REVIEW ARTICLE

Oman Medical Journal [2017], Vol. 32, No. 4: 269-274

Using Nanoparticles in Medicine for Liver Cancer Imaging

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ARTICLE INFO

Article history:
Received: 17 June 2017
Accepted: 24 Ocotber 2017

Online:
DOI 10.5001/omj.2017.54

Keywords:
Computed X-ray Tomography; Hepatocellular Carcinoma; Nanoparticles; Magnetic Nanoparticles.

ABSTRACT

One of the most important types of liver cancer is hepatocellular carcinoma (HCC). HCC is the fifth most common cancer, and its correct diagnosis is very important. For the quick diagnosis of HCC, the use of nanoparticles is helpful. The major applications of nanoparticles are in medicine for organ imaging. Two methods of liver imaging are X-ray computed tomography (CT) and magnetic resonance imaging (MRI). In this review, we attempt to summarize some of the contrast agents used in imaging such as superparamagnetic iron oxide nanoparticles (SPIONs) and iron oxide nanoparticles (IONPs), various types of enhanced MRI for the liver, and nanoparticles like gold (AuNPs), which is used to develop novel CT imaging agents.

Hepatocellular carcinoma (HCC) is the fifth most common cancer universally and the third most common cause of cancer mortality.[1] Therefore, a quick diagnosis is important. The liver is the organ most complex in metastases because of its blood volume, the appropriate size of sinusoids for enticement cells, and healthy environment for fast development.[2] For the early diagnosis of the liver cancer, the use of nanoparticles is the best method. Studies of contrast-enhanced computed tomography (CT) have also shown the capability to identify the scope of hepatic fibrosis and liver disease using various nanoparticles.[3] Nanoparticles have been evaluated for use in liver imaging due to their higher uptake by Kuepfer cells than by other cell types.[4,5]

The technology that deals with small matter is called nanotechnology.[6] The size range of nanoparticles is 1–100 nm. The use of nanoparticles has many benefits including enhanced penetrance into the cell, cell survival, and use in diagnostics and therapeutics.[7-11] However, the transfer of nanoparticle to target tumors has been restricted by fast clearance of the nanoparticles by the reticuloendothelial system.[12] The major applications of nanoparticle in medicine are toward imaging such as using contrast enhancement of magnetic resonance imaging (MRI) and CT. X-ray CT is a useful method of imaging for research and clinical purposes. CT merges high-resolution, three-dimensional data with fast utilization to obtain a solid platform for non-invasive human or specimen imaging.[12] Various investigators have studied the use of CT for the diagnosis of hepatic disease.[13,14] X-ray and CT imaging have attracted much attention in diagnosis and therapy due to increasing rates of liver metastases and various cancers.[14,15] X-ray contrast agents are injectable or ingestible compositions. Most agents combine atoms (like iodine, gold, or barium) due to their capability to absorb X-rays and convey contrast to a given organ system. Recently, the maximum attention is toward gold nanoparticles (AuNPs) as novel CT imaging agents have heavy weights and create greater contrast agents than the conventional iodine agents (gold: 5.16 cm^2g_1; iodine: 1.94 cm^2g_1 at 100 KeV).[15,16] Micro-CT has been also used to image liver tumors in mice using the specific contrast agent.[16]

MRI is a powerful instrument for diagnosis, which obtains noninvasive, three-dimensional imaging for living organisms.[17] Liver MRI is a common method in the diagnosis and follow-up therapeutics of patients with hepatocellular diseases such as HCC.[18] The basic mechanism of MRI is the excitation and relaxation of hydrogen nuclei. Relaxation times (intrinsic longitudinal (T1) and transverse (T2)) mark changes in MRI signal intensity.[19] Nanoparticles encapsulating contrast agents could have various effects on the future of MRI for the earliest diagnosis of tumors. Many types of nanoparticles have been utilized as MRI contrast agents such as super magnetic nanoparticles.[20]

