REVIEW PAPER

A review on theranostic applications of iodine nanoparticles: Recent findings and perspectives

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ABSTRACT

Application of nanoparticles have in the core of researchers attention for both imaging and therapy of cancers. This review article aimed to prepare an outline on recent applications of iodine nanoparticles (INPs) as theranostic agents in both diagnosis and therapies. Among various strategies are used in treatment of cancers, radiotherapy with radiopharmaceutical agents especially radioisotope of iodine displays satisfactory results for numerous types of cancers. In recent years, new investigations were done in order to develop the novel structure of INPs. These nanoprobes could act as efficient theranostic purposes. Iodine nanoparticles may be applied in nuclear medicine imaging and may be effective with mega voltage (MV) photons in cancer therapy, but this remains to be tested with different cancer cells. By using INPs, effective steps can be taken in the future in both diagnosis and treatment of cancers. This review emphasized the recent research findings on the application of INPs in medical imaging and therapeutic of cancers. The current challenges and the perspectives for their future applications were also represented and discussed.

Keywords: *Iodine nanoparticles (INPs), Medical imaging, Radiation therapy, Theranostic*

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INTRODUCTION

Cancer, which remains as one of the leading causes of mortality around the globe in recent years, is a multicellular disease that can arise from all cell types and organs with a multi-factorial etiology. Mortality rate of cancer significantly increases by diagnosing in the early stages, following by appropriate treatment [1]. The most common strategies to manage the aforementioned are surgery, chemotherapy, radiation therapy (RT) and combinational therapy. Along with surgery and chemotherapy, radiation therapy remains an important method used in cancer therapy [2].

The most goal of RT is to deliver of maximum dose to the cancer cells and sparing the normal surrounding tissues. However, damage of surrounding healthy tissues by the radiation still remains a big obstacle in the therapeutic approaches [3]. To manage these challenges, it is necessary to decrease side effects, enhance patient selection and estimate eventual toxicity. Taking these factors into account, the combination of therapy and targeted cancer imaging is a significant procurement [4].

Nuclear medicine imaging include positron emission tomography (PET) or single photon emission computed tomography (SPECT) allow scientists to focus on bio-distribution and tumor targeting efficacy based on drug accumulation in the tumor site and also monitor the cancer progression [5-7].

As concerns nuclear medicine contest, there are many radionuclides particularly suitable for theranostic approaches such as iodine-131 (^{131}I), luthetium-177 (^{177}Lu), actinium-225 (^{225}Ac), bismuth-213 (^{213}Bi) and yttrium-90 (^{90}Y) [8-10]. In nuclear medicine history, the first theranostic radiopharmaceutical was radioiodine, which used for imaging and therapy in thyroid diseases [11]. Since then various radioisotopes of iodine have been used in medical imaging purposes. Iodine-123, a pure gamma emitter, has excellent imaging characteristics as a result of its optimal

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photon energy of 159 keV, which has sufficient energy to detect by the scintillators. In many studies, results showed the superior imaging quality of the ^{123}I in comparison with ^{131}I [12, 13]. Iodine-124, used as theranostic agent in thyroid cancer is a proton-rich isotope of iodine with positron emitting [14]. Its 4.2 days half-life indicated that it could be promising for long biological imaging processes and implementation of positron emission tomography/computed tomography (PET/CT). Moreover, a variety of materials have been labeled with iodine-124 for PET imaging purposes; ^{130}I and ^{131}I are used for therapy of thyrotoxicosis [15]. Iodine-131 has the advantage of emitting both gamma and beta rays, which make it suitable for both medical diagnosis and treatment procedures. It also plays a major role as a radioisotope present in nuclear fission products. Nowadays, application of INPs have in the core of researchers attention for both imaging and therapy. The aim of this review is to prepare an outline of recent findings in theranostic iodine based nanoparticles applications.

Theranostic applications

The concept of theranostic refers to simultaneous combination of therapeutics and diagnostics for specific targeted therapy and also guided imaging in order to achieve a personalized treatment in the early stage. Various categories of nanomaterials such as polymer-, carbon- and metal nanoparticles have been utilized as theranostic purposes [11]. Fig 1. showed the properties of nanotheranostics such as molecular structure, biological interactions, and therapeutic methods.

