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# Recent Applications of Titanium Dioxide Nanoparticles as Cancer Theranostic Agents

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**Abstract**
In medicine, the application of nanotechnology is related to the use of nanoscale materials to improve and develop new diagnostic and therapeutic methods. Due to the unique physicochemical and optical characteristics of titanium dioxide nanoparticles ($TiO_2$ NPs), such as high biocompatibility, surface properties, and relative stability, they have been widely investigated for medical purposes, particularly as a theranostic agent in cancer diagnosis and treatment.
This review concentrates on current progress in the applications of $TiO_2$ nanostructures in cancer diagnosis and treatment domains. Studies have shown that $TiO_2$ NPs can be promising in various medical imaging techniques. In the field of cancer treatment, researchers have evaluated the ability of $TiO_2$ NPs in up-to-date therapeutic approaches, including drug delivery, sonodynamic, photodynamic, photothermal, and ionizing radiation therapies. In the current review, we focus on the ability of $TiO_2$ NPS as a radiation sensitizer to improve the efficiency of cancer diagnosis and treatment. Finally, according to the studies that have been conducted on controlling and optimizing the factors involved in the $TiO_2$ NP radiosensitization, the mechanism of $TiO_2$ NPs in producing the radiosensitivity effect has been discussed.
**Keywords**: Titanium dioxide nanoparticles, Drug delivery system, Sonodynamic therapy, Photothermal therapy, Photodynamic therapy

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## Introduction

Nanotechnology refers to a branch of science in which scientists synthesize materials with dimensions less than 100 nanometers and apply them in various fields.[1,2] Since the size of some nanoparticles (NPs) is smaller than the pores on the cell surface, NPs can enter the cell through endocytosis or actively through molecules on the cell surface.[3] Over the past decades, various materials with specific structures, shapes, and sizes have been synthesized for biomedical applications. Today, nanomedicine technology concentrates on the application of NPs for designing effective clinical strategies which accurately diagnose and treat various diseases.[4,5] Recent advances in the nanomedicine domain are a great help in the development of organic and inorganic nanostructures such as nanotubes, nanorods, nanowires, and nanoshells with unique properties. Many researchers around the world are doing research in the field of nanomedicine, but the United States made a greater contribution to the number of studies. It is noteworthy that 28.8% of the nanomedicine articles belong to the United States, and China is in second place with 20.47%.[6] According to the European Science and Technology Observatory, at least 150 organizations are active in the applications of NPs to medicine to perform adequate diagnostic and therapeutic techniques.[7]

Every year, cancer kills more than 760 million people worldwide.[8,9] For this reason, cancer treatment and diagnosis have attracted the attention of many researchers in the nanomedicine domain. Based on the National Cancer Institute reports, nanostructures can play a prominent role in cancer diagnosis, prevention, and treatment.[10] In addition to the conventional approaches in cancer treatment (e.g., chemotherapy, radiotherapy, and surgery), some recent treatment techniques such as photodynamics, photothermal, and sonodynamic also seem extremely promising.[11] In radiotherapy, a highly effective non-invasive treatment to kill cancer cells,

the goal is to plan the treatment so that the lowest dose reaches the healthy tissue while a sufficient radiation dose is given to the tumor.[12] Radiation therapy is continuously developing to enhance the quality of dose delivery to cancerous cells and promote the effectiveness of treatment. By synthesizing metal NPs, nanotechnology can help deliver the maximum ionizing radiation dose to the tumor and reduce the dose effects on the surrounding healthy tissue.[13]

Over the last decades, numerous investigations have been carried out on the application of the metal NPs in the medical field such as in cancer diagnosis and treatment. In different domains of investigation, titanium dioxide ($TiO_2$) NPs have received much attention because of their non-toxic effects and biological compatibility characteristics.[14-16] First, the current review study describes the synthesis and characteristics of titanium oxide NPs and then studies the $TiO_2$ nanoparticle applications in diverse domains of cancer diagnosis and treatment. Finally, this review discusses the effect of enhanced radiation on various beam energies from kilo to megavoltage regarding the existence of these NPs.