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The superparamagnetic iron oxide nanoparticle (SPION) and the super magnetic iron oxide nanoparticle (IONP) are commonly used contrast agents for the liver. IONPs have been found useful at lower concentrations and can better serve as contrast enhancement agents for MRI.[21–24] SPIONs have demonstrated their utility as an effective tool for enhancing magnetic resonance contrast due to their superparamagnetic property. Larger nanoparticles are used for hepatic imaging. When these SPIONs are taken up by Kuepfer cells in malignancies, we can detect and compare between the healthy and the diseased tissues.[25–27]

In this paper, we summarize the growth in the use of SPION, IONP, and other types of enhanced MRI for the liver and the use of nanoparticles such as gold (AuNPs) in the development of novel CT imaging agents. We also compared the methods and nanoparticles used in CT imaging especially micro-CT and MRI. The purpose of this paper is to aid researchers in choosing the best nanoparticles for imaging of the liver cancer to facilitate the earliest diagnosis of cancer. All the studies given used animal models.

Nanoparticles

Nanotechnology uses the particles 1–100 nm in size.[6–11] This modern technology has opened a new area in cancer imaging and medicine and is a useful method to diagnose tumors rapidly. Some nanoparticles are helpful when used for MRI or CT imaging to better diagnose liver malignancies. The early diagnosis of HCC is important for effective therapy.[6]

SPIO as a contrast agent in MRI

The core of SPIONs include magnetite (γ-Fe_2O_3) and maghemite (Fe_3O_4).[28] The small particle size SPIONs are used as ingestible contrast agents, and the large ones are applied in cell tracking and as contrast agents for the gastrointestinal tract. SPIONs range in size from 300 nm (oral SPION) to 30 nm (monocrystalline iron oxide nanoparticles (MIONs)).[28]

In many of ferromagnetic materials, the unpaired electron spins have aligned. The range of the two dominants of these materials is called the Bloch wall, and it is formed by a single crystal in the superparamagnetic state.[29,30]

The SPIONs align in the magnetic field they change the direction of the protein and that of the MRI signal.

SPIONs also reduce the spin–spin relaxation (T2) time for the best contrast.[29,30] SPIONs are used for spleen, liver, and lymph node imaging as MRI contrast agents. SPIONs are useful contrast agents in MRI due to their high transverse relativity, and ability to rapidly detect some pathologies. Arsalani et al,[19] performed a study of polyglycerol bound to the surface of SPION and found that it could be used as a useful contrast agent in MRI. Classes of different type of SPION.

There are two types of superparamagnetic nanoparticles defined by the size: SPION with the diameter of more than 50 nm and the ultra small SPION (USPION), which have a smaller size.[31] Some USPIONs have the same composition as the SPION but a smaller size and diameter. The nanoparticles with large size are faster than nanoparticles with small size.

SPION and USPION can uptake in many cell types. However, due to the small size of USPIONs, they are less available in the liver. Another important factor is the half-life of these particles, which is different in animals and humans. The half-life of USPION in animal blood is three- to 10-times lower than in humans. The half-life in animals depends on the size of the species and increases with the size. SPION is known as a negative contrast agent, but USPION is a positive contrast agent because of its very short T2 relaxation time, basic T1-weighted acquisition, and dephasing gradient effect on slice axis.[31]

IONPs between 8–30 nm functionalized and coated with various surface polymers and bear IONPs have been used to investigate the signal changes.[32] Oghabian et al,[32] studied the detection of USPION using a liver phantom and performed on the rat with the 1.5T MRI (GESigna) system. After anesthesia of the rat in the MRI system, a high sensitive protocol was performed, and the USPION was injected into the rat tissue. The signal intensity was investigated, and the lymphatic system of the rat was also assessed. Detection sensitivity of nearly 98% was achieved.[31,32] However, in some protocols, even a small change from the optimum imaging parameters caused an unexpected change of the signal. In this situation, diagnosis might be misunderstood between the tissues with normal USPION uptake and free USPION uptake. However, the type of coating surface, the characteristics of coating such as thickness were important factors for MRI signal

intensity in both T1 and T2 protocols. Based on the effect of monoclonal antibody conjugated IONPs on signal intensity changes, the USPION was recommended as a contrast agent MRI studies for tumor-specific imaging.[32]

