Recent topics of the clinical utility of PET/MRI in oncology and neuroscience

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Abstract

Since the inline positron emission tomography (PET) / magnetic resonance imaging (MRI) system appeared in clinical, more than a decade has passed. In this article, we have reviewed recently-published articles about PET/MRI. There have been articles about staging in rectal and breast cancers by PET/MRI using fluorodeoxyglucose (FDG) with higher diagnostic performance in oncology. Assessing possible metastatic bone lesions is considered a proper target by FDG PET/MRI. Other than FDG, PET/MRI with prostate specific membrane antigen (PSMA)-targeted tracers or fibroblast activation protein inhibitor have been reported. Especially, PSMA PET/MRI has been reported to be a promising tool for determining appropriate sites in biopsy. Independent of tracers, the clinical application of artificial intelligence (AI) for images obtained by PET/MRI is one of the current topics in this field, suggesting clinical usefulness for differentiating breast lesions or grading prostate cancer. In addition, AI has been reported to be helpful for noise reduction for reconstructing images, which would be promising for reducing radiation exposure. Furthermore, PET/MRI has a clinical role in neuroscience, including localization of the epileptogenic zone. PET/MRI with new PET tracers could be useful for differentiation among neurological disorders. Clinical applications of integrated PET/MRI in various fields are expected to be reported in the future.

Keywords: PET, MRI, FDG, PSMA, AI

Introduction

An inline positron emission tomography (PET) - magnetic resonance imaging (MRI) scanner has been developed and used this century, following the widespread use of a combined PET/CT scanner. Combining MRI, which yields higher tissue contrast, and PET images, providing metabolic information with higher resolution and quantification, precise functional information can be available with morphological data. In addition, fused images between PET and MRI obtained by most PET/MRI devices, unlike sequential acquisition with PET/CT, are acquired simultaneously, allowing us to get more accurate registration [1]. For this reason, more reliable information can be obtained in several specific organs likely to be influenced by respiratory motion or peristalsis [2]. On the other hand, the higher cost of an inline PET/MRI system has not been replacing PET/CT because the side-by-side reading of PET/CT and MRI is often sufficient for determining therapeutic management in clinical. More appropriate clinical applications of PET/MRI have still been explored [3].

In this review article, we overview the recent reports to consider the future perspectives of the clinical application of PET/MRI.

PET/MRI with FDG in Oncology

Catalano et al. compared the diagnostic accuracy of FDG PET/MRI with Fluorodeoxyglucose (FDG) and pelvic MRI in evaluating T and N stages in 62 patients with rectal cancer [4]. They clarified that PET/MRI provides a more precise assessment of the local extent of rectal cancers in evaluating cancer length, N status, and external sphincter involvement. PET/MRI outperformed MRI in evaluating tumor size (42.5 ± 21.03 mm per the reference standard, 54 ± 20.45 mm by MRI, and 44 ± 20 mm by PET/MRI, $p=0.004$) and in identifying N status (correct by MR in 36/62 patients [58%] and by PET/MRI in 49/62 cases [79%]; $p=0.02$) and external sphincter infiltration (correct by MRI in 6/10 and by PET/MRI in 9/10; $p=0.003$). Queiroz et al. [5] compared the diagnostic accuracy of detecting distant metastases for baseline rectal cancer staging between FDG PET/MRI and conventional staging (pelvic MRI and thoracic and abdominal contrast-enhanced CT) in 101 patients. They demonstrated that PET/MRI exhibited a higher accuracy in detecting metastatic disease than conventional

staging in all patients (88.4% vs. 82.6%, p=0.003) and patients with extramural vascular invasion (88.9% vs. 85.5%, p=0.013). The detection rate of PET/MRI was superior to that of conventional staging for all lesions (84.1% vs. 68.9%, p=0.001), as well as those in the liver (89.2% vs. 84.2%, p=0.023), non-regional lymph nodes (90.0% vs. 36.7%, p=0.001), and lungs (76.4% vs. 66.9%, p=0.019). Moreover, Gassert et al. compared the cost-effectiveness of FDG PET/MRI with hepatocyte-specific contrast agents and standard-of-care imaging (pelvic MRI and chest and abdominopelvic CT) for the initial staging of rectal cancer [6]. They clarified that FDG PET/MRI was identified as a feasible diagnostic strategy for the initial staging of rectal cancer from a cost-effectiveness perspective.

