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Original Article

Semiconductor Nanomaterials for Radiotherapy, Radiotherapy Combined with Nano-Biomaterials and Various Approaches to Enhance Radiosensitization in Cancer

Ahmed Hamza Oribi Hassan[1], Aqeel Faisal Waheed Ahmed[2], Hussein Abd AL-Ameer Salal[3], Rusul Falih Abd AL-Hadi[4]

[1,2,3]Department of Medical Physics, Hilla University College, Iraq

[4]Department of Chemistry, College of Sciences, University of Babylon, Iraq

Abstract:- Radiotherapy often fails and tumours recur after treatment because of acquired radiation resistance. To improve the safety and effectiveness of radiation therapy while reducing radiation resistance, many methods have been employed. Radiation therapy has been greatly improved in three main ways: (I) by making tumour tissue more radio-sensitized; (II) by making tumour tissue less resistant to radiation; and (III) by making healthy tissue more radio-resistant. Because of their dual role as a treatment and a carrier for other medicines, nanoparticles have been essential in improving radiation therapy. We summarise the current studies on improved radio-sensitization in cancer utilising several species of nanoparticles in this review. Because it is both noninvasive and highly adaptable, radiation therapy (RT) is a crucial component of tumour treatment. Scientists and physicians alike are understandably worried about the newfound ability of radiation therapy to trigger an immune response that fights tumours. This review focuses on the most up-to-date research on radiotherapy-activated immunotherapy using nano-biomaterials. To improve the efficacy of radiotherapy and promote the tumour immune response, we first explore the combination of several radio sensitising nano-biomaterials with immune checkpoint inhibitors. Afterwards, different tumour oxygenation techniques that utilise nano-biomaterials are implemented to improve the hypoxic tumour environment and enhance the immunomodulatory effect. Radiotherapy revitalises the immune system of the host by means of adjuvants and nano-vaccines. There is an increase in anti-tumor immunity mediated by the innate immune system when using nano-biomaterials that are responsive to ionising radiation. Lastly, we review the state of the art in immune modulatable nano-biomaterials and address the main obstacle to their further development for tumour radio-immunotherapy. Clinical radiotherapy and immunotherapy can be optimised and new combinational therapeutic modalities developed with an understanding of nano-biomaterials-assisted radio-immunotherapy.

Keywords: Radiotherapy, Nano-biomaterials, Radio-sensitization, Cancer

Corresponding Author: Ahmed Hamza Oribi Hassan†, Department of Medical Physics, Hilla University College, Iraq

Introduction:

Development of resistance to the therapeutic method is a key contributor to the failure to achieve a cure and the subsequent return of tumours. The main therapeutic approaches for cancer treatment are radiation therapy, surgery, and chemotherapy. It entails precisely targeting tumour tissue with high-intensity ionising radiations in order to kill tumour cells. One of the risks of radiation therapy is that it could harm healthy tissue in the area. However, some tumour cells may be located further away from the radiation source, which could result in a weaker beam of radiation reaching them [1, 2]. In addition, the cells have the potential to become radiation resistant. Mitotically active tumour cells typically have a somewhat elevated sensitivity compared to the healthy tissue around them. Therefore, the minimal radiation dose needed to destroy tumour tissue might only cause harm to healthy tissue and leave normal tissue unharmed. On the other hand, when tumour cells become resistant to radiation, higher dosages are needed, which in turn kills off healthy tissue [3]. Ionising water and/or biological components is the primary function of high-energy ionising radiations like gamma rays and X-rays. Some cancer treatments also make use of particle radiations like alpha or beta particles, or beams of electrons, protons, or neutrons to specifically target cancerous tissues. These ionising radiations cause radiation-mediated lysis of the molecule, which primarily targets water because of its importance to cells. Unlike chemical lysis, radiolysis produces a wide variety of free radicals, including hydrogen (H•), hydroxyl (OH•), and superoxide (O2 -) radicals, as well as charged water species (H2O+) and other radicals. Although many other cellular components are also destroyed, DNA is the principal target of ionising radiations and radicals [4, 5]. Apoptosis is induced when free radicals interact with membrane structures, which destroys those structures. certain significant problems with the treatment persist, even though radiation oncology has led to improved targeting and more controlled administration of ionising radiation. The therapeutic benefits and physiological drawbacks must be carefully considered due to radiation resistance and the system's inherent shortcomings. To improve its effectiveness while decreasing its toxicity, many methods have been employed. I improving radiosensitization of tumour tissue, (II) reversing radiation resistance in tumour tissue, and (III) improving radioresistance of healthy tissue will be the three main points covered in this brief overview. There is a summary of the radiosensitization methods in Figure 1.

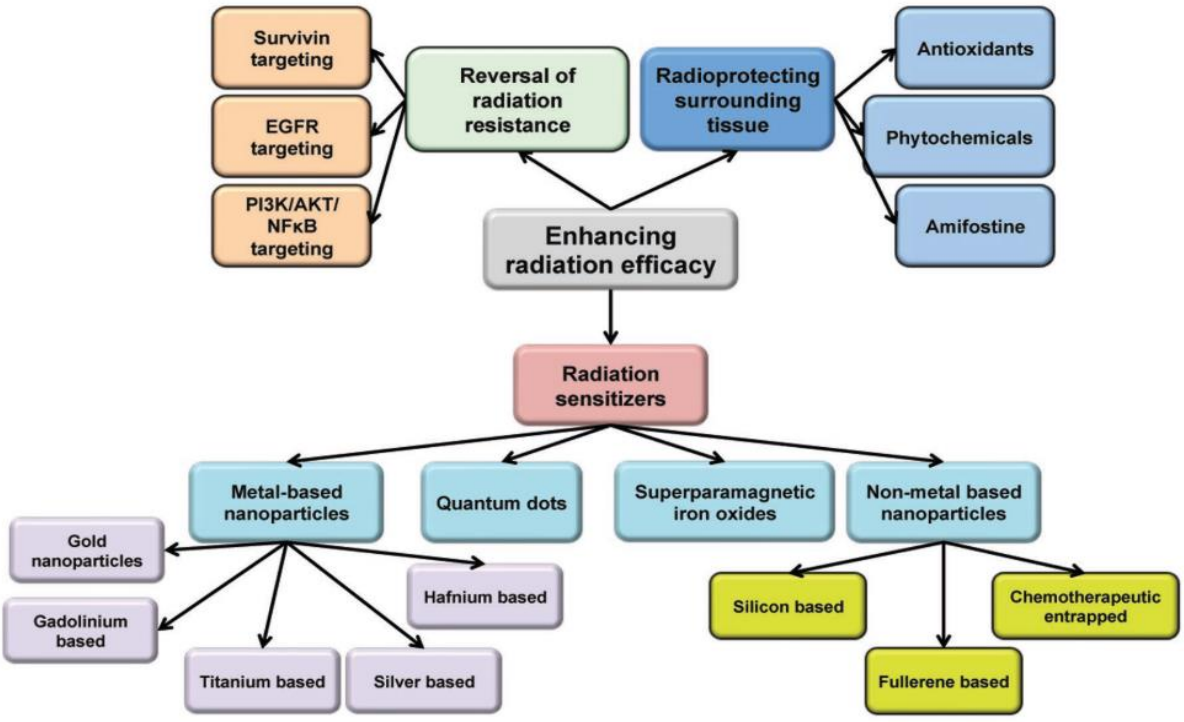

Figure 1. A Review of Methods for Raising Cancer Cell Radiosensitization.

