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Main applications of hybrid PET-MRI contrast agents: a review

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In medical imaging, the continuous quest to improve diagnostic performance and optimize treatment strategies has led to the use of combined imaging modalities. Positron emission tomography (PET) and computed tomography (CT) is a hybrid imaging existing already for many years. The high spatial and contrast resolution of magnetic resonance imaging (MRI) and the high sensitivity and molecular information from PET imaging are leading to the development of this new hybrid imaging along with hybrid contrast agents. To create a hybrid contrast agent for PET-MRI device, a PET radiotracer needs to be combined with an MRI contrast agent. The most common approach is to add a radioactive isotope to the surface of a small superparamagnetic iron oxide (SPIO) particle. The resulting agents offer a wide range of applications, such as pH variation monitoring, non-invasive angiography and early imaging diagnosis of atherosclerosis. Oncology is the most promising field with the detection of sentinel lymph nodes and the targeting of tumor neoangiogenesis. Oncology and cardiovascular imaging are thus major areas of development for hybrid PET-MRI imaging systems and hybrid contrast agents. The aim is to combine high spatial resolution, high sensitivity, morphological and functional information. Future prospects include the use of specific antibodies and hybrid multimodal PET-MRI-ultrasound-fluorescence imaging with the potential to provide overall pre-, intra- and postoperative patient care. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: PET; MRI; hybrid; contrast agent; multimodal imaging

1. INTRODUCTION

Today, various imaging modalities based on different physical properties are used in medicine, including computed tomography (CT), ultrasonography, single-photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI). In clinical practice, the current trend is to combine all these imaging modalities in order to improve diagnostic performance and subsequently adapt treatment accordingly (1). The complementary nature of MRI and PET is recognized, as the combined modalities offer the excellent spatial and contrast resolution of MRI and the high sensitivity and molecular information of PET (2–9). Regarding neurodegenerative disorders, coupling a morphological image from MRI with a metabolic image from [^{18}F]fluorodeoxyglucose (FDG) PET offers superior diagnostic capability compared to the use of one of these examinations alone (10). Likewise, in oncology, current recommendations advocate combining MRI and FDG-PET in the management of certain tumors, thus improving diagnostic accuracy and treatment planning (11,12).

The recent emergence of "hybrid" imaging devices combining PET and MRI modalities now enables two diagnostic tests to be performed on the same system simultaneously, thereby avoiding multiple tests and improving registration performance, all of which prove useful for planning radiation therapy. In parallel with the emergence of these hybrid PET-MRI devices, "hybrid" PET-MRI contrast agents are under development in preclinical setting. To overcome the limitations of a single device there is an increasing trend to combine two contrast agents. Molecular and cellular imaging is the primary target for this development. Macromolecules and cells need ligands for selective binding, and these ligands need to be conjugated with MR and/or PET contrast agents in order to be detected (13). They open up new diagnostic and research possibilities and notably provide access to functional and molecular imaging (9).

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Nothing to disclose.

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Abbreviations: *CT, computed tomography; SPECT, single-photon emission computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; FDG, [^{18}F]fluorodeoxyglucose; SPIO, superparamagnetic iron oxide; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; SUV, standardized uptake value.*

Biography

Anita Kiani is a fifth year resident in the University Hospital of Rennes, France. In 2011, Miss Kiani finished her first years of medical school and started a radiological residency. She is titular of a Master 2 about "image signals in medicine and biology". She is also running several research programs aiming at improving patients care in diffuse hepatic diseases. She is specializing in abdominal imaging and is about to begin a career in France in a University Hospital including research and student teaching activities.

The purpose of this article is to review the literature on hybrid PET-MRI contrast agents currently under development and their creation, to discuss their possible clinical applications, and lastly to consider their prospects.

2. CREATING A HYBRID PET-MRI CONTRAST AGENT

2.1. Added value of a true hybrid contrast agent

With the recent emergence of PET-MRI imaging devices, it makes obvious sense to develop hybrid contrast agents as this reduces the need for several chemical agents. The aim of a "hybrid" is to study the same target with the same imaging agent and multimodal device. With a bi-modal agent you can be sure that both images reflect the same biological process due to with an exact co-localization of the agents, and that the two modalities are combined into a single image under the same physiological conditions. The resulting synergistic effect allows more accurate quantification of the signal, and could allow for quantification of both relaxivity and concentration.

