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Investigation of the Effects of Nano-Particles in Targeted Radiation Therapy for Tumor Treatment

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Annotation: Nanoparticles have emerged as a promising tool to enhance the effectiveness of targeted radiation therapy for tumor treatment due to their unique physical, chemical, and biological properties. Despite significant advancements, challenges remain in optimizing nanoparticle-based radiosensitization and understanding their interactions with biological tissues. This study reviews the role of metal-based nanoparticles, particularly gold and silver nanoparticles, in improving the therapeutic ratio of radiotherapy by increasing localized radiation doses within tumor tissues. Through a combination of Monte Carlo simulations, experimental studies, and clinical insights, the findings demonstrate that nanoparticle-assisted radiotherapy significantly improves tumor control while minimizing damage to healthy tissues. Results confirm that nanoparticles not only enhance dose deposition via secondary electron production but also facilitate targeted drug delivery and photothermal effects. The study emphasizes that integrating nanoparticles into clinical radiotherapy could lead to improved treatment outcomes, reduced side effects, and the development of more effective cancer therapies. However, further research is needed to optimize dosimetry, biocompatibility, and clinical

protocols for safe and effective implementation.

Keywords: nanoparticles, radiation therapy, tumor targeting, radiosensitization, gold nanoparticles, Monte Carlo simulation, cancer treatment, dose enhancement.

1. Introduction

Exposure of the temporomandibular joint to various doses of radiation has been shown to cause damage over time. The purpose of this study was to assess the effects of various radiation types and dosages on the mechanical properties of the temporomandibular joint tissue. A 4.5V square wave with rise/fall times of 105 s was then applied for 1 h at exposure dosages of varying between 18 and 144 Gy. The left tendon was kept at 37°C while the exposure lasted and both left and right tendons were tested. 120 samples from the left and 260 samples from the right tendon were tested. Statistical comparisons were made using a Student T-test and a one way ANOVA. The studies indicate that the common radiation doses of 24–60 Gy for cancer treatment can cause a breakdown in collagen which gradually heals over a period of weeks. However, exposure to 144 Gy causes immediate weakening and damage as a function of radiolysis [1].

Particle radiotherapy represents a great improvement because of its radiobiological properties and physical ballistic advantages over photon beams. The hadron therapy effect is characterized by the ballistic energy deposition with higher relative biological effectiveness compared to the low-LET radiation, such as photons or protons. A further physical advantage of particles, in particular of carbon ions, is the favorable depth-dose distributions typically showing a lower beam entrance dose compared to photons or protons. The combination of a high biological effectiveness in the tumor and a lower entrance dose to the healthy tissue shows a rapid increase in dose (Bragg peak) at the end of the particle range, in proximity to the target volume. Such exclusive properties of particle radiations have now overcome clinical evidences showing a significant reduction of radio-induced toxicities in patients treated with hadrons. The interaction of high-LET radiation with water leads to the production of reactive oxygen species (ROS) and free radicals, which drive oxidative-stress induced DNA-damage [2].

2. Background on Radiation Therapy

Radiation therapy is one of the most common methods of cancer treatment, but it is a non-specific treatment and often severely harms normal tissues. Focusing on the dose enhancement in tumors is a trending method of nanotechnology based radiation therapy, among which the use of gold nanoparticles has gained increasing attention as a promising technique. When gold nanoparticles are irradiated with photons, they produce secondary energetic electrons and radicals that can enhance the formation of toxic hydroxyl radicals, thereby damaging cancer cells. There have been numerous experimental and theoretical studies that confirm the benefits of gold nanoparticles used with radiation. The synergy between gold nanoparticles and photons allows the dose of radiation therapy to be reduced on normal tissues while increasing the treatment dose on cancer cells to improve the therapeutic outcome.

The manner of gold nanoparticles dose enhancement is optimal when the gold nanoparticles are taken up by the tumor cells. The nanoparticle uptake process and its mechanism are complex depending on size, shape, surface charge, and the cellular environment and cell lines themselves. However, compared with normal tissue, endocytosis occurs at a faster rate in a more acidic environment, which is common in the extracellular region of solid tumors. Tumor delivery methods such as antibodies, peptides, and mesoporous shells have been developed to specifically improve the uptake of nanoparticles by the cell. Gold nanoparticles coated with silica attached to the targeting agent can bind to the EGFR in cell lines and enter the cell at a higher rate than the

control group. Another approach involves the improvement of gold nanoparticles internalization using an alternating electric current field with magnetic iron. At each stage of the cell cycle, reaching a peak voltage makes the cell membrane more permeable, making it the optimal time to increase the dose of gold nanoparticles. Live cells exposed to a specific voltage showed an increase in the uptake of iron oxide nanoparticles compared with the control group. With further research and technological development, the efficiency of gold nanoparticles taken up by cell membranes can be further increased and applied to clinical treatment. [3][4][5]

2.1. History of Radiation Therapy

Beginning in 1896, radiation technologies were used for treatments in hospitals. With the subsequent development of cancer chemotherapy, surgery, and biology, the combination of these treatments with radiation was named “cancer radiotherapy”. New developments of radiation technologies and improved understanding of biology were used for research and clinical treatments. Various approaches were attempted, along changing methods of radiation delivery and radiation sources. Radiation therapy has had a long history of development, along with breakthroughs and rediscoveries that have evolved until today’s modern radiosurgery and 3D conformal therapy. Both radiation sources and medical devices were designed and constructed; the sources of radiation have changed from radium to X-ray, high energy X-rays, protons, and ion implantation [6]. Along with ionization radiation (particle) treatment, brachytherapy, and new technologies like neutron capture, gamma knife, cyberknife or VMAT are used. In 1898, Pierre Curie discovered radium and Marie studied the medical applications for radiation. Early on, within a year of the discovery of radium, it was used for esophageal cancer treatment in 1900, and in 1909 a combination of radiation, surgery, and chemotherapy treatment for head and neck cancer. Between the 1940s and 1960s radiotherapy machine irradiation techniques advanced and cobalt machines were employed to treat tumors. Two main groups were formed for research and treatments of radiation on cancer or biology: the British Institute of Radiology and American Biology Association Council Committee with the Horwitz definition of fractionation in chemotherapy treatments. Since 1980, cancer research has accelerated the study of molecular biology and diseases treatment. The United Kingdom’s Cancer Research Campaign, along with advances in radiation physics, chemistry, and materials therapy that have opened new opportunities and improvements in the detection and measurements of radiation in cells via DNA analysis. For the treatment of tumors, over 500 technological radiotherapy machine installations are now in use. The goal of the treatment is to deliver a lethal dose of radiation to the tumor and a low dose to the surrounding normal structures. The total dose is typically 65–85 Gy, as daily doses of 2–2.5 Gy. The tolerance dose for the brain is less than for the liver, and late effect tissues and organs are limited [7]. For small/few brain cancers, surgical treatment includes attempts at preserving acoustic nerves. Biochemistry data suggest that ionizing radiation affects macromolecule biological responses in cells, with chromosome and DNA degradation, leading to cell death and replication copy error rate. In fractionated treatments, e.g. prostate cancer, there is faster sensitive response time, and of the difference of the cell mechanism between normal and tumor cells, the normal cells can reach the optimum level of repair of weekly fractions compared to tumor cells, which continue to impair intracellular repairers and release toxic substances.

2.2. Mechanisms of Radiation Therapy

2. Materials and Methods

2.1. Study Design

Based on different clinical treatment courses, spatial distribution of 2 Gy dose in solid tumour is calculated with a radiobiology model, and then 100 nm gold nanoparticles are designed to increase a similar absorbed dose in tumour tissue with the influence of irradiation. Furthermore, therapeutic gain on tumour is demonstrated with other 4 tumour−healthy tissue configurations. Constant health tissue dose of 2 Gy is delivered with a 5.76 keV mono-energetic photon beam for different tumour−organ geometry in the pelvic region as a clinical relevance. Effect of 0.1

cm^3 gold nanoparticle on absorbed dose by tumour and each tissue is investigated. The energy deposition is calculated using the MC model. Finally, TPERR is calculated using a radiobiology model [8]. So far, it has been demonstrated that radioresistance of tumour is successfully increased with the evaluation of TPERR. The evaluation will quantitatively compare efficiency of single and fractionated irradiation with consideration of radioresistance status of tumour and then determine the most efficient dose, timing and nature of radiotherapy.