How metal-based formulations work as radiosensitizers Numerous outcomes are possible when X-rays interact with metals. Cancer radiation makes use of scattered X-rays/photons, photoelectrons, Compton electrons, Auger electrons, and fluorescence photons, among other outputs. An electron in an atom gains energy from an incoming radiation wave, which it then uses to expel itself from its orbital with kinetic energy equal to the wave's energy minus the electron's binding energy. The range of the electron within the tissue is determined by the kinetic energy of the

outgoing electron radiation [3, 4]. (Z/E)3 determines the photoelectric effect, where E is the incoming photon's energy and Z is the atomic number of the targeted molecule. As energy is released, the ejected electrons are replaced with electrons falling from higher orbits, resulting in the production of Auger electrons or fluorescence photons [5]. Fluorescent photons have a larger covering range despite their low energy. Auger electrons can produce a far larger ionisation density in a small area, but their range of coverage is significantly shorter.

Nanoparticles made of gold characterise Gold nanoparticles are an excellent photosensitizer among high Z particles due to their many beneficial properties, such as:

1. Gold being very inert, it is highly biocompatible.
2. The gold nanoparticles enhance the effect of the radiation over a large area of tumor thus eliminating the need of the nanoparticles to be delivered to all the cells of the tumor tissue;
3. Nanoparticles are known to have low systemic clearance as compared to low molecular contrast agents such as iodine allowing the photosensitizing material enough time to get absorbed into the tumor tissue.
4. Nanoparticles are known to be well absorbed into systemic circulations, better permeation into the tumor tissue. This along with lower clearance rate results in the enhanced permeation and retention (EPR) effect;
5. By attaching targeting moieties such as antibodies, large number of the gold atoms can be specifically delivered to the tumor tissue as compared to using solutions of iodine. A nanoparticle of 10-15 nm in size contains 50-75 thousand atoms within it resulting in a much higher efficiency of delivery;
6. The gold nanoparticles can be varied in size or shapes (such as spheres cube, rods, cones or other 3D structures) based on the delivery requirements of the tumor tissue (such as its size and location) so as to achieve optimum delivery and effect;
7. It is much easier to perform overall and tissue specific pharmacokinetic studies with the gold nanoparticles.

Gold nanoparticles for radiosensitization: a therapeutic application

To demonstrate that gold nanoparticles can mitigate the radiosensitization effects of high-energy electrons on DNA, Zheng and colleagues conducted a proof-of-principle research [6]. They employed plasmid DNA and subjected it to 60 keV electron bombardment either singly or in combination with gold nanoparticles at a 1:1 or 1:2 ratio. As a result, the frequency of double-stranded fractures surged by a factor of around 2.5. According to the research, the increased impacts were caused by the gold particles producing low-energy electrons, and the effects were shown to be directly related to the amount of particles near the DNA. Brun and colleagues conducted one of the earliest systemic optimisation studies using comparable approaches. They went on to investigate aspects including nanoparticle size (8-92 nm), molar ratio, incoming X-ray energy (14.8-70 keV), and more [7]. Results were greatest when large-sized gold nanoparticles were used at high molar concentrations and exposed to 50-keV photons in these investigations. A sixfold improvement compared to controls was achieved by combining these two factors. Extra optimisation investigations conducted by Lechtman and colleagues also produced intriguing results. Their research showed that the auger cascade is dominating at photon energies below the k-edge, therefore tiny nanoparticles should be placed near the target areas in the cellular compartments as soon as possible. Nanoparticle size and localization are irrelevant when using photon sources above the k-edge, which necessitates a larger concentration of gold in the tumour region. A Monte Carlo model for radiosensitization prediction using gold nanoparticles that accounts for detailed nanoscale energy deposition was also recently generated by the authors. However, McMahon et al. cast doubt on these writers' assertions, suggesting a possible discrepancy between theoretical predictions and real clinical outcomes. The delicate balancing act between the effects of size on uptake, photon generation, and range determines the role of size in determining the final sensitization outcome of nanoparticles. So, it's possible that the best result would be to increase particle absorption into cells while making the particles larger in diameter. In addition, Ngwa and colleagues have demonstrated the use of gold nanoparticles as radiosensitizing agents for low dose rate gamma radiation therapy, specifically with I-125 brachytherapy seeds. The therapeutic efficacy was shown to be 70-130% higher when the nanoparticles were present. Toxicological reactions are mostly caused by the buildup of gold and liver damage. More precise dosimetry is now possible thanks to the development of more sensitive detection methods made possible by the growing interest in using gold nanoparticles in cancer therapy.

Radiotherapy and the necessity of Radioactive agents

Ionising radiation has a lengthy track record of effectiveness in cancer treatment. One of the most influential factors in cancer management is radiation, even if the focus of research has changed in recent years to treatments that are more tumor-specific and molecularly focused. Its function in noninvasively destroying, debulking, and regulating cancer cells is indispensable. One advantage and one disadvantage of ionising radiation is its lack of specificity. It kills tumours as well as healthy tissue [8, 9]. When tumour biology and genetic mutation evolve, radiotherapy's efficacy remains mostly unchanged, in contrast to chemotherapy. Radiation therapy with high doses can kill tumours even when it damages healthy tissues around them.

