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Review: Application Trends of Contrast Media in PET/MRI

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Abstract - Research on medical imaging contrast agents to improve diagnostic performance and optimize treatment strategies has been ongoing for a long time. Recently, hybrid imaging technology in which two different devices such as PET/CT, SPECT/CT, and PET/MRI are fused is emerging as a new trend in medical imaging. The high spatial resolution of Magnetic Resonance Imaging (MRI) and the high-sensitivity molecular-level information of Positron Emission Tomography (PET) by these convergence devices are leading to the development of new hybrid imaging technologies along with hybrid contrast agents. To create a hybrid contrast agent for simultaneous PET-MRI devices, the radiotracer for PET should be combined with the MRI contrast agent. The most common approach to achieve this is to coat radioisotopes to the surface of small superparamagnetic iron oxide (SPIO) particles. These contrast agents are used for pH change monitoring, non-invasive angiography, and early imaging diagnosis of atherosclerosis. In addition, tumor detection and cardiovascular imaging are becoming important research areas for the development of simultaneous PET/MRI imaging systems and hybrid contrast agents. Therefore, tumor detection and cardiovascular imaging are major areas for development of simultaneous PET/MRI imaging systems and hybrid contrast agents. The goal of developing hybrid contrast agents for this purpose is to combine high spatial resolution, high sensitivity, and morphological and functional information. The future prospect is considered to be the development of a multimodal hybrid contrast agent that detects diseases early, provides information before and after surgery for treatment, and provides treatment prognosis.

Key word: Medical Imaging, Simultaneous PET/MRI, Contrast agents, Hybride contrast agents

I. Introduction

Imaging technology plays an important role in medical diagnosis[1]. In the field of medical image, imaging techniques such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography(PET), and Single-Photon Emission Computed Tomography(SPECT) have provided clinicians with information of the human body[2]. The limited information provided by single modal medical images cannot meet the need of clinical diagnosis which requires a large amount of information, making medical image fusion research

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become a hot field[3]. Medical image fusion can be divided into single-mode fusion and multimodal fusion. Due to the limitation of the information presented by single-modal fusion, there are many researchers engaging in the study of multimodal fusion[2]. Different imaging methods keep different characteristics, and different sensors obtain different imaging information of the same part. The purpose of the fusion is to obtain better contrast, fusion quality, and perceived experience[4]. The result of the fusion should meet the following conditions: (a) the fused image should retain the information of source images completely; (b) the fused image should not produce any synthetic information, such as artifacts; and (c) bad states should be avoided, such as misregistration and noise[5]. With the recent advent of "hybrid" imaging devices that combine PET and MRI modalities, it is now possible to perform both diagnostic tests simultaneously on the same system, avoiding multiple tests and improving registration performance[6]. It is useful for planning radiation treatment. With the advent of these hybrid PET-MRI devices, "hybrid" PET-MRI contrast agents are being developed in preclinical settings[7]. Tendency to combine two contrast agents are more and more to overcome the limitations of a single device. These hybride contrast agents are aimed to obtain Molecular and cellular imaging[7]. Macromolecules and cells require ligands for selective binding, and these ligands must be conjugated with MR and PET contrast agents[8]. They open up new diagnostic and research possibilities and provide access to functional and molecular imaging in particular. The purpose of this paper is to review the literature on hybrid PET-MRI contrast agents, discuss the clinical applications of hybrid PET-MRI contrast agents, and review the prospects.

II. Developing a hybrid PET-MRI contrast agent

1. Simultaneous PET-MRI

The major technical challenge from the PET perspective was that photomultiplier tubes (PMTs), used until recently in virtually all commercially available PET scanners, are very sensitive to even small magnetic fields and cannot be operated inside modern preclinical or clinical high-field MR devices[9]. To overcome this limitation in the early days of PET/MRI, long optical fibers were used to channel the light from the scintillator crystals placed inside the MR system to PMTs located at a safe distance[9]. Several generations of small animal imaging devices have subsequently been built using PMTs in an effort to increase the PET performance in terms of the spatial resolution uniformity and axial coverage. All these efforts required substantial modification of the PET detectors to maximize compatibility with existing MRI devices. Alternatively, minimally modified PET detectors have been integrated in specialized MRI scanners. In spite of this very important pioneering work, PET/MRI would have likely failed to transition from small animal to human imaging if it were not for the emergence of MR-compatible photon detector technology that allowed the placement of the PET detectors inside the magnet's bore. Fortunately, solid-state photon detectors have reached a level of maturity that allowed them to replace PMTs for this application. Avalanche photodiodes (APDs) were the first such photon detectors that were demonstrated to work even inside ultra-high-field magnets and were used to build MR-compatible PET inserts for small animal imaging. More importantly, this technology allowed Siemens to build the first PET/MRI prototype scanner for human brain imaging. This device was called BrainPET and was designed to fit