Morawitz et al. compared FDG PET/MRI, MRI, and CT for nodal staging (lymph node station (axillary levels I–III, supraclavicular, and internal mammary chain)) in 182 patients with breast cancer and clarified FDG PET/MRI outperformed MRI or CT in detecting nodal involvement on a patient-based analysis and a station-based analysis [7]. FDG PET/MRI detected 193 stations in 75 patients, MRI detected 123 stations in 56 patients, and CT detected 104 stations in 50 patients, respectively.

An international expert opinion statement has shown the utility of FDG PET/MRI for imaging skeletal metastases with several advantages compared with FDG PET/CT (higher detection, better characterization of skeletal lesions, and better delineation of extra-osseous tumor spread and spinal cord compression) [8]. They concluded FDG PET/MRI should be considered for the staging of malignancies where there is a high likelihood of metastatic osseous disease based on the characteristics of the primary malignancy, high clinical suspicious and in cases where the presence of skeletal metastases will have an impact on patient management.

Lung evaluation with FDG PET/MRI is associated with technical issues and diagnostic image quality challenges. One review article has discussed the FDG PET/MRI utility of non-small cell lung cancer staging (4 papers) and lung nodule detection (5 papers) [9]. They showed that FDG PET/MRI and FDG PET/CT had similar diagnostic performance for T- and N-staging in non-small cell lung cancer. Although FDG PET/MRI is often helpful in detecting pleural/liver/bone/brain metastasis, the data material on M-stage was too small for meaningful analysis. The

lung nodule detection rate of PET/MRI was comparable to that of PET/CT for FDG-avid nodules larger than 10 mm. Still, the PET/MRI detection rate for non-FDG-avid nodules smaller than 5 mm was low in oncologic patients, but the clinical significance hereof is unknown. Biondetti et al. compared lung nodule detection on FDG PET/MRI versus standard-of-care imaging CT in 126 patients with primary abdominal malignancies [10]. They investigated the impact of missed nodules on clinical management in primary abdominal malignancies. The sensitivity of PET/MRI for detecting pulmonary nodules was significantly lower than that of chest CT and influenced by the size, with improved performance for nodules >7 mm. The missed lung metastasis by FDG PET/MRI did not affect patients' management, probably because of established advanced disease (stage III in 28 cases and stage IV in 80 cases). However, the fact that 22.3% of missed nodules grew at follow-up, likely representing metastases, is a significant red flag. This should alert about the need to perform a diagnostic quality chest CT to detect lung nodules in patients whose oncologic whole/body staging FDG PET/MRI was negative for both extra-thoracic metastases and lung nodules, especially if detection of lung metastases might change management.

PET/MRI with PSMA and FAPI in Oncology

Apart from FDG, various PET tracers have been developed in the oncologic field, and innumerable studies have been published to date. Here, we focus on two representative imaging targets: prostate-specific membrane antigen (PSMA) and fibroblast activation protein (FAP).

PSMA is the most popular target for detecting prostate cancer (PCa) lesions using PET. The U.S. Food and Drug Administration (FDA) approved two PSMA-targeting PET tracers, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, in December 2020 and May 2021, respectively. Clinical values of PSMA-PET would be more elevated considering the spread of the "radio-theranostics" approach to metastatic castration-resistant PCa such as ^{177}Lu- or ^{225}Ac-labeled PSMA-ligands [11]. Evangelista et al. performed a systematic review and meta-analysis extracting 50 studies to assess pooled diagnostic ability of PET/MRI in prostate cancer patients [12]. They revealed high pooled sensitivity in detecting primary PCa lesions of 94.9%. At restaging, the pooled detection rate was

high (81.8% and 77.3% for radiolabeled PSMA and radiolabeled choline, respectively), in which PET/MRI showed comparable ability to PET/CT (93.9% vs. 95.4%, respectively).

Multiparametric MRI (mpMRI) is often performed before ultrasound-guided prostate biopsies. PET/MRI has additional information on PSMA expression in the local PCa lesion and might be more helpful in guiding biopsy sites. Ferraro et al. performed a prospective study enrolling 42 patients to evaluate the usefulness of ^{68}Ga-PSMA-11 PET/MRI as guidance for prostate biopsy [13]. Per-patient sensitivity, specificity, and accuracy of PET/MRI for detecting clinically significant PCa were 96%, 81%, and 90%, respectively. They concluded that PSMA PET/MRI is a promising tool to select patients suspected of PCa for biopsy. Bodar et al. compared the accuracy of advice for potential image-guided prostate biopsy between ^{18}F-DCFPyL PET/MRI and mpMRI in a prospective analysis enrolling 30 patients (420 segments of the prostate) who underwent radical prostatectomy [14]. Both modalities correctly detected the segment, including PCa, with the highest grade group in 27 patients (90.0%). However, in this study, areas under the curve calculated from receiver operating characteristics analyses were larger in mpMRI than ^{18}F-DCFPyL PET/MRI (0.75 vs. 0.70). Solari et al. evaluated the performance of the radiomics approach in PSMA PET/MRI for predicting postsurgical Gleason score (GS) in primary PCa [15], with the overall best-performing model of the combination of PET and apparent diffusion coefficient (ADC). (see next chapter of Artificial Intelligence)

