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Review Article

Nanoparticles for targeted cancer radiotherapy

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ABSTRACT

Radiotherapy, where ionizing radiation is locally delivered either through an external beam or by surgically implanting radionuclide-based seeds in the tumor, is one of the gold standard treatments for cancer. Due to the non-selective nature of radiation, healthy tissue surrounding the cancerous region is usually affected by the treatment. Hence, new strategies, including targeted alpha therapy, are being studied to improve the selectivity of the treatment and minimize side effects. Several challenges, however, limit the current development of targeted radiotherapy, such as the functionalization of the therapeutic agent with targeting vectors and controlling the release of recoiling daughters. Nanoparticles offer unique opportunities as drug delivery vehicles, since they are biocompatible, enhance the cellular uptake of drugs, and are easily functionalized with targeting molecules. In this review, we examine how nanoparticles can be used for targeted radiotherapy, either as sensitizers of external beams or as delivery vehicles for therapeutic radionuclides. We describe the clinical relevance of different types of nanoparticles, followed by an analysis of how these nanoconstructs can solve some of the main limitations of conventional radiotherapy. Finally, we critically discuss the current situation of nanoparticle-based radiotherapy in clinical settings and challenges that need to be overcome in the future for further development of the field.

KEYWORDS

radiotherapy, targeted cancer radiotherapy, nanoparticles, cancer, targeted alpha therapy, external beam

1 Introduction

Therapy based on ionizing radiation is used to treat primary tumors as well as to prevent cancer relapse after the main tumor has been surgically removed [1–3]. For example, radiotherapy and surgery are the standard protocols to treat risky localized prostate cancer patients [1]. Radiotherapy can also interact synergistically with other treatments; it is frequently applied either before, during or after chemotherapy [4–6]. Radiation can be delivered to cancer cells either externally via a beam or internally (brachytherapy) through an implanted radiation source (Fig. 1) [7, 8]. Ionizing radiation damages multiple intracellular components, such as DNA, through molecule ionization that generates a free radical cascade [9, 10]. Although it is very effective at damaging tumor cells, ionizing radiation also affects surrounding healthy tissue. Hence, control over the administered radiation dose is fundamental to minimizing toxicity for normal tissues, and new strategies to target cancer cells are under investigation to achieve tumor-specific radiotherapy [11, 12].

Nanoparticles offer unique opportunities for radiotherapy [13, 14] because of their high surface-to-volume ratio [15], enhanced cellular uptake [16–19], and ease of functionalization [20–26]. Nanoparticles can be made of high-*Z* elements, acting as radiosensitizers for external ionizing radiation beams, or they can be used as delivery vehicles for therapeutic radionuclides. By functionalizing the nanoparticle surface with targeting molecules, tumor-specific delivery of therapeutic dose can be achieved [27, 28]. Alternatively, tumor accumulation can be

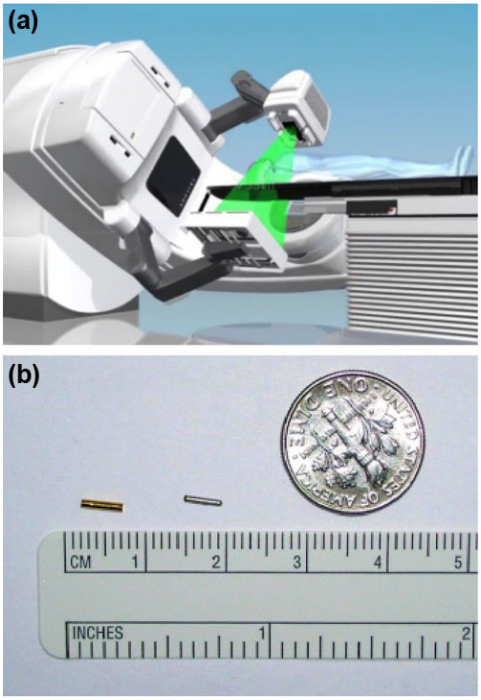

Figure 1 Two different types of radiotherapy used in clinical setups. (a) Scheme of external beam radiotherapy. Adapted from Ref. [45], © Ren, X. C. et al. 2019. (b) Radioactive brachytherapy seed, next to a USA coin worth 10 cents. Adapted with permission from Ref. [46], © Elsevier B.V. 2016.

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achieved by engineering nanoparticle coating and controlling the nanoconstruct circulation time (known as passive targeting) [29, 30]. Furthermore, the unique optoelectronic properties of inorganic nanoparticles, which are controlled through crystal engineering [31–34], can be exploited for combining radiotherapy with other treatments, such as phothermal therapy [35, 36] or theranostics [37]. Because this manuscript focuses on the application of nanoparticles for targeted radiotherapy, we also recommend previous reviews that covered nanoparticle fundamentals, including syntheses [38, 39], properties [21, 40], functionalization strategies and other biomedical applications [41–44].