Image interpretation is also simplified. If data are obtained on stand-alone PET and MRI scanners, the images must be fused with retrospective image registration. Abdominal regions are the most challenging due to breathing and physiological changes in the time between the two scans. In the case of follow up therapy, the interval between the two measurements must be as short as possible, and this is not always possible with two separate devices and injections. Moreover, a hybrid contrast agent has the same pharmacokinetic properties and reduces both the number of injections required and the time spent by patients in the scanner and could ultimately reduce costs. These are true benefits for the patient in terms of physical and psychological comfort.

PET and MRI agents could be injected simultaneously but there are likely to be validation and registration problems given the difference in pharmacodynamic properties. PET agents are very small and used in picomolar concentrations whereas MRI agents are larger and require millimolar concentrations (14).

A hybrid PET-MRI contrast agent can be created by combining a PET tracer with an MRI contrast agent (15,16).

2.3. PET tracers and MRI contrast agents

2.3.1. PET tracers

The β+ particle emitting radioisotopes currently described for PET-MRI hybrid tracer development are ^{64}Cu, ^{124}I, and ^{18}F (17). Tracers agents labeled with these radioisotopes are usually very small and nano-sized. The radioisotopes can be chelated and incorporated within nanoparticles, for example. They provide highly sensitive functional information but with poor spatial resolution of a few millimeters (Table 1).

2.3.2. MRI contrast agents

The MRI contrast agents used to create hybrid contrast agents provide two types of contrast, namely positive contrast with the well-known gadolinium contrast agents, and negative contrast with superparamagnetic iron oxides (SPIOs) and microbubbles. The latter are more commonly used to create hybrid contrast agents. Unlike PET tracers, MRI contrast agents are generally larger (longer biological half-life, longer retention in large vascular cavities, lower imaging contrast at earlier time points) and detected at typical concentrations 1,000 times higher than those required for PET but with much better spatial resolution (Table 1) (7).

2.3.2.1. Gadolinium. At present gadolinium chelate, a T1-positive MRI contrast agent, may be used but it exhibits low relaxivities, even more so after cellular internalization. Furthermore, the cellular toxicity of gadolinium is unknown as it is not biocompatible (13). Gadolinium chelates are therefore rarely used in hybrid PET-MRI contrast agents (18). They can, however, be incorporated into nanoparticles or combined with a PET radiotracer in a multifunctional approach (19).

2.3.2.2. Microbubbles. Microbubbles were first used as contrast agents in ultrasonography, allowing enhanced lesions to be studied with relative safety and rapid clearance. However, they may also be useful as a vascular MRI contrast agent, either without any structural modification, or with the addition of an agent with magnetic susceptibility such as hyperpolarized gas (^{3}He or ^{129}Xe) which increases detection. Adding a radioactive isotope is straightforward, making hybrid contrast agent development a simple procedure (20).

2.3.2.3. Superparamagnetic iron oxides (SPIOs). SPIOs contain a biodegradable iron oxide core coated with a hydrophilic protective layer of dextran or another polysaccharide, allowing chemical linkage of functional groups and ligands (6,13,21,22). Iron in SPIOs is biocompatible and can be either reused or recycled by cells via physiological iron metabolism (13). SPIOs have superparamagnetic properties. Unlike paramagnetic materials, these particles do not have any magnetic properties in the absence of an external magnetic field. When placed in an external magnetic field, their crystals align and create very high local magnetic field gradients inducing water proton spin dephasing and consequently reducing the T1 and T2 relaxation times of the surrounding water magnetic field (22,23). SPIOs therefore produce a dark signal with a T2/T2* sequence. In some cases, positive enhancement using a T1 sequence can be observed when low concentrations of SPIO are present in the tissue. They are considered to be non-toxic, have favorable pharmacodynamic and pharmacokinetic features, and achieve high image quality and contrast (23).

