Journal of Current Medical Research and Opinion
Received 19-06-2024 | Revised 20-06-2024 | Accepted 13-07-2024 | Published Online 14-07-2024

DOI:https://doi.org/10.52845/CMRO/2024/7-7-18 ISSN (O) 2589-8779 | (P) 2589-8760
CMRO 07 (07), 3253-3265 (2024) www.cmro.in

Original Research

Nanoparticle-Enhanced Radiotherapy Techniques: Cellular Targeted Radiation Therapy with Nanoparticle-Mediated Radiosensitizing Drug Delivery to Tumours and GNRT

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Abstract:
For cancer patients, radiotherapy has proved a lifesaver. Innovations in the biological, engineering, and physical sciences gave rise to and advanced the subject. Continual incorporation of innovations from different domains is crucial to the advancement of radiation oncology. Nanomedicine is a very young scientific field with the potential to influence radiation oncology. Nanoscale materials are ideal for use in radiation oncology because to their numerous desirable characteristics, including improved permeability, retention effect, and superparamagnetism. Radiation therapy for cancer often falls short of expectations due to several limitations. Normal tissues are also at risk from radiation therapy, which is why it is not used as a focused anticancer treatment. Radiation treatment is often unsuccessful because tumours have characteristics that make them resistant. Because of their ability to interact directly with ionising radiation, a number of nanoparticles have demonstrated the potential to improve the feasibility of radiation treatment by increasing cellular radiation sensitivity. Nanoparticles made of metal, quantum dots, silica, polymeric materials, etc., have all been studied for their potential as radio-sensitizers, with the goal of increasing the effectiveness of radiation therapy and overcoming radio-resistance. The use of nanoparticles to improve and enhance radiation therapy for cancer treatment still faces significant obstacles, despite all the research and development in the field. Problems in guaranteeing large-scale production of nanoparticles with enhanced characterizations and specific biological obstacles limit their potential uses as radiosensitizers. Enhancing the treatment is possible by resolving the issues with nanoparticles, such as pharmacokinetics and physical/chemical characterisation. Further research into nanoparticles and their therapeutic effects could pave the way for the creation of radiation treatments based on nanotechnology that effectively combat a range of malignancies in the years to come.

Keywords: Nanoparticle, Radiotherapy, Radiation Therapy, Drug Delivery, Tumours.

Introduction:

Mild temperature hyperthermia makes tumours more sensitive to radiation (thermoradiotherapy), whereas targeted heating of cancer cells can directly lead to tumour ablation. Achieving hyperthermia in a regulated and consistent form has proved elusive, despite its recognition as a valuable adjunct to more traditional anticancer therapy. The majority of the current methods for producing hyperthermia, whether it's external or interstitial, are not only non-invasive but also do not have the capability to track temperature during the thermal treatment process [1, 2]. As a result, these therapies are reported based on temperature measurements taken at specific points inside the tumour, which might introduce substantial sampling errors depending on where the probe is placed. There is little control over temperature patterns due to the unusual use of real-time monitoring and adaptive feedback control, and the temperature increase within tumours is both non-uniform (with "cold spots" or "heat-sinks" along vasculature) and changing over time. An alternate method of tumour heating is possible with metal nanoparticles, especially iron and gold. The distinctive optical characteristics of intense scattering and absorption of particular wavelengths of light are brought about when noble metals, like gold, are shrunk down to nano-meter dimensions on par with those of light waves. The reason behind this is that when activated with light of the right wavelength, the free electrons exhibit resonant oscillations—a phenomenon called localised surface plasmon resonance. Radiation (Mie scattering) or heat (absorption) can be used to disperse the resonant energy. During these periods of nanoscale size, metallic nanoparticles delivered intravenously seep into tumours through the bigger fenestrations and pores in the vascular endothelium linings of tumour blood vessels, which are naturally unorganised, immature, and incomplete. The phrase typically used to describe the phenomenon where nanoparticles are more effectively retained in tumours as opposed to normal tissues is the "enhanced permeability and retention" (EPR) effect. Because of their excellent thermal conductivity, gold nanoparticles (GNPs) rapidly transport the heat from a laser beam directed at a tumour to the surrounding tumour tissues (Jain et al. 2008). Ferrromagnetic nanoparticles (iron, iron oxide, or core-shell combinations of these) can also be heated up by applying an external alternating magnetic field; other nanoparticles have also been tested for thermotherapy. There is a lot of hype surrounding nanoparticle thermotherapy (NPTT) as a standalone anticancer treatment, but concerns about the nanoparticles' uneven distribution inside the tumour and the difficulty of reaching ablative temperatures inside the tumour without harming nearby healthy tissues put a damper on the enthusiasm. The basic notion of NPTT can be used more effectively as a supplement to RT when nanoparticles are used to induce mild-temperature hyperthermia (rather than thermoablation) inside tumours.

