Abstract

Cancer, as one of the most attention-grabbing medical problems, has been tried to solve with various methods. With the development of nanotechnology, diagnosis and therapy based on nanoplatforms have become new dawn for overcoming cancer problems. Biocompatible nanoplatforms integrating diagnosis and therapy technology for cancer have been extensively studied. Most of the reported works focus on the diagnosis and therapy of subcutaneous tumor. To promote clinical application, it is of great significance to develop efficient methods for deep tumors. This work reviews the latest research progress and future development prospects for the diagnosis and therapy of deep tumors based on biocompatible nanoplatforms. It mainly introduces four cancer diagnostic technologies (fluorescence imaging (FI), computed tomography (CT), magnetic resonance imaging (MRI), and photoacoustic imaging (PAI)) and four tumor treatment methods (phototherapy, ultrasound therapy, radiotherapy (RT), and microwave therapy (MWT)) based on the nanoplatforms. Several diagnostic techniques and treatment methods are systematically summarized and compared, and the advantages and limitations of different methods in tumors are discussed. At last, the application prospects and challenges of the nanoplatforms for the diagnosis and therapy of deep tumors are discussed. It is hoped that this review will provide some useful information for the research in this field.

KEYWORDS

cancer, deep tumors, diagnosis and therapy, imaging, nanoplatforms
1 | INTRODUCTION

Cancer is one of the most difficult medical problems in the world and has become one of the biggest killers threatening human health. Due to the poor development of cancer screening and early diagnosis technology, most cancers are already at an advanced stage when they are discovered, which makes patients miss the best treatment period. In addition, traditional treatment methods, such as surgery, chemotherapy, and RT alone, have shown positive results in the clinical application of tumor therapy, but the side effects are equally serious, such as drug resistance, toxicity to normal tissues, and high rates of metastasis and recurrence. Especially for deep tumors, these inconvenient limitations have led to the failure of treatment strategies to some extent. Therefore, in recent years, scientists have proposed to combine diagnosis and therapy, that is, integration of theranostics. This imaging-guided cancer treatment method achieves precise treatment of deep tumors with minimal side effects, which brings a glimmer of hope for the survival of cancer patients. Therefore, the development of nanoplatforms with good biocompatibility that can simultaneously achieve diagnostic and therapeutic functions has become the latest focus of current cancer research.

With the development of materials science and nanotechnology, the application of nanoplatforms with good biocompatibility in nanomedicine, especially oncology medicine has received more attention. The basic framework of nanoplatform is to combine chemistry, biology, medicine, diagnostics, and nanotechnology by taking advantage of the unique physical and chemical properties of nanomaterials. The nanoplatforms are used as a carrier to deliver contrast agents/antitumor drugs to the tumor site, which can achieve precise treatment of deep tumors under the guidance of imaging. Due to the variety of nanomaterials, choosing nanoplatforms with good biocompatibility as a platform for diagnosis and therapy can ensure less toxic and side effects. Therefore, the excellent physicochemical and biological properties of nanoplatforms make nanotechnology have broad application prospects in the field of cancer diagnosis and therapy.

This article summarizes the latest research progress and future development prospects in the diagnosis and therapy of deep tumors based on the emerging biocompatible nanoplatforms. We mainly review four cancer diagnosis techniques and four treatment methods based on the nanoplatforms (Scheme 1). The diagnosis techniques introduce CT, FI, MRI, and PAI imaging with nanoplatform as the medium, and systematically summarized and compared several methods. We also review the multimodal imaging that combines two or more of these imaging techniques through the nanoplatform, and discuss the advantages of multimodal imaging compared to monomodal imaging. The treatment methods mainly introduce the application of nanoplatforms in phototherapy, ultrasound therapy, RT and MWT, and discuss the advantages and limitations of different treatment methods in deep tumors. Finally, the application prospects and challenges of the nanoplatform in the diagnosis and therapy of deep tumors are prospected, which can be used as references in future research and development.

2 | TUMOR DIAGNOSIS

In vivo imaging has a pivotal position in the field of biomedicine. Through a visual system, it can monitor the state of the lesion in real time and accurately locate it, which is indispensable for further treatment and prognostic detection. Especially in cancer treatment, the best imaging technology can provide information about treatment strategies and individualize treatments in the early stages of tumor development, making diagnosis and/or treatment more effective. Generally speaking, the most common imaging methods are FI, CT, MRI, and PAI. They can conduct real-time monitoring during tumor treatment to improve the accuracy of treatment.

Nanomaterials are widely used as carriers in biomedicine because of their controllability of structure size, good biocompatibility, and unique physical and
TABLE 1 Summary and comparison of four tumor diagnosis techniques

| Diagnostic technology | Advantages                                                                 | Limitations                                                                 |
|-----------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|
| FI                    | Simple operation, wide range of marking objects and high sensitivity        | Relatively low spatial resolution, strong background noise and low signal-to-noise ratio |
| CT                    | High image resolution, accurate diagnosis results and high diagnostic efficiency | Expensive equipment, high inspection costs, and lower soft tissue imaging resolution |
| MRI                   | Non-invasiveness and deep tissue penetration                                | Low sensitivity                                                              |
| PAI                   | Deeper penetration, higher spatial resolution and high sensitivity           | Small imaging area and long imaging acquisition time                          |

chemical properties, which can accumulate in tumor sites. Recent advances in nanoscience and nanotechnology have made nanomaterials as a platform for imaging and treatment of various cancers. Nanoplatforms for cancer treatment include, but are not limited to nanogels, dendrimers, microbubbles, carbon nanotubes, grapheme, SiO₂ nanoparticles, and nanoscale metal organic framework (NMOFs) materials. In order to effectively treat cancer, the ideal method is to combine imaging elements and anticancer drugs into nanoplatforms, which can achieve precise treatment under the guidance of imaging. However, when a single type of imaging is used to guide cancer treatment, the accuracy and imaging effect are not satisfactory. Therefore, researchers sometimes combine several imaging methods to guide precision treatment under multimodal imaging. This article will discuss from the following two aspects, one is monomodal imaging, and the other is multimodal imaging. Table 1 summarizes and compares the advantages and limitations of the four tumor diagnosis techniques. Table 2 summarizes the emerging biocompatible nanoplatforms for tumor bioimaging including monomodal imaging and multimodal imaging.

2.1 Monomodal imaging

Monomodal imaging refers to the use of only one imaging techniques for the diagnosis and therapy of cancer under the guidance of imaging. The nanoplatform can be directly used as a contrast agent or used as a carrier to load materials with contrast agent functions. After that, the contrast agent is enriched in the tumor microenvironment, which can significantly enhance the imaging sensitivity. In the diagnosis of cancer, common monomodal imaging techniques mainly include FI, CT, MRI, and PAI. The following will specifically introduce these four monomodal techniques.

FI mainly uses fluorescent imaging molecules or contrast agents to generate fluorescent signals at the target or enhance the fluorescent signals between the tumor and surrounding tissues. It has the advantages of simple operation and wide range of marking objects. However, the limitations of relatively low spatial resolution, strong background noise and low signal-to-noise ratio also limit its clinical application. Nanoplatforms have good biocompatibility and modifiability, and are expected to be used as contrast agents for FI in vivo. At present, a large number of photosensitive materials which can be used as fluorescent contrast agents have been developed, such as photosensitive dyes (e.g. indocyanine green (ICG) and Rhodamine 6G, etc.), NMOFs nanomaterials (e.g. MOFs with maleimide-attached ligands or lanthanide metal center, etc.), and fluorescent quantum dots (e.g. gold clusters, and CQDs etc.). Among them, the poor water solubility of photosensitizing dyes, sensitivity to tumors, and poor specificity of FI limit its clinical application in tumor diagnosis. Therefore, researchers usually use nanoplatforms as carriers to encapsulate photosensitive dyes to reach tumors, which can enhance FI. For example, Jia and her colleagues used glioma cell membrane to load ICG to obtain biomimetic ICG-loaded liposome (BLIPO-ICG) NPs (Figure 1A). Due to homologous targeting, BLIPO-ICG NPs can cross the blood-brain barrier (Figure 1B). At 12 h after injection, ICG showed significant aggregation in brain tumors with a signal to background ratio of 8.4. At this time, near-infrared FI can clearly see the glioma and its margin. Therefore, under the guidance of FI, glioma tissue can be completely removed. The fluorescent quantum dot nanoplatform can also be used as a good fluorescent imaging contrast agent. For example, Ai et al. designed and synthesized ZnGa₂O₄Cr₀.₀₀₄ NPLNP (ZGC) quantum dots that can be used for liver cancer luminescence and imaging-guided surgery. ZGC is a kind of non-toxic nanoparticles based on near-infrared continuous luminescence, which can guide the operation of deep tissues, especially liver tumors. Although the nanoplatform can improve the use of fluorescent contrast agents for tumor imaging, the shallow penetration depth of light limits the application of FI in deep tumors.