Their size varies from 25 nm for ultrasmall SPIOs, to 350 nm for large SPIOs (17). After injection in the human body, the

Table 1. Properties, advantages and disadvantages of MRI contrast agents, PET tracers and hybrid PET-MRI contrast agents

	Labeling type	Physical properties	Resolution	Sensitivity	Advantages	Disadvantages
MRI	- SPIO	- Magnetic field modifications	+++	+	- No ionizing radiation	- High cost
	- Gadolinium				- No tissue penetration limit	- Long imaging time
	- Microbubbles				- Morphological imaging	
PET	- Radioisotopes	- Positron annihilation	+	+++	- No tissue penetration limit	- Detects only one type of radionuclide
					- Functional and molecular imaging	- Radiation
						- High cost
						- Long imaging time
PET-MRI	- SPIO + radioisotope (46,61)	- Positron annihilation and magnetic field modifications	+++	+++	- Morphological imaging	- Radiation
						- High cost
	- Gadolinium + radioisotope				- Functional and molecular imaging	- Long imaging time
	- Microbubbles + radioisotope (20,31)				- Multimodal imaging	
					- Theranostic	
					- No tissue penetration limit	

MRI: Magnetic resonance imaging
PET: Positron emission tomography
SPIO: Superparamagnetic iron oxide

SPIOs are mostly taken up by the liver (useful for hepatic imaging) and spleen, but also by the lymph nodes and bone marrow (23). Due to their physical features and if not entirely taken up by the liver and spleen, they are endocytosed by circulating macrophages and subsequently incorporated into cytoplasmic lysosomes. In this case, they can be used as inflammation markers or markers for some degenerative diseases associated with intense macrophage activity (22,24). Examples of SPIOs that are used or under development include Ferumoxide (Endorem®/Feridex®, Guerbet and AMAG) for hepatic lesion characterization; Ferumoxsil (Lumirem® in Europe/Gastromark® in the USA, Guerbet and AMAG) for digestive tract visualization, and Ferumoxtran-10 for lymphatic imaging (Sinerem®/Combidex®, Guerbet and AMAG). Further examples include Ferucarbotran (Resovist®, Bayer-Schering), Feruglose (Clariscan®, GE Healthcare) and Ferristen (Abdoscan®, GE Healthcare) (23).

2.4. PET tracer combined with an MRI contrast agent

The solution most often used to create a hybrid contrast agent is to bind the PET tracer to the MRI contrast agent, and particularly a radioactive isotope to the SPIO's surface (Fig. 1). This required a rethink of strategy and new syntheses for introducing the PET tracer, often recalcitrant to traditional coupling methods. Examples of developments include:

- A fluorine atom (^{18}F) that was incorporated into an MR agent GdDOTA-4AMP modified with versatile Cu(I)-catalyzed Huisgen cycloaddition (25).
- A ^{64}Cu atom and a SPIO that were bound to a bifunctional chelating agent, bis(dithiocarbamatebisphosphonate) $(DTCBP)_2$ (26).
- A more complex incorporation process that involved a ^{64}Cu atom chelated with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and labeling dextran sulfate coated iron oxide nanoparticles (27).

The advantage of these hybrid PET-MRI contrast agents is that they offer spatial resolution, sensitivity, and morphological and functional analysis with a single molecule (Table 1).

Many other molecules can also be incorporated onto the SPIO surface, in particular specific ligands such as antibodies for targeting a specific group of neoplastic cells.

3. HYBRID PET-MRI CONTRAST AGENTS AND THEIR APPLICATIONS

Most hybrid PET-MRI contrast agents currently under development are still at the animal testing stage. However, they offer a wide and promising range of applications, as summarized in Table 2.

3.1. Physicochemical property monitoring via "smart" contrast agents

"Smart" hybrid contrast agents are triggered by environmental factors or enzymatic activities. The MR relaxivity of a "smart" agent can be changed in the presence of an enzyme, a certain pH, a specific metal ion concentration, partial oxygen pressure

