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Dual nano-sized contrast agents in PET/MRI: a systematic review

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Nowadays molecular imaging plays a vital role in achieving a successful targeted and personalized treatment. Hence, the approach of combining two or more medical imaging modalities was developed. The objective of this review is to systematically compare recent dual contrast agents in Positron Emission Tomography (PET)/Magnetic Resonance Imaging (MRI) and in some cases Single photon emission computed tomography (SPECT)/MRI in terms of some their characteristics, such as tumor uptake, and reticuloendothelial system uptake (especially liver) and their relaxivity rates for early detection of primary cancer tumor. To the best of our knowledge, this is the first systematic and integrated overview of this field. Two reviewers individually directed the systematic review search using PubMed, MEDLINE and Google Scholar. Two other reviewers directed quality assessment, using the criteria checklist from the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) tool, and differences were resolved by consensus. After reviewing all 49 studies, we concluded that a size range of 20–200 nm can be used for molecular imaging, although it is better to try to achieve as small a size as it is possible. Also, small nanoparticles with a hydrophilic coating and positive charge are suitable as a T_2 contrast agent. According to our selected data, the most successful dual probes in terms of high targeting were with an average size of 40 nm, PEGylated using peptides as a biomarker and radiolabeled with copper 64 and gallium 68.

Keywords: dual contrast agent; PET/MRI; nano probe; tumor uptake; biodistribution; targeting

1. INTRODUCTION

1.1. Molecular imaging

Nowadays most clinicians trying to reach a successful targeted and personalized treatment believe that molecular imaging plays a vital role in achieving this aim. Thanks to molecular imaging the biological targets can be visualized and their complexities for diagnosis and treatment of the disease can be better understood (1–3). As the Society of Nuclear Medicine has described, molecular imaging can lead to the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems, therefore imaging of biological targets results in early detection of various diseases effectively (4). There are different imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Ultrasound (US), and Optical Imaging (OI). Each of the mentioned modalities has its own pros and cons. In order to obtain all the required information about the biological processes and function of an organ, we need to combine two or more modalities to use their advantages and weaken their disadvantages. This approach results in a better reliability of the images (1). Table 1 lists the different types of devices used in molecular imaging and describes their advantages and disadvantages. Also, it briefly mentions some current probes utilized in the imaging device.

1.2. Multimodality imaging

Concerning the advantages and disadvantages of imaging modalities to obtain a combination of anatomical, functional and molecular information, multi-modality imaging was suggested. In this approach, images from different modalities taken at the same point are combined in order to use the strengths of the different modalities and yield a hybrid imaging platform with characteristics superior to those of any of its constituents considered alone. In fact, utilization of the high- resolution information coming from an anatomical or functional image in order to improve the imaging performance of the low-resolution modality is the most important feature.

At the beginning, images of different modalities were acquired separately and then merged. However, due to the possibility of different positioning of the patient in the two modalities and also of inaccurate co-registration due to movement, the simultaneous acquisition of images was suggested. The first multimodal devices (SPECT/CT and PET/CT) were introduced commercially in 1998 (5).

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Biographies

Afsaneh Lahooti is a PhD student in Medical Physics at Tehran University of Medical sciences. She has received some awards such as the outstanding lecturer in the 11th Annual General Meeting of ARCCNM in Seoul, Korea, (2012), best poster award from IAEA in the 2nd World Congress on Gallium-68 and Peptide Receptor Radionuclide Therapy (PRRNT) in Chandigarh, India, (2013) and she won several grants from IAEA. At present, she is in the fourth year of her thesis. Her research interest is development and evaluation of the dual modality nano probe in PET/MRI for Molecular imaging of Breast cancer. She is currently focused on development of active targeting of breast cancer cells in in-vitro and in-vivo studies using SPION conjugated with a peptide. Her previous research was on external dosimetry in Radiotherapy and also internal dosimetry in Nuclear medicine based on MIRD protocol for estimating human dose from rat data.

Prof. Saeed Sarkar is a full professor of Medical Physics at Tehran University of Medical Sciences. He recived his PhD degree with specialization in Nuclear Medicine from University of Surrey (UK) in 1994. At present, he is the head of Research Center for Science and Technology in Medicine (RCSTIM) from 2002 till now. He is the co-author of two books, 8 international patents in the field of nanotechnology and several published papers.

Dr. Sophie Laurent was born in 1967. Her studies were performed at the University of Mons-Hainaut (Belgium), where she received her PhD in Chemistry in 1993. She then joined Professor R. N. Muller's team and was involved in the development (synthesis and physicochemical characterization) of paramagnetic Gd complexes and superparamagnetic iron oxide nanoparticles as contrast agents for MRI. She is currently working on the vectorization of contrast agents for molecular imaging. She is associate professor and co-author of around 240 publications and more than 350 communications in international meeting. She collaborates actively with the Center for Microscopy and Molecular Imaging (CMMI) in Gosselies, Belgium. Since October 2016, it is the head of General, Organic and Biomedical Chemistry Unit in the University of Mons and of the UMONS part of the CMMI.

Dr. Saeed Shanehsazzadeh obtained his Ph.D. in Medical Physics from Tehran University of Medical Sciences (TUMS) with specialization on developing dual modality contrast agents in SPECT/MRI via superparamagnetic iron oxide nanoparticles (SPIONs) in 2013. He has received many awards such as the outstanding lecturer in the 6th International Conference Isotopes held in Seoul, Korea (2008), Best Poster award in Medical Physics Section in the 2nd Asian Congress of Radiation Research (ACRR 2009) Korea and distinguished researcher at Tehran University of Medical sciences in 2010. He has gotten his first post-doctoral in nano medicine under the supervision of Professor Mohammad Ali Oghabian and Dr. Morteza Mahmoudi, respectively. He has worked also as an Assistant Professor in Radiation Application Research School, Nuclear Science and Technology Research Institute (NSTRI), Tehran, Iran for 2 years. Now he is doing his second post-doctoral under the supervision of Professor Sophie Laurent at UMONS, Belgium. His current research involves the SPION for simultaneous diagnosis and therapeutic (theranostic) applications.

Using dual modality probes in the clinic, physicians may benefit from not only anatomical data but also physiological (or functional) data from a single image. In addition, since some contrast agents in MRI produce negative contrast, using dual modality images enables them to ensure the existence of the probe and quantification of the uptake quantity. Therefore, the combination of anatomical and functional data by multimodal techniques, enhancement of contrast in molecular imaging and, therefore, the increase of diagnostic capabilities are other benefits (6).

Furthermore, the use and development of dual-modality contrast agents in some cases, such as manipulation of nano agents, will increase the tumor uptake and tumor retention.

1.3. PET/MRI

Combining positron emission tomography (PET) and magnetic resonance imaging (MRI) was presented as an idea even before PET/CT (7). The first PET/MRI systems consisted of PET and MRI elements individually and connected by a table; there were some limitations, such as misregistration due to temporal separation of the data acquisition and the need for a large room to place the equipment (8). In order to remove these problems, the fully integrated PET/MRI was designed. The main goal in the development of this dual-modality imaging system was benefiting from the high anatomical spatial resolution and good soft tissue contrast of MRI and the unparalleled sensitivity and noninvasive functional molecular imaging of PET (4,9,10). Another advantage of this hybridization was a shorter scan time (8).