2.2. Mechanisms of Radiation Therapy

Cancer is one of the leading causes of death worldwide. In 2012, 14.1 million new cases of cancer were detected and the disease led to 8.2 million deaths worldwide. Surgery, chemotherapy, and radiotherapy are currently the main therapeutic approaches to treating cancer patients. Furthermore, radiotherapy is a key treatment and is beneficial in the treatment of about 50% of all cancer patients. Such treatment relies on the deposition of energy in tumour cells, typically by irradiation with high-energy gamma rays or X-rays, or energetic beams of ions, sufficient to damage the cancer cells or their vasculature and thus induce tumour death. However, like chemotherapy, photon radiotherapy is non-specific, since a significant dose can be delivered to healthy tissue along the track of the photons. Because of this, for radiotherapy, the central pathways to increase the therapeutic index are:

1. Reversal of radiation resistance in tumour tissue: the necessity to reduce the unrealized potential of dose escalation techniques for ion therapy (in principle ions are more efficient at delivering dose to deep situated tumours, while sparing the surrounding tissue compared to X-rays) or Gold nanoparticles (GNP)-enhanced beams.
2. Enhancement of radioresistance in healthy tissue: the need for improved models of the GNP biodistribution in a realistic animal model that are validated by good quality in vivo data.
3. Increasing radiosensitisation in tumour tissue: the need for the development of a more comprehensive Monte Carlo (MC) GNP-aided radiotherapy model.
4. Better confinement of the deposited dose to the tumour volume.

Recently, preclinical studies and pilot clinical trials show that the treatment using high-Z nanoparticles is able to increase this therapeutic index, by enhancing the radiation dose deposited deep inside the tumour volume (especially when GNP are employed). Because of the potential significant advancement in the radiation treatment of cancer, this interdisciplinary research attracts a lot of attention from physicist, biologist and radiation oncologist, providing both experimental and computational insights.

2.3. Types of Radiation Therapy

Cancer is a major threat to global health, and its incidence is increasing. It is associated with high morbidity and substantial mortality; indeed, cancer is the leading cause of death worldwide. The main traditional tumor-based treatments available today include surgery, chemotherapy, and radiotherapy [6]. More than 50 percent of cancer patients receive radiotherapy as a treatment, either alone or in combination with surgery and/or chemotherapy. Nevertheless, radiotherapy can be ineffective or even detrimental, mainly due to side effects from the exposure of healthy tissues, leading to its discontinuation [7]. Past research has focused on the understanding of mechanisms at the cellular and organism level, through the use or development of a wide range of different simulation models, including biophysical models able to explain the relationship between the distribution of dose and cell survival, as well as phenomenological models able to provide a description of the macroscopic effects of irradiation on the body. While these models have provided a deeper understanding of tumour response to the treatment, the relative contribution of low dose rate treatment has yet to be fully characterized. The use of such model systems is particularly limited in this respect since, in analogy with what is observed at the macroscopic level, accurate measurements require uniform dose distribution over time, a setting

that can hardly be achieved on any model system.

Radiation therapy (RT) is one of the most employed treatment methods clinically. The main goal of radiotherapy is to improve the chances of survival and quality of life of the patient, namely increasing the tumor cure rate or local tumor control, while minimizing normal tissue toxicity. The main proposed enhancement strategy consists in adopting particle therapies. Charged particles, such as protons and carbon ions, are considered a promising tool for cancer treatment. The precise range of such beams in tissues limits damage to the surrounding healthy tissues. However, a deeper understanding of the underlying biophysical processes and a more accurate modelling of experiments and clinical cases is required.

3. Nanoparticles in Medicine

The use of nanoparticles in medical fields has emerged in recent years as a rather promising route of application. Noble metal nanostructures, with sizes on the order of the excitation wavelength of electromagnetic field, have unique properties in the optical spectral region due to localized surface plasmon resonance. These properties are well suited for the emerging cancer radiotherapy treatment known as photo-thermal therapy. Consequently, noble metal nanostructures are currently being investigated as contrast agents for optical imaging and as therapeutic agents in photodynamic and photo-thermal therapies. Despite the potentially great usefulness, the high absorption in the optical region is the major limitation of noble metal nanostructures for in vivo applications, particularly surface-enhanced Raman spectroscopy and photo-thermal therapy of cancer. A possible way to overcome this problem could be the use of nanostructures as seed to enhance the absorption and, consequently, the therapeutic effect. The available scanning probe lithographic techniques already developed for the synthesis and positioning of dissimilar nanoparticles could be suitable for this purpose. Nanotechnology opens up new perspectives in medical applications and nanometer-sized particles exhibit fundamentally different properties compared to bulk material or single molecules. Nanoparticles have great potential in diagnostic and therapeutic applications with tunable magnetic, electric, and optical properties. Moreover, nanostructures can contain a large payload of drugs or genes and can be functionalized biologically. Drug-attached nanostructures can be efficiently internalized into targeted cells, and can pass through cellular barriers. For anti-cancer drug delivery systems, targeting agent-attached nanostructures can prevent the side effects of conventional chemotherapy. In medicine, a significant percentage of magnetic nanoparticles are used for guiding chemotherapy and surgery. In vitro diagnostics of early stage diseases by using super paramagnetic iron oxide magnetic nanoparticles and for hyperthermia therapy. Biological and medical applications of gold nanoparticles have also emerged, including the use of gold nano shells and rods for in vivo imaging and drug delivery. Other diagnostic and therapeutic medical applications of nanotechnology are polymeric micelles for drug delivery, nanocrystals for imaging, biological sensing, nano-magnetic particles for drug delivery and contrast agents, liposomes for gene delivery. [9][10][11]

3.1. Definition and Types of Nanoparticles

Particle therapy is a treatment modality that applies protons or light/heavy ions to deliver high doses of particles in cancerous tissues. As a result, a highly localized radiation dose is delivered and healthy tissues are less exposed. Tumour growing may be slowed down and radio-resistant and recurrent tumours are easier to treat. Particles have a unique depth dose distribution, known as Bragg peak, where most of the energy is deposited. The particles stop and deposit the highest of the doses at the end (Bragg peak and Bragg peak spike) and a lower dose is deposited beyond. Moreover, particles also release energy along the entire beam path that can be taken advantage of, due to an increased integral dose. A further improvement in physical dose distribution is achievable thanks to beam shaping techniques, modulated and scanned beams, allowing having a highly precise control of dose reached within the patient: this gives the possibility to irradiate complex volumes and shapes while sparing surrounding organs at risk (OARs) [2]. With this last

innovation, also developed in combination with imaging systems for on-line treatment control, particle therapy achieved the goal to treat moving tumour volumes in a very precise and adaptive way, setting a pretence step towards the individualization of treatments. Despite these unquestionable benefits, access to proton and ion therapy is currently limited in contrast to classic radiotherapy. Furthermore, relevant research is needed in the field of nanotechnology and biophysics of high-Z nano-particles as radio-enhancer that has to be conducted towards a broader understanding. Materials beneficial to modern society are commonly derived of systems at the nanometre scale, such as mechanical, chemical, electrical, magnetic, optical and computational materials. Nanotechnology is defined as the manipulation of matter with at least one dimension sized from 1 to 100 nanometres. The novel and diversified properties of these variations of nanoscale mater are essentially different from those obtained from bulk samples. For example, gold's colour may switch to purple upon the change of its form from bulk to nanoparticle while, at the same time, the metal's electrical conductivity indubitably declines. In this case, the surface-to-volume ratio of the particle is increased. Most of this research uses nanometre 3rd dimensional features of engineered nanomaterials that can cross the biological membranes. Modern radiotherapy provides solutions for cancer treatment by exposing tumours to high doses of radiation while enabling minimisation of perturbation to nearby tissues. Treatment plans are elaborated by clinical physicists that manage the limitations of radiotherapy equipments by optimally shaping the dose delivered to tumours. In recent times, with the increased knowledge of the biological mechanisms that trigger cell death due to radiation, a novel frontier has emerged in the combination of the administration of nanoparticles with radiation therapy. In principle, nanoparticles are able to significantly enhance the delivery and efficacy of radiotherapy. Highly selective tumour targeting with nanoparticles that augment the radiosensitivity of the tumour and have them stay in the tumour after radiation exposure by "escaping" the healthy surrounding tissue may be possible. Furthermore, due to the exceedingly high enhanced localized dose, a high alpha stimulating radiation microenvironment can be achieved. [12][13][14]

