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Neogi, Newton
Nano Research Centre

Kristi Priya Choudhury
Nano Research Centre

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Utilization of Metal Based Nanoparticles in Biomedical Imaging Technologies

Newton Neogi[1]*, Kristi Priya Choudhury[1]
[1]Nano Research Centre, Bangladesh
*Corresponding author email: newtonneogi@gmail.com

Abstract: *In recent years, Nanoparticles (NPs) have gotten a lot of attention because of their multifunctionality, multivalency, and the capacity to carry payloads. Metal nano-particles (MNPs) are of current interest for their promising uses in biomedical imaging technologies for many diseases including cancer. The charge, shape, size, and hydrophilicity of MNPs are still critical for their successful distribution to their target sites in the human body. Imaging in the biomedical field are increasingly relying on nanomaterials (NMs) including nanoparticles, nanorods, and nanospheres. Metal oxide NPs (MONs) are extensively employed in functional imaging, treatment and synergistic combinational platforms. MRI, PET, CT, SPECT, and US imaging are the imaging methods in both clinical areas. There are many studies underway to improve the performance of imaging methods in complicated settings due to the necessity for reliable imaging of tiny biological targets. This review extensively discussed utilization of MONs in several bio imaging techniques.*

Keywords: Imaging; Metal-based system; Nanoparticles; Biomedical; CNT

1. INTRODUCTION

NPs have lately been proven to be effective in a variety of applications. Applications for metal oxide nanoparticles that are photocatalytic are currently being investigated [1][2]. These NPs can also be used for biological imaging. Recent breakthroughs in the production of many kinds of NPs clearly demonstrate the significance of NPs in biological imaging applications [3]. NMs have lately prompted initiatives to enhance biological detection and imaging because of their unusual passive, dynamic, and structural focusing characteristics. Tiny NPs have enhanced permeability retention (EPR) effects in tumors, leading to an increase in local contrast agent concentrations inside tumors compared to surrounding healthy tissue [4]. Additionally, nanoparticle surface labeling with multiple target receptor ligands might improve imaging contrast agent localization in lesions by specifically binding to those receptors in addition to passive targeting procedures [5][6][7]. Prostate-specified membrane antigen RNA aptamer-coated gold NPs have been demonstrated to have a computed tomography (CT) density that is greater for imaging prostate cancer cells [8]. The size and other features of nanoparticles play a big role in tumor imaging. Nanoparticle size has an impact on toxicology, blood movement half-life, tumor localization, tumor penetration, cellular absorption, and targeted delivery [9]. Organs of the lymph nodes, the liver, the spleen, and the lung are all constituents of the mononuclear phagocyte system (MPS), which concentrates NPs as well as rapidly recognizes particles larger than 100 nm, which can be subsequently identified through macrophages [10]. As they are close in size to significant naturally occurring NPs like viruses, slightly bigger particles in the biomedical field are typically classified as NPs as well. NPs can target tumors via the EPR or molecular sieving in certain organs, such as the lymphatic system, without the need for external targeting ligands [11][12]. NPs with diameters ranging from 10 to 60 nm had improved cellular uptake [13]. Tumor-specific nanoparticle probes with high specificity can be created by conjugating tumor-targeting ligands (such as peptides, small chemical compounds, or antibodies) to the particles [14]. MRI utilizes NPs in biomedical applications. Currently, clinical MRI uses superparamagnetic iron NPs (SPIOs) and ultra-small superparamagnetic iron NPs (USPIOs) to enhance imaging contrast in cancer and heart disease diagnosis. Complementary imaging modalities such as MRI and CT are routinely employed in interventional radiology. To keep pace with the fast expansion of interventional radiology's clinical applications, an integrated contrast agent suited for both CT and MRI would be very helpful for medical imaging and less invasive transcatheter treatments. Due to the success of "single component" NPs, a multicomponent nanomaterial may be able to take their place in the clinic [15]. The aim of our study is to give an overview of the utilization of metal oxide NPs in these processes. In section two we introduced some bioimaging techniques and section three has an overview of advances with MNPs in bioimaging techniques. Section four stands for utilization of MNPs for multimodeling imaging and section five has an overview of the challenges in this field.