In actual fact, x-rays are able to deposit radiation doses throughout the beam path, penetrating tissues and reaching deep-seated tumours for treatment. The tumor's contour can be followed to create a uniform high-dose zone using intensity-modulated radiation. The transition region to the surrounding normal tissue has a somewhat steep dose gradient [10]. Here, a very evenly high dose covers the injury while protecting the spinal cord admirably. Due to the greater dosage gradient compared to traditional radiation, image-guided radiotherapy has allowed for more precise setup in the treatment room. These advancements allow for much greater tumour doses, which in turn improves the likelihood of tumour control, and this has been accomplished in multiple dose escalation studies without surpassing patient tolerance to therapy [11]. Radiotherapy is one of a kind due to its durability, affordability, geometric correctness, and accurate dosimetry. However, the physical laws of x-ray travel are unchangeable, regardless of how well-planned or delivered a therapy may be. Redistribution of x-ray doses away from functionally vital and sensitive organs like the spinal cord and parotids and towards less crucial and radio-resistant tissues like muscle and fat has been proposed as a possible explanation for improvements in the therapeutic ratio. While changing the number of beams and intensity modulation can produce different organs-at-risk (OARs) sparing, calculations on integral doses vs treatment mode demonstrated that the integral doses are nearly constant [12, 13]. Dose restrictions on both the tumour and the OARs become more difficult to meet simultaneously when the tumour is surrounded or adjacent to OARs, necessitating compromises. Because of this, radiotherapy is not as effective for large tumours or those that are resistant to radiation. Even though particle therapy can enhance dosimetry, most patients won't be able to afford it anytime soon. One possible solution that could help solve the problem is adjuvant therapy that increases tumour toxicity selectively. To make tumour cells more sensitive to radiation, researchers have created chemical radiosensitizers [14] that target different biological pathways. One example is the use of electrophilic compounds to decrease radioresistance associated with hypoxia [15, 16]. A greater number of tumour cells that have developed resistance to radiation have been treated with tirapazamin, which is more lethal when exposed to hypoxia. Poggi et al. (2001) found that DNA containing bromine or iodine-substituted pyrimidines increased free radical damage. There have been conflicting findings on the evaluation of drugs that are involved in DNA repair. The Ras family of proteins and other cell signalling proteins are promising radioresistance targets. Researchers have also looked for ways to inhibit radioprotective thiols. These applications may have some potential, but they usually damage normal tissues and make them less radiation-tolerant. What's more, their mechanisms of action are often unclear, and they sometimes depend on a modulating cellular target that might vary over time [17, 18].

It has been determined that these chemical radiosensitizers have only provided modest clinical benefits [19]. The synergistic effect occurs at the cellular level, which is common to all of these chemical radio-sensitizers, even though their mechanisms are different. The sensitizer can make cells more susceptible to damage from ionising radiation or it can prevent cells damaged by radiation from healing themselves. Due of the incredibly complicated biology of tumour cells, the results of radiation treatments that do not directly involve the medicine are frequently unpredictable and unreliable. Scientists have been trying to come up with a new kind of sensitizer that would specifically target tumour cells and increase the amount of radiation that damages them. While semiconductor nanoparticles aren't typically utilised to boost radiation absorption, the energy transfer channel is important for the semiconductor nanoparticle-photosensitizer combination utilised in combined radiation-photodynamic therapy.

The Idea Behind Physical Radiation Accelerator

An increase in the physical radiation enhancer's cross section with x-ray photons is necessary to raise x-ray dosages for enhanced tumour cell death. A combination of the photoelectric effect, Compton scattering, and pair creation is responsible for the energy loss of X-rays as they interact with matter. A greater absorption of energy proportional to

the cube of the atomic number is possible when low-energy x-rays interact with high-Z materials via the photoelectric effect [18, 19]. Around 1217 (793/7.43) times that of normal tissue with an average atomic number of 7.4 is the relative absorption coefficient of gold at the K-edge compared to this. In the energy range of 100 keV to 10 MeV, the main mechanism by which x-rays lose energy is the Compton scattering, the cross-section of which is directly related to the electron density in the medium and little affected by the atomic number. Consequently, compared to typical human tissue, the relative absorption coefficient of an electron-dense material like gold (density 19.3 g/cm3) is approximately twenty times higher. The significance of pair creation increases as the energy level rises. By transforming the kinetic energy of photons into their rest mass, a positron and electron can be created in the process of pair synthesis. High-Z materials have an advantage up to photon energies greater than 10 MeV, but this advantage is negligible until the mass attenuation coefficient from pair creation is proportional to Z2 [20, 21]. Nowadays, tumours are rarely treated with low-energy kV x-rays that have strong photoelectric components due to their weak penetration. Extern beam therapy is reserved for the use of high-energy x-rays (6 MV or higher) and isotopes, such as Co-60, that emit gamma rays of energy 1.25 MeV, when treating tumours that are deeply seated. Conversely, isotopes that release lower-energy gamma rays allow for better normal tissue sparing when the radiation source can be positioned close to the tumour in brachytherapy (the Latin word for contact therapy). I-125, which emits 35.5 keV gamma rays, is a popular isotope because it provides a large dosage to a region within a few millimetres of the source, but a rapid decline in dose beyond this range is required for typical tissue sparing [22]. The dosage enhancement achieved with the same quantities of high-Z materials in the same tissues at different x-ray energy will obviously vary. When it comes to x-rays with energy at the K-edge of gold, a 0.1% mass concentration of gold in the tumour can double the radiation dose, but with MV x-rays, it won't have much of an impact.

Several cell and animal devices for radiation sensitization have taken use of the possibility of using a broad cross section of kV x-rays with high-Z materials. Since it is easily integrated into DNA with agents like iododeoxyuridine (IUdR), iodine (Z = 53) was among the first elements studied in vitro (Santos Mello et al. 1983; Matsudaira et al. 1980). Following incubation in IUdR solution, radiation treatment resulted in a threefold increase in tumour cell death [23, 24]. Using iodine contrast medium and 100 kVp x-rays, animal studies observed an increase in tumour growth delay (Santos Mello et al. 1983; Iwamoto et al. 1987). The use of computed tomography (CT) iodine contrast medium and orthovoltage (140 kVp) x-rays from a CT scanner resulted in a 53% improvement in survival rates for dogs with tumours. A collimator was used to alter the scanner's regular open beam geometry so that conformal radiation could be delivered to the tumour while avoiding the surrounding normal tissue. Phase I clinical trials including iodine contrast and the modified CT scanner were performed on eight human patients, all of whom had numerous metastatic brain tumours, following the animal tests. One of the metastatic tumours was treated with kV x-rays for 15-25 Gy following contrast injection, adding to the total radiation dose to 40 Gy for the same patient. The other tumour was spared from this further irradiation.

Although two tumours that were given the extra dose exhibited full response, the limited sample size prevented any statistical conclusions from being reached (Rose et al. 1999). As a physical radio-enhancer, iodine has a few drawbacks. One is that it doesn't penetrate deep enough to cure most tumours, and only a small fraction of the 140-kVp x-ray falls within its greatest absorption energy, which is directly above its K-edge at 33.2 keV. The fraction of thymine that must be substituted by iodouracil in order to obtain large dose enhancement effects in vivo with more practicable higher energy x-rays is unreasonably high.