Even a little rise in temperature causes a first rise in tumour perfusion and a subsequent decrease in the amount of hypoxia inside the tumour core when near-infrared (NIR) laser light is directed at tumours that contain gold nanoshells. There is a well-established direct association between tumour oxygenation and radiosensitivity, and this decrease in hypoxia allows tumours to respond more strongly to thereafter administered radiation. In addition, as a result of the perivascular localization of these relatively large nanoparticles (150 nm diameter) that do not penetrate [6-10] deep into tumour parenchyma, vascular disruption and extensive tumour necrosis are unique outcomes of combining hyperthermia with radiation. Also, magnetic resonance thermal imaging can measure the increase in temperature without causing any harm. This new approach to NPTT offers up the possibility of combining it with other traditional anticancer treatments by integrating localised vascular disrupting and antihypoxic measures. Atkinson et al. (2010) showed that nanoparticle-induced hyperthermia may be more harmful to cancer stem cells, leading to more effective eradication of tumours, which further indicates the originality of this NPTT technique when paired

with radiation. This finding lends credence to the idea that NPTT plus radiation therapy might be a promising therapeutic combination. A number of ongoing clinical experiments are demonstrating the safety and efficacy of GNPs as oral insulin delivery vehicles or for plasmonic thermal ablation of atherosclerotic plaques (clinicaltrials.gov). According to personal discussions with Nanospectra Biosciences Inc.'s Glenn Goodrich and two ongoing early phase clinical trials[12,13], all of which are targeting cancer. The federal drug authorities currently classify GNPs as "devices" rather than "drugs"; this dramatically cuts down on the time and money needed for clinical translation, which is a major benefit of subjecting GNPs to both preclinical and clinical testing.

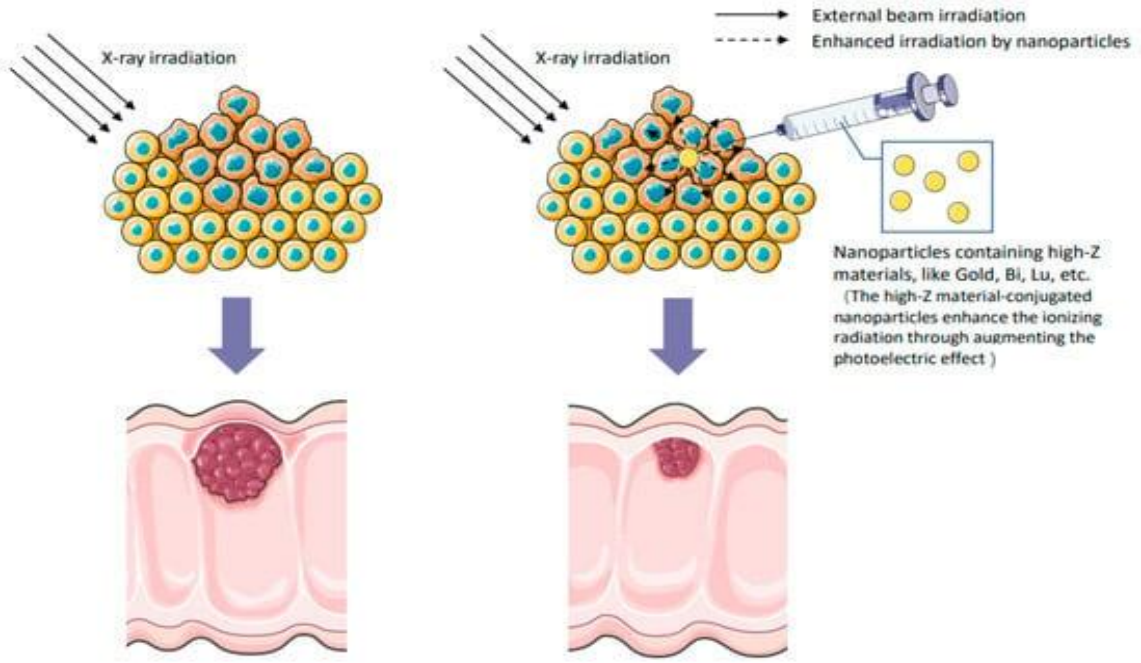

Figure 1. This is a schematic comparison of the effects of radiation therapy alone against nanoparticles of high Z-effect metals (Au, Bi, Lu) that include radiosensitizing chemical moieties, with the goal of reducing tumour growth by increasing the X-ray irradiation-induced damage.

