Recent progress in imaging technology combined with nanomaterials for medical applications

Ziyao Ding, Ke Xu ✉

School of Information & Control Engineering, Shenyang Jianzhu University, Shenyang 110000, People's Republic of China
✉ *E-mail: xksky1234@163.com*

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The development of medical imaging technology has led to progress in nanomedical diagnosis, prevention, and detection. In this study, the latest applications of single-mode imaging, dual-mode imaging and multimode imaging in nanomedicine are reviewed. Meanwhile, in the single-mode imaging section, several imaging techniques such as magnetic resonance imaging and computed tomography illuminate their respective characteristics and medical applications. In the part of dual-mode imaging, nanoprobes and nanodrug carriers as nanobiotechnology applications, which combined with dual-mode imaging are conducive to the accurate cancer diagnosis and efficient delivery of drugs, respectively. In the application of multimodal imaging, owing to the combination of treatment and multimodal imaging, functional diversity and fewer side effects are obtained. Each section outlines the current utilisation and potential of imaging in nanomedicine, illustrating the potential applications in the future. This review is supposed to provide some ideas for the multifunctional application and accelerate another technical leap of fusion imaging technology in medicine.

1. Introduction: In recent years, nanotechnology has shown great superiority and potential in the clinical diagnosis and medical research and even brings significant breakthroughs. In nanomedicine, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) (positron emission CT) are indispensable for the medical treatment. Medical imaging is routinely used to provide information about all aspects of the human body and aid the decision-making processes of diagnosis. In 1895, the German physicist W.C. Roentgen invented X-ray with cathode tube and discovered that it could penetrate human tissues. The invention of X-ray for treating fractures and gunshot wounds promoted the development of non-invasive imaging diagnosis which was an important milestone in the history of medical development [1]. In 2003, Lauterbur [2] of the United States and Peter Mansfield of the United Kingdom invented MRI, which has made great contributions to the anatomical image and surgery. The results show that imaging technology has great potential in nanomedicine. Therefore, the application of medical imaging is one of the hottest disquisitive foci in the current research of nanomedicine.

Imaging technology mainly applied to nanodiagnostics and nanomedicines. The two are the mode of different applications. In nanodiagnostics, with medical imaging technology, the nanomaterials has been labelled transformed and strengthened. As an example, labelled molybdenum disulfide (ReS2) nanosheets has made an enormous contribution to the destruction of tumours under the effect of Photoacoustic (PA imaging)/CT combined with photothermal radiotherapy [3]. The technology of nanomedicines takes the nanomaterials as the carrier, combined with pharmacological actions, in order to achieve the targeted drug delivery. Moreover, the function is diverse in different images. Single-mode imaging only retains its own characteristics and functions, which has great limitations on medical treatment. Image fusion is an efficient applicable method and can be applied to preclude the inherent limitations of single modal images. With the improvement of treatment accuracy, researchers have made further exploration in imaging technology. Multimodal imaging has integrated a greater abundance of information, compared to dual-mode tomography, for instance, the combination of CT, Fluorescence and PA imaging is conducive to the enhancement in sensitivity and imaging range [4].

In this review, we aim to highlight the research progress of image technology in nanomedicine, concentrating on the application of the dual-mode or even multimodal fusion in medical field, in particular. The help of fusion of different imaging in medical treatment and method of improving accuracy is investigated in detail. Moreover, this paper puts forward some potential applications and possible challenges. Finally, the future development direction of fusion imaging is proposed, which aims at providing reference for the future research and development of medical imaging technology.

2. Single-mode imaging

2.1. Magnetic resonance imaging: With the development of nanomedicine, MRI has been the most extensive medical image diagnostic technology. MRI has great potential for disease diagnosis, owing to the amount of information provided by MRI which is greater than others. However, the relaxation times of some different tissues overlap each other, leading to difficulty in diagnosis. Therefore, people began to increase the contrast of imaging by injecting contrast agents.

