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A Survey on Nanocontrast Agents for Cancer Diagnosis from MRI

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Abstract - **Contrast agents show its important function in spotting diseases from Magnetic resonance imaging (MRI) images. This will demand the development of novel MRI contrast agents which improves the sensitivity of an image. Although several contrast agents have been proposed for enhancing MRI images, nano- based contrast agent improves the image quality and increases diagnosing accuracy. T1-weighted contrast agents have the ability to enhance the intensity of the low-signal tissues where as T2-weighted Contrast agents have the ability to enhance the intensity of the images in high-signal tissues. This paper gives the overview about the involvement of nano-contrast agents in MRI images for cancer detection.**

Keywords: MRI, contrast agents, gadolinium, nanoparticles and cancer detection.

I. INTRODUCTION

Contrast agents (CA) are indispensable in the practice of radiology. Significant improvements in their composition during the past few decades have made them safer and better tolerated, as evidenced by their use in vast numbers of examinations, often in severely ill patients. The contrast agents come in to a commercial use at the time of invention of X-Rays. The main aim of administration of contrast agent is to change the the absorption of x-rays. These CA may be positive or negative. Negative CA absorbs small amount of x-rays when compared to tissues due to its low density. Similarly positive CA absorbs large amount of x-rays compared to tissues due to their high density and higher atomic number [1]. Contrast media are chemical matter administered during imaging examinations such as X-ray, MRI, Computed Tomography (CT), etc.

A perfect contrast agent should have the properties like good visualization, low toxicity, persistence until imaging is completed, low cost, and minimal or no side effects and no residual effects within patients. Effect of nanocontrast agents on brain MRI is shown in figure 1. The key characteristics of contrast agents are, ability of agents to mix with body fluids, viscosity, and ionic strength, persistence in the body, iodine content, osmolarity (HOCA/LOCA) and potential for toxicity. During the administration of contrast media, the radiotherapists (RT) or radiologists should take care of some aspects.

1. Administered under the supervision of a radiologists
2. Patient assessment and history
3. Patient comfort and education
4. Recognize signs and symptoms of reaction and act appropriately
5. Patient care and surveillance
6. Post exam considerations for patient

Most commonly iodine based contrast are used for computed tomography (CT) imaging, gadolinium based contrast agents are used for MRI and lipid bubble contrast agents are used in ultrasound imaging. Iodine and Barium based CA are the most commonly used CA for radiography. There are more types of iodinated CA with varying osmolarity, viscosity. Also each iodinated CA has absolute iodine content [2]. In MRI, *Gd* is most widely used CA [3]. Generally lipid bubbles based contrast agents are used for ultrasound examinations.

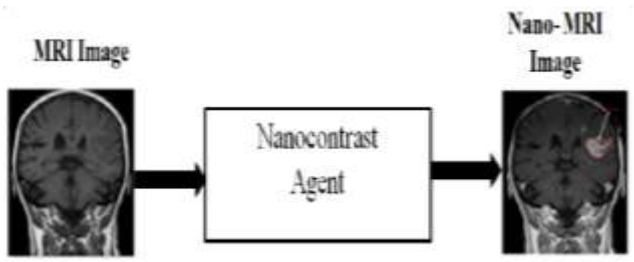

Figure 1: Effect on nanocontrast agents on brain MRI

II. NANOCONTRAST AGENTS FOR DETECTING CANCER FROM MRI IMAGES

MRI is a noninvasive technique and it has lot of advantages when compared with other imaging techniques. It also provides high resolution and contrast on soft tissues [4, 5]. MRI can be classified into two types such as T1-weighted imaging (longitudinal relaxation time) and T2-weighted imaging (transverse relaxation time) as shown in Fig.2. The main issue of MRI is its low sensitivity. Contrast agent will address this issue and improves the sensitivity and specificity.

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Contrast agents play a major role in MRI in order to differentiate tumor from normal healthy tissues during cancer/tumor diagnosis which further improves the efficacy of the treatment. A list of FDA (Food and Drug Administration) approved gadolinium based MRI contrast agents are given in table1. Currently, most of the MRI scans uses magnetic metal ions based contrast agents that will increases the intensity of signals [4, 6].