Improving Radiation Treatment using Gold Nanoparticles

Applying bulk materials like foil on gold makes it difficult to obtain uniform dose enhancement, as the range of dose enhancement with foil is about 50 μm. The infiltration of gold microspheres into tightly packed tumour cells was unsuccessful (Herold et al. 2000). An appealing alternative to the challenges associated with using gold materials to enhance radiation therapy [24, 25] is the use of gold nanoparticles. Kong et al. (2008) demonstrated the effectiveness in vitro by comparing cell survival following treatment with kV radiation alone against kV radiation combined with gold nanoparticles. Gold nanoparticle-containing cells had a much lower survival rate, and its dark toxicity was determined to be insignificant.

Gold nanoparticles are more adaptable and biocompatible than micron-sized gold particles, but they nevertheless have the potential to radiosensitize to the same extent at the same dose. Scientific evidence suggests that gold particles

smaller than 2 nm can successfully avoid detection by the immune system and liver retention when they are unmodified on their surface. At 1.6 tumor/liver concentration ratios, they can take advantage of the tumor's vascular structure's leakiness [26]. In the investigation carried out by Hainfeld et al. (2004), mice were given an injection of 0.01 mL/g of gold nanoparticles with a size of 1.9 ± 0.1 nm. Not long after that, it was noted that xenograft tumours absorbed gold nanoparticles. Mice lacking gold nanoparticles and those exposed to 250 kVp x-rays were then compared. Twenty percent of patients in the radiation-only group survived one year after treatment. The long-term survival rates were 50% and 86% in the groups that were exposed to lower doses of gold nanoparticles (135 mg Au/kg) and larger doses (270 mg Au/kg), respectively. With the exception of a handful of surface and intraoperative applications, MV x-rays have mostly supplanted the 250-kVp x-rays, also known as orthovoltage x-rays, in human patient treatment. This study shown that high-Z nanoparticles could significantly improve radiation therapy while causing little adverse effects. Due to size selection alone, tumours had somewhat larger quantities of gold nanoparticles than the liver, even without surface modification or tumour targeting [27]. Tumours still have a lower concentration than the kidneys and blood, but it's comparable to other tissues that would have gotten a higher dose due to the interaction between gold and kV x-rays. Thus, without precise targeting of tumours, the cumulative impact is comparable to that of increasing radiation dosage, which is anticipated to result in a comparable enhancement of animal survival. To increase the therapeutic ratio of physical radio-enhancers, one must increase the particle concentration delivered to the tumour while avoiding the normal tissue around it.

To improve tumour specificity, it is necessary to make surface modifications that lengthen the serum half-life, enhance affinity for a tumour hosting environment, and bind specifically to tumour cell receptors. Breast cancer cells selectively internalised glucose-coated gold nanoparticles, and the selectivity could be adjusted by changing the surface charge, as demonstrated by Kong et al. [28]. In a study conducted by Li et al. (2009), it was found that tumour cells absorbed gold nanoparticles functionalized with transferrin four times more effectively than normal cells. While there was an increase in absorption on prostate cancer cells, the augmentation in cell death was not directly proportional to the loading of gold nanoparticles, suggesting that there is a saturation mechanism in the effectiveness. Gold nanoparticles have been coupled with antibodies and peptides for more precise tumour cell targeting, in addition to nonspecific coating molecules.

Nanoparticle physical radiosensitizers' benefits are easily observable. A thorough description of the radiation-nanoparticle interaction exists. However, there are several issues with the present version. Megavoltage x-rays, which are now used to treat most cancer patients, can reach deeper layers of tissue with less radiation while still sparing the skin and achieving better dose conformity. In this environment, when photoelectric contact is absent, gold nanoparticles have only a limited impact. Radiosensitization requires a very high loading (0.5-5%) that may saturate cell absorption [28]. The specificity of tumour targeting is crucial for dramatically boosting the therapeutic ratio, but this is no easy feat due to the multiple physiological hurdles in entering a solid tumour. Although more precise targeting of tumours is desirable, it is not enough to make physical radio-enhancers much more effective; controllability is also required. The goal is to find a new approach to kill cells that makes use of radiation. Using semiconductor nanoparticles as energy mediators, there has been a growing interest in providing radiation therapy and photodynamic therapy (PDT) concurrently.

Treatment using light beams

There are a lot of similarities between radiation treatment and photodynamic therapy (PDT). Both derive their power from radiation emitted by the sun. Through the action of secondary molecules like free radical species or singlet oxygen molecules, both of these processes indirectly harm tumour cells. There are some shared features between PDT and radiation therapy, but there are also important distinctions. A distinct medication, the photosensitizer, is required for photodynamic therapy (PDT). Light activates the photosensitizer. The excited state can remain for a few microseconds as a metastable triplet through intersystem crossing. The triplet state of photosensitizers allows them to release energy through type I and type II mechanisms as they react with environmental chemicals. Anion species of superoxide radicals and other free radicals are produced in the type I reaction [29] by means of hydrogen-atom abstraction or electron transfer. The main reaction in photodynamic therapy (PDT) is the type II reaction, which involves the direct reaction of a photosensitizer in its triplet state with a ground state molecular 3O2. This reaction produces excited singlet 1O2, a kind of radical that is extremely reactive and harmful to mitochondria, lysosomes, and

cell membranes.

Dermatologic, oesophageal, bladder, and head and neck cancers are among the numerous that PDT treats, in addition to its non-oncologic uses. Potent and effective, PDT has few long-term negative effects when used as directed. One big drawback of PDT, meanwhile, is that the activation light only penetrates very deeply. For instance, Photofrin, a photosensitizer approved by the FDA [30], has an activating light wavelength of 620 nm. This wavelength has an attenuation coefficient of about 1 mm-1 in tissue, allowing for an effective treatment depth of 5 mm before the light intensity drops to less than 1% of the surface intensity. Phthalocyanines (Pcs) are one of the new kinds of photosensitizers that were created to activate at longer wavelengths. You can practically raise the therapy depth from less than 1 cm to several centimetres by activating in the near-infrared band [31]. Inserting optic fibres into patients through orifices or incisions to treat deeply seated solid tumours greatly complicates the operation. So yet, only a few of institutes have the expertise to perform PDT to nonsuperficial areas. It is challenging to accurately predict the light dosimetry, and shallow penetration is another issue. Oxyhemoglobin is a powerful red light absorber, and its distribution, as well as scatter and reflecting light, affect the estimate. Since the photosensitizer tissue concentrations can be adjusted and the light dosimetry is crude, PDT dosimetry is more of an empirical than a quantitative method. To the contrary, 3-dimensional radiation dosimetry has an accuracy of about 2% to 3%. The use of photosensitizers in conjunction with radiation, excited by the very measurable and penetrating x-rays, has been a promising concept for some time now [32]. Multiple aggressive human and mouse cell lines showed moderate radiosensitization in vitro and in vivo. Since the photosensitizers utilised in these research, porphyrins, have limited absorption spectra and cannot be stimulated directly by x-rays to form singlet oxygen, the mechanism has not been fully understood.