CT, as a commonly used diagnostic tool, uses the high energy and high penetration of X-rays for imaging. Due to its significant advantages in high image resolution, accurate diagnosis results, and high diagnostic efficiency, it has
| Nanoplatform          | Imaging unit | Imaging type | Cell lines         | Animal models                    | Ref. |
|----------------------|--------------|--------------|--------------------|----------------------------------|------|
| BLIPO-ICG            | ICG          | FI           | C6 glioma and MCF-7| Nude mice bearing C6 glioma      | 23   |
| PEG-TaS$_2$ NSs      | Ta           | CT           | HeLa and PC3       | Nude mice bearing PC3             | 24   |
| IL@ZrO$_2$           | Zr           | CT           | HepG2              | Balb/c mice bearing H22           | 25   |
| Iron oxide nanocubes | Fe           | MRI          | TRAMP-C1           | C57BL/6 mice bearing TRAMP-C1     | 26   |
| MnFe$_3$O$_4$@MOF-PEG| Mn, Fe       | MRI          | 4T1                | Balb/c mice bearing 4T1           | 27   |
| UMFNPs-CREKA         | Mn           | MRI          | 4T1-Luc            | Balb/c mice bearing 4T1           | 28   |
| NaGdF$_4$@PDAPEG-2000| Gd           | MRI          | A549               | Nude mice bearing A549            | 29   |
| pTBCB-PEG            | Pd           | PAI          | HepG2, 4T1 and MCF-7 | Nude mice bearing 4T1            | 30   |
| SPNs                 | SPNs         | PAI          | RAW 264.7          | Living mice                      | 31   |
| Fe-MOF@BSA-AuNCs NPs | Fe, Au       | FI, MRI      | HepG2, H22         | Balb/c mice bearing H22           | 32   |
| ZnGa$_2$O$_4$Cr$_{0.004}$ NPLNP | Zn, Ga, Cr | FI, CT     | HepG2 and Huh7     | Balb/c mice bearing Huh7 and HepG2 | 33   |
| MnSe$_2$Bi$_2$Se$_3$-PEG | Bi, Mn | CT, MRI      | 4T1                | Balb/c mice bearing 4T1           | 34   |
| MnWO$_3$-PEG         | Mn, W        | MRI, CT      | 4T1                | Balb/c mice bearing 4T1           | 35   |
| AuNR-PEI             | Au           | FI, PAI      | MCF-7 and HeLa     | Nude mice bearing MCF-7           | 36   |
| NaDyF$_4$:50%Lu@PB   | Dy, Lu       | CT, MRI      | HCT116             | Nude mice bearing HCT116          | 37   |
| GMs                  | Ga, In       | CT, MRI      | C8161, 3T3 fibroblasts | Nude mice bearing C8161          | 38   |
| CDPGM NPs            | Gd           | PAI, MRI     | U87MG              | Balb/c mice bearing U87MG         | 39   |
| CP Ncs               | Cu(II)       | MRI, PAI     | HeLa               | Mice bearing U14                  | 40   |
| Fe-MOF@HA@ICG NPs   | Fe, ICG      | FI, MRI, PAI | MCF-7              | Balb/c mice bearing MCF-7         | 41   |
| C-Fe$_3$O$_4$ QDs    | CQDs, Fe     | FI, MRI, CT  | HeLa               | Nude mice bearing HeLa            | 42   |
| Au@SiO$_2$(Gd)@DOX@HA| Au, Gd      | PAI, CT, MRI | MDA-MB-231 and MCF-7 | Nude mice bearing MDA-MB-231     | 43   |
| FeSe$_2$/Bi$_2$Se$_3$-PEG | Fe, Bi | MCR, CT, PAI | 4T1                | Balb/c mice bearing 4T1           | 44   |
| Fe$_3$O$_4$ NPs      | Fe           | FI, PAI, MRI | 4T1                | Balb/c mice bearing 4T1           | 45   |

a dominant position in other imaging methods. CT imaging is suitable for the detection of neoplasms in all parts of the body, the localization diagnosis of a small part of the tumor, the tumor distribution, infiltration and metastasis, and in vivo detection under CT guidance. However, due to expensive equipment and high inspection costs, the inspection of some specific parts has certain limitations, making CT imaging unsuitable for routine diagnosis. Therefore, designing a nano-platform with high X-ray absorption as a contrast agent can significantly improve the resolution and diagnostic accuracy of CT examination of certain organs. For example, Liu and co-workers reported a tantalum-based multifunctional nanoplatform (PEG-TaS$_2$ NSs), which is composed of tantalum sulfide (TaS$_2$) nanoflakes (NSs) with good biocompatibility (Figure 2A). Due to the high X-ray attenuation coefficient of Ta, PEG-TaS$_2$ NSs can be used as an efficient CT imaging contrast agent. The results of in vitro imaging experiments showed that the Hounsfield unit (HU) value of PEG-TaS$_2$ NSs was linear with the concentration (Figure 2B).

In order to further test the potential of in vivo imaging, time-dependent whole body CT imaging was performed by intravenously injecting PEG-TaS$_2$ NSs into the tail vein of prostate cancer PC3 tumor cells-bearing mice. The results showed that the cardiac CT signal of PEG-TaS$_2$ NSs was still significantly stronger than that of pre-injection 2 h after injection, which indicated that the circulation time of PEG-TaS$_2$ NSs was longer (Figure 2C). Therefore, PEG-TaS$_2$ NSs can become a unique and effective platform for the combined treatment of cancer under the guidance of CT imaging. In addition, IL@ZrO$_2$, MnSe$_2$Bi$_2$Se$_3$-PEG, C-Fe$_3$O$_4$ QDs, and so on are also good nanoplatforms, which can be used in tumor therapy guided by enhanced CT imaging.

MRI plays a vital role in molecular imaging and clinical diagnosis. Due to its non-invasiveness, low toxicity,
high spatial resolution, and deep tissue penetration, MRI is widely used in tumor diagnosis, such as Alzheimer’s disease, liver disease, and enteropathy, etc. However, the spatial resolution of MRI is not as good as that of CT, so patients with cardiac pacemakers or some metal foreign bodies cannot be examined by MRI. In addition, MRI is more expensive, relatively long scanning time, and more artifacts than CT. Therefore, contrast agents are usually used to improve the sensitivity of MRI, especially to distinguish tumors from normal tissues clinically. MRI contrast agents include positive contrast agents that produce bright signals, also known as T1-weighted contrast agents, and negative contrast agents that produce dark signals, also known as T2-weighted contrast agents. However, the MRI images produced by T2-weighted contrast agents are dark, similar to bleeding, metal deposition, or calcification, which may lead to false positive diagnosis. Moreover, the magnetic moment of T2-weighted contrast agents is large, which is easy to form susceptibility artifacts, and the display images are not clear. Therefore, the main limitation of MRI is the relatively low sensitivity of the contrast agent. In order to improve the sensitivity of MRI, scientists have developed various contrast agents to improve the detection capability of MRI, such as Fe, Mn, Gd-based nanoplatforms. For example, Yu and co-workers synthesized hybrid core-shell vesicles (HCSVs). The triggering of HCSVs in the exogenous circularly polarized magnetic field (MF) can lead to the increase of Fe²⁺. The occurrence of Fenton reaction caused the change of the ratio of Fe³⁺/Fe²⁺ to decrease R²*. Therefore, the change of MRI-R2* signal can be used to monitor Fenton reaction and the tracking of HCSVs. In addition, Li et al. reported a T1-weighted MRI contrast agent UMFNP-CREKA with ultra-sensitivity by coupling ultrafine manganese ferrite nanoparticles (UMFNPs) with tumor-targeted pentapeptide CREKA (CYS-Arg-Glu-Lys-ALA) (Figure 3). UMFNP-CREKA can release manganese ions (Mn²⁺) in the tumor microenvironment. The interaction of Mn²⁺ with proteins makes the T1-weighted magnetic resonance signal significantly amplified. In vivo T1-weighted MRI experiments showed that UMFNP-CREKA can detect metastases with the unprecedented minimum detection limit of 0.39 mm, which greatly extends the detection limit of previously reported MRI probes.

