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REVIEW

Advances in Nanotechnology in the Diagnosis and Treatment of Gynecological Cancers

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Abstract: Nanotechnology platforms facilitate therapeutic drug delivery and offer various advantages over conventional drugs, such as biocompatibility, non-inflammatory effects, high therapeutic output, biodegradability, non-toxicity, and biocompatibility. Due to the inherent drawbacks of conventional drug delivery to cancerous tissues, nanotechnology-based alternatives have been developed for such diseases. Gynecologic malignant tumors (GCs), include various types of cervical, endometrial, and ovarian cancers. The epidemiological characteristics of the tumors show that their incidence is increasing significantly and tends to be younger, which is a serious threat to women's physical and mental health. This article provides a systematic review of the latest research results on nanomaterials in the diagnosis and treatment of gynecological malignancies, including 2 sections on nanomaterials-based diagnostic and therapeutic strategies in gynecological cancers. In particular, the article also analyzes the challenges faced by nanotechnology, including toxicity, technology, and clinical translation issues. These applications not only improve the therapeutic efficacy of gynecological cancers, but also reduce the toxicity and side effects, and provide a new direction for the precise treatment of gynecological cancers.

Keywords: gynecologic cancer, nanomaterials, diagnosis, treatment, emerging tools

Introduction

The Current Situation of Gynecological Cancer

Nowadays, the three major gynecological malignancies, ovarian cancer, cervical cancer and endometrial cancer, together constitute a heavy disease burden.[1–3] Ovarian cancer has the highest mortality rate among gynecologic malignancies.[4] Cervical cancer is the most common malignancy in gynecology and the fourth leading cause of cancer deaths in women worldwide.[5] Although the incidence of cervical cancer has declined in many regions over the past three decades, its global incidence and burden remain high.[6] In addition, endometrial cancer has increased in incidence and age of onset, significantly affecting female fertility and quality of life.[7]

Significance of Nanomaterials in Gynecological Cancer Diagnosis and Treatment

For patients after tumor reduction surgery, chemotherapy with platinum-based drugs and paclitaxel is the currently recommended treatment of choice. However, the survival rate of patients with advanced gynecologic cancers is still unsatisfactory due to the problems of late diagnosis and chemotherapy resistance and tumor recurrence, invasion, and metastasis.[8] Late diagnosis of advanced gynecologic cancers and limited treatment options are key factors contributing to high mortality rates, thus highlighting the need and urgency for further research and development in this area.[9]

Nanotechnology has emerged as a promising field that offers great solutions to the limitations of conventional therapies.[10] Nanomaterial-based targeted drug delivery systems, biosensors, and thermotherapy offer more options for cancer patients than conventional surgery, chemotherapy, and radiotherapy.[11,12] These technologies demonstrate significant potential in treating gynecological malignancies, enabling the reduction of toxicity, enhancement of therapeutic efficacy, suppression of cancer cell metastasis, and countering drug resistance.[13–15] In recent years a variety of novel

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nano-delivery systems have been developed for the treatment of gynecological malignant tumors,[15] such as targeted nano-delivery systems, tumor microenvironment-specific drug release systems, nano-probes, nano-sensors, nanoimaging technology and other diagnostics, in addition, emerging technologies such as vaccines designed from nanomaterials have also demonstrated great potentials in the field of gynecological cancer.

Types of Nanomaterials

Nanomaterials used in the biomedical field can be broadly categorized into two main groups, organic and inorganic, based on their composition.[16] Organic nanoparticles, including lipid nanoparticles and polymer nanoparticles, are synthesized from carbon-containing organic molecules. In contrast, inorganic nanoparticles are usually made from non-carbon-based compounds, such as metals and metalloids. These inorganic nanoparticles are further classified into oxide nanoparticles and non-oxide nanoparticles (Figure 1). In conclusion, the unique physicochemical properties of nanomaterials provide new avenues and strategies for cancer diagnosis and treatment. Nanomaterials provide customized solutions for targeted drug delivery, cancer immunotherapy, imaging/biosensing, and therapy monitoring.[17,18] However, further studies on their in vivo metabolism, toxicological properties and long-term safety are needed.

In this review, we first explore a variety of diagnostic techniques using nanomaterials as carriers, covering areas such as ultrasound imaging, magnetic resonance imaging, fluorescent probes, and biosensors. Next, we present recent developments in nanotechnology-based therapeutic strategies, including targeted drug delivery systems, external energy-coordinated therapeutics for the treatment of gynecological cancers, and emerging nanovaccine technologies. Finally, we look at the future prospects of nanomaterials in the field of gynecologic cancer therapy and the challenges they face.

Nanomaterials for Diagnosis and Treatment of Gynecological Cancers

Diagnostics

The application of nanostructured materials in gynecological cancer diagnosis mainly includes the use of their high sensitivity, high specificity and biocompatibility to achieve precise detection and localization of tumor cells by means of nanoprobes, nanosensors, and nanoimaging techniques (Figure 2).

