SYSTEMATIC REVIEW

Applications of Nanoparticles in Magnetic Resonance Imaging: A Comprehensive Review

Ali Yadollahpour[1], Halime Mansoury Asl[2]*, Samaneh Rashidi[2]

[1]Department of Medical Physics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, [2]Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Technology advancements in synthesis and modification of nanoscale materials have advanced the development of different medical applications. Nanoparticles (NPs) have demonstrated promising potentials in diagnostic medicine especially for magnetic resonance imaging (MRI). Iron oxide, gold, and gadolinium NPs have been used in preclinical and clinical studies as contrast enhancing agents. Studies are ongoing to find the optimum parameters of these NPs as contrast agents (CAs) of MRI. This study aims to review the recent applications of iron oxide, gold, and gadolinium NPs as contrast enhancing agents in MRI for diagnosis of different disorders. The databases of PubMed (1980-2016), Web of Science (1980-2016), Scopus (1980-2016), and Google Scholar (1980-2016) were explored using the search terms "Nanoparticles," "Contrast agents," "Magnetic Resonance Imaging" and "disease." The obtained results were screened for the title and abstract and comprehensively reviewed. MRI CAs are divided into T1 and T2 CAs, respectively, used for T1 and T2 weighted protocols in MRI. Iron oxide, gadolinium, and gold NPs are the most common CAs used in MRI. High magnetization values, small size, narrow particle size distribution are the main features of NPs as CAs in MRI. Gadolinium is the most common T1 CAs used in MRI. However, it is associated with toxicity which is a serious concern in patients with renal failure. Iron oxide NPs can be used for these patients. However, the main limitation of iron oxide NPs is limited relaxivity. The relaxivity strongly depends on the size of NP. Paramagnetic NPs serve as T1 CAs and super paramagnetic NPs as T2 CAs. Modulating the size of NPs is the main parameter to adjust different NPs for different MRI protocols. Recent years to overcome the problem of gadolinium and iron oxide NPs, different paramagnetic and super paramagnetic NPs are developed.

Key words: Contrast agent, gadolinium, gold, iron oxide, magnetic resonance imaging, nanoparticle

INTRODUCTION

Noninvasive assessment and imaging of internal organs of a human body has been always a main challenge to physicians and researchers.[1] Magnetic resonance imaging (MRI) is the most common diagnostic imaging modality in clinical medicine due to its excellent spatial resolution, noninvasive and nondestructive nature.[2] MRI is imaging of soft tissue and in some cases cannot generate a sufficient contrast. The development of MRI to one of the most powerful techniques in clinical diagnosis is accompanied by the progress in the design of contrast agents (CAs), which enhance image quality.[3] MR images frequently rely on the differences in tissue relaxation times, both longitudinal (T1) and transverse (T2), to generate image contrast.[4] After protons are excited with a radiofrequency (RF) pulse applied perpendicular to the magnetic field, the protons will realign themselves with the magnetic field, a process referred to as relaxation. MRI signals are modulated by the rates at which protons return to equilibrium after an RF pulse. The difference in T1 and T2 relaxation times allow differentiation between soft tissues, bone, air, and liquids in the body.[5] Disease detection with MRI is often difficult because areas involved in the disease have similar signal intensity compared to the surrounding healthy tissue; therefore, requiring signal enhancement using CAs.[6] CAs

Address for correspondence:
Halime Mansoury Asl, Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: halime_mansoury@yahoo.com

Received: 10-11-2016
Revised: 14-01-2017
Accepted: 25-01-2017

interact with water molecules, leading to altered proton T1 or T2 relaxation times.[7] Contrast in MRI is most often defined by "T1" (spin–spin) or "T2" (spin–lattice) relaxation times, depending on the exact pulse sequence used to excite and then measure the relaxing spins. Exogenous CAs may be employed to alter local T1 or T2 relaxation times to produce highly enhanced tissue contrast as compared with the expected background T1 or T2 signals.[8]