into the bore of the standard 3T whole body MRI scanner. Although only a handful of BrainPET prototypes were ever built and only three of them are still in use, these inserts have been used for many studies ranging from those aimed at investigating the mutual interference between the two devices and the performance of the APD-based PET detector technology. It is developing methods to use the information obtained from one device to improve the other modality, and demonstrating the tremendous potential of PET/MRI through proof-of-principle studies in small animals, non-human primates, and humans. Additional challenges such as the need to carefully shield the PET detectors to minimize the electromagnetic interference with the MR system or to control for temperature variations in the detectors caused by the eddy currents induced by the switching MR gradients had to be considered when using these solid- state photon detectors. More recently, Geiger mode APDs (also called solid-state photomultipliers (SSPM), silicon photomultipliers (SiPMs) or multi-photon pixel counters (MPPC)) have emerged as very promising candidates for replacing APDs as the photon detector of choice for simultaneous PET -MR imaging and several groups have developed small animal scanners using this technology. There are also now companies that offer MR-compatible PET inserts designed to operate inside existing small animal MRI devices[10].

2. PET and MRI contrast agent

Recently, medical imaging using hybrid technology has been widely accepted and used in clinical practice. Since simultaneous PET/MRI offers significant advantages over well-established PET/CT, including superior contrast and resolution and reduced ionizing radiation[11], simultaneous PET/MRI is useful in oncological imaging of areas such as the brain, head and neck, liver , and pelvis. Nanoscale particles can exhibit special physical and biological behaviors and unique interactions with biomolecules [12]. Nanoparticles have a large surface area and unique functions that alter pharmacokinetics, prolong vascular circulation time, improve extravasation capacity, ensure enhanced biodistribution in vivo, and induce sustained and controllable delivery[13]. In addition, when a specific targeting ligand is conjugated to a nanoparticle, the nanoparticle can realize its target binding ability to a diseased region[14]. Nanocarriers penetrate through microvessels with improved permeability and are then absorbed into cells, resulting in highly selective payload accumulation at the target site[15]. Over the past few decades, many traditional medical imaging techniques have been established for routine laboratory and clinical use. These imaging techniques, including optical imaging (OI), computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and PET-single photon emission computed tomography (PET/SPECT) radionuclide imaging, have been widely applied in small-scale experiments and have shown excellent performance[16]. Molecular imaging differs from conventional imaging in that it is used to image specific targets or pathways using probes known as biomarkers. Biomarkers must interact very specifically with their surrounding environment and change their image in response to molecular changes occurring within the region of interest (ROI). Molecular imaging agents are endogenous molecular or exogenous probes used to visualize, characterize, and quantify biological processes in living systems. Different imaging techniques in terms of sensitivity, resolution, and complexity often require specific

contrast agents to achieve satisfactory contrast enhancement in visualization reconstructions [16].

2.1. PET Radiotracers

A PET radiotracer (also known as PET tracer) is a positron-emitting radiopharmaceutical used in positron emission tomography (PET). Each tracer consists of a positron-emitting isotope (radioactive tag) bound to an organic ligand (targeting agent). The ligand component of each tracer interacts with a protein target, resulting in a characteristic distribution of the tracer throughout the tissues. The ideal PET radiopharmaceutical should only interact with the protein target and not give accumulation phenomena. For example, the pre-eminent PET radiotracer fluorodeoxyglucose (FDG) is comprised of a fluorine-18 isotope bound to 2-deoxy-2-glucose, an analog to glucose. The 2-deoxy-2-glucose ligand is a substrate for the hexokinase/glucokinase enzymes involved in the early carbohydrate metabolism; Thus, FDG is chemically linked to cellular metabolic activity. It serves as a particularly good tracer agent because it tends to stay "trapped" within metabolically active cells due to the absence of the hydroxide group ("deoxy-"). There is an increasing list of chemical compounds which are being used for PET imaging.

Table 1 shows the compounds and radioactive isotopes of PET contrast agents currently developed and used.

Table 1. Compounds and radioactive isotopes of contrast agent for PET

chemical compounds	radioactive isotope
Acetate	C-11
choline	C-11
fludeoxyglucose	F-18
sodium fluoride	F-18
fluoro-ethyl-spiperone	F-18
methionine	C-11
prostate membrane antigen	PSMA, Ga-68
DOTATOC, DOTATATE	Ga-68
florbetaben, florbetapir	F-18
rubidium	Rb-82 chloride
ammonia	N-13
FDDNP	F-18
Labeled water	O-15
FDOPA	F-18

The synthesis of PET tracers begins in cyclotrons with the formation of small molecules called precursors. For example, the isotope carbon-11 can be produced both as carbon dioxide (C-11 CO2) and as methane (C-11 CH4), respectively the most oxidized and the most reduced chemical form.