According to the magnetic composition, MRI contrast agents can be divided into three categories: paramagnetic, ferromagnetism, and superparamagnetism. Metelkina *et al.* [5] developed a magnetite-nanofiber material which was tested as an MRI contrast agent. The relaxivities $r_1 = (0.7 \pm 0.3)$ mM s^{-1} and $r_2 = (268 \pm 13)$ mM s^{-1} were determined by linearly fitting the data. The determined r_2/r_1 ratio was 38,026, far exceeding the best pharmacy in the market. These materials have limited toxicity to healthy and malignant cells. The demonstrated MRI contrast agent may contribute to the release of magnetically induced drugs, the follow-up of the disease combined with the stratified nanomedicine treatment. Gadolinium is a commonly used paramagnetic contrast agent in clinic. Holbrook *et al.* [6] prepared a new Gd (III) contrast agent. Animal gold nanoparticles (AuNPs) were administered to evaluate its performance in the pancreas. As shown in Fig. 1, the image contrast of animals incubated with LIP-DTPA@AUNP and LIP-DO3A@AUNP was significantly enhanced and pancreas was identified obviously, which had high contrast-to-noise ratios (CNRs) in all subjects. It was found that despite the high accumulation in liver and spleen, only significant contrast enhancement of MRI was observed in the pancreas. Contrast agents synthesised in that work can improve imaging capabilities of pancreatic tissue.

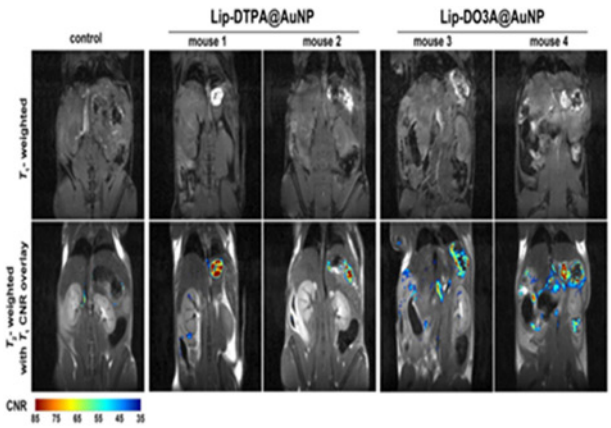

Fig. 1 *T1-weighted FLASH images were obtained at 9.4 T to assess contrast of Lip-DTPA@AuNPs and Lip-DO3A@AuNPs. CNR relative to muscle, computed from T_1-weighted FLASH images, were overlaid on TurboRARE T_2-weighted anatomical images at 9.4 T after administration of Lip-DTPA@AuNPs, LipDO3A@AuNPs, and no agents (control) following 24 h incubation. Upon administration of both Lip-Gd@AuNP constructs, significant contrast enhancement is observed in the region of the pancreas*

However, the application of gadolinium chelate in magnetic resonance molecular imaging is limited due to its difficulty in modification and lack of targeting. Superparamagnetic iron oxide nanoparticles (SPIONs) are a new direction in the development of MRI. Song *et al.* [7] prepared low cytotoxic SPION liposomes encapsulated with polyethyleneimine. The uptake of particles with different weight ratios is different in different cells, and the signal intensity decreases with the increase of weight ratios. The particles prepared can be used as magnetic resonance contrast agents to help the diagnosis of tumours. In drug delivery, nanotechnology can maximise pharmacological effects and overcome the limitations and shortcomings of drugs themselves. Yang *et al.* [8] prepared a self-assembled nanoscale metal-organic particle through Mn^{2+} and organic bridging ligand. This nanoparticle can minimise long-term toxicity. The R1 relaxation was same or higher than that in commercial contrast media. These Nanoscale metal-organic particles (NMOPs) were coated with dopamine (PDA) which promoted further modification of the polyethylene glycol (PEG). Affective tumour accumulation and rapid delivery of urine through the kidneys are showed in the MRI images of mice injected intravenously with Mn-IR825@PDA – PEG NMOPs. The nanoscale metal-organic particles prepared in the paper improve the sensitivity of MRI imaging for tumour targeting imaging is accelerated by combining it with photothermal therapy. Xiao *et al.* [9] synthesised a cRGD peptide functionalised polylactic acid-polyglycolic acid block copolymer for encapsulating doxorubicin (DOX) and SPIO. The synthesised micelles have lower toxicity than DOX drugs. The particles can be used for targeted delivery and vivo therapy by MRI. Based on cholera toxin B subunit (CB), Chen *et al.* [10] designed an efficient, stable and easy-to-construct nanosystem (CB-GD-CY5.5) for the treatment of Alzheimer's disease. CB, a nontoxic receptor binding subunit. Combining with the chelating effect of Gd^{3+}, its high RI relaxation rate at low concentration indicates that it has excellent imaging ability. The nanoparticles prepared in this paper provide a new idea for protein multifunctional drug delivery system targeting the brain.