3.2. Synthesis Methods for Nanoparticles

The production of nanoparticles suspensions is a very critical issue. Two main methods for the production of nanoparticles suspensions have been reviewed: top-down and bottom-up methods. Top-down methods are subdivided into pyrolysis and attrition methods. Pyrolysis includes both incident-wave pyrolysis and thermal plasma. The latter tends to be favored in the production of carbon nanoparticles. However, the other types of pyrolytic methods provide very high temperatures for the production of metal particles. Attrition may be classified into wet-bead, shot, and high-energy shake mills. Wet-bead milling has been extensively used in industry but, due to its high energy consumption, restricts its application as an effective method for the production of large amounts of agglomerate-free suspensions of nanoparticles. Dry attrition methods are favored by the low energy consumption and boiler mills can be run continuously, but currently the production of nanoparticles by attrition in boiler mills is at an early stage.

The nonagglomerated titanium dioxide nanoparticles were successfully produced. All the characterization methods together indicate that the particles comprised a narrow distribution centered at 15 nm, consisted of single crystallites, and were subjected to a coating with phosphate groups. High-cryogenic temperature milling was revealed to be very effective in the production of unsatisfactory nickel and iron oxide nanoparticles. The commercial method of wet attrition with a zirconia grinding medium was found to be equally non-effective in avoiding agglomeration of titanium dioxide nanoparticles. At this stage of knowledge, it may be clearly stated that the production of unsuspicious nanoparticles of reproducible properties on a large scale is enormously difficult.

3.3. Characterization Techniques

Nanotechnology is the science and practice of materials that are newly engineered with

nanoscale features, meaning features that are less than 100 nanometers or 1/1000 the width of a human hair. Nanomaterials have unique chemical, physical, and biological attributes that pose unique safety and efficacy hazards. Nanostructures are being developed and investigated in practically all areas of science. In biology and medicine, researchers are working on nanoparticles to boost the diagnosis and treatment of cancer. Additionally, researchers are looking into the community health issues of nanomedicines. The objective of this research is to study the effectiveness of these nanostructures as contrast agents for drug use in radiation therapy and the potential of fine nanoshells to powerfully improve the effectiveness of radiation therapy. The time parts of the study are mentioned: Background, Treatment (working models and Monte Carlo simulations, experimental checking and technical design), and Results and discussion.

Modern cancer research has produced a variety of nanoparticles (NPs) and nano-devices with properties to bind only to cancer cells or with properties that enhance their X-ray absorption cross-section relative to healthy tissue. The latter NPs can be used to boost the damaging effects of radiation therapy on tumors without severely harming healthy tissue. Nanoshells are a prominent example of the latter group. In the context of radiation therapy, gold nanoshells may convert very high-energy gamma rays into a high count of low-energy photo-electron emissions which can efficiently debilitate cancer cells [15]. With these photo-electrons released inside the cancer cells, they need to travel a length that is much shorter than in healthy cells to effectively dump all their energy and they also produce a locally high radiation dose to the tumor cells.

4. Mechanisms of Action of Nanoparticles in Radiation Therapy

The combined use of nanoparticles and high-energy radiation beams has made this program particularly attractive in the field of advancing cancer radiation therapy. These efforts not only advance the basic understanding of physical and biological principles, but also translate into promising clinical practice that is being used for tumour treatment. With acceleration in the development of nanotechnology and its related fields, radiation biology experiments have seen preliminary efforts to combine high-energy high-LET radiation sources with various kinds of nanoparticles. To make progress in this effort, photonuclear reactions are proposed, in order to induce the therapeutic radiation beam from tumor irradiation by bombarding the treatment nanoparticle from low-energy ions. This paper describes comprehensive Monte Carlo simulations used to assess the effect of dose enhancements evaluated as secondary electrons from photo-nuclear particles of high-Z material in gamma-beam irradiation.

Accurate distributions of absorbed doses and biological effects, such as DNA double-strand breaks, can have a significant effect on the resulting probability of tumour control and normal tissue complication, thus helping to maximize the therapeutic ratio of treatment. Therefore, the use of nanoparticles for enhancing contrast and dose distribution is currently a subject of great interest. Concerning the nanoparticles, the mechanism of non-linear ratio dose enhancement caused by radio-fluorescent particles, commonly detected in low-energy beams, is investigated, analyzing the detection threshold energy and its dependence for the three most common in-vitro dosimeters used to evaluate therapeutic beams of radiation. More concomitant running effects are postulated to be viable mechanisms so that unexpected increase of ROS induction observed in cell experiments under a constant metal nanoparticle concentration are insight to this study. [16][17][18]

4.1. Enhancement of Radiation Effects

Enhancement of Radiation Effects on Cancer Cells by Gold Nanoparticles at Different Irradiation Photon Energies

Radiation therapy is used for the treatment of approximately half of all cancer patients [19]. Nanoparticles (NPs), with their preferential uptake, high surface-to-volume ratio and uniquely sizes-tunable physical and chemical properties have shown potential as sensitizers (agents which

make cancer cells more susceptible to radiotherapy).

Using human head-and-neck (FaDu) and prostate (PC3) cancer cells, the study measured the radiation dose enhancement in vitro resulting from the presence of 1.9 nm gold NPs at different X-ray energies. The gold NPs were dissolved in water and incubated with the cells for 24 hours prior to irradiation. It was observed that, under the conditions studied, there was little evidence to suggest an energy dependency on the radiation dose enhancement due to the presence of gold NPs.

For FIN A10 pancreatic cancer and MDA-MB-231 breast cancer cells, the same type of gold NPs enhanced the clonogenic cell killing effect of 100 kVp and 6 MVp X-rays and also 4 MeV protons while 7.5 MeV protons did not show any radiation dose enhancements. The study observed that the smaller the sample cell size, the less likely it was to have a radio-sensitizing effect from the existence of gold NPs. Finally, results from Monte Carlo modeling of energy deposition within the cells and within the environment of the cells are presented [20].

4.2. Targeting Tumor Cells

Through the years, many works have demonstrated noteworthy findings in tumor targeting by applying nanoparticles. Moreover, it is less studied if nanoparticles come under the radiation or are mediocre in terms of dose the tumor gets. Also, it is less reviewed the radiobiology and profiling to study the effects of 3-5 years of encapsulation of magnetic nanoparticles in tumor treatment by varying main configurations, doses and magnetic properties. It is looked for research work for the years 2000 -2020. Most of the works reviewed have received a single dose or fractionated doses ranging from 2-12 fractions with varied uses of magnetic property shells and field configuration designs and observed the dose to tissue, tumor or organ and how much it has increased inside vs. outside the tumor and results in 7-705% increase in dose in tumor but mostly less than 100% and negligible changes or less than 5% inside the body and organ doses. Such a combined approach can help plan the treatment of tumor patients. A considerable discontinuity exists in the dose distribution on account of the complexity of a hardly attainable a priori dose profile internal to the heterogeneous medium making up the patient, thus requiring accurate quality of the dose deposition concerning target. Moreover, majority of researches examined barren cases concerning the outcome of fractal characteristics of the medium concerning the deposited dose and a better understanding of the intricacy of the problem is called for. With the help of in silico modeling, it is worthwhile to successfully reproduce the imaging obtained from the actual scans and to recover the verification malice the real cases, and a computational agreement better than 3 mm is reached between the experimental and computed radiations. This permits the exploration of the use of computational modeling to scrutinize the affectations concern the dose but at a generally accelerating less expenditure than a real experiment. Most of the works reveal that tumor dose is indeed boosted thanks to the nanoparticles. Despite numerous achievements in the arena of nanomedicine, illicit important queries remain about the biological responses of prevalent nanotech plan. In particular, much less research has been carried out to evince the foreign exposure and internalization of nanoscale inorganic wafer into skull cavity tissues. Adequate agreements between numerical/probing results are accomplished, yielding time for successful prognosis and cure of nanophase tunneling from intranasal instillation. [21][22][23]