2.2. MRI contrast agents

Most MRI contrast agents are paramagnetic gadolinium ion complexes or superparamagnetic (iron oxide) magnetite particles. Paramagnetic contrast agents are usually made from dysprosium (Dy^{3+}), the lanthanide metal gadolinium (Gd^{3+}), or the transition metal manganese (Mn^{2+}) and have water-soluble properties. The metal atom of choice most commonly used in MRI contrast agents is the lanthanide ion gadolinium, which has a high magnetic moment and is the most stable ion with an unpaired electron. The presence of unpaired electrons gives these contrast agents paramagnetic properties. Gadolinium has 7 electrons, dysprosium has 4 electrons, and manganese has 5 unpaired electrons. Contrast agents containing gadolinium shorten the T1 and T2 relaxation times of adjacent water protons. These effects increase the signal intensity of T1-weighted images and decrease the signal intensity of T2-weighted images[17,18]. T1 shortening occurs at lower gadolinium concentrations, whereas T2 shortening occurs at higher gadolinium concentrations, which is of limited clinical use due to the increased risk of toxicity. Therefore, in conventional clinical practice T1 is evaluated after

the administration of extracellular agents[19]. Contrast agents containing transition metal ions, such as high spin manganese, and superparamagnetic iron oxide such as iron oxides, affect the T2 relaxation strongly [20,21].

(1) Gadolinium

Gadolinium cholate is a coordination complex consisting of a gadolinium ion bound to a hexadentate organic chelating agent such as diethylenetriaminepentaacetic acid. Chelates of gadolinium are frequently utilized as magnetic resonance imaging(MRI) contrast agents and can be used to track nanoparticle-mediated drug delivery. Gadolinium chelate is a coordination complex consisting of a gadolinium ion bound to a hexadentate organic chelating agent such as diethylenetriaminepentaacetic acid. Chelates of gadolinium are frequently utilized as magnetic resonance imaging(MRI) contrast agents and can be used to track nanoparticle-mediated drug delivery. Table 2 all trials on the list are NCI-supported clinical trials, which are sponsored or otherwise financially supported by NCI.

Table 2. NCI-supported clinical trials

N	clinical trials
1	Brain-Directed Stereotactic Radiation Therapy with or without AgulX Gadolinium-Based Nanoparticles for
2	Seterotactic Magnetic Resonance-Guided Adaptive Radiation Therapy with pr without AgulX for the Treatment of Central Lung Tumors and Locally
3	Convection –Enhanced Delivery of Topotecan in Treating Patients with Recurrent or Progressive WHO
4	An Investigational Scan (Fluciclovine F-18 PET) for the Diagnosis of Cervical or Endometrical Cancer
5	Rapid Motion-Robust Quantitative DCE-MRI for the
6	Disposable Perfusion Phantom for Accurate DCE-MRI Measurement of Pancreatic Cancer Therapy Response
7	[^{18}F]FMISO-PET/MRIScanfortheMonitoringofTreatmentResponseinPatientswithHER2+StageII-IIIBreastCancerReceivingTherapybeforSurgery
8	Arterial Spin Labeled MR Imaging for Assessment of Therapy Response in Patients with Metastatic Renal
9	MR with Gadobenate Dimeglumine or Gadoxetate Disodium for the Diagnosis of Liver Metastases from
10	Magnetic Responance Imaging for Imaging of Tumor Microenvironment of Metastasis in Patients with
11	Advanced MRI Scan Befor and After Radiation Therapy for the Detection of Intracranial Metastasis
12	Abbreviated MRI Protocol for the Diagnosis of Woman with Findings Highly Suspicious for Breast
13	Whole-Body MRI for the Detection and Assessment of Therapy Response in Multiple Myeloma
11	Contrast-enhenced MRI in Detecting Denign and ^{18}F-DCFPyL PET/MRI for the Diagnosis of Prostate
1	PET/MRI Scan for the Evaluation of Resectable Stage
17	Pron to Supine MRI Scan for the Imaging of Breast Cancer Tumors, P2S2 MRI study
18	Effect on Body Movement and Mental Skills in Patients Who Received Dadolinium-based Contrast Media for Magnetic Resonance Examination Multiple
19	Diffusion MRI for the Assessment of Response during Chemoradiation Treatment in Patients with Heas and Neck Squamous Cell Cancer That Is Metastatic to the
20	Advanced Perfusion MRI Scan for the Study of Treatment Response and Progression in Glioblastoma

(2) Microbubbles

Microbubbles were initially used as contrast agents in ultrasonography, allowing the study of enhanced lesions with relatively safe and rapid clearance. However, it may also be useful as a vascular MRI contrast agent without structural modifications or with the addition of an agent with magnetization sensitivity such as a hyperpolarized gas (^{3}He or ^{129}Xe) that increases detection. Adding radioactive isotopes is straightforward, making hybrid contrast agent development a straightforward procedure [22].