In this review, we analyze the development of nanoparticles for targeted cancer radiotherapy. We describe the current challenges that therapy based on radiation presents, including confining therapeutic dose to the tumor region and controlling recoiling daughters. We then identify how different type of nanoconstructs can be used to solve these issues, highlighting the design principles, such as nanoparticle materials and structure, and targeting vectors that allowed for the overcoming of main difficulties. The nanoparticles covered in this work are classified either as sensitizers for external beam radiation or as drug delivery formulations for therapeutic radionuclides. Lastly, we list future research opportunities the field may hold as well as current questions that need to be solved before nanoparticle-based radiotherapy can move to clinical settings.

2 Nanoparticles as enhancers for external beam radiotherapy

Ionizing radiation is usually produced by a linear accelerator, and the beam is directed to the cancerous region. There are different classes of external beam radiotherapy, which are chosen based on the tumor type. The most common therapies rely on high-energy X-rays, where megavoltage (over 1,000 kV) or orthovoltage (100 to 500 kV) photons are used to treat deep-seated or superficial tumors, respectively [47–49]. Alternatively, energetic particles, such as protons and neutrons, are also used for cancer therapy [50]. The latter are advantageous over traditional X-rays because the region where the energy is delivered is more confined due to the particles' sharp Bragg peak (Fig. 2) [50]. Nevertheless, particle-based radiotherapies, where protons, neutrons or heavier ions are used as ionizing radiation, are less common than conventional ones based on X-rays due to their high costs.

As previously described, ionizing radiation is non-selective and damages cells without discrimination. Hence, nanoparticles functionalized with biomolecules that target tumors can improve treatment efficiency by increasing their selectivity towards cancer cells.

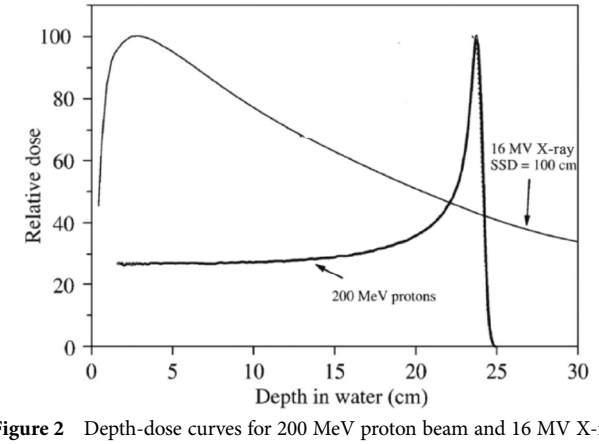

Figure 2 Depth-dose curves for 200 MeV proton beam and 16 MV X-ray beam. Adapted with permission of Ref. [50], © Elsevier B.V. 2016.

2.1 X-ray as ionizing radiation

The interaction between X-ray and a material can result in four major types of processes: photoelectric effect, Compton effect, pair production or Rayleigh scattering [51]. The probability of interaction between an atom and a photon increases with atomic mass because of the larger attenuation cross section (Fig. 3) [52].

High-Z elements show higher photoelectric absorption coefficients that can deliver more significant dose to the surrounding cells [54]. Dose enhancement by high-Z elements is known as the radiosensitization effect. The collision between energetic photons and heavy atoms also produces Auger electrons, which enhance radiotoxicity through DNA damage as well as ionizing water molecules, producing cytotoxic reactive oxygen species [55, 56]. Following this principle, iodine nanoparticles were used to treat advanced human gliomas grown orthotopically in mice [57]. The use of nanoparticles more than doubled the median life extension in mice compared to radiotherapy alone. Furthermore, iodine nanoparticle-based radiotherapy improved the effect of chemotherapy, leading to long-term mouse survivors. The use of multi-component nanoparticles also allowed for the obtaining of multiple therapeutic effects with only one formulation. For instance, poly(vinylpyrollidone)- and selenocysteine-modified Bi_2Se_3 nanoparticles were used as a versatile agent that (1) acted as a radioenhancer due to their high X-ray attenuation, (2) showed high near-infrared absorption ability for photothermal therapy, and (3) released a small amount of Se that enhanced the immune function and reduced radiotherapy side-effects *in vivo* [37]. Bi_2Se_3 nanoparticles have also been used to overcome hypoxia-associated resistance to radiotherapy.

The efficiency of ionizing radiation is highly dependent on cellular oxygenation level [58], where high levels of oxygen facilitate the formation of organic peroxides at the broken ends of DNA that are more difficult to repair, enhancing the radiotherapy-induced cell damage. Hence, hollow Bi_2Se_3 nanoparticles were loaded with the oxygen carrier perfluorocarbon, providing both high X-ray-absorbing performance and release of oxygen (Fig. 4(a)) [59]. A similar concept was developed using porous platinum nanoparticles (Fig. 4(b)), where the metal showed high X-ray absorption attenuation as well as increased tumor oxygenation by transforming intracellular H_2O_2 to O_2 [60].