PAI plays an important role in modern biomedicine, especially in the imaging technology of various deep tissues. PAI is an emerging hybrid imaging technology that combines light excitation and ultrasound detection. Compared with traditional optical technology, PAI has deeper penetration and higher spatial resolution, while maintaining rich contrast and high sensitivity. Compared with the first near-infrared (NIR-I) PAI window, the second near-infrared (NIR-II) biological window has lower absorption and scatter of skin tissue, deeper tissue penetration, and can be used to guide FI and PAI imaging, which has a greater prospect for deep tissue diagnosis. However, it is reported that most contrast agents cannot emit NIR-II PAI signals, which limits its clinical application. Therefore, in order to overcome the obstacle of clinical
application of NIR-II PAI, it is particularly important to have a nano-platform contrast agent with good biocompatibility. For example, Zhang et al. combined an amphiphilic polymer semiconductor as a light-to-heat converter, a PA emitter, and an iron-chelated Fenton catalyst to synthesize a semiconductor nanozyme (HSN, pTBCB-PEG). HSN can emit PA signals in the near-infrared second zone, and can be used for NIR-II PA imaging-guided iron therapy and photothermal therapy (PTT) combined cancer treatment. In addition, Jiang and co-workers synthesized semiconducting polymer nanoparticles (SPNs) using optical polymers (PA generators) and hydrolyzable amphiphilic polymer polymers (Figure 4A). SPNs can be degraded by a large number of peroxidases and lipases in phagocytic cells, and then transformed from non-fluorescent nanoparticles (30 nm) to near-infrared fluorescent ultra-fine metabolites (1 nm). Furthermore, these nanoagents have a high photothermal conversion efficiency and emit a bright PA signal at 1064 nm (Figure 4B). Therefore, at low doses, through the complete skull of a living animal, NIR-II PAI can be sensitive to subcutaneous tumors and deep brain vascular systems.

2.2 | Multimodal imaging

The ideal tumor diagnosis and therapy platform should provide excellent therapeutic effects and reliable assessment of tumor characteristics and details. Among them, FI, CT, MRI, and PAI imaging are the most conventional imaging diagnostic techniques. However, each model has some drawbacks and cannot provide complete information. For example, in vivo FI has high sensitivity but low spatial resolution. On the other hand, CT imaging provides high spatial resolution and three-dimensional tomography
FIGURE 3 Schematic diagram of the bio-inspiring UMFNP-CREKA nanoprobe, which has a multi-level response $T_1$-weighted MRI signal amplification function and can illuminate ultra-small metastases. Reprinted with permission. Copyright 2020, Wiley

FIGURE 4 (A) Scheme of NIR-II PAI for brain and tumor. (B) After intravenous injection of SPN-PT in live mice, the PAI of the tumor at the designated time point. Reprinted with permission. Copyright 2019, Wiley
information for the tissue structure of interest, but its application is often limited by poor soft tissue contrast caused by low sensitivity. In addition, MRI provides superior soft tissue imaging resolution, but its sensitivity is lower than CT. In addition, due to the relatively moderate laser energy, PAI can only image a small area of the body. Therefore, due to the insufficient diagnostic information provided by monomodal imaging technology, the development of multimodal imaging technology has attracted people's attention.\textsuperscript{61} Multimodal imaging combines the complementary information of two or more imaging methods to obtain more disease information.\textsuperscript{62} Early diagnosis of tumors can significantly improve the cure rate of tumor patients, while multimodal imaging can greatly improve the accuracy of early diagnosis and reduce the risk of misdiagnosis. Therefore, scientists have integrated several different imaging functions into a single nanoplatform to promote the application of multimodal imaging. This approach can overcome the limitations of a single imaging technique and allow for more accurate diagnosis of diseases such as cancer.

Compared with the NIR-I biological window, the NIR-II biological window has lower absorption and scatter of skin tissue, deeper tissue penetration, and can be used to guide FI and PAI imaging. For example, Guo and co-workers reported the organic contrast agents (CP NPs) with dual NIR-II fluorescence and PAI capabilities (NIR-II FI/PAI) (Figure 5A).\textsuperscript{63} CP NPs have good biocompatibility, light stability, and high temporal resolution, which can monitor deep cerebrovascular and blood flow in the micron range in real time. Furthermore, focused ultrasound opened the blood-brain barrier and combines with NIR-II FI/PAI imaging to provide unprecedented clarity in locating microscopic brain tumors (<2 mm in diameter) through intact scalp and skull (high signal background ratio 7.2). Therefore, dual-function NIR-II FI/PAI is expected to provide powerful performance, including good temporal and spatial resolution, deep penetration, and large signal-to-background ratio for accurate brain diagnosis. Multimodal imaging has a significant guiding effect on the diagnosis and therapy of tumors, and it can be more accurate in the treatment of cancer. Wang et al.
designed and synthesized Fe₃O₄@Au SPs to be used as multimodal imaging agents (Figure 5B).⁴⁵ Fe₃O₄@Au SPs showed excellent CT imaging and MRI capabilities, and also showed good biocompatibility both in vivo and in vitro. From the results of CT experiments, it can be seen that 12 h after intravenous injection of SPs, visible signals appeared at the tumor site. And the signal intensity was stronger after 24 h, which indicated that Fe₃O₄@Au SPs was an ideal contrast agent for in vivo CT imaging. Due to the magnetic properties of Fe₃O₄@Au SPs, it can also be used for T₂-weighted MRI imaging. The experimental results showed that after 24 h of injection of Fe₃O₄@Au SPs, a clear dark signal appeared in the tumor area, indicating that Fe₃O₄@Au SPs can be used as T₂-weighted NMR contrast agents. Moreover, Fe₃O₄@Au SPs also had the PAI imaging function. In Hela solid tumors, it can be clearly observed that PAI imaging becomes more obvious with the extension of time. In short, Fe₃O₄@Au SPs had highly integrated multimodal imaging functions and had broad prospects in the diagnosis and therapy of clinical deep tumors.

All in all, imaging technology has a great determinant effect on diagnosis and therapy, because it is important to have clear lesions compared with images of surrounding tissue. The selectivity and sensitivity of contrast agents play a vital role in imaging. Therefore, it is very important to develop an effective nanoplatform as an imaging contrast agent. Nanoplatform can integrate diagnosis and therapy, and improve the treatment effect of tumors. Next, we reviewed the latest developments of some nanoplatforms in several tumor treatments.

3 TUMOR THERAPY

At present, the morbidity and mortality of malignant tumors are high and showing an increasing trend, making them one of the most dangerous “killers” threatening human life and health. How to effectively prevent and treat cancer has become one of the most important tasks of scientific research. Traditional cancer treatments include surgery, chemotherapy and RT, but these treatments have their own shortcomings.⁶⁴ Surgical treatment has high risks and large wounds. Chemotherapy and RT can effectively kill cancer cells, but they can also severely damage normal cells. The defects of traditional cancer treatment methods will seriously affect the quality of life of patients, which can no longer meet the needs of clinical treatment. Consequently, the development of more efficient, low-toxic, and less traumatic treatments is of great significance for the development of cancer diagnosis and therapy.⁶⁵,⁶⁶

In recent years, many researchers have been exploring new treatment strategies, especially nanomedicine. Many interesting nanomaterials or nanotechnology are involved in improving the efficacy of commonly used cancer treatments.⁶⁴ Therefore, nanoplatforms with unique properties have brought new opportunities for early diagnosis and therapy of tumors.⁶⁷ The next part mainly introduces the progress of nanomaterials in phototherapy, ultrasound therapy, RT, and MWT. Table 3 summarizes and compares the common irradiation sources, advantages, and limitations of the four treatment methods. Table 4 summarizes the emerging biocompatible nanoplatforms for tumor treatment.