Combination of SPIO with quantum dots

A simple extraction method is the combination of nanoparticles with quantum dots (QD). Hybrid nanoparticles luminesce at the same wavelength as the parent QD, and include biocompatible sliver sulfide quantum dots (Ag_2SQD). When this QD bind with SPIO, the simple complex is produced. This complex is used in multimode imaging and magnetic targeting.[33] Ag_2SQDs have been stimulated with visible light, and they are also emitted at the near-infrared region. This combination has many advantages such as stimulation in the visible region, enhancement of depth of penetration, decreased or no absorbency of emitted photons by SPIONs, optical resistance, and a potent luminescence and response to magnetic field. Hocaoglu et al,[34] suggested that this method had major potential as new theranostic nanoparticles. But, they only studied in-vitro imaging and did not compare it with animal cell toxicity assays. They mentioned in their paper that in animal cells the blood reaction was more sensitive.[33] However, there are few reports where this complex sample (Ag_2S and SPION) was reported as hemocompatible.[33–35]

Each imaging modality (e.g., MRI, optical, and nuclear) has its limitations. The image taken for one biomarker should also be accompanied with contrast agents such as QD.[36,37] Using SPION probes for molecular imaging could reduce costs and avoid cellular sequestration, and is also an effective probe and contrast agent for this method.[37]

Different types of IONPs and Feridex

There are four types of IONPs. SHP is a group of water soluble IONPs with amphiphilic polymer coating. Their reactive group is carboxylic acid and they range in size from 10 nm (SHP-10) to 30 nm (SHP-30). Bu et al,[18] used synthesized IONPs with different core diameters (10 and 30 nm) by pyrolysis and subsequently coated these with a copolymer containing either carboxyl (SHP) or methoxy groups (SMG) as termini. They compared their four synthesized nanoparticles to in-vivo Feridex I.V. to determine their suitability for use as liver contrast agents. SHP-30 outperformed Feridex suggesting that the SHP-30 could be an effective alternative to Feridex for liver imaging as an contrast agent intravenously.[18]

Nanoparticles as contrast agent in micro CT imaging

Some nanoparticles are used in micro-CT. For example, gold nanoparticles (AuNPs) for specific CT imaging of the liver, and iodinated contrast agents. However, commonly available iodinated contrast agents are not appropriate for multicolor CT because of their low k-edge absorption energy profile. There are also two nanoparticle-based non-iodinated contrast agents ExiTron Nano 6000 and ExiTron Nano 12000 which accumulate in the liver (due to gradual clearance) and provides long-term X-ray contrast.[38]

Many nanoparticles such as gold and alkaline earth (e.g., ExiTron™) for CT imaging of some organs have been used, but we have only reviewed cases of liver imaging.[39] Kuepfer macrophages take up ExiTron™ two minutes after injection. Novel CT contrast agents are biocompatible with higher weight atoms such as gold, tantalum, and bismuth. The use of lanthanides could overcome the limitation of detecting different materials with single imaging and heparin-covered gold particles.[14]

Gold nanoparticles

Synthesis of gold nanoparticles using *Candida albicans* cytosolic extract has been demonstrated.[40] Synthesized gold nanoparticles are used in spectroscopy, transmission electron microscopy, microscopy of atomic force, and micro-CT.[40]

Studies of nanoparticle bioconjugation have been reported, including synthesis of gold nanoparticles directly conjugated with bovine serum albumin. The unique optical and electronic properties of gold nanoparticles make them ideal candidates for cell targeting and also as efficient tools for bioassays.[40,41] These gold nanoparticles could then differentiate between healthy and cancerous cells by specifically binding to the surface antigens of the cancer cells. Gold nanoparticles could be developed to target cancers and hormones.[40,41] Comparing the non-iodinated agent with the iodinated.