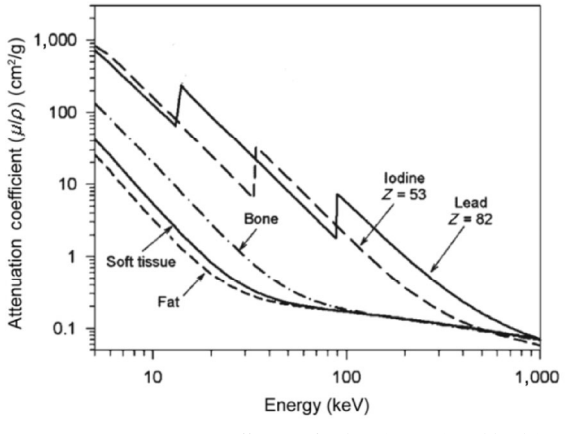

Figure 3 Mass attenuation coefficient of iodine (Z = 53) and lead (Z = 84) compared to biological materials. Under the same photon energy, heavier elements tend to show higher X-ray mass attenuation coefficients. Adapted with permission of Ref. [53], © Society of Nuclear Medicine and Molecular Imaging 2005.

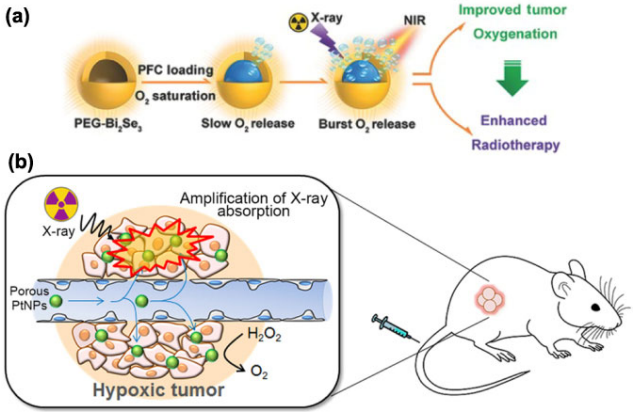

Figure 4 Bifunctional nanoparticles that acted as radio sensitizers and anti-hypoxic agents. (a) Hollow Bi_2Se_3 nanoparticles loaded with oxygen precursor perfluorocarbon (PFC). Adapted with permission of Ref. [59], © WILEY-VCH Verlag GmbH&Co. 2016. (b) Porous platinum nanoparticles that promote intracellular oxygen generation. Adapted with permission from Ref. [60], © Elsevier Ltd. 2019.

Alternatively, nanoparticles that release cytotoxic carbon monoxide or nitric oxide upon irradiation also showed on-demand therapeutic effect without reliance on oxygen [61, 62]. All these nanoparticle-based strategies against hypoxia-associated radioresistance promoted tumor remission *in vivo* in mice.

Gold as a high-*Z* element shows strong radiosensitization effect when delivering a dose to tumors [63]. Furthermore, gold nanoparticles are some of the most studied nanoparticles because of their ease to functionalize and biocompatibility [64, 65]. For example, gold nanoparticles were conjugated with Arg-Gly-Asp (RGD) peptides to target cancer cells that express RGD receptors, such as α5- and αv-integrin [27]. This nanoparticle-based radiotherapy decreased cell viability and inhibited the invasive activity of breast cancer cells (MDA-MB-231). Gold nanoparticles have also been used for targeted prostate cancer radiotherapy in mouse models, where prostate-specific membrane antigen was functionalized on a nanoparticle surface to achieve the specific therapeutic response [66]. Similar to other gold nanoparticle-based therapeutics, radiotherapy performance is affected by particle morphology. A systematic study with different shaped gold nanoparticles showed that spherical ones performed better over other commonly used in nanomedicine, such as rods and stars [67]. Because gold nanoparticles can be easily functionalized with drug-loaded polymers, nanoconstructs for synergistic radiotherapy and chemotherapy have been prepared by capping gold nanocrystals with chitosan and loading them with anti-cancer doxorubicin [68]. Similar work has been done with other high-*Z* element-containing nanoparticles, such as biomimetic copper sulfide functionalized polyethylene glycol, which were used as drug carriers for chemotherapeutic agents [69]. Because gold also displays strong imaging contrast on computer tomography, gold nanoparticles have been used in theranostics where particles acted as both radiosensitizers and contrast agents [70, 71]. Other nanoparticles that have been explored for radiation-based theranostics include those made of silica, which can adsorb high loads of therapeutic agents in their pores [72, 73], and thulium oxide and bismuth oxide [18, 28].