Nanotechnology has revolutionized the potentials of the MRI imaging modality. Nanoparticles (NPs) continue to receive attention in the field of medical imaging for their potential as specific CAs *in vitro* and *in vivo*.[9-11] The combination of multimodal imaging and theranostics will lead to cutting-edge technologies in which the potential of the NPs can be maximized.[12] However, the sensitivity at cellular/molecular imaging level is obviously lower than positron emission tomography and fluorescence imaging. MRI CAs, such as superparamagnetic iron oxide NPs (SPIONs), are emerging as one of the most promising probes for improving contrast at cellular or even molecular levels.[13-19] The use of CAs in MRI facilitates a more accurate diagnosis by enhancing the contrast between tissues. Recently, CAs have also been combined with target-directing molecules to visualize specific tissues and molecules.[20,21] In this regard, SPIONs, which induce the dark contrast enhancement in T2-weighted MR images, have been commercialized as T2 CAs.[16,22-27]

In this paper, we will review the characteristics of different types of NPs including iron oxide, gold, and gadolinium which have been developed as contrast enhancing agents in MRI. Characteristics such as size, clinical applications, protein/ligand, relaxivity, and toxicity for each type of NPs are discussed.

METHOD

The databases of PubMed, Web of Science, and Google Scholar were searched from the first data available to 2016. The following key words were used "MRI" and "CA" and "NP." The obtained records were reviewed for the title and abstract by two authors independently. Then, a consensus decision was made whether the studies are relevant for the review topic. Human and animal studies including the use of NPs the NPs used in MRI. Limited number of studies in this field and heterogeneity in the design and methodology of the studies, we aimed to provide a comprehensive and descriptive overview of all aspect of applications of NPs for more accurate diagnostic MRI.

Search method

The scientific records were retrieved by a systematic search of multiple bibliographic databases and the last update of the search was performed on to December 10th 2016 including PubMed (1980-2016), Web of Science (1980-2016), Scopus (1980-2016), and Google Scholar (1980-2016). The language of the search was limited to English. The search key words based on the MeSH heading included "MRI" and "CA" and "NPs." The titles and abstracts of all the records retrieved by the search strategy were reviewed by two authors (AY and HM) and the relevant papers with full texts available were used for further assessments. Moreover, the reference lists of the relevant papers were checked manually to identify additional eligible studies. These papers also were included for the full review.

Inclusion and exclusion criteria

The identification and screening of the titles for inclusion or exclusion were performed independently by the two reviewers (AY and HM) and disagreements were resolved by discussion. Only original articles were eligible if they provided the following characteristics: (1) Human and animal studies that used of NPs in MRI, (2) *in vivo* and *in vitro* studies, (3) articles that evaluated diagnosis variety of cancers and tumors using NPs. Studies were excluded if: (a) abstract only, (b) review or meta-analysis, (c) books, (d) letters, (e) conference documents, (f) case reports, (g) editorial, (h) guideline, and (i) pilot study. The flowchart of the study process is depicted in Figure 1.

RESULTS

Characteristics of studies

A total of 508 records were retrieved in the searching process. Studies were excluded if abstract only, review or meta-analysis, books, letters, conference documents, case reports, editorial, guideline, and pilot study. Finally, 17 articles fulfilled the criteria to be included in the final reviewing.

Table 1 presents descriptive information of all studies. The trials were conducted until 2016 in China, Australia, Korea, Taiwan, U.S.A, Japan, etc.