2. BIOIMAGING TECHNIQUES

The complicated chain of obtaining, processing, and displaying structural or functional pictures of live objects or systems, as well as the extraction and processing of image-related information, is known as biomedical imaging. Biomedical imaging is becoming more widely recognized as a fundamental clinical investigative tool [16]. Positron emission tomography (PET), single photon emission computed tomography (SPECT), CT, Magnetic resonance imaging (MRI), Optical imaging, Ultrasonography, MR imaging etc. are the most frequent imaging procedures (see Fig. 1). MRI benefits to spot the difference between healthy brain tissue and stroke-damaged brain tissue. The utility of MRI for prostate cancer staging and monitoring has been improved including demographic statistics. CT creates a 3D picture of an object's interior using a higher number of 2D pictures when recorded on the device's cross-sectional plane. CT is a widely available and reasonably priced diagnostic imaging technology. Image contrast is provided by using X-ray CT. To better distinguish between healthy and malignant tissue on X-rays, it is

preferable to utilize contrast agents to boost the contrast of sick tissue. CT and MRI provide several options for undertaking functional assessments of many bodily systems due to fast technological advancements that result in great spatial and temporal resolution. The introduction of functional MR imaging and radionuclide imaging has revolutionized the investigation of numerous bodily systems' functioning [17][18]. MR spectroscopy has become commonplace in clinical practice as a result of fast technological advancements over the past decade [19][20].

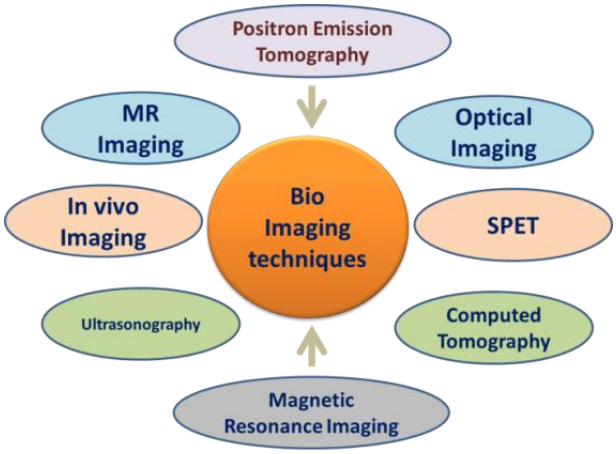

Figure 1. Several types of bioimaging techniques for various purposes in the clinical area.

It is usually applied as an auxiliary technique to MRI in pre-therapeutic diagnosis monitoring of patients' responsiveness to treatment as well as therapeutic monitoring for cancers of the brain, breast, and prostate [21][22][23]. It is possible to see the relative concentrations of important chemical components, including citrate and choline, using MR spectroscopy. Tumor volume, extracapsular extension, and post-radiation recurrence have all been estimated with the use of MR spectroscopy [24][25]. PET and SPECT are cutting-edge imaging modalities that can capture live images of metabolic processes in the body. In oncology, PET and SPECT are often used to monitor a patient's treatment-induced development of cancer and other disorders. Novel functional and metabolic imaging techniques such as hybrid SPECT/CT and PET/CT/MRI afford information regarding the disease's pathology in addition to morphological aspects. PET/CT fusion provides greater benefits over either imaging modality alone and has proven useful in a variety of medical imaging applications, including cardiac imaging. Coronary artery disease can be detected and located with greater precision with PET/CT imaging than with PET or CT alone [26][27][28]. The characteristics of radionuclides are used in PET and SPET modalities. Magnetic fields are used in MRI to detect molecules of water in various tissue settings [17]. Most widely used methods in the field of nuclear medicine are PET and SPECT, which make use of radiotracers to provide visual representations of Alzheimer's disease, neurodegenerative disease as well as vascular brain pathology. Visualizing organs and tissues in detail is performed using optical imaging making advantage of light and the exclusive features of photons. It makes use of light released by fluorescence or bioluminescence to illuminate diseased area or tumor. NIR fluorescence or optical coherence tomography are commonly used methods of optical imaging [29].