1.4. Advantages

From a scientific and clinical point of view, an integrated PET/MRI may have some benefits over PET/CT imaging:

1. The greater contrast of soft tissue obtained with MRI (compared to CT), even without the use of contrast agents, allows

Table 1. Molecular imaging devices and their advantages and disadvantages

Devices	Advantages	Disadvantages	Probes	Ref.
Ultrasound systems	Low cost; Portable; Safe (lack of ionizing radiation); High frame rate (Widely available real-time imaging modality (200 f/s)); and has a better depth of penetration than optical imaging; Spatial resolution about: • 0.01–0.1 mm for superficial (few mm depth) applications • 1–2 mm for deeper (few cm depth) applications Flow information; Good temporal resolution; Quantitative data; Real-time practice; Non-invasiveness; Relatively inexpensive cost	Low Numbers of Retained Contrast Agents; High Background from Freely Circulating Agents (waiting period); Limited Field of View; Lack of Quantitative Ability; Possible Immune Responses; Low sensitivity (at least 10^7 bubbles needed)	Microbubbles	(31,90,91)
Optical imaging (Phosphorescence and bioluminescence)	Safe (non-ionizing); High sensitivity; Low cost; Portable; Vascular and Intravascular signals; High temporal sensitivity	Low depth resolution <1 cm; Poor spatial resolution; Surface weighted imaging; Auto fluorescence; Tomography challenges	Fluorophore, Fluorescent Protein, Luciferine, Quantum dot, etc.	(91,92)
Computed Tomography (CT)	Best clinical spatial resolution (0.5–1 mm); No limitation in depth; Good temporal resolution; Clinical utility; Widely available; Relatively cost effective; Highly efficient	Poor sensitivity (requires heavy mass of imaging agents); Ionizing radiation; Limited soft tissue resolution; Limited molecular imaging applications	Bromid and Iodine complex, Iodinated Nanoparticles, Gold Nanoparticles, Alkaline Earth-based Nanoparticles	(91,93,94)
Magnetic Resonance Imaging (MRI)	No limitation in depth; High spatial resolution; Safe; Good soft tissue contrast; Provides both anatomical and functional information	Low sensitivity (10^{-5} M); Relatively long acquisition time; No direct quantitative data; Requires expensive equipment	Gadolinium complexes (Dotarem, Gadovist) Iron oxide nanoparticles (USPIO, SPION), Manganese complexes, Cobalt nanoparticles	(91,95,96)
Single Photon Emission Computed Tomography (SPECT)	No limitation in depth; High sensitivity and quantifiability; Potential to detect multiple probes simultaneously in contrast to PET (cocktail therapy or using two or more radionuclides simultaneously)	Low spatial resolution (8-10 mm clinical); Lower sensitivity than PET (10^{-11} M); Lack of anatomical parameters	Most of the radionuclides which emit gamma rays (^{99m}Tc, ^{67}Ga,^{111}In,^{123}I, …)	(91,95)

(*Continues*)

Table 1. (Continued)

Devices	Advantages	Disadvantages	Probes	Ref.
Positron Emission Tomography(PET)	No limitation in depth; High sensitivity and quantifiability (10^{-12} M); Metabolic imaging; Better spatial resolution than SPECT (5–7 mm)	Lack of anatomical parameters; Requires specialized equipment; Requires radio-nucleotide facilities; Requires expensive equipment	Radionuclides which emit positrons (^{68}Ga, ^{76}Br, ^{94m}Tc, ^{11}C, ^{13}N, ^{15}O, ^{18}F,^{64}Cu)	(91,95,96)
PET/CT	Better attenuation correction; Time of flight; Relatively cheaper than PET/MRI and variable; Relatively faster techniques than PET/MRI; Ability to detect cortical lesions, lung lesions and lymph nodes (PET/CT superior to PET/MRI)	Higher absorbed dose compare to PET/MRI; Lower soft tissue contrast; Reduced sensitivity to detect metastases in organs with high glucose uptake such as the brain.	Au nanoparticles labeled with positron emitters	(97–101)
PET/MRI	Higher soft-tissue contrast; Reduced radiation exposure; Advanced MRI techniques such as perfusion imaging, Diffusion imaging, and MR spectroscopy. It is superior than PET/CT for patients who need multiple follow-up examinations because of lower radiation dose (75% reduction in dose); PET/MRI showed superior lesion detectability compared to PET/CT	Halo artifact; Needs higher technology; Needs more time for reconstructions and attenuation correction calculation; Challenging due to the presence of magnetic field (it needs avalanche photodiode (APD)), Increased eddy currents and heating; The highest costs (5 million euros)	Magnetic nanoparticles labeled with positron emitters	(97,98,101–104)

enhanced anatomical visualization of soft tissue structures and bone marrow. Therefore, it is beneficial for a number of malignant diseases, such as brain tumors, head and neck cancer, malignant melanoma, malignancies of the prostate, cervix, and potentially the breast, liver tumors, and metastatic disease of the liver (11,12). However, to show small lung nodules, bone, and bone structures, CT is still more sensitive than MRI (13).

Also, MRI is capable of measuring other factors that can characterize malignancies and their patient-specific biological properties (12). These factors regularly evaluated today include blood vessels generated by a tumor and perfusion properties through dynamic contrast enhancement [DCE] imaging (14). DCE without the rather high radiation dose, as compared to CT-based perfusion measurements, can help evaluate intravascular treatments. Another MRI method called Diffusion Weighted Imaging (DWI) provides information related to tumor cells and the integrity of the cellular membrane. It has the ability to determine treatment response to chemotherapy and radiation treatment (12,15,16).

2. Real-time image acquisition enables temporal co-registration of dynamic PET data acquisition and anatomical/functional MRI data (17). MRI can provide a range of functional information, e.g. perfusion (micro vessel density, vessel leakage, etc.), diffusion (cell density, microstructure, etc.), and metabolism (cell death, proliferation, etc.) (18,19).
3. A great number of papers about evaluating and determining the application of PET/MRI have been published. Some studies comparing whole-body MR with PET/CT have shown potential advantages of MRI particularly regarding the early detection of brain, liver and bone marrow metastases (17). For T-staging of tumors, PET/MRI is very accurate in some cancers such as head and neck cancer and primary bone and soft tissue tumors (20). But for N-staging, the performances of MRI and PET/CT are similar. It should be mentioned that the use of new lymphotropic superparamagnetic nanoparticles (NPs) can offer new opportunities for the detection of nodal micro metastases that is not possible with PET/CT (21). For M-staging, it has been claimed that MRI may provide higher accuracy for detection of lesions, particularly in the brain, liver, and bone (20).

   Furthermore, PET/MRI offers interesting opportunities for use of dual modality probes in both research and clinical fields (20).

   In recent years, the interest in hybrid imaging, especially PET/MRI, in cardiovascular studies is increasing. This is because of MR-based motion correction of PET images that allows improved evaluation of myocardial perfusion, providing viability information in plaque imaging and MR angiography (22).

   Further interesting applications of PET/MRI are the early diagnosis of neurodegenerative disorders and dementia (23), the detection of epileptic foci (24), monitoring glucose metabolism and cerebral blood flow or oxygen consumption for the investigation of focal brain ischemia (12).

4. In fully integrated systems, MRI could also be used to provide a gating signal in addition to imaging. However this is only advantageous when MR data acquisition, MR gating data, and PET data are acquired simultaneously and for similar amounts of time, as otherwise MR is just an expensive device to provide gating information for PET.
5. The main advantage of MRI is a lack of ionizing radiation especially for a patient with a non-oncological disease or a potentially curable oncological disease. But it is not important for oncological patients (17,25,26).
6. Combined PET/MRI may decrease the imaging time; thus, by reducing appointment periods, department logistics have to be improved (17,26).

1.5. Disadvantages (challenges)

Although several investigations were performed to find solutions for some disadvantages of PET/MRI, there are still several challenges in combining PET and MRI. Therefore, more studies must be designed and implemented to solve them properly. We will mention some of these disadvantages and their solutions.

1. One of the main challenges in totally integrated PET/MRI system is developing a PET detector that is compatible with MRI. Whereas the conventional detectors cannot operate accurately in or even near a magnetic field, especially between of 0.5 to 10 tesla (indeed the paths of electrons are perturbed by the magnetic field) (27), some solutions have been proposed:

   a) Shielding electronics against the magnetic field for avoiding the effects of the changing gradient field and radiofrequency pulses of MRI.
   b) The new generation of detectors, avalanche photodiode detectors (APD), can be used as a detector in PET instead of photomultiplier tubes (PMT) (28). Magnetic fields do not affect these new detectors (29,30); therefore, they can be placed in an MRI magnet without any degradation in performance. In addition, the potential of another type of detector called silicon photomultiplier (SiPM) as a possible replacement in PET has been confirmed recently (31).
2. The gradient magnetic field in MRI is one of the other interferences in a PET system. Since the fast switching of magnetic fields can induce eddy current loops in conductive components, heating, and mechanical vibration, this must be solved for example by shielding electronics, as was mentioned in the previous item (27).
3. In addition, radio frequency (RF) interference created by the MRI transmission coil may affect electronic components. RF shielding around PET is the effective way to decrease its effect. But unfortunately, the shielding can induce eddy currents and heating individually (27).
4. The additional challenge is placing the PET detectors inside the limited space of the MRI bore, which imposes other challenges to the detector technology (27).
5. Attenuation correction for PET images is vital, since one of the causes of image degradation in all nuclear medicine emission imaging techniques (especially PET) is variable photon attenuation in different tissues (12,32). It should be mentioned that MR images give information about tissue proton densities and magnetic relaxation times, not photon attenuations (12,17). Although the attenuation correction methods proposed by combined MRI/PET systems, based on segmentation methods of MR images for preparing the total attenuation map, are developed enough to use them clinically, the problem is not yet completely solved and remains an active area of research (27,33,34).
6. Because PET imaging usually takes a long time, motion problems are inevitable (34). This leads to blurring of tumors in PET

images and may even entirely obscure the presence of smaller lesions (33). Also, in the case of motion with large amplitude, it causes severe artifacts (34). In general, motion can be one a source of errors in both lesion localization and quantification (35). Three major types of motion are (33):

a) Gross motion: head movement or subtle patient repositioning due to discomfort.
b) Periodic movement: cardiac and respiratory motion.
c) Internal shifting and distortion in the pelvic and abdominal regions.