NPs should be biocompatible, nontoxic, and stable for *in vivo* applications. These features can be controlled by changing the size and the coating's properties of NPs.[13,28] MRI CAs are divided into T1 and T2 CAs, respectively, used for T1 and T2 weighted protocols in MRI. Iron oxide, gadolinium, and gold NPs (AuNPs) are the most common CAs used in MRI. High magnetization values, small size, narrow particle size distribution are the main features of NPs as CAs in MRI. Gadolinium is the most common T1 CAs used in MRI. However, it is associated with toxicity which is a serious concern in patients with renal failure. Iron oxide NPs can be used for these patients. However, the main limitation of iron oxide NPs is limited relaxivity. The relaxivity strongly depends on the size of NP. Paramagnetic

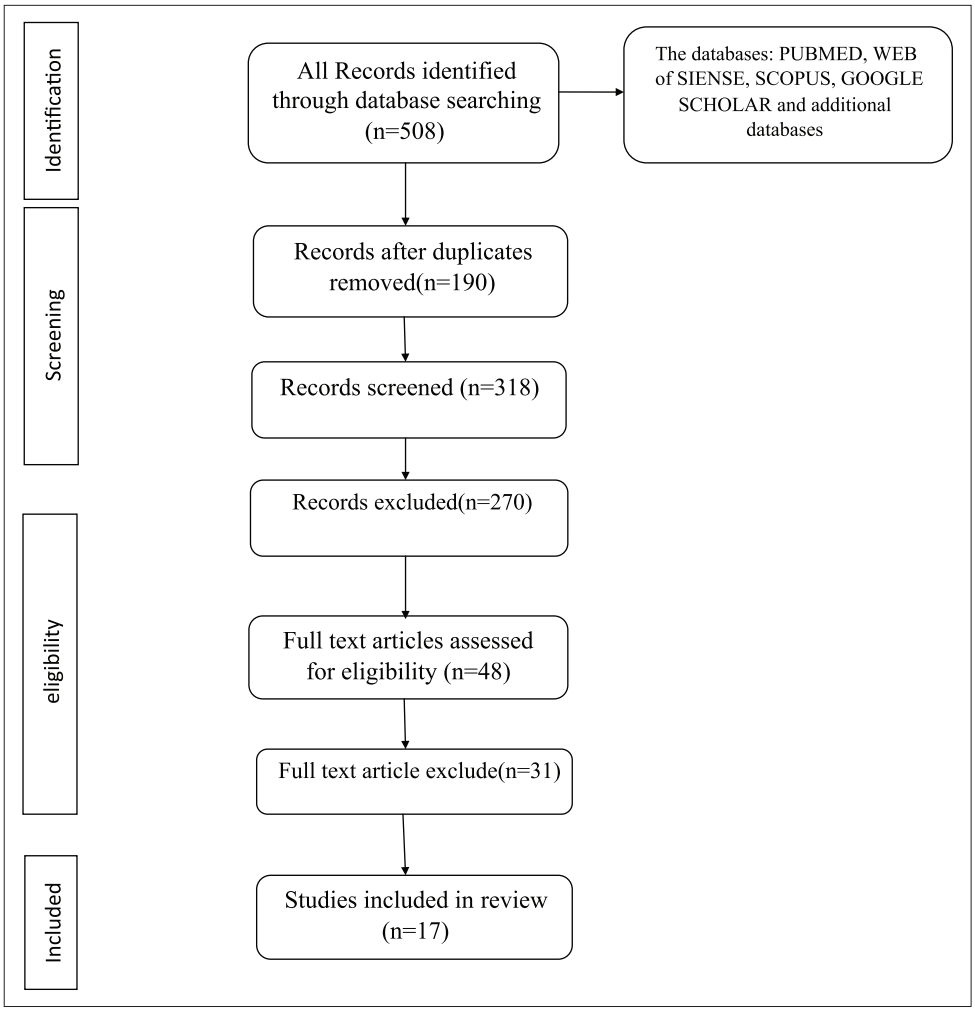

Figure 1: The flowchart of the study design process

NPs serve as T1 CAs and super paramagnetic NPs as T2 CAs.

