

**Review article:****Molecular imaging modalities using nanoprobes for cancer diagnosis**

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**Running head:** Cancer diagnosis using imaging modalities

## Molecular imaging modalities using nanoprobe for cancer diagnosis

### Abstract

Molecular imaging modalities are used for different type of cancers detection and diagnosis. In recent few years, there has been an increased focus on developing novel nanoparticles as new imaging contrast agents for early detection of cancer. The aim of this review article is to summarize molecular imaging technologies accompanying with using nanoparticles to improve potential imaging for cancer detection and hence valuable therapy in the future. Nanoprobes are rapidly becoming potentially transformative tools on cancer diagnostics for a wide range of imaging modalities such as CT, MRI, SPECT, PET, Ultrasound and Optical imaging. The study results seen in the recent literature are provided and discussed the diagnostic performance of imaging modalities for cancer diagnosis and their future directions. With knowledge of the correlation between the application of nanoparticles and molecular imaging modalities and with the development of targeted contrast agents or nanoprobe, they may provide better cancer diagnosis in the future.

**Keywords:** Molecular imaging, nanoparticles, cancer diagnosis, imaging modalities.

### Introduction

At present, molecular imaging (MI) is an emerging subject that integrates advanced imaging technology with cellular and molecular biology. Molecular imaging has the strength to enhance all feature of cancer care (1). Notable sophisticated technologies with the purpose of improving diagnostic accuracy and also individualizing treatment methods to make the most of effectiveness when reducing short-term mobility. Hence, MI is sophisticate to characterize and measure the biological process at the cellular and subcellular of living organism (2). Therefore, the mortality rate of cancer will increase significantly for earlier detection of disease, precise diagnosis of diseases and enhancing the results of treatment using appropriate imaging probes. Molecular imaging probes can be categorized as follows: A) phenotypic probes, b) targeted probes, c) cell-tracking probes, and d) reporter gene probes. The first category is utilized to determine general features of malignant physiology, such as angiogenesis, cell proliferation, apoptosis, and the expression of certain receptors in Tumor cells. The second category is employed to images specific biomolecules which are characteristic of a Tumor or even class of Tumors. The third category is employed to localize and follow the movement of cells that may

be of importance for tumor survival. The cells can be labelled directly with tags or indirectly via the insertion of marker genes. Last of all is the reporter gene probes which are used to monitor the action of genes in biologic in vivo systems (3).

Molecular imaging requires high resolution in addition to very sensitive features to detect and recognise specific imaging agents that link the imaging signal with molecular size. Molecular imaging techniques also may consider tumor characterization and cancer diagnosis without any invasive operations like biopsy or even surgery (4). Recently, there are many types of MI agents such as small molecules, peptides, aptamers, high-molecular-weight antibodies, and various nanoparticles.

Molecular imaging probes include targeting component such as antibody (5, 6), peptide (7), or small molecule and a signalling component including a radionuclide (8), fluorochrome for optical imaging (9) or a paramagnetic chelate for magnetic resonance imaging (10, 11). Nano-sized probes with unique properties have emerged a potential class of MI (12).

Clinicians are using six imaging modalities to diagnose and treat the cancer. Only four of them including computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET), are widely used for three-dimensional in cancer staging (13). Virtually all four 3-D imaging modalities suffer from deficiencies in sensitivity as well as resolution. The ability to solve many of the most important clinical problems in terms of scale, for enhance their ability for diagnosis; they simply were not designed to image small numbers of cancer cells (14). The aim of cancer imaging should be to detect the smallest possible number of cancer cells, before the angiogenesis. In recent years, nanoparticles have extended significant attention as contrast agents for the primary detection of cancer in current imaging system such as molecular imaging. Using nanoparticles, it is possible to (1) achieve great specificity toward a target, thus eliminating the hazard of side effects; (2) deliver a large payload quantity in a single dose and (3) simultaneously deliver both imaging agents and therapeutics.

In this review article, the current state of the art and advanced approaches in MI using nanoprobables for cancer diagnosis was considered.

### **Positron Emission Tomography (PET)**

PET is the MI modality most extensively used in current clinic routine (15). Its image originated from the radioactive decay of neutron-deficient or positron-enrich radioisotopes including  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{18}\text{F}$ , and  $^{131}\text{I}$ , which they are prepared as radiopharmaceutical and intravenously injected into the body. In another word, PET modality are designed to detect the

paired 511 keV photons generated from the annihilation event of a positron and electron. The paired annihilation photons travel in opposite directions (180° apart) along a line. A PET detector surrounding the target can prepare signal and convert it into tomographic images.

Due to high sensitivity of PET, limitless depth of penetration, and quantitative capabilities, it becomes a powerful tool for clinical diagnosis and basic research including neurology, cardiology, and particularly oncology (16). In the clinical application, PET scan is essential for cancer detection and staging, in addition to evaluate the response of cancer to therapy. The main disadvantage of PET is the lack of anatomical parameters to identify molecular events with accurate correlation to anatomical findings, and this disadvantage has recently been compensated by merging these devices with either CT or MRI known as dual modalities named PET/CT and PET/MRI (17, 18). PET/CT improves the accuracy of cancer diagnosis and staging. With the widespread of instrument, it has become an important tool for predicting therapeutic response, providing useful information for the decision to stop ineffective treatment or switch to a more efficient treatment (19).