Wathen et al,[39] compared two non-iodinated contrast agents, ExiTron Nano 6000 and ExiTron Nano 12000, with the iodinated agent eXIA T160

Table 1: Summary of some types of nanoparticles available for liver imaging.

Nanoparticles	Size	Properties	Application	Other
SPION	> 50 nm	- High transverse relaxation - Rapid detection of some pathogens	Liver and spleen imaging at MRI, hyperthermia, cell labeling	Negative contrast agent
USPIO	< 50 nm	- Short T2 time - Less uptake in liver than SPIO	MRI of liver	Positive contrast agent
SPIO+ QD(Ag_2S)		- Noninvasive - Great luminescence - Good response to magnetic field - Correct diagnosis and anatomical information - SPIO is effective probe as contrast agent	Molecular imaging	Mixed procedures
IONPs	10–30 nm	Large size = high r^2 = effective agent	MRI of liver	There are 4 type and SHP-30 is good contrast agent
AuNPs	Smaller or larger than 25 nm (almost 99 nm)	- Unique optical and electronic property - Effective device - Cost-effective - Greater contrast agent for imaging	For diagnosis of different cancers, liver imaging with micro-CT, CT imaging, spectroscopy	Negative contrast agent
Iodinated-based (exiA-160)	55–100 nm	- Common accessible - Low energy of k-edge - Not good formulation	Micro CT imaging	-
Non-iodinated (alkaline earth, ExiTron-6000, ExiTron-12000)	-	- Low clearance - Long-term contrast - Biocompatible	Micro CT imaging	- ExiTron-12000 is the highest contrast enhancement

SPION: superparamagnetic iron oxide nanoparticle; USPIO: ultra small superparamagnetic iron oxide; QD: quantum dots; IONs: iron oxide nanoparticles; AuNPs: gold nanoparticles; MRI: magnetic resonance imaging; CT: computed tomography.

(55–100 nm). The authors evaluated the contrast agents for imaging lesions of the liver in mice with HCC. There was no uptake of the contrast agents by the HCC lesions. Nano 12000 demonstrated the greatest liver-to-tumor contrast. The novel nanoparticle-based ExiTron Nano 12000 obtained the highest contrast enhancement in the normal liver and the foremost contrast in HCC mice.[42] There were no contrast between HCC lesions and normal liver parenchyma in native CT.[39]

Recent research has focused on nanoparticles such as gold as contrast enhancing agents. They also use nano contrast agent in CT to better diagnose liver lesions as a negative contrast agent, and in many imaging planes (coronal, sagittal, and transverse axial).[39] The various types of nanoparticles are reviewed in Table 1.

Comparing of dual methods as contrast agent in MRI and CT imaging

Pandit et al,[43] compared preclinical MRI and micro-CT to determine the best method for following metastatic liver diseases using a liposomal blood stream agent. After injection of nanoparticles into mice, the contrast to noise ratio (CNR) was calculated using the equation:[43]

$$CNR = \left(\frac{SI_{liver} - SI_{tumor}}{\sigma noise} \right)$$

The results of their studies showed that two methods had a lower augmentation at later time points and that the CNR in the T2-weighted MRI was more contrast-enhanced than those of CT images.

Micro-CT allowed faster utilization (< 10 minutes) with the biggest spatial resolution (88-micron isotropic resolution). MRI was slower (30 minutes), but its use decreased the requirement for a contrast agent. The contrast-to-noise between the tumor and the normal parenchyma became high.[43] On the other hand, in-liver metastasis of colon carcinoma showed that the contrast enhancement of micro-CT imaging obtained a better resolution than MRI. In MRI, however, the augmentation of the signal-to-

noise ratio could identify the small lesions sooner.[43] MRI was more appropriate for longitudinal studies.[43]

