides an insight into myocardial structure, function and the pattern of injury (late gadolinium enhancement) which can be combined with the ^{18}F-FDG PET that maps myocardial and extracardiac inflammation. In both cases, the changes can be subtle and therefore combining PET and MRI increase disease detection (*14*). In a direct comparison of PET/CT and PET/MRI using ^{18}F-FDG in cardiac sarcoid,

PET was considered equivalent while MRI provided additional pathological insights not afforded by CT (*15*).

Myocarditis is another inflammatory condition where the addition of ^{18}F-FDG PET to MRI may provide additional insight into inflammation or myocyte necrosis not evident on MRI alone but is not a commonly performed procedure (*16*). While 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 reported in one study (*17*).

There is an emerging role of PET/MRI with 18F beta 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*).

Protocol considerations

Attenuation correction on PET/MRI remains a challenge with a risk of artefact, especially when imaging smaller structures (eg. coronary arteries, valves). Given MRI attenuation correction methods remain confounded by cortical bone and air, the proximity of the heart to both bone and lung mean even recently developed solutions remain imperfect. This 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 does not reflect direct comparison of PET/CT and PET/MRI or provide any insight into potential loss from de-coupling 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 with diffusion-weighted imaging of 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 in nature and when combined with the rapid acquisition for CT compared to the prolonged PET bed position, this can result in inaccuracy associated with small lesions or misregistration associated with physiological motion (respiratory or cardiac). Indeed, in wholebody PET acquisitions where the CT is performed prior to or after the PET acquisition, it is possible for physiological movement or altered biodistribution to impact registration or attenuation correction (eg. bladder filling, movement in the gastrointestinal tract). This is largely overcome by simultaneous acquisition in 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 where MRI is superior to CT (*19*).

Breast cancer

Since MRI plays an integral role in diagnosis and staging (and re-staging) of the breast cancer patient, the role of ^{18}F-FDG PET/MRI in breast cancer is important (*20*). Pet can also be performed with tracers that target hypoxia (18F FMISO), estrogen receptors (^{18}F-fluoro-17β-estradiol or ^{18}F-FES) and HER2 (^{89}Zr trastuzumab, ^{68}Ga-HER2-nanobody or ^{64}Cu-NOTA-Trastuzumab). The multiparametric radiomic data associated with PET/MRI is likely to drive improved management. Breast MRI provides excellent contrast and spatial resolution, the assessment of vascular permeability and evaluation of neoangiogensis which allow high sensitivity in detection of malignancy (*21*). The combination with ^{18}F-FDG PET produces the metabolic insights that improve specificity, in one study reported to improve specificity from 53% to 97% (*22*). Breast focused PET/MRI is useful in pre-operative staging of breast cancer although there is less value in wholebody surveillance over PET/CT using ^{18}F-FDG. There is significant potential in the future for wholebody PET/MRI using targeting estrogen receptors or HER2.

Prostate cancer

PET/MRI can be useful for the initial staging of prostate cancer before therapy and detecting intermediate and high-risk patients (*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 68Ga-PSMA PET/MRI is superior to MRI alone for initial staging of prostate cancer, detection of recurrence and therapy surveillance (*4*), however, the data does not reflect direct comparison of PET/CT and PET/MRI or provide any insight into potential loss from de-coupling PET/CT that would be offset by a PET/MRI gain not seen with an independent PET/CT and MRI scan.

Lung cancer

While there was no difference in patient management associated with PET/MRI versus PET/CT in non-small cell lung cancer, PET/MRI has poorer sensitivity associated with small lesions in the lung due to respiratory motion (*20*). Furthermore, limitations associated with MRI imaging of 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 tumor, 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 liver in these patients. ^{68}Ga DOTATATE PET/MRI with contrast was shown to detect more lesions and with improved contrast over PET/CT (*24*) but the addition of a biliary specific contrast agent will yield more liver lesions (*25*).

Other malignancies

PET/MRI is particularly useful in the evaluation of liver metastases with hybrid techniques providing higher accuracy than PET or MRI individually (*26*). Key protocol requirements include biliary contrast agent imaging on MRI and respiratory gated list mode PET data (*23*). In one study, 22% of colorectal carcinoma patients had their management changed as a result of PET/MRI but they noted PET/MRI was problematic (inferior to PET/CT) in pulmonary lesion detection (*27*). ^{18}F-FDG PET/MRI has also been used for the staging, therapy planning, evaluation of response to therapy and detection of recurrence in ovarian and cervical malignancies (figure 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*).