3. METAL BASED NPs FOR BIOMEDICAL IMAGING

Proton density, T2, and T1 impact the MR image. The contrast in MRI images is mainly due to differences in the relaxation times of protons within and between specimens. Several MNPs can be utilized for several bioimaging techniques (Table 1). Manganese oxide (MnO) nanoparticles coated with human albumin are utilized as a contrast agent for MRI tumor imaging [30]. Iron oxide-coated gelatin nanoparticles are utilized as a contrast agent for MRI [31]. Surface-modified nanoparticles are utilized for imaging purposes. Hybrid nanocrystals consisting of Fe3O4 and MnO are utilized for T1- and T2-weighted MR imaging with dual contrast agents [32]. Due to their greater selectivity, improved in vitro and in use stability, and longer half-life in circulation, gold NPs are the most beneficial. It will be significantly more effective to use as a contrast agents. The selectivity of nanoparticle-tumor interactions can be improved by the inclusion of specific ligands. NPs can be functionalized using a variety of specific ligands, including small molecules, peptides, proteins, and antibodies [33]. Gold-coated iron oxide nanoparticles are utilized as imaging agents for MR and CT scans. Barick et al. [34] employed Fe_3O_4 NPs with carboxyl groups on these for MRI imaging. The transverse relaxivity (r2) value obtained from the analysis of the T2-weighted MRI images of these NPs in water was 215 mM-1s-1. These NPs have a high r2 value and are colloidally stable, which makes them suitable candidates for a high-efficiency T2 contrast agent in MRI. Cho et al. [35] fabricated ^{68}Ga labeled Fe_3O_4 nano-biocomposite for dual utilization as imaging agent in PET/ MRI. SK-BR-3 and CT-26 cell lines both show a significant level of cellular absorption of this NP despite its relatively low cytotoxic potential. Researchers searched for better option for MRI when they found the performance of currently used gadolinium chelate based T1 contrast agents (CAs) was unsatisfactory. Researchers have found a new plan of action to enhance the capacity of nanoparticle based T1 CAs by utilize the photoinduced superhydrophilic assistance (PISA) effect significantly. Citrate-coated Gd-doped TiO_2 ellipsoidal nanoparticles (GdTi-SC NPs) was synthesized by researchers. In presence of UV radiation their r1 increased notably. The decreased water contact angle and the enhanced number of surface hydroxyl groups proved the existence of PISA effect. It notably promotes the efficiency of paramagnetic relaxation enhancement (PRE). As a a result the imaging performance was aggravated. GdTi-SC NPs could serve as a high-performance CA for fine imaging of blood vessels and proper diagnosis of vascular lesions, and this is demonstrated by rats with GdTi-SC NPs. This ensures the success of researchers' plan of action. The research for improved alternatives to current gadolinium chelate-based T1 contrast agents for MRI has been prompted by their inadequacy. Researchers have proposed a new method that uses the photoinduced superhydrophilic aid effect to improve the effectiveness of nanoparticle-based T1 contrast agents. Researchers synthesized ellipsoidal Gd-doped TiO_2 nanoparticles and coated them with