CONCLUSION

There are many nanoparticles used for liver imaging. The most practical nanoparticles used in MRI and micro-CT imaging are SPION, Au, ExiTron™ Nano. The value of SPIO in the liver and spleen has been recognized by the medical research community, particularly in liver imagine where more detail is needed for the best diagnosis. Other agents used in micro-CT imaging can better define the anatomy of organs. The use of nanoparticles in MRI requires a higher level of technical expertise to operate the instruments compared to X-ray CT, which will form a barrier to some researchers who wish to use the technique. However, new developments in MRI systems aide to decrease the technical obstacles using the equipment for many applications.[44] According to some studies, the use of nanoparticles could help to identify the liver abnormalities. It is expected that combination of molecular imaging and multiple modalities with nanoparticles will help to detect diseases such as liver cancer and other liver malignancy. This review only looked at animal studies.

Al Sukaiti et al,[45] performed studies on humans using CT, which they declared helpful for the diagnosis of liver malignancies.It is noteworthy that using of this nanoparticles for animal study is expensive, the author did not have any experience working with nanoparticles for liver cancer imaging.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

Acknowledgements

The authors are grateful to Mr. Hassan Farokhi Moghadam for his help with this paper.

REFERENCES

1. Mickler FM, Möckl L, Ruthardt N, Ogris M, Wagner E, Bräuchle C. Tuning nanoparticle uptake: live-cell imaging reveals two distinct endocytosis mechanisms mediated by natural and artificial EGFR targeting ligand. Nano Lett 2012 Jul;12(7):3417-3423.
2. Robinson PJ. Imaging liver metastases: current limitations and future prospects. Br J Radiol 2000 Mar;73(867):234-241.
3. Varenika V, Fu Y, Maher JJ, Gao D, Kakar S, Cabarrus MC, et al. Hepatic fibrosis: evaluation with semiquantitative contrast-enhanced CT. Radiology 2013 Jan;266(1):151-158.
4. Poeckler-Schoeniger C, Koepke J, Gueckel F, Sturm J, Georgi M. MRI with superparamagnetic iron oxide: efficacy in the detection and characterization of focal hepatic lesions. Magn Reson Imaging 1999 Apr;17(3):383-392.
5. Ward J, Guthrie JA, Wilson D, Arnold P, Lodge JP, Toogood GJ, et al. Colorectal hepatic metastases: detection with SPIO-enhanced breath-hold MR imaging–comparison of optimized sequences. Radiology 2003 Sep;228(3):709-718.
6. Feynman RP. There's plenty of room at the bottom. Eng Sci 1960;23(5):22-36.
7. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat Rev Drug Discov 2008 Sep;7(9):771-782.
8. Desai N. Challenges in development of nanoparticle-based therapeutics. AAPS J 2012 Jun;14(2):282-295.
9. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. Nanomedicine (Lond) 2010 Jun;5(4):523-528.
10. Peng XH, Qian X, Mao H, Wang AY, Chen ZG, Nie S, et al. Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. Int J Nanomedicine 2008 Sep;3(3):311-321.
11. Sun C, Lee JS, Zhang M. Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliv Rev 2008 Aug;60(11):1252-1265.
12. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res 2008 Mar;14(5):1310-1316.
13. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol 2009 Sep;51(3):433-445.
14. Sun IC, Eun DK, Na JH, Lee S, Kim IJ, Youn IC, et al. Heparin-coated gold nanoparticles for liver-specific CT imaging. Chemistry 2009 Dec;15(48):13341-13347.
15. Ackerman NB, Lien WM, Kondi ES, Silverman NA. The blood supply of experimental liver metastases. I. The distribution of hepatic artery and portal vein blood to "small" and "large" tumors. Surgery 1969 Dec;66(6):1067-1072.
16. Weber SM, Peterson KA, Durkee B, Qi C, Longino M, Warner T, et al. Imaging of murine liver tumor using microCT with a hepatocyte-selective contrast agent: accuracy is dependent on adequate contrast enhancement. J Surg Res 2004 Jun;119(1):41-45.
17. Burtea C, Laurent S, Elst LV, Muller RN. Contrast Agents: Magnetic Resonance. In: Semmler W, Schwaiger M, editors. Molecular Imaging I: Handbook of Experimental Pharmacology. Heidelberg: Springer-Verlag Berlin; 2008. p. 135–165.
18. Bu L, Xie J, Chen K, Huang J, Aguilar ZP, Wang A, et al. Assessment and comparison of magnetic nanoparticles as MRI contrast agents in a rodent model of human hepatocellular carcinoma. Contrast Media Mol Imaging 2012 Jul-Aug;7(4):363-372.
19. Arsalani N, Fattahi H, Laurent S, Burtea C, Vander Elst L, Muller RN. Polyglycerol-grafted superparamagnetic iron oxide nanoparticles: highly efficient MRI contrast agent for liver and kidney imaging and potential scaffold for cellular and molecular imaging. Contrast Media Mol Imaging 2012 Mar-Apr;7(2):185-194.
20. Xie J, Huang J, Li X, Sun S, Chen X. Iron oxide nanoparticle platform for biomedical applications. Curr Med Chem 2009 Feb;16(10):1278-1294.
21. Cormode DP, Jarzyna PA, Mulder WJ, Fayad ZA. Modified natural nanoparticles as contrast agents for medical imaging. Adv Drug Deliv Rev 2010 Mar;62(3):329-338.
22. Fattahi H, Laurent S, Liu F, Arsalani N, Vander Elst L, Muller RN. Magnetoliposomes as multimodal contrast agents for molecular imaging and cancer nanotheragnostics. Nanomedicine (Lond) 2011 Apr;6(3):529-544.
23. Laurent S, Boutry S, Mahieu I, Vander Elst L, Muller RN. Iron oxide based MR contrast agents: from chemistry to cell