## Titanium Dioxide Nanoparticles

The use of $TiO_2$ NPs is not unprecedented, and the first study dates back to 1985, which was related to photocatalytic disinfection.[5] The main properties of $TiO_2$ NPs depend on their size, shape, and synthesis strategy.[17] There are various methods for NP synthesis, but in general, physical, chemical, and biological techniques are the most common ones.[18] The small size of the synthesized NPs (less than 100 nm) compared to the organelles inside the human cells (less than 5 μm) increases the possibility of their interaction with these organelles. The ability of the NPs to interact with intracellular contents has led to the emergence of various medical applications in the field of diagnosis and treatment.[19] During the last years, due to the particular characteristics of $TiO_2$ NPs, they have been used for cancer diagnosis and treatment in different medical domains, including cancer cell imaging, drug delivery, radiotherapy, and photothermal, photodynamic, and sonodynamic therapies. The particular characteristics of TiO2 $NP_S$ are listed below:

1) It is easy to synthesize them in different sizes and shapes.
2) They can bind various biological agents to their surface. Due to the propensity of TiO2 NPs to interact with thiols and amino groups, biological ligands, including DNA, proteins, peptides, and antibodies may be used on the surface.[20,21]
3) They have optical characteristics. Surface plasmon resonance (SPR) is a phenomenon associated with the metal surface of $TiO_2$ NPs, which results in the unique optical characteristics of these NPs. SPR effect happens because of the fluctuation of the outermost electrons of the solids when the incident light is irradiated on them. Following light absorption by NPs, the photons radiate isotropically in all directions with identical frequency. The SPR characteristics of TiO2 NPs enable NPs to absorb incident light with near-infrared (NIR) or visible wavelengths.[22] These properties of $TiO_2$ NPs can be employed in cancer therapy techniques such as photothermal therapy (PTT) and cancer diagnosis approaches such as optical imaging modality.
4) Biocompatibility and stability[23]
5) Desirable uptake by mammalian cells via endocytosis[24]
6) The high atomic number and subsequently the high radiation absorption coefficient of these NPs have made them suitable agents for therapeutic and diagnostic applications in medicine. After the synthesis of $TiO_2$ NPs, their properties can be evaluated by several techniques as follows:

1) Dynamic light scattering device is used for the investigation of the distribution of nanoparticle size.
2) Ultraviolet (UV) spectroscopy is used to assess the size and optical characteristics of $TiO_2$ NPs after synthesis. The amount of light absorption of NPs is directly related to their dimensions and concentration in a solution.[22]
3) Microscopic techniques such as atomic force microscopy (AFM) and transmission electron microscopy (TEM) are used to directly image $TiO_2$ NP and control their dimensions (size), surface coating, and shape.
4) X-ray photoelectron spectroscopy (XPS) is employed for the quantitative assessment of surface elemental compositions of $TiO_2$ NPs.[25] Due to these unique features, $TiO_2$ NPs have been widely investigated in different cancer treatment and diagnosis domains. The specific properties of these NPs are provided in Figure 1.

## Recent Strategies for Using TiO2 NPs as a Contrast Agent in Cancer Diagnosis and Treatment

Current investigations have demonstrated that TiO2 NPs can improve diagnostic accuracy and cancer staging by enhancing the quality of various imaging techniques such as magnetic resonance, optical, and X-ray imaging.[26-28]

## Imaging Techniques Using X-ray

Medical X-ray imaging is based on the absorption amount of irradiated tissue. In the range of kilovolt energies used for diagnostic imaging, a photoelectric effect can occur, which depends on the X-ray beam energy (E) and the atomic number of the irradiated tissue (Z).[29] One of the most common X-ray imaging techniques is computed tomography (CT), which is usually conducted with a contrast agent. CT scan usually uses iodine to diagnose

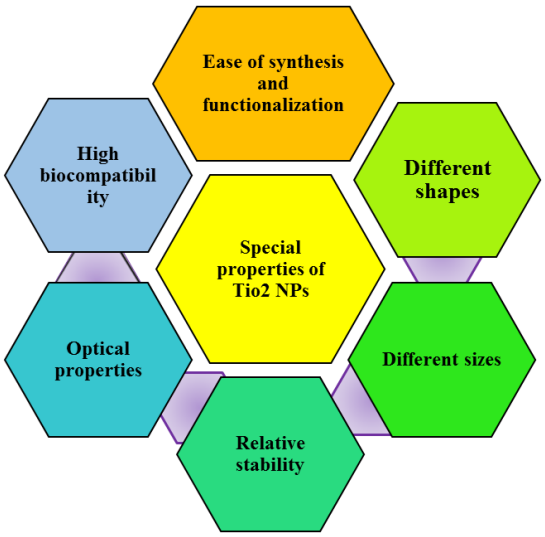


**Figure 1.** Prominent Properties of TiO2 NPs. *Note.* TiO2 NPs: Titanium dioxide nanoparticles

tumors, which increases the accuracy in assessing tumor volume and determining its stage by improving the photoelectric effect.[2]