SPIONs

Iron oxide NPs are iron oxide particles with diameters between 1 and 100 nm. The two main forms are magnetite (Fe_3O_4) and its oxidized form maghemite (γ-Fe_2O_3). Magnetite has an inverse spinal structure with oxygen forming a face-centered cubic crystal system. In magnetite, all tetrahedral sites are occupied by Fe3+ and octahedral sites are occupied by both Fe3+ and Fe2+. Maghemite differs from magnetite in that all or most of the iron atoms are in the trivalent state (Fe3+) and by the presence of cation vacancies in the octahedral sites. Maghemite has a cubic unit cell in which each cell contains 32 O ions, $21\frac{1}{3}$Fe3+ ions, and $2\frac{2}{3}$ vacancies.[13,22,29-33]

Gadolinium NPs

Gadolinium (Gd^{3+}) ion is the most commonly used metal ion as CA in MRI. The main characteristic of Gd^{3+} ion is the presence of seven unpaired electrons combined with a long electron spin relaxation time that makes this metal a very efficient relaxation enhancing agent.[34,35] The five MRI CAs approved by the FDA are based on the Gd^{3+} ion, the material has high ability to catalyze the relaxation of the water signal and create positive contrast in MRI.[3] Several methods are known for the synthesis of gadolinium oxide NPs, mostly based on precipitation of the hydroxide by the reaction of gadolinium ions with hydroxide, followed by thermal dehydration to the oxide. The NPs are always coated with a protective material to avoid the formation of larger polycrystalline aggregates.[3,4,7,33,36-38] Gadolinium oxide NPs are potential CAs for MRI. Sizes of these NPs are <65 nm. Gadolinium oxide NPs have a relaxivity of <20/s/mM. The main clinical challenge of using gadolinium NPs is high toxicity of these agents. Gadolinium is very toxic in ionic form (Gd^{3+} ion) which extremely interferes with calcium channels and protein binding sites so that cannot be administered directly.[19,39-44] Free Gd ions accumulate in the liver, spleen, kidney, and bones. To reduce the side effects of toxic ions and prevent tissue interaction, Gd^{3+} ions are combined with chelating ligands. However, toxic Gd^{3+} ions may still be released from some chelates via transmetallation with other metal ions such as Zn^{2+}, Ca^{2+}, and Cu^{2+} inside the

Table 1: Characteristics of the reviewed studies

Study	Contrast agent	Size	Test	Disease	Dose	Relaxivity mM/S)	Outcome
Xie *et al.*, 2011; China[32]	Lf-SPIONs	75 nm	*In vivo* (animal)	Brain gliomas	51 emu/g Fe	r2=75.6	Enhanced T2W after 48 h
Yang *et al.*, 2011; China[33]	Fe_3O_4 at SiO_2	21 nm	*In vitro* and *in vivo* (animal)	Glioblastoma tumors	200 mL (2 mg/mL)	r1=4.2 r2=17.4	Extended for fabricating other biologically active NPs
Im *et al.*, 2012; Korea[49]	Fe_3O_4/MnO hybrid	5, 11, and 21 nm	*In vitro* and *in vivo* (animal)	HCC	20 ml	r1 remained unaffected, r2 78.9 and 141	Detection of HCC with a high degree of conspicuity
Cha *et al.*, 2011; Korea[30]	PCM-CS	43.1±6.3 nm	*In vivo* (animal)	SCC 7 tumor bearing xenografted	0.05 ml PCM-CS 0.15 mg Fe/mL		NIRF signal of tumor increased up to 12 h post injection
Andreas *et al.*, 2012; Germany[29]	Citrate SPIONs	80-160 nm	*In vivo* (animal) and *ex vivo*	MSCs	25 mg Fe/ml citrate, 500 mg Fe/ml Endorem		Very efficient intracellular magnetic labels for *in vivo* stem cell tracking by MRI
Hu *et al.*, 2011; China[31]	Ultra-small PEGylated iron oxide	5.4 nm	*In vitro*	HeLa cell		r1=19.7 and the lowest r2/r1 ratio of 2.0	SPIONs have little effect on HeLa cell viability
Chou *et al.*, 2010; Taiwan[50]	FePt	3, 6, and 12 nm	*In vitro* and *in vivo*	MBT2 tumor			The 3 nm-FePt showed higher brain concentrations
Lu *et al.*, 2009; China[51]	Mn-SPIO	80 nm	*In vitro* and *in vivo*	Hepato carcinoma		r2=270	High sensitive identification of small liver lesions
Zhang *et al.*, 2012; China[43]	GH	-	*In vitro* and *in vivo*	Blood pool and liver	10 mL, 24.2 mM of Gd^{3+}	r1=15.0 r2=19.7	*In vivo* T1W in living mice shows GH nanoparticles have an intravascular half-life up to 1 h, much longer than that of Gd-DTPA
Zhang *et al.*, 2013; China[44]	Gd-DTPA-FA		*In vitro* and *in vivo*	AP			Highly efficient and specific to detect early AP
Xu *et al.*, 2012; South Korea[42]	Fluorescein PEI coated gadolinium oxide (Gd_2O_3)	3.92 and 7.5 nm	*In vivo*	Liver tumor	0.1 mmol Gd/kg	r1=6.76 r2=20.27	Excellent MRI-CL dual functionality
Liu *et al.*, 2011; China[37]	PLA-PEG-PLL-Gd	69.8±5.3 nm	*In vitro* and *in vivo*	HCC	0.6 mM e12.0 mM		Showed great potential in the early diagnosis of liver tumors
Faucher *et al.* 2012; Canada[41]	Ultra-small PEG-Gd_2O_3	1.3 nm	*In vitro* and *in vivo*	Glioblastoma multiform	0.3-1.1 pg Gd per cell	r1=14.2 r2/r1=1.20	Strong positive contrast enhancement effects in T1W