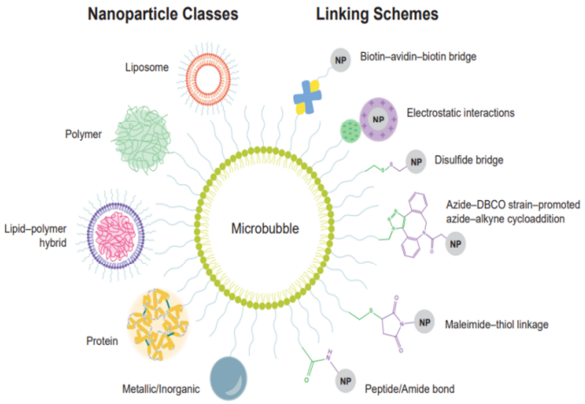

Figure 1. Examples of microbubble contrast agent[22]

(3) Superparamagnetic iron oxide NPs (SPIONs)

SPIONs are a promising and multifunctional tool in various cancer therapies and may help to overcome the limitations of conventional therapies. Moreover, it is still necessary to develop new methods of treatment with expected properties, such as lower toxicity, long-lasting effectiveness and higher selectivity. Analyzing the literature data, we found that currently SPIONs are used in the transport of drugs, immunotherapy and hyperthermia. The main aim of this review is to present various cancer treatment therapies utilizing SPIONs, the importance of the experiments carried out by research groups and further perspectives in the nanotechnological use of SPIONs.

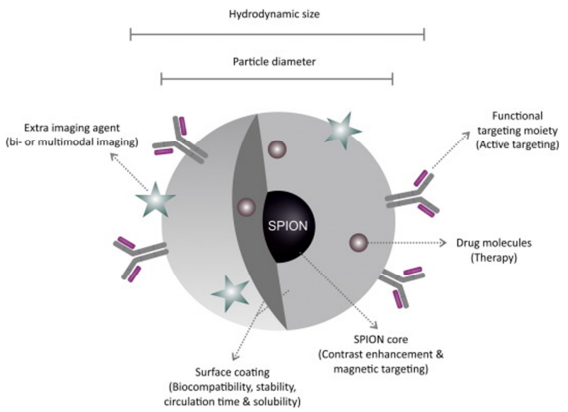

Figure 2. Examples of SPIONs [23]

Table 3. Superparamagnetic iron oxide agents available for MRI cell trafficking[24]

Category	Trade name	Company	Size(nm)	Coating material	Other application
MION	VSOP-C184	Ferropharm	7	Citrate	Blood pool contrast agent
	CLIO		45	Crosslinked aminated dextran	MRI molecular imaging
USPIO	Sinerem/ Combidex	Guerbet Advanced Magnetics	20-40	Dextran T10T1	Metastatic lymph node imaging, Macrophage imaging, Blood pool agent
	CODE 7228	Advanced Magnetics	18-20	Carboxyl-methyl-dextran	Macrophage imaging, Blood pool agent
SPIO	Feridex/ Endorem	Guerber Advanced Magnetics	80-150	Dextran T10	Liver imaging
	Resovist	Schering	62	Carboxy-dextran	Liver imaging
MPIO	Bangs Particle	Bangs Laboratories	760-1630	Styrene/ Divinyl benzene with dragon green fluorescent dye	Magnetic cell sorting

(CLIO crosslinked iron oxide, MION monocrystal line iron oxide nanoparticles, MPIO micrometer-sized paramagnetic iron oxide, SPIO superparamagnetic iron oxide, USPIO ultrasmall superparamagnetic iron oxide)

3. PET tracer combined with MRI contrast agent

Iron oxides (IONPs) are favored for T2 and T2*-weighted MRI imaging. There are several methods for the chemical synthesis of iron oxide nanoparticles. Among these methods, coprecipitation of Fe^{2+} and Fe^{3+} ions in a basic aqueous medium (NaOH or NH_4OH solution) is the simplest, but generally polydisperse non-crystallized nanoparticles are obtained[25]. To avoid these disadvantages, iron oxide nanoparticles that are monodisperse and of uniform crystallinity were prepared using a thermal decomposition method. Then, the hydrophobic iron oxide nanoparticles can be coated with phospholipids, silica, or an amphiphilic polymer as a shell to exhibit excellent solubility and biocompatibility in vivo[25]. In the simultaneous PET/MRI units, the PET is placed within the MR bore. To acquire simultaneous PET/MRI images, a combined imaging agent must be metabolized simultaneously in the body[26]. Therefore, the MRI and PET contrast agents should be synthesized as one agent. Used N-(p-maleimidophenyl) isocyanate (PMPI) to crosslink magnetic nanoparticles (MNPs) for MRI imaging with fluorodeoxyglucose (^{18}F-FDG) for PET imaging as a single contrast agent for combined PET/MRI imaging (Figure 3).