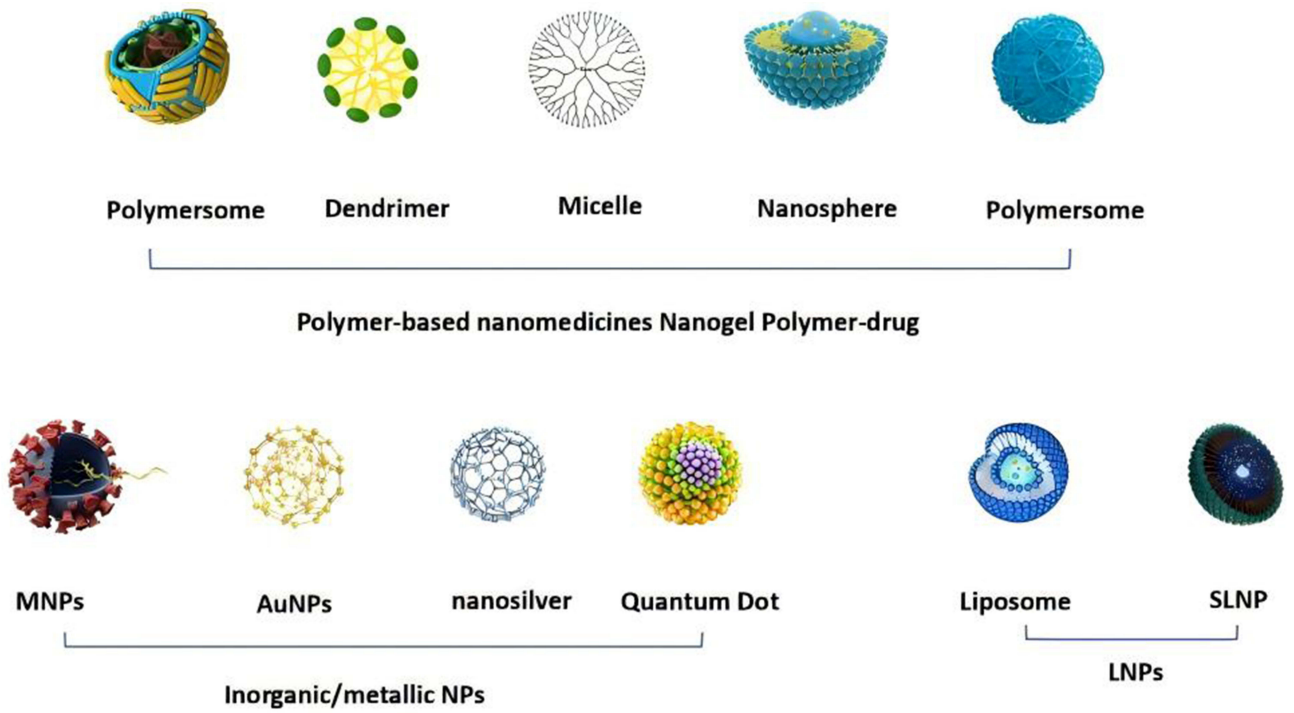

Figure 1 Graphical summary of commonly reported nanomedicines. Abbreviations: np, nanoparticles; LNPs, lipid nanoparticles; SLNP, solid lipid nanoparticles. Created in BioRender. ruimin, z. (2025) https://BioRender.com/ih6xhrk.