Head and neck cancer

Recent studies suggest there is no difference in the overall performance of PET/MRI compared to PET/CT in head and neck cancers and, given the complexity and cost, could be an argument against PET/MRI (*20*). PET/MRI may improve lymph node metastases detection (*20*). Compared to 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 T, N and M staging, radiation therapy planning, and treatment response surveillance; predominantly using ^{18}F-FDG (*28*). There are challenges associated with PET/MRI in the head and neck associated with the interface between bone, air and soft tissue that undermine the accuracy of attenuation correction and quantitation.

Neurological Applications of PET/MRI

There are a number of potential applications of simultaneous PET/MRI in neurological conditions including neurodegenerative, oncology and epilepsy. While 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 co-registered without hybrid systems is perhaps the biggest barrier to more widespread use of neurological simultaneous

PET/MRI. That is, PET/MRI can be readily performed without hybrid simultaneous systems for neurological imaging. For clinical sites without hybrid PET/MRI for neurological use, there is not a strong independent justification for investment, despite the advantages of PET/MRI. Nonetheless, there is a convenience in simultaneous PET/MRI that should not be discounted that is especially beneficial where CT is not part of the imaging request. Brain PET can also forgo the CT for attenuation correction as the calculated methods used before hybrid system were developed offers an accurate option independent of MRI based methods. Given brain imaging is performed in a single bed position, protocols are significantly more convenient than oncology protocols.

Alzheimer's 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 anatomical map of physiological and molecular level 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 beta amyloid (figure 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 beta amyloid plaque deposition and neuronal injury/degeneration (*6*). Likewise, there is a theoretical benefit for performing simultaneous PET/MRI in Parkinson's disease using ^{18}F-FDOPA or other dopamine radiopharmaceuticals.

Neurological 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 neurological malignancy. Clinically, the most important opportunity for PET/MRI in neurological malignancy is differentiating tumor recurrence from treatment effects (surgery or radiation) (*14*). MRI is the gold standard in brain tumor imaging, however, molecular imaging provides crucial insights not captured by anatomical imaging. A number of PET radiotracers are currently used to evaluate brain tumors, including but not

limited to ^{18}F-FDG, ^{18}F-fluoroethyltyrosine (^{18}F-FET), ^{18}F-FDOPA, ^{18}F-fluorothymidine (^{18}F-FLT), ^{18}F-choline and ^{18}F-Fluoromisonidazole (^{18}F-FMISO) (*30*). PET/MRI using the amino acid metabolism radiopharmaceutical ^{18}F-FLT enhances MRI evaluation of recurrence in glioma and metastatic brain lesions (*14*). PET/MRI using ^{18}F-FLT 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 suffering epilepsy with 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 reduced radiation dose associated with not using CT. Indeed, ^{18}F-FDG PET/MRI provides improved seizure foci detection over either MRI or PET alone (*29*). As with all PET/MRI applications, there is also the convenience to the patient that may undergo both PET and MRI in one visit, as opposed to traditionally coming in for two separate appointments. This is one of the biggest benefits for patients that suffer from frequent seizures, where they may have difficulty making it to two separate appointments and care maybe delayed while waiting to undergo two separate imaging procedures.

Pediatric Applications of PET/MRI

An important application of simultaneous PET/MRI is in the assessment of oncology 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 doses 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, with being limited to:

- Staging, restaging and response to therapy for lymphoma predominantly but also leukemia, neuroblastoma, neurofibromatosis type I, and sarcoma.
- Seizure foci localization using ^{18}F-FDG and fused interictal MRI to guide surgical intervention.

- Infection (eg. pyrexia of unknown origin) and inflammation (eg. inflammatory bowel disease).

While these applications relate to ^{18}F-FDG PET, newer developments may see emergence of broader applications of PET/MRI in the pediatric population. For example, ^{18}F-meta-fluorobenzylguanidine is a PET alternative to ^{123}I-mIBG imaging for neuroblastoma and ^{18}F-FLT 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. While the potential applications of PET/MRI are very broad, the applications where 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 level PET provides improved sensitivity and specificity in some pathologies. 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 neuro-oncology, neurodegeneration, epilepsy, prostate cancer, neuroendocrine/pancreatic tumor, pediatric malignancy, cardiac inflammation associated with sarcoidosis, myocarditis and plaque vulnerability, and cardiac amyloidosis.