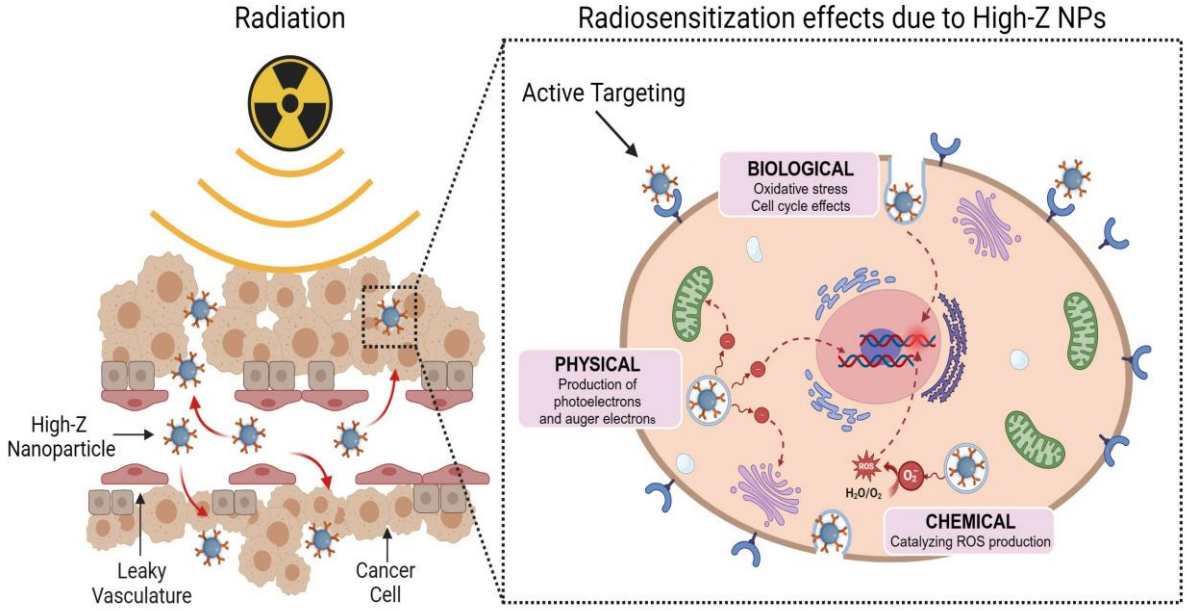

Figure 2. Nanoparticles to Improve Today's Radiation Therapy

Finding beneficial therapeutic settings for GNP-mediated hyperthermia is the biggest hurdle. Despite its ability to penetrate deep tissues, near-infrared light (NIR) cannot effectively heat nanoparticles located just a few centimetres beneath the surface of intact skin. In addition, only a tiny fraction (as little as 1% of the injection dose) reaches the tumour, even though targeting is achieved through active ligands and PEGylation, which results in longer circulation durations. All of these things add together to make it very tough to heat deep-seated tumours adequately.

Consequently, GNPs should only be administered to patients undergoing hyperthermia in specific clinical settings where their heat production capabilities are adequately demonstrated. The tumour may be located in a cavity that a laser probe can access (e.g., colon cancers with a modified colonoscope)[15,16], be sufficiently superficial (e.g., skin tumours, post-mastectomy chest wall, tumours of the head and neck), or be within tissues with low attenuation coefficients for near-infrared light (breast). At the same time, research into how tumour size, shape, and surface makeup affect circulation times and uptake is ongoing, with the goal of optimising particle concentration within tumours.

Substituting iron oxide nanoparticles for graphene nanoparticles and near-infrared radiation for an alternating magnetic field can increase the electromagnetic radiation's penetration into the body, therefore heating the nanoparticles. By utilising a combination of hysteresis and Neel relaxation, magnetic nanoparticles can be safely heated using alternating magnetic fields (AMF), which pose no danger to humans. Due to these intrinsic physical features of ferromagnetic nanoparticles, the temperature within the nanoparticles rises and is subsequently dispersed into the tissues [17, 18]. While this method isn't ideal for thermoablation—the concentration of ferromagnetic nanoparticles needed to produce a big enough specific absorption rate in an alternating magnetic field is usually not achievable via systemic nanoparticle administration—it can be utilised for hyperthermia to enhance the effects of chemotherapy and radiotherapy. Still, the present iteration relies on direct interstitial injection as the main entry point for these particles into tumours. While not ideal from a distributional perspective, this has the benefit of being imageable by MRI (at tissue concentrations high enough) and allowing for the targeted injection of interstitial fluid to remedy distributional deficiencies. Magforce AG, a Berlin-based German company, has commercialised this procedure for tumour heating utilising water-soluble 15-nm particles with a magnetic core and a silane coating. With the patented NanoTherm therapy having received European regulatory approval and attracted over US$30 million in equity funding, the method's effectiveness has recently garnered great acclaim. This treatment is now the subject of at least three active clinical trials: one for pancreatic cancer, one for prostate cancer, and one for glioblastoma. Phases I and II of the glioblastoma trials have already been successfully completed, paving the way for regulatory approval from the European Union. The process of getting into the American market is still in its early stages; to get permission from the FDA, the nanoparticle, alternating magnetic field generator, and adaptive treatment planning software will likely all need independent approvals.