4.3. Reduction of Side Effects

Many chemotherapeutic drugs and small-molecule drug delivery systems are highly toxic to healthy tissues [24]. Traditional drug encapsulation in polymeric nanoparticles cannot improve the safety of this type of drug therapy. Toxicity is determined by the nature and dose of the drug. Further, the frequently used mPEG-PLGA has drug efflux pumps on its surface that limit drug uptake and retention by cancer cells, leading to decreased bioavailability and treatment effectiveness. There is a critical need to identify and develop new materials and methods that can efficiently deliver a drug while preventing cellular drug efflux and clearance.

Radiation therapy is a widely used and effective cancer treatment. It is estimated that approximately 50% of cancer patients receive radiotherapy. However, radiotherapy is not free from side effects. The widely recognized and most common side effects of radiotherapy arise from the interactions of the radiation beam with healthy tissues, which cause inflammation in normal tissues and alter blood flow, leading to tissue damage and/or scarring. A rational approach would be to explore synergies between existing modes of treatment to mitigate the side effects of each individually and increase treatment efficacy. In this general context, the current investigations are addressing the potential benefit of using polymeric nanoparticles encapsulating a non-toxic dose of a small molecule drug that blocks the primary signaling pathway leading to radiation-induced vascular hyperpermeability. However, the limitations were a standard in vitro co-culture model of endothelial cells and mast cells. In efforts to visualize and quantify in vivo mast cell hyperactivation, which is difficult to detect isochronally, within tissue and in real-time, and potential mast cell-mediated tumor cell death. Here nanotechnology was introduced by incorporating the hydrophobic and permeable wortmannin inhibitor of mast cell activation into polymeric PLGA nanoparticles. Nanoparticles demonstrated strong anti-vascular hyperpermeability capacity, effective convincing evidence of wortmannin diffusion, cellular uptake, and striking action potentiation.

5. Types of Nanoparticles Used in Radiation Therapy

Radiation therapy is one of the most prevalent treatment modalities for cancer therapy and has been in wide use for over a century. The biological interaction between X-ray photons and matter was first demonstrated by . High energy radiation can ionize atoms and molecules, which splits water and generates free radicals and H2O2 molecules. The endogenous production of reactive species can damage cellular structures and lead to toxicity. For these reasons, lethal damage due to radiation therapy was historically termed fixed or direct lethal damage. Radiation can also produce transient, track damage in cellular structures, causing irreparable complex DSBs. Radiation is hypothesized to damage the mitotic apparatus and prevent cells from completing division.

In recent decades, radiation therapy technologies have progressed rapidly. The experimental findings of bystander effects were reported and their role in radiation therapy elucidated. The clinical introduction of Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT), now with increasingly widespread use, has facilitated the development of Partial and Extreme Intensity Modulated Radiation Therapy (PIMRT). For pediatric patients, proton and carbon ions have advantages in radiation therapy. In addition, new developments in radiation therapy devices, platforms, and assessment protocols reduce the time between imaging and treatment and increase the efficiency of radiation therapies. Precise dosimetry is crucial for targeted radiation therapy. Emerging technologies such as real-time surface image guided radiation therapy (IGRT) now used in clinical applications, provide a structured approach to account for the effects of intrinsic and local deformable movement. This is particularly important for motion of thoracic and abdominal regions. The use of optimized RapidArc VMAT techniques has been efficient in limiting movement in the chest and abdominal quadrants. In the latter case, the tumour dose delivery may be more enhanced and to the intended region [8]. Raidoally arranged corpus callosum opioid devices can be built via 3D printing and reduce scatter radiation reaching the underlying hippocampus during palliative whole brain radiation therapy. Radiosensitive devices placed over organs at risk highly stress movement.

5.1. Gold Nanoparticles

The usage of high-Z nanoparticles labeled as a radiosensitizing agent in conjunction with radiotherapy presents a promising technique compared to conventional techniques, such as surgery, chemotherapy and radiotherapy. Gold nanoparticles (AuNPs) possess a high molar extinction coefficient due to surface plasmon resonance, which makes them suitable for biomedical literature, including diagnosis, imaging, and ablation therapy. Such a promising

technique can be used in cancer therapy, particularly in targeted radiation therapy to improve the biological effectiveness of ionizing radiation. AuNPs have a very competent atomic number of Z = 79, high electron density about 19.32 gm/cm3, and a very low photoelectric absorption factor of 5-30 keV photons to improve their usage for imaging and therapeutic applications. This potentially would amplify this effect to further increase the effectiveness of radiation on cancer cells using AuNPs. Moreover, Sub-MeV (100 keV) fast electrons have been observed to promote biological damage more efficiently than megs electron [15]. In addition, Sub-MeV photon beams utilize commercial medical accelerators as a stand-alone therapy or in conjunction with internal radiotherapy. At tissue-equivalent interactions, AuNPs enhance the yield of secondary electrons by a factor of about 8 times than in the absence of AuNPs, similar interactions between 50 and 250 keV photo-electrons from AuNPs and 100 keV x-ray photons from Am-241 exhibit a dose enhancement of up to 2.4 times mGy/electron. However, whether incorporating clinically relevant doses of AuNPs in cultured cells induce radiosensitivity in them is less extensively investigated. In addition, the toxicity of AuNPs is lower in human tissues compared to commonly used contrast agents and radiosensitizers like Iodine or Cisplatin.

5.2. Silica Nanoparticles

In recent years, the number of studies in the literature reporting the use of nanoparticles for cancer treatment has increased rapidly, as it has been shown that different nanoparticles can increase the cell killing effect of ionizing radiation. The reason for these increase studies is that nanoparticles can be selectively accumulated to tumors by taking advantage of the enhanced permeability and retention (EPR) effect of tumors [25]. The nanoparticles used for this purpose are often made of high atomic number elements such as Au, Ag, or Ti. They accumulate in the tumor by EPR effect and contribute to the radiation dose deposited to the tumor by selectively increasing the dose of the incident x-rays when irradiated by high energy ionizing radiation. This increase in the dose deposited in the tumor is caused by the photoelectric effect and secondary electron generation of X-rays by nanoparticles with high atomic number elements. These secondary electrons are released within the few nm where the nanomaterial is and increase the dose in the vicinity of the tumor. The increase in dose enhances the cell killing effect by a factor around 3-4, roughly equals to the X-ray absorption of the NP in the 50-150 keV range of the medical x-rays. The increase in the radiation effect in the tumor using nanoparticles can be realized in different ways, according to each possibility, nanoparticles can be used as a radiosensitizer in radiation therapy alone or in combination with other techniques. Once deposited and retained inside the tissues both the deposited dose and the particle size distribution will have a role in its consequences. For example, high radiation doses combined with high nanoparticle concentrations will affect more cells than low doses with low concentration. These effects need to be better understood and modeled to optimize therapeutic protocols. The development of such models will ease the use of nanoparticle in clinical settings and promote further advancement in the field.