As previously mentioned, the oldest example of theranostic approach to cancer therapy refers to radioactive iodine therapy. After expanding the idea of using radioactive iodine in case of patients having thyroid diseases, the first clinical application was performed with ^{131}I [16]. The combination of iodine with other therapeutic techniques has led to more effective recognition and treatment of cancers. In 2015, a research team have designed iodine containing nanoparticles by dropping ^{131}I in CuS nanoparticles and coating with PEG (CuS-^{131}I -PEG), which were used as the theranostic agents for imaging-guided combined radiotherapy and photothermal therapy (PTT-RT) [17]. Their intrinsic high near-infrared (NIR) absorbance and the doped ^{131}I made them utilized in photothermal therapy and radiotherapy, respectively. Due to the high NIR optical absorbance of PEG (CuS-^{131}I-PEG) as well as its radioactivity properties it is an optimal choice for using combined PTT and internal RT of tumor ablations [18]. In another work, it was conducted on a subcutaneous mouse tumor model by direct or systematic injection into tumors, which were then exposed to a low power density NIR laser with wavelength of 808 nm, achieving a remarkable synergistic therapeutic effect as a suitable material for PTT [19].

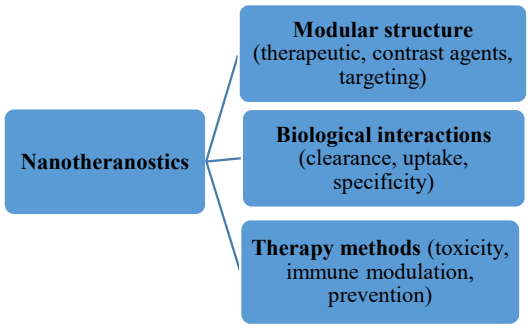

Fig 1. Properties of nanotheranostics [11]

Moreover, their ability of radioactivity and x-ray absorbing made them suitable for *in vivo* gamma- and CT imaging. The cytotoxicity of these nano-agents could be efficient for metastatic tumors, and it prolonged the survival of animals [20]. In another work, the iodine containing nanoparticles were prepared and coated with gold (Au) shell and finally functionalized with hyaluronic acid (PMATIB/PEI/Au nanoshell/HA). This nano-platform provided appropriate condition for CT imaging and photothermal therapy by x-ray- and near infrared (NIR) absorption [21]. In 2019, a research team in South Korea, designed radioiodine-124-labeled gold nanoparticles with crushed gold shells (^{124}I-Au@AuCBs) as a theranostic nanoplatform (photothermal therapy/PET/CT imaging). They labeled macrophages with this nanoparticle and found that it could display antitumor effects both *in vitro* and *in vivo* conditions [22]. To elevate the efficiency of photodynamic therapy, in 2020, Wen Zhou and his colleagues prepared semiconducting polymer nanoparticles with high iodine density (SPN-I) being utilized in CT/fluorescence dual-modal imaging with high level of sensitivity and deep penetration in tissues. In their work, the iodine induced intermolecular heavy atom effect (HAE) and boosted the O2 generation. In addition,

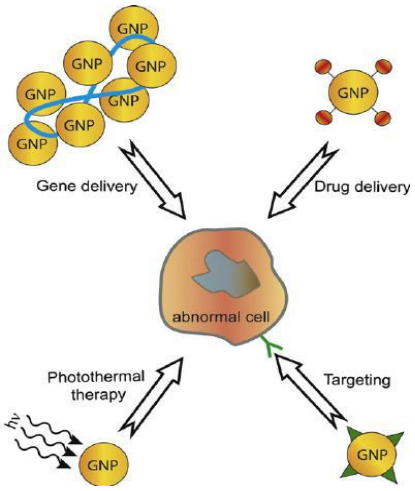

Fig 2. Nanotheranostic applications of nanoparticles (NPs) in diagnosis and therapy of cancers

high fluorescence quantum yields of SPN-I and the presence of iodine as contrast agent made it efficient for fluorescence and CT imaging, respectively. Antitumor activity of nanoparticles was also tested *in vivo* on Lewis cell xenograft tumor mouse and demonstrated higher inhibition rate (98.7%) than that of its counterpart nanoparticles (SPN-I) (85.1%) [23]. Nanotheranostic applications of nanoparticles (NPs) in diagnosis and therapy of cancers are presented in Fig 2.

As an example of combined imaging and chemotherapy, iodine contacting disulfide cross-linked nanoparticles (cRGD-XIPs) were fabricated as non-toxic and smart nanostructures, which enhanced CT imaging and effectively loaded Dox (Doxorubicin) with properties of stability, high drug loading and fast intracellular release. *In vitro* and *in vivo* effects of iodine nanoparticles were studied and exhibiting more potential in the preventing growth of B16 melanoma cells compared to non-targeted XIPs-Dox [24]. Several years after, nanotheranostics applications were done by sing different biocompatibility materials combination with various imaging modality contrast agents [25, 26].

