International Journal of Nanomedicine

Dovepress
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REVIEW

Research Progress of Nanodelivery Platforms in the Diagnosis and Treatment of Esophageal Cancer

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Abstract: Esophageal cancer treatment has long been limited by the toxicity of radiotherapy and chemotherapy, multidrug resistance, and low immune response. Nanotechnology, with its precise targeting advantages, offers a new solution. This article reviews its core advances: first, achieving enhanced efficacy and reduced toxicity of radiotherapy and chemotherapy, and reversing drug resistance; second, empowering photodynamic, gene, and immunotherapies, utilizing co-delivery strategies to reshape the microenvironment to activate "cold tumors"; and third, constructing a visualized integrated diagnostic and therapeutic platform. Although clinical translation still faces challenges related to biological barriers and mass production, the integration of biomimetic design, intelligent response, green manufacturing, and organoid screening technologies holds promise for bridging the translational gap and significantly improving patient prognosis.

Keywords: nanodelivery system, multidrug resistance, immunotherapy, therapeutic integration, clinical translation

Introduction

Esophageal cancer (EC) is a highly aggressive malignant tumor with a very poor prognosis, with a five-year survival rate of only 10%–30% in most parts of the world. As the sixth leading cause of cancer death globally, EC places a heavy burden on public health, especially in high-incidence areas in East Asia such as China, where the five-year survival rate hovers below 30%.[1]

EC is mainly divided into two subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The former is closely related to long-term physical and chemical irritants (such as smoking and alcohol consumption) and is dominant in developing countries; the latter is mostly caused by gastroesophageal reflux disease (GERD) and obesity and is more common in Western countries.[2] Its risk factors include gastroesophageal reflux disease (GERD), obesity, and smoking. In addition, Barrett's esophagus is its direct precancerous lesion.[3] The treatment of EC is mainly based on the TNM stage and pathological type of the tumor.[4] Surgery is the main treatment for early EC. For early lesions, the 5-year survival rate of surgical or endoscopic resection can be as high as 90%. However, for patients with more common locally advanced lesions, the effect of surgery alone is not ideal, and the recurrence rate after surgery is extremely high. Therefore, the current mainstream treatment model has shifted to "neoadjuvant therapy + surgery", which can increase the 5-year survival rate to 40% – 50%. Nevertheless, the biggest bottleneck of surgical treatment is still the high recurrence rate, and about half of the patients still face the risk of tumor recurrence or metastasis after surgery. As a neoadjuvant therapy before surgery, radiotherapy and chemotherapy can effectively shrink the tumor and

https://doi.org/10.2147/IJN.S588613
Received: 12 December 2025
Accepted: 20 March 2026
Published: 31 March 2026

create conditions for surgery; for patients with locally advanced disease who cannot be operated on, radical concurrent chemoradiotherapy can achieve a long-term survival of about 20% – 30%. However, the drug resistance gradually generated by tumor cells eventually leads to treatment failure.

Targeted therapy is difficult to apply in the field of EC, and a highly effective target has not yet been found.[5] But immunotherapy has changed the EC treatment landscape. To break this deadlock, immunotherapy (especially PD-1/PD-L1 inhibitors) has reshaped the treatment landscape of EC in recent years, becoming the new standard of care for advanced-stage cancer.[6,7] However, clinical reality shows that immunotherapy is not a panacea: only a portion of patients benefit from it, and nearly half still exhibit primary resistance.[8] An even more serious challenge is that current biomarkers often fail to accurately predict efficacy, leading to difficulties in patient stratification and causing many patients to miss the window of opportunity due to ineffective treatment. This "precision treatment gap", along with the systemic toxicity of traditional radiotherapy and chemotherapy, urgently requires us to find a novel treatment strategy that can enhance drug delivery efficiency, overcome resistance mechanisms, and modulate the tumor microenvironment.

Nanomaterials can be defined as materials with a size between 1 and 100 nanometers. They affect the boundaries of nanomedicine, from biosensors, microfluidics, drug delivery and microarray testing to tissue engineering. Nanoparticle (NP)-based drug delivery systems have received widespread attention due to their excellent physicochemical properties. Compared with traditional tumor drug therapy, due to the high permeability of tumor blood vessel walls and obstructed lymphatic drainage,[9–11] macromolecular materials exhibit an enhanced permeability and retention (EPR) effect in tumor tissues, enabling nanoparticles (NPs) to accumulate in tumor tissues compared to normal tissues.[12,13] Subsequently, specific ligands bound to the surface of the nanocarrier can precisely bind to tumor cells. Furthermore, nanocarriers can encapsulate drug components, protecting them from premature degradation, preventing premature interactions with the biological environment, significantly improving drug solubility and biostability, and controlling drug pharmacokinetics and tissue distribution characteristics.[13]

Current EC tumor therapy still faces many challenges, such as systemic toxicity, tumor drug resistance, and low response to immune checkpoint inhibitors (ICIs).[4] Nanodelivery platforms, with their precise delivery, controlled release, and multifunctional integration[14–16] have great potential for development in addressing current challenges in EC treatment, such as chemotherapy resistance, radiosensitization, and insufficient response rates to immunotherapy.[17,18]

The multifunctional integration of nanoplatforms enables them to synergize with chemotherapy, radiotherapy, and immunotherapy, potentially overcoming the limitations of monotherapy. However, the field of nanomedicine is vast, and to avoid generalizations and provide practical guidance, this review focuses on nanodelivery platforms closest to clinical application in esophageal cancer, rather than encompassing all nanotechnology. We will summarize the latest advances in nanotechnology in overcoming chemotherapy resistance, radiosensitizing, and improving immune response rates, and critically discuss the challenges and prospects of their transition from the laboratory to the clinic.

Development History of Nanodelivery Platforms

Before delving into specific nanotherapy strategies, it is necessary to first trace the historical evolution of nanomedicine in esophageal cancer treatment. Over the past thirty years, the development of nanomedicine has not been a sudden leap, but rather has progressed through three stages, from basic drug encapsulation to precision medicine.

The first stage (1990s–2000s): Passive targeting and safety optimization. The core objective of this period was to reduce the systemic toxicity of traditional chemotherapy drugs and improve their solubility. A landmark milestone was the clinical approval of nanocarriers utilizing high permeability and retention effects, such as liposomal doxorubicin and albumin-bound paclitaxel. While these "first-generation" nanomedicines did not achieve active tumor recognition, they significantly improved drug biodistribution and safety.[19,20]

The second stage (2000s–2015s): Active targeting and functional modification. With advancements in materials science, research focus shifted to addressing the inefficiency of passive targeting. Researchers have begun modifying the surface of nanocarriers with specific ligands, such as EGFR antibodies targeting EC high expression, folic acid, and RGD peptides, to endow nanomedicines with the ability to "actively recognize" tumor cells, thereby enhancing cellular uptake and overcoming physiological barriers.[5,21,22]

The third stage (2015s–present): Intelligent response and multimodal therapy. Current research is at the forefront of this stage, focusing on developing intelligent stimulus-response systems that can respond to the tumor microenvironment (such as pH, GSH, and enzymes), and multifunctional platforms that integrate immunotherapy, gene therapy, and therapy.[23,24]

Given the above development trajectory, this review will follow the logical depth of this technological evolution, first exploring how nanotechnology optimizes traditional chemotherapy and radiotherapy, and then delving into emerging fields such as photodynamic therapy, immunotherapy, and therapy-integrated treatment.

Evolutionary Timeline of Nanotherapeutic Strategies

Nanochemotherapy with Enhanced Efficacy and Reduced Toxicity

As is shown in Figure 1, esophageal cancer (primarily ESCC) still relies on radiotherapy, chemotherapy, and concurrent chemoradiotherapy as core treatment methods, but these are limited by factors such as tumor hypoxia and radioresistance, chemotherapy side effects, and post-chemotherapy drug resistance. Nanotechnology offers strategies to enhance the efficacy and reduce the toxicity of traditional radiotherapy and chemotherapy. Even though the application of nanotechnology in some treatments is still in the clinical trial stage, and there is a lack of reliable nanocarriers, overall, nanotechnology has made significant contributions to the precision and personalized treatment of esophageal cancer based on many traditional therapies.