PET/CT has changed the diagnostic algorithm in oncology by substantially influencing the management of patients with cancer (20, 21). Among a variety of radiopharmaceuticals for molecular and metabolic imaging with PET, the most relevant biomarker for cancer remains the glucose analog FDG (FDG-PET/CT). In contrast to conventional imaging modalities such as CT, Ultrasound and MRI, which detect tumors based on morphologic alterations, PET detects and characterizes tumors based on molecular alterations and known as functional imaging modality. Following intravenous injection, FDG is taken up by cancer cells, similarly to normal glucose. The subsequent conversion of FDG to FDG-6-monophosphate by the intracellular enzyme hexokinase leads to trapping of the metabolite within the cancer cells (22, 23). PET imaging using FDG takes advantage of one of the hallmarks of cancer, namely the Warburg effect: increased glucose metabolism and conversion of glucose carbon to lactate are characteristics of cancer cells as compared to normal cells (24). This increased glucose metabolism in malignancies is mediated via an increased expression and activity of glucose transporters in the cell membrane as well as via changes in the glycolytic enzyme expression and activity. This alteration in glucose metabolism represents one of the early events in carcinogenesis. PET/CT is also helpful in the localization of tumors in cases where conventional diagnostic methods are unable to localize the cancer of unknown primary. For cancer staging, PET/CT offers many advantages over conventional imaging strategies. FDG-PET has high accuracy for staging cancer such as non-small-cell lung, gastrointestinal tract cancers including colorectal and esophageal, thyroid, head and neck, and breast (25-28).

Moreover, a novel radioligand was reported for PET which can detect the expression of urokinase-type plasminogen activator receptors on breast cancer, urinary bladder and prostate cancer. The new radioligand was tested on patients whom diagnosed with mentioned cancers and no adverse events was found after administration and imaging by PET/CT (29).

Rowe et al. conducted a study that finally introduced [ $^{18}\text{F}$ ]DCFPyL, a novel low molecular weighted radiotracer. They reported that, the novel radiotracer was targeted PSMA in patient with metastatic prostate cancer (30). Also, Rowe et al. (31) evaluated the ability to combine MR imaging and PSMA-based PET biomarker for detection of prostate cancer by utilizing imaging biomarker including  $^{18}\text{F}$ -DCFBC PET.

In another study, Ellison and co-workers (32) introduced a novel image-guided radioarsenic-labelled thiolated mesoporous silica nanoparticle using PET scan for cancer patients. Indeed, for PET imaging of tumor vasculature, Chakravarty et al. (33) developed the hollow mesoporous silica nanoparticles conjugated  $(64)\text{Cu}$ -NOTA -PEG-cRGDyK.

Also, to evaluate the biodistribution of three different fabricated contrast agents ( $^{111}\text{In}$ -SPION,  $^{56}\text{Fe}$ -SPION, and  $^{14}\text{C}$ -SPION) conjugated SPION for PET and SPECT imaging an in-vivo study carried out by Wang et al. (34). The lower level of  $^{14}\text{C}$  was reported in reticuloendothelial organs compared to  $^{111}\text{In}$  and  $^{56}\text{Fe}$ .

Furthermore, PET imaging can act as guided device for different types of cancer treatment such as photothermal therapy. Pang and colleges (35), confirmed great enhancement of targeting breast cancer of  $^{64}\text{Cu}$ -Doped PdCu@Au Tripods for photothermal therapy.

Pascual's group interestingly conjugated Mesoporous silica nanoparticle with MUC1 aptamer as radiolabelled tracer for PET and SPECT. They reported that  $^{99\text{m}}\text{Tc}$ (S1-ap-MUC1-Tc) showed significant targeting in tumor-bearing Balb/c mice model (36).

Additionally, SPECT as an excellent nuclear imaging technique which is based on detection of gamma-ray photons, utilized for imaging due to its fast detection time, specificity and more affordable compare to PET. However, SPECT is generally less sensitive and the spatial resolution of PET (5-7 mm) is higher than SPECT (8-10 mm). It was reported that, the spatial resolution of micro-SPECT that is employed in preclinical examination is higher than that of PET due to advancement of imaging tools (37). Micro-SPECT is more accessible in preclinical examinations such as drug development in animal researches. The heavy radioisotopes such as  $^{123}\text{I}$ ,  $^{99\text{m}}\text{Tc}$ , and  $^{133}\text{Xe}$  have utilized for SPECT (38). Zhao et al. (39) conjugated  $^{199}\text{Au}$  with D-Ala 1-peptide T-amide which could detect mouse triple negative breast cancer and its malignancy using SPECT for in vivo studies. The  $^{99\text{m}}\text{Tc}$ -labeled PEG iron oxide developed by Mardu and colleagues displayed multicontrast agent for sentinel lymph node.

Recently, Rainone et al. (40) developed dual probe,  $^{99m}\text{Tc}$ -radiolabeled nanosilica system conjugated with a trastuzumab half-chain for aggressive HER2-positive breast cancer. Moreover, SPECT and MRI provided pre-surgical information like location of the sentinel lymph node. It was reported that the multicontrast could be used for malignant melanoma as well as breast cancer imaging (41). Misri et al. (42) conjugated iron oxide nanoparticles with  $^{111}\text{In}$  anti-mesothelin monoclonal antibody (Mab) targeting antigens for malignant mesothelioma, the dual-modality imaging probe was suggested for MRI/SPECT. Their results showed great uptake of  $^{111}\text{In}$ -MabMB-SPION and signal drop after 24 hrs post-injection.