Although the function of MRI is becoming more and more powerful, there are still some factors restricting its technological development. For example, the diagnosis of lesion tissue needs further qualitative analysis. The development of polarisation imaging in the future can magnify magnetic resonance signal 10,000 times, which makes magnetic resonance metabolic imaging possible. Imaging speed is also a drawback of MRI. The cost of high magnetic field is high, and the safety of high gradient field cannot be improved. Parallel acquisition technology needs to coordinate its internal interference. If there is great technological innovation, the development of MRI will become more important imaging equipment.

2.2. X-ray CT imaging: Like MRI imaging, X-ray CT imaging appears the distribution of a certain physical quantity in space. However, CT imaging has higher density resolution than others, in which images reconstructed by electronic computers do not overlap with images of adjacent layers. X-ray construction of three-dimensional (3D) tomographic images has been fully utilised in medicine. The same principle has been extended to the nanoscale; however, its low soft-tissue sensitivity is a major obstacle to the development process. NP-based CT imaging technology raises substantially spatial resolution with the paramount aid of contrast agents.

The commonly used contrast agent for CT is iodine-containing organic molecules. Zou *et al.* [11] prepared iodinated polypyrrole (I-PPy) by chemical oxidation combined and iodination. CT imaging of I-PPy revealed that CT value presented a linearly increasing trend with the concentration of I-PPy solution. The nanoparticles have low toxicity. I-PPy nanoparticles were injected into different organs, and the contrast of heart, aortic arch, posterior vein and renal vein was immediately enhanced. The results showed that I-PPy had great potential in blood pool imaging and could effectively enhance the imaging level of liver diagnosis.

However, iodine ions ionised by iodine-containing substances have stronger toxicity, gold nanoparticles have better contrast effect and X-ray absorption ability, which can overcome the shortcomings of traditional CT contrast agents. Kesharwani *et al.* [12] designed a dendritic macromolecule encapsulated AuNP, which has strong CT signal intensity and can be used as a contrast agent for CT imaging. Combining with photothermal effect, it can kill cancer cells effectively. However, due to the associated toxicity of free amino groups and dendritic macromolecular complexes, dendritic complexes need to be minimised by pegylated or acetylated surface amines. The particles designed in this paper can enhance CT imaging, and with the cancer cell ligand, the contrast agent can be transferred to the cancer cells for imaging.

Although gold nanoparticles present high-resolution images, their high daily cost is not reasonable for clinical applications. Bismuth nanoparticles are antibacterial, non-toxic, and low-cost. It has an appropriate response to X-ray radiation and is often used for concentrated radiation therapy for cancerous tumours. Mohammadi *et al.* [13] studied the performance of Bi_2O_3 as a CT contrast agent. Bi_2O_3 was coated with glutaraldehyde cross-linked chitosan molecules, and CT images of Bi_2O_3 and iodine were performed, respectively. The image showed that the CT value of Bi_2O_3 was larger than that of iodoethanol, and increases as the particle concentration increases. MTT analysis showed no significant toxicity. This article demonstrates that Bi_2O_3 is a replacement for iodine contrast agents.

CT imaging can obtain incompletely continuous 3D structural information, which is helpful for drug monitoring and therapeutic monitoring. Fan *et al.* [14] designed a special carrier system using self-decomposing SiO_2 nanoparticles (nanoparticles), drug loading at the centre, and AuNPs as imaging agents loaded on SiO_2 nanoparticles, CT 3D imaging of drug release process, showing the more severe the gold nanoparticles are aggregated, the higher the CT intensity, and vice versa. The nanoparticle drug delivery system enables non-invasive real-time monitoring of local drug release, providing a new strategy for drug release. Wu et al [15] prepared new nanorattles with three functions PEG-IL/ZrO_2-Ag@SiO_2. The shell and silver content of ZrO_2 enhanced the CT imaging effect. The method has lower ionizing radiation. Owing to the good antimicrobial property of silver, it can be used as an antimicrobial agent. With the increase of the

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concentration of the material, the CT imaging signal enhances. Good CT imaging characteristics can be used for real-time monitoring of the treatment process. The three-function nanorattles can be used in microwave hyperthermia and anti-bacterial infection of brain tumours under CT imaging, and have great potential in cancer treatment.