Overexpressed in aggressive tumour cells are ligands of peripheral benzodiazepine receptors, which could potentially inhibit cell development, according to a theory put up and tested by Luksiene et al. (2006) [33]. Such receptors are liganded by dicarboxylic porphyrins. The fact that the photosensitizers had a mostly antiproliferatory effect in these trials, as opposed to inducing apoptosis, which is more typical with singlet oxygen, lends credence to the theory. Consequently, x-rays are not necessary for the mechanism of action of photosensitizers as radiosensitizers. But an energy mediator is required to use more penetrating x-rays.

Radiation therapy using nanobiomaterials in conjunction with immune checkpoint inhibitors

Tumour immunotherapy has demonstrated clinical efficacy in cancer fighting, making it the most promising treatment approach. Immune checkpoint blocking therapy, which includes anti-Programmed Death 1 (αPD-1), anti-Programmed Death Ligand 1 (αPD-L1), anti-Cytotoxic T-Lymphocyte Antigen 4 (αCTLA-4), anti-Lymphocyte activation gene-3 (αLAG-3), anti-T cell immunoglobulin-3 (αTIM-3), and anti-T cell immunoreceptor with Ig and ITIM domains (αTIGIT), has shown to be effective in treating numerous advanced malignancies [34]. Seven immune checkpoint inhibitors have been approved for the treatment of over 20 different types of cancer by the FDA since the market launch of CTLA-4-targeting ipilimumab in 2013 [35]. Even though immunotherapy has been showing promising results recently, about 80% of patients still do not respond to treatment that blocks immunological checkpoints with a single drug [36, 37]. Furthermore, severe autoimmune-like side effects and secondary resistance restrict the clinical usage of immune checkpoint inhibitors. Several studies, both in the lab and in the clinic, have shown that radiation can increase the effectiveness of checkpoint blocking treatments by stimulating the growth and activation of cytotoxic T cells that target tumours. In comparison to using only αTIM-3 and RT, research has demonstrated that RT+αTIM-3 significantly slowed tumour growth. Furthermore, as compared to patients with metastatic melanoma who only received immune checkpoint inhibitors, the overall progression-free rate of individuals treated with radiation and immune checkpoint inhibitors is approximately 36-50%. Despite an improvement in patient survival, combinational radio-immunotherapy still has limited therapeutic effects and response rates due to issues such tumour metastasis and inadequate radiotherapeutic efficacy. Luckily, new methods have been discovered by scientists to increase the rate of immune response and therapeutic efficacy by combining radio-immunotherapy with various functionalized nano-biomaterials. Activated CD8+ T cells express the PD-1 receptor, which is common knowledge. When it attaches to tumour cells' PD-L1 ligand, it stops CD8+ T lymphocytes from doing their jobs and from multiplying. Thus, increasing the effector CD8+ T cell activity in tumours can be achieved by inhibiting the interaction of PD-1 with its ligands using αPD-1 or αPD-L1. Activated and potentially fatal T cells display an exceptionally high expression level of PD-1 in comparison to other immune checkpoints. By raising the number of activated and deadly T cells, the

introduction of nano-biomaterials into radiotherapy improves the function of αPD-1 or αPD-L1, which in turn raises the amount of PD-1. Extensive research has been conducted on the idea of enhancing the immune response generated by X-rays by combining nano-biomaterials that capture antigens with PD-1 or PD-L1. One example is the work of Wang et al., who developed various kinds of antigen capturing poly(lactic-co-glycolic acid) nanoparticles (AC-NPs). These nanoparticles could carry X-ray-stimulated tumor-specific proteins to cells that present antigens. This enhanced the effectiveness of αPD-1 checkpoint inhibitors and caused abscopal effect. The cure rate of distant tumour went up from 0% to 20% after AC-NPs were added. In addition to transporting tumor-specific proteins, nano-biomaterials have the potential to increase radiotherapy's immunogenicity by making patients more sensitive to the radiation. To illustrate, WSP NPs including WO2.9-WSe2-PEG nanoparticles and αPDL1 antibody were created by Dong et al. for the purpose of cancer ablation. Combining WSP NPs with αPD-L1 led to a significant reduction of both the primary tumour (>90%) and distant tumours (>80%) when exposed to X-rays (Fig. 2a-d). Another study utilised a nanoplatform based on tannic acid and Mn2+ chelation to treat tumours through the integration of αPD-L1. The survival rate of tumour tissue treated with a combination of αPD-L1 and other agents was one-and-a-half times higher than that of the αPD-L1-treated group (Fig. 2e-g). The findings supported the idea that X-ray irradiation in conjunction with nano-biomaterials could enhance PD-1 immunotherapy by either increasing the visibility of tumor-derived specific proteins or boosting the immunogenicity and radiosensitivity of tumours. Internal radiotherapy, which involves a longer exposure to low-dose radiation, has been found to have substantial radio-immune effects and a higher rate of αPD-L1 response, in contrast to external radiation. Pei et al. found that 177Lu@Au NCs could promote the expression of PD-L1 on distant tumours, which increased the likelihood of αPD-L1 binding to the tumour, in addition to effectively stimulating the maturation of dentritic cells (DCs). This was achieved by labelling metabolizable gold nanoclusters with the therapeutic radionuclide lutetium-177 (177Lu). Transgenic mice with tumours that had metastasized on their own were used to test the efficacy of this approach. 177Lu@Au NCs and αPD-L1 together effectively halted tumour growth and metastasis, and the mice's survival cycle was lengthened. It is worth mentioning that eliminating PD-L1+ cells or downregulating PD-L1 ligands can also enhance the anti-tumor immune response by reducing the immunological escape of tumour cells. In their study on glioblastoma radio-immunotherapy, Zhang et al. created lipid nano-biomaterials (LNP) that were targeted at PD-L1 and included both αPD-L1 and the cyclin-dependent kinase inhibitor dinaciclib. Due to the up-regulation of PD-L1 on tumor-associated myeloid cells, the transport efficiency of the medicinal payload was significantly improved when exposed to X-ray radiation. Treatment with αPD-L1-LNP/Dinaciclib not only stops PD-L1 from working, but it also stops new PD-L1 synthesis. In the end, αPD-L1-LNP was able to eradicate tumor-associated myeloid cells, and when administered alongside radiation therapy, it significantly prolonged the survival of the mice. To combat glioblastoma, Erel-Akbaba et al. developed solid lipid nanoparticles (SLN) that target tumours and release small interfering RNAs. The nano-biomaterials that emerged from the brain tumour area were a direct outcome of the enhanced uptake of SLN by low-dose radiation.