Moreover, NPs synthesized for use in radiotherapy can be beneficial for CT imaging because the CT imaging technique is usually for cancer treatment planning before starting radiotherapy. An old CT scanner can be upgraded using CERT iodine to provide therapeutic radiation doses. The therapeutic radiation dose distributions provided by this modernized CT scanner are almost similar to those obtained from 10-MV energy, thus permitting simulation, multimodality imaging, and treatment on the comparable strategy.[30] An identical option would be more acceptable for developed contrast agents. This option could be $TiO_2$ NPs because they can be used as a contrast agent in diagnostic imaging and enhance radiation therapy in cancer treatment. However, medical imaging and radiotherapy enhancement using dual-mode contrast agents is an integrated domain of NP application that has not yet been fully explored. Khalid et al [30] showed that the unmodified $TiO_2$ NPs with a size of less than 100 nm present a significant enhancement in image contrast obtained from CT, varying from $0 \pm 3$ HU (without NPs) to $283.7 \pm 3$ HU (0.23 g/mL concentration). Chen et al[31] designed a hollow mesoporous $TiO_2$ NPs, as a radiosensitizer, based on tumor microenvironment responsive antigen-capturing. This radiosensitizer demonstrated a strong abscopal effect to destroy breast tumors. Radiosensitizers can improve the efficacy of radiotherapy by releasing significant amounts of tumor-associated antigens. The released tumor-associated antigens could be additionally trapped and enhanced by the radiosensitizers to create a platform named nano-vaccine for anti-cancer therapy. Tumor heterogeneity is one of the factors that reduce the efficiency of treatment. Nano-vaccine platforms can effectively solve this problem and increase the speed of the immune system's response to radiation therapy.

By employing a solvothermal synthesizing method, Nakayama et al[32] synthesized samarium-doped $TiO_2$ NPs to increase their efficiency. The results showed that the combination of samarium-doped TiO2 NPs and 6 MV photon beams evoked higher call cytotoxic effect and reactive oxygen species (ROS) production in the A549 and DU145 cancer cell lines than that with TiO2 NPs and 6 MV photon beams. Further, the results indicated that CT numbers of samarium-doped TiO2 NPs were higher than those of $TiO_2$ NPs.

## Magnetic Resonance Imaging and Computed Tomography

Magnetic resonance imaging (MRI) is a non-invasive, effective, and commonly used imaging method for clinical diagnosis because of its excellent ability to create contrast between soft tissues, high spatial resolution, and suitable penetration depth. One of the effective ways to improve contrast is to use different metal-based NPs as contrast agents before MRI and CT scans.[26] Contrast agents in MRI enhance the contrast of the tissue by accelerating proton relaxation in areas where they are more concentrated than in other parts of the body. If the sensitivity of the contrast agent is higher, adequate contrast will be obtained even with low concentrations of the contrast agent. Therefore, the possible toxic effect caused by these compounds in the body is reduced. Today, global attempts are underway to develop new $TiO_2$ NPs that present both contrast and anti-cancer properties. In Sherin and colleagues' study,[26] the new curcumin-incorporated $TiO_2$ NPs bonded with the MCP-1 antibody could increase the image contrast of MRI. Metal ions with unpaired electrons have paramagnetic properties that create a suitable contrast in imaging. Studies have demonstrated that carbon compounds improve the paramagnetic properties of $TiO_2$, which is essential for increasing MRI contrast. Leon Smith et al[33] found that the CT number of synthesized $TiO_2$ NPs with a concentration of more than 15 mg/mL makes observable changes in these numbers. In another study, the contrast-enhancing properties of $TiO_2$ NPs with a size of about 50 nm were investigated using MRI and CT techniques. The results displayed that $TiO_2$ NP has excellent potential for use in T2 sequences of MRI.[34] In an MRI study, Liu et al suggested citrate-coated gadolinium (Gd)-doped ellipsoidal $TiO_2$ NPs as a suitable alternative to conventional T1 contrast agents. They significantly improved the ability of nanoparticle-based T1 contrast agents using the photoinduced super hydrophilic assistance effect. This effect considerably improves the paramagnetic relaxation enhancement efficiency and, consequently, the MRI performance of the NPs. Furthermore, in vivo results have demonstrated

that these GdTi-SC NPs have excellent performance for sensitive blood vessel imaging and vascular lesions diagnosis.[23]

## Optical Imaging Technique

There are various strategies for employing the optical characteristics of $TiO_2$ NPs using optical imaging, the most important of which are optical coherence tomography (OCT) and photoacoustic imaging.[35,36]

OCT is a well-known optical technique that can present high-quality images from the cross-sectional views of a biological sample. Barkhade et al[14] compared the effects of $TiO_2$ and iron (Fe) content $TiO_2$ NPs as an exogenous contrast agent in terms of optical imaging efficacy using a swept-source OCT system in the chicken breast tissue. Fe bonding in the $TiO_2$ decreased the toxic effect of this NP on the skin and provided a biocompatible exogenous contrast agent. Furthermore, the results showed that the scattering coefficient improved with increasing exposure time to $TiO_2$ NPs.