2.2 Protons as ionizing radiation

Initially, nanoparticles made of high-*Z* elements were mainly applied to X-ray therapy, since they were not expected to sensitize particle-based radiation (i.e. the interaction between ionizing particles and materials shows little *Z* dependence) [74]. Nevertheless, the first *in vitro* experiment that employed gold nanoparticles in proton radiotherapy showed limited but promising results [75]. Although only moderate therapeutic effect was observed in colorectal and breast cancer cell lines when a proton external beam and gold nanoparticles were combined (between 2 and 12% decrease in survival fraction of treated cells), these results sparked interest in the use of nanoparticles as proton radiosensitizers. Subsequent studies improved the radiotherapeutic performance (up to 19% higher relative biological effect compared to conventional X-ray therapy) by optimizing the administrated doses [76]. Since then, other nanoparticles made of platinium and gadolinium have been explored *in vitro*, showing the induction of DNA nanosize damage that is lethal for cells [77]. *In vivo* experiments with colorectal carcinoma model Balb/c mice showed between 58% and 100% one-year survival rates for animals treated with both gold nanoparticles and proton radiotherapy (depending on the dose), compared to 11% to 13% survival rates for mice treated solely with proton-based therapy [78]. Unlike previous experiments performed with non-targeting nanoparticles, recent studies have developed gold nanoparticles conjugated with the targeting vector cetuximab [79]. By exploiting nanoparticle accumulation on EGFR-overexpressing A431 cells, selective proton radiotherapy was demonstrated.

Because experimental data contradicted initial expectations that high-*Z* element nanoparticles would perform poorly as radiosensitizers, several computational studies have been performed to understand the mechanism of sensitization. Although different conclusions have been reported depending on the method used, all simulations agreed that radial dose enhancement is localized around the nanoparticle surface, fading after a few nanometers [80–82]. Hence, it has been proposed that the physical radiation-based effect is not primarily responsible for an enhanced therapeutic response, and other nanoparticle-induced biological or chemical processes may be involved [81]. Interest in better understanding the biological effect of these nanoparticles has prompted new mechanistic studies, which have identified the inhibition of thiredoxin reductase as one of the main targets of the nanoparticle-based proton radiotherapy [83].

2.3 Neutrons as ionizing radiation

Similar to proton radiotherapy, external neutron beams are also used to treat certain type of tumors. In order to minimize damage to healthy tissue, a boron-10-based therapeutic agent that produces secondary radiation particles upon collision with neutrons is frequently used to induce cancer cell death [84]. This strategy is known as neutron-capture therapy, and it is a two-step process, where a drug that contains boron-10 is initially injected into the patient with the tumor, and then epithermal neutrons are irradiated [85–87]. The cross section for neutron capture of boron-10 is several orders of magnitude higher than biological tissue [88]. After the neutrons are captured by boron-10, high-energy alpha particles are emitted that kill the surrounding cancerous tissue [88]. Because the energy of the beam is pimarily distributed around the boron-10 compounds, this therapy provides higher spatial control than conventional electron beam radiotherapies. Boron neutron capture therapy has been studied as an alternative treatment for several radioresistant tumors, including gliomas, meningioma and superficial melanomas [89, 90].

Nanoparticles have been explored to deliver boron-10 more efficiently to tumor cells. For example, poly(DL-lactide-co-glycolide) (PLGA) nanoparticles have been used as carriers in tumor-bearing mice because of the polymer biocompatibility

and biodegradability (Fig. 5(a)) [91]. The administration of boron-10 through the polymeric nanoparticles allowed boron to be excreted through urine without accumulation in other organs. Moreover, targeted boron neutron capture therapy was achieved by functionalizing anti-HER-2 antibodies on boron10-containing gold nanoparticles (Fig. 5(b)) [92]. During the neutron capture reaction, γ-rays are also emitted [95, 96], which cause side-effects, such as inflammation, through reactive oxygen species generation [97]. Hence, cluster-containing redox nanoparticles have been synthesized to simultaneously delivery boron-10 as well as reactive oxygen species scavengers (Fig. 5(c)) [93]. Another challenge of boron neutron capturing therapy, particularly in glioblastoma treatment, is achieving selective imaging, targeting and tissue accumulation to kill tumor cells without affecting surrounding healthy neurons. This challenge was overcome by developing a boron-10 core silica shell nanoparticle that displayed a targeting peptide on the surface that could pass through the blood barrier and selectively bind to glioblastoma tumor cells (Fig. 5(d)) [94]. In addition to their therapeutic effects, these nanoparticles contained gadolinium-based contrast agents to enhance the contrast of magnetic resonance imaging, allowing image guided therapy and prolonging the 50% mouse survival span from 22 to 39 days.

Because the ^{157}Gd isotope shows a 66-fold higher thermal neutron cross section than ^{10}B, gadolinium has been explored for use as an alternative therapeutic agent [98]. For instance, calcium phosphate nanoparticles, which show high biocompatibility and biodegradability [99], loaded with ^{157}Gd-based contrast agents have been studied for neutron capture therapy [100]. Mice treated with these nanoparticles and irradiated showed up to four times higher tumor suppression than control groups.