Although chemotherapy drugs have long occupied a dominant position in the drug treatment of esophageal cancer, current chemotherapy drugs have many problems, such as adverse reactions after chemotherapy and tumor drug resistance.[25,26] Nanodelivery platforms have improved the pain points of traditional chemotherapy to some extent by encapsulating drugs within nanocarriers to achieve enhanced efficacy and reduced toxicity.[27,28] The specific mechanisms are divided into passive delivery and active delivery.

Passive delivery is the most classic mechanism of action of nanochemotherapy, the core of which is to utilize the EPR effect of tumor tissue (Figure 2). Currently, various nanodelivery systems have shown great potential in the field of EC therapy, such as liposomes, polymer micelles, and albumin NPs. Liposomes are one of the earliest nanocarriers used and

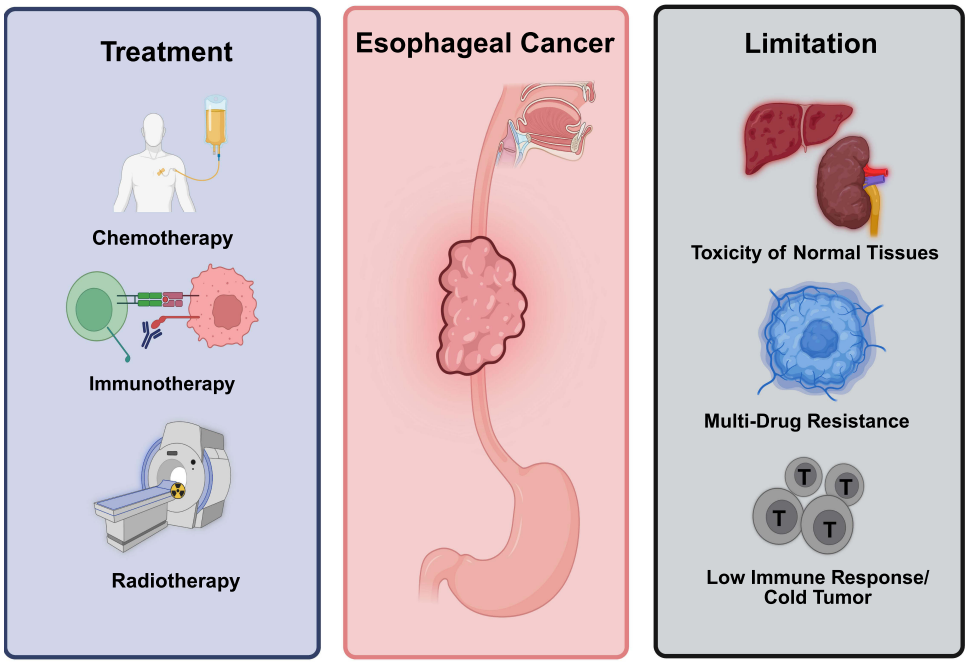

Figure 1 Nanomaterials combined with radiotherapy and chemotherapy in the treatment of esophageal cancer.

https://doi.org/10.2147/IJN.S588613

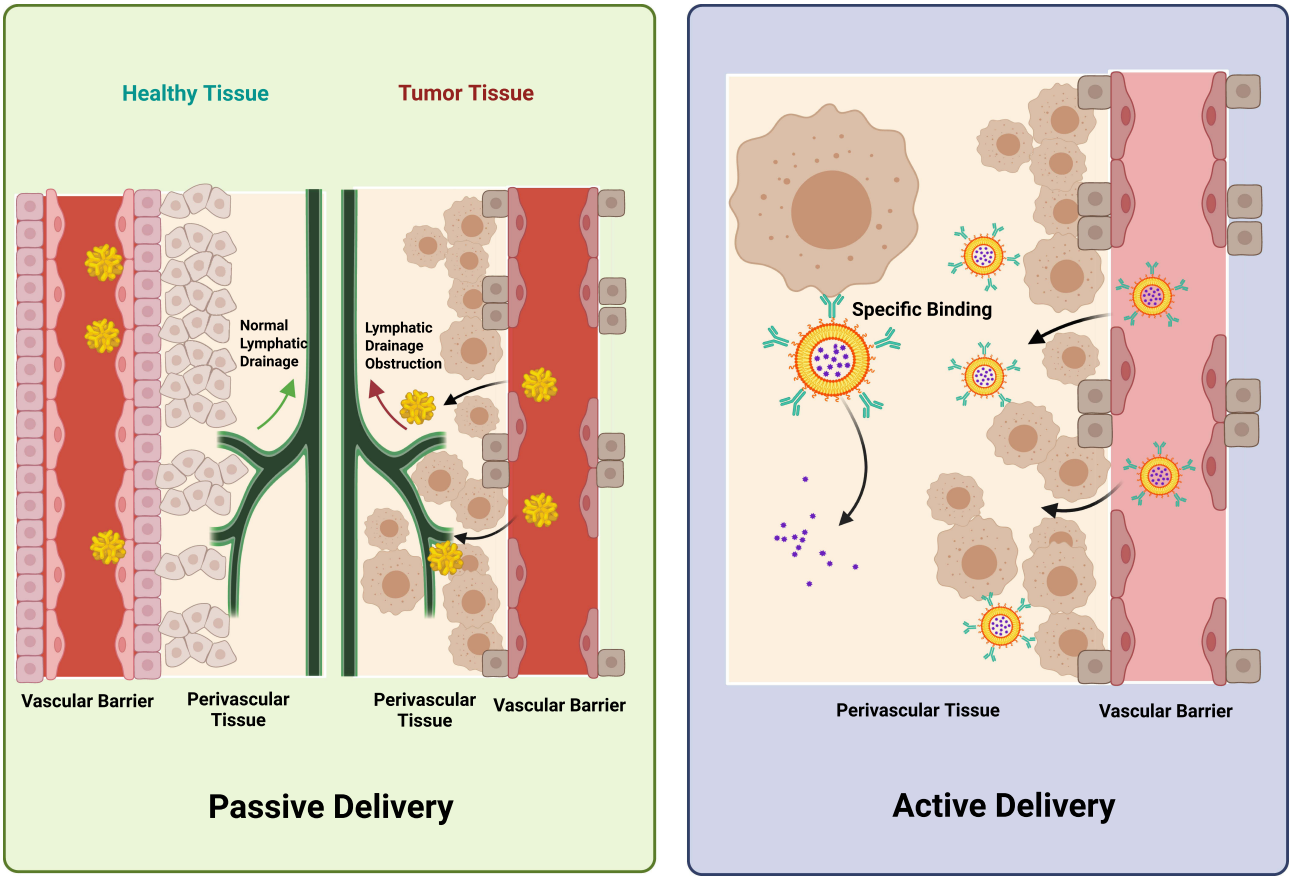

Figure 2 Passive delivery and active delivery. Yellow star-shaped symbols, nanoparticles; Orange spherical particles with green ligands, actively targeted nanocarriers; purple dots, loaded therapeutic agents.