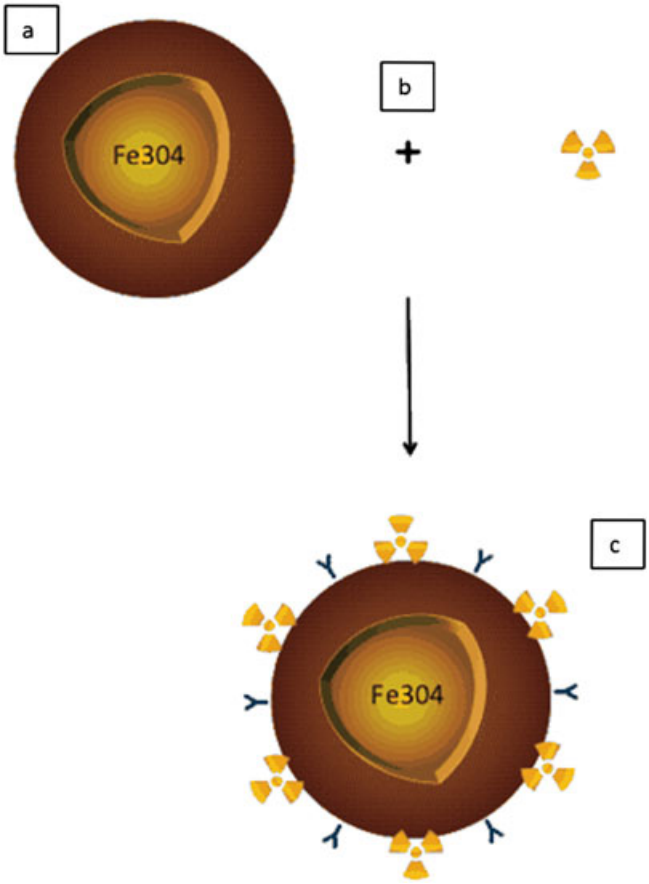

Figure 1. Hybrid PET-MRI contrast agent developed by combining SPIOs and PET radiotracers. (a) Superparamagnetic iron oxide (SPIO) coated with a hydrophilic shell. (b) The radionuclide is combined, either directly with the envelope shell or through a ligand, which is generally DOTA-based. (c) An antibody can be added to the complex to allow specific targeting by RGD peptide (e.g. targeting of the $\alpha v\beta 3$ integrin expressed in the tumor).

or a certain temperature (28–30). These agents are therefore capable of monitoring physicochemical properties in vivo and detecting enzyme deficiency or disorders (25). At a known concentration, any gadolinium signal change is related to relaxivity change. The main problem in vivo is that the gadolinium concentration is unknown. Coupling with PET imaging offers the possibility of gadolinium quantification. The counts registered in a PET study are directly proportional to the concentration of tracer present in the voxel and can thus be used to quantify gadolinium absolutely (11).

In vivo pH variation monitoring with a hybrid PET-MRI agent could reveal crucial clinical and therapeutic information since an extracellular pH decrease is associated with tumors and ischemic diseases (stroke, ischemic heart disease, kidney disease).

A bimodal hybrid molecule combining gadolinium and ^{18}F was created: Gd-DOTA-4AMP-F. The aim of this molecule was to provide quantitative, non-invasive assessment of pH levels in vivo. The PET signal is linear with radiochemical concentration and the MRI T1 signal is related to relaxivity and the pH level. The results have shown a good correlation with invasive pH measurement methods (25).

3.2. Vascular and atheroma imaging

3.2.1. Non-invasive angiographic sequences

Currently, vascular imaging generally involves injection of an iodinated contrast agent or gadolinium chelate. These agents are excreted by the kidneys and may cause kidney disease in some patients, especially those who already have kidney insufficiency. The population requiring angiographic imaging generally has cardiovascular risk factors and associated kidney insufficiency. In such cases, these agents are more or less contraindicated and another agent may be useful instead. Tartis *et al*. developed ^{18}F-labeled microbubbles to assess biodistribution and pharmacokinetic characteristics (31). Willmann *et al*. also worked with ^{18}F-labeled microbubbles but with VEGFR2, a vascular receptor, also as a target (20,32,33). Microbubbles filled with a specific MRI agent such as a polarized gas (^{3}He or ^{129}Xe) can be used to increase the signal-to-noise ratio, which is low in these conditions. These gas-filled microbubbles proved effective in vascular imaging with a high signal-to-noise ratio and no known side effects. Thus, in the future, they could be an interesting alternative to iodine or gadolinium labeled agents (33,34).

3.2.2. Atheroma imaging

The possibility of preventing atheroma-related diseases, responsible for vascular and/or coronary attacks, through early diagnosis prompts the search for non-invasive imaging methods, to allow detection before symptoms appear (35). In clinical routine, the risk of complications and operating indications reported for stenosis are mostly assessed by artery lumen measurements. Recent studies show that the riskier atheromatous plaques are the ones with vascular inflammation (36). These plaques present a greater risk of fissure and rupture and consequently ischemic