In addition, Ivan et al[27] used the TiO2 @ RhdGd multimodal therapeutic-imaging probe, in which $TiO_2$ NPs created a contrast between tissues in optical and MRI techniques. In this study, fluorescence microscopy and MRI were used to visualize the NPs in the cells, and results showed that the therapeutic-imaging probe can be considered a tumor cell-killing agent when irradiated with UV light. Since these nanoprobes do not cause toxicity to T-lymphocytes, HeLa, and mesenchymal stem cells, they are highly promising for diagnostic and therapeutic applications. Berkova et al[37] attached gadolinium (III) complexes to $TiO_2$ after labeling with rhodamine (TiO2@RhdGd). The results indicate that this nanoprobe design is an excellent contrast agent for imaging pancreatic islet cells. The photoacoustic imaging technique is another approach that integrates both optical and ultrasound imaging and plays a role in early and accurate cancer diagnosis. This technique is based on biological sample irradiation using short non-ionizing laser pulses. Absorbing the energy of the incident pulse increases the temperature and local pressure of the tissue, which subsequently leads to the production of a detectable ultrasound wave.[38-40] He et al[28] found that mesoporous $TiO_2$ NPs (mTiO2NPs) can improve the diagnosis accuracy in ultrasound/photoacoustic imaging. Polypyrrole (PPY)-coated mesoporous and honokiol-loaded (HNK) TiO2 NPs (mTiO2@PPY-HNK) showed satisfactory cytotoxicity in HepG2 and 4T1 cells under laser and ultrasound irradiation. The capability of $mTiO2NP_S$ coated with mesopore as a contrast agent for ultrasound irradiation and photoacoustic imaging is studied both in vivo and in vitro investigations. The findings indicated that mTiO2@PPY-HNK has theranostic properties and provides a fantastic possibility for tumor therapies as a new nanoprobe. Several applications of $TiO_2$ NPs in cancer imaging have been presented in Figure 2.

## The Application of Titanium Dioxide Nanoparticles to Cancer Treatment Using Drug Delivery Techniques

The use of NPs as a nanosystem for drug delivery applications has increased the efficiency of cancer diagnosis and treatment by about 10 to 100 times more than the molecular drug administration to the tumor environment.[10] Furthermore, since the uptake of NPs by the reticular-endothelial system is reduced, the persistence of the drug in the circulatory system

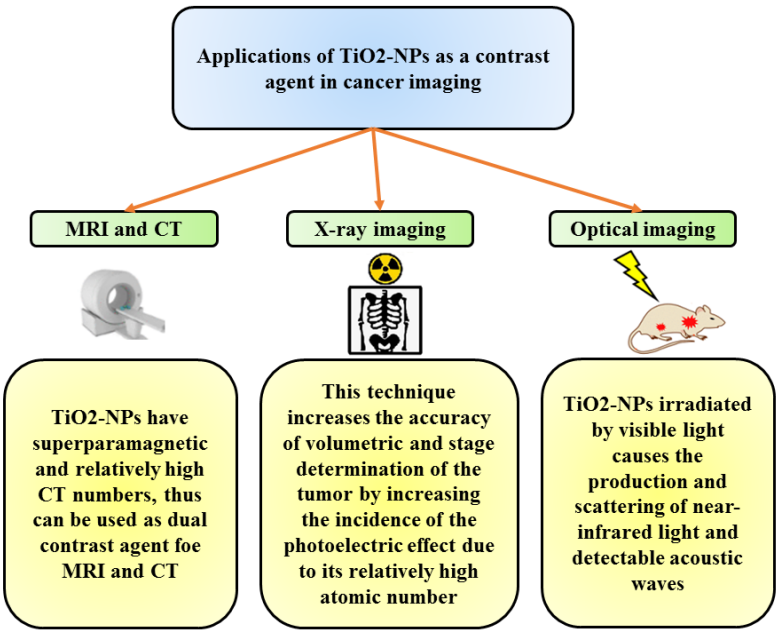


**Figure 2.** Different Applications of Tio2 NPs in Cancer I. *Note.* TiO2 NPs: Titanium dioxide nanoparticles; MRI: Magnetic resonance imaging; CT: Computed tomography