have shown good results in EC therapy. Studies have shown that the targeting and tumor cell inhibition effects of liposomes are significantly better than those of traditional chemotherapy drugs. For example, Sun et al successfully developed nanoscale EA2-modified pH-sensitive liposomes (EA2-PSL-PTX/LUT). 72 hours after administration to ex vivo organ imaging, the fluorescence intensity of the targeted liposomes in tumor tissue was 2.6 times that of the non-targeted liposomes. In vivo imaging data showed that the tumor burden in the traditional chemotherapy group was 2.28×10^7 a.u., while the tumor burden in the EA2-PSL-PTX/LUT group was only 0.084×10^7 a.u., which improved the efficacy by about 27 times.[29] Chen X et al also developed a liposomal nanocarrier, DOX/ORD NLP. In vivo studies showed that DOX/ORD NLPs had a significant targeting effect on subcutaneous tumors. Apoptosis was detected by TUNEL staining with terminal deoxynucleotidyl transferase dUTP nick end marker. The results showed that DOX/ORD NLP treatment significantly induced apoptosis and inhibited tumor growth.[30] It is worth noting that liposomes not only excel in cutting-edge research but are also the most successfully translated nanocarriers into clinical applications. Among them, PEGylated liposomal doxorubicin and liposomal irinotecan are landmark drugs in this field. Doxil™, the world's first FDA-approved nanomedicine, significantly prolongs the drug's in vivo half-life through polyethylene glycol modification, utilizes the EPR effect to achieve tumor enrichment, and greatly reduces the cardiotoxicity caused by free doxorubicin. Onivyde™, on the other hand, utilizes a highly stable drug delivery technology to improve the pharmacokinetics of irinotecan, demonstrating significant survival benefits in the treatment of refractory metastatic pancreatic cancer. The successful launch and widespread application of these two classic drugs powerfully demonstrate the enormous clinical value of liposome-based nanomedicine delivery systems in optimizing the biodistribution of chemotherapeutic drugs and improving the therapeutic index.

The representative drug of albumin NPs is albumin-bound paclitaxel (Nab-PTX), which has been widely used in solid tumors such as breast cancer, lung cancer, and pancreatic cancer,[19] In addition, albumin-delivered chemotherapeutic drugs such as cisplatin and doxorubicin have also attracted widespread attention,[20,31–33] Albumin NPs have higher remission rates and better safety than traditional drugs. Gradishar WJ et al found in a Phase III clinical trial on breast cancer that Nab-PTX showed a significantly higher response rate (33% vs 19%, Respective; P =0.001) and a significantly longer time to tumor progression (23.0 vs 16.9 week, Respective; RR = 0.75; P =0.006).[34] Socinski MA et al found that in patients with non-small cell lung cancer, the Nab-PTX plus carboplatin group showed a significantly higher objective response rate (ORR) than the solvent paclitaxel plus carboplatin group.[35] Von Hoff DD et al found that for patients with metastatic pancreatic adenocarcinoma, Nab-PTX plus gemcitabine significantly improved overall survival, progression-free survival and response rate.[36] As for EC treatment, the Nab-PTX plus cisplatin chemotherapy regimen has become the first-line treatment for EC in China.[37,38] Compared with the maturely applied Nab-PTX, most other types of albumin nanomedicines are in the early stages of clinical research, and the current research progress is still in the preclinical, Phase I or Phase II clinical trial stage.[39,40] At present, the academic and industrial communities lack key late-stage clinical data that can prove their clinical value and promote their market launch.

Unlike passive delivery, active targeted delivery strategies, based on passive targeting, specifically recognize and bind to the overexpression of tumor cells through ligands on the surface of nanocarriers (Figure 2). This triggers receptor-mediated endocytosis,[41] allowing the drug to accurately enter tumor cells and increase the drug concentration within tumor cells.[27] Active delivery systems are often used in combination with penetrating peptides (such as iRGD) or vascular targeting (αvβ3) to improve intratumoral distribution.[21,42] In EC, epidermal growth factor receptor (EGFR), CD44, and integrin αvβ3/αvβ5 are common targets, highly expressed in EC cells,[5,22] These targets are expected to be key targets for nanodelivery systems and represent a new direction for drug development.

Even with the widespread use of chemotherapy in the treatment of EC, the benefits of chemotherapy rapidly decrease in patients with multidrug resistance (MDR).[25] MDR has many mechanisms, one key pathway being the overexpression of P-glycoprotein (P-gp) encoded by the MDR1 gene.[43] P-gp is an energy-dependent drug efflux pump that reduces intracellular drug concentration by pumping various chemotherapeutic drugs out of the cell. Although some studies have attempted to combine small molecule P-gp inhibitors,[44] the final results are often unsatisfactory due to the toxicity of first- and second-generation P-gp inhibitors and their pharmacokinetic mismatch with chemotherapeutic drugs.[43] However, Singh MS et al successfully prepared two P-gp inhibitors into polymeric NPs and evaluated their inhibitory effects on P-gp resistance proteins. Calcein AM and rhodamine-123 were used to assess their inhibitory effect on P-gp. Cytotoxicity studies revealed that in cells expressing P-gp, the NP formulations were significantly more effective than the original compounds in reversing drug resistance.[45] Furthermore, breast cancer resistance protein (BCRP), which has a similar mechanism to P-gp, also acts as a drug efflux pump, and its inhibitors have attracted widespread attention.[46–48] Unfortunately, despite decades of effort, no specific BCRP inhibitor has yet been effectively applied clinically. Clinically, drugs that inhibit BCRP are often dual-action drugs, such as many tyrosine kinase inhibitors (TKIs).[49]

Nanoscale Radiosensitization

Radiotherapy, like surgery and chemotherapy, is an important treatment for solid tumors such as EC. However, its practical application faces many problems: First, in order to ensure complete destruction of tumor tissue and reduce the chance of tumor metastasis, radiotherapy uses high doses to destroy the tumor, which sometimes damages adjacent tissues (lungs, heart), causing serious side effects; Second, studies have shown that hypoxic cells in the center of the tumor have stronger resistance to radiation,[50] which will reduce the effectiveness of radiotherapy. Therefore, the core goal of radiotherapy is to reduce damage to normal tissues and increase the sensitivity of tumor tissue to radiation.

The current mainstream solution is to use radiosensitizers.[51,52] Currently, the research and application of radiosensitizers have expanded from traditional hypoxic cell sensitizers,[53] to multiple cutting-edge fields such as targeted DNA damage repair and regulation of the tumor microenvironment (TME)[54] Utilizing high atomic number (High-Z) elements (NPs) as radiosensitizers is also a very promising research direction. These NPs have a photoelectric absorption cross section much higher than that of human soft tissue to amplify radiation in the tumor. By generating a large number of reactive oxygen species (ROS), especially the most toxic hydroxyl radicals (•OH), they cause irreparable double-

strand breaks (DSBs) in the DNA of tumor cells, and damage mitochondria and cell membranes, thereby increasing the killing effect of radiation on tumor cells.[51] In addition, functionalized noble metal nanomaterials can promote the generation of ROS, switch the cell cycle to a radiosensitive state,[55] and inhibit the p53 signaling pathway to induce autophagy and lysosomal dysfunction, thereby improving radiosensitivity.[51] This strategy has shown great potential in the preclinical study of EC. Related in vivo and in vitro studies have demonstrated its strong radiosensitizing effect.[56] Butterworth KT et al found that gold NPs caused significant cell type-specific cytotoxicity, apoptosis and oxidative stress. Among them, AGO-1522B cells showed the highest dose enhancement at a NP concentration of 100 μg/mL, reaching 1.9-fold, which induced a series of cell line-specific responses, including decreased clonal viability, increased apoptosis, and induction of DNA damage,[56] Li X et al developed a novel lipid-modified manganese diselenide nanoparticle (MnSe2-lipid) with excellent spherical morphology uniformity and responsiveness to TME, which can overcome radio-resistance and reduce radiation side effects. Notably, they verified that EC radiosensitization therapy with this particle can provide radiosensitivity through cGAS-STING pathway-mediated immunostimulation and chemokinetic therapy, while protecting normal tissues.[57]

Nanodelivery Platforms for Emerging Therapies for Esophageal Cancer

In recent years, with the development of nanomedicines, photodynamic therapy (PDT) has made breakthrough progress, and the rapid development of nanomedicines has provided new ideas for PDT.[58] By combining photosensitizers (PS) with NPs, ROS for treatment[59] and fluorescence signals for diagnosis are generated in tumor tissue. This not only achieves precise and minimally invasive diagnosis and treatment, but also greatly improves the actual effect of photodynamic diagnosis (PDD) and PDT.[60,61]