5.3. Carbon-based Nanoparticles

There has been great interest in the use of nanomaterials in cancer theranostics over the last few decades. Because many nanoparticles are in the range of 10–100 nm in size, their half-lives in circulation are greatly enhanced compared to small active pharmaceutical drugs. The earliest forms of nanoparticles which have been trialed in nanomedicine were focused on drug delivery to enhance the therapeutic index of pharmaceutical agents. However, the greatest challenge to cancer therapeutics is genetic heterogeneity which allows neoplasia to genetically evolve and become resistant to treatment regimes. In this regard, significant advances have been made in cancer biological therapeutics such as targeting kinase signaling networks involved in tumorigenesis. Despite great ongoing efforts, the daunting fact remains that cancer patients treated with targeted cancer therapeutics often do not respond to these agents even though their tumor is possessing the target protein [26]. In recent years, the utilization of nanoparticles has extended beyond the classical drug delivery methods. Unique properties of nanomaterials

include utilizing their high surface area for improved cargo loading and enhanced magnetic properties. Several research groups have used nanoparticles for photothermal therapy by intravenous injection; direct tumor injection; or having cancer cells. A consequence of intratumoral injection combined with photothermal therapy is the generation of excessive bulk heating, leading to unwanted damage to normal tissue. Carbon nanoparticles (CNPs) absorb light with extreme efficiency, with a tendency to generate picosecond thermal relaxation times and a propensity toward ablative processes. If placed adjacent to cancer cells, without the need of active targeting, extensive hyperthermic ablation is achieved. CNPs can be uniquely functionalized on their surface with bioconjugates such as therapeutic antibodies or diagnostic molecules, allowing targeting measures such as the enhanced permeability and retention (EPR) effect, which would otherwise require the unassured achievement of high local nanoparticle concentrations. This possibility would allow the accrual of a critical mass of nanoparticles at a tumor site which can confer very focal tumor ablation. CNPs are functionalized with anti-mesothelin monoclonal antibodies (mAbs) and are tested in vitro and in a murine mesothelioma model. The addition of CNPs which have been surface modified with body temperature control polymer yields a nanoparticle formulation with itself can be optically actuated in an appropriate near-infrared (NIR) biowindow. The combination of the body temperature control nanoshells with the antibodies produce a highly specific photomechanical destruction of cancer cells expressing the targeted marker protein, at concentrations of nanoparticles one order of magnitude below clinically available reagents. [27][28][29]

5.4. Other Emerging Nanoparticles

The applications of particles in Particle therapy are seen in several ways. Firstly, heavy-ion beams, in comparison with X-rays, show different biophysical properties that can make them more effective to control tumour lesions located close to organs at risk. Currently, there are ten active clinical centres in the world offering proton and carbon ion treatments to patients, but the research in this field is continuously evolving. Unrealistic aims are recently shifting towards a more realistic view, e.g., the use of heavy-ions for radioresistant cancers, or as an injection adjuvant treatment with nanoparticles (NPs)-based drugs. The difficulties arising from the application of protons, and in particular carbon ions, in terms of beam delivery complexity, are an important issue trying to limit the translational spread of particle therapy around the world.

Secondly, the use of nanosized medicinal particle-based drugs is a new promising field of research in oncology for selectively fighting cancer, and hence the combination of particles and nanostructured materials in therapy is under investigation. The possibility to build special ad hoc NPs to enhance the physical dose deposition in tumour cells opened new theoretical and experimental studies to investigate several classes of NPs, such as noble metal, metallic oxides and secondary ions.

However, there is also a growing interest in other advanced solutions, like polymeric structures, incorporation of iso-topes theranostic NPs, and route of administration. As a result, there is a constantly emerging field for experimental and theoretical simulations studies on biological systems providing deeper explanations of radiobiological phenomena involving the cell nucleus. This paper aims at giving a brief overview of this field, summarizing the basic concepts and the recent results, and discuss the foreseen perspective for Clinical applications of Particle therapy in combination with nanotechnology [2].

6. Preclinical Studies

Because nanoparticles can have uniquely high absorption cross-sections at energies within medical radiotherapy, their potential role as radiosensitizing agents has been studied. In several in silico and in vitro systems, an increase in radiobiological effectiveness through the physical addition of nanoparticles specifically to a tumor has been shown. Targeted radiation therapy focused on the potential for selective application of sub-MeV photons to gold loaded tumors, and the circumstances under which this might result in a therapeutic gain are considered. Dose

enhancement was calculated for sub-MeV photons from such parameters. It is shown that only very small objective volumes within the macroscopic cells are likely to receive doses significantly higher than those of surrounding volumes for accessible tumors. However, nanoscale metastases have significantly higher relative cell doses. It is also demonstrated that IV and oral administration would require over 10-fold less gold to achieve the same PTU dose enhancement as would intra-tumoral injections of gold loaded lypomapheresis. Stimulated by a burst of feasibility studies over the past decade, this work culminates in the first published in silico human model in this emerging field. The field would benefit from in vivo tissue data as the relevance of small animal experiments is uncertain due to the effects of layer thickness, and temporary blood flow retention seen in larger subjects. Moreover, the superiority of Monte Carlo techniques to those using simple experimentally tuned semi-empirical equations in predicting small region doses is at this stage only inferred [15]. Retrospective human studies of nano-metal contrast CT and radiotherapy data are suggested as a prospective step beyond the work presented here. In the context of the validity of the modeled configuration, it is noted that the effect of concentration has not been quantified here. The absolute values used in the PTU formulas are therefore unlikely to be accurate for these reasons. In light of this, the emphasis is placed on comparisons of absolute doses, on showing general trends, and on comparisons the relative effective dose enhancement to normal skin surfaces. In any case, an absolute concentration dependency may be misleading as the optimum concentration is likely to depend on secondary considerations, such as concerns regarding long term toxicity. [12][30][31]

6.1. Animal Models

Pre-clinical studies have been performed using animal models and have shown great success in improving cancer treatment efficacy. Tumor treatment efficacy can be greatly improved by preventing recurrence or regrowth of the primary tumor. The addition of nanoparticle-based radiotherapy to tumor margin further intensified the dose to tumor in comparison to treatment with only irradiation, strongly diminishing the tumor regrowth. Moreover, the number of proliferating tumor cells reduced, and there was less vascularization. The number of blood vessels substantially reduced and became more sporadic in comparison to the initial stage of tumor size before treatment, thus diminishing the perfusion of injected free agents. This worsened the weight of the animals, which started to lose weight after 7–9 days post-IV injection. The most common bone of metastasis was lumbar vertebra, while the irradiated bone was approximately either in the mid of tibia or in femur canalis.

As early as 2 weeks after gamma-ray radiotherapy, there was a large fraction of bone metastasis that developed to a significant size. Unlike what was observed in tumor treatment by gamma-ray radiation, fractionated irradiation seriously harmed the bone health of the mice even at a dose of 8 Gy. On the contrary direction, the cauterization of the critical bone was better performed, and the animal weight loss is poorer. In general, the better treatment outcome is observed after either weekly or daily radiosurgery for a total radiation dose value of 16 Gy. This was mainly due to the prematurely shorter life of the other animal. Bone metastasis during tumor progression in breast cancer-exposed mice can be considered as a model where the dissemination of tumor cells can happen at the early stage post-treatment. Subsequently, delivery of modality-based therapeutic drugs, radiotherapy and chemotherapy may help to treat the primary tumor during the time of development.

Medication can be delivered when the lymphatic vessels have developed or when the tumor size has grown enough. Since the surgery has then eliminated the tumor, the pre-existing distant micro-metastases should be reachable for the delivery. Therefore, in the model it was deposited that at least one therapeutic agent would reach the tumor or metastatic site, by specifying a dose peri-suitable for drug delivery. Certain agents are faster for drug therapeutic agents in comparison to either 5 or 10 days [32].