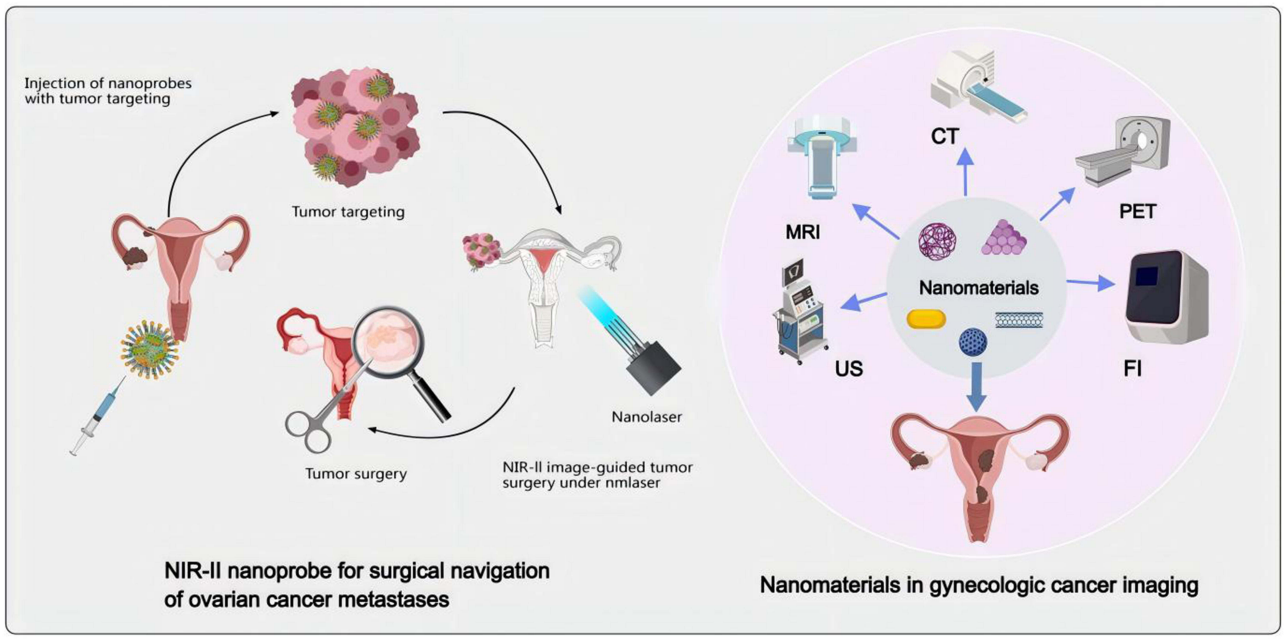

Figure 2 Graphical summary of diagnostic methods of common nanomaterials. Created in BioRender. ruimin, z. (2025) https://BioRender.com/fdqlyi8.

Application of Nanoprobes in Surgical Tracing of Gynecological Cancer

Nanoprobes are able to specifically identify tumor cells and achieve precise localization of tumor tissues by techniques such as Fluorescence Imaging (FI).[19] Nanoprobes have great potential in the diagnosis, treatment monitoring and surgical navigation of gynecological cancers, especially ovarian cancer. During surgical resection of ovarian cancer models, nanoprobe-labeled fluorescence imaging provides real-time, high-resolution, and high-specificity detection advantages over conventional visual inspection and preoperative imaging. For example, Tao Pu et al[20] synthesized NIR-II down-converted rare-earth nanoparticles (DCNPs) by taking advantage of the deep tissue penetration and low autofluorescence of near-infrared two-region fluorescent probes (NIR-II,1000–1700 nm) and modified paired DNA and targeting proteins on their surfaces, which enabled long-term and stable labeling of the probes within the tumor. The application of this technique greatly improves the signal-to-noise ratio of optical imaging, enabling the successful resection of tiny lesions (≤1 mm) in peritoneal metastasis models of ovarian cancer under the guidance of near-infrared imaging, which improves the precision and safety of surgery. In addition, the results of this research also indicate that the probe molecules obtained from the modification of target proteins and complementary DNA are expected to achieve precise resection of early lesions of peritoneal metastasis of ovarian cancer as well as lymph node metastatic tumors under the guidance of fluorescence imaging. The results of this preclinical trial demonstrate the enormous potential of nanoprobes in surgical navigation for gynecological cancers, especially in improving surgical precision and reducing healthy tissue damage. In the future, this technique may be further optimized and more extensively tested in ex vivo models for eventual clinical application.

It has been shown that folate receptor-α (FR-α) has elevated tumor tissue expression in 76–89% of patients with epithelial ovarian cancer;[21,22] meanwhile, it is barely expressed in normal ovarian epithelium.[23,24] Therefore, when it is combined with fluorescent dyes, the background fluorescence level of the healthy tissues is low, making it an ideal target for intraoperative imaging. In addition, chemotherapy does not affect FR-α expression, so application of this protein allows targeting tumor tissues during primary and interstitial tumor cytoreduction.[25,26] FA-ICG liposomes are smart nanoprobes that combine folate receptor targeting (FR-α) and near-infrared fluorescence imaging (NIR),[27] primarily used for real-time tumor localization, margin delineation, and metastasis detection during ovarian cancer surgery. Ovarian cancer cells often overexpress folate receptor α (FRα) on their surfaces. FA-ICG liposomes can specifically bind to FRα, creating a distinct contrast between tumor tissue and normal tissue. Compared to traditional ICG, the lipid-encapsulated

formulation enhances the stability and penetration of the fluorescent signal, enabling clearer visualization of microscopic metastatic lesions.[28] Under the assistance of a near-infrared fluorescence imaging system, FA-ICG liposomes can real-time mark tumor boundaries and occult lesions, aiding surgeons in precise tumor resection, reducing residual lesions, and lowering the risk of postoperative recurrence.[29] Clinical studies have shown that this technology can significantly improve the R0 resection rate (no residual cancer cells at the tumor margin). Currently, FA-ICG liposome-related technology is in the clinical research stage, and some research findings have confirmed its effectiveness in ovarian cancer surgical navigation. If validated through large-scale clinical trials in the future, it has the potential to become an important auxiliary tool for precise ovarian cancer surgery.[30]

Nanosensors for Gynecologic Cancer Biomarkers

Nanosensors are small devices that can be implanted inside the human body to monitor changes in biomarkers in real time,[31] such as circulating tumor cells (CTCs), tumor exosomes, and microscopic nucleic acids (miRNAs).[32] Recent advances in nanotechnology have led to the development of highly sensitive nanobiosensors in recent years, and ultrasensitive nanobiosensors are used to improve the sensitivity and accuracy of cancer biomarker detection.[18] Recently, many scientists have focused their attention on volatile organic compounds (VOCs). These are gaseous molecules that are easily collected from the breath as they travel from the bloodstream into the lungs and also from the bloodstream into the urine. They can provide information on a wide range of diseases.[33–35] Nanobiosensors can enable early detection of tumors by detecting volatile organic compounds (VOCs) in a patient's breath.[36] Several studies by Horvath et al have shown that human ovarian cancer has a specific odor.[37,38] Prof. HAICK's team, which detects ovarian cancer through exhaled breath samples, diagnosed the disease by measuring changes in electrical resistance through the development of a sensor array integrating aromatic ligands and gold nanoparticles that react with VOCs associated with ovarian cancer. The nano-array measured VOCs with good sensitivity (79%) and specificity (100%) in detecting ovarian cancer patients compared to controls. It also differentiated well between early and advanced ovarian cancer. Not only does this sensor provide high diagnostic accuracy, it also simplifies device design from the traditional need for multiple sensors to just one sensor, while maintaining high performance.[39] In addition, emerging nanotechnologies such as carbon nanotube nanosensor arrays targeting ovarian cancer show great potential for application.[40] With further research and optimization of the technology, it is expected to revolutionize the early diagnosis and treatment of cancer.