increases, and the tumor cells have more time to receive the drug.[41] The high biocompatibility, non-toxicity, and high affinity of $TiO_2$ NPs have caused them to be considered for specific targeting of tumors by binding various ligands and antibodies to their surface. Accurate delivery of anti-tumor drugs right at the tumor site can enhance the efficiency of cancer treatment while reducing the harmful drugs' side effects.[18,42] Several studies have documented the benefit of $TiO_2$ NPs for delivering anti-cancer drugs, including doxorubicin,[24] paclitaxel,[43] and platinum-based drugs (e.g., cisplatin) to enhance cancer treatment efficiency.[44]

## Photodynamic Therapy Technique

Photodynamic therapy (PDT) is a promising technique that employs a photosensitizer to generate ROS to kill cancerous cells.[12] The photosensitizer is excited when exposed to light irradiation and generates ROS.[15] In general, clinical photosensitizers such as porphyrins and phthalocyanines are hydrophobic, so they need a suitable carrier to cross the lipid membrane and enter cancer cells. In this technique, NPs act as carriers for the delivery of light-sensitive drugs.[45] It is noteworthy that the conjugating of NPs to photosensitizing agents can promote the production of ROS.[46,47] Several studies have demonstrated that $TiO_2$ NPs conjugated with photosensitizer agents can enhance PDT efficiency.

Xu et al[20] used $TiO_2$ NP bound to a monoclonal antibody to treat human metastatic cancerous cells of the colon (LoVo). In this study, the electroporation technique was used, which causes micro-pores in cancer cell membranes, thus increasing membrane permeability. Using this technique led to a 100% and 44% decrease in the LoVo cell population, respectively, after 365 nm UV light irradiation to these cells in the presence of NPs and when only the cells were exposed to radiation (in the absence of $TiO_2$ NPs). Similar to antibodies, folic acid increases the tendency of NPs to enter tumor cells. Due to the increased folate receptor expression in tumors, NPs conjugated with folic acid more efficiently enter tumors by passing through the membrane of cancer cells with excessive expression of folate. Feng et al[48] synthesized folic acid-conjugated $TiO_2$ NPs coated with silica as a new photosensitizer. The results indicated that the synthesized NPs have significant permeability in human fibroblast and nasopharyngeal epidermoid cancer cells and exert the best photodynamic effect on reducing KB cell viability by up to 57% at 100 μg/mL. Studies have detected that a thin silicon dioxide layer of about 5.5 nm may be optimal for fully preserving the photodynamic properties and improving the biocompatibility of $TiO_2$ NPs.[49]

Akram et al[15] indicated that the gold (Au) TiO2 NPs alone generate considerable ROS and can kill about 70% of cancer cells, but this reduction was 82% for doxorubicin (DOX)-loaded Au-$TiO_2$ NPs irradiated with a UV laser. DOX-loaded Au-$TiO_2$ NPs release ROS when irradiated with laser, and they also prevent the MCF-7 cells proliferation by enhancing oxidative pressure. The results showed that in irradiation of Au-$TiO_2$ NPs under laser light, DOX operates as a photosensitizing agent and makes Au-$TiO_2$ NPs conjugated to DOX have more potential than pure Au-$TiO_2$ in PDT. In addition, Zhang et al[50] incubated SMMC-7721 hepatocarcinoma cells with $TiO_2$ NPs and demonstrated that these NPs can induce ROS in the hepatocarcinoma cells after UV irradiation. The caspase-dependent apoptosis induction was the cause of the anti-cancer activity of TiO2 NP. Yurt et al[51] observed that 131I-SubPc and 131I-SubPc-$TiO_2$ NPs are appropriate agents for the treatment of liver and colon cancer cells using PDT. Their findings showed that SubPc-$TiO_2$ could be a suitable theranostic agent in nuclear imaging and PDT.