### **Magnetic resonance imaging (MRI)**

MR imaging is one kind of problem-solving imaging modalities for diagnostic due to its high anatomical and temporal resolution as well as contrast in soft tissue in the clinical application. Basically, the alignment of protons from water molecules in an external magnetic field which due to magnetism property of body tissue is the basic physics of MRI. The spin of protons according to the strength of external magnetic field are affected by the radiofrequency (RF) pulse. When the RF pulse is turned off, the protons can return to the original state by transferring energy to general structure of material and generating an RF signal. The entire process is known "relaxation." After measuring the relaxation by receiver coils, the relaxations turned into an image (43). In contrast to PET/CT, the ability of MRI to deliver functional and biological information is limited. By using MRI contrast agents to enhance the  $T_1$  and  $T_2$  relaxation rates and coupling imaging techniques such as magnetic resonance spectroscopy (MRS) may the limitation of this image modality is decreased.

During the past decades, improvement in instrument brought MRI into a new era of MI. The excellent feature of MRI as an imaging modality for MI are comparably high temporal and spatial resolution, excellent tissue contrast and tissue penetration, no ionizing radiation, non-invasiveness for serial studies, and simultaneous acquisition of anatomical structure and physiological function (44). However, some limitation of molecular MRI is including low sensitivity, and this requires the introduction of imaging agent and development of powerful signal amplification strategies. Imaging agent design is hence an important topic in molecular MRI.

MR imaging contrast agents are mainly divided into two categories: ferromagnetism and paramagnetic. The former is considered as negative contrast agents which mainly reduce the signal in  $T_2$ -weighted images, while the latter is referred to as positive contrast agents that increase the signal in  $T_1$ -weighted images. The most representative negative contrast agents are

superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO), Gd-encapsulated silicon micro-particles, Gd-contained UCNPs and typical positive contrast agents are small molecular weight compounds involving a single Lanthanide chelate as signal producing element (5,45,66).

A lot of works have been done on Gd-based contrast agents for MR imaging, which is among the world most recognized non-invasive techniques employed in clinical diagnosis of patients. At ionic state, Gd is considered toxic but less toxic in chelate form. A variety of nano-carriers, including gadolinium oxide ( $Gd_2O_3$ ) nanoparticles have been used by researchers to improve the  $T_1$  and  $T_2$  contrasts of MR images. Even more recently, a few researchers have tried to the use of graphene oxide (GO) and layered double hydroxides (LDH) as candidates for theranostic applications (45,46).

So far, there are plenty of MR molecular imaging which have proved the potential of this technology. Shahbazi-Gahrouei et al. (47) put forward a conjugated SPIONs-C595 against ovarian cell surface, MUC1 using heterobifunctional linker sulfo-SMCC for early detection of ovarian cancer which offered the best hope for cancer diagnosis. Abdolahi et al. (48) introduced SPIONs conjugated J591 Mab coupled with the extracellular domain of PSMA using sulfo-SMCC linker. MRI data and cell uptake experiments confirmed the high potential of the nanoprobe as a specific MRI contrast agent for detection of PSMA-expressing prostate cancer. In another study, Shahbazi-Gahrouei et al. (49) conjugated 9.2.27 and WM53 Mabs against human melanoma and leukaemia cells, respectively, with cyclic anhydride gadolinium-diethylenetriaminepenta-acetic (DTPA) using 7 T MRI. In-vitro data showed novel contrast agent detected colorectal cancer. However, it was reported that its enhancement effect is not stable at higher concentrations. In this regard, Shahbazi-Gahrouei et al. (50) conducted a study to evaluate the linear relationship between signal intensity for different concentrations of Gd-DTPA. The results revealed that by increasing the concentration of contrast agent the MR signal intensity decreased. Also, Shahbazi-Gahrouei et al. (51-53) synthesised non-toxic Gd-hematoporphyrin, Gd-tetra-carboranyl-methoxyphenyl-porphyrin (Gd-TCP), Gd-DTPA-WM53, and Gd-DTPA-9.2.27 as specific MR imaging contrast agents for melanoma (MM-138), leukaemia (HL-60) and breast cancer (MCF-7) cells. Data revealed 16%, 20% and 21% enhancement of  $T_1$  relaxation times with human melanoma (MM-138) 24 hrs after injection of the dual imaging probes Gd-hematoporphyrin, Gd-DTPA-9.2.27, and Gd-TCP for MRI and boron neutron capture therapy (54).