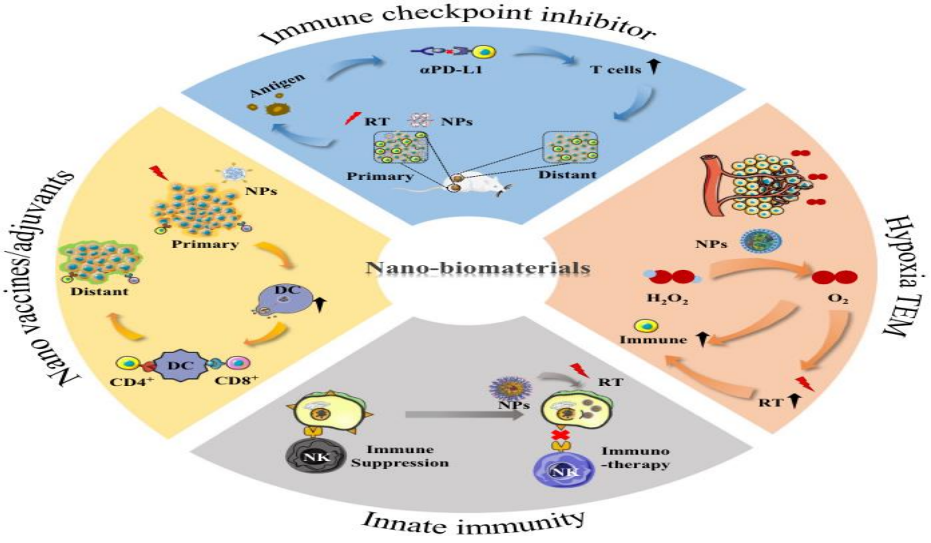

Figure 2. A schematic depicting the primary process of cancer radio-immunotherapy utilising radiotherapy in conjunction with nano-biomaterials.

Radiotherapy and Photodynamic Therapy in Combination Implementing QDs

Initial testing of nanoparticles as photosensitizer delivery vehicles occurred outside of the realm of radiation. Because of their poor solubility in water, most photosensitizers, such as porphyrins and Pcs, cluster in tissues, reducing the efficacy of their photochemical actions. A more effective hydrophilic PDT delivery system was created by synthesising gold nanoparticles coated with Zn-Pc. Another method for delivering photosensitizer molecules to tumour locations was the use of biodegradable liposome nanoparticles. Conjugating photosensitizers to fluorescent semiconductor nanoparticles improves the energy transfer efficiency, which is an additional benefit of delivery vehicles. Samia et al. (2003) were the first to show that CdSe QDs can act as a Förster resonance energy transfer (FRET) mediator, transferring energy from UVA light to a PDT agent. It is not possible to use QDs for biological applications since the conjugates are not water-soluble and the quantum yield is quite low (~5%). For enhanced water solubility, Shi et al. (2006) produced QDs coated with peptides related to phytochelatin. In their 2007 study, Tsay et al. covalently linked QD with a surface coating that was identical to Rose Bengal, a photosensitizer. This led to reports of three to four times greater singlet oxygen output from the QD/photosensitizer conjugate compared to the photosensitizer alone, in addition to outstanding colloidal characteristics. Using this platform, one might boost the quantum yield by increasing the amount of photosensitizer molecules on each quantum dots (QD) and reducing the link between the QD and photosensitizer to improve FRET efficiency. The investigations did not address the fundamental restriction of PDT treatment depth, and they used visible or UV lamps.

Enhancement of radio immunotherapy with nano vaccines and adjuvants

Vaccine treatment has the potential to activate the innate immune system and improve the peripheral tumor-specific T cell response. Classical cancer vaccines have a number of serious drawbacks, such as restricted tumour antigen transmission to lymph nodes due to enzymatic degradation and rapid renal clearance, ineffective cross-presentation of tumour tissue specific antigens, and poor vaccine release efficiency. It is well-established that radiation therapy leads to immunogenic cell death, which in turn produces tumour antigens and enhances the efficacy of antigen presentation. Patients with hepatocellular carcinoma can safely and effectively undergo proton-beam radiation in conjunction with an in situ vaccination, according to clinical trials [70]. Abei et al. demonstrated the efficacy of the "in situ vaccination" approach in the first clinical experiment. Four patients achieved progression-free survival for over a year, and nine patients had a median progression-free survival of 6.0 months (range: 2.1–14.2) [18]. After radiotherapy, DCs are better able to absorb antigens from nano-biomaterial vaccines, which allows for easier antigen cross-presentation and stimulates the antitumor T-cell response. Inspiring by this characteristic, Ni et al. developed a locally activable immunotherapeutic approach utilising nMOFs loaded with CpG oligonucleotides. These frameworks have been extensively studied as vaccine adjuvants for DCs maturation and the release of pro-inflammatory cytokines. The release of tumour antigens and DAMPs was activated by producing large amounts of reactive oxygen species (ROS) under X-ray radiation. Concurrently, CpG oligonucleotide delivery enhanced antigen-presenting cell adhesion, and the combination treatment approach increased cytotoxic T cell numbers in lymph nodes draining tumours. In the end, the combination treatment resulted in a strong immunological memory effect, and both the primary and distant tumours significantly decreased. When combined with ionising radiation, nanovaccines containing immune adjuvants such stimulator of interferon (IFN) genes (STING) agonists and CpG oligodeoxynucleotides can enhance cancer immunotherapy. As an example, in order to enhance the systemic T cell response specific to cancer, Luo et al. created STING activating nanovaccines using antigen-loaded polymeric PC7A NPs. In comparison to single treatment, which not only killed the main tumour but also caused an abscopal effect, combining local STING pathway activation with X-ray radiation resulted in a synergistic treatment effect against large tumours. In addition to blocking DNA damage repair, ATR kinase inhibitors (ATRi) can alter the immune system and promote a stronger immunological response when used as an adjuvant. Hafnium oxide (HfO2) nanoparticles and a hydrophobic ATRi VE-822 (Berzosertib) were combined to form a nanocomposite by Liu et al. If HfO2 NPs are indeed radiosensitizers, then exposing tumour cells to external X-ray radiation might significantly damage them. Afterwards, the local radiotherapeutic efficacy is significantly improved because the loading VE-822 inhibits ATR and slows DNA damage repair (Fig. 4a). Crucially, by increasing immunogenicity via the cGAS-STING pathway and encouraging immune cell infiltration, the combination of VE-822 with HfO2 NPs-mediated RT can effectively stimulate the immune system to fight cancer.