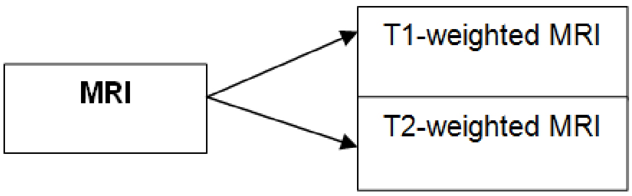

Figure 2: Types of MRI

a) T1-weighted MRI contrast agents

For the most part, T1-weighted MRI contrast agents (T1 contrast agent) are gadolinium based and manganese based (*Gd*3+ or Mn2+) due to the reduced serious side effects [6-8]. The strength of this gadolinium can be increased by adding some chemotherapeutic agents. Gadolinium ethoxy benzyl diethylene triamine penta acetic acid (*Gd*-EOBDTPA) [9] is a type of the mixing which is used to detect small hepatic metastases. This *Gd*-EOB-DTPA enhanced MRI showed higher accuracy than diffusion weighted MRI. Labeling the cell is the step towards the development of CA for cell tracking. In [10] the glioblastoma multiforme cells are labeled using ultra small gadolinium oxides [10] which are followed by the localization. This causes high amounts of *Gd* retainment in cells and those labeled cells were visualized using 1.5 Tesla. This labeling procedure allowed the clear visualization of signal-enhanced cancer cells in a vascularized model in vivo, using high-resolution T1-weighted MR imaging. Generally, the antibody modified nanoparticles proved higher uptake of cells when compared to non-targeted NPs. To use manganese as a T1 relaxation agent for enhancing contrast of MRI is a different approach. In general, Coating of nanoparticles can significantly improve their stability, biocompatibility, and relaxivity. Mesoporous silica-coated hollow manganese oxide (HMnO @ mSiO2) nanoparticles [11] is a novel T1 magnetic resonance imaging (MRI) contrast agent. These novel nanoparticles can provides a positive contrast on T1-weighted images at high magnetic field strengths.

TABLE 1
FDA approved *Gd* based MRI contrast agents

Contrast Agents	Approved year
Magnevist	1988
Prohance	1992
Omniscan	1993
Optimark	1999
Multihance	2004
Eovist	2008
Ablavar	2008
Gadavist	2011

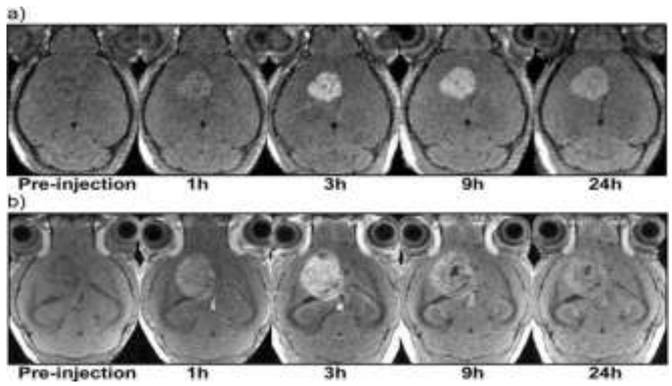

Figure 3: a) T1-weighted MRI of breast cancer cells with the functionalized MnO nanoparticles b) T1- weighted MRI with the non functionalized MnO nanoparticles

It showed a high cellular uptake by adipose-derived MSCs, using electroporation, and was detected with MRI both in vitro and intracranially in vivo over a prolonged time period. Manganese oxide (MnO) is a usable form of T1 weighted MRI contrast agent which provides fine anatomical structure of internal regions. The clear T1-weighted MR images of the brain, liver, kidney, and spinal cord can be obtained through the administration of MnO nanoparticles [12]. Functionalized MnO nanoparticles prepared by conjugation with a tumor-specific antibody can also be used for selectively imaging breast cancer cells in the metastatic brain tumor which can be shown in figure 3. This figure clearly shows that the visualization tumor in MRI after the administration contrast agent is clear compared with pre injection MRI images.

b) T2-weighted MRI contrast agents

T2 MRI contrast agents are a type of negative contrast agent which decreases the intensity and can be used when

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there is a need of reduction in intensity for better visualization of diseases.

Super paramagnetic nanoparticles based contrast agents with different coating layers are often used as T2- weighted MRI contrast agent (T2 contrast agent) [12]. These super paramagnetic iron oxides can be prepared by different methods. Super paramagnetic iron oxides can provide a high relaxivity with a typical r2value of 100 mM−1s−1 and r1 value of 30 mM−1s−1, together with a prolonged contrast enhancement [13-15]. Gold coated nanoparticles are the new era of MRI contrast agent. Keshtkar M.et.al., [16] synthesized a gold-coated iron oxide nanoparticles. Transmission electron microscopy (TEM) study was performed for characterizing the size and structure of the nanoparticles. Spectroscopic properties of the nanoparticles were analyzed using X-ray diffractometry (XRD) and UV-Visible spectrophotometer.