2.4 Heavier ions as ionizing radiation

Heavier ions, including carbon, neon or iron, benefit from a sharper Bragg peak than protons and neutrons [101], confining the therapeutic dose in a narrower range. Moreover, heavier ions show higher linear energy transfer at the Bragg peak, inducing stronger biological effect [102]. Hence, a smaller dose from a heavier ion can result in higher therapeutic effect than in other radiotherapies based on photons or lighter particles. This type of external beam radiotherapies, however, are rare due to the elevated costs.

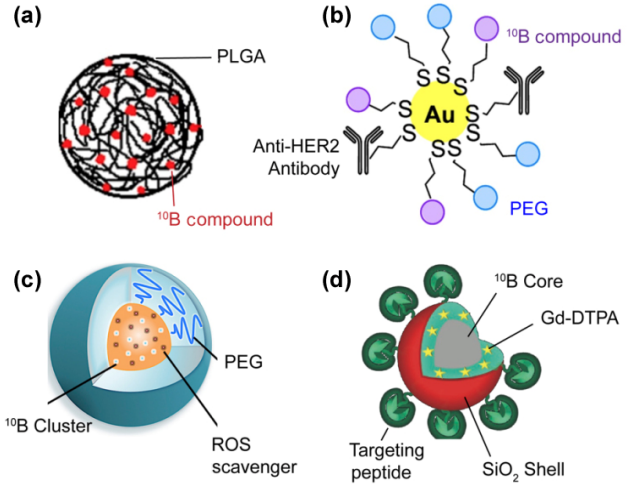

Figure 5 Different types of nanoparticles used as sensitizers for boron-10 neutron capture therapy. (a) Polymeric PLGA nanoparticles loaded with hydrophobic ^{10}B compounds. Adapted with permission from Ref. [91], © Elsevier B.V. 2017. (b) Gold nanoparticles functionalized with ^{10}B compounds, anti-HER2 antibodies, and polyethylene glycol (PEG). Adapted with permission from Ref. [92], © Elsevier B.V. 2017. (c) Bifunctional nanoparticles containing both ^{10}B cluster and ROS scavenger agents. Adapted with permission from Ref. [93], © Elsevier B.V. 2016. (d) Bifunctional core-shell nanoparticles containing ^{10}B cluster and DTPA-Gd, and functionalized with targeting peptides for theranostic applications. Adapted with permission from Ref. [94], © WILEY-VCH Verlag GmbH&Co. 2017.

Only two reported studies have used nanoparticles as radiosensitizers for heavier ion electron beam [103, 104]. In both cases, the viability of HeLa cells was studied after irradiation with carbon ions (up to 4.6 Gy dose). The administration of untargeted gold nanoparticles before irradiation increased the cytotoxic effect between 24.5% and 41% depending on the nanoparticle size and capping agent, and dose used.

3 Nanoparticles as therapeutic agents for internal radiotherapy

The most common form of internal radiotherapy is brachytherapy, where dozens of radioactive millimeter-long rods (known as seeds) are inserted into a tumor [105, 106]. Because high conformal dose distribution is achieved, it is an attractive therapeutic strategy [107]. Brachytherapy has been used as monotherapy for patients with low and intermediate-risk prostate cancers, and as an adjuvant to other therapies for higher risk patients [108]. Nevertheless, because it is a very invasive technique where a large number of radioactive seeds need to be implanted in each prostate, adverse effects occur, including swelling and discomfort [109]. Furthermore, the activities of the seeds are produced at fixed values (usually between 0.5 and 2 mCi per seed), which does not allow for precise dose tuning. Hence, there is a need for developing new and less invasive ways to administrate the radioactive materials that allow a more precise control over the dose.

An alternative to brachytherapy is targeted therapy, where radionuclides are conjugated to a carrier, such as a chelator coupled to a targeting molecule, in order to deliver the cytotoxic radiation dose to tumor cells [110]. Although monoclonal antibodies are the most common targeting vectors [111–113], other biomolecules, such as peptides [114, 115] and ligands [116], are also used. Because nanoparticles can be simultaneously functionalized with chelators and targeting agents [117, 118], and can enhance the cellular uptake of therapeutic agents [17, 119], they are being explored as delivery systems for targeted internal radiotherapy.

3.1 Beta-emitters as therapeutic agents for internal radiotherapy

Beta-emitters are preferred over their alpha counterparts during radiolabeling due to the large recoil energy (in the order of 100 keV) during decay of the latter [121], which significantly exceeds the binding energy between ligand and radionuclide, causing the release of daughters from the chelator [122]. Nanoparticles made of radioactive gold-198 and gold-199 have been used in nuclear medicine, including therapeutics and diagnostics, because of their beta emission [123]. For instance, gold nanoparticles containing ^{198}Au (β of 0.96 MeV and half-life of 2.7 days) have been coated with magniferin, a glucose-functionalized xanthonoid that promoted the accumulation of nanoparticles in prostate tumor cells (PC-3) through binding with the overexpressed laminin receptor [124]. The mice treated with the gold nanoparticles showed a 5-fold higher tumor volume reduction compared to the control groups after three weeks. Similarly, gold nanoparticles containing ^{199}Au have been developed for targeting the αvβ3 receptors of melanoma tumor cells in mice [125].