Nanophotodynamic Diagnosis and Therapy

Nano PDT is a therapy that integrates the concept of minimally invasiveness. By combining PS with nanocarriers to form NPs, ROS is generated by irradiating specific wavelengths of light under an endoscope to kill tumor cells. Under the influence of light and oxygen, PS stimulates the production of ROS,[62,63] thereby causing damage to tumor cell double-stranded DNA, mitochondrial membranes, and cell membranes, while also causing tumor vascular occlusion and immune activation (Figure 3A).[64–66] Nanotechnology can give PS more superior properties, enhancing drug stability, reducing systemic phototoxicity, enabling release in TME, and guiding tumor imaging.[15] It can even enhance ROS killing power by co-loading oxygen-producing substances (such as MnO2, CaO2) to deplete glutathione (GSH);[67–70] Like other parts of the digestive tract, the natural lumen of the esophagus makes endoscopic irradiation therapy under EC possible, giving PDT/photothermal therapy (PTT) unique clinical advantages in EC treatment: minimally invasive, capable of repeated treatment in a short period, reducing damage to normal tissues, and can be performed simultaneously with endoscopic procedures such as biopsy, dilation, and stent placement.[71]

Nanoparticle-based drug delivery systems (PDTs) benefit from the unique advantages of nanotechnology: 1. Enhanced targeting and safety:[72] Due to the high permeability of tumor blood vessels and the obstruction of lymphatic drainage, nanoparticles can passively accumulate in the tumor site, increasing the drug concentration in the lesion while reducing damage to healthy tissues. 2. Increased drug loading and delivery efficiency: Compared with traditional delivery methods, nanoparticles (NPs) have extremely high specific surface areas, allowing them to bind a large number of substances required for diagnosis and treatment. Furthermore, thanks to their small size, nanoparticles can penetrate blood vessel walls, promoting the internal absorption of drugs by cancer cells. 3. Provided drug protection: Through surface modification of nanoparticles, biomolecules can be simulated, effectively protecting the internal PS from being cleared or prematurely degraded by the body's immune system, giving it a longer effective time, and allowing the drug to effectively reach the tumor tissue.

Currently, many nanoparticles are widely used in PDDs and PDTs, and many nanoparticles designed for them have been developed to achieve better targeting effects.[73–75] These include two main categories: organic and inorganic substances. Organic nanoplatforms (such as liposomes and micelles) are characterized by good biocompatibility, low toxicity, and easy encapsulation of PS. They can achieve targeted localization of tumors by improving drug solubility and delivery efficiency.[65] In contrast, the core advantages of inorganic nanoplatforms (such as gold NPs and iron oxides) are

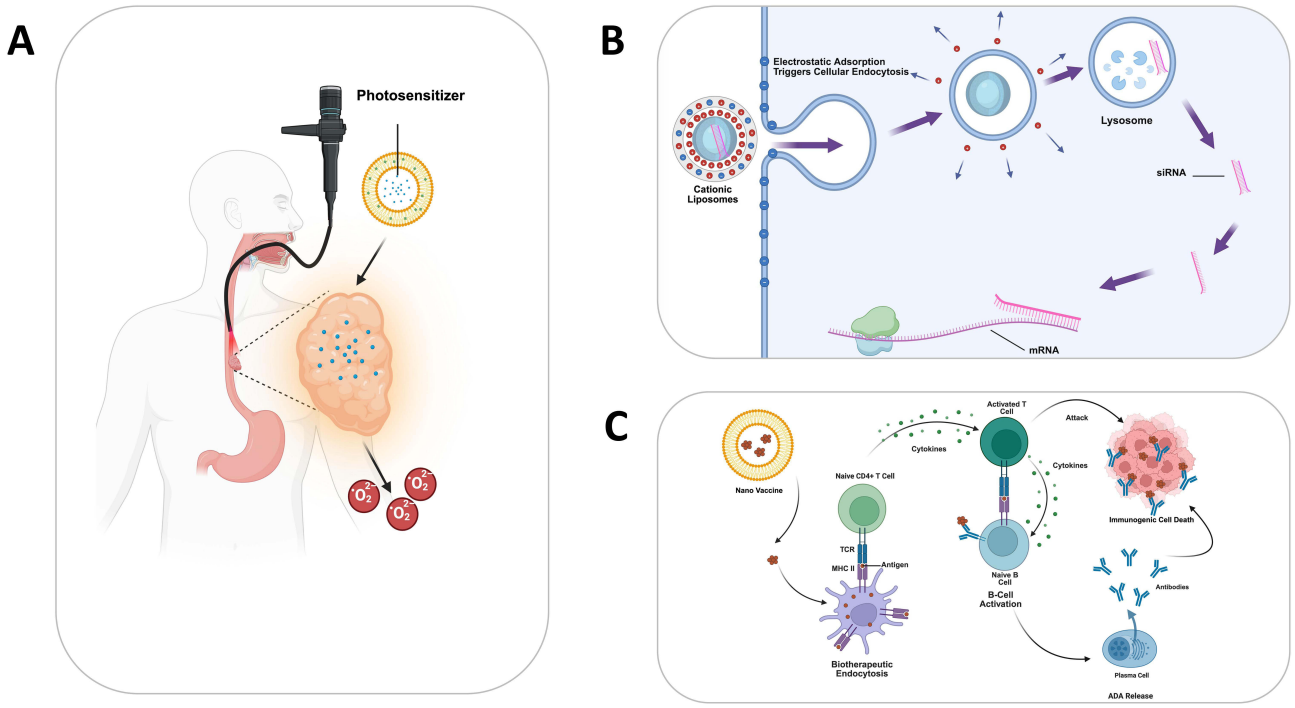

Figure 3 (**A**) Nanophotodynamic diagnosis and therapy: Nanoparticles enhance ROS generation and fluorescence imaging under endoscopic light irradiation. (**B**) Nanoparticle immunotherapy: Nanocarriers deliver antigens to activate dendritic cells or modulate the immune microenvironment. (**C**) Nanogene therapy: Non-viral vectors protect and deliver siRNA to regulate tumor-related gene expression. In (**A**), blue dots, photosensitizer molecules; red circles, reactive oxygen species. In (**B**), red dots, positively charged components; pink strands, siRNA. In (**C**), Orange spherical particles, nanovaccines; small brown particles, antigens or therapeutic payloads; green dots, cytokines.

tunable physicochemical properties (size, shape), high drug loading capacity, efficient accumulation in tumors, and amplification of therapeutic effects.[76] In particular, inorganic nanoplatforms have excellent optical or magnetic properties and can be directly used for tumor imaging and diagnosis, and can be used for both diagnosis and treatment.

It is worth noting that among many nanomaterials, carbon-based nanomaterials are ideal materials for PDD and PDT,[77] Compared with other nanomaterials, carbon-based nanomaterials combine good optical properties, high drug loading capacity, and enhanced ROS generation, making them suitable for integrated diagnosis and treatment; their surfaces are easy to modify, allowing the connection of targeting groups to enhance tumor targeting; in addition, they have good biocompatibility and low toxicity. Previous studies have reported relevant cases: Xue et al successfully constructed an integrated nanoprobe (NBCD-PEG-Ce6-Tf) using carbon dots (CDs) prepared from litchi shells. This probe has both diagnostic and therapeutic functions, enabling tumor imaging through near-infrared fluorescence and also efficiently generating ROS under light to kill cancer cells.[78] This study verified the advantages of carbon-based nanomaterials and to some extent proved the feasibility of using carbon-based nanomaterials for photodynamic therapy and their great potential in drug development.