labeling. Curr Med Chem 2009;16(35):4712-4727.

24. Sun C, Du K, Fang C, Bhattarai N, Veiseh O, Kievit F, et al. PEG-mediated synthesis of highly dispersive multifunctional superparamagnetic nanoparticles: their physicochemical properties and function in vivo. ACS Nano 2010 Apr;4(4):2402-2410.
25. Reimer P, Jähnke N, Fiebich M, Schima W, Deckers F, Marx C, et al. Hepatic lesion detection and characterization: value of nonenhanced MR imaging, superparamagnetic iron oxide-enhanced MR imaging, and spiral CT-ROC analysis. Radiology 2000 Oct;217(1):152-158.
26. Shamsi K, Balzer T, Saini S, Ros PR, Nelson RC, Carter EC, et al. Superparamagnetic iron oxide particles (SH U 555 A): evaluation of efficacy in three doses for hepatic MR imaging. Radiology 1998 Feb;206(2):365-371.
27. Vogl TJ, Hammerstingl R, Schwarz W, Mack MG, Müller PK, Pegios W, et al. Superparamagnetic iron oxide–enhanced versus gadolinium-enhanced MR imaging for differential diagnosis of focal liver lesions. Radiology 1996 Mar;198(3):881-887.
28. 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 Jun;108(6):2064-2110.
29. Josephson L, Tung CH, Moore A, Weissleder R. High-efficiency intracellular magnetic labeling with novel superparamagnetic-Tat peptide conjugates. Bioconjug Chem 1999 Mar-Apr;10(2):186-191.
30. Kachra Z, Beaulieu E, Delbecchi L, Mousseau N, Berthelet F, Moumdjian R, et al. Expression of matrix metalloproteinases and their inhibitors in human brain tumors. Clin Exp Metastasis 1999 Jul;17(7):555-566.
31. Oh J, Feldman MD, Kim J, Condit C, Emelianov S, Milner TE. Detection of magnetic nanoparticles in tissue using magneto-motive ultrasound. Nanotechnology 2006 Aug;17(16):4183-4190.
32. Oghabian MA, Guiti M, Haddad P, Gharehaghaji N, Saber R, Alam NR, et al. Detection sensitivity of MRI using ultra-small super paramagnetic iron oxide nano-particles (USPIO) in biological tissues. Engineering in Medicine and Biology Society 2006. EMBS'06 28th Annual International Conference of the IEEE. p. 5625-5626.
33. Zhao H, Saatchi K, Häfeli UO. Preparation of biodegradable magnetic microspheres with poly (lactic acid)-coated magnetite. J Magn Magn Mater 2009 May;321(10):1356-1363.
34. Hocaoglu I, Demir F, Birer O, Kiraz A, Sevrin C, Grandfils C, et al. Emission tunable, cyto/hemocompatible, near-IR-emitting Ag2S quantum dots by aqueous decomposition of DMSA. Nanoscale 2014 Oct;6(20):11921-11931.