To solve the problems related to motion:

a) The first way is using high spatial resolution MR images to correct for PET motion with affectedly reduction of the spatial blurring and artifacts associated with PET movement of solid organs (34). But inappropriately, this imaging covers a large field of view (FOV) and takes a few minutes that can cause motion individually (33).
b) Another solution is the use of external tracking devices and video cameras to record the movements as used in cardiac and respiratory gating (36,37).

2. OBJECTIVE

The objectives of this review is to evaluate the detection efficiency, specificity, and targeting capability of dual contrast agents in PET/MRI and SPECT/MRI for early detection of primary cancer tumor and specially breast cancer.

3. METHODS AND MATERIALS

3.1. Identifying studies search strategy

Two reviewers individually directed the systematic review search using PubMed, MEDLINE, and Google Scholar. The following keywords were used: ('Dual contrast agent' or 'Multimodal imaging' or 'hybrid imaging' or 'dual probe') AND ('magnetic resonance imaging' or 'positron emission tomography' or 'PET/MRI'). There was a restriction date between 2008 to the end of 2015 and confined to English language articles.

3.2. Selection of studies

Studies were included according to the following criteria: 1) published in English with full-text available; 2) using NPs as the base of the contrast agent; 3) using PET/MRI or SPECT/MRI imaging; 4) performing *in vivo* imaging or *in vivo* biodistribution or both; and 5) using radionuclides with or without chelator. Studies were excluded if they included PET/CT imaging. Differences of opinion between the two reviewers were resolved by compromise. In order to have a precise comparison of our data, we asked for additional data from the authors of eleven studies. Nine responded whereas two did not respond and had to be excluded.

3.3. Quality assessment

Two reviewers directed quality assessment, using a criteria checklist from the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) tool, and differences resolved by consensus.

4. RESULTS AND DISCUSSION

We extracted the important data from the 49 selected studies. All data are presented in Table 2. The data is shown is the clearest way possible.

4.1. Liver uptake

In the 49 selected studies, we evaluated the liver uptake and the reasons for that. Some studies aiming at lymph node (LN) imaging, report LN uptake; although, liver uptakes were not considerable. Iron oxide and superparamagnetic iron oxide nanoparticles (SPION) are the base of the agents used. In order to achieve the desired diameter (in a narrow size range) of those SPIONs essential for LN imaging, they should be produced in a systematic way. For two compounds, ^{68}Ga-SPION and ^{99m}Tc-SPIONs, the biodistribution data showed that a small amount of them were transported by the lymph through other nodes and finally accumulated in the liver and spleen (38,39).

Table 3 presents the best three studies which had the highest amounts of lymph node uptakes. Since the benefits of using PET in comparison with SPECT imaging in the clinic are higher sensitivity, reduced dose, greater resolution, and critically reduced partial volume effects, the development of PET/MRI contrast agents like ^{89}Zr-ferumoxytol can allow mapping of the draining lymphatics and provide information-rich preoperative mapping as well as increase intraoperative confirmation (40). Among all three studies in Table 3, the liver uptake of ^{89}Zr-ferumoxytol was the highest, 6.11 %ID/g, maybe because of the dextran coating (40), since the other compounds had PEG coating and had lower liver uptakes. On the other hand, the comparison between the Sentinel Lymph Node (SLN) uptakes showed that a bigger size of contrast agent causes a greater SLN/Liver uptake (38). However, we cannot state that as a rule since there are contradictory results in other articles, like that of Natarjan *et al.* (41). The section in this review dedicated to size will discuss in more detail the effect of size on liver uptakes.

From all studies which mention the amount of liver uptake at different time points, we conclude that the highest liver uptake belongs to ^{99m}Tc-DPA-ale-Endorem (Dipicolylamine-alendronate (DPA-ale)), with an uptake of 96.9 ± 0.9 %ID. Since Endorem is a clinically approved and colloidally stable MRI contrast agent and is taken up by cells of the reticuloendothelial system (RES), such as monocytes, macrophages, and Kupffer cells, this result was expected. Moreover, the size of this compound (106 ± 60 nm) and its dextran coating are other reasons that cause high liver uptake. In the reported study, by measuring and evaluating the variations of T_2* values from the short-axis images, the accumulation of ^{99m}Tc-DPA-ale-Endorem in the liver was calculated as well (42).

In three of the studies, we found approximately equal liver uptake 24 hours after administration (43–45). The large accumulation in the liver is because of scavenging and phagocytosis by cellular elements of the RES. Furthermore, all of the NPs used had PEG coating. These reasons could be the cause of a nearly equal liver uptake.

Finally, the lowest liver uptake was found in one of the studies which used two compounds, ^{68}Ga-NODAGA-AGuIX and ^{68}Ga-DOTAGA-AGuIX, as a dual-modality PET/MRI probe (46). Actually, due to the small size (2.5 ± 0.1 nm) and the biodegradable properties of AGuIX, the NPs were cleared from the blood quickly into the urine via the kidneys. The small amount of remaining activity

Table 2. Characterizations of multimodality contrast agents from selected studies