(*Contd...*)

Table 1: (*Continued...*)

Study	Contrast agent	Size	Test	Disease	Dose	Relaxivity (mM-1 S-1)	Outcome
Park *et al.*, 2010; Korea[38]	Au at GdL: (AuNP)	14 nm	*In vivo* and *in vitro*	Kidney and liver	0.03 mmol Gd/kg	r1=4.6*10^5 r2=7.2*10^5	Demonstrated by histological and TEM images as well as CT and MR
Chen *et al.*, 2013; China[47]	Gd-Au DENPs-FA	4.0 nm	*In vivo* and *in vitro*	Xenograft tumor	0 to 200 mM		Used as dual mode nano-probes for targeted CT/MRI
Alric *et al.*, 2007; France[36]	Au at DTDTPA-Gd	2.4 nm	*In vivo*			r1=4.1	Dual modality imaging freely circulate in the blood vessels without undesirable accumulation in the lungs, spleen, and liver
Wen *et al.*, 2012; China[48]	GdeAu DENPs	4.6 nm	*In vivo* and *in vitro*	DOTA	0.124 mmol Gd/kg	r1=1.05	Good contrast agent MRI for liver, bladder, and heart

HCC: Hepatocellular carcinoma, MRI: Magnetic resonance imaging, CT: Computed tomography, SPIONs: Superparamagnetic iron oxide NPs, NPs: Nanoparticles, AuNP: Gold nanoparticle, PEI: Poly ethylene mine, TEM: Transmission electron microscopy, AP: Acute pancreatitis, MSCs: Mesenchymal stromal cells, SCC: Squamous cell carcinoma, GH: Gadolinium-based hybrid, T1W: T1-weighted, T2W: T2-weighted

body and protonation of the ligands in the low pH mediums which may cause the separation of scheelite within the body.[45,46]

AuNPs

AuNPs, for instance, have demonstrated a great potential as an excellent substitute for iodine. Advantage of AuNPs comes from the fact that facile surface modification may lead to the formation of various functionalities applicable to multiple imaging modalities such as MRI. The common size distribution of these NPs is <13 nm.[36,38,47,48]

CONCLUSION

New nanotechnologies have great promise for achieving high MR contrast. They have the potential of reducing the risk of toxicity or intolerance due to the release of free metal. Various NPs are already used. Each type has its advantages and disadvantages in terms of chemistry, availability, production costs, and biocompatibility properties. Important factors to consider when choosing a specific NP are the biocompatibility, size, shape, and the payload or relaxivity per volume. Modulating the size of NPs is the main parameter to adjust different NPs for different MRI protocols. Recent years to overcome the problem of gadolinium and iron oxide NPs, different paramagnetic and super paramagnetic NPs are developed.