Radioimmunotherapy via triggering innate immunity using biological materials A wide variety of myeloid-lineage cells are involved in innate immunity. These include dendritic cells (DCs), monocytes, mast cells, polymorphonuclear cells, and innate lymphoid cells (including NK cells). Many research have focused on manipulating innate immune cells to lyse malignant cells, leveraging their potent activities such as tumour recognition, adaptive immunity regulation, and tumour cell death. The potential of radiation to enhance the efficacy of innate immunotherapy is a topic of growing interest in the field of immunomodulatory adjuvant research. Ionising radiation, for instance, has the ability to induce macrophage phenotypic changes that confer anti-tumor and pro-inflammatory properties. Efforts to enhance anticancer immune responses by combining nano-biomaterials with radiation and immunotherapy have received substantial attention in light of the combination therapy's limited success. Following radiation, dendritic cells (DCs) would absorb tumor-associated antigens (TAAs), convert them into peptides, and then show them to the cell surface's major histocompatibility complex (MHC). The next step in the immunological response could be for T cell receptors to identify Te MHC-antigen complexes and activate T cells. Unfortunately, post-radiation TAA synthesis is low, and lysosome degradation renders most TAAs internalised by DCs useless for optimal antigen cross-presentation. Radio-immunotherapy can be improved with nano-biomaterials by boosting the synthesis of tumor-associated antigens (TAAs), facilitating their lysosome escape, and fostering cross-presentation. On one hand, there is a synthetic antigen-capturing stapled liposome that has been demonstrated to enhance TAA generation, facilitate lysosomal escape, and cross-present TAAs in vitro. This liposome contains N,N′- methylenebis(acrylamide), 2-(hexamethyleneimino) ethyl methacrylate (C7A-MA), maleimide (Mal), and L-arginine. Additionally, when combined with RT, it encouraged a longer survival time. Figure 5b, c) [85] shows that after 45 days, 75% of the mice in one treatment group survived, while all of the other groups died. Endocytosis, processing, and antigen presentation are the primary functions of tumor-associated macrophages (TAMs), which can be broadly classified into two phenotypes: the conventionally activated tumoricidal M1 and the tumorsupportive M2 [86]. Subsequently, initiatives have been launched to enhance macrophage tumor-negative function by retraining them from M2 phenotype to M1 phenotype. For instance, in order to improve radio-immunotherapy, Cao et al. described CpG adorned gold (Au) nanoparticles. The study found that by utilising Au NPs as radioenhancers, antigen production was boosted and CpG re-educated M2 TAMs to M1 TAMs, innate immunity was aroused and T cell activation was primed simultaneously. Combining RT with nanoparticles significantly increased M1 cell expression and decreased M2 cell expression, respectively [31–36]. Furthermore, the mice with bilateral colorectal tumours were treated by Ni et al. with HFDBA MOF that was loaded with IMD αCD47 and combined with αPD-L1. The platform was able to repolarize immunosuppressive M2 macrophages to immunostimulatory M1 macrophages, eliminate distant tumours, and accelerate X-ray energy deposition and ROS generation, according to this study. It also improved antigen presentation performance. Because of their ability to both kill tumour cells and regulate the immune system, NK cell-based medicines have recently come to the forefront of tumour immunotherapy for some malignancies. Overexpression of human leukocyte antigen E (HLA-E) in tumours prevents natural killer cells (NK cells) from lysing tumour cells of different origins. Overexpressing human leukocyte antigen E (HLA-E) prevents natural killer cells (NK cells) from destroying tumours because HLA-E suppresses NK cell function. The NK cells can't get rid of tumour cells because of this. Recent research has shown that selenic acid can inhibit HLA-E expression and promote cell death in tumour cells, leading to anticancer action mediated by NK cells. Nevertheless, selenic acid administered systemically may increase NK cell cytotoxicity towards normal cells expressing HLA-E. Consequently, NK cell-based treatments greatly benefit from selenic acid in situ produced inside the tumour site [37, 38]. It has been suggested that ionising radiation has the ability to break diselenide bonds, resulting in the formation of seleninic acid. To lessen the harm that NK cells can do to healthy tissues, it is possible to create nano-biomaterials with radiation-sensitive diselenide linkages that can absorb NK cell-activated tumour therapy. This is why Gao et al. created a nanomedicine called PSeR/DOX, which combines the X-ray-sensitive polymer skeleton based on diselenides with the chemotherapy drug doxorubicin. Ionising radiation could oxidise diselenide bonds into selenic acid, which NK cells could then use to their advantage in cytotoxicity. A combination of radiotherapy, selenic acid-mediated immunotherapy, and chemotherapy was associated with an increase in tumour infiltration of NK1.1(+) NK cells, a decrease in the expression level of HLAE, and an improvement in the tumour inhibition rate in mice treated with PSeR/DOX and exposed to X-rays. To disrupt diselenide bonds, X-rays aren't the only option; γ-rays, which are more penetrating, are also utilised. Through γ-radiation-sensitive hydrogen bonding, Li et al. coassembled pemetrexed nano-biomaterials with cytosine disselenides, making cancer cells more responsive to NK cells and significantly reducing tumour metastasis. By releasing payloads through radiation in situ, tese ionising

radiation-responsive nano-biomaterials [39] are able to accomplish total tumour treatment.
Further investigation into the practical use [40] and clinical transformation is necessary, but nano-biomaterials that are responsive to ionising radiation offer a new approach to immunotherapy that is regulated by ionising radiation and broaden the field of radiotherapy. Although radiation may enhance controlled penetration, further research into the internal mechanism between radiation dose and material sensitivity is necessary.

Role of Free Radical Scavenger in Radiation Protection

Working from the opposite direction, the therapeutic ratio can be improved by protection of normal tissue more than tumor tissue from radiation damage. Since radiation-induced injury to cells is caused primarily by free radicals generated by excitation [41] and ionization events during the interaction of radiation with the tissue, free radicals have been the primary target of research in radiation protection. Amifostine is the only approved treatment for radioprotection in patients with head-and-neck cancer (Spencer and Goa 1995).

In normal cells, amifostine hydrolyzes by alkaline phosphatase to the active thiol metabolite, WR-1065, which scavenges super-oxide radicals generated from ionizing radiation. However, common side effects of amifostine include hypocalcemia, diarrhea, nausea, vomiting, sneezing, somnolence, and hiccups. Serious side effects include hypotension (found in 62% of patients) and erythema multiforme. These side effects have prevented the wider application of amifostine in radiation therapy.