The insensitivity of CT imaging to density resolution may lead to further development of photonic CT and 3D CT in the future. In addition, CT imaging has certain ionizing radiation; the choice of CT contrast agent still needs to be explored.

2.3. Positron emission CT imaging: Positron emission CT (PET) is now the only new imaging technology to emerge biomolecular metabolism, receptors and neuronal activity in vivo that is different from the rest, which is mostly available for the diagnosis on account its high sensitivity and resolution. The working principle of PET is that essential substances in biological life metabolism are marked with short-lived radionuclides to reflect the metabolic activities of the life through the accumulation of the substance in the body.

However, PET is susceptible to radiopharmaceuticals. Pang *et al.* [16] prepared a radioactive labelled PdCu@Au core–shell tripod. PET imaging of a ^{64}Cu-doped core–shell tripod was performed 24 h after injection with 4T1 tumour-bearing mice, which indicated that CCR5-targeting tripod had better tumour targeting, absorption and high stability. This multifunctional nanoparticle (core–shell tripod) is utilised in accurate intravital PET imaging, guiding photothermal cancer treatment. Through PET imaging of ^{64}Cu and ^{52}Mn liposomes (Cu-LIPO and Mn-LIPO), Xia *et al.* [17] found that the PET imaging probe based on liposomes can greatly increase the blood circulation time, and quantitatively characterise the biological distribution of liposomes, evaluating the targeting accumulation ability. The results showed that non-targeting liposomes had a high uptake rate of tumours. This article provides an idea for the application of liposomes in PET imaging and plays an important role in inhibiting the growth of tumours.

PET can dynamically obtain fast (second-order) kinetic data, and can rapidly visualise physiological and pharmacological processes for drug delivery. Edmonds *et al.* [18] demonstrated a PET radiolabelling method that made metal ions as a carrier and utilised the metal-chelation properties of certain drugs, which could quantitatively analyse the biological distribution of stealth liposomal nanodrugs containing alendronate radiolabelled in a model of breast cancer. That PET labelling method has played a significant role in the treatment of liposomal drugs, not only improving the clinical value of liposomal drugs, but also guiding submicrodosing imaging studies of liposomal nanomedicines.

Nanoscale metal–organic framework (nMOF) materials are an attractive tool for a variety of biomedical applications. Chen *et al.* [19] combined the essentially radioactive UIO-66 nMOF (^{89}Zr-UiO-66) with the isotope zirconium-89(^{89}Zr). ^{89}Zr-UiO-66 was further functionalised with pyrrole-derived PEG (Py-PGA-PEG) and bound to the nucleolar protein with the peptide ligand (F3). This particle did not impose acute or chronic toxicity to the test subjects. PET imaging in mice bearing orthotopic MDA-MB-231 tumours, showed that this nanomaterial rapidly accumulated in tumours. The results showed that it could be available for guiding images as a tumour-selective cargo transport nanoplatform, which illustrated tremendous potential for tumour targeting and drug delivery. Mukai *et al.* [20] used dynamic PET imaging and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to analyse about 100 nm liposome nanoparticles WS wrapped with sirna and found that it has a good protective effect to 18-Mer phosphorothioate oligodeoxynucleotide. This combination method is helpful for the development of nanoparticle-encapsulated nucleic acid drugs and is of great significance for medical drug delivery technology.

With the use of metal-binding drugs in tumour chemotherapy and various liposome nanodrugs, PET will be more widely used in the future to track the progress of drugs in the body and test whether the drug reaches the target site with effective therapeutic concentration. And in order to solve the limitation of radiopharmaceuticals, the exploration of the characteristics of nanoparticles is still necessary.