As stated before, MI is a technique that provides detailed picture in cellular level. Moreover, cell surface antigens as biomarkers offer tremendous potential for early diagnosis, prognosis,

and therapeutic response in a variety of diseases such as cancers (55). In a study Shahbazi-Gahrouei et al. (56) took advantage of the feature and performed an in-vitro study on synthesised Gd-porphyrins, MR T<sub>1</sub> contrast agent, by using an inversion recovery pulse sequence using 11 T Bruker instrument. Results confirmed the MCF-7 cell membrane uptake of synthesized contrast agent, indicating selective delivery and detection of breast cancer. Also, Shahbazi-Gahrouei et al. (57-60) introduced Gd-DTPA-C595 that promised contrast agents for the detection of MCF-7 breast cancer cells and Gd-hematoporphyrin, for detection and diagnosis of melanoma, colorectal as well as breast cancer in MRI. Mirzaei et al. (11) introduced dual probe, nano-dendrimer which C595 Mab Gd<sup>3+</sup>-ALGDG2-C595 that could be used as therapeutic and imaging agents for breast cancer. Indeed, Shahbazi-Gahrouei et al. (61, 62) conducted a study using SPIONs-C595 for detection of MUC1-expressing ovarian cancer. Their findings revealed great tumor accumulation and detection of ovarian cancer by the nontoxic nanoprobe as a specific ovarian MR imaging contrast agent.

One category of magnetic nanoparticles is magnetic iron oxide nanoparticles (MIONs) which has been notably suggested due to its great advantages. Because of extensive application of MIONs in biomedicine, before they can be used in vivo, their cytotoxicity must be investigated (63). In this way, Keshtkar et al. (64) prepared a novel aptamer-conjugated nanoparticle using AS1411 aptamer which was conjugated to Fe<sub>3</sub>O<sub>4</sub>@Au nanoparticles on mouse mammary carcinoma (4T1) cells that overexpressed nucleolin. The results showed that the synthesized nanoprobe produced strongly darkened T<sub>2</sub>-weighted (90% reduction of signal intensity) in 4T1 cells at 45 µg/mL concentration. Recently, Khaniabadi et al. (5,6) demonstrated study on SPION conjugated C595 Mab, MR T<sub>2</sub> contrast agent for early detection of overexpressed MUC1 breast cancer.

True MR-based MI strategies that are clinically available include MRS. Conventional MRI is able to provide high-resolution localization of prostate tumors via their reduced T<sub>2</sub> signal in comparison to the surrounding healthy prostate (65). In patients with moderate and high-risk tumors, staging using the combination of MRS and MRI has been reported to be of incremental prognostic significance. Information on tumor metabolism provided by endorectal MRI/MRS may serve as a predictive marker in prostate cancer, as it can be used to identify patients with a high risk of relapse after radical prostatectomy. MRS, however, has limitations for whole-body imaging in part due to its susceptibility to respiratory and bowel motion.

Liu K et al, synthesized and applied hydrophilic CaF<sub>2</sub>:Yb,Er@CaF<sub>2</sub>:Gd nanoparticles modified using PEG-PAA di-block copolymer benefited from the presence of Gd only in the outer CaF<sub>2</sub>



layer of the nanoparticles  $Gd^{3+}$ -doped  $CaF_2$ -based core-shell nanoparticles for efficient magnetic resonance angiography (MRA) and tumor diagnosis (66).

Gd-based bovine serum albumin (BSA) hybrid-coated hollow gold nanoshells (Au@BSA-Gd) was applied for nanotheranostic agent due to its hollow and porous structures, hence possessing photodynamic/photothermal property and near-infrared fluorescence (NIRF)/PA and excellent  $T_1$  contrast agent for MRI capability as shown in Fig. 1 (67).

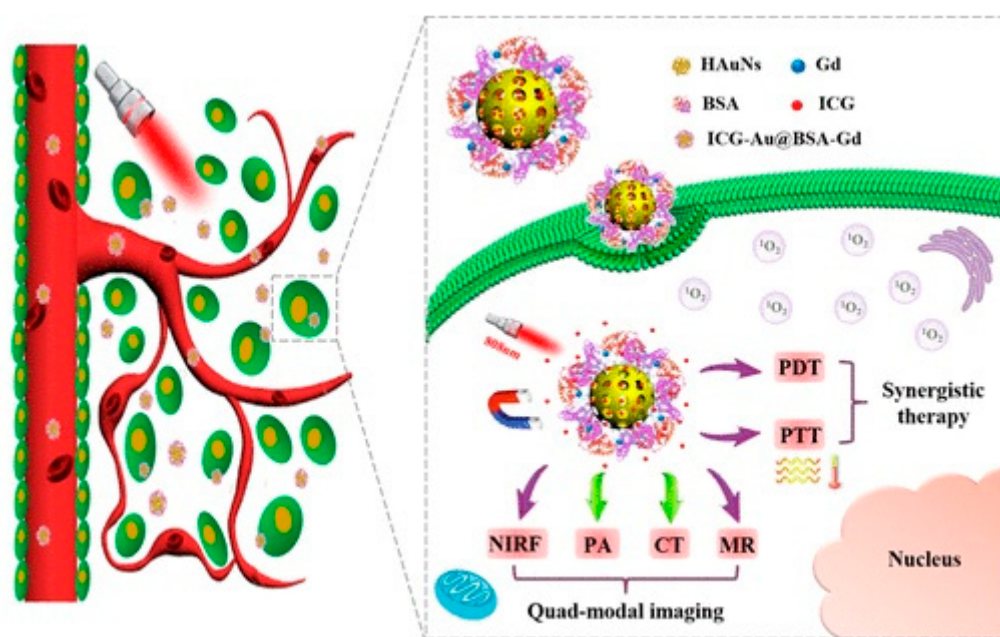


Figure (1): Schematic diagram for multimodal imaging, using ICG-Au@BSA-Gd  $T_1$  contrast media for cancer imaging and therapy (67).