After the success of using ^{198}Au and ^{199}Au as therapeutic agents for internal cancer radiotherapy, a further work compared the performance of the two isotopes. Geometrical models of human prostate were used to identify which isotope could concentrate the dose better within the tumor region [126]. Although both nanoparticles (made of either ^{198}Au or ^{199}Au) confined their dose within the tumor region, ^{198}Au nanoparticles induced higher overall dose, suggesting that ^{198}Au was a better candidate for radiotherapy, while ^{199}Au could be better suited for imaging applications. These results were consistent with a previous work that used nanoparticles made of both isotopes as contrast agents for SPECT imaging [127]. The use of noble metal radioisotopes was further expanded to ^{103}Pd, where core–shell nanoparticles made of palladium and gold were used to treat xenograft prostate cancer in mice [120]. Instead of functionalizing the particle surface with targeting vectors, the nanoparticles were co-injected with alginate, a biocompatible polymer that polymerized upon contact with Ca^{2+} in the tumor environment, and promoted nanoparticle accumulation in the cancerous region (Fig. 6). 4-weeks after treatment, a 56% tumor volume reduction was observed in the treated mice compared to the controls.

Because gold nanoparticles are easily functionalized and can be biocompatible, cold gold nanoparticles have been used to deliver other radionuclides that undergo beta decay. For example, the β-particle emitter ^{177}Lu (energy of β(max) of 497 keV (78.6 %), 384 keV (9.1 %) and 176 keV (12.2 %) [128]) was attached onto the surface of gold nanoparticles through polyethylenglycol chains linked to DOTA [129]. The nanoparticles were also conjugated with panitumumab, which targets epidermal growth factor receptors overexpressed in several cancer cells, and the survival of treated mice with breast cancer tumors was prolonged up to 120 days. Alternatively, high tumor accumulation of ^{177}Lu (15.6% injected dose per gram) was achieved with porphyrin-PEG-nanocomplex as delivery systems [130]. This nanocomplex has also been used for the delivery of other therapeutic radioisotopes, such as ^{89}Zr, in Cherenkov light-activated phototherapy [131].

Internal radiotherapy with beta emitters has also been combined with other types of therapy by employing multifunctional nanoparticles. As an example, polymer-coated copper sulfide nanoparticles were labeled with ^{131}I for combined photothermal therapy and radiotherapy [132]. In addition to its anti-cancerous properties, photothermal therapy relieved the tumor hypoxia, which enhanced the radiotherapeutic effect of ^{121}I, resulting in a synergistic treatment. Nanoparticles labelled with iodine radioactive isotopes could also be used as agents for single-photon emission computed tomography and Cherenkov radiation imaging, providing theranostic capabilities [133].

3.2 Targeted alpha therapy

Alpha particles have advantages over beta or gamma radiation, short penetration depth and higher linear energy transfer, that concentrate the cytotoxic effect [134, 135]. The recoiling daughters of alpha emitters, however, can cause undesired damage to healthy tissue if they are not contained within the tumor. Nanoparticles have the potential of minimizing side effects by confining or encapsulating the radionuclides, and enhancing their delivery to the tumor cells.

Although multiple alpha-emitting radionuclides have been proposed as therapeutic agents, only a few are realistic since most of them have either too short or too long half-lives, show complicated decay pathways, and are scarce [134]. As an example, ^{213}Bi has been explored as an alpha-emitting agent in clinical setups. Its 46-minute half-life limits its use to very accessible tumors. For short-lived α-emitters, an alternative is to generate them *in situ* through the decay of their parent, such as decaying ^{225}Ac for the generation of ^{213}Bi.

Radium-223 is the first α-emitter approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to treat bone metastatic tumors that originated from castration resistant prostate cancer [137, 138]. ^{223}Ra (half-life of 11.4 days) emits four alpha and two beta particles in its decay pathway down to ^{207}Pb, inducing high therapeutic dose (27.9 MeV) to the tumor [134]. Nevertheless, one of its daughters is ^{219}Rn, which is gaseous and can recirculate in the body, damaging healthy tissue. A method for both targeting cancerous cells and controlling recoiling daughters is to use bioconjugated nanozeloite particles as delivery systems, which show between 90% and 95% retention of decay products after 6 days and target NK-1 receptors overexpressed in glioma cells [139]. An