III. FDA ABOUT *Gd* BASED CONTRAST AGENTS

Gadolinium-based contrast agents (GBCAs) are a type) drugs used for enhancing the contrast of MRI. These agents are a rare earth metals which is applied through an IV (intravenous) in the arm [17]. Food and Drug Administration (FDA) suggested that small amounts of GBCAs may be deposited in certain brain areas. This conveys that these types of contrast agents was not entirely removed from the body.

IV. SAFETY, RELAXIVITY AND TUMOR-SPECIFICITY OF CONTRAST AGENTS

Safety is the first and foremost major factor for the usage of contrast agents in clinical applications. The direct administration of *Gd* (III) ions into the subject is not recommended by FDA as these ions are highly toxic in nature. So *Gd* (III) should be acutely interfered with calcium and protein bindings. These *Gd* (III) ions can be conjugated with the ligands to avoid acute interaction with tissues and to reduce the toxicity. Sometimes the usage of this type of contrast agents cause severe adverse effect called nephrogenic systemic fibrosis (NSF) to the small percentage of patients with the renal infections. The FDA issued a warning to forbid the exploit of such contrast agent in the patients with renal infections. This type of agents should be excreted form the patients with in an hours of administration.

The contrast agent's relaxivity defines its capability in altering the water proton relaxation rates. The attainment of high relaxivity in a contrast agent is difficult. In general *Gd* based contrast agents will increase T1 relaxation rates and T2 relaxation rates. The relaxivity can be measured in a unit of $mM^{-1}S^{-1}$ which can be represented by the equation

$$\left(\frac{1}{T_{1,2}}\right)_{obs} = \left(\frac{1}{T_{1,2}}\right)_{d} + r_{1,2}[Gd\ ]$$

Where $\left(\frac{1}{T_{1,2}}\right)_{obs}$ - The observed water proton relaxation rate,

And $\left(\frac{1}{T_{1,2}}\right)_{d}$ - Relaxation rate without a contrast agent.

The delivery of contrast agents into the targeted tumor tissue is crucial task. The physical appearance of timorous tissue is different from the normal tissues. Thus the accumulation of nano sized contrast agent in tumor is easier. These tumor tissues also have numerous cancer biomarkers in a cell surface. Thus the contrast agents can easily enhance the contrast of such tumors.

V. DISCUSSION

In the most of the literatures discussed in this paper, majority of the authors used *Gd* based contrast agents for T1 weighted MRI and Super Paramagnetic Iron Oxide (SPIO) based contrast agents for T2 weighted MRI. Even though this *Gd* based contrast agents is most widely used in MRI applications, its administration is restricted in the patients with renal infections. It is the major drawback of such agents. At this situation the place of *Gd* is replaced with Manganese oxide based contrast agents in T1 MRI. This manganese has good electronic configuration and improved biochemical features. As the altering property of SPIOs is superior, it is more useful than *Gd* (Gadolinium). This type of agent is used in T2 MRI. They can also be used in lower concentrations, which is the main advantage over *Gd* based agents. They also have low toxicity profiles, have long blood retention times and are biodegradable. The toxicity of the MRI contrast agents can be limited by conjugating these agents with any other ligands. Also the coating helps the agents to reduce the toxicity. From this study, it is noted that almost all of the nano contrast agents are investigated in animal model. Yet up to date the clinical applications of such contrast agents are limited. One of the major reasons behind this limitation is time consumption required for clinical trials and its associated costs. Also the specificity of such agents has to be improved for the usage in clinical applications.

VI. CONCLUSION

From this critical review on contrast agents, it may be noted that gadolinium based contrast agents (GBCAs) are used for enhancing the contrast of T1-weighted MRI. It is reported that, for each year approximately 10 million MRI studies were done using GBCAs. Specifically *Gd*-DTPA and *Gd*-DOTA

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are the most widely used T1- MRI contrast agents. Even though they utilized frequently, these types of contrast agent yields to poor sensitivity and require hasty renal clearance. So, the incorporation of *Gd* onto nanoparticles can reduce the toxicity and enhancing the T1-weighted MR signals. In addition to this the conjugation of antibodies to nanoparticles can generate a product that combines the properties of both nanoparticles and antibody. It is also noted that, in this elaborated review most of the T2 contrast agents are based on iron oxides. Through this review, we can conclude that the use of nanocontrast agent will improve the disease diagnosis as it enhances the internal structure of the diseases.

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