35. Cerda-Cristerna BI, Flores H, Pozos-Guillén A, Pérez E, Sevrin C, Grandfils C. Hemocompatibility assessment of poly(2-dimethylamino ethylmethacrylate) (PDMAEMA)-based polymers. J Control Release 2011 Aug;153(3):269-277.
36. LaConte LE, Nitin N, Zurkiya O, Caruntu D, O'Connor CJ, Hu X, et al. Coating thickness of magnetic iron oxide nanoparticles affects R2 relaxivity. J Magn Reson Imaging 2007 Dec;26(6):1634-1641.
37. Thorek DL, Chen AK, Czupryna J, Tsourkas A. Superparamagnetic iron oxide nanoparticle probes for molecular imaging. Ann Biomed Eng 2006 Jan;34(1):23-38.
38. Rothe JH, Rudolph I, Rohwer N, Kupitz D, Gregor-Mamoudou B, Derlin T, et al. Time course of contrast enhancement by micro-CT with dedicated contrast agents in normal mice and mice with hepatocellular carcinoma: comparison of one iodinated and two nanoparticle-based agents. Acad Radiol 2015 Feb;22(2):169-178.
39. Wathen CA, Foje N, van Avermaete T, Miramontes B, Chapaman SE, Sasser TA, et al. In vivo X-ray computed tomographic imaging of soft tissue with native, intravenous, or oral contrast. Sensors (Basel) 2013 May;13(6):6957-6980.
40. Chauhan A, Zubair S, Tufail S, Sherwani A, Sajid M, Raman SC, et al. Fungus-mediated biological synthesis of gold nanoparticles: potential in detection of liver cancer. Int J Nanomedicine 2011;6:2305-2319.
41. Yang L, Xing R, Shen Q, Jiang K, Ye F, Wang J, et al. Fabrication of protein-conjugated silver sulfide nanorods in the bovine serum albumin solution. J Phys Chem B 2006 Jun;110(21):10534-10539.
42. Yang L, Cao Z, Sajja HK, Mao H, Wang L, Geng H, et al. Development of receptor targeted magnetic iron oxide nanoparticles for efficient drug delivery and tumor imaging. J Biomed Nanotechnol 2008 Dec;4(4):439-449.
43. Pandit P, Johnston SM, Qi Y, Story J, Nelson R, Johnson GA. The utility of micro-CT and MRI in the assessment of longitudinal growth of liver metastases in a preclinical model of colon carcinoma. Acad Radiol 2013 Apr;20(4):430-439.
44. Schmid A, Schmitz J, Mannheim JG, Maier FC, Fuchs K, Wehrl HF, et al. Feasibility of sequential PET/MRI using a state-of-the-art small animal PET and a 1 T benchtop MRI. Mol Imaging Biol 2013 Apr;15(2):155-165.
45. Sukaiti RA, Robinson K, Menias C. Retrospective Review of Cross Sectional Imaging Findings of Pancreatic Non-functional Islet Cell Tumor (NFICT) and its Hepatic Metastases. Oman Med J 2011 Jan;26(1):39-42.