3. Dual-mode imaging: Disparate modality images obtained by different medical imaging devices supply diverse emphases for the same detection part of the human body, which is difficult for doctors to accurately diagnose and treat diseases based on the medical images of a single mode. On comparison with single imaging method, dual-mode imaging overcomes the limitations and broadens the application range of molecular imaging technology.

Nanobiotechnology has been widely used in the field of medicine and health. As one of the important applications, the establishment of nanoprobes is essential for improving imaging level. Wen *et al.* [21] synthesised bovine serum albumin (BSA)-based PDT nanoparticles (Gd@BSA-Ce6) employing Ce6 as photosensitiser and BSA as skeleton material by biomineralisation. Toxicity test shows that it is harmless to human body. The therapeutic effect was evaluated relying on fluorescence and transmission electron microscopy imaging in the venous tails of mice, which were injected with nanoparticles. Gadolinium-based nanoparticles in combination with imaging and therapeutic approaches help in providing new ideas for the synthesis of nanoprobes. Zhao *et al.* [22] reported a magneto ferritin nanoprobes made from ^{125}I radionuclide-conjugated human H-ferritin iron nanocages (^{125}I-M-HFn). The particle has low radioactivity to surrounding tissues. The simultaneous binding and uptake of transferrin and HFN emerged from MRI/SPECT image of tumour-bearing mice injected with ^{125}I-M-HFn nanoparticles, manifesting the endocytosis of M-HFn nanoparticles through TfR1. The work has provided a way out of excessive non-radioactive labelled probe obstruction caused by large sensitivity difference in nuclear imaging process. The combination of dual-mode imaging and nanodrug carriers also plays an important role in improving drug release efficiency. Asem *et al.* [23] proposed a biodegradable nanoparticle system. SPIONs were encapsulated in poly (ethylene glycol)-co-poly (caprolactone) (PEG-PCL) micelles by emulsion evaporation. The particle does not cause toxicity due to nucleic acid drugs. The mice biological distribution was observed through fluorescence imaging with injection of PEG-PEC, no organ lesions were found. The drug release was in a continuous state within 10 h and SPION-PEG-PCL micellar took on the contrast enhancement in T_2-weighted MRI. The results indicated that the PEG-PCL micelle's with extremely high drug-loading capacity can be conducive to sustained drug release. Sun *et al.* [24] proposed an oval-shaped Fe_3O_4@Gd_2O_3 nanometer platform (FA-PYFGN) functionalised by PEG and folic acid. The mice tumour site treated with FA-PYFGN showed the brightest T_1-weighted and darkest T_2-weighted magnetic resonance images, indicating that FA-PYFGN can availably accumulate in the tumour area. The platform could be transmitted to tumour tissues and released anticancer drugs to eliminate cancer cells.

Exploring the properties of nanoparticles to exploit their potential functions can also enhance dual-mode imaging quality. Yang *et al.* [25] synthesised a biocompatible GD integrated CUS nanotherapeutic agent (GD: CUS @BSA). In the image of the vein of tumour-bearing mice in which the enhanced MRI imaging was monitored the PA intensity obtained from the tumour site continued to increase. No significant systemic toxicity was observed. This nanoparticle makes a great contribution to the realisation of high-resolution and sensitive tumour treatment. Yang *et al.* [26] accurately synthesised size-dependent Ag_2S nanodots (NDs) with the restricted growth of Ag_2S in hollow human serum albumin nanomaterials, which showed its ultrasensitive second near-infrared (NIR-II) fluorescence imaging and microscopic PA imaging ability with spatial resolution by fluorescence/PA imaging.

The results showed that Ag_2S-NDS could promote NIR-II fluorescence PA imaging and synergistic photothermal therapy for tumour ablation.

4. Multimode imaging: Multimodal imaging achieves maximum resource savings and demonstrates extraordinary capabilities in the illness diagnosed that are unmatched by single-mode and dual-mode. With the increasing demand of medical imaging information, dual-mode imaging has a simpler fusion process, but its efficiency and completeness in diagnosing diseases are lower than multimode imaging, which cannot meet the needs of fine treatment. In addition, the multiple functions of multimode imaging can be better combined with medical therapy for cancer treatment.