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
^{68}Ga-SPION	30 nm	SPION ~13 nm	PEG	Sentinel Lymph Nodes and Iliac Lymph Nodes	SLN: 123% IA/g Iliac Lymph Node: 47% IA/g Liver: 0.3% IA/g Spleen: 0.1% IA/g Kidneys: 0.05% IA/g 3 hpi	NM	T_2 and T_2* weighted imaging	SLN mapping	(38)
^{64}Cu-NOTA-SPION-cRGD-DOX	68 ± 2 nm	SPION 10 nm	Hetero bifunctional poly (PEG)	U87MG cells (human glioblastoma cells)	Tumor: 5.6 ± 1.7 %ID/g Liver: 9.7 ± 2.7 %ID/g Blood: 1.8 ± 0.3 %ID/g 6 hpi	cRGD conjugation increases the cytotoxicity of the SPION	T_2 weighted imaging 101.9 $mM^{-1}s^{-1}$ at 200 MHz	Combined tumor targeting drug delivery and PET/MR imaging	(49)
^{64}Cu-DOTA-IO-RGD	45 ± 10 nm	Iron Oxide 5 nm	Polyaspartic acid (PASP)	U87MG human glioblastoma cell line, Tumor $\alpha_v\beta_3$ integrin expression	Liver: 22.6 ± 2.9 %ID/g Kidney: 4.9 ± 0.8 %ID/g Tumor: 10.1 ± 2.1 %ID/g 4 hpi	PASP has low toxicity.	T_2 weighted imaging 105.5 $mM^{-1}s^{-1}$	Dual PET/MRI scanning of tumor integrin $\alpha_v\beta_3$ expression	(50)
^{99m}Tc-DTPA-SPION-LBA	30 nm	SPION 12 nm	Dopamine	ASGP-R on hepatocytes	Liver: 38.43 ± 6.45 % ID/g Spleen: 18.69 ± 5.12 % ID/g Blood: 4.88 ± 1.18 % ID/g 1 hpi	NM	T_2 weighted imaging	Hepatocyte targeted imaging and the diagnosis of various liver diseases	(105)
^{64}Cu^{II}-dtcbp-SPION	108 ± 60 nm	SPION	Dextran	Draining lymph nodes	Popliteal lymph nodes and iliac lymph nodes	NM	T_2* weighted imaging	Lymph node mapping	(106)
^{124}I-SA-MnMEIO	32 nm	MnMEIO 15 nm	Serum Albumin (SA)	Sentinel lymph node	High lymph node uptake at 1 h post-injection to the forepaw and still remaining until 6 days post injection	NM	T_2 weighted imaging 321.6 $mM^{-1}s^{-1}$	Axillary and Brachial Lymph Nodes imaging	(107)
^{69}Ge-SPION (chelator free strategy)	23 nm	SPION 10 nm	PEG	Sentinel lymph node	Dominant liver uptake, Spleen, popliteal lymph node	NM	T_2* weighted imaging	Lymph node mapping	(108)
^{99m}Tc-DPA-ale-Endorem	106 ± 6 nm	SPION 5 nm	Dextran	RES system (liver and spleen)	Liver: 96.9 ± 0.9 %ID/g Spleen: 1.3 ± 0.4 %ID/g Rest of body: 1.8 ± 0.7 % ID/g 1 hpi	NM	T_2* weighted imaging 26 $mM^{-1}s^{-1}$ at 400 MHz	Dual modality probe for SPECT/MRI RES system imaging	(42)
^{64}Cu-DOTA-mSPIO	20.3 ± 1.9 nm	SPION 6.2 nm	PEG+ micelle	Heart and carotid arteries (atherosclerosis and cancer models)	Liver: 33.42 ± 1.85 % ID/g Spleen: 19.96 ± 2.27 % ID/g Heart: 9.46 ± 1.76 % ID/g Blood: 37.31 ± 12.87 % ID/g 1 hpi	no toxicity for ^{64}Cu	T_2 weighted imaging 209 ± 26 $mM^{-1}s^{-1+}$ at 20 MHz	Disease detection and treatment in atherosclerosis and cancer models	(109)
^{11}C-SPION		SPION 16 nm	COOH	Liver	Liver	NM	T_2* weighted imaging	PET/MRI of Liver	(110)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
^{64}Cu-MoS_2-IO-(d)PEG	NM	MoS_2 50-200 nm	PEG	Breast cancer (4 T1 tumor)	Tumor: 5.70 % ID/g Liver: 30 % ID/g Spleen: 11 % ID/g 24 hpi	Low cell toxicity	T_2 weighted imaging 93.59 $mM^{-1}s^{-1}$ at 128 MHz	Triple modal PET, Photoacoustic Imaging and MR imaging for 4 T1 murine breast tumor	(43)
^{99m}Tc-SPION-RGD	200 nm	SPION 10 ± 2 nm	Aminosilane	$\alpha_v\beta_3$ integrin receptors in U87MG glioblastoma cells	Tumor: 9.01 ± 0.19 % ID/g Liver:10.36 ± 0.87 % ID/g Spleen: 31.14 ± 3.78 % ID/g Blood: 8.88 ± 0.19 % ID/g 1 hpi	The non-observable toxicity of IO-NPs, RGD-NPs has dose dependent toxicity.	T_2 weighted imaging	Dual PET/MRI scanning of tumor integrin $\alpha_v\beta_3$ expression	(51)
Fe_3O_4-Ag^{125}I heterodimers	NM	Fe_3O_4-Ag 14 nm	PEG	NM	Liver: 31.98 ± 2.44 %ID/g Spleen: 41.87 ± 4.41 %ID/g 1 hpi	Low cell toxicity	T_2 weighted imaging 139.8 $mM^{-1}s^{-1}$ at 60 MHz	Dual modality probe in SPECT/MRI	(111)
^{59}Fe-SPION	17 ± 6 nm	SPION 4.3 ± 1.3 nm	PAA-DOP-PEG	NM	Liver: 45 ± 6 %ID/g Kidneys: 21 ± 5 %ID/g Brain: 4 ± 6 %ID/g 24 hpi	NM	T_1 and $^*T_2$ weighted imaging 97 ± 3 $mM^{-1}s^{-1}$ at 300 MHz	Dual modality probe in SPECT/MRI	(44)
^{89}Zr-DFO-ferumoxytol	NM	Iron oxide 15-35 nm	Carboxymethyl dextran	Prostate cancer and Lymph node	Liver, Kidney, Axillary and Brachial Lymph Nodes	NM	T_2 or T_2* weighted imaging 89 $mM^{-1}s^{-1}$ at 20 MHz	Diverse nanomedical diagnostic applications	(40)
^{111}In-DMPE-DTPA-SPION	40 ± 7 nm	SPION	PEG	NM	Liver: 37.28 ± 1.03 %ID/g Spleen: 21.48 ± 2.41 %ID/g 24 hpi	NM	NM	SPECT/MRI	(45)
^{124}I-c(RGDyk)$_2$-UCNPs	32 ± 9 nm	Upconversion nanophosphors ($NaGdF_4$:Er^{3+}/Yb^{3+})	PEG	$\alpha_v\beta_3$ integrin expression tumors, U87MG tumor cells and Xenografted tumor	Tumor: 2.8 ± 0.8 %ID/g	UCNPs have a low cytotoxic effect (below a 50 mg/mL concentratio)	T_1 weighted imaging	Dual PET/MRI scanning of tumor integrin $\alpha_v\beta_3$ expression	(52)
^{68}Ga-NOTA-hydrazine-Fe_3O_4NPs (GaNHFCNP)	15.3 nm	Fe_3O_4NPs (11.5 nm)	NM	Colon cancer cell (CT-26) and breast cancer cell (SK-BR-3)	CT-26 cell line: 8.778 % SK-BR-3 cell line: 15.491 % 2 hpi	non-toxic property	NM	Dual PET/MRI imaging of Colon cancer cell (CT-26) and breast cancer cell (SK-BR-3)	(112)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
^{64}Cu-DOTA-MSN-Gd^{+3}	76.8 ± 8.3 nm	mesoporous silica nanoparticles 60 nm	NM	Sentinel Lymph Nodes (SLNs)	T-SLNs: 76.7 ± 2.21 %ID/g N-SLNs: 2.3 ± 0.12 %ID/g 1 hpi	Nontoxicity	T_1 weighted imaging	Mapping SLNs and identifying tumor metastasis	(112)
^{64}Cu-TNP or ^{64}Cu-DTPA (64Cu-DTPA-CLIO-VT680)	20 nm	Iron oxide5 nm	dextran	Inflammatory Atherosclerotic Plaques	Blood half-life:$T_{1/2}$ 259 ± 39 min Liver: 33.6 %ID/g Small Intestine:15.8 %ID/g Kidney: 13.8 %ID/g Lung: 11.0 %ID/g Spleen: 9.4 %ID/g Heart: 6.0 %ID/g Aorta: 5.2 %ID/g Lymph Nodes: 4.3 %ID/g Thymus: 2.4 %ID/g 24 hpi	NM	T_2 weighted imaging	Triple PET/MRI/ optical contrast agent	(113)
^{18}F-CLIO	38 nm	Iron Oxide 3 nm	Cross-linked dextran	aortic aneurysms (AAs)	Blood half-life:$T_{1/2}$ = 192 ± 14 min	NM	T_2 weighted imaging	PET/MRI quantitation of macrophage content in a mouse model of AAs.	(114)
^{68}Ga/^{111}In-IONP	100 nm	Fe_2O_3 10 nm	aminosilane coating with NH_2	RES & efficient cell labeling	Liver: 2.18 ± 0.05, 2.74 ± 0.29 and 2.33 ± 0.2 %ID/g Spleen: 1.46 ± 0.02, 4.24 ± 0.21 and 5.06 ± 0.25 %ID/g Kidneys: 4.67 ± 0.08, 6.3 ± 0.35 and 7.91 ± 0.34 %ID/g Blood: 4.67 ± 0.52, 1.82 ± 0.28 and 0.98 ± 0.24 %ID/g Lung: 14.98 ± 1.22, 3.24 ± 0.85 and 1.16 ± 0.13 %ID/g 2, 24 and 48 hpi	Nontoxicity	T_2 weighted imaging	Dual PET/MRI contrast agent	(115)
^{68}Ga-NODAGA-AGuIX and ^{68}Ga- DOTAGA-AGuIX	2.5 ± 0.1 nm	gadolinium oxide (Gd_2O_3) 1.7 nm	polysiloxane	U87MG (human primary glioblastoma cell line)	Kidney: 22.4 %ID/g Blood: 0.62 %ID/g 2 hpi	AGuIX nanoparticles displayed at least 80% cell viability	T_1 weighted imaging $r_1 = 10.3\ mM^{-1}s^{-1}$ $r_2 = 13.4\ mM^{-1}s^{-1}$ at 60 MHz	Dual PET/MRI contrast agent	(46)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