Nanoparticles in Gynecologic Cancer Imaging

Imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-CT (PET-CT) are widely used for diagnosis and staging.[41–43] However, these methods exhibit low resolution, insufficient for tiny tumor (<5 mm) detection and long acquisition times.[43] Nanomaterials show great promise for imaging gynecologic cancers. Nanoparticles as imaging contrast agents can significantly improve the accuracy and efficiency of imaging, especially in the visualization and diagnosis of ovarian cancer. A large number of published articles have reported the application of nanomaterials in gynecological cancer imaging. It has been shown that the use of nanoparticles as a biomarker detection platform can greatly enhance the diagnostic efficiency and accuracy of gynecological cancers. Currently, imaging techniques used for the diagnosis and treatment of various diseases include Fluorescence imaging (FI), Magnetic resonance imaging (MRI), X-ray computed tomography (CTI), photoacoustic imaging (PAI), and positron emission tomography (PETI).

Specifically, the use of quantum dots coupled with specific antibodies allows specific binding of cancer biomarkers such as CA-125 at the cellular level, resulting in the detection of trace amounts of cancer-associated proteins through the enhancement of fluorescent signals.[44] Chitosan is a carrier in NPs and is used as a drug delivery agent with multiple delivery options. Studies have shown that chitosan-based NPs are suitable for parenteral drug delivery for a variety of diseases, including cancer, gastrointestinal diseases, lung diseases, and brain and eye infections. A recent study in a mouse model of ovarian cancer investigated a positron emission tomography (PET) agent composed of chitosan and poly(γ-glutamic acid).The NP reagent was radiolabeled with 68 Ga ions. Both in vitro and in vivo tests confirmed that the absorption of the drug is mediated by the folate receptor. In summary, the results suggest that this NP could be used for

diagnostic purposes in cancers that overexpress the folate receptor.[45] In addition, Jinsui et al[46] prepared an NP consisting of carboxymethylhexanoyl chitosan and perfluoropentane, an ultrasonic gas precursor. The results showed that carboxymethyl-hexanoyl chitosan-perfluoropentane-DOX was absorbed by tumor tissues. In addition, it can be used as an ultrasound visualizer at body temperature. In addition, the combination of ultrasound with this drug resulted in an enhanced killing effect of chemotherapy. Thus, this NP is able to be an agent for imaging and drug delivery.

In summary, nanomaterials are playing an increasingly important role in the diagnosis of gynecologic cancers, not only improving diagnostic accuracy, but also providing new methods for treatment. The development of these technologies heralds a new stage in the management of gynecologic cancers.[47]

Therapeutic

In the field of gynecologic oncology therapy, nanotechnology has unique advantages especially in improving the targeting of therapeutic agents and reducing systemic toxic side effects.Specifically, approaches based on nanomaterials improve the delivery of therapeutic/targeting agents to tumor sites and cellular uptake, thereby enhancing tumor suppression efficacy.[48,49] In the field of gynecology, nanotechnology-based therapeutic approaches are advancing rapidly, overcoming inherent limitations of traditional cancer diagnostics and treatments. They hold broad prospects across chemotherapy, radiotherapy, phototherapy, chemodynamic therapy, immunotherapy, and combination therapies (Figure 3).