Nanoparticle Immunotherapy

Nanodelivery platforms can deliver a variety of drugs, not only in combination with immune checkpoint blockade (ICB) drugs, but also for delivering tumor-associated antigens, adjuvants, immunosuppressants, and agonists.[16]

Currently, immunotherapy represented by ICB plays an important role in neoadjuvant therapy for EC, but many patients still experience non-response and drug resistance, which is related to the tumor immune microenvironment of EC.[16,79] Whether the addition of nanomaterials can improve the efficacy of ICB by activating a specific immune response against EC is attracting widespread attention. At present, the combination of immunotherapy and nanotechnology in the field of EC is still in its infancy and lacks corresponding research support. However, it has made great progress in other tumors such as breast cancer and melanoma, and these progresses will also provide ideas for EC nanoimmunotherapy.

https://doi.org/10.2147/IJN.S588613

Pembrolizumab is an IgG4 monoclonal antibody that blocks PD-L1. It is currently used in EC treatment for neoadjuvant, adjuvant and advanced/metastatic malignancies,[80] PD-L1 is a key target in immunology. Currently, many people have tried to combine NPs loaded with chemotherapy drugs with anti-PD-1 antibodies and achieved significant results. Some articles have shown that its expression level is an important biomarker for predicting the response to PD-1/PD-L1 inhibitor therapy and is correlated with the progression of metastatic diseases.[81] Lin's team combined PD-L1 with NPs to develop Zn-pyrophosphate NPs (ZnP@pyro) encapsulating the photosensitizer pyrrole ester, and used them in combination with anti-PD-L1 antibodies for the treatment of metastatic breast cancer. Notably, they found that the combination therapy not only effectively eradicated the growth of the primary tumor, but also prevented lung metastasis.[82] Moynihan's research[83] was the first to achieve significant results in the treatment of tumors through a combination of T-cell vaccines, interleukin-2 (IL-2), anti-PD-1 antibodies, and tumor antigen-targeting antibodies. In melanoma syngeneic transplantation models and genetically engineered mouse models that were previously difficult to clear by endogenous immune clearance, even high tumor burdens could be completely cleared. At the same time, they found that the efficacy may be related to the enhancement of antigen uptake and transmission, the increase in the secretion of anti-tumor cytokines, and the more complete infiltration of immune cells. Some also believe that NPs-mediated chemotherapy also has a synergistic effect with ICB. Researchers prepared nanodisks that mimicked high-density lipoprotein to load doxorubicin (DOX). They found that using nanodisc DOX could enhance CD8+ T cell responses to achieve anti-tumor effects. When further combined with PD-1 antibodies, more than 80% of tumors in both CT26 and MC38 tumor models showed complete regression.[84]

To further enhance the efficacy of immunotherapy by improving the delivery efficiency of anti-PD antibodies, many researchers have explored NP delivery systems loaded with ICIs. One study developed a self-degradable microneedle patch containing anti-PD-1 and glucose-specific enzyme NPs, which is released on demand. In a mouse melanoma model, this delivery system efficiently elicited an anti-tumor immune response.[85] Furthermore, anti-PD-1 and 1-methyl-DL-tryptophan (1-MT) were co-loaded into m-HA NPs and delivered transdermally using microneedles, this time showing satisfactory synergistic anti-tumor effects.[86] Overall, this system shows great promise for the single or combined delivery of ICIs and is expected to reduce the side effects of conventional drug therapy.

Cancer vaccines, especially esophageal cancer vaccines, are being developed at an accelerated pace using nanotechnology platforms. With advantages such as good safety, controlled release, targeted delivery to dendritic cells (DCs), and enhanced antigen uptake, NPs can serve as carriers of tumor antigens and adjuvants, precisely delivering drugs to the tumor environment, thereby altering immunosuppression in TMEs, increasing tumor immunogenicity, reducing inflammatory responses, and further enhancing vaccine efficacy.[87] By co-encapsulating EC-specific antigens and adjuvants in the same nanocarrier, efficient synergistic delivery of both to antigen-presenting cells (APCs) in lymph nodes can be achieved. On the one hand, antibodies protect antigens and adjuvants from phagocytosis and degradation; on the other hand, they greatly enhance the activation level of APCs, further activating and amplifying cytotoxic T lymphocytes (CTLs) (Figure 3B). Commonly used EC-related antigens include neoantigen peptides, whole tumor lysates, or tumor cell membrane/exosome-derived antigens; common immune adjuvants include CpG, Poly I:C, STING agonist cGAMP, etc.;[88] commonly used nanocarriers include liposomes, PLGA polymers, metal-organic frameworks, and injectable hydrogels. Surface ligands (such as mannose and anti-DEC-205) play a targeting role and can be delivered to DCs. Unlike other treatments, vaccine-induced immunogenic cell death (ICD) can further release intracellular antigens from tumor cells, which can also cause a stronger immune response, thus transforming the tumor from an immunosuppressed cold tumor to an immune-active hot tumor.[68,89] Currently, many innovative nanostrategies are being used for immunotherapy, and a new nanomaterial,[90] has been developed and demonstrated to significantly enhance the efficiency of antigen-activated immune levels. Researchers have developed a nanodisc that mimics high-density lipoprotein (HDL), which can efficiently deliver antigens and adjuvants to DCs and persistently activate the immune response. Experiments have shown that the ability of the nanodisc to stimulate anti-tumor T cells after binding antigens and adjuvants is 47 times higher than that of traditional vaccines, and even 31 times higher than that of existing potent adjuvants. When used in combination with PD-1/CTLA-4 inhibitors, this therapy successfully cleared established tumors in mice, opening up broad prospects for the development of a new generation of cancer vaccines. Kroll et al developed a biomimetic nanovaccine,[91] which interestingly uses a polymer core wrapped in a cancer cell membrane to deliver the patient's

own tumor antigens to APCs. The vaccine showed satisfactory preventive effects and could prolong survival. When used in combination with PD-1/CTLA-4 inhibitors, it also showed excellent therapeutic effects.

Nanogene Therapy

Gene drugs commonly include small interfering RNA (siRNA), microRNA (miRNA), and plasmid DNA. Among them, siRNA is considered to play a central role in a phenomenon called RNA interference (RNAi).[92] These nucleic acid substances are extremely unstable in the internal environment[93,94] and are very easily degraded. On the other hand, because nucleic acids carry a negative charge on their surface, they are difficult to transport. Therefore, developing safe and efficient delivery vectors is crucial for the success of gene therapy. Non-viral nanocarriers have become a current research hotspot due to their high safety, low immunogenicity, ease of large-scale production, and functional modification.[95,96] There are two main types: cationic liposomes and cationic polymers. Similar to other carriers, they can protect drugs from degradation, have high safety, low immunogenicity, and can be surface-modified to target molecules for directed delivery to tumor tissues. Most importantly, cationic nanocarriers can better deliver drugs into cells by interacting with the cell membrane due to their charge.[97,98]

Cationic liposomes are spherical vesicles composed of positively charged lipid molecules. Due to their positive charge, they can stably carry negatively charged nucleic acid drugs, forming a lipid complex. However, the complex as a whole remains positively charged and can adsorb onto the negatively charged cell membrane, subsequently initiating endocytosis. Inside the cell, it can disrupt the endosomal membrane, allowing genes to enter the cell and exert their effects. The principle of cationic polymers is similar to that of cationic liposomes (Figure 3C). Common polymers include long-chain molecules with positive charges such as polyethyleneimine (PEI) and poly-β-amino ester (PBAE).