^{67}Ga-NOTA-MF-AS1411	68.1 nm	cobalt ferrite	Silica and PEG	Nucleolin (a cellular membrane protein highly expressed in cancer) C6 rat glioma cells	Intestine, liver and tumors	Nontoxicity	T_2 weighted imaging 82.1 $mM^{-1}s^{-1}$ at 60 MHz	Targeting nucleolin and monitoring by multimodal fluorescent, radioisotope and MRI modalities	(116)
^{64}Cu-bisphosphonat-$MnFe_2O_4$ And [18 F]-fluoride-$MnFe_2O_4$	49.8 nm	$MnFe_2O_4$ 4.8 nm	$Al(OH)_3$ PEG (5 K)	The ability to derivatise the surface with radiolabels and bisphosphonate groups suggests applications in molecular imaging.	Liver and spleen	Nontoxicity	T_2 and T_2* weighted imaging $r_2 = 121.9\ mM^{-1}s^{-1}$ at 128 MHz	Dual PET/MRI contrast agent	(117)
^{99m}Tc-SPIONs	18 nm	Iron oxide 13 nm	PEG	Sentinel lymph node	SLN: 211 ± 225 %ID/g Liver: 1.4 ± 0.7 %ID/g Kidney: 0.3 ± 0.08 %ID/g Spleen: 0.2 ± 0.1 %ID/g 4 hpi	Nontoxicity	T_2 and T_2* weighted imaging	Dual SPECT/MRI for Sentinel lymph node (SLN) mapping in breast cancer and malignant melanoma	(39)
^{166}Ho-DTPA-SPION	85 nm	Iron oxide 7 nm	Dextran	Liver and spleen (RES)	Liver: 60.1 %ID/g Spleen: 15.3 %ID/g 30 min pi	NM	T_2 and T_2* weighted imaging	Dual SPECT/MRI for RES theranostic purposes	(66)
^{99m}Tc-USPIO	80 nm	Iron oxide 5 nm	Cross linked Dextran	Liver and spleen (RES)	Liver & Spleen 78 %ID/g 15 min pi 25 %ID/g 48 hpi	NM	T_2 and T_2* weighted imaging	Dual SPECT/MRI for RES theranostic purposes	(67)
^{99m}Tc-USPIO	41 nm	Iron oxide 5 nm	Cross linked Dextran	Liver and spleen (RES)	Liver: 55.11 %ID/g Spleen:19.75 %ID/g 5 min pi Liver: 30.91 %ID/g Spleen: 10.68 %ID/g 1 hpi blood half-life was 90 seconds	NM	T_2 and T_2* weighted imaging	Dual SPECT/MRI for RES theranostic purposes	(68)
^{99m}Tc-USPIO-C595	114 nm	Iron oxide 5 nm	Cross linked Dextran	Breast cancer and RES	Very promising *in vitro* results but low *in vivo* tumor uptakes due to the protein corona effect	Nontoxicity	T_2 and T_2* weighted imaging	Dual SPECT/MRI for Breast cancer	(69)
^{124}I-TCL-SPION	40 nm	Iron oxide 4-11 nm	Cross-linked PEG	NM	No quantification but images show uptakes	NM	T_2 weighted imaging	Triple-Modality Optical/PET/MR	(77)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
					in tumor and lymph nodes (Front paw injection)		$r_2 = 283.7\ mM^{-1}s^{-1}$ at 60 MHz	Imaging imaging of 4 T1 breast tumor	
^{64}Cu-Cy5.5-IONPs	19 nm	Iron oxide 15 nm	Dopamine and albumin (HSA)	NM	Tumor: 5.46, 6.11 and 8.45 %ID/g at 1, 4 and 18 hpi	Nontoxicity	T_2 weighted imaging $r_2 = 314.5\ mM^{-1}s^{-1}$ at 300 MHz	PET/MR/Optical nude mice bearing U87MG tumors	(57)
^{64}Cu-DOTA-IO-c(RGDyK)	12 nm	Iron oxide 8 nm	ferritin	for tumor visualization of nude mice bearing U87MG tumors	Tumor: 6.4, 7.5, 8.1 and 7.5 %ID/g at 1, 4, 24 and 40 hpi	Nontoxicity	T_2 and T_2* weighted imaging	Triple PET/MR/ NIRF	(53)
^{111}In-mAbMB-SPION	69.6 nm	Iron oxide 17 nm	carboxy methyl dextran	^{111}In-labeled antimesothelin antibody () with SPIONs	Liver: 2.1, 8.1 %ID/g Spleen: 28.6, 48.4%ID/g Tumor: 2.2, 3.8 % ID/g 24hpi & 72hpi	Nontoxicity	T_2 and T_2* weighted imaging	for SPECT/MR imaging of mesothelioma	(56)
^{111}In-IONPS - ChL6	20, 30 & 100 nm	Iron oxide 5 nm	PEG-dextran	Breast Cancer	Tumor % ID/g ± SD of each SPIO 20 nm: 9.00 ± 0.8 %ID/g 30 nm: 3.0 ± 0.3 % ID/g 100 nm: 4.5 ± 0.8 %ID/g 48 hpi	Nontoxicity	T_2 and T_2* weighted imaging	Dual SPECT/MRI for Breast alternating magnetic field (AMF) therapy	(41)
^{67}Ga-DTPA-USPIO	85 nm	Iron oxide 5 nm	Cross linked Dextran	Liver and spleen (RES)	Liver: 62.25 & 22.75 %ID/g Spleen: 23.03 & 5.27 %ID/g at 15 min pi & 2 days pi	NM	T_2 and T_2* weighted imaging $r_2 = 16.3\ mM^{-1}\ s^{-1}$ $r_1 = 0.41\ mM^{-1}s^{-1}$ at 60 MHz	Dual SPECT/MRI for RES theranostic purposes	(70)
^{64}Cu-DOTA-IO	26.6 ± 7.3 nm	Iron Oxide 7.9 ± 2.0 nm	dextran	Macrophages	Atherosclerosis plaques	NM	T_2 and T_2* weighted imaging $r_1 = 14.46$ and $r_2 = 72.6\ s^{-1}mM^{-1}$ at 60 MHz	Dual PET/MRI probe for cardiovascular imaging of plaques	(118,119)
^{125}I-cRGD-USPIO	51.3 nm	Iron Oxide	Carboxymethyl dextran (CMD)	$\alpha_v\beta_3$ integrin receptors	Kidney: 11.60 %ID/g Liver: 9.28 ± 1.04 %ID/g Blood: 47.60 ± 6.63 & 2 %ID/g in 1 & 48 hpi Liver: 9.28 ± 1.04, 6.65 ± 0.33 & 1.69 ± 0.08 %ID/g at 1, 4 & 24 hpi	NM	T_2 weighted imaging	Dual SPECT/ MRI of integrin $\alpha_v\beta_3$ expression in breast cancer	(54)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
					Spleen: 8.08 ± 1.09, 4.96 ± 0.16 & 1.34 ± 0.06 %ID/g at 1, 4 & 24 hpi Tumor: 3.73 ± 2.40, 8.08 ± 0.30 & 3.65 % ID/g at 1, 4 & 24 hpi				
^{111}In-DOTA-di-scFv-c	20 nm	Iron Oxide 5 nm	Dextran PEG	Glandular epithelial cells express MUC-1	Tumor: 6 %ID/g Liver: 23 %ID/g Spleen: 9 %ID/g Kidney: 7 %ID/g 48 hpi	NM	T_2 weighted imaging	Dual SPECT/ MRI of MUC-1 expression in Glandular epithelial cells	(60)
^{68}Ga-NOTA-OA-IONP	66 nm	Iron Oxide 16 nm	PEG	Colon cancer (HT-29) cells	Tumor: 3.07 ± 0.76 %ID/g 1 hpi	NM	T_2 weighted imaging $r_2 = 157\ s^{-1}\ mM^{-1}$ at 200 MHz	Dual PET/MRI imaging agent for tumor diagnosis and analysis of tumor functionality and simultaneous tumor	(120)
^{64}Cu-DOTA-GdVO4:4%Eu-DGEA	Thickness = 5 nm and width = 150 nm	Gd	OA PAA	prostate cancer, high $\alpha_v\beta_3$ integrin expression	Tumor/Background contrast : 8.4% ID/g 20 – 24 hpi Tumor 7.2% ID/g 45 hpi	No significant decrease in the cell viability	T_1 weighted imaging	Dual PET/ MRI contrast agent of integrin $\alpha_v\beta_3$ expression in prostate cancer	(121)
^{64}Cu-DOTA-USPIO	140 ± 7 nm	USPIO 5 nm	PEG	MDA-MB-231 Human Breast cancer cell	Tumor: 3.5 ± 0.25 % ID/g Liver: 22.0±6.0 %ID/g 20 hpi	NM	T_2 weighted imaging $r_2 = 265 \pm 10\ s^{-1}mM^{-1}$ $r_2/r_1 = 123$ at 60 MHz	Dual PET/ MRI contrast agent	(122)
^{18}F/^{64}Cu-$Co_{0.16}Fe_{2.84}O_4$ @N aYF_4(Yb, Er)-BP-PEG	44 nm	Fe_3O_4@$NaYF_4$ and $Co_{0.16}Fe_{2.84}O_4$ @N aYF_4(Yb, Er) 10.3 ± 1.4 nm	PEG 2 K & PEG 10 K	NPs cleared from the blood pool more slowly than positively charged NPs	with 10 K PEG and lower charge -10 mV: Liver: 24.3, 32.1, 43.1 & 34.3 %ID blood: 22.7, 17.2, 8.6 & 6.5 %ID Spleen << 2 %ID Bone: 16.3, 17.2, 17.5 & 23.4 %ID with 2 K PEG and lower charge +10 mV: Liver:49.6, 66.4, 53.8 & 44.9 %ID Blood:7.3, 1.6, 1.4	not toxic	T_2 weighted imaging $r_2 = 325.9 \pm 10$ & $r_1 = 2.7 \pm 0.1\ mM^{-1}\ s^{-1}$ for PEG 2 K $r_2 = 102 \pm 2.6$ & $r_1 = 5 \pm 0.6\ mM^{-1}\ s^{-1}$ for PEG 10 K at 128 MHz	Dual PET/ MRI contrast agent	(61)