3.1 Phototherapy

As an emerging anti-cancer therapy, light-mediated phototherapy based on the thermal or dynamic effects of photosensitizers has been proven to be an effective method to kill cancer cells under the stimulation of a specific light source.⁶⁹ According to the types of light source, it can be classified into visible light therapy, near-infrared therapy (NIR), and laser therapy. Among them, NIR therapy has become one of the treatment methods that have attracted much attention in recent years because of its specific treatment of tumors and the reduction of side effects on normal tissues.⁷¹,⁷² As a non-invasive tumor treatment method, phototherapy is usually divided into PTT and photodynamic therapy (PDT).⁷³ In order to achieve a better therapeutic effect, the development of a variety of nanoplatforms and a collaborative treatment method based on integrated phototherapy are the application potential of nanomaterials in the field of biomedicine.

PTT is mainly a thermal treatment method that converts NIR energy into high temperature and induces necrosis and apoptosis of cancer cells.⁶⁸ It has the advantages of non-invasiveness, simple treatment process, and few side effects. It is worth noting that light-driven conversion nanomaterials (i.e. photosensitizers) are essential materials for PTT, which can convert NIR light energy into local heat.¹⁰⁷ An increase in the temperature of the tumor site will cause irreversible damage to tumor cells and tumor regression. Near-infrared light is divided into the NIR-I biological window (600-900 nm) and the NIR-II biological window (1000-1700 nm).¹⁰⁸ NIR-I can only be applied to superficial tumors due to its low tissue penetration depth (1-2 cm). However, the combination of NIR-I and interventional technology is expected to be used in the treatment of deep tumors. For example, Hu and co-workers used anti-urokinase plasminogen activator receptor antibodies, ICG, and polyethylene glycol-modified gold nanoshells to obtain uPAR-ICG-Au-PEG nanoparticles (uIGN).⁷⁰ By injecting (uIGN) into mice, under the combined treatment of interventional PTT (IPTT) and clinical iodine-125 (¹²⁵I)
TABLE 3  Summary and comparison of four tumor treatment methods

| Treatment       | Irradiation source | Advantages                                                | Limitations                                              |
|-----------------|--------------------|-----------------------------------------------------------|----------------------------------------------------------|
| Phototherapy    | Visible light, NIR-I, NIR-II | Non-invasiveness, simple operation and high precision | Shallow penetration, may require repeated treatment |
| Ultrasonic      | Ultrasound/HIFU    | Non-invasiveness, deep penetration, and high safety       | Treatment is susceptible to gas interference, small focus area, and may require repeated treatment |
| Radiotherapy    | X-ray, α-ray, β-ray, and γ-ray | Wide treatment range, non-invasiveness, and short treatment time | Treatment resistance, may harm normal tissues, and multiple treatments |
| Microwave       | Microwave plates or needles with frequencies of 433, 915, and 2450 MHz | Deep penetration, wide treatment range, high heating efficiency, simple operation, and high safety | The range of thermal diffusion is limited, the heat is difficult to control, and may harm normal tissues |

PTT tumors (Figure 6A, B). This smart PTT technology demonstrated highly sensitive H₂O₂-activated/acid-enhanced photoacoustic tomography signal changes and precise PTT in vitro and in vivo. NIR-II light-mediated tumor PAI and PTT ultimately lead to excellent deep tissue photoacoustic contrast and photothermal heating capabilities. (Figure 6C). Wang and co-workers used liposomes as a template to synthesize a HA-4-ATP-AuNFs-DOX which exhibited obvious photothermal effect, high absorbance, high photothermal stability and high photothermal conversion efficiency under NIR-II irradiation. And the interstitial brachytherapy (IBT-125-I), it was realized in the orthotopic xenograft model of human pancreatic cancer good treatment effect and prolong the survival time of mice. Therefore, the combination of interventional technique and PTT was expected to achieve the treatment of deep pancreatic tumor.

In recent years, due to the deeper tissue penetration, NIR-II has been widely used in the PTT for deep tumors. For example, in 2019, Wang et al. developed a microenvironmental stimulation-activated nanotheranostics (SHT, SiO₂@HRP/TMB) for NIR-II PAI imaging to guide NIR-II
| Nanoplatform          | Therapies | Cell lines                                | Animal models                     | Ref.  |
|-----------------------|-----------|-------------------------------------------|-----------------------------------|-------|
| POM@BP                | PTT       | Huh7, HepG2, Hepa-6 and HeLa              | Nude mice bearing Hepa-6 cells    | 68    |
| CuSCDB@MMT7           | PTT       | MCF-7, 4T1, L929 and RAW 264.7            | Balb/c mice bearing 4T1 cells     | 69    |
| uIGN                  | IPPT      | SW1990 and PANC-1                        | Nude mice bearing SW1990          | 70    |
| SiO2@HRP/TMB          | NIR-II PTT| 4T1                                       | NCr nude mice bearing 4T1 cells   | 71    |
| HA-4-ATP-AnFNs-DOX    | NIR-II PTT| MDA-MB-231                                | Nude mice bearing MDA-MB-231      | 72    |
| PEG/Ce-Bi@DMSN        | NIR-II PTT+PDT | HeLa, and L929                      | Mice bearing U14                   | 73    |
| Te-Gd                 | NIR-II PTT| 4T1                                       | Balb/c mice bearing 4T1 cells     | 74    |
| BPQD@PLPH/PEG NP      | PDT       | 4T1                                       | Balb/c mice bearing 4T1 cells     | 75    |
| CP/ChS-g-PSS NPs      | PDT       | MCF-7 and 4T1                            | Balb/c mice bearing 4T1 cells or MCF-7 | 76    |
| Ce6@MnO2-PEG          | PDT       | 4T1                                       | Balb/c mice bearing 4T1           | 77    |
| TNYL-ICG-HAuNS        | PTT-PDT   | CT26                                      | Balb/c mice bearing CT26          | 78    |
| Fl27-MnO2-ZIF@C/C3N4  | Chemo-PDT | 4T1                                       | Balb/c mice bearing 4T1           | 79    |
| UCNPs                 | Optical fiber and PDT | U87-MG                      | Balb/c mice bearing glioblastoma multiforme | 80    |

Indocyanine green, Fluorescein sodium

| Therapies          | Cell lines | Animal models                                    | Ref.  |
|--------------------|------------|---------------------------------------------------|-------|
| laser endomicroscopy | –          | Mice bearing orthotropic liver tumor              | 80    |
| P-Fe3O4/PFOB@OIHVs | HIFU       | –                                                 | 81    |
| IR780 NPs          | SDT        | 4T1                                               | 82    |
| DOX@FeCPs          | Chemo-SDT  | 4T1, CT26 and HUVEC                               | 83    |
| DHMS                | SDT        | 4T1                                               | 84    |
| GC2@M              | SDT        | 4T1, 231 and CT26                                 | 85    |
| HMME/R837@Lip      | SDT-Immunotherapy | 4T1 and CT26                           | 86    |
| TiH1.924 nanodots   | PTT-SDT    | 4T1                                               | 87    |
| N@CaFe2-BSN        | SDT        | 4T1                                               | 88    |
| Zn-TCPP/CpG        | SDT-Immunotherapy | CT26                                   | 89    |
| NaYF4:Gd/Tb        | RT         | A549                                              | 90    |
| Zr-MOF-QU NPs      | RT         | A549, HCC827 and 231                               | 91    |
| MnSe@Bi2Se3-PET    | RT         | 4T1                                               | 92    |
| PEG-Bi2Se3@PFO@O2  | RT         | 4T1                                               | 93    |
| HGNs                | RT-PTT     | SW1990                                            | 94    |
| Hf-MOL              | RT-RDT     | 4T1                                               | 95    |
| NaCeF3: Gd, Tb      | RT-RDT     | A549                                              | 96    |
| POMoNcs             | RT-RDT     | 4T1                                               | 97    |
| Hf-DBB-Ru           | RT-RDT     | MC38                                              | 98    |
| Hf-Ir               | RT-RDT     | MC38                                              | 99    |
| TBP-Zr nMOFs       | RT-RDT     | SQ20B                                             | 100   |
| IL@ZrO2            | MWTT       | HepG2                                             | 101   |
| PEG-IL/ZrO2-Ag@SiO2 | MWTT      | HepG2                                             | 102   |
| DPA@PFO/MG         | MWTT       | HepG2                                             | 103   |
| DOX@ZDNP@PEG       | MWTT       | HepG2                                             | 104   |
| Mn-ZrMOF Ncs       | MDT+MWTT   | HepG2                                             | 105   |
| PEG-IL-LM-ZrO2 SNPs | MDT+MWTT  | HepG2                                             | 106   |
| Fe-MOF@B3A-AnNcs NPs | MDT+MWTT | HepG2 and H22                                     | 107   |
| IDPC@Zr-PEG        | Chemo-MWTT | HepG2, H22 and L929                              | 108   |
| IQUS@Zr-PEG NSPs   | MWTT-RT    | A549                                              | 109   |