Radiosensitizing Drug Delivery to Tumours via Nanoparticle-Mediated Transport

Radiosensitization characteristics are known to exist in a number of compounds, and new ones are being discovered every day. Typically, these medications exhibit tumour selectivity due to differences in radiation damage repair capacities (tumours incorporate more bioreductive drugs), preferential cytotoxicity to rapidly proliferating cells, or preferential sensitization of hypoxic cells to radiation (normal tissues are less prone to hypoxia than tumour cores that have outgrown their blood supply). Radiation may counteract localised disease, while medications mainly target metastatic disease; hence, the synergy between the two may be geographical. More drug penetration

into the tumour microenvironment (beyond the biological and physical barriers provided by the interstitial collagen, glycosaminoglycan, and proteoglycan matrix that houses the most aggressive and radioresistant cells that thrive in low pO2, low pH environments) is highly desirable in all of these cases [19–22]. When the radiosensitizer is genetic material (siRNA, shRNA, miRNA, DNA, etc.), nanoparticles could act as practical chaperones that transport radiosensitizers to tumours more effectively than radio-sensitizers alone. The majority of nonviral methods of delivering DNA to cells involve nanoparticles. Reportedly, mouse squamous carcinoma cells were discovered to absorb poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles harbouring ataxia telangiectasia-mutated antisense oligonucleotides, rendering them irradiation sensitive in both laboratory and living organism settings. Nanoparticles encoding the antisense epidermal growth factor receptor (EGFR) gene were also shown to promote cell death through radiation in a separate study conducted by the same university on the same cell line [23, 24].

Conventional hypoxia radiosensitizers, such paclitaxel and etanidazole, can be made more effective by delivering them using nanoparticles. As the preferred vehicle for delivery, PLGA nanoparticles ranging from 80 to 150 nm were utilised. Hypoxic tumour cells were found to be radiation sensitive when the released medication was administered. Compared to nanoparticles loaded with a single drug, those carrying both paclitaxel and etanidazole seemed to have far superior radiosensitization. Prostate tumours that overexpress the NAD(P) H:quinone oxidoreductase-1 enzyme, which is a member of the cytoplasmic 2-electron reductase family, have also been targeted using beta-lapachone, a bioreductive medication, using PEG-PLA polymer micelles as delivery vehicles. Experiments on head and neck cancer cells and xenografts using folate-decorated nanoparticles with a PLGA core loaded with docetaxel and a lecithin and PEG capsule showed that nanoparticle-drug formulations can improve radiosensitization even further by targeting tumour cells with their payload.

Discovering short peptides that attach exclusively to irradiated tumour cells—but not to unirradiated or normal cells—and then decorating lipid-based nanoparticles loaded with chemotherapeutic drugs with these peptides is a new spin on the old nanoparticle-mediated delivery of cytotoxic radiosensitizers strategy. To find new peptides, scientists utilise a technique called "phage display," in which a bacteriophage virus displays a collection of peptides on its surface. The goal is to find peptides that can distinguish between cells that have been exposed to radiation and those that have not. On the other hand, researchers have used a photochemical strategy by using transition metal complexes, which are precursors to nitric oxide, to deliver therapeutic dosages of nitric oxide gas to tumour tissues via nanoparticles. Nitric oxide is known to be a radiosensitizer. The photochemical approach has the benefit of enabling the controlled delivery of a bioactive substance at a certain time and place with an exact dosage. Hyperthermia, in conjunction with site-specific drug release, makes tumours more radiosensitive, and in a similar vein, external spatiotemporal control of drug release within tumours is possible through the use of thermosensitive liposomes loaded with drug.

Radiosensitization and Enhancement of Radiation Dose via Nanoparticles

Physical and biological methods of increasing the radiation exposure to cancer cells are very similar. The two approaches share the goal of increasing the likelihood of radiation-induced cell death by loading nanoparticles preferentially into cancer cells. The two methods differ in the sensitization mechanism; one uses interactions between the nanoparticle and the incident radiation to reach the cells, while the other uses direct cell-to-cell contact.