Nanogene technology has achieved many results in the field of EC. Nanotechnology has solved the problems of gene drugs entering cells and easy degradation. The study by Yu et al found through bioinformatics analysis that the expression of miR-1-3p in ESCC tissue was significantly downregulated. To explore its function, they loaded miR-1-3p into extracellular vesicles and found that these vesicles not only effectively inhibited the proliferation, migration and invasion of EC cells in vitro, but also inhibited the colonization and growth of KYSE150 cells in vivo. Further analysis showed that miR-1-3p downregulated the expression of E2F5 protein by directly binding to the 3'UTR region of the mRNA of transcription factor E2F5, and subsequently inhibited the activation of the MAPK/ERK signaling pathway.[99] Zhang et al (2022) designed a multifunctional NP (CEAMB NPs) for the treatment of EC, which can synergistically deliver the chemotherapy drug DOX and siRNA targeting the MVP and BCL2 genes. Subsequent experiments showed that the NPs can not only effectively target tumors, but also significantly enhance DOX-induced apoptosis by inhibiting the expression of target genes, thereby greatly improving the anti-tumor treatment effect.[100] Jun et al (2020) developed a liposome nanocarrier encapsulated in leukocyte membranes that can simultaneously deliver the chemotherapy drug DOX and siRNA targeting the LPCAT1 gene. Studies have shown that this strategy combining chemotherapy and gene therapy produces a strong synergistic effect, with efficacy superior to the sum of individual therapies. At the same time, the encapsulation in leukocyte membranes also significantly prolongs the circulation time of the drug in vivo, making it a highly promising targeted delivery platform.[101] Many large pharmaceutical companies have developed related drugs for the treatment of various cancers such as breast cancer and ovarian cancer,[102] truly applying nanogene technology to clinical practice. However, there is a lack of drugs for clinical treatment in the field of EC, and most nanogene drugs are still in the preclinical stage.

Theranostics Nanoplatform for Esophageal Cancer Diagnosis and Treatment

With the rapid development of nanomedicine, theranostics nanoplatform, which integrates diagnostic, therapeutic, and efficacy assessment functions, has provided new ideas for the treatment of esophageal cancer (EC). Through more advanced molecular design, multiple functional modules are integrated onto nanoparticles (NPs), greatly enhancing the functionality of the nanoplatform while retaining the advantages of nanotechnology, thus significantly promoting the progress of personalized oncology (Figure 4).

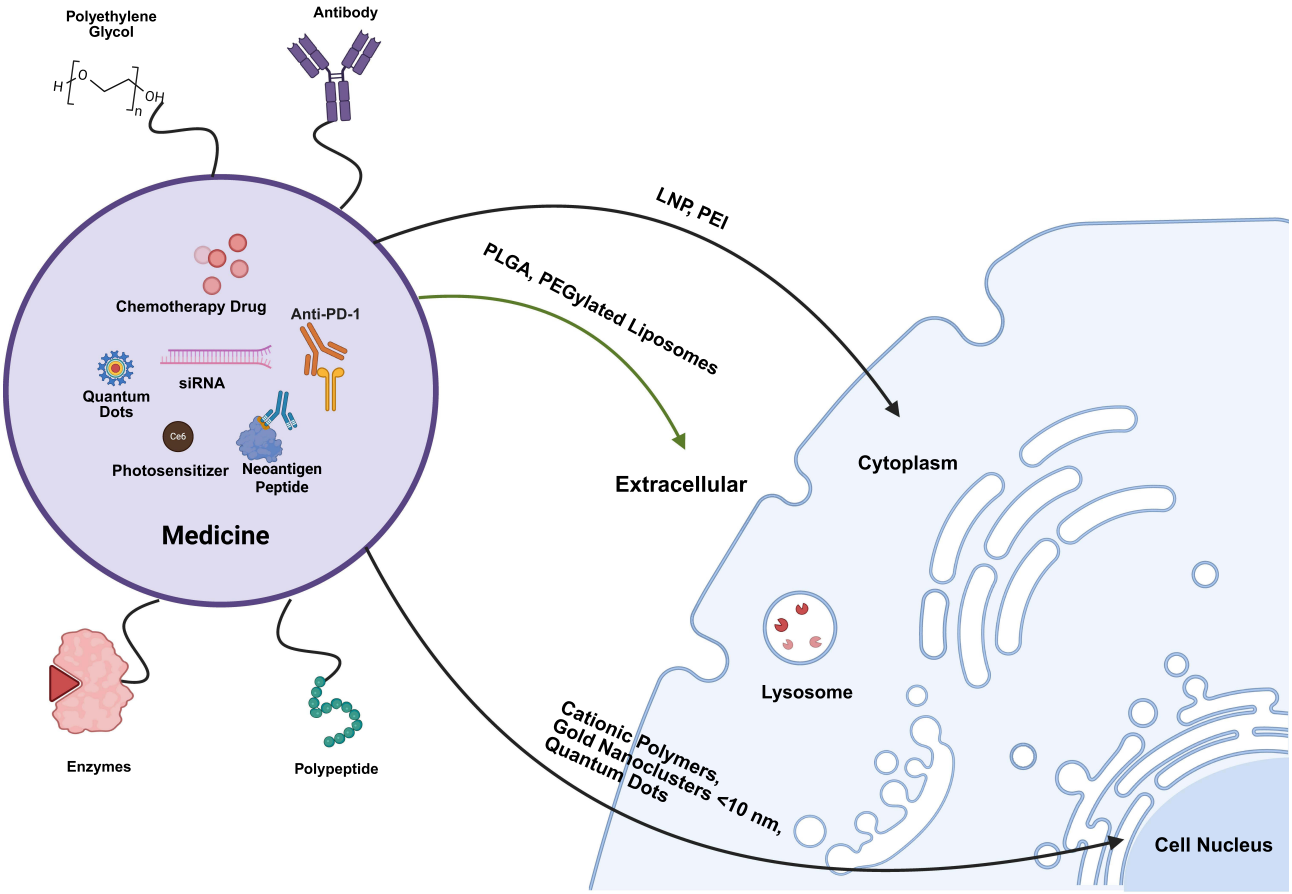

Figure 4 Composition of nanodelivery platforms.

Nanoprobes for Precise Imaging and Diagnosis

Early detection and accurate staging of EC are crucial for personalized treatment and improved patient prognosis.[103] However, traditional imaging techniques (such as CT and endoscopy) cannot meet the precision and accuracy required for early diagnosis.[104] Nanoprobes, with their excellent size characteristics and after surface functional module modification, exhibit excellent optical and magnetic properties.[105–107] Currently, nanoprobes are mainly used for tumor screening, staging, and intraoperative navigation.[107]

Fluorescence imaging primarily utilizes two methods: quantum dots (QDs) and upconversion nanoparticles (UCNPs). Both are fluorescence imaging techniques. QDs exhibit high fluorescence quantum yield, a broad excitation spectrum, a narrow emission spectrum, and good photostability, making them ideal for in vitro monitoring of tumor markers. In basic experiments, they can be used for tumor imaging in animal models.[108] UCNPs emit visible light under near-infrared (NIR) excitation. NIR light has strong tissue penetration and minimal interference from biofluorescence, making it suitable for intraoperative navigation in endocrine disruption (EC).[109,110] Preoperative injection of UCNPs allows surgeons to visualize tumor tissue and metastatic lymph nodes intraoperatively by emitting near-infrared light, facilitating more precise, safe, and reliable surgical procedures.

Conventional imaging examinations can only observe some differences between tumor and normal tissue. In many cases, relying solely on these differences is insufficient for accurately assessing tumor status through imaging. Contrast agents are used to enhance the imaging difference between tumor and normal tissue. Traditional contrast agents lack targeting and have low resolution, which nanoprobes effectively address. Magnetic polymer composite nanoprobes are based on magnetic molecules, with Fe_3O_4 being a representative example. These are typically modified with biocompatible materials,[111,112] showing great promise for early diagnosis. Gai et al covalently bound a chitosan to Fe_3O_4, obtaining novel chitosan-Fe_3O_4 NPs (CNFVs), which exhibited good magnetic properties and biocompatibility. They then

encapsulated fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR) within these NPs. Compared to patients undergoing CT imaging alone, CECT-CNFV demonstrated higher resolution, accuracy, and sensitivity in enhanced CT scans of suspected EC patients.[113]

Superparamagnetic iron oxide nanoparticles (SPIONs) are a type of contrast agent for T2-weighted magnetic resonance imaging (MRI). The principle is to shorten the T2 relaxation time of protons, resulting in low signal intensity on T2-weighted imaging due to the enrichment of the contrast agent.[114] By modifying the contrast agent with specific targeting modules, tumor tissue can be accurately located, and tumor staging and lymph node metastasis can be assessed. This method offers good imaging results, high resolution, and precise staging, providing a basis for developing radiotherapy and chemotherapy regimens.[115,116] Currently, the development of nanomaterials has greatly enhanced the imaging effect of EC tumors. Motoyama et al demonstrated that SPIONs can improve the detection rate of metastatic cervical lymph nodes in MRI scans of EC patients.[117] These cases demonstrate the excellent imaging effect of SPIONs and point the way for future EC MRI examinations.