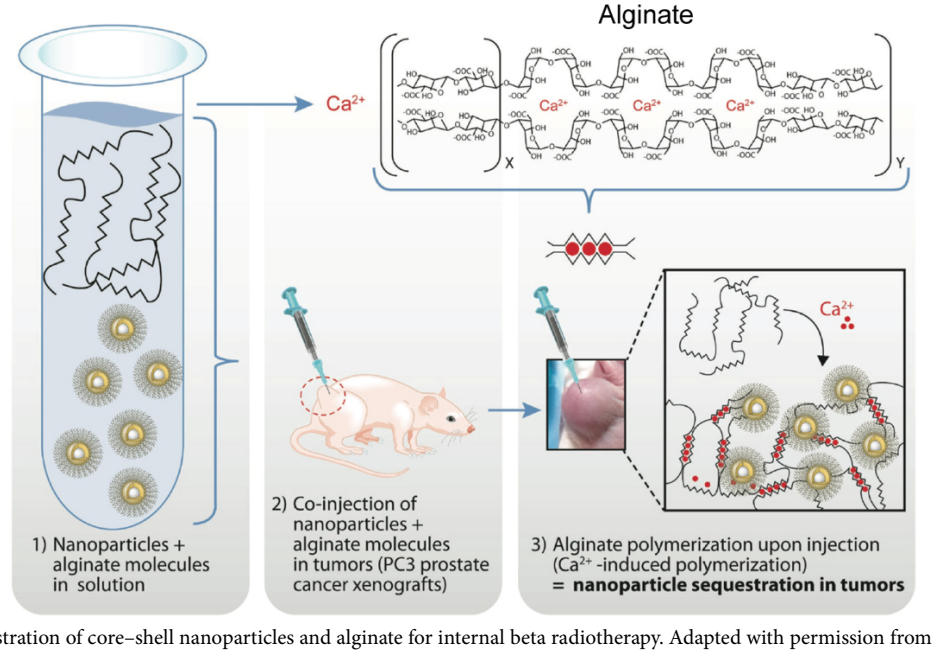

Figure 6 Co-administration of core–shell nanoparticles and alginate for internal beta radiotherapy. Adapted with permission from Ref. [120], © WILEY-VCH Verlag GmbH&Co. 2017.

alternative is to encapsulate the radionuclides inside core–shell nanoparticles, such as the ones made of cold $LaPO_4$, trapping both the ^{223}Ra and its daughters [140].

Another radionuclide proposed for targeted alpha therapy is ^{225}Ac, which has a half-life of ten days and generates four alpha and two beta-particle emissions for each decay event [141]. For instance, TiO_2 nanoparticles were radiolabeled with ^{225}Ac and biofunctionalized with a peptide fragment that targets NK1 receptors on glioma cells, showing high cytotoxic effect *in vitro* in T98G glioma cells [142]. ^{225}Ac was also formulated in liposome-based nanoparticles, which were capable of crossing the blood-brain barrier and delivering a therapeutic dose to glioblastoma cells through integrin alpha-v-beta-3-targeting (Fig. 7) [136, 143]. Although not explored for cancer yet, other radionuclides, such as ^{166}Ho, have been used for different radiotherapies, including using radiolabeled iron oxide nanoparticles for synovectomy (arthritis treatment) of knee joints in mice [144].

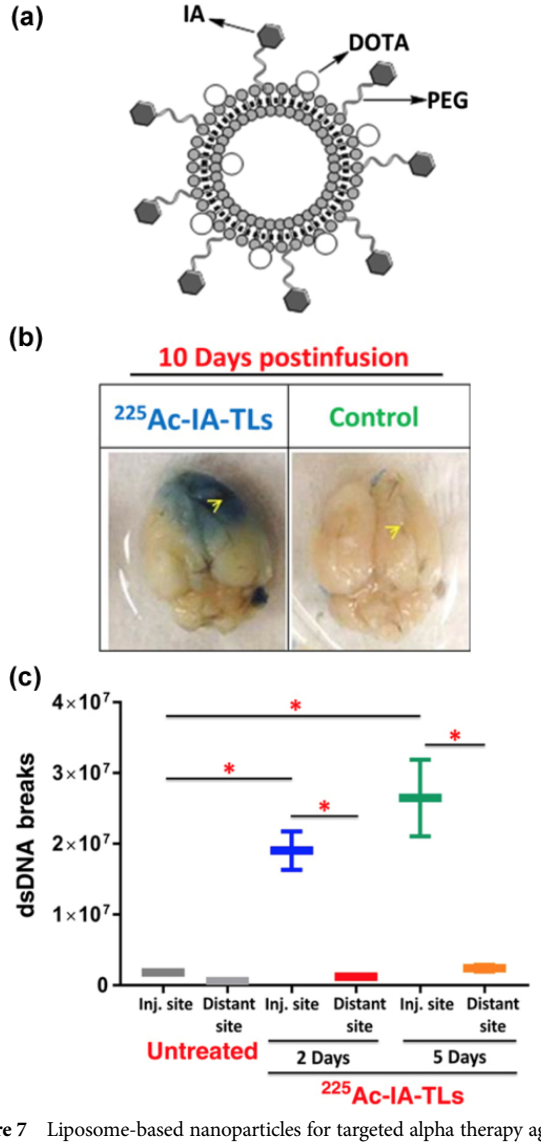

Figure 7 Liposome-based nanoparticles for targeted alpha therapy against glioblastoma. (a) Scheme of the liposome-based nanoparticles displaying targeting vector integrin alpha-v-beta-3, DOTA chelator with ^{225}Ac, and PEG. (b) Extravasation of intravenously injected Evans Blue dye showing blood-brain barrier opening after treatment with liposome-based nanoparticles. (c) Double strand DNA breaks present within the tumor region but absent within the surrounding tissue after nanoparticle treatment (*, $p < 0.001$). Adapted with permission from Ref. [136], © American Association for Cancer Research 2017.