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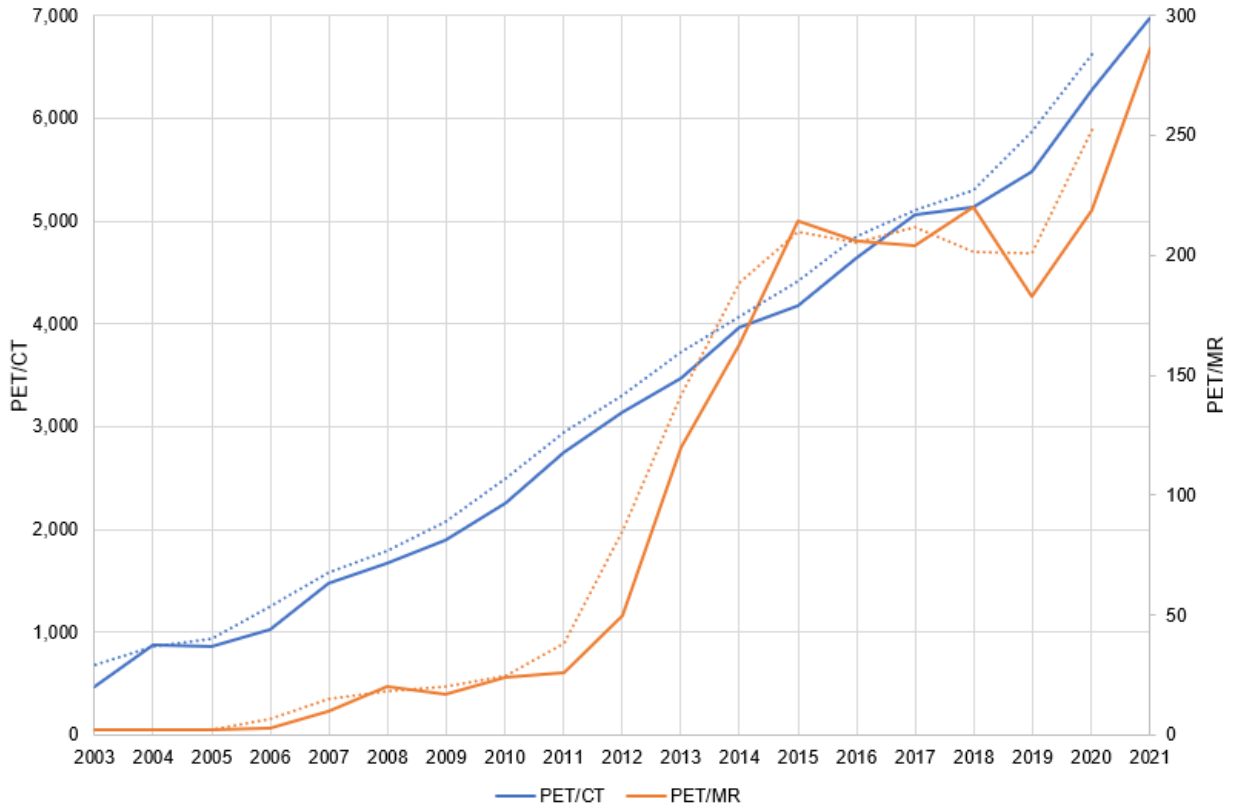

Figure 1: Yearly publication numbers from PubMed (www.pubmed.gov) for PET/MR (orange and right Y axis) compared to PET/CT (blue and left Y axis). The dashed lines are the corresponding moving averages. PET/MR showed almost exponential growth until 2015 before a flattening of the curve. 2021 data is adjusted based on projection from the data collection point 80% through the year.