Gold nanoparticles (AuNPs) are a promising type of nanoprobe. Compared with traditional iodine contrast agents, gold has a higher atomic number and a more significant X-ray attenuation capability.[118,119] Pharmacokinetically, AuNPs have a longer blood circulation time and can be enriched in tumor tissues through the EPR effect and active targeting.[120,121] They exhibit higher signal on CT, enabling higher resolution and longer effective observation time windows.[121] Chen et al assembled heterobivalent (HB) peptide ligands onto the gold nanoprobe HB-Au-NPs, achieving good imaging results by specifically targeting EGFR and tyrosine kinase receptor 2 (ErbB2) overexpressed on the surface of EC cancer cells. They showed strong contrast in photoacoustic and CT imaging and have good biocompatibility.[122] In summary, the development of targeted nanoprobes has significantly enhanced the imaging effects of CT and MRI, providing more reliable technical support for the early diagnosis, accurate staging, and intraoperative navigation of EC.

Integrated Diagnosis-Treatment-Evaluation System

In the future development of nanoprobe technology, the most cutting-edge research direction is to integrate the three major functions of nanotechnology—diagnosis, treatment, and efficacy evaluation—onto a single nanoplatform, forming a three-in-one integrated diagnosis-treatment-evaluation nanosystem. This powerful system has unique advantages,[123] enabling tumor imaging while treating tumors, real-time and in-situ monitoring of nanoprobe distribution, drug release, and tumor response to treatment, achieving simultaneous diagnostic evaluation, targeted therapy, and dynamic monitoring. This will provide greater potential for personalized EC treatment in the future.[124]

The integrated system benefits from the development of nanomaterials science; its essence is the integration of different functional modules onto a single nanocarrier. The diagnostic module can be the aforementioned magnetic NPs, AuNPs, or UCNPs,[125,126] used for fluorescence imaging or MRI and CT. The therapeutic module can carry chemotherapy drugs, PDT agents, or gene therapy drugs. Its key advantage lies in responsive release and real-time feedback. Like many NPs, the integrated system is designed to respond to specific signals of the TME (such as acidic environment, specific enzymes) or physical stimuli (such as near-infrared light, magnetic field) to trigger the activation and release of the loaded drug.[127] This makes it precise and targeted in treatment, reducing damage to normal tissues, while the imaging module can be used to track the tissue distribution of NPs.

Currently, nanotherapeutic integration mainly presents three core forms: (1) single-platform nanosystems integrating imaging and treatment functions; (2) responsive systems based on TME or physical energy activation; (3) intelligent diagnostic and treatment modes based on molecular recognition and immune regulation. The former is represented by polymers, liposomes, metal nanomaterials, etc., which integrate MRI, PET, optical imaging with chemotherapy, gene therapy or PDT in the same nanodelivery system to achieve visualized drug delivery and simultaneous monitoring of efficacy. It is currently the most complete nanointegrated technology.[127,128] Secondly, activation-responsive systems triggered by pH, ROS, GSH, specific enzymes, or hypoxia can enable drugs to undergo structural depolymerization, enrichment, or imaging signal transformation within the tumor, thereby significantly reducing adverse reactions in patients; exogenous energy sources such as light, ultrasound, magnetic fields, or X-rays can further achieve precise nanoactivation therapy in both time and space dimensions.[23] At the same time, molecular recognition and immune regulation diagnostic and therapeutic systems have attracted widespread attention. For example, DNA barcode nanoparticles can

screen drug sensitivity in situ within the tumor, enabling personalized drug decisions within 72 hours;[24] nanobodies, due to their high affinity and small size, are widely used in PET/NIR imaging of targets such as PD-L1 and HER2, and can be combined with toxins, radionuclides, or cell therapy modules to achieve integrated immune monitoring and immunotherapy.[129] However, this technology still has gaps in the diagnosis and treatment of EC. Overall, these different forms have promoted the rapid development of nano-diagnostic and therapeutic integration towards precision, visualization, and personalization.

Challenges and Future Prospects

Although nanodelivery platforms have broad prospects in improving chemotherapy resistance, enhancing radiosensitivity, reducing adverse reactions in patients, and achieving integrated diagnosis and treatment in EC, most studies are still in the animal model stage and pre-clinical trial stage. Few nanoplatforms in the EC field are suitable for clinical treatment. To truly translate these laboratory results into clinical practice, efforts are still needed to overcome biological barriers, drug safety, and difficulties in clinical translation.

Current Core Challenges

The EPR effect faces significant biological barriers in real-world clinical translation. While early nanomedicine design primarily relied on the EPR effect for passive enrichment, mounting evidence suggests that the heterogeneity of human tumors far exceeds that of animal models, leading to a weakened or even absent effect in clinical patients. The EPR effect is significant in rapidly growing, highly vascularized, and loosely structured rodent xenografts, but it is difficult to replicate in human esophageal cancer.[130] EC tissues (mainly ESCC) typically have a high degree of fibrous tissue formation and are often accompanied by high interstitial pressure, which constitute a physical barrier to the tumor, hindering the downgradient penetration of NPs into the tumor core.[131] Furthermore, the reticuloendothelial system of organs such as the liver and spleen sequesters NPs, meaning the actual drug dose reaching the tumor site is often far lower than the total dose, resulting in low therapeutic efficiency.[132] Therefore, this dual barrier, composed of dense interstitial tissue and high interstitial pressure, severely limits the deep penetration and distribution of nanomedicines in the human body. This interspecies pathophysiological difference reasonably explains why many nanomedicines, which show significant efficacy in preclinical models, fail to achieve the expected therapeutic concentrations in clinical trials, and also demonstrates the limitations of relying solely on passive targeting strategies.

To move nanomaterials from the laboratory to clinical applications, the high barrier of biosafety must first be overcome. Although inorganic materials such as AuNPs, carbon nanotubes, and QDs have shown great potential in imaging and photothermal therapy, their bioinertness also poses risks. Most of these materials are difficult to degrade in vivo and tend to remain in the RES for extended periods. This accumulation effect may induce persistent chronic inflammatory responses and even lead to potential organ damage.[95,133] In particular, for nanoplatforms loaded with heavy metal elements (such as QDs), the core components pose a risk of nephrotoxicity, a problem that remains unsolved.

On the other hand, nanodelivery systems based on organic materials such as polymers or liposomes have relatively lower risks, but still warrant attention. Some synthetic materials may be recognized as foreign substances by the body's immune system, thereby activating the complement system and triggering complement activation-related pseudoallergy (CARPA).[133] Furthermore, the accelerated blood clearance (ABC) effect that may occur after repeated administration not only raises unknown safety concerns but also reduces the effectiveness of subsequent treatments, posing a pressing problem for cancer patients requiring multiple cycles of therapy.[134]

In terms of the clinical translation of nanomaterials, there is also a significant technological gap between laboratory preparation and large-scale production to meet clinical needs. This is particularly true for therapeutic nanosystems, where the complexity of the preparation technology makes mass production extremely difficult. These systems typically integrate multiple functional modules, and their complex synthesis processes amplify uncertainties in the production process, making it extremely difficult to maintain high consistency in particle size distribution, drug loading efficiency, and surface chemical modification between different batches.[135] This complexity and batch-to-batch variation also present significant challenges to the establishment of pharmacokinetic assessment and quality control standards, leading

regulatory agencies to be more cautious in approving such cutting-edge drugs. High development costs and long approval cycles also make pharmaceutical companies hesitant to invest in complex nanomedicines.