A multimodal contrast agents for integrated preoperative MRI and intraoperative fluorescence image-guided surgery (FIGS) was performed by Payne et al., (68) in which self-assembled multimodal imaging nanoparticles (SAMINs) were developed as a mixed micelle formulation using amphiphilic HA polymers functionalized with either Gd-DTPA for  $T_1$ -weighted MRI. They employed simulated surgical phantoms that are routinely used to evaluate the depth at which near infrared (NIR) imaging agents can be detected by FIGS. Studied nanoprobe imaging agent efficacy was also evaluated in a human breast tumor xenograft model in nude mice.

## Computed Tomography (CT)

It could be daring express that CT is very useful clinical imaging modality for cancer diagnosis and treatment. A CT scan image provides two-dimensional cross-sectional images structures inside of the human body using a narrow x-ray beam. Each rotation of the doughnut shaped scanner provides a picture of a thin slices. Then, all of the slices are stacked together and saved as a group to form 3D image on a computer, in which important details could be difficult to image because of shadowing structures. Image contrast of anatomic structure is based on different x-ray absorption by tissue and lesion. Therefore, transparent tissues like cancers can be imaged by CT. However, low signal-to-noise ratio, reduced the ability of CT to distinguish between neighbouring tissues. Most important futures of x-ray contrast media are including, chemical stability, high solubility, denseness and toxicity. Recently, high resolution small animal CT is opened a new window for preclinical research in molecular level rather than organ and tissue (69, 70).

The integral role of MI is to match the traditional imaging technique modalities, using micro or nanoprobe which enhance the detections of cellular events in addition to early detection of different types of cancers. Fluorescence, radionuclides and paramagnetic chelates are small signalling moieties that have provided as contrast agents.

Several heavy atoms such as iodine, tungsten and barium as contrast media are enhanced the CT images due to great x-ray attenuation coefficient of mentioned metals. Moreover, somatostatin analogue such as  $^{68}\text{Ga}$ -DOTATATE PET/CT and  $^{111}\text{In}$ -octreotide improve the diagnostic of medullary thyroid and bone metastases (71). The iodine-based CT contrasts are either monomeric or dimeric forms of 1,3,5-triiodobenzene derivatives (71). Researchers are put so much efforts to develop and launch different types of contrast media, because the these are able to accumulate selectively at target either chemically or physically interaction with desired site of target. CT provides inexpensive and unmatched high spatial resolution images of anatomical structure as well as blood vessels; also, this imaging technique is much faster and available than MRI (73). Although limitations of CT are soft tissue resolution, deficiency of targeted molecular imaging, ionizing radiation, renal toxicity, functional CT imaging for cancer as well as lower sensitivity (74). CT is always emerged with other modalities for anatomical imaging such as MRI (75), SPECT (76), PET (77) as well as MI to enhance functional imaging and to reflect essentially anatomical conversion by employing novelties beacons that detect cellular events. Moreover, satisfactory contrast and side-effects in patients are inversely proportional. Therefore, expected doses of CT contrast moieties can be condensed when nanoparticles are used. For this reason, nanoparticles have low number density, viscosity

and osmolality in compare to same concentration of molecular contrast agents. Subsequently, by administration of nanoparticle CT contrast the imaging time and less renal toxicity will be expected.

Recently, Li et al. (78) evaluated 20 lung cancer patients with metastatic lymph nodes and 20 non-metastatic patients that diagnosed with lung cancer. All patients received normalized iodine concentration and imaged by dual energy CT. they found that utilizing dual energy CT with iodine quantification might differentiate the metastatic lymph node in lung cancer. Naha et al. (79) demonstrated the utilization of gold-silver alloy nanoparticle as contrast agent for CT and dual-energy mammography. They found that novel contrast agent might be useful for screening the breast cancer and blood pool. In addition, SPECT/CT may help the oncologist for surgical decision by utilizing  $^{99m}\text{Tc}$ -3PRGD2 SPECT/CT for patient whom raised with lymph node metastatic (80). Pandit-Taskar et al. (81) took advantage of the feature that  $^{89}\text{Zr}$ -DFO-huJ591 PET/CT targeted PSMA for prostate cancer. They proved that developed imaging biomarker detected positive soft tissue sites and positive bone lesion for prostate cancer using PET/CT. Li et al. (82) proved the ability of fabricated CT contrast agent, 2-deoxy-d-glucose (2-DG) labelled gold nanoparticle, for detection of human epithelial cancer cell. Aydogan (83) introduced 2-Deoxy-D-Gluucose conjugated onto gold nanoparticle as potential functional CT contrast for cancer detection.

Nanoparticles by surface modification have been functionalized to target affinity side of tumors by attaching to receptors such as the overexpression of folic acid or specific antigens on cancer cells. The mentioned operative approach for delivery of CT contrast media is called active targeting. Generally, there are three major applications of nanoparticles which utilize as x-ray contrast agents in diagnosis; (a) blood pool, (b) passive targeting as well as (c) active targeting. Shi et al. (84) used Au(III) ions to fabricate a novel dendrimer-stabilized gold nanoparticle for imaging and targeting cancer cells. They found that Au DSNPs targeted the cells that expressed folic acids and fluorescein isothiocyanate. Year later, Eck et al. (85) introduced CT contrast media which targeted CD4 receptor of peripheral lymph nodes conjugated gold nanoparticle. The contrast media enhanced CT images in live animal.