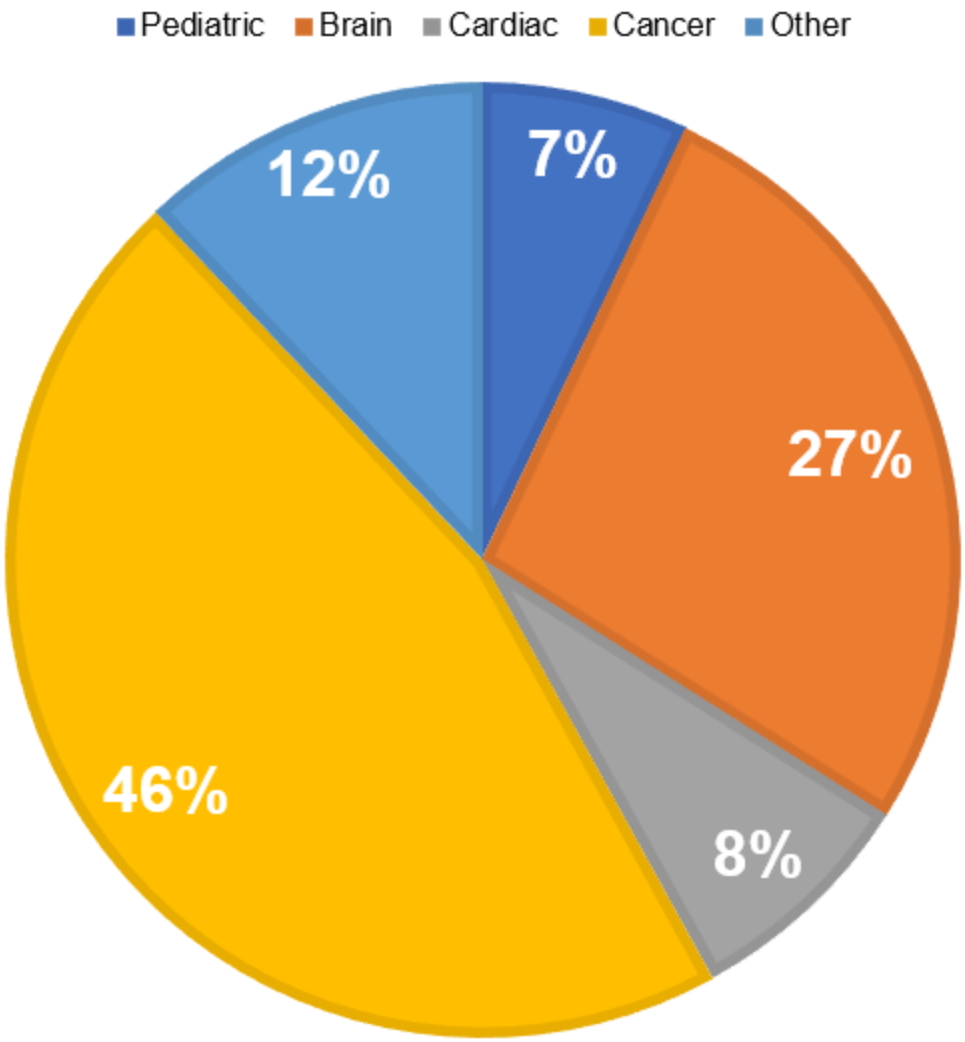

Figure 2: Yearly publication numbers for 2020 from PubMed (www.pubmed.gov) for PET/MR showing oncology has the greatest engagement followed by neurology, other applications not listed, cardiology and pediatric.