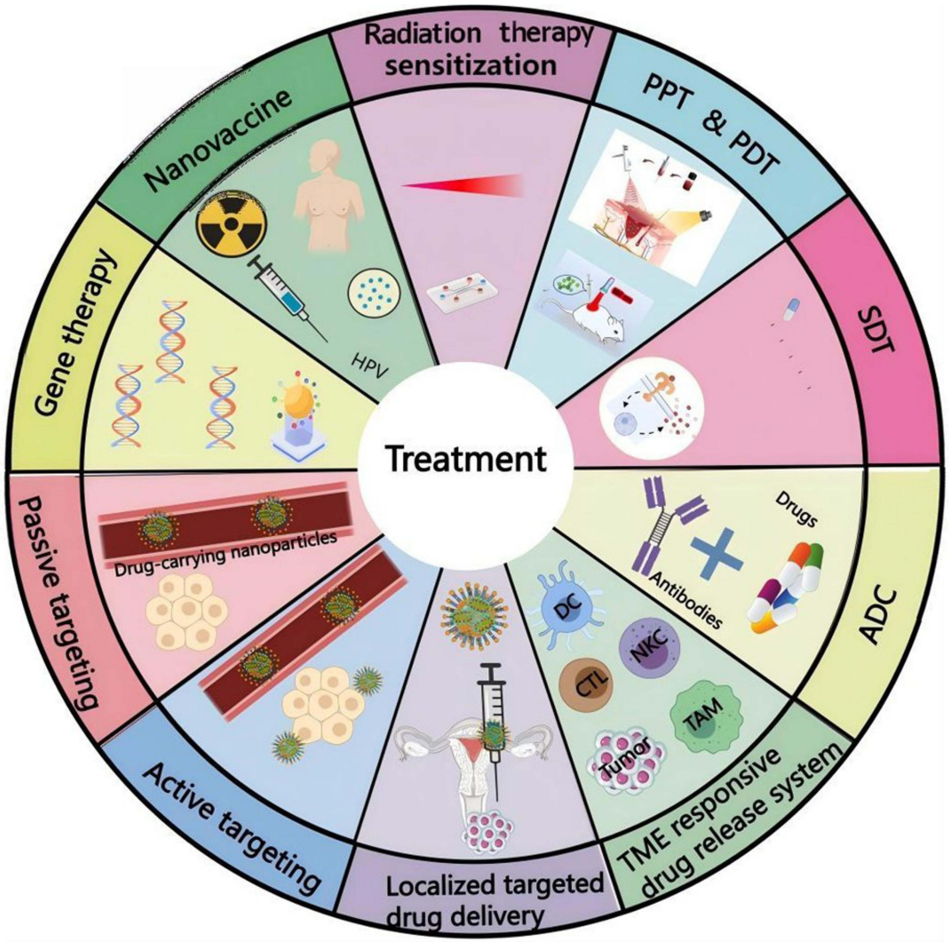

Figure 3 A graphical summary of common treatment methods for nanomedicines. Created in BioRender. ruimin, z. (2025) https://BioRender.com/ ow2dbw9.
Abbreviations: ADC, Antibody-Drug Conjugate; PDT, Photodynamic Therapy; PTT, Photothermal Therapy; TME, Tumor Microenvironments; SDT, Sonodynamic Therapy.

Nanocarrier Drug Delivery Systems

The rapid development of nanotechnology has provided new strategies for targeted therapy of gynecological cancers. Currently, a variety of nanoparticle drug delivery systems (NDDS) have been developed due to their advantages of improving drug pharmacokinetics, reducing drug side effects, inhibiting cancer cell metastasis, mitigating drug resistance, and combining therapies.[50,51]

For example, one study developed an injectable nanohydrogel by combining carboxymethyl chitosan (CMCS) with poly(lactic acid)-hyperbranched polyglycerol-based bioadhesive nanoparticles (BNPs). This system enables co-delivery of CD and ICI in the intraperitoneal cavity and prolongs drug retention time. In a mouse model, BNP/CMCS nanohydrogels loaded with paclitaxel (PTX) and anti-PD-1 antibody (αPD-1) significantly inhibited the peritoneal translocation of OC compared to all other tested groups. Thus, BNP/CMCS nanohydrogel as a drug delivery system can effectively co-deliver PTX and αPD-1 into the peritoneal cavity and improve the therapeutic efficacy of peritoneal metastasis of ovarian cancer, while decreasing the systemic side effects (inhibition of metastasis).[52] Chemotherapy is an important treatment for ovarian cancer, but the emergence of multidrug resistance (MDR) is the main reason for chemotherapy failure. Recently, a study has found a way to reverse MDR in ovarian cancer by developing a novel hyaluronic acid (HA)-targeted modified mesoporous silica-coated gold nanorods co-delivery system (HA-PTX/let-7a-GNR@MSN), which utilizes hyaluronic acid as a ligand for the cd44 protein, which is highly expressed on the surface of ovarian cancer cells, and enhances the endocytosis efficiently through ligand-receptor mutual recognition, forming a specifically targeted nano-delivery system with nearly 300% increase in tumor site uptake and a better inhibition of ovarian cancer proliferation in vitro. In the spf skov3tr balb/c-nu mouse subcutaneous tumor model, the nanosystem showed better therapeutic efficacy in reducing pgp levels in ovarian cancer tissues, reversing drug resistance, and enhancing the chemotherapeutic efficacy of paclitaxel (reducing drug resistance).[53]

In gynecological cancers, nanomaterials enhance drug delivery to the tumor site (enhanced delivery) in a variety of ways, eg, nanocarriers are able to take advantage of the enhanced permeability and retention effect (EPR) of cancer tissues to achieve passive targeting of tumors, thereby reducing toxic damage to normal tissues (passively targeted nanomedicine systems). At the same time, specific ligands or antibodies can be modified on the surface of the nanoparticles to achieve active targeting of tumor-specific biomarkers, further enhancing therapeutic selectivity (actively targeted nanomedicine system).[54] In the field of drug release, smart nanosystems, ie, tumor microenvironment responsive drug release systems, have been developed to address pH, enzyme, or redox conditions specific to the tumor microenvironment. The aim is to ensure that the drug is released under appropriate temporal and spatial conditions to maximize efficacy and minimize adverse effects. In addition, as drug therapy for cervical cancer faces challenges such as insufficient drug distribution at the focal site after systemic administration and severe side effects. Localized drug delivery is also an effective mode of drug delivery (local drug delivery system) (Figure 4).