ACKNOWLEDGMENT

This study was financially supported by the Student Research Committee of Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran (Grant No.: 94s58).

REFERENCES

1. Azhari H, Weiss JL, Rogers WJ, Siu CO, Zerhouni EA, Shapiro EP. Noninvasive quantification of principal strains in normal canine hearts using tagged MRI images in 3-D. Am J Physiol 1993;264:H205-16.
2. Mankoff DA. A definition of molecular imaging. J Nucl Med 2007;48:18N, 21N.
3. Caravan P, Ellison JJ, McMurry TJ, Lauffer RB. Gadolinium(III) chelates as MRI contrast agents: Structure, dynamics, and applications. Chem Rev 1999;99:2293-352.
4. Caravan P. Strategies for increasing the sensitivity of gadolinium based MRI contrast agents. Chem Soc Rev 2006;35:512-23.
5. Bottomley PA, Hardy CJ, Argersinger RE, Allen-Moore G. A review of 1H nuclear magnetic resonance relaxation in pathology: Are T1 and T2

diagnostic? Med Phys 1987;14:1-37.
6. Shellock FG, Kanal E. Safety of magnetic resonance imaging contrast agents. J Magn Reson Imaging 1999;10:477-84.
7. Caravan P, Farrar CT, Frullano L, Uppal R. Influence of molecular parameters and increasing magnetic field strength on relaxivity of gadolinium - and manganese-based T1 contrast agents. Contrast Media Mol Imaging 2009;4:89-100.
8. Cyrus T, Winter PM, Caruthers SD, Wickline SA, Lanza GM. Magnetic resonance nanoparticles for cardiovascular molecular imaging and therapy. Expert Rev Cardiovasc Ther 2005;3:705-15.
9. Ali Y, Zohre R, Mostafa J, Samaneh R. Applications of upconversion nanoparticles in molecular imaging: A review of recent advances and future opportunities. Biosci Biotechnol Res Asia 2015;12:131-40.
10. Yadollahpour A. Magnetic nanoparticles in medicine: A review of synthesis methods and important characteristics. Oriental J Chem 2015;31:271-7.
11. Yadollahpour A, Rashidi S. Magnetic nanoparticles: A review of chemical and physical characteristics important in medical applications. Oriental J Chem 2015;31:25-30.
12. Walia S, Acharya A. Silica micro/nanospheres for theranostics: From bimodal MRI and fluorescent imaging probes to cancer therapy. Beilstein J Nanotechnol 2015;6:546-58.
13. Bulte JW, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed 2004;17:484-99.
14. Smirnov P, Lavergne E, Gazeau F, Lewin M, Boissonnas A, Doan BT, *et al. In vivo* cellular imaging of lymphocyte trafficking by MRI: A tumor model approach to cell-based anticancer therapy. Magn Reson Med 2006;56:498-508.
15. Billotey C, Aspord C, Beuf O, Piaggio E, Gazeau F, Janier MF, *et al.* T-cell homing to the pancreas in autoimmune mouse models of diabetes: *In vivo* MR imaging. Radiology 2005;236:579-87.
16. Hao R, Xing R, Xu Z, Hou Y, Gao S, Sun S. Synthesis, functionalization, and biomedical applications of multifunctional magnetic nanoparticles. Adv Mater 2010;22:2729-42.
17. Yadollahpour A, Hosseini SA, Jalilifar M, Rashidi S, Rai BM. Magnetic nanoparticle-based drug and gene delivery: A review of recent advances and clinical applications. Int J Pharm Technol 2016;8:11451-66.