Table 2. Most promising hybrid contrast agents and their applications

Hybrid contrast agent	MRI contrast agent	PET tracer	Applications
Gd-DOTA-4AMP-F(25)	Gadolinium	^{18}F	In vivo pH measurements
SPIO-^{64}Cu (+/-Cu^{2}+) (10,58)	SPIO	^{64}Cu	Stem cell monitoring, Wilson's disease
^{18}F-lipid-labeled microbubbles (31,32)	Microbubbles	^{18}F	Non-invasive angiography
^{64}Cu-labeled-magnetic-nanoparticle (27)	SPIO	^{64}Cu	Atheromatous plaque imaging
^{124}I-SA-MnMEIO (61)	SPIO	^{124}I	Lymph node imaging
RGD-PASP-IO combined with ^{64}Cu (46)	PASP-IO	^{64}Cu	Tumor neoangiogenesis imaging

PET: Positron emission tomography
MRI: Magnetic resonance imaging
SPIO: Superparamagnetic iron oxide

complications. A hybrid PET-MRI contrast agent combining SPIO (dextran sulfate coated iron oxide nanoparticles) and ^{64}Cu is under development and has been evaluated in animals (37). This agent targets the circulating macrophages, thereby enabling detection of inflamed plaques (38). The authors emphasize that hybrid agent synthesis is complicated: nanoparticle labeling with ^{64}Cu was recalcitrant to traditional coupling methods and new syntheses had to be developed to achieve this.

Studies on that particular hybrid agent are currently being evaluated on animal models. In the long run, this hybrid contrast agent might be used for screening patients with a high cardiovascular risk profile, particularly diabetic patients. The contrast agent could also play a very important role in prognosis or influence major therapeutic decisions because it achieves detection of plaques with a high risk of complications.

3.3. Oncology

Enhanced visualization after administration of gadolinium chelate or detection of glucose hypermetabolism using FDG-PET are used in daily clinical practice for diagnosing or monitoring tumors. However, these imaging modalities can be inadequate for early assessment of lymph node metastasis. Furthermore, with improved understanding of genetic mutations and antigenic and vascular changes due to tumorigenesis, new molecules specifically targeting them have been developed and are used as hybrid agents.

3.3.1. Lymph node imaging

Early detection of lymph node metastasis of malignant tumors is needed to avoid under- or over-treatment and help optimize care. This is usually achieved with FDG-PET and MRI, which are sometimes combined with the sentinel lymph node technique (39). A major line of research currently involves an investigation to improve the sentinel lymph node technique with multimodal contrast agents (26,40,41). A hybrid PET-MRI contrast agent, ^{124}I-SA-MnMEIO, combining an SPIO and ^{124}I, was developed by Choi *et al*. (41,42). This agent significantly improved the detection of lymph node relays in rats. It has not yet been tested on humans but could ultimately improve surgical precision and lower morbidity due to unnecessary dissection (43).

3.3.2. Tumor neoangiogenesis imaging

Tumor spread is inevitably associated with neovessel formation, or neoangiogenesis. The endothelial cells from these neovessels overexpress specific markers such as the $\alpha v\beta 3$ integrin, which specifically recognizes peptides with an arginine-glycine-aspartic acid (RGD) sequence (18,44,45). A hybrid PET-MRI contrast agent, combining SPIO and ^{64}Cu with an RGD peptide and targeting the $\alpha v\beta 3$ integrin, has been developed by Ha-Young Lee *et al*. (46). This hybrid agent enabled tumor detection with very high sensitivity and specificity in mice. It also provided precise anatomical and functional information.

Ultimately, neoangiogenesis targeting could facilitate diagnosis and solid tumor monitoring as well as treatment (47) because neoangiogenesis inhibition induces apoptosis and subsequent tumor reduction (46).

3.3.3. Diffusion-weighted imaging (DWI)

In tumor imaging and cancer staging, whole-body imaging is recommended in clinical practice. Whole-body cancer staging using hybrid PET-MRI imaging was validated in comparison with PET-CT imaging (48,49). Unlike with PET-CT, different image contrasts are available. Diffusion-weighted MR imaging (DWI) is known to be a sensitive sequence for lesion detection in malignancy diagnosis. Some studies evaluated DWI as part of PET-MRI imaging protocols for lesion detection. The results still differ. Buchbender *et al*. found no benefit in lesion detection performance with DWI as part of whole-body [^{18}F]FDG PET-MRI (50). On the other hand, using non-Gaussian DWI in their FDG-PET MR protocol, Heusch *et al*. showed good correlation with standardized uptake values (SUV) and concluded that DWI might provide additional information in whole-body imaging (51).