External beam radiation therapy (EBRT) dose increases lead to better tumour control for radiosensitive tumours, all else being equal. Even with hyperfractionated dosing schedules, the

highest effective dose is limited to roughly 60-65 Gy due to radiation damage at higher doses. Without raising the radiation dosage, nanotechnology can help make radiation treatment more effective [31–33]. Two methods exist for achieving this goal: increasing the cells' radiosensitivity (biological dose enhancement) or physically "trapping" the ionising radiation so that it is more targeted towards the tumour as it travels through it (physical dose enhancement).

Tumour cells are damaged by ionising radiation in two ways: first, it breaks the DNA strands directly. Second, it releases secondary electrons through interactions between radiation and tissue elements, such as photoelectric absorption, the Compton effect, and pair production for photons. These interactions create short-lived highly reactive oxygen species (ROS), which further damage DNA and other vital cellular structures. Although various geometrical targeting techniques used for current RT can produce some tumour specificity of radiation, ionising radiation in general deposits its energy without discriminating between normal and tumour tissues. The radiation damage to tumour cells will be increased by "trapping" more energy into the tumour, while the damage to normal cells will be reduced. In principle, this may be achieved by loading the tumour with nanoparticles made of materials that can absorb more radiation energy than the tissue itself. These materials would have greater photoelectric absorption cross sections for gamma and x-ray photons, for instance. These incredibly absorbing elements generate a great deal of secondary electrons, such as photoelectrons and Auger/Coster-Kronig electrons, with low energies (approximately on the order of keV or lower), when exposed to radiation of the right wavelength [34, 35]. The secondary electron fluence within a tumour exposed to low energy (~100 keV) photon sources could be enhanced by a factor of two if the tumour was doped with GNPs at low concentrations (about 0.1 wt.%), as suggested by recent computational studies (Cho et al. 2009; Jones et al. 2010).

Electron energy deposition surrounding GNPs within the tumour would increase two orders of magnitude if the expected degree of increase in secondary electron fluence were to materialise. In most cases, the creation of these extra electrons occurs in a sequential manner (for instance, photoelectric absorption followed by the "Auger cascade") and is highly reliant on the atomic number (Z) of molecules (for instance, photoelectric absorption ∘ Z3). Compared to other possible methods of increasing the secondary electron generation (such as pair creation ↘ Z) for physical dose enhancement, these features provide clear benefits.

Many have sought to profit from the concept of utilising high-Z elements to increase tumour dose, often known as radiosensitizing the tumour, throughout the years. A number of high-Z media have been studied by researchers. These include gold, platinum, iodine, gadolinium, and bromine. Using the high-Z nature of the base metal and the high tumour specificity of nanoparticles under passive/active targeting scenarios, a lot of research has been focused on developing approaches using different metallic nanoparticles, such as gold and platinum, in recent years [36, 37]. Given that gold has a higher Z number than the other metals studied and a less toxic profile for human uses, for instance compared to platinum, GNP-based techniques appear to be the most promising of the different methods discussed in greater depth in the previous chapters.

In addition, bioconjugated GNPs for active tumour cell targeting provide a novel approach to modulating tumour radiation response under a specific irradiation scenario by inducing and controlling the location of physical dose enhancement [38, 39]. The potential consequences of this on the clinical application of GNP-aided radiation treatment (GNRT) are substantial (Cho et al. 2009). In the next section, we'll go into this topic further.

For the most part, physical factors can explain, at least in part, the radiobiological results observed in earlier in vitro and in vivo investigations with GNPs, such as radiosensitization of 20% or higher. In the first successful animal study by Hainfeld et

al. (2004), for instance, the significant increase in the photo-/Auger electron fluence within the tumour (including blood vessels) loaded with high-Z GNPs during kilovoltage x-ray irradiation may have explained the remarkable outcome (e.g., an 86% vs. 20% l-year survival rate for mice irradiated with/without GNP injection, respectively). Because there was more gold in the blood when the tumour was being irradiated with kilovoltage x-rays, the endothelial cells lining the tumour blood channels were likely the ones most physically damaged by the increased secondary electron fluence. Furthermore, in vitro models have indicated that GNP-mediated radiosensitization is conditional on a multitude of variables, including cell type, radiation type and energy, GNP size and concentration/internalization, and cell model.