Traditional cancer treatment methods cannot achieve the best treatment due to some side effects and limited curative effect. In order to overcome these disadvantages, the combination of treatment methods and multimode imaging can achieve more precise medical treatment with fewer side effects. Zhang *et al.* [27] developed a chemical photothermal heat treatment platform (RGD-^{125}IPT-PDA@GNRs). In SPECT and CT imaging, it could selectively accumulate in tumours, and in high-resolution PA imaging, shown to accumulate in the blood vessels alternatively. This platform could be efficaciously applied in the treatment of tumours, integrated with photothermal therapy to inhibit tumour recurrence. Shen *et al.* [28] synthesised a 2D transition metal diol disulfide (ReS_2) nanosheet, using single proton emission CT, PA and CT imaging to observe the effective tumour accumulation after injection of this nanosheet into mice, combined with in vivo photothermal radiation therapy devote to achieve impactful tumour treatment. The results showed that the multifunctional nanotherapeutic drugs with near-infrared intensity and strong X-ray attenuation could availably treat cancer through multimode imaging, which has a broad application prospect for nanostructures with highly integrated functions in cancer treatment.

Multimodal imaging also has more methods to improve accuracy than dual-mode imaging, such as the use of probes, nanoagents and contrast agents. Unlike double imaging probes, the operable multimode probes can enhance multiple imaging signals by targeting specific molecules. By using nanoparticles as carriers, multiple imaging probes can be integrated and multiple imaging examinations can be performed at a single injection. Zheng *et al.* [29] constructed a redox-activatable fluorescent/^{19}F-MRS/^{1}H-MRI trifunctional probe 1. The matrix glue solution of probe 1 (500 μM) mixed with GSH (10 mM glutathione) or nothing was immediately subcutaneously injected into two different parts of the same healthy nude mouse. The fluorescence image revealed a 2.2-fold increase in fluorescence compared to the injection site of the probe alone, which same conclusion could be obtained by MRI imaging. GSH has certain toxicity under long-term action. This nanostructure decomposition method facilitates the development of other stimuli-responsive trimodal probes for molecular imaging of living cells and different biological targets in vivo. Li *et al.* [30] prepared a Bi_2Se_3 nanoagent with a special morphology of nanosized spherical sponge. Bi_2Se_3 has less biological toxicity. Combined with X-ray CT, multispectral tomography and infrared thermography, it possessed a prominent performance in contrast imaging. This strategy of single-component nanoagent combined with multimode imaging furnishes an avenue for antitumour application. Xiao *et al.* [31] a novel ultra-small silicon quantum dot gadolinium (SiQD-Gd) synthesised by simple hydrothermal growth chelation. It showed low toxicity in normal and cancer cells. In vivo T_1−T_2 weighted MRI showed good contrast effect, and in vivo fluorescence imaging showed its potential in fluorescence tracking in mice. The nanoparticles show good multimode imaging ability and provide a new strategy for the preparation of multimode probes.

5. Conclusion: This review summarises the latest research on the imaging and fusion in nanomedicine. Medical imaging is one of the major research fields of nanomedicine, which contribute to nano diagnosis, nanodrug treatment, etc. In the process of modern clinical medicine sought for a root disease, organs even molecular level is demanded in elaborate and non-invasive presentation, which accelerate the development of nanometer imaging technology. One of the capital progresses in imaging technology embodied from a single mode to the fusion, and consequently bring about diagnosis treat model reformation.

Fusion meaning lies in overcoming the defect of low-resolution of space and tissue and exploiting the image information to the maximum extent. Nanometer medicine puts nanoparticles as a carrier for targeted drug delivery and contrast agents, which are immensely instrumental to clinical medicine. In the nanodiagnosis, fusion imaging can distinctly display the structure and adjacent relationship of the organ or tissue, which conduce doctors to comprehend its morphological characteristics, accordingly perform a more explicit qualitative diagnosis. In the future, image fusion may have broad application prospects in telemedicine, such as multimode imaging in the case of real organs registration to undergo remote surgery. We believe that image fusion for nanomedicine will drive another technical renewal and hope that this review will inspire more researchers into this innovation.

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