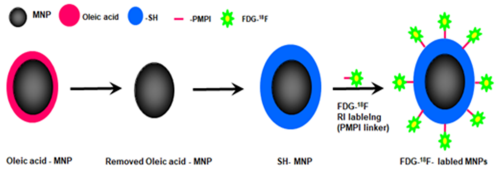

Figure 3. ^{18}F-FDG labeled MNPs[27]

III. Hybrid PET-MRI contrast agents and their applications

Currently, hybrid imaging technology that combines positron emission tomography (PET) and magnetic resonance imaging (MRI) is receiving great attention not only in clinical applications but also in preclinical fields. Several prototypes based on different types of PET detector technology have been developed in recent years, some of which have been used in first preclinical studies. We searched papers published between the 1990s and 2022 in scholar google, Cohrane review, PubMed, EMBASE, and NIH with search keywords in the order shown in Figure 4. Search keywords are "Medical imaging, contrast media, contrast agent, radioisotopes, radiotracer, nuclear medicine, PET, MRI, PET/MRT, PET radiotracers, MRI contrast media, MRI contrast agent, simultaneous PET/MRI, hybrid contrast media, hybrid contrast agent, hybrid PET/MRI contrast media, PET/MRI contrast agent, angiography, brain scan, cardiovascular angiography, molecular imaging agent, NMP probe". A literature search yielded 128 abstracts, of which 23 were duplicates. We reviewed 75 abstracts according to exclusion criteria.

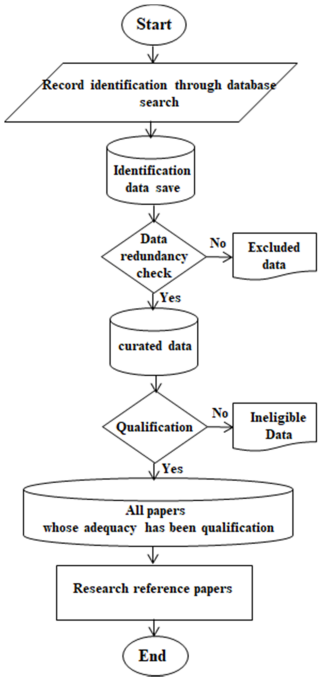

Figure 4. Flowchart of literature searching process

Table 4 shows hybrid PET/MRI contrast agents for tumor imaging through a literature search.

Table 4. Hybrid PET/MRI contrast agents for tumor imaging

Nano structure	MRI Component	PET Component	Chelator	Biological Traget
Hyaluronic acid+chitosan	Gd-DAPA	^{18}F-FDG	No chelator	Passive targeting
Iron oxide + ligands	Iron oxide	^{11}C	No chelator	Passive targeting
Iron oxide +	Iron	^{64}Cu	DOTA	Passive
Iron oxide +	Iron	^{64}Cu	DTCBP	Passive
Iron oxide +	Iron	^{64}Cu	DOTA	Passive
Iron oxide + mannose	Iron oxide	^{64}Cu	NOTA	Passive targeting
Iron oxide + micelle	Iron oxide	^{64}Cu	NOTA	Oleanolic acid
Iron oxide +	Iron	^{64}Cu	DOTA	RGD*
Iron oxide +	Iron	^{64}Cu	NOTA	Anti
Iron oxide + PLGA	Iron oxide	^{64}Cu	DOTA	Passive targeting
Iron oxide + polyglucose	Iron oxide	^{89}Zr	Desferri-oxamine	Passive targeting
Iron oxide + silica	Iron oxide	^{68}Ga	DO3A	Passive targeting
Liposome	Gd-DTPA	^{89}Zr	no chelator	Octerptid
Liposome	Gd^{3+}	^{64}Cu	DOTA	Passive

Liposome + nEG	Gd^{3+}	^{64}Cu	DOTA	Passive targeting
Melanine NP	Fe^{3+}	^{64}Cu	No	RGD*
Mesoporous	Gd^{3+}	^{64}Cu	DOTA	Passive
Micelle	Fe^{3+}	^{89}Zr	Desferrio-xamine	Passive targeting
MnMEIO + SA	MnMEIO	^{124}I	No chelator	Passive targeting

HSA: Human serum albumin, **RGD:** Arg-Gly-Asp, **PEG**: Polyethylene glycol, **PLGA**: polyactic-co-glycolic acid, **nEG**: n-ethylene glycol spacers, **MnMEID**: Mn-doped magnetism engineered iron oxide, **PASP**: polyaspartic acid, **DTCBP**: dithiocarbamatebisphosphonate, **EGFR**: epidermal growth factor receptor, **NOTA**:1,4,7-triazacyclonane-1,4,7-triacetic acid, **DOTA**: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, **DOTAGA**: 1,4,7,10-tetraazacyclododecane-1-glutaric anhydride-4,7,10-triacetic acid, **NODAGA**: 2,2'-(7-(1-carboxy-4-(2,5-dioxopyrrolidin-1-yl)oxy)-4-oxobutyl)-1,4,7-triazonane-1,4-diyl) diacetic acid, **NODAGA**: 2,2'-(7-(1-carboxy-4-((2.5-dioxopyrrolidin-1-yl)oxy)-4-oxobutyl)-1,4,7-triazonane-1,4-diyl) diacetic acid, **DO3A**: 1,4,7-tris(carboxymethylaza)cyclododecane-10-azzacetylamide, **FDG**: flurodeoxyglucowe

Table 5 shows the various application fields of hybrid PET-MRI contrast agents.