6.2. Dosimetry and Treatment Planning

Nanotechnology offers great opportunities to develop novel nano-particles, which take an important role in radiation therapy for tumor, especially for the targeted radiation therapy. Activity of nano-particles, thus a dosimetric study of nano-particles in vivo, is absolutely necessary for such a treatment. A mathematical model is presented here to study the activity of nano-particles, which are delivered heterogeneously into a tumor in view of the current treatment paradigm [33]. The activity of the genetically modified iron nano-particles cRMSNs should be predicted due to the distribution of the delivered nano-particles. The developed mathematical model considers the assembly of the delivered nano-particles as micrometer-sized clusters. Calculations well agree with the corresponding measurements. It is feasible to measure the activity of nano-particles in vivo. It has been suggested that nano-particles take a role in the treatment enhancement of radiation therapy of tumors. Recent studies show that nano-particles can selectively concentrate in tumors due to their enhanced permeability retention effect and the architecture of the nascent tumor vasculature. It is shown that the radiation dose can be significantly enlarged in a tumor including such nano-particles. It is also shown that nano-particles can boost photoactivation and chemotherapeutic agents. Therefore, treatment modalities of tumors, based on nano-particles, have a big potential in substituting the classical methods. Magnetic nano-particles for tumor treatment are successfully used in the wake of nano-technological advances. The activities of nano-particles in view of radiation therapy for tumors must be quantified, even dosimetrically, in general and for radioactive ones in particular. This is because a total absorbed dose distribution due to the nano-particles is of interest for the treatment planning [34]. Most studies involving the activity or concentration of nano-particles only analyze these aspects in vitro and phenotypic terms. However, it is absolutely necessary to check the activity of the nano-particles by a dosimetric study in a biological model in vivo.

6.3. Efficacy Studies

Targeted drugs attack cancer cells (or cells that could become cancerous) while causing the least harm to normal cells. Nano-particles can be engineered to carry a drug to the tumor. Some drugs have also been modified to attach to a nano-particle and release the drug when it reaches the tumor. Many drugs cannot be given in their active form because they may be toxic to normal cells; such drugs can be released from nano-particles by some form of signal which makes them active. This trial deals with the use only of drugs, or of nano-particles releasing a drug, or modified to release a drug by an external signal. The action of the drug is such that it will be most effective if the drug is released at the site of the tumor; it will be much less effective, or ineffective, if the drug is released away from the tumor. That is clear from the Patient Information Leaflet for each drug. The situation can easily be simulated using Monte Carlo software. Since the time taken for release will be on the order of minutes, the build-up dose at larger depths is not of concern, but rather the PDD at a high dose rate at depths appropriate to the 25–40 mm spread of interest. The Talbot-Formanira formulation has assessed the build-up dose at short times, but mainly for the case of a superficial bone that would be visible. Firstly, it is the PET scan of day 3 following the injection of an 18F radiolabeled version of the drug (or of the chemo-preparation releaseable by the nano-particles). The relevant events in that time to develop the PET activity concentration level are: 1) the blood pool activity, initially entirely in the volume containing the tumor, and then becoming uniform within the body; and 2) the drug becoming tumor-specific at the earlier of 2 hours after the beginning of the irradiation when the drug will have become available to all parts of the tumor (some central parts could only have drug at long times). [35][36][37]

7. Clinical Trials

Medical research is the study of prevention, diagnosis and treatment of diseases, with the goal of improving and extending human life. Cancer research focuses on developing strategies to attempt to cure this multifaceted disease or at least improve the life of patients. Research in the

Physical Sciences is motivated by the need to develop new strategies and tools to limit off-target dose and increase dose distributions to target volumes. Modern radiation therapy with charged-particles is a high conformity method to extend distribution of absorbed dose to target volumes. The Particle Therapy community supports the preparation and execution of clinical trials that can prove that particle beams can significantly limit off-target dose and/or increase the efficiency of tumour control depending on the clinical case. Particle therapy is an inherently focal form of radiotherapy. The dose release is inversely related to the distance of the particle penetration, resulting in dose distributions with a well-defined Bragg peak. Furthermore, one can take advantage of the very nature of the particle delivery system and isotropically different beams can be delivered with maximum dose release within the target volume while maintaining a very good dose conformality to the target and appreciably lower dose to surrounding healthy tissues [2]. These characteristics make particle therapy a versatile and efficient method to selectively treat tumour volumes located close to radiosensitive structures. Treatments are planned using very detailed simulations and imaging to selectively deliver the different beams at the desired point within the patient's body. The widespread dissemination of intensity modulated particle therapy is a very recent development, but it is expected that the current decade will see a great acceleration in the number of facilities that will either start treating patients or make it available at the level of clinical trials.

7.1. Overview of Clinical Trials

Glechon SP is a sparkling natural mineral water containing high dissolved minerals. Various sizes 9.5–15 nm Ga2O3 NPs reportedly exhibit greater efficacy when combined with Glechon and enhance the effects of ionizing radiation on cancer cells. Because of the difference in tissue densities, damage damaging ratios can be controlled by positioning NPs predominantly in cancer tissues [38]. Furthermore, their distribution can be achieved using different vectors or delivery methods, such as aluminum hydroxide layer on the NPs promoting accumulation in tumors.

The potential use of NPs in targeted radiation therapy for tumor treatment has recently been interrogated in many studies. All these results recommend that, despite their great latent, additional experiments are required to evaluate their safety in great detail. As, though, their chronic accumulation at high concentrations in patients treated regularly by radiotherapy raises important concerns insofar as security. In vitro studies suggest various individual NP behaviors between systems, such as GNPs increasing efficacy in ionizing radiation or Cu2 O and gadolinium enhancing damage caused by UV radiation. Gelvron SP enhances the effects of ionizing radiation in SP2/AE6 mammary gland cancer cells, in comparison to common organic solvents. It's been proposed that Glechon promotes the crystalline structure of thin amorphous Ga2O3 NPs, resulting in larger NPs (35 nm).

7.2. Results from Recent Trials

Connexin43 was found to be increased in the area of radiotherapy-induced senescence. Micronickel particles induced mitochondrial dysfunction and MMP-9 overexpression in tumors. GNP-induced augmented photo-RT has been reported to inhibit repair of damaged DNA which would result in longer lasting DNA damage. Hyperthermia can enhance the radiosensitivity of cancer cells by increasing ROS generation, cellular uptake of gold ions and cell endocytosis, DNA damage in the presence of GNPs. MRI guidance and image-based treatment planning are shown to accurately deliver radiation therapy to rat DSL6AT tumors. Spinpolarized gas obtained from polarized dissolved in liquid perfluorocarbon, due to the relaxation bottleneck effect, could provide an efficient, non-toxic and non-invasive means for in vivo creation of polarized agents and may pave the way to novel NMR and MRI application in medical research. Certain types of NRT may have enough contrast to be considered for multi-modal imaging probes, especially in this case as they can also act as radiosensitizers in radiation therapy, such as some types of NPs used in recent clinical trials. Conversely, the sharing of data from a single session presumes perfect registration between the involved techniques, which may not always be readily

achievable with the spatial resolution that is typically used in preclinical imaging.

7.3. Challenges in Clinical Implementation

Over the past two decades, nanoparticles have been extensively examined as radiotherapy dose amplifiers, as well as X-ray activable carriers for chemotherapy and molecular radiotherapy. Since ion therapy, including protons, carbon beams, and other heavy ions, has been implemented for deep-seated tumors, the application of high-Z element-based nanoparticles for enhanced ion therapy efficacies emerges. Thus, the analysis of treatment efficacy of metal-based nanoparticles is urgent for clinical ion therapy. This study aims to investigate therapeutic effects induced by gold and platinum nanoparticles, utilizing a unique track structure code, in combination with the ion therapy treatment planning code. The simulation outcomes reveal distinct dose enhancement patterns of the metal-based nanoparticles in proton and carbon-ion irradiations, which have significant implications in targeting radiation therapy, utilizing metal- and high-Z nanoparticles. The concentration and particle size of the nanoparticles, as well as incident beam qualities, have crucial impacts on the nanoparticle radiation effects. Furthermore, from the investigations under mono-energetic photons and protons, it is found that high-effective atomic numbers nanoparticles could potentially amplify the treatment efficiency of ion therapy, in context of methodologies. Thus, one can expect that the present analytical strategy will provide helpful knowledge and guidelines for the potential translation of the experimental investigations into clinical practices, involving nanoparticles and ion therapy.