Ebeid et al reported that[55] enhanced the therapeutic efficacy of paclitaxel (PTX) in uterine plasmacytoid carcinoma with mutant p53 through the use of polymeric nanoparticles (NPs), and that the optimal NP formulation was identified through a comprehensive analysis of release profiles, cellular uptake, and cell viability studies. Not only did PTX-loaded NPs outperform PTX in solution, but the combination of PTX-loaded NPs with the anti-angiogenic molecule inhibitor BIBF 1120 (BIBF) specifically triggered synthetic lethality in loss-of-function (LOF) p53 mutant cells. Experimental results showed that PTX-loaded lactic acid-hydroxyacetic acid copolymer (PLGA) nanoparticles (NPs) successfully aggregated in endometrial cancer tissues with the aid of the EPR effect, significantly inhibited tumor growth, and effectively prolonged survival.

Free paclitaxel is often used as a first-line treatment for ovarian cancer.[56] It is dissolved in Cremophor EL, which is a major cause of allergic reactions to paclitaxel. ABI-007 (Abraxane) is an albumin-conjugated 130 nm paclitaxel particle designed to reduce Cremophor-based Cremophor /ethanol toxicity and through albumin receptor-mediated endothelial transport.[57] ABI-007 utilizes nanotechnology to deliver paclitaxel to directly target cancer cells through an albumin-mediated receptor mechanism. This mechanism involves the gp60 receptor, which allows active drug transport in microvascular endothelial cells. Albumin binds to the gp60 receptor on endothelial cells, activating vesicle protein-1 and forming vesicles. These vesicles carry the albumin-drug complex and other fluid-phase components across the

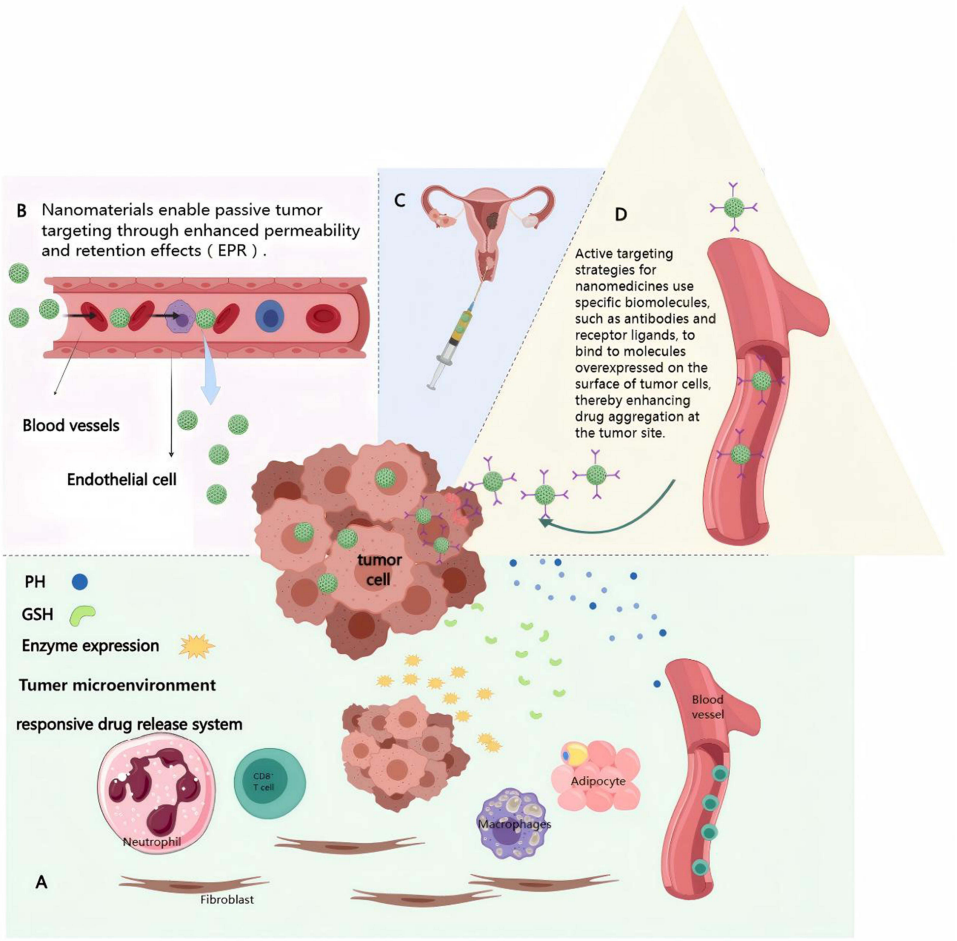

Figure 4 Common nano-loaded drug delivery systems: (**A**) Tumor microenvironment-responsive drug release system (**B**) Passively targeted nanomedicine system. (**C**) Localized drug delivery system (**D**) Active targeted nanomedicine system. Created in BioRender. ruimin, z. (2025) https://BioRender.com/ww86iuf.