(*Continues*)

Table 2. (Continued)

Compound	Size	Core	Coating	Targets	Uptakes	Toxicity	T_1 or T_2 contrast agent	Applications	Ref.
					& 0.9 %ID Bone:11.1, 10.1, 15.2 & 21.1 %ID Spleen: 3.3, 3.4, 3.1& 3.0 %ID at 15, 45, 75 and 120 min p.i. respectively.				
^{68}Ga-NOTA-IO-Man	10.12 ± 1.46 nm	Iron Oxide 5 nm	PEG	Lymph nodes	high LN uptakes after 30 min post footpad injection	Low toxicity	T_2 weighted imaging $r_2 = 449.9\ mM^{-1}s^{-1}$ at 600 MHz	Dual PET/ MRI contrast agent	(123)
^{68}Ga-NODA-Magh-1-PNPs	44 ± 55 nm	Iron Oxide (Fe_2O_3) 8-12 nm	PLGA-b-PEG-COOH	a promising tool for innovative PET/MRI diagnostic agents	Liver: 2.2 %ID/g Spleen: 2 %ID/g Kidney: 0.5 %ID/g Lung: 0.6 %ID/g Heart: 0.3 %ID/g (20,60,120 & 180 min post injection)	not toxic	$r_2 = 182\ mM^{-1}s^{-1}$ $r_1 = 0.5\ mM^{-1}s^{-1}$ at 60 MHz	PET/MRI	(124)
^{64}Cu-Apoferritin-	13.6 nm	Fe_2O_3 12.1 nm	Apoferritin	Good tumor uptake for human colon cancer	Tumor: 4.82, 6.14, 7.34, 7.26 and 6.74 % ID/g at 1, 2, 4, 18 and 26 hpi	not toxic	T_1 weighted $r_1 = 2.54\ mM^{-1}s^{-1}$ at 60 MHz	PET/MRI/Photo acoustic imaging	(76)
^{64}Cu-RGD-PEG-MNP	9.6 nm	USPION 4.5 ± 0.5 nm	PEG	Glioma Tumor and $\alpha_v\beta_3$ integrin U87MG cells	Tumor: 4.13, 5.79 and 5.95 % ID/g Liver: 22.76, 22.43 and 15.86 % ID/g Spleen:7.11, 6.94 and 6.62 % ID/g at 2, 4, 24 hpi	not toxic	$r_1 = 1.2\ mM^{-1}s^{-1}$ at 400 MHz	PET/MRI	(125)
^{68}Ga -DOTA-IO-GUL (glutamate-urea-lysine)	11.01 ± 1.54 nm	Iron oxide 5 nm	PEG	prostate-specific membrane antigen (PSMA)	Tumor uptakes:5.34 % ID after 1 h post i.v. injection SUV for Tumor was: 2.385 from PET images	not toxic	T_2 Weighted $r_2 = 185.13\ mM^{-1}s^{-1}$	PET/MRI	(126)

Table 3. Liver uptake of studies that were designed for Lymph node imaging

Lymph node type (LN)	LN uptake/Liver uptake	LN uptake (%ID/g)	Liver uptake (%ID/g)	Probe	Coating	Size	Charge	Ref.
SLN	410.0	123.0	0.3	^{68}Ga-SPION	PEG	30 nm	NM	(53)
Iliac LN	156.7	47.0	0.3	^{68}Ga-SPION	PEG	30 nm	NM	(53)
Brachial LN	150.8	921.2	6.1	^{89}Zr-DFO-ferumoxytol	Dextran	22 nm	16.4±0.8 mV	(67)
Auxiliary LN	56.1	343.0	6.1	^{89}Zr-DFO-ferumoxytol	Dextran	22 nm	16.4±0.8 mV	(67)
SLN	150.7	210.9	1.4 ± 0.7	^{99m}Tc-SPION	PEG	18 nm	5 mV	(77)

in all untargeted tissues, such as liver (0.25 %ID/g), showed that this agent could be a suitable probe (46).

4.2. Tumor uptake

One of the most important parameters for evaluating the efficiency of a contrast agent is tumor uptake in comparison with other organs (especially vital organs). First of all, it is better to begin by explaining the uptake mechanism. Most solid tumors have blood vessels with a defective structure; therefore, they exhibit enhanced vascular permeability known as enhanced permeability and retention (EPR). By EPR, drugs could be directed to the tumor environment in a passive way rather than through biochemical receptors (47). On the other hand, the transport of nanoscale hydrophilic biomolecules is usually done using endocytosis, which is a form of active transport. In this process, a cell absorbs materials by enclosing them in vesicles or vacuoles pinched off from its cytoplasmic membrane. There are various types of endocytosis and different types of NPs reveal a chosen pathway for cellular internalization. Also, whereas one of the main approaches in the development of nanomedicines for imaging and therapy is to confirm that the NPs can easily enter the cells, having knowledge about the effecting parameters on uptake is essential (48).

Studies have shown that the effecting factors on cellular uptake are size and shape, composition, charge, and surface chemistry of the NPs (48). From the analyzed studies we concluded that the size range of 20–200 nm can be used for molecular imaging, although it is better to try to achieve as small a size as it is possible.

After reviewing the 49 studies, we extracted the amounts of tumor uptake of 19 studies. Among the selected studies, Arginine-glycine-aspartic (RGD) peptide, which has high affinity to bind tumor with integrin a_vb_3 expression, was chosen for the synthesis of seven dual contrast agents (49–55). It was shown that the tumor uptake with agents conjugated to RGD was considerably higher than with agents not-conjugated to RGD. Therefore, the high tumor uptake could be due to RGD. As shown in Table 4, the highest uptake was found for ^{64}Cu-DOTA-IO-RGD (10.1 ± 2.1 %ID/g) at 4 h post injection in tumor $\alpha_v\beta_3$ integrin expression. In that study, the non-targeted particle (without RGD) ^{64}Cu-DOTA-IO showed considerably lower tumor uptake compared with the RGD conjugated nanoparticle, but their liver and kidney uptakes had no significant difference at different time points (50).