Bone is the most frequent site of distant metastases from PCa. Some previous studies have presented the superiority of MRI to CT in characterizing bone lesions. Thus it is expected that PSMA PET/MRI might be advantageous over PET/CT as well as in evaluating local prostate tumors [8].

FAP is highly expressed in cancer-associated fibroblasts (CAFs) and rare in normal tissues. ^{68}Ga-labeled FAP inhibitor (^{68}Ga-FAPI-04) is one of the novel PET tracers accumulating in CAFs in various carcinoma tissues [16]. Due to the lack of high background uptake in the brain and abdomen, it is expected that ^{68}Ga-FAPI-04 PET could achieve higher image contrast and better accuracy in assessing whole-body tumor distribution compared to FDG PET/CT [17, 18]. However, as is widely known in FDG,

^{68}Ga-FAPI-04 is not a completely tumor-specific tracer. Recently, Zhang et al. published a case series of false-positive ^{68}Ga-FAPI-04 uptake in the pancreas detected by PET/MRI [19]. According to their study, 7/103 patients (6.8%) showed a focal ^{68}Ga-FAPI-04 uptake, in which other imaging modalities, such as enhanced CT, MRI, and FDG PET, did not reveal any abnormality. They cautioned that ^{68}Ga-FAPI-04 uptake due to various inflammatory processes (activation of fibrotic reaction, fibrin formation, and FAP expression through wound healing) could cause misdiagnosis as malignant tumors.

Despite the abovementioned limitation, FAP-targeting PET has yet been expected as a useful tool that might potentially replace FDG PET. Backhaus et al. recently reported clinical data regarding PET/CT and PET/MRI using a new FAP-targeting PET tracer, ^{68}Ga-OncoFAP [20]. They also demonstrated its favorable radiochemical properties, rapid clearance from organs and soft tissues, and intense tumor uptake followed by excellent detectability of tumorous lesions throughout translational research.

Artificial Intelligence

The clinical application of artificial intelligence (AI), which is represented by machine learning (ML), has been reported in the field of PET/MRI [15, 21-25]. ML relies on the technique of identification of the complex interactions among all variables by learning from data with updating algorithms to make a prediction as accurate as possible. The benefits of ML comprise flexibility and scalability compared with conventional statistical approaches, making it deployable for several tasks, such as diagnosis and classification.

Romeo et al. examined whether the ML models using quantitative perfusion, diffusion, and metabolic data and radiomics features extracted from FDG PET/MRI could discriminate between benign and malignant breast lesions [21]. They constructed several ML models; perfusion radiomics model extracted from dynamic contrast-enhanced images, diffusion radiomics model extracted from apparent diffusion coefficient (ADC) map, and metabolic radiomics model extracted from FDG PET/CT and combined these models. Among them, the combined ML model using perfusion, diffusion, and metabolic radiomics features obtained the highest accuracy in