endothelium and into the tumor mesenchyme by means of active transport,[58] and bind to SPARC proteins on the surface of the tumor tissue to inhibit the growth of cancer cells (or to induce apoptosis).[59]

Adriamycin is widely used in the treatment of gynecological cancers, especially ovarian cancer, and works by interfering with DNA and RNA synthesis in tumor cells, and nano-delivery systems based on natural materials are an effective way to overcome drug resistance.[60] There have been attempts to introduce synthetic poly(γ-benzyl-L-glutamic acid) (PBLG) onto silk-glue protein peptides to create simple biocompatible and biodegradable capsules.[60] Sericin-PBLG -DOX has high loading and pH-responsive release properties that improve cellular uptake of adriamycin (DOX). Silk-gelatin-PBLG-DOX releases DOX in perinuclear lysosomes, and in vitro and in vivo experiments have shown its antitumor effect to be superior to that of DOX alone.These micelles exhibit good biosafety, enhanced cellular uptake, pH-triggered drug release, potent antitumor effects, and minimal endo-drug use, heralding the potential for overcoming drug resistance in cancer therapy.

Garbuzenko et al introduced an advanced nanotechnology-based strategy for personalized treatment of ovarian cancer based on the individual genetic profile of the patient's tumor.[61] Through a delivery system based on targeted nanoparticles, the most effective siRNA and anticancer drugs were selected for each patient. These personalized treatment regimens were demonstrated to significantly suppress drug resistance, block tumor progression, prevent metastasis, and reduce the adverse side effects commonly associated with traditional therapies.[62,63]

Compared with oral and injectable routes, novel nanocarrier-based drug delivery systems can also enhance drug absorption through localized delivery to effectively reduce drug toxicity and improve therapeutic efficacy, especially for

gynecological cancers such as cervical and peritoneal cancers. Inadequate drug distribution within the tumor and severe adverse effects are usually associated with systemic chemotherapy for cervical cancer. Considering the location of cervical cancer, vaginal access to the cervix may provide an alternative route of drug delivery for high doses of drugs at the tumor site, minimal systemic exposure, and the convenience of noninvasive self-administration. Hydrogels exhibit various advantages in terms of physicochemical and biological properties, which make them promising vaginal drug delivery systems. Especially for vaginal delivery, hydrogels are considered to be one of the most effective carriers due to their excellent viscosity and lubricating properties. Researchers have proposed a nanoparticle-hydrogel composite system to overcome this drawback, which contains mucus-penetrating nanoparticles in a mucosal-adherent hydrogel. These composite systems utilize nanoparticles and hydrogels to improve drug retention time and penetration, accelerate drug absorption into the vagina, and ultimately improve the treatment of vaginal infections.[64] Schubert et al doped liposomes into polyacrylate gels to overcome the drawbacks of hydrogel instability and achieve longer retention times. In vitro release studies showed that due to the hydrophilic and bioadhesive nature of hydrogels, liposomes doped into the gels achieved sufficient stability and desirable viscosity at low pH (pH 4.0 to 5.0), which may be promising for vaginal drug delivery. The results showed that less than 40% of the encapsulated drug was released from the liposomal gel after incubation in buffer at pH 4.5 for 24 h. Ning et al improved the physical stability of the liposomes by preparing the liposomal system into a 2% Carbopol gel.[65]

In addition, nanomaterials can enhance the cellular uptake of drugs to the tumor site in a variety of ways, such as transcytosis based on receptor-mediated or adsorption, and some studies have used specific receptor modifications of nanomaterials such as the CD44 receptor, which is highly expressed in ovarian cancer cells. Metal-ligand polymer nanoparticles (ha@pfg nps) coated with hyaluronic acid (HA) bind specifically to the CD44 receptor, leading to active targeting and a significant increase in cellular uptake efficiency.[66] In tumor microenvironments such as ovarian cancer intracellular glutathione (GSH) concentration is 2–3 orders of magnitude higher than extracellular. Based on this, redox-sensitive nanomicelles, such as ptx-ss-tmp-nps, can be constructed, and under the action of high GSH concentration in tumor cells, the disulfide bond breaks, and the nanosystem rapidly depolymerizes, releasing the drug, while at the same time the charge of the nanomaterials is changed and electrostatic adsorption with the cell membrane is generated, promoting the drug uptake into the tumor cells.[67] In addition, many nanomaterials such as liposomes and polymer nanoparticles are biocompatible and can reduce the risk of being recognized and cleared by the immune system while circulating in the body. For example, with polyethylene glycol (PEG)-modified nanoparticles, the PEG chains can form a protective film on the surface of the nanoparticles, which makes the surface properties of the nanoparticles hydrophilic and reduces its recognition by immune cells, thus prolonging the nanoparticle's circulating time in the body, and increasing its chances of reaching the tumor site, which in turn improves the drug's uptake in the tumor cells.Ding et al have investigated and synthesized the pH-sensitive Ding et al synthesized a pH-sensitive amphiphilic copolymer, poly(ethylene glycol)-poly(diisopropylamino)ethyl methacrylate (mPEG-PDPA), and then encapsulated the hydrophobic anti-apoptotic B-lymphoblastoma-2 inhibitor, navitoclax, and the hydrophilic chemotherapeutic drug, DOX, into the membranes and lumens, respectively, of nano-vacuoles formed by self-assembly of mPEG-PDPA. Environment-triggered release and the combined delivery of DOX and navitoclax enabled the nanomedicines to show superior anticancer efficacy and lower toxic side effects in endometrial cancer treatment.[68]