When more complex physical models are used to produce estimates of physical dose enhancement on a nano-cellular scale, the physical explanation for many of these radiosensitization factors becomes somewhat apparent. Even while one can get a rough idea of the physical picture of GNP-mediated radiosensitization by intuition, numerous research groups have been actively trying to figure out the specific molecular pathways that cause this fascinating event. The presence of GNPs in the cell culture (either surrounding or inside the cells) during irradiation has been the subject of numerous research that have sought to prove an increase in DNA double-strand breaks (DSB). According to a study by Chithrani et al. (2010), there is a positive link between the rise in the DSB and the amount of GNPs internalised within the cells, as measured by the number of radiation-induced foci such γ-H2AX and 53BP1. However, according to Jain et al. (2011), there was no increase in DSB formation in cells treated with GNP after irradiation, based on the counting of 53BP1 foci. The variation in experimental circumstances may account for some of the discrepancies in the results. The size of the particle is known to affect the efficacy of cellular uptake (or internalisation) of GNPs, for instance. Therefore, with the same experimental conditions, one would anticipate different results from experiments with GNPs with 50 nm and 1.9 nm diameters, based solely on the aforementioned physical factors at the nano- or cellular scale (e.g., the distance between GNPs and DNA, the range of secondary electrons from GNPs). While this case study demonstrates the feasibility of using a physical model to solve a biological problem, there are some problems that are so intrinsically biological that no amount of physical modelling can help. As an example, a study found that cells were accelerated in the G0/G1 phase and arrested in the G2/M phase when exposed to irradiation GNPs, which activated the CDK kinases. Additionally, the study found that cyclin B1 and cyclin E levels were enhanced. On top of that, a new study found that the widely used GNPs with a diameter of 1.9 nm interact directly with cells, leading to heightened oxidative stress, cytotoxicity, and cell death. These examples highlight specific difficulties in understanding the molecular mechanisms of GNP-mediated radiosensitization [39, 40]. In order to accurately identify all potential mechanisms linked to GNP-mediated radiosensitization, a substantial amount of research will be necessary.

GNTR as RT with enhancer for contrast

Compared to traditional high-Z contrast media, GNPs have a higher Z number and better tumour specificity, making them a potentially superior agent for contrast-enhanced radiation therapy (CERT) in terms of increasing the tumour dose. Actually, the CERT was successfully demonstrated in the aforementioned animal study by Hainfeld et al. (2004). The reason behind this is that the GNPs were immediately (within 2 minutes) followed by 250 kVp x-ray irradiation. At this early stage, the tumour gold content was mainly an indicator of the tumor's vascularity, and the GNPs acted only as contrast agents. Experimental and computational data clearly show the potential for potent radiosensitization, and the CERT approach assures a high overall tumour gold content (on the order of 1 wt.%, although het-erogeneously distributed), which is possibly comparable to what is achievable via intratumoral injection of GNPs. Even if

improved beam delivery methods, like rotational delivery, can deal with the uneven dose distribution from kilovoltage sources, the major problem remains the creation of disastrous collateral damage to normal tissue blood vessels, particularly those located along the beam path when EBRT is being administered. Bypassing the dose enhancement to the bone and skull with conventional or low-energy [41, 42] augmented megavoltage photon beams would solve the well-known problem of kilovoltage RT, but the level of dose enhancement would also diminish. Even after taking into account the potential collateral damage to normal tissue blood vessels, it is extremely unlikely that the utility of GNRT via contrast-enhanced kilovoltage RT goes much beyond the treatment of superficial tumours, despite a few encouraging results from purely computational studies. It stands to me that electron beams might likewise be used for GNRT of these tumours. Further investigation into the potential benefits of GNRT implementation using low-energy enhanced megavoltage photon beams should be undertaken, as these beams are now routinely available from the flattening-filter-free mode of linear accelerators and could still be useful in certain clinical scenarios (for a hypothetical example, see Figure 19.3) [42, 43].

At last, it's clear that GNRT, when administered by brachytherapy, might be a lot more practical and less problematic than what was previously said. Specifically, as previously stated (Cho et al. 2009), GNRT applications utilising 50 kVp x-ray and 169Yb sources, which are low-energy but deliver a high dose rate, show promise and necessitate additional research towards their potential clinical application.

GNRT as a form of radiation therapy that targets cells

A different strategy, known as passive targeting, involves injecting unconjugated GNPs intravenously and then irradiating the tumour at a later time, perhaps 24 hours later. Previous research has demonstrated that by this moment most GNPs should have been removed from the blood compartment, but extravasated GNPs (as a result of the EPR effect) should still be inside the tumour. Therefore, GNRT's effectiveness would be called into question due to the substantially lower overall tumour gold content compared to any CERT-type implementation; however, an EBRT implementation of GNRT might potentially reduce the likelihood of collateral damage to normal tissues, independent of radiation type. Nevertheless, there may be a high enough concentration of gold within the tumour, for example in the perivascular space where untargeted GNPs are believed to be concentrated in certain studies, to cause a noticeable increase in radiation damage to critical structures nearby, like tumour vasculature, and to induce a meaningful enhancement of microscopic dose.