Nude mice bearing Hepa-6 cells

Nude mice bearing SW1990

NCR nude mice bearing 4T1 cells

Nude mice bearing MDA-MB-231

Mice bearing U14

Balb/c mice bearing 4T1 cells

Balb/c mice bearing CT26

Balb/c mice bearing 4T1 cells or MCF-7

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1 cells

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing CT26

Nude mice bearing Lewis lung cancer

Nude mice bearing A549

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing Lewis lung cancer

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing A549

Rabbits bearing VX2 liver tumor

Balb/c mice bearing 4T1 cells

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Balb/c mice bearing 4T1

Nude mice bearing Lewis lung cancer

Nude mice bearing Lewis lung cancer

Balb/c mice bearing CT26

Balb/c mice bearing H22

Balb/c mice bearing H22

Balb/c mice bearing H22

Balb/c mice bearing H22

Balb/c mice bearing H22 and C57 mice bearing Hepa 1–6

Balb/c mice bearing H22

Balb/c mice bearing H22

Balb/c mice bearing H22
treatment of solid tumors guided by PAI/Raman dual imaging had a high tumor inhibition rate. In 2020, Dong and his colleagues synthesized a bacterial-like nanozyme (PEG/Ce-Bi@DSMN) by coating Bi$_2$S$_3$ NRs with dendritic mesoporous silica, and then modifying ultrasmall CeO$_2$ nanozymes into Bi$_2$S$_3$@DSMN nanocomposites. Under NIR-II irradiation, PTT activated by PEG/Ce-Bi@DSMN nanozymes significantly enhanced the consumption of peroxidase mimic activity, the depletion of GSH, and catalase-mimic activities. Both in vitro intracellular level and in vivo evaluation of xenograft tumors indicated that PEG/Ce-Bi@DSMN nanozymes could enhance PTT tumors and achieve higher tumor regression rate under NIR-II irradiation. In addition, Dong et al. used bovine serum albumin (BSA) modified Gd integrated Te 1D nanorods (Te-Gd) for CT and MRI-guided PTT under NIR-II irradiation. Te-Gd can effectively inhibit tumor growth and induce tumor regression.

PDT is another important direction of phototherapy. The therapeutic potential of PDT was discovered more than 100 years ago, but it was not widely used until the 1980s. PDT is mainly composed of three different non-toxic components (photosensitive drugs, light, oxygen) synergistically to produce reactive molecules, which are responsible for the therapeutic effects of PDT. Reactive molecules are mainly produced by two ways. One is photo-excited photosensitizers (PSs) that participate in redox to generate cytotoxic reactive oxygen species (ROS). The other is to release energy directly into oxygen to form highly reactive singlet oxygen (1$O_2$). Currently, PDT for solid tumors has two potential defects, one is the hypoxic tumor microenvironment, and the other is the low selectivity for cancer cells. Hypoxia is one of the characteristics of solid tumors. Therefore, alleviating the hypoxia of tumor cells can effectively improve the therapeutic effect of PDT. The use of nanoplatform to transport H$_2$O$_2$ to the tumor site and catalytically decompose it into O$_2$ under the excitation of light, which can effectively alleviate the problem of tumor hypoxia, thus effectively improving the therapeutic effect of PDT. Moreover, the nanoplatform combines PDT with other treatment methods, which can kill tumor cells more accurately and reduce side effects as much as possible. For example, in 2019, Li and co-workers used polyethylene glycol and ROS-sensitive polythiopropylene (PPS) to graft amphiphilic black phosphorous quantum dots (BPQD) vesicles, and prepared near-infrared/reactive oxygen (NIR/ROS) sensitive BPQD vesicles through self-assembly (BPNVs) (Figure 7). The light absorption of BPNVs in the near-infrared region is enhanced, and immune adjuvant oligodeoxynucleotides (CpG ODNs) have higher loading efficiency in the cavity of BPNVs. After near-infrared laser irradiation, BPNVs produce high levels of ROS, which triggers the transformation of hydrophobic ROS sensitive poly (propylene sulfide) (PPS) to hydrophilic polymers, leading to the decomposition of vesicles into BPQDs. Due to the simultaneous release of CpG with enhanced immunotherapy and BPQDs with deep tumor penetration, the BPNVs-CpG realizes potential photodynamic immunotherapy in vivo and
can block the growth and metastasis of distant tumors. In addition, Yang *et al.* developed a new amphiphilic polymer (ChS-g-PPS) to encapsulate chlorine e6 (Ce6) and paclitaxel (PTX) to synthesize CP/ChS-g-PPS NPs. CP/ChS-g-PPS NPs self-destructive ROS-responsive nanoparticles triggered by NIR can be used to enhance chemo-PDT. In vitro and in vivo experiments have proved that NIR laser irradiation can quickly release the drug and penetrate deep into the tumor tissue, which was conducive to the complete removal of tumor cells.

However, due to the limited penetration of light, it is only suitable for the treatment of superficial tumors. Recently, with further improvements in light transmission, such as built-in optical fibers, it has become possible to apply phototherapy for treating deeper tumors. Optical fiber is a fiber made of glass or plastic, which is widely used in the medical field. Among them, fiber optic endoscopes can be introduced into the heart and ventricles for measuring blood pressure in the heart, oxygen saturation in the blood, body temperature, etc. The laser scalpel connected with optical fiber has also been used in clinical practice. In recent years, due to its inherent long-distance light-guiding properties, optical fibers have microscopic cross-sections that can be constructed at the nanometer level to manipulate the transmission/reflection spectrum of light. Good biocompatibility enables it to be effectively integrated with biocognitive molecules, and it also has the characteristics of anti-electromagnetic interference, mechanical flexibility, and low cost, which has the potential for deep tumor treatment. The light energy is delivered to the tumor site through the optical fiber for the purpose of treatment. For example, Kennedy and co-authors developed an upconversion nanoparticle (UCNPs) implant with good biocompatibility to provide upconversion photon properties in a flexible optical waveguide design. In order to enhance its translatability, UCNPs implants were constructed with FDA-approved poly (ethylene glycol) diacrylate (PEGDA) core coated with fluorinated ethylene propylene (FEP). The emission spectrum of the UCNPs implant can be tuned to overlap with the absorption spectrum of the clinically relevant photosensitizer 5-aminolevulinic acid (5-ALA). UCNPs implants can wirelessly transmit up-converted visible light, up to 8 cm in length, and can be bent even when implanted in the skin or under the scalp. With this system, it is proved that chronic PDT based on NIR can be achieved in the mouse xenograft glioblastoma multiforme (GBM) model. In addition, Zheng and co-authors used dual-band confocal laser endomicroscopy (CLE) combined with image mosaic technology to guide liver cancer surgery. In the orthogonal liver tumor mouse model, CLE can accurately detect tumors with clinically available dyes fluorescein sodium (FS, excitation wavelength 488 nm) or indocytine green (ICG, excitation wavelength 660 nm). The mosaic of CLE images expands the imaging field of view and more accurately finds the edges of liver tumors. In the same tumor-bearing mice, the fluorescence intensity of CLE image of normal liver tissue was significantly higher than that of tumor tissue (*P* < 0.0001). Therefore, dual-band CLE imaging can effectively identify liver tumor tissues and margins, which can help achieve radical resection during surgery.