Furthermore, Zhang et al. (86) have evaluated AuNPs for imaging of microdamage in bone tissue using conventional method. They introduced AuNPs x-ray contrast agent. So far, Aydogan et al. (87) conjugated gold nanoparticles and 2-deoxy-D-glucose. They reported that by using microCT scanner, a novel fabricated CT contrast media was able to detect human alveolar epithelial cancer (in-vitro). Recently, a new cost-effective CT contrast agent is designed and expected to target overexpressing folic acid side of cancer cells by utilizing CT

imaging modality. The fabricated folic acid-targeted polyethylenimine-entrapped AuNPs showed potential CT contrast in both in vivo and in vitro studies (88). Additionally, it was reported elsewhere that Au PSNPs (methyl-orange-doped polystyrene gold nanoparticle) not only confirmed as CT contrast agent also it suggested to utilize for blood pool imaging (89). The slight difference in the size of AuNPs after modification is due to either specific localization of gold nanoparticle in targeted Tumor (90) or caused by conjugation of antibody onto it (91). Moreover, modification of the surface of AuNPs by coating with polymers such as glycol chitosan or other chemical compound is affected the biological behaviour of NPs at the target sides and increases the stability of nanoparticles, thus imaging capability may improve (92-96).

It was reported the unique biological properties of CT contrast media, Au DENPs (dendrimer-entrapped gold nanoparticle) with a neutral surface for SPC-A1 in-vitro as well as the xenograft tumor model (97,98). Moreover, Au-DENPs-FA presented as a potential CT contrast for human lung adenocarcinoma (99).

To increase the practicable and accuracy of tumor imaging, dual modality is necessary. For example, Au DENPs conjugated gadolinium and M-NPAPF-Au demonstrated as great specific nanoprobe to study the internal organs of mouse for CT/MRI and fluorescence/CT imaging, respectively (100,101).

### **Ultrasound molecular imaging**

Compared with other MI modalities, ultrasound imaging has many advantages including good temporal resolution, qualitative data, real-time practice, non-invasiveness, relatively inexpensive cost, and no ionizing radiation. In addition, it is a unique modality in some sense that it can be employed for diagnostic imaging and as a therapeutic tool. One type of contrast agent that applied in ultrasound (US) modality is Microbubble (MB). MB enhanced the specificity and sensitivity of cancer detection. However, micro meter range size of MB is an obstacle for extravasation from the vasculature. Therefore, only intravascular targets are potentially obtained. Besides, the reduction of unspecific background signals is observed by molecular US imaging. It is worth to mention that, many intravascular targets significantly diagnose inflammation and characterize angiogenesis (102).

Common targets for molecular ultrasound imaging are surface receptor molecules expressed on the luminal side of activated endothelium, either in response to inflammatory or to angiogenic stimuli. Angiogenesis, the process of new blood vessels formation, plays the main role of tumor neovascularisation. Neo-angiogenesis is the initiation of Tumors which can be

predicator of spreading cancer cells to other organs. Angiogenesis needs oxygen and other nutrients to remove useless cellular residues. US is able to expose flow dynamic of vessels less than 500 micrometres which is greater than angiogenic capillaries by using targeted microbubbles.

A study in cellular and molecular biology suggested identifying new angiogenic biomarkers and their molecular signalling path ways with the use of US contrast agent, US imaging enables specific and sensitive depiction of molecular targets (103).

Compared with other MI modalities, ultrasound MI has many advantages including good temporal resolution, quantitative data, real-time practice, non-invasiveness, relatively inexpensive cost, and no ionizing radiation. In addition, it is a unique modality in some sense that it can be employed for diagnostic imaging and as a therapeutic tool (104). Martins et al. (105) confirmed that the use of US for MI with microbubble targeting VEGFR-2 a receptor tyrosine kinas, might be a potential method for noninvasively detecting and quantifying of VEGFR-2 expression in colorectal cancer. Angiogenesis perform a major role in tumor growth in many types of cancers. BR55, VEDFR2-specific US molecular contrast agent confirmed the simplifying of the prostate cancer detection in men employing clinical standard technology (106).

Recently, Abu-Elkacem et al. (107) introduced novel molecular targeted MB, conjugated to 10th type of human-fibronectin. According to their in-vivo and in-vitro results the specific contrast, VEGFR2 was imaged on the neovasculature of breast cancer. In studies, Hao et al. (108,109) developed high molecular polymer MB which marked by quantum dots (MBQDs/PLGA/Her). They proved the diagnosis and treatment of ovarian cancer by ultrasound and photothermal therapy. Lutz et al. (110) developed a mouse model that might make easy the pre-clinical development of microbubbles targeted human vascular. The MILE SVEN1CD276/2008 ovarian cancer cells revealed the US signal significantly higher in compare with the control groups.