Future Development Directions

Bionic Camouflage and Active Targeting: To effectively circumvent the phagocytic clearance of the RES system and improve tumor targeting efficiency, researchers have drawn inspiration from natural cells and developed cell membrane biomimetic camouflage technology.[136] By coating the surface of an EC cell membrane onto the nanocarrier, its homology recognition properties can be utilized to achieve precise localization of primary and metastatic lesions, while simultaneously camouflaging itself as an autologous cell to evade immune surveillance. Future exploration will focus on hybrid cell membrane strategies, such as combining the long-circulation characteristics of erythrocyte membranes with the targeting capabilities of cancer cell membranes, aiming to create "super" nanocarriers with more powerful delivery performance.[137]

Logic-Gated Intelligent Response Systems: Single physicochemical signal responses (such as pH or specific enzymes) are insufficient in complex TMEs to meet the requirements for precise drug activation. The design of next-generation nanoplatforms will incorporate the concept of logic gating, giving them stronger environmental recognition capabilities. For example, a drug delivery system can be constructed that releases drugs only when both "low pH" and "high GSH" conditions are met simultaneously, thereby greatly avoiding premature drug release and toxic side effects in non-target areas such as normal esophageal mucosa.[138] Based on this, developing smart hydrogel-nanocomposite formulations with mucosal adhesion for oral administration or endoscopic local spraying is a promising method for improving local drug concentration and reducing systemic toxicity.[139]

Reshaping the tumor microenvironment and synergistic immunotherapy: The current treatment concept for EC has shifted from simply killing tumor cells to the more complex regulation of TME. Future nanomedicines will not only be used for drug delivery but also as TME modulators. The envisioned multifunctional nanosystems will be able to actively alleviate tumor hypoxia to sensitize radiotherapy, chemotherapy, or PDT,[140] or activate anti-tumor immunity by inducing ICD, or even transform immunosuppressive M2 tumor-associated macrophages into pro-immune M1 macrophages.[141] The integration of this type of nanotechnology with ICB therapy is expected to transform "cold tumors" like EC, which have poor immune responses, into "hot tumors" that are easily attacked by the immune system.

Green manufacturing and innovation of supercritical fluid technology: Supercritical fluid (SCF) technology is becoming a highly competitive solution to address the industrial bottlenecks in the clinical translation of nanomedicines, such as complex preparation processes, large batch-to-batch variations, and residual organic solvents.[142] In particular, supercritical carbon dioxide ($scCO_2$) assisted technology, with its unique gas-like diffusion and liquid-like solubility, can achieve efficient drug encapsulation under mild conditions. Compared with traditional preparation methods, the biggest advantage of SCF technology lies in its "green" attribute-it can significantly reduce or even completely eliminate the use of toxic organic solvents, reducing the toxicity risk of drugs from the source. Future research will focus on one-step synthesis strategies using SCF technology, such as through supercritical antisolvent (SAS) or rapidly expanding supercritical solution (RESS) processes, to precisely control the crystal form, particle size distribution, and surface morphology of nanoparticles. This not only significantly improves the drug loading and stability of esophageal cancer nanomedicines, but more importantly, the SCF process is easy to scale up for production, ensuring high consistency across different batches. This provides an efficient, environmentally friendly, and economically feasible technological path for nanomedicines to move from the laboratory to GMP-standardized industrial production.

Towards Personalized Precision Nanomedicine: With the rapid development of genomics and proteomics technologies, the design philosophy of nanomedicines is shifting from "universality" to "personalization". Using patient-derived organoids (PDOs) models constructed using microfluidic technology, we can rapidly and efficiently screen for optimal nanomedicine formulations for specific patients in vitro,[143,144] including but not limited to optimal particle size, targeting ligands, and drug combination schemes. This new paradigm of customized treatment aligns with the initial goal of "therapeutic integration," and this nanotechnology will lead EC treatment towards personalized precision medicine.

Conclusion

In summary, nanodelivery technology has evolved from a single drug carrier into an intelligent, multifunctional platform, fundamentally reshaping the landscape of esophageal cancer diagnosis and treatment. Its core breakthrough lies in achieving an integrated diagnosis and treatment strategy, significantly improving the efficiency and safety of targeted drug delivery and providing clinicians with real-time, visualized, and precise monitoring capabilities. Faced with the complex anatomical structure and immune microenvironment of esophageal cancer, nanotechnology demonstrates potential advantages over traditional therapies in synergistic effects with radiotherapy and chemotherapy, photodynamic therapy, and immune activation. In the future, as related research deepens its translation into clinical applications, nanotechnology is expected to become a key force in overcoming the bottlenecks in esophageal cancer treatment and achieving personalized precision medicine.

However, we must remain vigilant: Currently, the vast majority of esophageal cancer nanomedicines are still in the preclinical or early clinical stages, and there is still a long way to go before they are widely approved in clinical practice. Regulatory approval and large-scale production remain huge challenges. Additionally, a significant gap still exists between the microscopic design at the laboratory level and the macroscopic benefits at the clinical application level. Potential risks to biosafety, standardization challenges in industrial production, and the high heterogeneity of tumors themselves remain formidable challenges in translational research. Current research findings are largely based on animal models, and a lengthy validation period is still required before they can be readily applied in clinical settings. The key to future breakthroughs lies in deep interdisciplinary collaboration among materials science, pharmacology, tumor biology, and clinical medicine. We must, on the foundation of ensuring safety, utilize cutting-edge methods such as organoid screening to conduct more rigorous preclinical evaluations of nanodesign, thereby overcoming translational difficulties. With technological iteration and the deepening of translational research, nanomedicine is expected to become a significant emerging force in conquering endemic tumors (EC), bringing substantial breakthroughs in extending patient survival and improving quality of life.

Abbreviations

EC, Esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; PD-1/PD-L1, Programmed cell death protein 1/programmed cell death ligand 1; NP, Nanoparticle; EPR, enhanced permeability and retention; ICIs, immune checkpoint inhibitors; Nab-PTX, albumin-bound paclitaxel; ORR, objective response rate; EGFR, epidermal growth factor receptor; MDR, multidrug resistance; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; TKIs, tyrosine kinase inhibitors; TME, tumor microenvironment; ROS, reactive oxygen species; DSBs, double-strand breaks; PDT, photodynamic therapy; PS, photosensitizers; PDD, photodynamic diagnosis; GSH, glutathione; PTT, photothermal therapy; CDs, carbon dots; ICB, immune checkpoint blockade; IL-2, interleukin-2; DOX, doxorubicin; DCs, dendritic cells; APCs, antigen-presenting cells; CTLs, cytotoxic T lymphocytes; ICD, immunogenic cell death; HDL, high-density lipoprotein; siRNA, small interfering RNA; miRNA, microRNA; RNAi, RNA interference; PEI, polyethyleneimine; PBAE, poly-β-amino ester; QDs, quantum dots; UCNPs, upconversion nanoparticles; NIR, near-infrared; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; SPIONs, Superparamagnetic iron oxide nanoparticles; MRI, magnetic resonance imaging; AuNPs, Gold nanoparticles; HB, heterobivalent; RES, reticuloendothelial system; CARPA, complement activation-related pseudoallergy; ABC, accelerated blood clearance; SCF, Supercritical fluid; $scCO_2$, supercritical carbon dioxide; SAS, supercritical antisolvent; RESS, rapidly expanding supercritical solution; PDOs, patient-derived organoids.

Acknowledgments

Figures 1–4 were drawn by using templates from Biorender.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors report no conflicts of interest in this work.

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