The lowest tumor uptake reported was for ^{111}In-mAbMB-SPION. The quantities of tumor uptake are 2.2 and 3.8%ID/g at 24 and 72 hours post-injection, respectively (56). This result could be because of the size of the compound (69.6 nm) in comparison with another contrast agent, ^{64}Cu-NOTA-SPION-cRGD-DOX, which has higher tumor uptake (49). There is, however, no additional data about other time points.

Concerning the effect of particle size, by comparing two contrast agents, ^{64}Cu-Cy5.5-IONPs and ^{64}Cu-DOTA-IO-c(RGDyK), it is found that the tumor uptake for the smaller particle size is higher than for the other one (53,57).

4.3. Size effect

Size is one of the most important issues in the biodistribution of NPs. An earlier study showed that the uptake efficiency of 100 nm size particles by the intestinal tissue was 15–250 fold higher compared to larger size particles (58). Another study reported that moving from 200 nm to 70 nm leads to 27 times higher uptakes in target organs (59). Natarjan *et al*. investigated the tumor uptake and biodistribution of ^{111}In-IONPS-ChL6 with three different sizes and showed that the tumor uptakes at 48 h post injection were 9.0 ± 0.8 (for a size of 20 nm), 3.0 ± 0.3 (for 30 nm), and 4.5 ± 0.8 (for 100 nm) (60). Therefore, concluding that lower size always gives better tumor uptake may not be correct but as shown in Tables 2 and 4 the majority of the dual probes are below 100 (the minimum size being 2.5 and the average size about 43 nm). Among all studies presented in Table 2, the highest tumor uptake was observed for NPs with a hydrodynamic size of 45, 20 and 19 nm with the tumor uptakes of 10.1 ± 2.1 % (50), 9.0 ± 0.8% (60) and 8.45% (57) respectively. NPs with small size (less than 100 nm) are transported and taken up by the target organs more readily, whereas the larger NPs are likely to remain at the injection site (61).

4.4. Coating

Another crucial factor in tumor uptake is the coating. Among all 49 studies presented in Table 2, more than 36% used dextran, whereas about 26% used PEG, as a coating. Some studies show that a small hydrodynamic size (less than 100 nm) and low zeta-potential offer the opportunity to control circulation time and avoid immediate RES clearance, where this is desired for targeting applications (61,62). Cui *et al*. showed that the use of longer-chain PEGylated NPs (10 KDa, n ≈ 227 and −10 mV) resulted in a delayed clearance of NPs as compared to the shorter-chain PEGylated NPs (2KDa with n ≈ 45, and zeta potential of +10 mV). Therefore, the length of the PEG chain and the zeta potential of NPs play important roles in biodistribution (61). Previous studies confirm the fact that particle size and surface properties also play a significant role in enhancing lymphatic transport (63,64). PEGylation can improve the uptake in lymph nodes and increase accumulation at the disease site by reducing the nonspecific interaction between particles and proteins of the biological milieu, thus causing a longer blood circulation time (61,65). On the other

Table 4. Tumor uptake of some multimodality contrast agents

Compound	Size	Core	Coating	Tumor uptake (%ID/g)	Ref.
^{64}Cu-NOTA-SPION-cRGD-DOX	68 ± 2 nm	SPION	Hetero bifunctional poly (PEG)	0.5 h: 4.3 ± 0.6 3 h: 5.5 ± 1.9 6 h: 5.6 ± 1.7 24 h: 5.4 ± 2.0 48 h: 5.4 ± 2.1	(49)
^{64}Cu-DOTA-IO-RGD	45 ± 10 nm	Iron Oxide 5 nm	Polyaspartic acid (PASP)	1 h: 7.9 ± 0.8 4 h: 10.1 ± 2.1 21 h: 9.8 ± 3.2	(50)
^{64}Cu-MoS_2-IO-(d)PEG	NM	MoS_2 50-200 nm	PEG	24 h: 5.70 Tumor/Liver = 0.1425	(43)
^{99m}Tc-SPION-RGD	200 nm	SPION 10 ± 2 nm	Aminosilane	1 h: 9.01 ± 0.19 Tumor/Liver = 0.8476	(51)
^{124}I-c(RGDyk)$_2$-UCNPs	32 ± 9 nm	Upconversion nanophosphors ($NaGdF_4$:Er^{3+}/Yb^{3+})	PEG	4.5 h: 2.8 ± 0.8	(52)
^{99m}Tc-USPIO-C595	114 nm	Iron oxide 5 nm	Dextran	0.25 h: 4.88 2 h: 4.13 24 h: 3.45	(69)
^{64}Cu-Cy5.5-IONPs	19 nm	Iron oxide 15 nm	Dopamine and albumin (HSA)	1 h: 5.46 4 h: 6.11 18 h: 8.45	(57)
^{64}Cu-DOTA-IO-c(RGDyK)	12 nm	Iron oxide 8 nm	Ferritin	1 h: 6.4 4 h: 7.5 24 h: 8.1 40 h: 7.5	(53)
^{111}In-mAbMB-SPION	69.6 nm	Iron oxide 17 nm	carboxy methyl dextran	24 h: 2.2 72 h: 3.8	(56)
^{111}In-IONPS -ChL6	20, 30 & 100 nm	Iron oxide 5 nm	PEG-dextran	48 h: 9.00 ± 0.8 (20 nm), 3.0 ± 0.3 (30 nm), & 4.5 ± 0.8 (100 nm)	(41)
^{125}I-cRGD-USPIO	51.3 nm	Iron Oxide	Carboxymethyl dextran (CMD)	1 h: 3.73 ± 2.40 4 h: 8.08 ± 0.30 24 h: 3.65	(54)
^{111}In-DOTA-di-scFv-c	20 nm	Iron Oxide 5 nm	Dextran PEG	48 h: 6	(60)
^{68}Ga-NOTA-OA-IONP	66 nm	Iron Oxide 16 nm	PEG	1 h: 3.07 ± 0.76	(120)
^{64}Cu-DOTA-GdVO4:4%Eu-DGEA	NM	Gd	OA, PAA	45 h: 7.2	(121)
^{64}Cu-DOTA-USPIOn	140 ± 7 nm	USPION 5 nm	PEG	20 h: 3.5 ± 0.25	(122)
^{64}Cu-Apoferretin-	13.6 nm	Fe_2O_3 12.1 nm	Apoferretin	1 h: 4.82 2 h: 6.14 4 h: 7.34 18 h: 7.26 26 h: 6.74	(76)
^{64}Cu-RGD-PEG-MNP	9.6 nm	USPION 4.5 ± 0.5 nm	PEG	2 h: 4.13 4 h: 5.79 24 h:5.95	(125)
68Ga -DOTA-IO-GUL (glutamate-urea-lysine)	11.01 ± 1.54 nm	Iron oxide 5 nm	PEG	1 h: 5.34	(126)

hand, several studies confirmed that Dextran coated NPs resulted in RES uptakes due to the protein corona formation (see the section 4.6) (66–70).

4.5. Transverse relaxivity (r_2)

In some of these 49 studies, the values of the transverse relaxivity (r_2) have been mentioned precisely. There are some studies that investigated the relationship between r_2 and particle characteristics, such as size and coating. They showed that as coating thickness increases, r_2 and r_1 decrease dramatically and found no effect on relaxivity with changing pH (71,72). A recent study showed that the impact of charge on magnetic properties is much higher than that of coating thickness. Particles with positive surface charges showed higher r_2/r_1 ratios (73).

For a type of NPs commonly used as MRI contrast agent, i.e. superparamagnetic iron oxide NPs, r_2 is especially enhanced due to rapid diffusion and exchange of water molecules surrounding the magnetic contrast agents (74).

As mentioned, some studies examined the effect of coating type. They showed that iron NPs with silica coating have the highest r_2 (628 $mM^{-1}s^{-1}$ in a magnetic field of 1.5 T) in comparison with other coatings (75) and also that r_2 depends on the level of hydrophilicity of the coating material, with the highest r_2 mentioned in a study with hydrophilic Polyethylenimine (PEI) ligand coated nanocrystals (74).