Furthermore, for clinical features of US imaging, MBs are conjugated by gene or drug, specifically used for targeted therapy. On the other hand, targeted MB in US may enhance the permeability of cellular membrane. Hence, targeted microbubble conjugated with drugs are able to treat the cancer. Li et al. (111) developed a novel MB-10-HCPT, and they reported that the injection of 10-HCPT loaded MB and exposure to US might expand the drug concentration in tumor noteworthy, leading to a considerable boost in tumor inhibition rate (70.6%) contrast to entire 10-HCPT loaded MB (47.8%) additionally to commercial HCPT administration

(49.4%). Other studies have found that the combination of US and MB could significantly increase the transfection efficacy (112-113).

Also, MBs cannot permeate through the tumor vasculature to the cellular target site to generate the desired diagnostic and therapeutic effect (114). Therefore, researchers are paying more attention to developing nanobubble (NB)-based UCAs for tumor ultrasound imaging. Nano-sized bubbles with various shells composed of polymers or phospholipids and gas, liquid or solid cores have been applied in extravascular US imaging. One strategy for detection of the tumor is to apply specific antibody conjugated MB targeting ligands. Yang et al. (115) observed that a novel NB-Affibody conjugates significantly detected the HER-expressing tumor and launched as specific MI as well as targeted therapy. Recently, Li et al. (116) conducted in-vivo and in-vitro studies on fabricated PNBL-NPY modified nano-sized bubbles. The results significantly presented that, conjugated US contrast agent, targeted Y1 receptor overexpressed breast tumor with minimal toxicity in early stage (Figure 2).

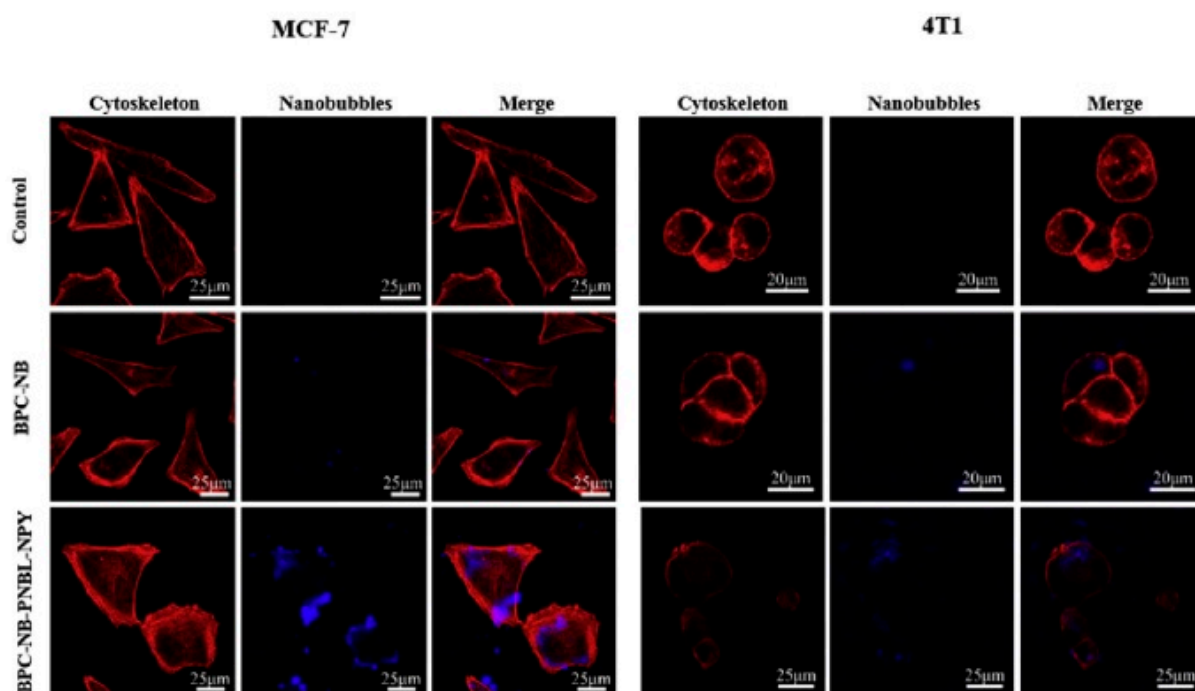


Figure (2): in-vitro images of MCF-7 and 4T1 cells after 12 h incubation with 0.5 mg/mL BPC-NB and BPC-NB-PNBL-NPY. NB are blue and cytoskeletons with rhodamine phalloidin are red (116).

## Optical imaging

Optical imaging is a non-invasive modality for looking inside the body, which uses visible light and the special properties of photons, infrared, and ultraviolet to obtain detailed images of organs and small structures like cells and molecules. These images are used by scientists for research and by clinicians for diagnosis and treatment of abnormalities, in particular cancers. In fact, by applying this modality, various colors of light are using to visualize and to measure various properties of a specific organ or tissue target. Moreover, combination of mentioned technique with other modality such as MRI, CT or X-ray, can enhance the information of disease.

Generally speaking, optical imaging includes a variety of techniques such as Endoscopy, Optical Coherence Tomography (OCT), Photoacoustic Imaging, Raman Spectroscopy, Diffuse Optical Tomography (DOT) and Super-resolution Microscopy.