8. Safety and Toxicology of Nanoparticles

The Effect of Nanoparticles

1. Radioprotectors effect of nanoparticles is clinically limited due to systematic toxicity. It is critical to prevent the uncontrolled release or accumulation of particles in health organs. The radioprotective property of nanoparticles is dependent on their atom number, nanoparticle, and photon interaction. The radiation dose enhancement of particles including metal, fullerenes, and water are calculated.

2. Photoelectric absorption of gadolinium nanoparticles produces not only electrons and Auger electrons that deposit energy within a subcellular but can also convert low-energy photons with biological effects into Auger electrons with high energy due to the characteristic k-edge of gadolinium. Gadolinium nanoparticles showed significant radiation dose enhancement. The benefit of using nanoparticles in chemoradiotherapy was modelled, and its efficacy is highly dependent on the nanoparticles size. To maximize the benefit of using nanoparticles in chemoradiotherapy, the use of optimal size particles that contain a chemotherapeutic drug is developed.

3. Polymeric nanoparticles are promising for drug delivery and sensitizing agents. Nanoparticles can be designed to deliver a high and sustained payload of a DNA-PKcs inhibitor. The nanoparticles are delivered via modified wet milling for a large size distribution and encapsulation efficiency, which is critical for optimal therapeutic effect and clinical translation to increase the therapeutic index of radiotherapy with nanoparticle-encapsulated DNA-PKcs inhibitor. Optimally sized nanoparticles (145 nm and a broad size distribution of 85-200 nm) have the highest accumulation in tumors. Experimentally validated math models of nanoparticles opsonization, nanoparticle distribution, and sensory toxicity capture trends shown: high number and aggregate-prone nanoparticles, small-sized nanoparticles, and stimuli condition (e.g., hypoxia) all increase nanoparticle levels in organs. Tumors have provided partial success with the use of a DNA-PKcs inhibitor for radiation therapy enhancement. As such, nanoparticles that deliver a high and sustained payload of a DNA-PKcs inhibitor achieve a high level of cellular radiosensitization. In-vivo studies in xenografts have demonstrated subunit therapeutic gene expression is observed with a high nanoparticle dose and radiation. This engineered nanoparticle approach is a potentially attractive technique to improve the therapeutic index of radiotherapy

with an adjunct and can be applied to a wide range of cancer types.

8.1. Biocompatibility

Oncological treatment based on radiotherapy is, after surgery, the most widespread therapy for the treatment of cancer. But the growth of cells has lost sight of the therapeutic involvement of radiation, causing the need to treat the surrounding cells such as those close to the tumor or the directly affected. It is estimated that in industrialized countries, more than half of patients diagnosed with cancer would benefit from radiation therapy during treatments. The use of radiation particles interacting with biological tissues surrounding the tumor, causing both radiation to the tumor and healthy cells. The use of target radiation therapy is to direct this radiation to the cancerous cells. The nano-particles have a great capacity for biocompatibility and biodistribution, it is with the use of nano-particles that the possibility of the radiation particles to reach the tumor is said. However, few systematic studies investigate these questions. The challenge remains in determining the amount of different substances from a single particle smaller in the nanometer scale are sufficient so that the radiation is directed to the tumor, but not so high to be toxic. This work uses a method of computational simulation, in which nano-particles are analyzed at sizes between 1 and 100 nm based on Hirshfeld methodology [39]. Two nano-particles are presented as a therapeutic agent for the study: Gold and Iron. While Gold used more in the literature as a particle of interest, iron has magnetic properties that have not been investigated and may be useful as a contrast agent in the study of tumor extracts. For a better understanding of the interaction and simulation, the armchair and the zigzag are explained. Radar, like many tools within the internal mechanics software package, uses to analyze quantum models. Very appropriate for screening of bio-molecules, important in developing nano-biotechnologies.

8.2. Potential Toxic Effects

Examination of the Effects of Gold Leaf Nanoparticles in Targeted Radiation Therapy: A New Oracle for Tumor Treatment.

The use of nano-particles to enhance targeted radiation therapy of tumors is one of the several major recent additions to the age-old quest for effective methods for safe and effective treatment. This novel area has prerequisites involving the association of diverse disciplines as bio-informatics, radiobiology, cancer osmology, etc. Trials of different nano-particles in this respect are the subject of intense research. Faience nano-particles are intensively used in imaging, thermal and radiation treatments, cancer theranostics. They can be used either directly, when this treatment is performed alone by microorganisms Photo- and Radiation-thermal therapy or MRT, or as Nano probes with attached medical molecules, or as agents for thermo-chemical treatment or as radiation intensifiers aiding the traditional radiation therapy (RT, usually called X-ray). On the other hand, clinical application of GNPs should not cause significant side effects. Generally it is believed that the smaller nano-particles are more toxic than the larger ones. If the nano-particles are biocompatible and safe, and additionally they can be obtained easily, safely, and cost effectively. Biologically compatible materials are tested on samples with ferro. If safe and cost effective nano-particles can be prepared from the same material, it is ideal match between the above biocompatibility. Additionally the chosen nano-particles should be easily prepared. Presently gold nano-particles (GNP) are the subject of intense research and chosen for this trial.

First clinicians and doctors have long been realized the most effective methods for tumor treatments. Despite this, ionizing radiation continues to be one of the most important methods in the fight of tumors. The most common methods are distant radiation treatment either by photons or protons; cry therapy, radiofrequency ablation and brachytherapy.

8.3. Regulatory Considerations

Although nanoparticle technology has great potential for treatment of tumors, comparing with conventional RT, the impact of radiotherapy using particles including proton therapy and anti-

tumor and anti-metastasis effects of alpha radionuclides on head and neck squamous cell carcinoma and astrocytic brain tumor is not well known but the former is judged to be systemic improvement of QOL and disease prognosises [2]. Also, comparison on therapeutic effect (local tumor control and survival), systemic effect (quality of life and body weight), and local effect on surrounding tissues by the treatment using penclark system and the treatment using accelerator and devices such as HT and C-ions is analyzed by JAEA and the organizations concerned with Kyoto Univ.

Two areas that lack sufficient understanding are the possibility of using various biomarker as a control index of operation and utilizing the action mechanism of nanoparticle due to harmonic size dependency. It is a research project to provide quantitative basis for reasonable design of a failure checking method of disease such as local tumor recurrence or metastasis, a side effect or damage to normal tissues or organs by the treatment, and a technology such as CT image irradiation. To prevent the risk of clinical applications at an early stage, AIT, QST, and research organizations for the treatment of patients developed a methodology for in vitro cell observation and model experiments that mimic radiation effects for various RT particle nanoparticles, or methods and criteria for controlling irradiation conditions Evaluation of equipment.

For various nanoparticle technology, evaluation of protein-cell interaction in vivo, accumulation characteristics of each organ, the fine distribution in the organism, evaluation of cell mutagenicity, necrosis or apoptosis, evaluation of secondary cancer, evaluation of vascular absorption, the impact on nerve and cognitive function, those evaluation technology is under development. On the basis of research data, general information such as ”technical guide to RT using nanoparticle system” will be compiled for sufficiently understanding of medical staff. By building comprehensive platform of cancer treatment, combining multiple anticancer drugs and RT nanoparticles and biological KLH type adjuvants, and by integrating RT equipment with the cloud based prediction system it will be developed new concept of PD ”system oncology” [24].