Carboxyfullerene

One definition of carboxyfullerene is a "free radical sponge" that can take in many radicals and store them in a single nanoparticle. This is why, ever since its discovery, there has been a great deal of interest from researchers in considering its potential use as a shield against cell oxidation damage. For its anti-oxidant properties, carboxyfullerene (C3) is a popular choice. Until recently, the mechanism by which carboxyfullerenes reduce ROS generation remained unclear, despite the fact that experimental evidence supporting this effect existed. The mechanism of the reaction between C3 and free radicals was revealed by a computer model [42]. By transferring the unpaired electron from superoxicide to C3, the free radical is neutralised. The whole reaction is limited by this phase, it turns out. Better free radical scavenging could result from fine-tuning this process. The second stage involves the reaction of a second superoxicide with an anion of the C3 radical that has an additional electron. Through a series of intermediate processes, the OO moiety becomes more stable by transferring electrons to it, and it obtains two protons from the COOH link on C3, resulting in the formation of a hydrogen peroxide molecule.

It is unclear, however, how the hydrogen peroxide molecule interacts with C3 in subsequent metabolism. Human keratinocytes were shown to be well protected from UVB radiation by carboxyfullerene [43]. Radioprotective function testing has also been conducted on C3. Normal hematopoietic progenitor cells showed a protection factor (the ratio of survival with and without C3) of up to 2.38, whereas mouse and human tumour cell lines showed significantly less protection. Sod2−/− mice, which do not have mitochondrial manganese superoxide dismutase, had a life span increase of 300% after being treated with C3, demonstrating the antioxidative stress action of C3 (Ali et al. 2004). Fullerenes significantly suppress ROS, superoxide radical anion, singlet oxygen, and hydroxyl radicals, according to additional research carried out by Yin et al. (2009). Additionally, this study showed that variations in electron affinity and physical characteristics, like aggregation degree, caused by surface chemistry impact the radical scavenging capacity [43]. The toxicity of carboxyfullerene, however, has been documented. Aqueous carboxyfullerene (nC60) may produce reactive oxygen species (ROS) depending on the particular car-boxyfullerene derivative. Embryo death and deformity were reported in investigations using nC60in zebrafish, however the results are extremely contentious [44].

The rate of free radical scavenging is the second obstacle to use carboxyfullerene as a radiation shield. C3 is slower than CeO2 nanoparticles at removing the superoxide anion [45–55]. While carboxyfullerene might be enough in a setting where free radical production is slow, a new study found that it only has modest radiation-protective activity in living organisms, suggesting that it might not be enough in a scenario where ionising radiation is present. The lack of proof of differential protection from irradiation to normal cells versus tumour cells was also highlighted as the third obstacle in the same study [56-57]. An important area of research involves modifying the surface chemistry to enhance radiation protection and ROS scavenging efficiency.

CONCLUSION

Despite the novelty of using semiconductor nanoparticles in radiation treatment, promising first findings have been reported. The energy reservoir in the form of semiconductor nanomaterials absorbs a broad spectrum of x-rays and transforms them into visible light with a wavelength tuned to the photosensitizer's absorption peak. This light then produces cytotoxic singlet oxygen molecules, which kill tumour cells more effectively. In contrast to the straightforward energy sink using high-Z materials, this application has the potential to circumvent radioresistance by activating new biological pathways that lead to tumour cell death. Along with tumor-specific targeting, other potential areas for future research include modifying particles to increase the cross-sectional area of high-energy x-rays and using photosensitizers that produce more singlet oxygen. It has not yet been demonstrated if nanoparticles selectively protect normal tissue from tumours, despite their great redox capacity, which makes them free radical scavengers for radioprotection. A new breed of sensitive and agile dosimeters has been developed through the nanoengineering of these semiconductor materials. While this area is still in its early stages of development, the fact that nanomaterials are not frequently utilised in patient treatment shows that it is mature. Improvements in efficiency, safety, pharmacokinetics, and affordability are necessary for nanotechnology to reach its maximum promise in radiation therapy. The use of nanomaterials in biology has long been plagued by many of these issues. Although a lot of ground has been covered, there are still no set standards for everything. Achieving success is typically done on an individual basis. Building a nanodevice that can do everything or meet every need is also very challenging, if not impossible. For any given use case, these characteristics must be prioritised. For patients with advanced cancer, the effectiveness of radiotherapy should take precedence above concerns about long-term toxicity and biological clearance.

The immunomodulatory effects of radioimmunotherapy, including tumour immunogenicity enhancement, inducing immune cell death (ICD), and triggering the release of cytokines and chemokines, have been extensively studied in recent years. The goal of developing different types of nano-biomaterials or nanomedicines for use in nano-biomaterials-assisted radio-immunotherapy was to increase the success rate of immunotherapy in conjunction with radiation therapy. One example is the potential for anti-tumor immunity when immune checkpoint blockades are used in conjunction with high Z nanoradiosensitizers exposed to X-ray radiation. Nanomedicines that produce oxygen improve the anti-cancer effects of radio-immunotherapy by adjusting the immunosuppressive tumour microenvironment (TME). New nano-vaccines and nano-adjuvants also improve antigen presentation capabilities, leading to synergistic effects that are super-additive. In conclusion, various approaches to radio-immunotherapy mediated by nano-biomaterials have produced outstanding synergistic results. Uncertainty regarding the adverse effects of nano-biomaterials-activated immunity, the intricate interaction between nanomedicine and radio-immunotherapy, and the unknown molecular processes of immune pathways are a few of the remaining hurdles. Some important concerns must be resolved in order to facilitate the clinical translation of radio-immunotherapy supported by nanobiomaterials. (1) Because present nanodelivery technologies are so complicated, very little is known about how nanoformulations interact with biological organs, tissues, or cells. More research is needed to fully comprehend how these intricate nanodrugs interact with a patient's immune system. Exploring the inner workings of radioimmunotherapy with nano-biomaterials. When the immune system interacts with the body, it leads to the development and spread of cancerous tumours. To create nano-biomaterials that are related to the immune system and tumours, a better knowledge of how the immune system works is necessary. It is not possible to conduct extensive analyses in animal models using samples generated from human tumours. Most of the pre-clinical studies in radio-immunotherapy use murine cell lines. Some humanised mouse models continue to face issues such as rejection, an inadequate or nonexistent immune response to MHC-restricting antigens, and a difficult modelling process. A lot of people are interested in using nano-biomaterials for tumour radioimmunotherapy because of how safe they are for biological systems. It is important to choose safer methods of drug delivery and to ensure that nano-biomaterials are highly biocompatible. Researchers are currently very interested in intra-tumoural administration. Drug availability in situ and body tolerance can both be enhanced by intratumoural injection, according to reports. One major benefit of intratumoural injection is that it reaches lymph nodes, which can then mount an immune response against the tumour. There will be significant advancements in radio-immunotherapy and the provision of synergistic cancer immunotherapy for clinical translation as a result of the creation of functionalized nano-biomaterials.

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