To sum up, photo-mediated phototherapy (including PTT, PDT, and built-in optical fibers) based on nanoplatform is another cancer treatment method after traditional cancer treatment methods (surgery, chemotherapy, and radiation therapy), which can further improve the rate of tumor cell degeneration.

### 3.2 Ultrasound therapy

Ultrasound, a mechanical wave with frequencies higher than the range of human hearing, is widely used in biomedical applications because of its non-invasive, deep penetration depth (penetration depth greater than 10 cm), and less energy attenuation. When ultrasound interacts with tissues, different tissues will lead to different acoustic characteristics, which forms a diagnostic method based on ultrasound imaging. Ultrasound imaging is not only non-invasive and safe, but also can realize real-time monitoring. In addition to ultrasound imaging, ultrasound is also widely used in the treatment of tumors, such as high intensity focused ultrasound physiotherapy (HIFU) and sonodynamic therapy (SDT).

HIFU can aim at deep tumors in vitro, which makes a large number of mechanical energy accumulated in the tumor site and quickly heat, thus killing cancer cells. Moreover, HIFU does not damage the surrounding normal tissues and has higher safety. The combination of diagnosis and therapy, through the real-time monitoring of imaging, HIFU can achieve accurate treatment, and the treatment effect is more obvious. Therefore, the development of nanoplateform is very important. In addition, the development of nanoplateform integrates ultrasonic imaging sensitizers and high-intensity focused ultrasound therapy drugs into one, so as to achieve precision treatment under real-time monitoring. For example, a facile self-assembly/sol-gel approach to fabricate PEGylated magnetite/PFOB co-loaded organic/inorganic hybrid vesicles (designated as P-Fe3O4/PFOB@OIHVVs) for both dual-modality ultrasound / MR imaging and imaging-guided HIFU ablation.

Another important application of ultrasound in tumor therapy is SDT. In 1989, Umemura *et al.* discovered SDT for the first time in an experiment, and it was further confirmed in 1990. Since then, SDT has received...
widespread attention. Like PDT, SDT can kill tumor cells by stimulating sonosensitizer agents to generate cytotoxic ROS, such as $^{1}\text{O}_2$ and $\bullet$OH, etc.\textsuperscript{114} Compared with PDT, SDT can penetrate deep tumors.\textsuperscript{115} In addition, SDT can accurately locate the tumor site without harming the normal tissue. Therefore, SDT can be used for the treatment of deep lesions. The mechanism of SDT is relatively complex, mainly including ultrasonic cavitation, ROS, singlet oxygen, ultrasonic induced cell apoptosis, etc., which is closely related to the types of sonosensitive agents. Although SDT performs well in various anticancer cell therapies, the results of in vivo treatments are not satisfactory. The emergence of nanoplatform enhances the therapeutic effect of SDT, which can increase the potential of sonosensitizer delivery, enhance ultrasonic cavitation, amplify the generation of ROS, and mediate combined therapy. Zhang et al.\textsuperscript{82} reported the application of nanodroplets (IR780 NDs) based on ultrasound-activated sonosensitizer (IR780) in SDT.\textsuperscript{82} IR780-NDs had the mitochondrial targeting ability, which improved the precision and accuracy of SDT delivery. In vitro evaluation experiments, overgeneration of ROS after mitochondrial targeting was observed, which made cancer cells more sensitive to ROS-induced apoptosis.

In order to further improve the therapeutic effect, nanoplatform-mediated combined therapy involving SDT has become one of the most concerned development trends at present. The combination of SDT and chemotherapy can effectively inhibit the growth of tumor and induce apoptosis and mitochondrial dysfunction of tumor cells. Xu and his colleagues prepared DOX-loaded hematoporphyrin monomethyl ether (HMME) with Fe (III) ions coordination particles (FeCPs), which was used as a new high-efficiency nanoplatform for combined treatment of deep tumor STD and chemotherapy under the guidance of MRI imaging (Figure 8A).\textsuperscript{83} FeCPs with SDT function can effectively kill cancer cells under ultrasound irradiation. Large surface area and porosity enable FeCPs to have higher DOX carrying efficiency and intracellular release capacity. The combination of SDT and chemotherapy can significantly inhibit the growth rate of deep tumors (Figure 8B). The combination of SDT and gas therapy can reshape the tumor microenvironment and also provide sufficient conditions for SDT to induce the generation of ROS. For example, Pan and his colleagues synthesized the MOF-derived two-layer hollow manganese silicate nanoparticles (DHMS), which can efficiently generate ROS after ultrasonic irradiation (Figure 8C).\textsuperscript{84} And DHMS can produce oxygen in the tumor microenvironment, which overcomes the hypoxia of solid tumors, and reshapes the tumor microenvironment. In vivo experiments showed that under the guidance of ultrasound imaging and MRI,
DHMS-mediated SDT can effectively inhibit tumor growth (Figure 8D).

Additionally, GSNO/Ce6@ZIF-8@homotypic cancer cells (GCZ@M), a multi-functional bionic nanoplatform designed by An and co-workers, was prepared by loading GSNO and Ce6 into ZIF-8 and then coating the membrane of homotypic cancer cells (Figure 9). GSNO/Ce6@ZIF-8@homotypic cancer cells (GCZ@M) had homologous targeting capabilities that accumulate in tumor tissues. The interaction between NO released by GSNO and ROS generated by Ce6 can produce highly active RNs such as ONOO, which can significantly enhance the tumor clearance ability. In addition, ultrasound can effectively alleviate tumor hypoxia by promoting tumor blood flow and improve the therapeutic effect of SDT. The combination of SDT and immunotherapy can not only enhance the therapeutic effect and inhibit the metastasis of tumor, but also produce immune memory effect and prevent tumor recurrence. Yue et al. reported a tumor treatment method using nanosonosensitizer (HMME/R837@Lip) for SDT combined with checkpoint immune blocking therapy. Using a variety of tumor models, it was proved that the combination of nanosensitizers and anti-PD-L1 can induce anti-tumor responses. This can not only prevent the progression of the primary tumor, but also prevent lung metastasis. In addition, the combination therapy strategy provided a long-term immune memory function, which can prevent the tumor from attacking again after eliminating the initial tumor.

All in all, as a non-invasive cancer treatment, ultrasound therapy has deep tissue penetration ability and can be used in the treatment of deep tumors. However, HIFU and SDT are susceptible to bone and gas interference, which limits their application in lung, intestine and bone. Therefore, synthesizing a more effective nanoplatform with good biocompatibility and powerful modification functions is an important research direction to promote the clinical application of ultrasound therapy technology.

3.3 | Radiotherapy

Radiotherapy, a traditional form of treatment that uses high-energy radiation (such as X-rays, γ-rays, etc.) to generate peroxide free radicals (e.g., ROO•, R₂HRtOO•, etc.) that destroy the DNA of tumor cells and kill cancer cells, has been used in medicine to treat more than half of cancer patients. It is unsatisfactory that the effective RT is restricted to a great extent by the uneven radiation response and radiation resistance. Because high energy radiation can generate oxygen-centered free radicals, which can cause DNA damage. Especially in sufficient oxygen environment, it can react with DNA breaks to generate stable and difficult-to-repair peroxides, thus greatly improving the therapeutic effect of RT. However, tumor microenvironment is more hypoxic than normal tissue, and as a result hypoxia-related RT resistance may occur. In addition, different organs and tumor tissues respond differently to radiation, which severely limits the effect of RT treatment. For example, the higher the degree of cell differentiation, the lower the sensitivity to
irradiation. And the proliferating cells were more sensitive than the nonproliferating cells. In order to overcome these problems, enhancing specific absorption of ionizing irradiation energy in tumor tissues and regulating tumor microenvironment to reduce irradiation resistance are commonly used methods.\textsuperscript{119} In recent years, nanoplatform-based combination therapy has attracted much attention in the field of oncology, which is safer and more effective than monotherapy.\textsuperscript{120} There are two ways to enhance the effect of RT by combining the nanoplatform with RT. On the one hand, the nanoplatform is used to improve the hypoxia problem of the tumor microenvironment and achieve the purpose of enhancing the effect of RT. On the other hand, by combining RT with other treatments, the side effects of RT can be minimized and the cancer cells can be killed more accurately and efficiently. At present, enhanced RT and radiodynamic therapy (RDT) are the two most popular RT.