4 Current challenges and clinical translation

As described in previous sections, nanoparticles have shown great promise in pre-clinical studies. Nevertheless, the selection of nanoparticle characteristics, including composition, size, shape, and ligand coating, is frequently based on research group preferences rather than on an experimentally well-established set of parameters.

Furthermore, the physicochemical characterization of the nanoparticles used in radiotherapeutics is not always thorough. Hence, calls for the standardization of nanoparticle characterization, as well as *in vitro* and *in vivo* studies, have been made to further improve and facilitate the comparison between studies [145]. Similar efforts have been successfully applied to other fields, such as coordination chemistry, where a set of standard conditions have been established to study metal-ligand complexation thermodynamics [146].

Although there are currently no nanoparticles approved for radiotherapy, several of them are being investigated in clinical studies. Nanoparticles made of polysiloxane matrix and gadolinium chelates (AGuIX; NCT02820454) have undergone a phase 1 study for treating patients with multiple brain metastases through whole brain radiotherapy [147]. Hafnium oxide nanoparticles (NBTXR3) are under a phase 1-2 study for treating liver cancer patients in conjunction with stereotactic body radiation therapy (NCT02721056). A phase 2-3 clinical trial (NCT02379845) has evaluated the safety and efficacy of the aforementioned NBTXR3 nanoparticles for preoperative treatment of soft tissue sarcoma in combination with external beam radiotherapy. A pathological complete response (i.e. absence of all signs of cancer in tissue after therapy) was observed in 18% of the patients that received both nanoparticles and radiotherapy, compared to 9% of the patients that only received radiotherapy [148]. Finally, the NBTXR3 particles are also in a clinical study (phase 2-3, NCT02805894) for the treatment of prostate cancer in combination with brachytherapy.

5 Summary and outlook

Therapy that involves radiation in combination with chemotherapy and surgery is one of the gold standard protocols in cancer treatment. Radiation is locally delivered either through an external beam or by surgically implanting radionuclide-based seeds in the cancerous area. However, radiation is non-selective and control over administrated dose is required to avoid damaging healthy tissue. New strategies, such as targeted alpha therapy, are currently being explored to focalize the damaging effect of radiotherapy in tumor cells and minimize side effects in the surrounding tissue. These targeted therapies, however, face several challenges, including the use and functionalization of a selective targeting vector, and dealing with radionuclide recoil. Hence, novel delivery systems capable of (1) transporting radionuclides, (2) displaying targeting vectors, and (3) retaining recoiling daughters, are necessary to bring these new therapeutic solutions to clinical settings.

Nanoparticles have emerged in recent years as exceptional drug delivery systems because of their biocompatibility, cellular uptake enhancing capabilities, and ease to functionalize with both biomolecules and therapeutic agents. Moreover, their unique physicochemical properties can be used in different therapeutic set ups, allowing for synergistic treatments.

In this comprehensive review, we summarize the progress of the use of nanoparticles for targeted radiotherapy (Table 1). Nanoparticles can be employed either as sensitizers for external beam radiation or as radionuclide delivery systems for internal radiotherapy. For external radiotherapy, nanoparticles are made

Table 1 Summary of nanoparticle-based targeted cancer radiotherapy

Nanoparticle role	Type of radiation	Nanoparticle core	Radioisotopes	Clinical trial
Radiosensitizers	X-ray	High-*Z* element		NCT02820454 NCT02721056 NCT02379845 NCT02805894
	Proton	High-*Z* element		
	Neutron	^{10}B or ^{157}Gd-containing core		
	Heavier ions	High-*Z* element		
Delivery systems	Beta	Variable	^{198}Au, ^{199}Au, ^{103}Pd, ^{177}Lu, ^{131}I	
	Alpha	Variable	^{213}Bi, ^{225}Ac, ^{223}Ra	

of high-*Z* elements, which show stronger radiation absorption cross sections. For internal radiotherapy, therapeutic radionuclides can be doped inside nanocrystal structures or can be attached to nanoparticle surfaces using a chelator. In both types of radiotherapy, nanoparticles are functionalized with biomolecules, such as antibodies, peptides or ligands, which target different cancer cell receptors. To understand the possible impact of nanoparticles in targeted radiotherapy, we identified current challenges in the field and highlighted how different types of nanoconstructs can overcome these challenges. We believe this review will help others understand the current status of the field as well as recognize research directions that may be important in the future.

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