Table 5. Applications of Hybrid PET/MRI contrast agents

Hybrid Agent	MRI Component	PET Component	Application
SPIO-^{64}Cu(+/-Cu^{2+})[28, 29]	SPIO	^{64}Cu	Stem cell monitoring, Wilson′s disease
Gd-DOTA-4AMP-F[30]	Gd	^{18}F	In vivo pH measurements
18F-lipid-labled Microbubbles[31]	Microbubbles	^{18}F	Non-invasive angiography
^{64}Cu-labled-magnetic-nanoparticle[32]	SPIO	^{64}Cu	Atheromatous palque imaging
^{124}I-SA-MnMEIO[33]	SPIO	^{124}I	Lymph node imaging
RGD-PASP-IO combined with ^{64}Cu[34]	PASP-IO	^{64}Cu	Tumor neoangiogenesis imaging
^{18}F-FDG labeled MNPs [34]	Iron oxcid	18F	molecular imaging

IV. Discussion

1. Physicochemical property monitoring via "smart" contrast agents

"Smart" hybrid contrast agents are triggered by environmental factors or enzymatic activity. The MR relaxivity of "smart" agents can be altered in the presence of enzymes, specific pH, specific metal ion concentration, partial oxygen pressure or specific temperature. Iron oxides (IONPs) are favored for T2 and T2*-weighted MRI imaging. There are several methods for the chemical synthesis of iron oxide nanoparticles. Among these methods, coprecipitation of Fe^{2+} and Fe^{3+} ions in a basic aqueous medium (NaOH or NH4OH solution) is the simplest, but generally polydisperse non-crystallized nanoparticles are obtained[35]. To avoid these disadvantages, iron oxide nanoparticles that are monodisperse and of uniform crystallinity were prepared using a thermal decomposition method. Then, the hydrophobic iron oxide nanoparticles can be coated with phospholipids, silica, or an amphiphilic polymer as a shell to exhibit excellent solubility and biocompatibility in vivo[35]. In the simultaneous PET/MRI units, the PET is placed within the MR bore. To acquire simultaneous PET-MRI images, a combined imaging agent must be metabolized simultaneously in the body[18]. Therefore, the MRI and PET contrast agents should be synthesized as one agent. Here, we used N-(p-maleimidophenyl) isocyanate(PMPI) to crosslink magnetic nanoparticles(MNPs) for MRI imaging with fluorodeoxyglucose(^{18}F-FDG) for PET imaging as a single contrast agent for combined PET/MRI imaging (Figure 3) .

2. Vascular and atheroma imaging

2.1. Imaging of Atherosclerosis

Noninvasive imaging of atherosclerosis could potentially move patient management towards individualized triage, treatment, and followup. The newly introduced combined positron emission tomography(PET) and magnetic resonance

imaging(MRI) system could emerge as a key player in this context. Both PET and MRI have previously been used for imaging plaque morphology and function: however, the combination of the two methods may offer new synergistic opportunities. It will give a short summary of current relevant clinical applications of PET and MRI in the setting of atherosclerosis. Additionally, our initial experiences with simultaneous PET/MRI for atherosclerosis imaging were presented. Future potential vascular applications exploiting the unique combination of PET and MRI was discussed[36].

2.2. Imaging of Atherosclerosis

Fluorine 18–labeled sodium fluoride PET/MRI characteristics were associated with the culprit atherosclerotic plaques in the carotid circulation of study participants with acute neurovascular syndrome; PET/MRI was also usable in the assessment of carotid stenosis, high-risk plaque features, and plaque biologic activity. Fluorine 18–labeled sodium fluoride PET/MRI characteristics were associated with the culprit carotid vessel in study participants with acute neurovascular syndrome[37].

3. Oncology

Hybrid imaging, incorporating positron emission tomography(PET) and magnetic resonance imaging(MRI), has the advantages of high-resolution anatomical data from MRI and functional imaging data from PET, with the potential to improve diagnostic evaluation of various types of cancer. Clinical oncology applications of this newest hybrid imaging technology are evolving, and efforts are underway to adapt the role of PET/MRI in routine clinical use. Papers published to date suggest that PET/MRI may play an important role in evaluating patients with certain types of malignancies involving anatomical locations such as the pelvis and liver. In this paper, we reviewed the currently published PET/MRI literature for specific oncology applications.