Recently, many studies have focused on the application of nanoparticles in optical imaging and has garnered attention. In a study, Depalo et al. (117) fabricated silica coated PbS quantum as optical nanoprobe to target the  $\alpha\beta3$  integrin receptor on angiogenic tumor in near infrared region for in-vivo studies. Elsewhere, Indrasekara et al. (118) demonstrated spherical gold nanoparticle tag as potential tumor targeting and surface-enhanced Raman scattering based detection. In another work, Xi et al. (119) discovered as a novel nuclear targeting nanoprobe, Au NPs conjugated to SV-4. They showed that fabricated probe, could assess the cell nucleus, hence, provide the significant information in living cells which employed surface-enhanced Raman scattering for the research of drug delivery and cancer therapy. Also, complementary features of iron oxide and Au-NP attract the attention of researcher to develop the multimodal probes for non-invasive imaging modalities. Reguera and co-workers (120) took advantage of this feature and discovered Janus magnetic-plasmonic nanoparticles as multipurpose versatile probe for surface-enhanced Raman scattering as well as MRI, and CT. Atabaev's group designed a non-toxic dual mode nanoprobe, Au,Gd-Codoped Yttria that successfully enhanced  $T_1$ -weighted images. Simultaneously, the mentioned nanoprobe was used for optical imaging of L-929 (121). Today, scientists put much effort to develop and synthesis the new versatile nanoprobe to provide prominent information on the tumor by improving contrast for bioimaging. Xu et al. (122) demonstrated Au-Gds by bio-mineralization method and summarized the capability of Au-Gds as tri-modal agent for optical imaging, MRI, and CT. Kang et al. (123) conjugated optical imaging and chemotherapeutic for cancer theranostic. For this purpose they conducted a study on a novel theranostic NP, C-hMOS, which could solve non-achieved key for cancer diagnostic and treatment using drug delivery (Figure 3).

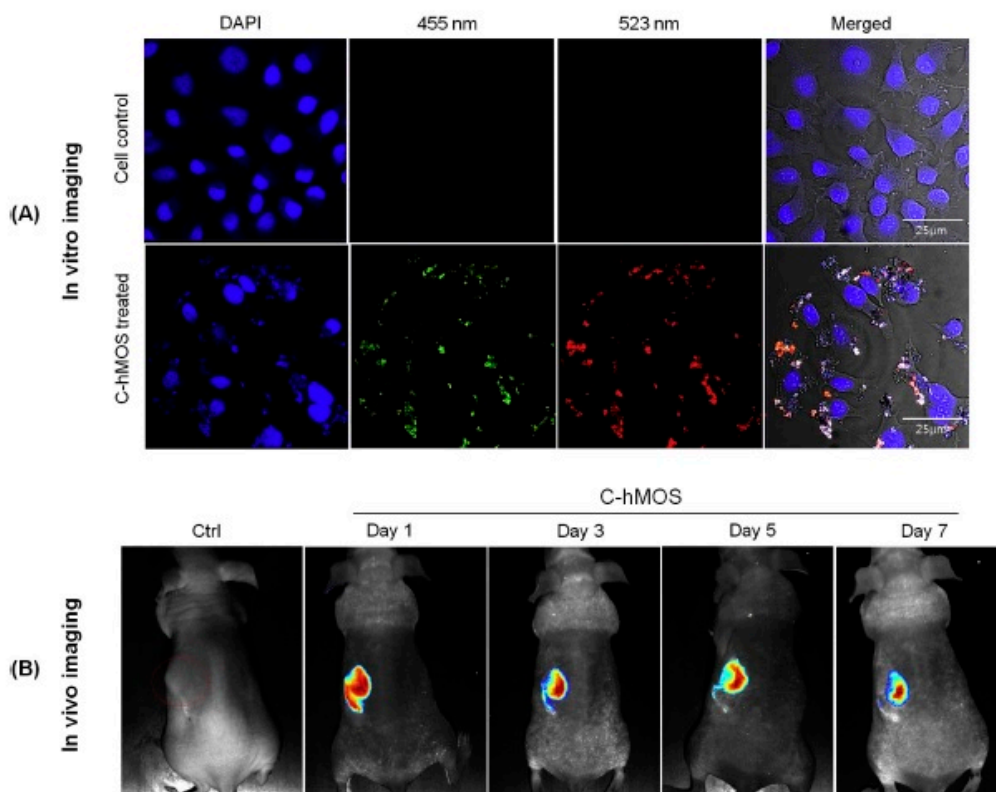


Figure (3): (A) images of treated cells by 40  $\mu\text{g/ml}$  dose of C-hMOS after a period of 4 h. To visualize NP inside cells, different wavelength used. (B) in-vivo images of nude mouse which treated by C-hMOS and monitored for 7 days (123).

### Conclusions

In this review, a broad overview of nanoparticles applications in molecular imaging modalities was provided for cancer detection. These modalities are of great importance in diagnosing of cancer at early stages. This review article could be useful from a point of tutorial and educational view for all medical students and nanotechnology researchers who are interested in cancer imaging and therapeutic. The limitation of this article is that it has not covered every aspect of all imaging modalities for cancer detection in details.

With knowledge of the correlation between the application of nanoparticles and molecular imaging modalities and with the development of targeted contrast agents or nanoprobe, they may provide better cancer diagnosis in the future.



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