According to r_2 data extracted from the 49 studies, the lowest r_2 (2.54 $mM^{-1}s^{-1}$ at 60 MHz) results from using ^{64}Cu-Apoferritin-as a triple-modality contrast agent. This could be because of the relatively high coating thickness (76). However, the highest value (283.7 $mM^{-1}s^{-1}$) in the same magnetic field, relates to ^{124}I-TCL-SPION as an Optical/PET/MRI contrast agent. The main cause could be the size of NPs (77).

Consequently, based on the specified papers and other investigations on r_2, an appropriate contrast agent in images using MRI and other dual modality systems that include MRI is an agent with a high r_2 that decreases the signal in T_2-weighted images. Also, for *in vivo* biomedical applications such as biomarker targeted delivery and molecular imaging, it is important to use NPs with smaller overall size in order to achieve efficient delivery and rapid clearance of bioconjugated NPs (74). Therefore, small NPs with hydrophilic coating should be suitable.

The transverse relaxivities of some multimodality contrast agents mentioned in the analyzed studies are shown in Table 5.

4.6. Protein corona

When NPs are exposed to the biological milieu, their surfaces become covered with a variety of proteins and biomolecules, which are called the protein corona (78–80). Studies showed that the protein corona reduces the targeting capability of surface modified NPs by covering or affecting the active sites of these nanoprobes (80–82). Usually, *in vitro* results (i.e. serum-free medium or 10% serum) are very promising and confirm the high capability of the new functionalized NPs for targeting the desired cells. However, the *in vivo* results are often disappointing and show lower targeting yields and undesirable biodistribution (i.e. NPs taken up by the RES instead of the desired tumor tissue) (69,83,84). In a study carried out by Shanehsazzadeh *et al*. after obtaining very promising *in vitro* results the *in vivo* results were disappointing (>80% of ID/g of the nanoprobe was taken up by RES). This was not only due to the targeting site being covered by the protein corona, but also because of absorption of opsonin-based proteins at the surface of nanoprobes (69). Studies have shown that there are two main reasons for high RES uptakes: first, the opsonin based proteins are absorbed to the

Table 5. Transverse relaxivity of some of multimodality contrast agents

Contrast agent	r_2 ($mM^{-1}s^{-1}$)	Size (nm)	Core	Coating	Ref.
^{64}Cu-NOTA-SPION-cRGD-DOX	101.9 at 200 MHz	68 ± 2	SPION (10 nm)	Hetero bifunctional poly (PEG)	(49)
^{64}Cu-DOTA-IO-RGD	105.5	45 ± 10	iron oxide (5 nm)	Polyaspartic acid (PASP)	(50)
^{124}I-SA-MnMEIO	321.6	32	MnMEIO (15 nm)	Serum Albumin (SA)	(107)
^{99m}Tc-DPA-ale-Endorem	26 at 400 MHz	106 ± 60	SPION (5 nm)	Dextran	(42)
^{64}Cu-DOTA-mSPIO	209 ± 26 at 20 MHz	20.3 ± 1.9	SPION (6.2 nm)	PEG + micelle	(109)
^{64}Cu-MoS_2-IO-(d)PEG	93.59 at 128 MHz	-	MoS_2 (50-200 nm)	PEG	(43)
Fe_3O_4-Ag ^{125}I heterodimers	139.8 at 60 MHz	-	Fe_3O_4-Ag (14 nm)	PEG	(111)
^{59}Fe-SPION	97 ± 3 at 300 MHz	17 ± 6	SPION (4.3 ± 1.3 nm)	PAA-DOP-PEG	(44)
^{89}Zr-DFO-ferumoxytol	89 at 20 MHz	22	iron oxide (15-35 nm)	Carboxymethyl dextran	(40)
^{68}Ga-NODAGA-AGulX and ^{68}Ga- DOTAGA-AGulX	r_1 = 10.3 r_2 = 13.4 at 60 MHz	2.5 ± 0.1	gadolinium oxide (Gd_2O_3) 1.7 nm	polysiloxane	(46)
^{67}Ga-NOTA-MF-AS1411	82.1 at 60 MHz	68.1	cobalt ferrite	Silica and PEG	(116)
^{64}Cu-bisphosphonat $MnFe_2O_4$ and [^{18}F]-fluoride- $MnFe_2O_4$	r_2 = 121.9 at 128 MHz	49.8	MnFe2O4 4.8 nm	Al(OH)3 PEG (5 K)	(117)
^{124}I-TCL-SPION	283.7 at 60 MHz	40	iron oxide (4-11 nm)	Cross-linked PEG	(77)
^{64}Cu-Cy5.5—IONPs	314.5 at 300 MHz	19	iron oxide (15 nm)	Dopamine and albumin (HSA)	(57)
^{67}Ga-DTPA-USPIO	r_1 = 0.41 r_2 = 16.3 at 60 MHz	85	iron oxide (5 nm)	Cross linked Dextran	(70)
^{68}Ga-NOTA-OA-IONP	157 at 200 MHz	66	iron oxide (16 nm)	PEG	(120)
^{64}Cu-DOTA-USPIOn	r_2 = 265 ± 10 r_2/r_1 = 123 at 60 MHz	140 ± 7	USPIOn	PEG	(122)
^{18}F/^{64}Cu-$Co_{0.16}Fe_{2.84}O_4$@NaYF$_4$(Yb, Er)-BP-PEG	r_2 = 325.9 ± 10 & r_1 = 2.7 ± 0.1 for PEG 2 K r_2 = 102 ± 2.6 & r_1 = 5 ± 0.6 for PEG 10 K at 128 MHz	44	Fe_3O_4@$NaYF_4$ and $Co_{0.16}Fe_{2.84}O_4$@NaYF$_4$(Yb, Er) 10.3 ± 1.4 nm	PEG 2 K & PEG 10 K	(61)
^{68}Ga-NOTA-IO-Man	r_2 = 449.9 at 600 MHz	10.12 ± 1.46	iron oxide 5 nm	PEG	(123)
^{68}Ga-NODA-Magh-1-PNPs	r_2 = 182 r_1 = 0.5 at 60 MHz	44 ± 55	iron oxide (Fe_2O_3) 8-12 nm	PLGA-b-PEG-COOH	(124)
^{64}Cu-Apoferritin-	r_1 = 2.54 at 60 MHz	13.6	Fe_2O_3 12.1 nm	Apoferritin	(76)
^{64}Cu-RGD-PEG-MNP	r_1 = 1.2 at 400 MHz	9.6	4.5 ± 0.5 nm USPIO	PEG	(125)
^{68}Ga -DOTA-IO-GUL (glutamate-urea-lysine)	r_2 = 185.13	11.01 ± 1.54	5 nm iron oxide	PEG	(126)
^{64}Cu-DOTA-MDIO	83.9 at 60 MHz	62.7	IONP (7–8 nm)	Dextran	(127)

surface of NPs, and, second the ability of the protein corona to cover the targeting species. For instance, Dawson *et al*. showed that the targeting ability of transferrin-conjugated NPs was significantly reduced after interaction of NPs with serum proteins (85). More specifically, the protein corona shielded transferrin from binding to its targeted receptors. This second mechanism is related to low blood circulation time of the nanoprobes.

Protein corona not only alters the biological fate of the NPs but it also changes their magnetic properties (86–88). Studies show that the r_2 is very much dependent on the functional group and the surface charge of the SPIONs' coating. Therefore, due to changes in hydrodynamic size and charge of NPs after being exposed to the biological milieu, their magnetic properties changed (73,88,89).

5. CONCLUSION

In this review we analyzed the main factors that affect the uptakes of the dual modality probes in PET/MRI. Evaluating the liver uptake of selected studies showed that the bigger size of contrast agent NPs causes the more liver uptake. The kind of coating is another important reason for high liver uptake (dextran causes higher liver uptake). Furthermore, some molecules and proteins such as opsonins are taken up by cells of the RES. From the published studies we concluded that a size range of 20–200 nm can be used for molecular imaging; although since tumor uptake is higher with smaller particle size, as small a size as possible should be achieved.

In terms of the biomarkers, the best targeting results among the published studies were related to nanoprobes that used peptides. One of these molecules is RGD, which has been conjugated with some contrast agents and shown to result in a higher tumor uptake than others.

In conclusion, the best targeting results according to the selected studies are generally with peptide or engineered mAb (with lower molecular weights) with an approximate hydrodynamic size of 40 nm, PEGylated radio labeled with ^{64}Cu or ^{68}Ga. However, there are some exceptions and some surprising nano probes with a different composition.

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