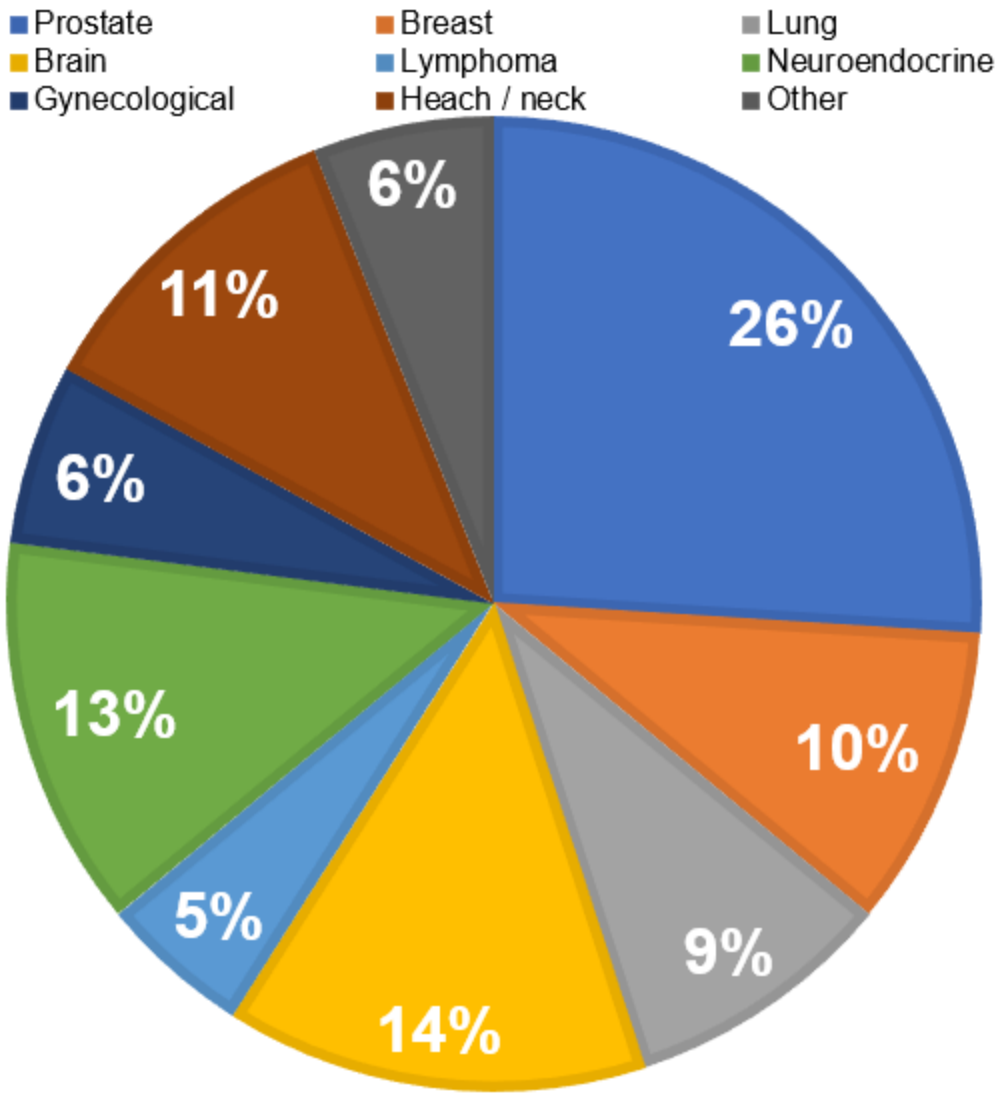

Figure 3: Yearly publication numbers for 2020 from PubMed (www.pubmed.gov) for PET/MR for various oncology applications suggests prostate, brain and neuroendocrine (including pancreatic) are the most significant applications.