discriminating between benign and malignant breast lesions, with an area under the curve (AUC) of 0.983 (95% CI: 0.962-1.000), which achieved a greater AUC than clinical interpretation of FDG PET/MRI by an expert reader (AUC 0.868). They concluded that AI-enhanced functional and metabolic breast imaging had excellent performance and outperformed expert readers, thus having the potential to assist human readers in correctly classifying suspicious breast lesions and preventing unnecessary invasive breast procedures. As was mentioned earlier, Solari et al. examined the usefulness of the ML approach using ^{68}Ga-PSMA PET/MRI-based radiomics to predict the postsurgical Gleason scores (pGS) in primary prostate cancers [15]. The following ML models were constructed for predicting the pGS; four single-modality radiomics models (PET, T1WI, T2WI, ADC) and three PET + MRI double-modality models (PET + T1WI, PET + T2WI, PET + ADC). The overall best-performing model was the combined PET + ADC radiomics with a diagnostic accuracy of 82.5%. Moreover, the diagnostic accuracy for predicting the pGS was higher in this combined PET + ADC radiomics model than in biopsy GS (82.5% vs. 72.4%). Thus, the authors concluded that the combined ^{68}Ga-PSMA PET and MRI radiomics model helped predict pGS in primary prostate cancers. It might be a reliable tool for urologists and radiologists in their daily decision-making process. Similarly, Papp et al. examined the diagnostic performance of ^{68}Ga-PSMA PET/MRI for predicting low-vs-high lesion risk with ML in patients with prostate cancer [22]. All patients were treated with radical prostatectomy, and the lesions were dichotomized as low (≤ GS 3) and high (≥ GS 4) risk. In this study, the AUC of the ^{68}Ga-PSMA PET/MRI-based radiomics ML model for predicting the high-risk group was higher than that of the ^{68}Ga-PSMA SUVmax (0.86 vs. 0.80). They suggested that there was the feasibility of ^{68}Ga-PSMA PET/MRI in combination with radiomics and ML for risk prediction in patients with prostate cancer.

It has also been reported in image denoising using AI algorithms for PET/MRI [23, 24]. One disadvantage of PET/CT is the additional exposure to ionizing radiation, while PET/MRI saves radiation by replacing CT with radiation-free MRI scans, and it would reduce more redundant exposure if it is possible to reduce the injected radiotracer dose. However, increasing image noise is a significant problem with reducing the injected

radiotracer dose. Wang et al. examined generating the diagnostic FDG PET images of pediatric cancer patients from low-dose FDG PET images using the convolutional neural network (CNN) algorithms in PET/MRI studies [23]. They demonstrated the proposed CNN model reduced image noise of the ultra-low-dose PET scans (0.18mBq/kg, 6.25% of standard dose) and produced the image quality on AI-reconstructed PET images similar to standard-dose PET images (3 MBq/kg), with clinically relevant information in terms of diagnostic accuracy and quantitative values. Chen et al. also reported the potential of CNN algorithms for synthesizing the diagnostic-quality PET images from ultra-low injected dose simultaneous amyloid PET/MRI data [24]. In this study, 18 participants underwent two separate ^{18}F-florbetaben PET/MRI studies in which an ultra-low-dose (6.64 ± 3.57 MBq, 2.2 ± 1.3% of standard) or a standard-dose (300 ± 14 MBq) was injected. The inputs for the model were the ultra-low-dose PET and multi-contrast MR (T1-, T2-, and T2 FLAIR–weighted) images. The image quality of the generated deep learning (DL)–enhanced images was evaluated using three quality metrics (peak signal-to-noise ratio, structural similarity index, and root-mean square error), as well as the coefficient of variation (CV) for regional standard uptake value ratios. The DL-enhanced PET images showed marked improvement on all quality metrics compared with the low-dose images ($p < 0.001$ for all comparisons), as well as having generally similar regional CVs to the standard dose.

There is an issue with attenuation correction of PET scans acquired using PET/MRI scanners due to the errors in PET quantification arising primarily from incomplete bone information or lack thereof. Pozarurk et al. examined whether the AI approach overcomes this issue [25]. They developed an MR-based attenuation correction method for whole body PET imaging using a novel augmented DL-based generative adversarial network algorithm. The augmented DL method improved bone identification and quantification in the attenuation correction μ-maps, demonstrating a more accurate whole-body PET image than MR-based methods. Thus, they conclude that the proposed method has the potential to significantly improve the quantification accuracy of reconstructed PET images using simultaneously acquired MR PET image datasets.

In summary, AI algorithms have been applied in PET/MRI, and promising results

have been reported in image diagnosing and reconstruction.

PET/MRI for neurology

The clinical/investigational use of PET/MRI is also active for neurological disorders. Especially epilepsy is one of the diseases for which functional imaging is most expected. Guo et al. investigated the morphometric analysis program (MAP) generated from 3-D T1 brain volume imaging and quantitative FDG PET (QPET) to identify the epileptogenic zone (EZ) [26]. Among the 71 patients investigated, 45 reached Engel I seizure outcomes (free of disabling seizures after surgery). Regarding localizing EZ, the sensitivity and specificity were 66.4% and 69.2% by MAP, and 73.3% and 65.4% by QPET, respectively. Then, the authors ensembled the two modalities in 'AND' (MAP+QPET) and 'OR' (MAP/QPET) methods. They found that MAP+QPET had lower sensitivity (53.3%) but higher specificity (88.5%), while MAP/QPET had 86.7% and 46.2%, respectively. The authors concluded that QPET was superior to MAP in terms of sensitivity when used as a single modality and that combining simultaneous PET/MRI information, more specifically by the MAP+QPET method, may improve the specificity in EZ localization.