citrate. UV light exposure greatly enhances R1. The PISA effect is manifested through a reduction in water contact angle and an augmentation in surface hydroxyl groups. Certain factors significantly influence the efficacy of paramagnetic relaxation enhancement. The photography functionality has been enhanced. The research illustrates that GdTi-SC NPs are an effective contrast agent for in vivo MRI of rats, allowing for precise imaging of blood vessels and diagnosis of vascular lesions with high sensitivity. The results confirm the efficacy of the method [36]. Scientists found that novel surface-enhanced Raman scattering (SERS)-active materials is essentially needed for efficacious cancer cell diagnosis. SERS active materials possess some significant properties like excellent biocompatibility, low biotoxicity, and good spectral stability. Herein, they developed black TiO_2 nanoparticles (B-TiO_2 NPs) with crystal-amorphous core shell structure. From synergistic effect of the promising crystal-amorphous core-shell structure they derived observable SERS activity. Scientists generated plenty of excitons by high-efficiency exciton transitions in the crystal core. Enough charge sources can be provided by this feature. Scientists found that the unique crystal-amorphous heterojunction allows efficient exciton detachment at the crystal-amorphous interface. As a result of this they can successfully facilitate charge transfer from crystal core to amorphous shell which results in exciton improvement at amorphous shell. They found this NP can successfully assist vibration coupling with desired molecules. They also found that MCF-7 drug-resistant (MCF-7/ADR) breast cancer cells can be diagnosed rapidly and correctly based on high-sensitivity B-TiO_2-based SERS bio probe. Moreover scientists explore the crystal-amorphous core-shell heterojunction enhancement of TiO_2-molecule by PICT process and open up application of semiconductor-based SERS platforms in accurate diagnosis and treatment of cancer [37]. A novel bimodal time-gated luminescence (TGL)–MRI nanoprobe has been developed for the purpose of monitoring cancer cells both in vitro and in vivo. The nanoprobe was fabricated through the application of functional silica shells onto superparamagnetic Fe_3O_4 nanoparticles. The present study involved the surface decoration of encapsulated luminescent Eu^{3+} complexes with tumor-targeting molecules, specifically folic acid. The artificially created nanoprobe exhibits robust and persistent luminescence, remarkable magnetic characteristics, and exceptional stability, biocompatibility, and aqueous dispersibility [38]. CT contrast enhancers are generally made of tiny organic iodinated compounds that are very water-soluble. Compared to the regularly used iodine contrast agent iopromide, PEG-coated NPs administered intravenously into rats had a substantially longer blood circulation period (> 4 h). Researchers found that injecting PEG NPs intravenously into hepatoma-bearing rats increased the contrast between the cancerous and healthy liver tissue [31][32]. The ligand exchange approach was used to make these PEG-coated NPs. The reaction of $HAuCl_4$ with sodium citrate yielded gold NPs. By combining citrate-gold NPs with PEG-SH and stirring for one hour, the gold NPs were covalently modified with PEG in the ligand exchange process. CT, unlike MRI and other nuclear medicine imaging modalities, was not previously thought of as a molecular imaging modality (SPECT, PET etc.). Nevertheless, the utilization of Au NPs to identify head and neck cancer in vitro using a typical clinical CT has been has established. Instead of spherical gold NPs, the researchers employed gold nanorods. Despite particle size and form, the quantity of gold present per unit volume is critical in CT imaging. Gold nanorods with UM-A9 antibody attached to them were used to treat squamous cell carcinoma (SCC) selectively. Nikoobakht and El-Sayed technique was used to make gold nanorods. EDC/NHS chemistry was used to attach the polyacrylic acid (PAA)-adsorbed gold nanorods with the UM-A9 antibody conjugate. The cancer cell solution was then combined with antibody-coated gold rods for one and a half hours, rinsed, and redistributed, and CT images were taken using a CT scanner [14].

Table 1. NPs for imaging

Imaging Techniques	Nanoparticles	Synthesis technique	NP size	Applications	Ref.
MRI/OI	GQDs-folate-DOX-Gd	sol-gel	Thickness of 1.5 nm	Imaging and tumor targeted drug delivery	[39]
MRI	Gd(III)-thiolated DNA–Au nanostars (DNA-Gd@stars)	salt aging	50 nm	Imaging pancreatic cancer cells	[40]
MRI/US/CT	Gd- Au microcapsules	Biological process via islet cells	Diameter of 2.0–2.5 nm	Multimodal cellular imaging of transplanted islet cells	[41]
MRI/CT	Gd(III)-decorated Au NPs	grafting	12.1±1.6 nm	Improving the relaxometric properties of Gd(iii) complexes	[42]
MRI/US	Liposomes-Gd-rhodamine	thin-film hydration method	77.5 nm	MRI monitoring and quantification of US-induced drug delivery	[43]
MRI	Liposome-Gd	Solvothermal	125 nm	Placenta imaging	[44]
MRI/PET	PEGylated liposome (LP)-(Gd)-positron-emitting ^{89}Zr	radiolabeling strategy	115±2 nm	Cancer cells imaging	[45]