## Photothermal Therapy Technique

The agents used in the PTT technique can change the NIR radiation into heat with the smallest waste of energy, and while accurately delivering heat to the desired regions, they can also prevent heat damage to normal tissues.[52,53] The ability of TiO2 NPs to absorb energies in the range of visible and NIR has made them an ideal option for use in the PTT technique. In this technique, temperatures above 50°C are produced via the light absorption of TiO2 NPs, which can cause cancer cells to die. It is noteworthy that light absorption and the consequent increase in temperature in the NIR is higher than that in the visible wavelengths.[54]

Electrons in biological samples irradiated with NIR beams are excited to go to higher atomic energy levels. When they return to a stable energy state, they release the obtained energy as heat to the surrounding tissues.[55] Low cytotoxicity and high absorption of NPs employed in this therapeutic technique are among the main features.[56] Various in vitro and in vivo studies have effectively treated cancer cell lines using PTT and TiO2 NPs.[19,55,56] Behnam et al[56] synthesized PEGylated TiO2 NPs and evaluated the ability of these NPs to reduce melanoma tumor size after PTT. In vivo results showed that PEGylated $TiO_2$ NPs are exponentially strong in killing melanoma cancer cells using the PTT. Biocompatible and safe Ti8O15 NPs were able to absorb more than 98% of NIR light and exhibited a significant photothermal therapeutic effect in a mouse model.[19] Moreover, Zhao et al[52] synthesized peptide c(RGDyK) conjugated $TiO_2$ NPs with excellent biocompatibility and targeting ability. These NPs improved the PTT efficiency by 38.5% with high absorption properties in the NIR wavelength and good stability in biological conditions. Considering the tendency among peptide c(RGDyK) and avb3 integrin, TiO2 RGD NPs exhibited a high targeting property for U87-MG cells (human glioblastoma cell line) with

overexpression of avb3 integrin.

The survival of MCF-7 cells with deficient expression of avb3 integrin and U87-MG cells after incubation with 100 mg/mL$TiO_2$ RGD NPs and under NIR laser irradiation was about 71% and 31%, respectively.

## Sonodynamic Therapy Technique

Sonodynamic therapy (SDT) is a non-invasive anti-tumor treatment technique that employs ultrasound waves. In this technique, the gathering of sonosensitizing agents inside tumoral tissue and subsequent exposure to ultrasound waves cause cavitation bubbles.[57] However, cavitation bubbles are known to produce ROS when they collapse.[58,59] Different investigations have studied the applications of $TiO_2$ NPs in the SDT technique. He et al[28] indicated that ultrasound waves have little influence on the cancerous cells, but the cell killing was enhanced in HepG2 and 4T1 cells in the presence of HNK-loaded mTiO2@PPY. Kim et al[60] encapsulated DOX-coordinated $TiO_2$ NPs using polymeric phenyboronic acid. Loaded DOX was released when irradiated with US waves because of the ROS-cleavable properties of the phenylboronic ester bond.

Furthermore, pPBA@TiO2NPs-DOX exhibited excellent ability to be used in combination techniques to kill MCF-7 and MDA-MB-231 cells using sonodynamic and chemotherapy techniques. High biocompatibility, the application of polymeric phenyboronic acid as a ligand for targeting cancer cells, the proper dimension of NPs for the enhanced permeability and retention effect, the specific and accurate release of the drug using ultrasound waves, and the synergistic effect of sonodynamic and chemotherapy are among the factors that increase the anti-cancer effect of this functionalized NP. You et al[61] synthesized hydrophilic $TiO_2$ NPs (HTiO2NPs) with high stability in the bloodstream. The results showed that ultrasound irradiation in the presence of HTiO2-NPs could generate significant ROS that inhibits the growth of liver cancer cells at least 15 times more than when the animals did not receive ultrasound radiation (only HTiO2-NPs). Bai et al[62] synthesized iron-doped TiO2 nanodots as sonosensitizers to improve SDT. Due to the combination of the chemodynamic therapy and SDT, Fe-TiO2 nanodiscs (NDs) NPs modified with polyethylene glycol exhibited biocompatibility and in vivo therapeutic efficiency much better than commercial $TiO_2$ NPs. Further, no apparent long-term toxicity was observed in the treated mice. In the SDT technique, bandgap plays a crucial role in ROS production, meaning that reducing the bandwidth makes the NPs more easily stimulated by ultrasound, resulting in more ROS generation.[63] The mechanism behind the increase in sonodynamic efficiency by Fe-TiO2 NDs than by pure TiO2 NDs lies in a cyclic conversion between $Fe^{3+}$and $Fe^{2+}$, which leads to much ROS generation.[63]

## Radio-Sensitivity of Titanium Dioxide Nanoparticles in Radiotherapy

Approximately 60% of patients with cancer receive radiation therapy during their medical treatment procedure.[64] An appropriate radiotherapy approach to decrease the side effects of ionizing radiation on healthy tissues around the tumor and maximize the killing of cancer cells includes using radiation protectors and sensitizer agents.[13]

Compounds containing high atomic numbers such as iodine as a conventional CT contrast agent can also be useful as a radiation sensitizer. However, conventional CT contrast agents cannot be absorbed, specifically by tumor cells. In addition, such compounds may have several harmful effects on the kidney, thyroid gland, and other body organs.[65] In recent years, most studied radiation sensitizers have been inorganic NPs based on elements such as silver, gadolinium, platinum, and titanium.