3.1. Breast cancer

The value of FDG-PET in local breast cancer evaluation is still controversial. The primary utility of PET is believed to be in the evaluation of distant metastatic disease. It has been shown in PET/CT that PET has higher sensitivity and specificity in detecting distant disease as well as assessing response to treatment compared to conventional imaging[38]. Similarly, the role of MRI in breast cancer evaluation has also been established, suggesting its usefulness for lesion characterization, multiple disease detection, and diagnosis of unsuspected contralateral cancer. However, a recent study by Grueneisen et al[39] showed that integrated PET/MR provides no advantage over MRI alone for local staging evaluation. Additionally, it is not yet clear whether the aforementioned potential segmentation errors in bone evaluation for PET/MR may reduce the value of this technique compared to PET/CT, which has been shown to be superior to conventional imaging. PET/MR may eventually appear to be of value in breast cancer management, but currently its role is limited and largely undefined.[40]

3.2. Lung cancer

Lung cancer is the leading cause of cancer-related deaths worldwide. Additionally, lung metastases frequently occur with many cancer types, and detection and accurate characterization of pulmonary nodules is critical in oncologic imaging.

Characterization of pulmonary lesions, which are commonly found incidentally on imaging studies, is very important for appropriate patient management[41]. PET/CT has been shown to be useful in characterization of pulmonary lesions with an overall sensitivity and specificity approaching 90% for solitary pulmonary nodules >10 mm[42]. However, FDG-PET is limited in evaluating pulmonary nodules <1 cm. MRI also is limited in the detection of small pulmonary lesions. Thus, diagnostic CT is still considered the method of choice for detection of small pulmonary lesions. A recent study compared the differences in image quality, lesion detection rate, and radiotracer uptake of the pulmonary lesions in patients with different types of malignancies using PET/CT and PET/MRI[43]. In this study, PET/MR consisted of a coronal 2-point Dixon 3D VIBE T1W MR in shallow respiration for attenuation correction and a fat-suppressed CE 3D VIBE pulse sequence performed in deep inspiration while imaging the lungs. A total of 47 pulmonary lesions with various sizes (mean size ± SD: 10.0 ± 11.4 mm; range 2–60 mm) were detected. All patients underwent a separate low-dose CT in deep inspiration; Additional CE diagnostic CT was performed in some patients. Diagnostic CT and/or low-dose CT at full inspiration was considered the reference standard, which classified 24 pulmonary lesions malignant[44], most likely unspecific/benign, and 2 indeterminate. Lesion SUVs measured on PET/CT and PET/MR were significantly correlated ($r = 0.9$; $P = 0.0001$). While the quality of PET images was similar on PET/CT and PET/MR, the image quality of CT was superior to Dixon and VIBE MRI for nodule visualization. More lesions were detected on the CE VIBE than on the Dixon, but a greater number of indeterminate lesions were seen on MR images. For lesions <1 cm, the MR detection rate was significantly lower than CT ($P < 0.0001$), but there was a high correlation in the size of the pulmonary lesions detected by CT and MR. Thus, while an additional imaging sequence is essential for detection of pulmonary lesions, the diagnostic value of CE MRI is still inferior to CT, especially for detection of small pulmonary lesions. CT detected 66 pulmonary nodules in 85% of the patients, whereas water and in-phase MR images detected 56 and 58 pulmonary nodules, respectively, in 83% of the patients, and the size of the nodules was significantly smaller on water and in-phase phase MR images compared with CT ($P < 0.05$ and $P < 0.01$, respectively)[41]. In this study, while the detection rates for pulmonary nodules were lower for MRI, there was no statistically significant difference between MRI and low-dose CT on a patient-based analysis. Thus, PET/MRI using a dedicated pulmonary imaging protocol takes much longer than PET/CT and does not provide any advantage in thoracic staging in NSCLC patients in comparison with PET/CT. However, the performance of whole-body PET/MR in detection of M stage may prove to be different and, at the minimum, it may increase the confidence of CT-negative/PET-positive findings such as lesions in the bone marrow. In addition, MRI may be able to more reliably stage organs such as the brain, adrenal glands, and the liver in these patients[45].

3.3. Gastrointestinal malignancies

As the liver is a common site for metastatic disease in many primary tumors, an area of interest and potential benefit of PET/MR compared to PET/CT is to evaluate liver lesions. In the only study comparing PET/MR combined with contrast-enhanced CT (PET/CECT), PET/MRI with T1-W/T2-W sequences had comparable diagnostic accuracy to PET/CECT for the detection of liver metastases[46]. The authors concluded that the non-contrast PET/MR protocol was more sensitive but less specific for liver lesion

evaluation than PET/CECT. Dynamic contrast enhanced MRI(CEMRI) sequences have been recommended to significantly improve the characterization of liver lesions[47]. There are several studies comparing liver MRI and contrast enhanced CT(CECT) to detect metastases, and many studies show improved sensitivity and specificity of CEMRI compared to CECT[48]. Integrating MR with hepatobiliary contrast agents (e.g., gadoxetate disodium) and DWI can provide optimal sensitivity and specificity for detection and characterization of metastatic liver lesions. For colorectal cancer, optimal diagnostic accuracy is essential given the current treatment paradigm of resection of liver metastases in selected patients with one to multiple liver metastases. PET/CT has been shown to be useful in detecting extrahepatic disease for early staging[49]. Due to variable uptake of FDG in some colorectal liver lesions, low spatial resolution for small lesions, and reduced uptake of FDG in lesions after treatment, PET/CT may be limited in assessing liver disease burden for surgical staging purposes[50]. The use of PET to rule out extrahepatic involvement combined with MRI for liver evaluation may provide the most accurate imaging option that provides both accurate liver evaluation and sensitive detection of extrahepatic disease. No studies have evaluated the diagnostic accuracy of PET/MR or compared it with other imaging modalities for detecting and diagnosing liver lesions in colorectal cancer staging. A potential area of synergy between PET and MRI is in early staging and assessment of response to neoadjuvant therapy, with the goal of predicting complete pathological response in some patients with rectal cancer[51]. MRI evaluation of tumor regression can help predict survival, and a decrease in tumor SUV after chemoradiation is associated with an increased likelihood of complete pathological response[52]. Although neither modality has been demonstrated to reliably predict pathological response as a stand-alone, combining information from both modalities may help identify patients with a complete response.