MRI/SPECT	^{127}I-RGD-DOTA conjugate	Sol gel	-	Tumor targeting	[46]
MRI	Fe_3O_4 NPs	coprecipitation method	12.8 nm	Imaging, targeting hepatocellular carcinoma	[47]
MRI	FeCo MNPs	thermal decomposition of metal-complex precursors	7 nm	Tumor imaging	[48]
MRI	FePt MNPs	thermal decomposition of metal-complex precursors	12nm	Tumor imaging	[48]

4. MULTI-MODAL IMAGING WITH METAL BASED MAGNETIC NANOPARTICLES

Multimodal imaging is a term that describes the use of numerous imaging techniques at the same time. Complication rises with the capacity to integrate multimodal imaging data sets (e.g., mix PET/CT/SPECT/MRI data sets) and creative diagnostic procedures as tools for feature analysis and computer-assisted diagnosis are also required [49][50]. The advantages of multi-mode systems are that each mode works in concert with the others to maximize efficiency. Nanoparticle surfaces may act as conjugating sites for additional imaging modalities or functional biomolecules by attaching various chemical moieties. MRI contrast effects of MNPs may be improved by adding imaging active moieties such as fluorophores and radioisotopes. This may be done by adding extra ligating molecules that can detect the presence of certain chemicals or elements in the surrounding environment [51]. There are two techniques to magnetic NMs multi-modal imaging (MMI). MNPs coupled with secondary imaging components are used in imaging. NPs can be utilized in MRI, CT, and SPECT because of their extremely high sensitivity and fine resolution. The biological targets may be scanned with great precision when these signals are integrated in a complimentary way. Instead of using extra imaging moieties, magnetic NPs' intrinsic magnetic capabilities are used to generate MMI signals. The position of biological organs may be detected by the MMI methods by using NPs. It is possible to combine magnetic nanoparticle in imaging methods with more traditional imaging approaches. Image sensitivity and accuracy may both be improved by using MMI methods. In other words, combining MRI with PET or optical modalities yields superior resolution and sensitivity, as well as more extensive and accurate imaging data than if each modality were used alone. When used as a substrate for the inclusion of fluorescent chemicals or radioisotopes, MNPs have served as a multimodal integrator. MNPs have recently been developed for T1–T2 contrast agent of MMI such as MRI-optical and PET/SPECT MNPs [52]. Tumors larger than 0.5–1 cm3 are often imaged using a pair of PET and CT. Gold NPs have harvested a lot of interest due of their biocompatibility, low short-term toxicity, and higher physical density and absorption coefficient than iodine. When gold NPs (AuNPs) were introduced, imaging methods gained a whole new dimension. By using tumor-specific antibodies on MNPs, imaging methods like as CT get the benefits of molecular, tumor-specific imaging. Because of combination with the particular properties of AuNP in clinical imaging, the techniques provide a powerful new imaging tool. Photon-counting detectors like those used in the development of spectral CT capture the interactions between individual photons, resulting in an energy spectrum that can be used to create a color picture [53]. Colloidal super paramagnetic iron oxide (SPIO) particles coated with dextran have been reliable, well-characterized, and easily accessible contrast agent for MRI and micro-CT (mCT) long-term monitoring of transplanted cells. As a consequence, SPIO NPs are being evaluated for six months and a year in Lewis's rat hearts as a multi-modal contrast agent to mark off progenitor cells in specified tissues put in the atrioventricular groove. SPIO particles are thought to be safe to decompose through standard iron recycling channels when exempted from dying cells due to their biological inertness [54]. Iron oxide NPs may be tagged with radiolabeled bisphosphonates conjugates to create SPECT/PET-MR dual-modality imaging agents. Endorem/Feridex, a clinically authorized SPIO, can act as MRI agent of the reticuloendothelial system (RES). It has been used in in vivo imaging of liver and spleen [17]. Stable intracellular composition of the core-corona-shell CoFe2O4@Au@TiO2 nanocomposite is a nanocrystal of gold corona and superparamagnetic core. This NPs is a promising multimodal imaging agent with potential applications in biological imaging [15].