On the other hand, Liu et al. investigated the usefulness of delayed FDG PET/MRI for EZ localization [27]. A PET/MRI scanner acquired FDG images in the early phase (~40 minutes) and delayed phase (3 to 4 hours). They calculated the asymmetry index, which is 0 when symmetrical between EZ and the contralateral region, while it was a positive value when EZ showed a lower signal than the contralateral region. According to the investigation results of 41 patients, the asymmetry index was ~3.7 higher for delayed images than for early images. The change in the asymmetric index was more significant for MRI-positive cases than MRI-negative cases. In the qualitative assessments, 2 of 2 radiologists determined that delayed images had more obvious asymmetry.

The differential diagnosis of Parkinson's disease (PD) vs. multiple system atrophy (MSA) is clinically significant but not always easy. Hu et al. applied PET/MRI-based radiomics and machine learning to solve this issue [28]. They used sophisticated machine learning methods for model building. A total of 1172 radiomics features were

extracted from the putamen and the caudate nuclei on FDG PET and MRI using two standard software packages (LIFEx and pyradiomics). The study population consisted of 60 PD and 30 MSA patients, for whom a 7:3 train-test split was performed. The optimal model was based on T1WI, susceptibility-weighted image (SWI), and FDG signals, with the area under the curve (AUC) of 0.957 for the test dataset. Higher AUC was achieved when a model combining radiomics and clinical symptoms (disease duration, dysarthria, and autonomic failure) was used (AUC=0.994). They concluded that the radiomic analysis with metabolic, structural, and functional information provided by hybrid FDG PET/MRI might achieve promising diagnostic efficacy for distinguishing between PD and MSA.

Research for new drugs is another attractive use of PET/MRI. Tiepolt et al. reported the first-in-human study of (+)-^{18}F-Flubatine, which is a novel ligand targeting α4β2 nicotinic acetylcholine receptors [29]. They compared several kinetic models to distinguish Alzheimer's disease (AD) vs. healthy controls (HC). They found that 97% of injected compound was chemically unchanged at 270 minutes post-injection and that the 1-tissue compartment model without metabolite correction was adequate. The study subjects (9 mild AD and 11 HC) also underwent ^{11}C-PIB PET. In AD patients, (+)-^{18}F-Flubatine binding and ^{11}C-PIB SUVR were negatively correlated in several regions, while these tracers showed a positive correlation in the white matter of HC. They concluded that (+)-^{18}F-Flubatine has a favorable characteristic (safe and stable) and will be helpful α4β2 nAChR-targeting PET ligand in future clinical trials. Finally, ^{18}F-FLUDA, a radiotracer for adenosine A_{2A} receptor, was pre-clinically investigated by Lai et al. [30]. The adenosine A_{2A} receptor is a therapeutic target for several diseases, such as Parkinson's disease and Huntington's disease. ^{18}F-FLUDA is a deuterated isotopologue of ^{18}F-FESCH. The authors hypothesized that substituting deuterium (i.e., heavy hydrogen, ^{2}H) near the ^{18}F position improves the imaging properties. In the in vivo evaluation of mice, they found that ^{18}F-FLUDA was more stable than ^{18}F-FESCH, and thus brain-penetrating radiometabolites of ^{18}F-FLUDA were absent. PET/MRI studies showed the high specific binding of ^{18}F-FLUDA toward the striatal A_{2A} receptor with a maximum specific-to-nonspecific binding ratio of 8.3. The toxicity study did not show any adverse effects. The authors concluded that FLUDA is ready for human

applications.

Conclusion

There has been an increasing number of articles demonstrating the clinical efficacy of combined PET/MRI scanners, indicating their contribution to daily clinical use. Evaluating bone metastasis with FDG PET/MRI and pre- or post-therapeutic evaluation of primary or metastatic prostate cancer by PSMA-PET/MRI could be an efficient imaging test as a one-stop shop. The clinical application of AI for images obtained by PET/MRI would also be promising. Several articles describe PET/MRI with new PET tracers for differential diagnosis among neurological disorders. Due to the higher cost of the PET/MRI system, its diffusion has been gradual, but we need to continue clinical studies to use this state-of-the-art modality properly.

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