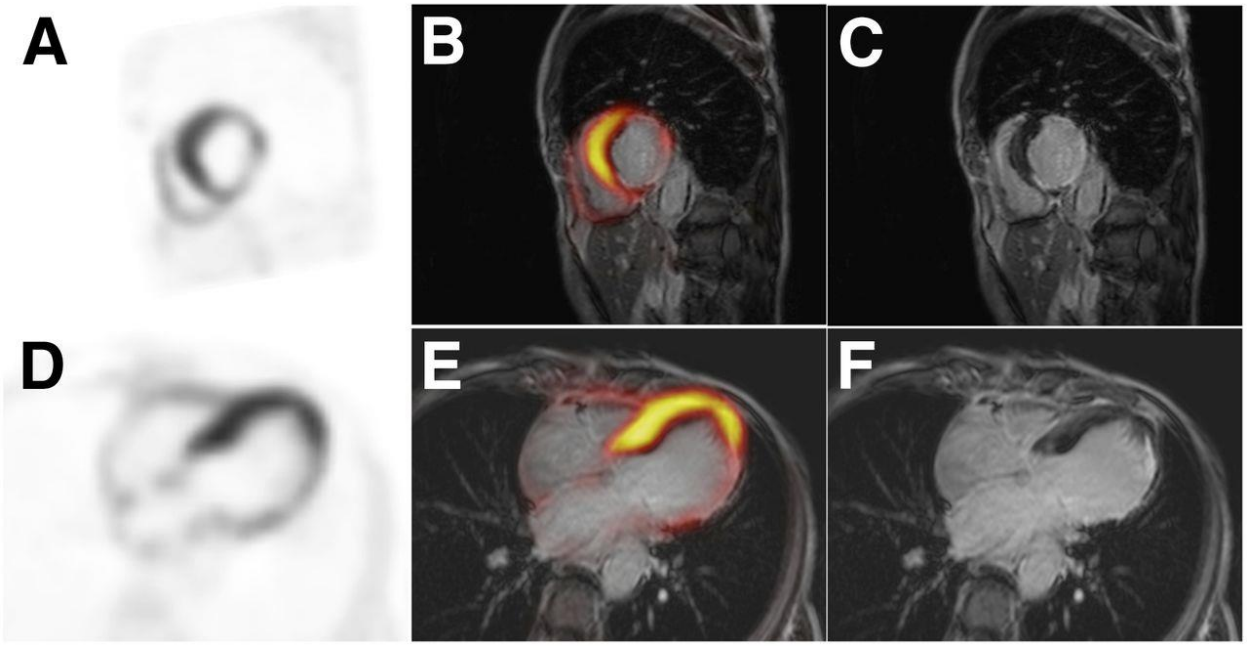

Figure 4: A patient with a left ventricular ejection fraction of 30% with inferior-to-posterolateral akinesia on echocardiography. 18F FDG PET/MRI shows decreased metabolic activity of posterolateral wall (A and D) corresponding to late gadolinium enhancement on MR images (C and F) confirmed on fused images (B and E). Reprinted with permission (*31*).