4. PROSPECTS

Hybrid PET-MRI contrast agents are currently under development, mainly in oncology and cardiovascular imaging, supported by the recent emergence of hybrid PET-MRI devices.

The prospects for these new contrast agents are numerous and wide-ranging, including the development of hybrid multimodal contrast agents, i.e. not only PET-MRI but also PET-MRI-fluorescence-ultrasound agents, for instance (52). These could be useful for pretreatment diagnosis, surgical identification and tumor follow-up.

Other hybrid contrast agents are also under development or have development potential for applications in the following areas:

- Detection of micromolecular changes in copper-related diseases such as Alzheimer's disease, Menkes' disease, Wilson's disease, amyotrophic lateral sclerosis and prion disease (10).
- Identification of hypoxia, which affects most solid tumors. Measurement of tumor oxygenation levels could be very useful for targeting therapies. Non-invasive imaging of hypoxia could help to select patients likely to benefit from anti-angiogenesis therapies or predict therapeutic response (53). Applications in fields other than oncology are possible, and in particular include ischemic stroke investigations, cardiac or vascular conditions and osteoarthritis.
- Molecular imaging targeting specific tumors using antibodies. Coupling with specific tumor antigen antibodies is one of the most exciting prospects based on molecular imaging targeting a specific tumor group and providing initial diagnostic and prognostic information (54–57).
- Stem cell monitoring. Cell labeling can be very useful for monitoring cells used in regenerative medicine (40,58).

These hybrid PET-MRI contrast agents, with or without the addition of antibodies, could also be used as theranostic agents, i.e. serve both diagnostic and therapeutic purposes (59,60). Chemotherapy drugs such as cisplatin could easily be incorporated or β- isotope emitters (^{131}I, ^{90}Y, ^{177}Lu, ^{188}Re) even implanted in microbubbles or SPIOs.

Ultimately, overall patient care could benefit from these hybrid contrast agents. PET-MRI agents with a specific tumor group antibody targeting a glioblastoma, for example, could be injected shortly before an operation and localized to provide a highly accurate preoperative lesion evaluation. During the operation, this same agent, detected with specific positron emitter probes, could help guide the surgeon. Then, on the day following the operation, the contrast agent, still detectable, could facilitate postoperative surveillance. During the subsequent follow-

up period, the agents could help in early detection of recurrence and even treat it by enabling targeted therapy to be tailored as closely as possible to the particular tumor.

5. FUTURE CHALLENGES AND LIMITATIONS

The design of multi-modal hybrid agents has moved from research laboratories to pre-clinical and clinical applications. A vast body of literature has emerged on the subject as they are highly complementary to the hybrid imaging systems being developed. This imaging approach offers a high degree of sensitivity and provides both anatomical and molecular information about the same given target with two (or more) different imaging modalities.

Creating 'smart' agents or finding new ways to deliver agents are topics to be addressed. The future lies in the interface between imaging and disease treatment with "theranostic" agents. New imaging agents are being developed to help monitor chemical, biological and genetic therapies. The integration of anatomical, functional, molecular and cellular imaging with therapeutic and drug delivery capabilities is the ultimate aim. Absolute quantification of MRI contrast agents through quantification of PET tracer concentration is also one of the next challenges of dynamic contrast-enhanced MRI or dynamic susceptibility contrast MRI. Hybrid contrast agents are based on advances in knowledge and technology, as well as the collaborative efforts of engineers, chemists, biologists and clinicians.

The use of nanoparticles to create hybrid agents has significant advantages and is widely used for multimodal imaging and theranostics. However, a potential limitation is clearance from the bloodstream as detection depends mainly on concentration. The reticuloendothelial system, spleen, kidneys and liver rapidly remove nanoparticles according to their size. The physicochemical properties of nanoparticles such as size, hydrophobicity and surface charge should therefore be optimized to ensure a reasonable blood half-life and good biodistribution (6). Linking a PET agent to a nanoparticle could improve circulation half-life and yield high initial blood retention with only moderate liver uptake (11).

6. CONCLUSION

Many hybrid contrast agents are currently under development, particularly in oncology and cardiovascular imaging. In the long run, these agents could radically change our methods, delivering highly accurate morphological and essential functional information, and sometimes even a targeted treatment, by means of a single examination and injected product.

CONFLICT OF INTEREST

none declared.

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