Iodine based nanoparticles in imaging

The rapid development of medical imaging has facilitated cancers detection in the early stages. In another words, medical imaging applications have the role of prediction, detection, localization, screening, diagnosis, and staging, assessment of tumor care and tumor response. It constitutes a fundamental part of cancer clinical researches and is used in all stages of cancer management [27]. High performance in imaging requires improvements in sensitivity and contrast agent targeting. Different radiopharmaceutical agents and radiotracers are used for this purpose based on properties of the tumor. Various radioisotopes of iodine have diagnostic potential and used for cancer imaging strategies [28-31].

In a nuclear medicine study, a nanoprobe was prepared by attaching iodine-125 to modified gold nanoparticles (cRGD-PEG-AuNP) and was used as SPECT/CT imaging agent. *In vivo* studies on nude mice showed that they could reach cancer cells (U87MG cells) in a short time after 10 minutes injection with high stability [30]. In another work, a research team designed ^{124}I labeling polymeric nanoparticles, which had potential to detect endothelium by functionalizing with different ligands of determinants present on the surface in animal studies. The properties of nanoparticles made them stable, non-invasive probes, for which they were used in PET imaging of the lung in mice [27]. In a study, researchers have developed nano-hybrid structure containing cyclic Arg-Gly-Asp-conjugated gold nano-rods combined with ^{131}I ([^{131}I]GNR-PEG-cRGD) for targeting imaging purposes, with description of AuI had utilized in specific SPECT/CT imaging [22].

Application of different nanoparticles labeled with radioisotopes, in particular iodine-125 were reported in many research works as nuclear imaging agent for *in vivo* imaging and biodistribution analysis [32-34]. For instance, Chrastina and Schnitzer have applied functionalized iodine-125 labeled to silver nanoparticles (Ag NPs) as a single-photon emission computerized tomography (SPECT) imaging probe [29]. They conducted an *in vivo* study by systemic administration of ^{125}I-Ag NPs on BALB/C mice to investigate its eminent uptake in the spleen (41.5%ID/g) and liver (24.5%ID/g). This method enables rapid iodine-125 radiolabeling of silver nanoparticles with a specific activity sufficient for *in vivo* imaging and biodistribution analysis [35, 36].

The distribution of the nano-probes was also investigated in breast cancer cells such as B16F10 and MCF-7 [27]. Consequently, the specific nanoparticles were synthesized by integration of iodine and carbon quantum dots

(I-CQDs) introduced as well-organized probes for fluorescence/CT imaging 30]. In addition, to enhance the potential of specific diagnosis, the surface of nano-probes was functionalized with an antibody, cetuximab, which is highly expressed in lung, head and neck cancers and is capable of binding with EGF receptor (I-CQDs-C225) [31, 32]. The targeting tests was done *in vitro*, on three different types of cells including HCC827, H23 and HLF with high sensitivity. In 2020, Han et al., conjugated ^{124}I to gold nanoclusters, which were modified with luteinizing hormone releasing hormone (LHRH) peptide, as therapeutic targeting agent. The receptor of LHRH is excessively expressed in diverse kinds of cancers, breast and lung cancer are some examples. Both PET and fluorescence imaging studies of A549 xenografted tumor model and A549 lung tumor model demonstrated that these nanostructures had a potential to be exploited or the early detection of lung cancer [33]. In a study, Clark et al. [34] have conducted two types of nanoparticles based on iodine and gold in dual micro-CT imaging for using in small animals to measure fractional blood volume and vascular permeability as a potential imaging methods. In another work, Ashton et al. [37] showed that dual-energy micro-CT using contrast agents of gold and iodine nanoparticle can be accurately measured functional vascular parameters in mice model and has the potential for better diagnosis of different types of lung cancer.