18. Yadollahpour A, Jalilifar M, Rashidi S. A review of the feasibility and clinical applications of magnetic nanoparticles as contrast agents in magnetic resonance imaging. Int J Pharm Technol 2016;8:14737-48.
19. Yadollahpour A, Venkateshwarlu G. Applications of gadolinium nanoparticles in magnetic resonance imaging: A review on recent advances in clinical imaging. Int J Pharm Technol 2016;8:11379-93.
20. Terreno E, Castelli DD, Viale A, Aime S. Challenges for molecular magnetic resonance imaging. Chem Rev 2010;110:3019-42.
21. Louie A. Multimodality imaging probes: Design and challenges. Chem Rev 2010;110:3146-95.
22. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, *et al.* Magnetic iron oxide nanoparticles: Synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem Rev 2008;108:2064-110.
23. Schladt TD, Schneider K, Schild H, Tremel W. Synthesis and bio-functionalization of magnetic nanoparticles for medical diagnosis and treatment. Dalton Trans 2011;40:6315-43.
24. Xie J, Chen K, Lee HY, Xu C, Hsu AR, Peng S, *et al.* Ultrasmall c(RGDyK)-coated Fe3O4 nanoparticles and their specific targeting to integrin alpha(v)beta3-rich tumor cells. J Am Chem Soc 2008;130:7542-3.
25. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, *et al.* Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003;348:2491-9.
26. de Vries IJ, Lesterhuis WJ, Barentsz JO, Verdijk P, van Krieken JH, Boerman OC, *et al.* Magnetic resonance tracking of dendritic cells in melanoma patients for monitoring of cellular therapy. Nat Biotechnol 2005;23:1407-13.
27. Lee JH, Huh YM, Jun YW, Seo JW, Jang JT, Song HT, *et al.* Artificially engineered magnetic nanoparticles for ultra-sensitive molecular imaging. Nat Med 2007;13:95-9.
28. Nitin N, LaConte LE, Zurkiya O, Hu X, Bao G. Functionalization and peptide-based delivery of magnetic nanoparticles as an intracellular MRI contrast agent. J Biol Inorg Chem 2004;9:706-12.
29. Andreas K, Georgieva R, Ladwig M, Mueller S, Notter M, Sittinger M, *et al.* Highly efficient magnetic stem cell labeling with citrate-coated superparamagnetic iron oxide nanoparticles for MRI tracking. Biomaterials 2012;33:4515-25.
30. Cha EJ, Jang ES, Sun IC, Lee IJ, Ko JH, Kim YI, *et al.* Development of MRI/NIRF 'activatable' multimodal imaging probe based on iron oxide nanoparticles. J Control Release 2011;155:152-8.
31. Hu F, Jia Q, Li Y, Gao M. Facile synthesis of ultrasmall PEGylated iron oxide nanoparticles for dual-contrast T1- and T2-weighted magnetic resonance imaging. Nanotechnology 2011;22:245604.
32. Xie H, Zhu Y, Jiang W, Zhou Q, Yang H, Gu N, *et al.* Lactoferrin-conjugated superparamagnetic iron oxide nanoparticles as a specific MRI contrast agent for detection of brain glioma *in vivo*. Biomaterials 2011;32:495-502.
33. Yang H, Zhuang Y, Sun Y, Dai A, Shi X, Wu D, *et al.* Targeted dual-contrast T1- and T2-weighted magnetic resonance imaging of tumors using multifunctional gadolinium-labeled superparamagnetic iron oxide nanoparticles. Biomaterials 2011;32:4584-93.