3.4. Prostate cancer

Hybrid PET/MR of the prostate has the advantage of combining high-resolution MR images, functional studies, and metabolic/molecular PET imaging[53]. There is moderate agreement between diffusion limitation on DWI and uptake of [^{18}F]fluorocholine in prostate cancer[54] and [^{18}F]fluorocholine-PET/CT and PET/CT in prostate cancer[55]. There is a significant correlation between MR and SUV. A recent study in men with recurrent prostate cancer showed better detection of prostate bed recurrence with MRI and better detection of pelvic lymph node metastases with [^{11}C]choline-PET[56]. These results suggest that PET and MRI are complementary in assessing the extent of pelvic disease. Compared to PET/CT, PET/MR is most likely to improve T stages.The use of [^{11}C]choline-PET/MR rather than [^{11}C]choline-PET/CT[57] seems to improve the anatomical assignment of lesions, especially in the bone and prostate or surgical bed. Other novel PET tracers, such as ^{68}Ga-labeled prostate-specific membrane antigen(PSMA) using PET/MR, have been shown to be promising for evaluating prostate cancer[58].

3.5. Hematologic malignancies

Imaging is important in initial staging, therapy response evaluation, and follow-up in lymphoma. Several studies have evaluated MRI and PET in multiple myeloma for assessment of disease activity.

In a small study of patients with biopsy-proven myeloma, whole-body MRI with diffusion slightly outperformed PET/CT, displaying higher sensitivity (69% vs. 59%) and specificity (83% vs. 75%). In another study of patients undergoing PET and spine MRI, MRI again performed slightly better than PET[59]. This slight superiority of MRI compared to PET held true in another longitudinal study of patients evaluated after treatment[60]. There are no studies to date that have compared simultaneous PET/MRI to PET/CT or whole-body MRI alone in myeloma patients.

4. Prospects

In the future, translational stem cell research will benefit from innovative applications of PET/MR. Experiments demonstrating the differentiation of stem cells to dopaminergic neurons and their function might be replicated in humans by ^{11}C-2β-carbomethoxy-3β-(4-fluoro) tropane PET and perfusion-weighted MRI[61];

1. Accumulation of implanted iron-labeled stem cells in border zones of brain tumors[62] and migration of such stem cells to ischemic lesions can be demonstrated[63],

2. and experiments to even detect the mobilization of endogenous neural stem cells and their migration to and proliferation around ischemic lesions (3′-deoxy-3′-fluorothymidine PET and MRI of iron oxide–labeled cells) might be established [64]..

The viability of stem cells can be documented by MRI combined to PET imaging of reporter genes [65]. Another interesting field is angiogenesis, which can be investigated by PET of 18F-galacto-RGD and dynamic contrast-enhanced MRI, and might be a new target for selective tumor therapy[65].

V. Conclusion

The development of PET/MR simultaneous and sequential scanners represents major technological achievements in hybrid imaging. Thus, many hybrid contrast agents are developing in oncology and cardiovascular imaging. The clinical role of combined PET/MR in oncology applications is evolving with the potential to improve diagnostic accuracy for specific applications. Although current data are limited, there are certain indications that are particularly promising for PET/MRI. Pelvic malignancies including cervical cancer, rectal cancer, and prostate cancer may benefit from the increased soft-tissue contrast provided by MRI compared to CT. Liver evaluation with state-of-the-art MRI combined with FDG-PET for staging of metastatic disease, especially in select patients with colorectal cancer and neuroendocrine tumors, may be of benefit. PET/MRI may yield similar results with less radiation than PET/CT in younger patients with potentially curable malignancies such as lymphoma who will undergo multiple PET studies over their course of treatment. While PET/MRI is the most recent clinical hybrid imaging modality to be developed, it is not currently widely available and may not outperform PET/CT in some instances, such as pulmonary nodule evaluation and detection of small pulmonary metastases. Widespread adoption of PET/MRI into routine clinical practice will require the identification of specific indications that benefit sufficiently from PET/MRI to justify the added cost and complexity of both equipment acquisition and imaging interpretation.

Competing interests

The authors declare that there are no competing interests.

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