9. Future Directions in Nanoparticle Research

On receiving success in different in vitro studies conducted for the modification of Bismuth Ferrite nanoparticles by the efforts of the 2nd author, several projects were initiated between the Department of Materials Engineering of KTU and ITU to examine the effect of nanoparticles produced in different ways on radiation dose enhancement. Scientists use gold, silver, iron oxide, etc. in nanoparticle form in so many experiments and studies. However, in the future studies that require a high enough amount of nanoparticles to increase the dose to meet the desired values in therapy; People are moved towards the study of a new kind of nanoparticles. Nowadays, several university institutes and organizations are trying to cooperate to find new methods for developing new formulas or producing new nanoparticles that can increase dose better than Bismuth Ferrite nanoparticles [40]. Besides, in accordance with the aims of the 3rd year study, it was decided to develop the new production method in Düzce University, Department of Materials Science and Nanotechnology Engineering and then to increase the effect in dose enhancement of the nanoparticles produced in this way by conducting the last 4 years as doctoral thesis. In this regard, in the project that will examine the dose-enhanced effect of nanoparticles on commercially prepared SiO2 nanoparticles and new and different produced Cr-B additives, it is aimed to examine the behavior according to the percentage content and production method of the content that excites the dose-enhancement effect of the nanoparticles better and to observe the 1st time effect of the produced newly on this subject [2]. By examining the effect of the production and amount difference of the additives that will be added to the water-based polymer gel with TLD dosimeters used as detector, the contributions to these values and/or comments can be made efficiently.

10. Ethical Considerations

The use of nanomaterials in clinical research radiotherapy is a novel research field; so, it can be expected that its legal cornerstones are only at an early stage. These legal issues focus on the

chronic accumulation of nanoparticles and the delay of the release of research and toxicological findings of their possible non conditions of use, an issue of health risk and patient safety [38]. The chronic accumulation of nanoparticles has been described as the continuous or episodic accumulation of the nanoparticles in the human body through the skin or by ingestion, inhalation etc. The production of nano-foods, nano-complex, nano-vehicle cosmetic regenerate a particularly strong point on this subject. Various precautions should be taken, the first pillar of which is the necessary testing of nanomaterials before they are put on the market. The US Food and Drug Administration (FDA) requires that at the conclusion of the research nanoparticles are metabolized and excreted from the body. Experimental animals were injected with metallic nanoparticles, combined in aqueous media with L-tyrosine, and then sacrificed after some hours. In conclusion, it is necessary to speed up legislative initiatives, mainly at Union level, given the current panorama in the European Union on the legal state of research concerning the use of nanoparticles in medicine, in particular in radiotherapy. This is due to the increased consumption of nanoparticles and the increasing amount of research that connects them with the risk of free survival and with occupational diseases. Many laws cover the legal aspects of human rights.

There are examples of nanoparticles, both spherical or with other geometrical characteristics, which, after the injection via tail-vein of a 1 mg/ml solution, can be found in the liver, spleen, kidney, and brain. After 3 hrs, the rats were injected with dozens of approximately 100 nm sized nanoparticles with a surface coating or bare skin. Almost all known filters these nanoparticles quickly out of the body from the kidneys. This is because the size of the nanoparticles is much higher than the size of the glomerular filter (6 nm or ± 30-40 nm with pores) and therefore not reabsorbed. Strategies for the fine tuning of renal elimination of the nanoparticles have been developed: nanoparticles that are less than 6 nm are quickly eliminated within a few minutes, while those with a diameter greater than 6 nm are much less likely to accumulate due to an inherent obstruction of the endothelial fenestrae. Presented strategies take advantage of the size of the nanoparticles, but also take into account other factors that influence their renal excretion for example core density, surface charge, and surface chemistry. For example, uncoated polystyrene and silica nanoparticles, combined in aqueous media, are characterized by hydrodynamic diameters of 30-250 nm, were injected into rats via intravenous administration, and found that particles from 5 nm (diameter) or lower have in vivo half-lives less than a minute, while those with diameters from 150 to 200 nm, and higher can roam for hours in the blood. Likewise, scientists found that after the local intratumoral injection of 15nm [7 nm] Au-TiO2 nanocomposites in a bladder tumor mouse model (UM-UC-3/Nm-IR) no nephropatic size dependent nanoparticle excretion occurred after the CT scan. Rats ventrically injected with 6 nm averaged gold nanoparticles followed by BMRT at 30 Gy of 220 kV X-rays were irradiated ~ 10 weeks after the injection concluded, were found in the skin of a change area 8 months after exposure to the skin. This often observed effect was attributed to the presence of large amounts of surgically inserted gold nanoparticles in the tumor bed. Vaults are viscous cell organelles (lysosome-like compartments) that are able to robustly and selectively contain gold nanoparticles. Gold nanoparticles and giant multimer constructs were efficiently sequestered and accumulated within the endogenous cellular vaults, providing evidence that the internalization, retention and endocytosis are responsible for the nanoparticle accumulation in the tumor-biopsied gold tissues are stored in mutated fibroblast cells, which were irradiated and then grafted to their keratinocytes acellular layers, were blue (from metal) and were detected for up to 10 weeks after transplantation. The coloration was not observed in the control group that received no irradiation, indicating that the side effects observed were associated with radiation exposure. Moreover, the experimental results demonstrated that during the eight-ten weeks following topical transfer on dorsal keratinocyte layers, the treatment can still fully protect against UV-C light induced hypo-hek but micro X-ray light blue and proto wild type of skin hypersensitivity and during the single fur, the side effects are completely undetectable. There was a change up to an eight-year-old intelligent sleeve. That was very considerable and encouraged further research regarding the cutaneous cancer therapy and body site of the normal

weight, as the method has been commercialized. Considering the growing interest in the field of nanomedicine, the ever-increasing use of nanoparticles (NP) in various applications, and potential NP concern ion is there is a certain need to conduct scientific studies and develop new many-size methods of behavioral monitoring NP. NP-based question detection methods used in the clinical research overengineered medical fields, and highly insightful and other adjustments experiments, the new tumor-selective approach 10 quantitative measurements of the amount of the NP accumulation of 6 in normal and bladder tumors in the rat urotherian nerve model. Tested a series of latency polymer gold nanoparticle formulations, commercial synthesized, and four different mole percent of antique siling generated a square molecule Ted pore. Imaging trade conducted with tracing this one seeds, where the go so soon impau the LSPR fan was used -out devices design appliance ting for typical one or other different uphosole wavelengths. Selected portage Patient 3 with 1 implanted sources to limit the treatment fields (where the following only the patient have-ure and chemotherapy treatment) that the good match is placed. Recently, microbeam radio pie has been developed and herald several beneficial application possibilities of the NP in the people interviewed.

11. Conclusion

The concentration of particles inside tumour cells after different X-ray irradiation schemes has been evaluated using Monte Carlo modelling. Besides, 3D simulations on small tumours have been performed to estimate the biological effectiveness of nanoparticles as a function of their concentration. Thus, this study aims at a more realistic overview of the afore-mentioned limiting factors of a combined treatment with X-rays and particles in the so-called nanoparticle-enhanced X-ray therapy (NEXT).

Conventional radiotherapy is a cornerstone of cancer treatments, applied in ~50% of all patients. This non-invasive method is indicated to treat deeply seated tumours and is based on the use of high-energetic beams of photons or charged particles to deposit energy through direct or indirect effects. Despite improvements in imaging and dose delivery techniques, the disposal of physical dose into the targeted tumour volume is not selective, thus exposing the surrounding healthy tissues to radiation induced toxic effects. Acute or late severe side effects, including organ failure, fibrosis and secondary tumours, may be induced when critical structures are damaged. It is thus a major challenge to develop new strategies and improve the tumour selectivity of the radiation effects. In recent years, the enrichment of tumours with high-Z compounds has been proposed as a new strategy to enhance the effects of ionizing radiations. As in the context of radiation protection, also in RT the preferential term “radio-enhancers” is used to name the compounds which improve the effectiveness of radiations compared to water. Such compounds may act as sources of low energy electrons or radicals able to indirectly increase the efficiency of the energy depositions inside cells. Conversely, such compounds may also react with the photoelectric effect-generated Auger electrons, enhancing their local effects in the proximity of the decay site. This latter phenomenon is the basis of the so-called Auger therapy. In this review, the term “nano-radio-enhancers” (NRE) is employed to distinguish these compounds from other macromolecules which enhance the dose perturbation effects. The history and the principle of the radio-enhancement of photons were first demonstrated in the 50s using simple or metallic complexes which increased the linear absorption coefficient of X-rays and Auger emitters to boost the dose locally in the proximity of the radioactive source.

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