This injury to the tumor's blood vessels may explain why an earlier in vivo investigation using an electron beam found a substantial radiation sensitization effect. Expanding on this idea, GNPs could be coupled with peptides or antibodies that target tumour or tumour vascular antigens, allowing for GNRT to be delivered more specifically to tumours. In addition to increasing the gold content in tumours, this active targeting strategy has the ability to localise GNPs at the surface of cells or even within them. This could lead to more severe damage, such as double-strand breaks (DSBs), to the cellular nucleus or DNA—the primary target of radiation damage—through short-range secondary electrons emitted by GNPs.

In order to achieve a substantial reduction in the number of GNPs needed to elicit a radiosensitization effect during GNRT treatments, active targeting would be helpful in improving the efficiency of GNP-mediated radiosensitization. Actually, this theory is backed up by our unpublished research using anti-EGFR antibody-conjugated gold nanorods. To determine how effective active targeting is for GNRT using different types of radiation that can produce secondary electrons from GNPs, additional research is required. Successful completion of these studies will allow GNRT to have less restrictions and be used more broadly.

Cancer treatment using internal radiation Utilising nanoparticles that emit radiation Tumours can be internally irradiated in two ways: either naturally occurring radioactive isotopes are transported to or injected into the tumour, or a nonradioactive nanoparticle can be activated by an external trigger to produce a radioactive isotope. As with radioactive iodine and the thyroid gland, the most elegant way to deliver radionuclides to tumours through systemic administration is to use metabolic pathways that guarantee the radioisotope accumulates specifically in tumours. Radioimmunotherapy, which uses antibodies that have been radiolabeled, is another option for targeting tumours using radioisotopes. The ideal target for localised implantation of radioisotopes in tumours is liver tumours, as these tumours get most of their blood supply from the hepatic artery (which is cannulated and infused with the microparticles), while normal livers get most of their blood supply from the portal vein. This technique is employed in interventional radiology and involves intra-arterial instillation of radioactive microparticles (beads or resins) to cause embolisation within tumour vessels preferentially. Up until now, tumor-directed RT has been mostly accomplished by methods that do not involve nanoparticles. Combining the benefits of minimally invasive methods of introduction into the body with highly efficient methods of concentrating radioactivity within tumours through passive accumulation and targeting ligands presents an opportunity for the introduction of nanoparticles carrying payloads of radionuclides that are specifically targeted to tumours. In contrast to traditional radioimmunotherapy, which makes use of single-atom-labeled monoclonal antibodies, nanoparticles, micelles, dendrimers, hydrogels, and liposomes coated with antibodies provide a higher radiation dose for each recognition event. A model of this scenario demonstrated that tumour cells can be exposed to doses as high as 50 Gy when treated with a nanoparticle of the beta-emitting radionuclide 90Y2O3, which is attached to an antibody and has a diameter of 5 nm. Nevertheless, similar to GNPs, the deposited dose was found to be significantly affected by vascular irregularities and the existence of a necrotic core.

There have been a number of outstanding reviews outlining the developments in the field of radioactive delivery by nanoparticles (and microparticles). Radioactive yttrium enclosed within a protein shell has been reported, taking use of the one-of-a-kind peptide structure of apoferritin with its empty core. To facilitate additional shell painting with tumor-targeted antibodies, the 8-nm-diameter nanoparticle was biotin functionalized. Similarly, lipid-polymer hybrid nanoparticles loaded with a mixture of radionuclides (111In and 90Y) and chemotherapeutic medicines (docetaxel) have demonstrated good therapeutic activity in prostate cancer models, and these nanoparticles are biodegradable and biocompatible.

Additional Approaches to Enhancing Radiation Treatment Make use of nanoparticles

Using quantum dots to combine photodynamic therapy with RT and nanoparticulate radioprotectors of normal tissues to broaden the therapeutic window for RT are two examples of the evolving tactics outlined in earlier chapters of this book that enhance radiation response of tumours.