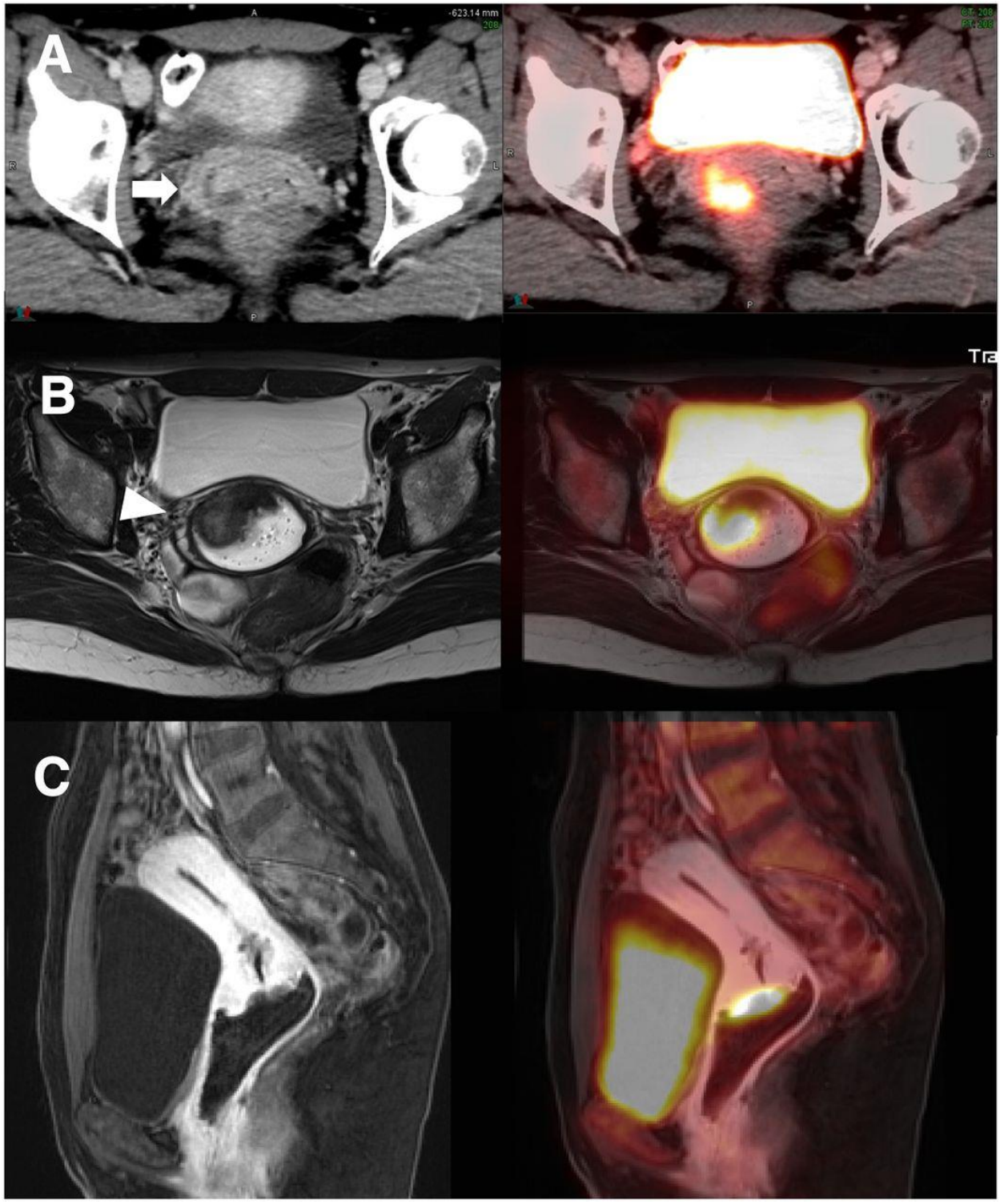

Figure 5: Poorly differentiated squamous cell carcinoma of cervix showing CT (A; left) and PET/CT (A; right) with corresponding unenhanced T2-weighted turbo spin-echo (B; left) and T2-weighted turbo spin-echo PET/MRI (B; right). Contrast enhanced sagittal MRI T1-weighted Dixon-visual background extractor) (C; left) and PET/MRI (C; right) are also shown. Reprinted with permission (*32*).

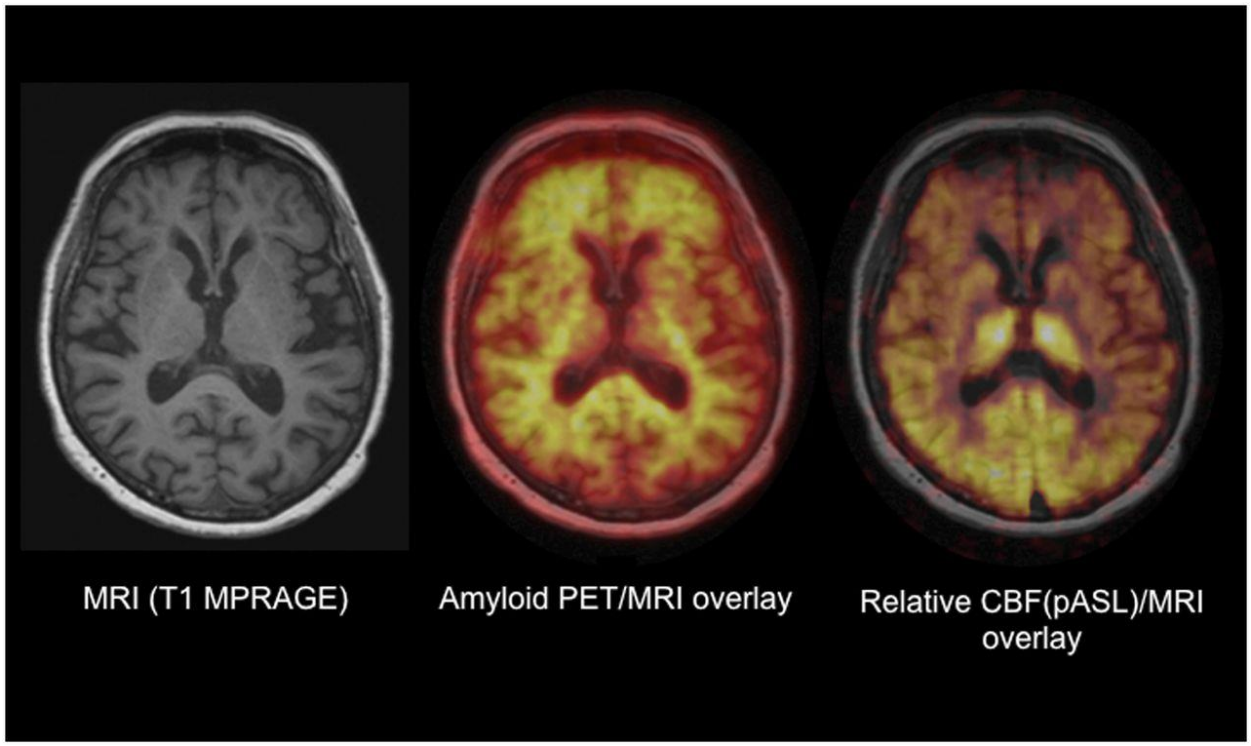

Figure 6: Simultaneous PET/MRI in dementia using ^{18}F-florbetaben PET and pulsed arterial spin labeling (pASL) MRI. Reprinted with permission (*33*).