One way to sensitize cancer cells to radiation is to stop them at a stage of the cell cycle that is most vulnerable to radiation damage. Notably, the 7-Ethyl10-hydroxy-camptothecin (SN-38) can arrest the cell cycle at the G2/M phase. In other words, the regulation of the cell cycle by SN-38 makes cancerous cells more sensitive to radiation-induced impairment. Thus, transporting SN-38 into the nucleus of cancerous cells using mesoporous TiO2 NPs can act as a radiation sensitizer.[66]

TiO2 shows luminescence when exposed to X-rays. Therefore, a suitable photosensitizer can produce photodynamic effects by absorbing photons emitted during radiation therapy. In such cases, the concern of the limited photo-penetration depth related to PDT is resolved. In a study, the calculation of radiosensitivity parameters showed that the survival fraction for SNB-19 and U87MG cells treated with $TiO_2$ NPs and radiation dose of 2 Gy was reduced by 0.36 and 0.6, respectively, compared to the control group. In this study, the radiation sensitivity of $TiO_2$ NPs in both cell lines in the lowest dose caused a significant increase in the alpha parameter, and high doses caused a significant decrease in the beta parameter in the survival fraction curve.[16]

The concentration, shape, dimensions, and surface coating of $TiO_2$ NPs are among the key features that affect their application as radiation sensitizers. Molina Higgins et al[67] assessed the radiosensitivity effect of Au@TiO2 by investigating the methylene blue decomposition in the presence of NPs. The effects of factors such as gold loading, surface chemistry, dose rate, TiO2 NPs size, and activation voltage were evaluated on the methylene blue decomposition rate, which indicates the radiation sensitivity. The highest radiation enhancement response was obtained using $TiO_2$ NPs with an average size of 6.5nm, loading of 10% gold, and sodium hydroxide as the ligand. Au@TiO2 nanocrystals synthesized using sodium hydroxide exhibited up to 50% higher radiosensitization

than those synthesized with urea. Figure 3 presents several applications of $TiO_2$ NPs in cancer treatment.

Studies have documented that there is a strong dependence between increasing the size of $TiO_2$ NPs up to 30 nm and the amount of ROS generation. It is noteworthy that for sizes larger than 30 nm, this relationship remains almost constant.[68] Furthermore, studies have indicated that the radiosensitizing effect of TiO2 NPs can be increased by including Ti peroxide and increasing the molar fraction of oxygen atoms.[2] In vitro studies have also demonstrated that titanium nanotubes and $TiO_2$ NPs can remain in the cytosol of human glioblastoma cells for 10 days without causing cytotoxicity after irradiation with megavoltage energies.[69] An in vivo study revealed that when rare-earth-doped $TiO_2$ NPs are irradiated with X-rays of 200 kV, the tumor volume is significantly reduced.[2] In Youkhana and colleagues' study,[29] DU145 and HaCaT cell lines were treated using different concentrations (0.5 to 4 mM) of $TiO_2$ NPs with a size of 30 nm. It was found that the irradiation of NPs with megavoltage photons causes significant radiosensitivity in the prostate (14-67%) and keratinocytes (9-50%) cancer cells.

## Combined Therapies

Since tumors differ in terms of heterogeneity, complexity, and microenvironment, the response to tumor treatment is different for a specific treatment. Studies have indicated that the use of combined treatment techniques may enhance the efficiency of anti-cancer treatment. Hence, the focus of research has shifted to combination therapy, which can improve the therapeutic efficacy of different tumors by creating synergistic effects.[60,70] SDT is an effective technique and provides a strong clinical approach to treating cancer cells when combined with the chemotherapy technique. As mentioned in the sociodynamics section, Kim et al[60] used NPs carrying the chemotherapy drug (DOX). By receiving ultrasound irradiation, pPBA@TNP-DOX showed a considerable anti-cancer effect on MCF-7 and MDA-MB-231 cell lines, which can be attributed to a synergistic effect of a combination of chemotherapy and SDT. Further, the synergistic anti-tumor effect of sonodynamic and PDT has been investigated in squamous cell carcinoma. The results displayed that using only SDT had no significant anti-tumor effect compared to using 5-ALA alone. Applying SDT after the administration of the 5-ALA/$TiO_2$ mixture exhibited a more negligible anti-tumor effect than applying PDT. Furthermore, the authors used sonodynamic followed by PDT and revealed that combined therapy significantly improved the anti-tumor activity because the ultrasound can penetrate more in-depth into the tumoral tissue than the laser light (635 nm).[71] Another promising multifunctional agent for future works is mTiO2@PPY-HNK which was introduced by He et al.[28] When this agent is exposed to laser radiation, it can effectively cause photothermal effects, photodynamic effects, and the release of chemotherapy drugs, thus significantly increasing the efficiency of cancer treatment.