34. Brasch RC. Work in progress: Methods of contrast enhancement for NMR imaging and potential applications. A subject review. Radiology 1983;147:781-8.
35. Brasch RC. 6.5 Contrast-Enhanced NMR Imaging: Animal Studies Using Gadolinium-DTPA Complex. Classic Papers in Modern Diagnostic Radiology; 2005. p. 423.
36. Alric C, Taleb J, Le Duc G, Mandon C, Billotey C, Le Meur-Herland A, *et al.* Gadolinium chelate coated gold nanoparticles as contrast agents for both X-ray computed tomography and magnetic resonance imaging. J Am Chem Soc 2008;130:5908-15.
37. Liu Y, Chen Z, Liu C, Yu D, Lu Z, Zhang N. Gadolinium-loaded polymeric nanoparticles modified with Anti-VEGF as multifunctional MRI contrast agents for the diagnosis of liver cancer. Biomaterials 2011;32:5167-76.
38. Park JA, Kim HK, Kim JH, Jeong SW, Jung JC, Lee GH, *et al.* Gold nanoparticles functionalized by gadolinium-DTPA conjugate of cysteine as a multimodal bioimaging agent. Bioorg Med Chem Lett 2010;20:2287-91.
39. Lansman JB. Blockade of current through single calcium channels by trivalent lanthanide cations. Effect of ionic radius on the rates of ion entry and exit. J Gen Physiol 1990;95:679-96.
40. Biagi BA, Enyeart JJ. Gadolinium blocks low - and high-threshold calcium currents in pituitary cells. Am J Physiol 1990;259:C515-20.
41. Faucher L, Tremblay M, Lagueux J, Gossuin Y, Fortin MA. Rapid synthesis of PEGylated ultrasmall gadolinium oxide nanoparticles for cell labeling and tracking with MRI. ACS Appl Mater Interfaces 2012;4:4506-15.
42. Xu W, Park JY, Kattel K, Ahmad MW, Bony BA, Heo WC, *et al*. Fluorescein-polyethyleneimine coated gadolinium oxide nanoparticles as T 1 magnetic resonance imaging (MRI)–cell labeling (CL) dual agents. RSC Adv 2012;2:10907-15.
43. Zhang B, Jin H, Li Y, Chen B, Liu S, Shi D. Bioinspired synthesis of gadolinium-based hybrid nanoparticles as MRI blood pool contrast agents with high relaxivity. J Mater Chem 2012;22:14494-501.
44. Zhang HW, Wang LQ, Xiang QF, Zhong Q, Chen LM, Xu CX, *et al.* Specific lipase-responsive polymer-coated gadolinium nanoparticles for MR imaging of early acute pancreatitis. Biomaterials 2014;35:356-67.
45. Laurent S, Elst LV, Copoix F, Muller RN. Stability of MRI paramagnetic contrast media: A proton relaxometric protocol for transmetallation assessment. Invest Radiol 2001;36:115-22.
46. Greenberg SA. Zinc transmetallation and gadolinium retention after MR imaging: Case report. Radiology 2010;257:670-3.
47. Chen Q, Li K, Wen S, Liu H, Peng C, Cai H, *et al.* Targeted CT/MR dual mode imaging of tumors using multifunctional dendrimer-entrapped gold nanoparticles. Biomaterials 2013;34:5200-9.
48. Wen S, Li K, Cai H, Chen Q, Shen M, Huang Y, *et al.* Multifunctional dendrimer-entrapped gold nanoparticles for dual mode CT/MR imaging applications. Biomaterials 2013;34:1570-80.
49. Im GH, Kim SM, Lee DG, Lee WJ, Lee JH, Lee IS. Fe(3)O(4)/MnO hybrid nanocrystals as a dual contrast agent for both T(1)- and T(2)-weighted liver MRI. Biomaterials 2013;34:2069-76.
50. Chou SW, Shau YH, Wu PC, Yang YS, Shieh DB, Chen CC. *In vitro* and *in vivo* studies of FePt nanoparticles for dual modal CT/MRI molecular imaging. J Am Chem Soc 2010;132:13270-8.
51. Lu J, Ma S, Sun J, Xia C, Liu C, Wang Z, *et al.* Manganese ferrite nanoparticle micellar nanocomposites as MRI contrast agent for liver imaging. Biomaterials 2009;30:2919-28.

Source of Support: This study was financially supported by Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (No.:94S58).
Conflict of Interest: Nil.