The photodynamic therapy method uses a photosensitizer that accumulates inside tumours and is activated by light to produce cytotoxic, tumor-confined singlet oxygen species. When combined with RT, these singlet oxygen species can increase the number of DNA strand breakage and cell death. Here, the photosensitizer is attached to a nanoparticle, which, when exposed to radiation, produces light. This, in turn, activates the photosensitizer, causing it to produce singlet oxygen species that are specific to tumours. This way, the antitumor effects of radiation are amplified. One distinct benefit of this method is that it can be used to perform photodynamic therapy in nonluminal organs inside the body using deep-penetrating ionising radiation, rather than just on superficial or endoscope-accessible tissues. Another advantage is that it can approximate the photodynamic therapy in space and time and can tailor the localization of nanoparticles and photodynamic/radiation therapy to the tumor's geographical contours.

One effective strategy to decrease RT-associated morbidity is the targeted supply of radioprotective medicines to healthy tissues, which is similar to the delivery of radiosensitizing medications to tumour tissues. This is of utmost importance for radiosensitive tissues, like the lining of the digestive tract or bone marrow, particularly in cases where they will inevitably be exposed to radiation during treatment. Unfortunately, nanoparticles naturally extravasate more from tumour vasculature into tumours than from normal vasculature into normal tissues, which is a major drawback when trying to passively administer radioprotectors to normal tissues using nanoparticles. Therefore, radio-protection with normal endothelium penetrating nanoparticles could be the way to go when radiation isn't being used to treat tumours at the same time (for example, to prevent radiation syndromes in healthy people who are accidentally exposed to radiation) or when normal tissues can be selectively targeted to accumulate through active targeting. The first concept is shown by the creation of an orally accessible [45] version of amifostine, the sole radioprotective drug currently utilised in clinical settings, which primarily functions by scavenging reactive oxygen species (ROS). The higher conversion of amifostine to its active metabolite N-(2-mercaptoethyl)1,3-diaminopropane (WR-1065) in normal tissues compared to tumours is due to the stronger alkaline phosphatase activity in the former. Mice administered a PLGA nanoparticle carrying WR-1065 orally had a markedly reduced risk of bone marrow and intestinal toxicity, as well as improved survival rates compared to control groups, after whole body irradiation. An interesting idea for radioprotection by nanoparticles is to use cerium oxide (CeO2) nanoparticles, which shield healthy tissue from radiation by removing reactive oxygen species (ROS), the main culprits in radiation-induced cell damage. By administering the CeO2 nanoparticles to living animals that were exposed to high radiation doses, an in vivo mouse model was able to demonstrate that they were well-tolerated and avoided the development of radiation-induced pneumonitis. While nanoceria are known for their ability to regenerate and autocatalyze free radical scavenging cycles, they do not have any innate selectivity that would make them useful for radioprotecting healthy tissues rather than tumours. Similarly, fullerene nanoparticles have radioprotective characteristics in both laboratory and living organism studies, indicating their potential as ROS scavengers. The radioprotective qualities of melanin, a naturally occurring pigment, were used to create melanin-coated silica nanoparticles, which were then given intravenously to nude mice with melanoma. Less hematologic toxicity without detectable tumour protection was related with nanoparticles localised in bone marrow within 3 hours of treatment and subsequent radioimmunotherapy with 188Re-labeled 6D2 melanin-binding antibody.

Conclusion:

Nanotechnology has recently experienced a rise in attention due to the discovery of unique properties of matter when limited to nano-scale dimensions and breakthroughs in characterisation and visualisation of these features. This is despite the fact that nanoparticulate formulations have been available for centuries. The most promising biomedical application that could transform cancer imaging and treatment is the spontaneous trapping of circulating nanoparticles inside tumours via their extravasation from leaky tumour vasculature. Active targeting, in which biomolecules adorning nanoparticle surfaces dock to tumour cells and transport the nanoparticulate payload to tumours more efficiently, in vivo sensing and monitoring of biomarkers, dual imaging and therapeutic constructs allowing image-guided therapy, and various other applications are all possible from this platform for passive accumulation of nanoparticles in tumours. Without a doubt, nanoparticles' adaptability in form and function can be utilised in many ways to improve nearly every therapeutic process.

There is a wide range of potential interactions between nanoparticles and radiation that could be used for therapeutic purposes. These include nanoparticulate radioactive isotopes, neutron

activatable nonradioactive isotopes, photodynamic therapy with radiation, localised heating using plasmon resonant or magnetically activated particles, transporting radiosensitizing agents to tumours or radioprotective agents to healthy tissues, and many more. In its early stages, research at the intersection of nanotechnology and radiation oncology has focused mostly on modelling and proof-of-principle experiments. However, due to the high level of enthusiasm surrounding these initial experiments, there is hope that these methods may be used in clinical settings in the near future to achieve meaningful improvements in RT treatment. At the same time, more effective ways to advance this new frontier might be revealed by a deeper comprehension of the biological and physical foundations of nanoparticle-radiation interactions at the nanoscale.

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