Iodine based nanoparticles in radiation therapy

For many years, numerous fascinating ideas have been proposed and tested in order to increase the radiation dose delivered to the tumors, while keeping normal cells. High atomic number radio-sensitization is an efficient approach for improving RT effectiveness. Iodine is a heavy element recognized as successful progress of non-toxic x-ray contrast media, leading to radio-sensitization clinical trials. In 1982, the studies of a research group estimated that the radiation dose absorbed from low-energy x-ray (kV) or gamma ray source could be enhanced when the tissue was loaded with iodine. As a result, they witnessed that the dose was increased because of contrast-medium (CM) and this enhancement is caused by the absorption and photoelectric effects of the iodine atoms [28]. In this line, a study was done with rabbit brain tumors involved injections of CM, by irradiation of implanted tumors, meaning that the addition of CM shortly prior to RT contributes to an even more increase in survival among the early dying rabbits, with the iodine being the main grounds for the aforementioned [38]. By the combination of human brain tumors and modified CT, in 1999, higher iodine concentrations in the tumor led to improved absorption of x-ray. It was demonstrated that computerized tomography scanner (CTRx) irradiation of brain tumors having 10 mg of iodine per gram of tumor was as good as the dose distribution originating from conventional 10-MV x-rays [39].

In another study carried out by Adam and collaborators in 2016, using synchrotron stereotactic radiation therapy (SSRT), patients were injected with iodinated contrast agent intravenously; this was followed by the irradiation with 1 to 10 coplanar isocentric beams and this intratumoral iodine concentration (1.94 to 0.12 mg/ml) led to a 20% local averaged dose increase [40]. Current standard clinical x-ray contrast agents have some deficiencies such as rapid kidney clearance, because of low molecular weight providing the capability of vascular imaging for very short time. This is not appropriate for preclinical microCT imaging due to longer scan time required for high resolution imaging. To overcome these insufficiencies, in 2018, Hainfeld et al., have designed a new polymer iodine nanoparticle (INP) with small size (20 nm) properties, results in having better tumor penetration, covalent construction for stability, show long blood half-life of 40 hrs, steady whole body clearance (50% over 6 months). Moreover, possess non-toxic properties after an intravenous injection of 4 g iodine/kg leading to exploitations anticipated by vascular imaging and tumor therapy [41]. After that, in 2019, they used these INPs for glioma therapy in a mouse model and they targeted 20 nm nanoparticles into brain tumors after intravenous injection. Using the combination of RT and iodine nanoparticles, they understood that more than two times in comparison with RT alone increased life extension. Furthermore, these nanoparticles could improve the effectiveness of chemotherapy when combined with chemotherapeutic drugs like Doxil [42].

In the next investigation, the non-toxic INPs were delivered into triple negative breast cancer (TNBC) tumors, growing in the brains of athymic nude mice that showed high uptake of iodine

(with uptake peaks at 4.5%, an average of 2.9% of 7 g iodine/kg body weight). It is considerable that the number of mice with pretreatment INPs witnessed longer life extensions, reaching more than 10 times of that provided merely by RT. It is estimated that the combination of INP-RT with synergistic chemotherapy and other therapies using equipment utilized for optimized irradiation results in enhance therapeutic approaches toward human brain metastases [43].

CONCLUSION AND PERSPECTIVE

Many metal nanoparticles, such as gold nanoparticles (AuNPs) are highly colored and high doses of IV injection NPs are necessary for the high tumor concentration in tumor site, which resulting in skin discoloration and poor clearance. Using INPs can overcome many of AuNPs problems and have some properties like; non-toxicity at high doses (7 g I/kg), colorless, highly x-ray absorbing, long blood half-life (40 h), high uptake in tumors, slow but consistent liver clearance (50% by six months, 70% by 12 months), organic (not non-degradable metal) and reasonable in cost [44, 45]. Therefore, developed INPs that are almost colorless, non-toxic, lower cost, and have reasonable clearance, can overcome major drawbacks of the AuNPs.

Recently, INPs have been attracted increasing attention due to their potential applications in both imaging and therapy. Following by Hainfeld et al., studies [42], in 2019, which used Doxil + INPs and RT to increase of life of mice 2 times more than RT alone. Many research works by the author and his colleagues focusing on the use of INPs + RT + Chemotherapy drug (Oxaliplatin) as a nanotheranostic agent in colorectal cancer cells (HT-29) are underway

As mentioned earlier, the INPs may be effective with mega voltage (MV) photons, but this remains to be tested with different cancer cells. By using INPs, effective steps can be taken in the future in both diagnosis and treatment of cancers. Of course, radioactive properties of some iodine radionuclides in the synthesis process and their side effects and radiobiological considerations are main questions need to investigation and answer.

Overall, authors hope that this article will present recent progresses in INPs applications and will be useful as a scientific reference to researchers and those who learn more about this new area of nanomaterials in medical imaging and therapeutics.

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