The method of overcoming hypoxia-related RT resistance by regulating the hypoxia tumor microenvironment has been widely studied. For example, Jiang and co-workers used X-ray to trigger NaYF\textsubscript{4}: Gd/Tb scintillator to release NO (deep tissue up to 3 cm), which can overcome the hypoxic state of the tumor microenvironment.\textsuperscript{90} This strategy reduced the RT resistance of the tumor and improved the RT effect. Ma et al. designed a stable nanoplatform to overcome tumor hypoxic properties using 1, 4-phthalic acid ligands as carbonic anhydrase (CA-IX) inhibitors (Figure 10A).\textsuperscript{91} During RT, the Zr-MOF decomposition producted 1, 4-benzoic acid ligand can effectively inhibit the expression of CA-IX and down-regulate the expression of hypoxia inducible factor (HIF-1\textalpha), thereby alleviating hypoxia-induced resistance and promoting cell apoptosis. In addition, the strategy of adding high-Z elements to the nanoplatform to enhance the absorption of X-rays can also improve RT treatment resistance. For example, Song and co-workers synthesized multifunctional MnSe@Bi\textsubscript{2}Se\textsubscript{3} core-shell nanostructures by cation exchange method.\textsuperscript{[34]} This kind of nanoplatform can not only concentrate irradiation energy in tumor,
but also can improve oxygenation level in tumor and overcome hypoxia related irradiation tolerance to enhance the effect of RT. Using the same method, they further synthesized hollow Bi$_2$Se$_3$ nanoparticles, which were then functionalized with polyethylene glycol (PEG) and injected with Perfluorocarbon (PFC) for oxygen loading. In the PEG-Bi$_2$Se$_3$@PFC@O$_2$ system, Bi$_2$Se$_3$ can be used as a radiosensitization agent to enhance the efficiency of RT, while the PFC loaded in the cavity can be used as an oxygen carrier to moderately improve the hypoxia state of the tumor. More importantly, because Bi$_2$Se$_3$ has a strong near-infrared spectrum absorbance, it can produce a strong light effect under near-infrared laser irradiation, which triggered the release of oxygen and further overcame hypoxia-related RT resistance. Therefore, effective in vivo therapeutic outcomes were achieved through NIR-enhanced RT treatment by using PEG-Bi$_2$Se$_3$@PFC@O$_2$. More interestingly, Zhang et al. implemented an interventional photothermal brachytherapy (IPT-BT) strategy using a biodegradable honeycomb gold nanoparticle (HGNs) as an internal photothermal agent and radiosensitizer (Figure 10B). Interestingly, HGNs-mediated IPT-BT synergistic treatment (Figure 10C), the tumor inhibition rate of orthotopic pancreatic cancer was as high as 96.6%. This strategy provides a new idea for the treatment of deep tumors.

Inspired by PDT, high-energy radiation-stimulated photosensitizer was used to generate ROS for RDT, so as to further improve the effect of RT. In the past decade, the use of X-ray induced RDT has become a promising treatment for malignant tumors, but the energy conversion efficiency is low and the treatment effect is not ideal. Therefore, the use of the nanoparticle to combine RT and RDT can not only reduce the toxic and side effects of RT, but also improve energy conversion efficiency, so as to kill tumor cells more accurately and efficiently. For example, Ni and co-workers designed a new nanoscale metal organic layer (nMOL), Hf-MOL, based on electron-dense SBUs and photosensitive ligands. Hf-MOL can trigger the generation of ROS under low-dose X-rays, which can activate RT-RDT to effectively treat tumors. Due to the reduced dimensionality, Hf-MOL allowed easy diffusion of ROS and exhibits excellent antitumor effects on colon, head and neck, and breast cancer bilateral models, and had significant antitumor effects on lung metastasis triple-negative breast cancer orthotopic models. Therefore, the reasonable adjustment of Hf-MOL composition and structure was expected to lead to more effective RT-RDT enhanced checkpoint blockade immunotherapy in the treatment of metastatic tumors. (Figure 11). Zhong et al. synthesized
a photosensitizer NaCeF₄: Gd, Tb scintillating nanoparticle (ScNPs) that can generate ROS under X-ray irradiation (Figure 12). ScNPs have good biocompatibility and can achieve CT/MRI imaging at the same time. After intravenous injection of ScNPs, synchronized RT-RDT that significantly inhibited tumor progression was achieved under X-ray irradiation. In addition, Maiti and colleagues functionalized chitosan (CS) and polyethylene glycol (PEG) on the surface of polyoxymolybdate to obtain polyoxymolybdate nanoclusters (POMo NCs). POMo NCs can significantly inhibit tumor growth by RT-RDT under low-dose X-ray radiation.

All in all, RT, as one of the three traditional treatment methods for cancer, has the advantages of deep penetration and can be used for the treatment of deep tumors. However, uneven radiation responses, non-selectivity to normal tissues, and radiation resistance limit the use of RT as the primary treatment for cancer. Therefore, the development of effective nanoplatforms, the study of the relationship between the tumor microenvironment and the efficiency of RT, and the combination of RT with other treatment methods are essential to further improve the curative effect.

### 3.4 Microwave therapy

MWT, as a minimally invasive method for tumor treatment, mainly uses ultra-high frequency electromagnetic waves with a wavelength of 1 mm ~ 1 m (400 ~ 2500 MHz) to act on the tumor for the purpose of treatment. It has the advantages of deep tissue penetration, safe without radiation, and free from gas and bone interference. At present, MWT mainly includes microwave thermal therapy (MWTT), microwave dynamic therapy (MDT) and microwave gas therapy (MGT).

MWTT mainly uses the biothermal effect of microwave to inactivate tumors. Its material basis is dipole heating caused by polar molecules such as carbohydrates and proteins of the human body, and ion heating caused by charged ions such as Na⁺, K⁺, and Cl⁻. The rise of temperature in the tissues causes a series of physiological
changes in tumor cells, such as changes in intracellular ion concentration, chromosomal aberrations in G1 and S phase cells to form multinucleated cells and then split the death, DNA/RNA polymerase inactivation leads to DNA and inhibition of protein synthesis, cell proliferation capacity loss and so on. These effects directly or indirectly lead to the apoptosis of tumor cells, thereby alleviating or curing the tumor. MWTT has the advantages of simple operation, high heat conversion efficiency, small trauma, and is widely used in the clinical treatment of tumors. However, there are also some technical difficulties that restrict the application of MWTT. For example, microwave is not selective for tumors, and it is difficult to avoid damage to surrounding normal tissues while killing tumor cells by microwave ablation. Moreover, the current microwave ablation technology has limited thermal diffusion range, and monotherapy is difficult to completely eliminate large tumors. In addition, MWTT was still unable to effectively control the metastasis and recurrence of tumors. Therefore, in order to better apply microwave to treat malignant tumors, especially deep tumors, the above problems must be solved. The emergence of nanoplateform has found a solution to the limitations of MWTT. For example, in 2014, Shi and his colleagues used computer-simulated model to theoretically verify that in a confined space, ions have high microwave sensitization characteristics, that is, strong confinement effect (Figure 13A-C). Afterwards, the team designed a hollow mesoporous structure of ZrO2 nanosphere and loaded it with ionic liquid (IL) to obtain IL@ZrO2 nanoparticles (Figure 13D). After that, IL@ZrO2 was injected into the mice through the tail vein (Figure 13E), the tumor inhibition rate of
Apatinib (DPA@PEMG) were obtained by loading doxorubicin (DOX) and NaCl to obtain DOX&NaCl@liposomes.\textsuperscript{132} The results showed that under thermal effects of IL. In 2016, Jin et al. used liposomes to encapsulate doxorubicin (DOX) and NaCl to obtain DOX&NaCl@liposomes\textsuperscript{132} The results showed that under microwave irradiation, the limitation of NaCl ion concentration in the small size of liposomes made the temperature of liposomes rise faster than dissociative ions, showing strong microwave responsiveness. In addition, due to MWTT usually exists in a warm zone, tumor cells cannot be completely killed, which is often accompanied by metastasis and recurrence of tumor cells. Inhibiting the metastasis and recurrence of tumor cells can effectively improve the therapeutic effect of tumor. In 2020, Sun et al. designed a small graphene, which has good biocompatibility, low-frequency microwave absorption performance and good thermal conversion ability.\textsuperscript{101} PEG-Graphene@PCM-Apatinib (DPA@PEMG) were obtained by loading the neovascular inhibitor Apatinib into graphene. After the nanoparticle reaches the tumor microenvironment, it can significantly downregulate the expression of VEGF, thereby inhibiting the recurrence and metastasis of tumor cells. Therefore, graphene combined with MWTT showed a high tumor ablation rate of 86.7%. The several successful cases mentioned above prove that the development of nano-microwave nanoplatform provides a new idea for improving the effect of MWTT for deep tumors.