## Conclusion and Future Perspectives

In recent years, TiO2 NPs have attracted much attention from many scientists due to their unique characteristics in the cancer diagnosis and treatment domains. The present review has described various aspects of TiO2 NP applications as important theranostic agents in cancer diagnosis and treatment. Studies have demonstrated that TiO2 NPs are extremely valuable in various imaging techniques, including ionizing imaging (e.g., CT and X-ray) and non-ionizing imaging (e.g., MRI, OCT, and

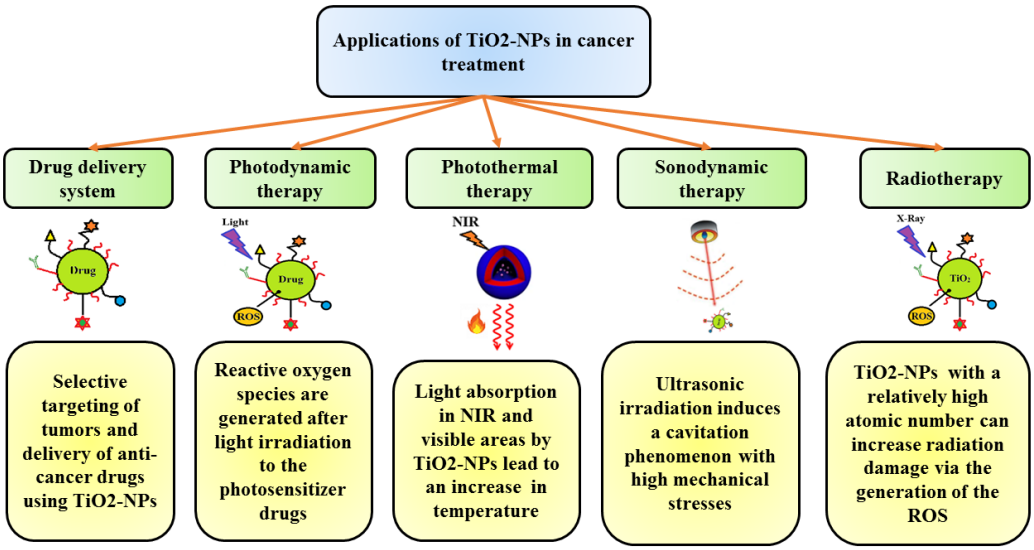


**Figure 3.** Diverse Applications of TiO2 NPs for Cancer Treatment. *Note.* TiO2 NPs: Titanium dioxide nanoparticles; NIR: Near-infrared; ROS: Reactive oxygen species

optical imaging). In addition, these NPs can promote the efficiency and effectiveness of various recent anti-cancer treatment techniques such as radiation therapy, drug delivery, PTT, SDT, and PDT. TiO2 NPs can be used as a radiation sensitizers due to their physical and biological effects. They can increase the probability of the photoelectric effect when irradiated with kV photons. Most studies have reported that TiO2 NPs have many potential capabilities in cancer diagnosis and treatment techniques.

Although TiO2-based nanomedicines have achieved significant attainments in cancer therapy, they are still in their primary phases, and additional investigations are needed for clinical translation. In the first step, a deeper understanding of the mechanisms that effectively synergize the therapeutic effect of sonodynamic, photodynamic, photothermal, and radiation therapy techniques for treating cancer cells is needed. A better understanding of these mechanisms will allow us to provide an optimal combination therapy approach. For the second step, the biosafety, biocompatibility, and biostability of sonosensitizers, photosensitizers, and radiosensitizers should be comprehensively investigated by targeted studies in in vitro, in vivo, and preclinical experiments.

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## Competing Interests

The authors declare that they have no conflict of interests.

## Ethical Approval

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