5. LIMITATIONS OF USING METAL BASED NPS IN IMAGING

Because the use of NPs in biomedical research is rapidly growing, the toxicity of these materials must be thoroughly investigated. It is difficult to establish a relationship between nanoparticle toxicity and a broad variety of materials. Various toxicity pathways have been thoroughly investigated in the literature, both in vitro and in vivo. For varied forms of NPs, detailed bio distribution, pharmacokinetics, and local and systemic toxicity research will be required for overall toxicity evaluations. Despite significant advances in the development of biomedical NMs, nanotoxicology research has trailed [14]. When using NPs in vivo, it is important to think about how dangerous they might be. The emissions of harmful ions from metallic NPs and reactive suffering generated by the nanoparticle's inherent features are associated to nanotoxicity [55]. The subject of

nanotoxicology faces several challenges as a result of the introduction of NPs with a variety of unique properties into dynamic, complex biological systems. While it is feasible to characterize NPs throughout their interaction with the biological system, technical constraints make it difficult to accurately quantify nanoparticle uptake location and concentration. Many of the evaluation techniques were created to examine molecular toxicants, which are believed to interact with cells differently than NPs, whereas a range of in vivo and in vitro nanotoxicity tests were performed to define the toxicology of synthetically designed NPs. When NPs are present, the in vitro toxicity tests used in this research may not correctly predict in vivo response. Because of the increased surface area provided by the porosity of these NPs, they have the potential to be more cytotoxic due to the presence of more reactive surface atoms [56]. With regard to tumor imaging, CT imaging is the most often utilized method since it scans quickly and has good spatial resolution over a vast area of the body. PET is typically used in conjunction with CT to get functional molecular imaging. Certain constraints, on the other hand, have an impact on the clarity of the tumor image. On the other hand, tumor cell metabolism must be much higher than in normal tissue for PET imaging to be effective with 18F-FDG. Ionizing effects are required for PET-tracers, which raises patient risk of DNA mutation. The creation of spectral-CT analyzers, which employ the k-edge discrimination of elements to allow for their precise identification within the body, was a strategy to overcome the limitations of PET/CT. Another advantage of spectral segmentation is the possibility to utilize several contrast agents during a single imaging session, therefore reducing the patient's X-ray exposur [53].

6. CONCLUSION

In the conclusion NPs are auspicious for their applications in imaging technologies. Metal NPs have shown great potential in bioimaging, with the ability to significantly impact the fields of biomedical diagnostics and imaging. Metal nanoparticles possess distinct physicochemical properties that enable the achievement of high-resolution and sensitive nanoscale imaging of biological structures. Nanoparticles possess enhanced adaptability and utility in various imaging modalities, including optical, magnetic, and photoacoustic imaging, due to their adjustable optical properties, surface functionalization capabilities, and biocompatibility. Before metal NPs can be widely used for bioimaging in clinical settings, it is crucial to address concerns related to their biocompatibility, potential toxicity, and long-term stability. Comprehensive investigations of the biodistribution, clearance, and potential adverse effects of these substances are imperative to ensure their safe utilization in clinical settings. With these things metal NPs are expected to have a significant impact on bioimaging due to technological advancements and increased knowledge. This is likely to lead to groundbreaking advancements in both fundamental and clinical research.

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