As a new dynamic therapy, MDT, different from PDT, uses microwave as an exogenous stimulus energy source to trigger sensitizers to generate cytotoxic ROS. ROS has a redox reaction with tumor cells, which in turn induces tumor cell apoptosis. For example, in 2018, Fu et al. designed an Mn\textsuperscript{2+} doped Zr-MOF nanocomposite for the first time that can significantly enhance the generation of ROS under MW irradiation, which provides a new idea for MWTT of deep tumors.\textsuperscript{103} In addition, the Mn\textsuperscript{2+} doped Zr-MOF nanocomposites exhibited excellent synergistic therapeutic effects of MDT and MWTT, and the growth of tumor cells was significantly inhibited. In addition, Wu and his colleagues took advantage of the fact that liquid metals (LM) could generate ROS under microwave irradiation (Figure 14A).\textsuperscript{104} The dual-functional supernanoparticles (SNPs) of PEG-IL-LM-ZrO\textsubscript{2} SNPs was designed by loading LM and MW sensitizer IL into mesopore ZrO\textsubscript{2} nanoparticles. PEG-IL-LM-ZrO\textsubscript{2} SNPs can generate ROS under microwave irradiation and also have a significant thermal effect (Figure 14B), thereby enhancing the combination therapy of MDT and MWTT. Moreover, under the combined treatment of MDT and MWTT, the tumor inhibition rate of subcutaneous tumor model mice was as high as 92.2 ± 6.8%, and even 40% of tumor-bearing mice in orthotopic liver cancer mouse models were completely cured. Therefore, MDT will be a very promising method for the treatment of deep tumors.

MGT refers to the use of microwave as an exogenous stimulus energy source to stimulate nanomaterials to produce gases (e.g. O\textsubscript{2}, NO, H\textsubscript{2}, and H\textsubscript{2}S, etc.) in the tumor microenvironment to reshape the tumor microenvironment and thereby improve the therapeutic effect of the tumor. For example, in 2018, Chen et al. designed a multifunctional nanocomposite of IL-DOX-PCM-CuO@ZrO\textsubscript{2}-PEG (IDPC@Zr-PEG) to alleviate hypoxic state in tumor microenvironment based on microwave-triggered CuO to produce oxygen (Figure 14C).\textsuperscript{105} IDPC@Zr-PEG can produce oxygen in the tumor microenvironment during MWTT (Figure 14D), so as to alleviate the hypoxia state of tumor cells and improve the therapeutic effect. In vivo antitumor experiments showed that the tumor inhibition rate was as high as 92.14%. In addition, Chen and co-workers designed a multifunctional nanosuperparticle of IL-Quercetin-CuO-SiO\textsubscript{2}@ZrO\textsubscript{2}-PEG (IQuCs@Zr-PEG NSPs) that can generate oxygen under microwave irradiation and reshape the tumor microenvironment.\textsuperscript{106} After IQuCs@Zr-PEG NSPs were injected into mice via tail vein, it can continuously release oxygen under microwave irradiation, thereby downregulating the expression of hypoxia-inducible factor HIF-1\textalpha. Therefore, the reoxygenation of tumor cells by microwave irradiation can significantly enhance the combined treatment effect of MWTT and RT, and the tumor inhibition rate was as high as 98.62%.

Above all, MWTT has the characteristics of high heating efficiency, deep penetration depth, and wide treatment range, and is one of the effective methods for the current clinical treatment of tumors. Using microwave as an exogenous stimulus source, the combination of microwave and nanoplatform for deep tumor treatment can improve treatment failure caused by low treatment efficiency due to insufficient penetration depth.

## 4 SUMMARY AND OUTLOOK

In summary, in recent years, the application of nanoplatforms in nanomedicine has received more attention. In particular, the integration of diagnosis and therapy based on the nanoplatform has brought hope to the precise treatment of cancer. This article reviews the latest research progress in the diagnosis and therapy of deep tumors based on the emerging biocompatible nanoplatform. It mainly introduces four cancer diagnosis techniques (CT, FI, MRI, and PAI) and four treatment methods (phototherapy, ultrasound therapy, RT, and MWT). The four imaging technologies have their own advantages and limitations in cancer diagnosis. Therefore, multimodal imaging that combines two or more of these imaging
methods is more accurate in cancer diagnosis. Compared with traditional treatments in clinical applications, several treatment methods have fewer side effects and more precise and effective treatments. Among them, the NIR-II biological window has lower absorption and scatter of skin tissue, deeper tissue penetration, which is more suitable for PTT of deep tumors. Moreover, the combination of interventional technology and PTT can also achieve better treatment of deep tumors. Sonodynamic therapy (SDT) has attracted a wide range of attention in recent years. Although SDT is susceptible to bone and gas interference, SDT based on the biocompatible nanoplatform still has great application potential in the treatment of deep tumors. Radiotherapy (RT), as one of the three traditional treatment methods for cancer, has the advantages of deep penetration. But uneven radiation responses, non-selectivity to normal tissues, and radiation resistance limit the use of RT as the primary treatment for cancer. Radiodynamic therapy (RDT) can overcome the radiation resistance limit, and the combination with RT can effectively improve the therapeutic effect of resistant tumors. Microwave therapy (MWT) has the characteristics of high heating efficiency, deep penetration depth, and wide treatment range, and is one of the effective methods for the current clinical treatment of tumors. In addition, synthesizing a more effective nanoplatform with good biocompatibility and powerful modification functions is an important research direction to promote the clinical application of integrated diagnosis and treatment technology.

Although cancer research based on nanoplatforms have made vigorous progress, it has not yet been popularized in clinical applications, and there are still major challenges to be solved urgently. Firstly, it is necessary to develop new strategy and technology to achieve minimally invasive/non-invasive accurate therapy of deep tumor. For example, the combination of clinical interventional technology with thermal and dynamic therapy. Secondly, it is highly desired to design and synthesize suitable nanoplatforms with high tumor targeting, good biosafety, easy degradation or excretion, excellent imaging, and
therapeutic functions. There are many kinds of nanomaterials prepared for diagnosis and therapy, but there is still a need for further development of nanomaterials that can be mass-produced, and the synthesis method is simple, easy to repeat, and economical. The biocompatibility of nanomaterials will be verified through acute toxicity experiments in experiments, but the chronic toxicity of materials has not been studied. The EPR effect of nanomaterials can be used to target the tumor, but its targeting is not enough. There are still a large number of nanomaterials that will penetrate into normal tissues and organs. Therefore, further research is needed to improve the targeting of nanomaterials and reduce the accumulation of drugs in other tissues. Last but not the least, the establishment of deep tumor model still needs more stringent experimental conditions. It is of great significance to develop a systematic and easy-to-operate method for the establishment of deep tumor, especially for the orthotopic carcinoma of liver, lung, stomach, colon, and pancreas of mice or rabbits. It is hoped that diagnosis and therapy based on the nanoplatforms can overcome the limitations of cancer treatment and no longer let cancer become the shackles of human health.

ACKNOWLEDGMENTS

W. N. Guo and Z. Z. Chen contributed equally to this work. We are grateful for the financial support from National Key R&D Program of China (2018YFC0115500, 2020YFE0100200), National Natural Science Foundation of China (U20A20335, 91859201, 81971745, 61975214, 2020YFE0100200), National Natural Science Foundation of China (2202057, 7212208, 4202075), and Beijing New Star Program of Science and Technology (Z19110000119042).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: W. Guo, Z. Chen, L. Tan, D. Gu, X. Ren, C. Fu, Q. Wu, X. Meng. VIEW 2022, 3, 20200174. https://doi.org/10.1002/VIW.20200174