External Energy Assisted Drug Release System

Nanomaterial-mediated externally activated therapeutic modalities, as an alternative therapeutic modality that relies on the transfer of energy to generate or release reactive oxygen species (ROS) from energy-converting therapeutic agents in response to external stimuli including light, ultrasound, radiation, and magnetic fields,[69–71] thermotherapy, photovoltaics, Compton's effect, cavitation, mechanical effects, or apoptosis/necrosis induced by the microwave electric field of chemotherapeutic drugs, or radio frequency The term "energy conversion nanomedicine",[72–74] includes photodynamic therapy (PDT) and photothermal therapy (PTT) triggered by single near-infrared (NIR) light,[75,76] destroys cancer cells by photothermal or photodynamic therapy under light irradiation of a specific wavelength,[76] thereby making non-invasive therapeutic strategies provide new insights into the treatment of gynecologic cancers.[77]

The study used polyethylene glycol-modified WS2 nanosheets as nanocarriers loaded with adriamycin and doped with the NIR fluorescent probe indocyanine green. A novel biomimetic system (WID@M-FA NPs) with high biocompatibility, prolonged circulation time, and significant NIR photothermal function was developed for targeted therapy of cervical cancer through erythrocyte membrane and folate molecule modification. In vitro tests showed that the photothermal effect of ICG enhanced drug cell uptake and tumor cell killing efficiency. Targeted accumulation and synergistic treatment of DOX in cervical cancer tissues resulted in tumor elimination rates of more than 95%, with no side effects on normal tissues. These results suggest that WID@M-FA NPs may be an effective therapeutic modality for cervical cancer.[78]

Although PDT and PTT are effective in treating a wide range of cancers, they have limited effect on deep-seated tumors.SDT is an emerging noninvasive therapy that triggers apoptosis/necrosis of cancer cells by generating cytotoxic ROS from acoustic sensitizers stimulated by low-intensity ultrasound.[79] Conventional light-triggered PDT is usually limited to the treatment of superficial tumors due to the poor tissue penetration of NIR light in deep tumors. Compared with NIR lasers, ultrasound offers low tissue attenuation, high precision, minimal invasiveness, and ideal biocompatibility, allowing for deeper penetration into biological tissues with less energy attenuation and the ability to activate acoustic sensitizers with greater spatial precision.[80–82] AgNPs are one of the most discussed nanomaterials in medicine, with applications ranging from antimicrobial to biomedical diagnostics.[83,84] Studies have shown that Ag nanoclusters can be activated by exogenous visible light to generate ROS for PDT, leading to apoptosis or necrosis of cancer cells.[85] However, PDT is not suitable for deep site tumors due to its limited light penetration depth. Therefore, there is a need to explore the SDT effect of Ag NPs for effective cancer therapy.Bernard et al[86] investigated the effects of applying a therapeutic ultrasound field in the presence of <100 nm silver nanoparticles on human ovarian cancer cells A2780. The results showed that the combined effect of the ultrasound field and silver nanoparticles significantly reduced cell viability compared to exposure to silver nanoparticles or the ultrasound field alone. In the presence of silver nanoparticles, the ultrasound field significantly affected cell viability.

Overall, external energy synergistic therapy has the advantages of being minimally invasive, highly targeted and low toxicity, and enhances targeted delivery and localized release of chemotherapeutic agents. However, its disadvantage is that it may cause side effects at the radiation site, such as burning sensation, pain and edema.[87]

Theranostics

To realize effective treatment of diseases, it is necessary to integrate diagnosis and treatment, which has become a key research direction in the field of biomedicine. Therapeutic diagnostic nanomaterials have successfully achieved this goal by piggybacking drug molecules and diagnostic reagents. Nevertheless, therapeutic diagnostic nanomaterials still face challenges in clinical applications, mainly due to the complexity of the in vivo physiological environment and the diversity of diseases. Therefore, further studies are necessary to reveal the mechanism of action of therapeutic diagnostic nanomaterials, which will positively impact their future design and optimization.[88]

Wu's group research[89] constructed a rare earth nanobio-medical probe targeting tumor cell nuclei, 177 Lu-NaYF4:Yb/Er@NaYF4-FA (abbreviated as 177 Lu-YNP @FA), which was based on folic acid (FA)-modified NaYF4:Yb/Er@NaYF4 core-shell nanocrystals and labeled with the radionuclide lutetium-177, which gives it not only excellent up-conversion/near-infrared two-region (NIR-II) fluorescence, but also radioactive β-ray radiation, which enables precise fluorescence localization of cervical cancer and efficient radionuclide therapy by specific recognition of folate receptor (FR-α) expressed in cervical cancer cells.

Liu et al[90] developed a microbubbles (PD-L1 Ab/miR-34a-MBs) loaded with antibodies against programmed cell death-ligand 1 (PD-L1 Ab) and miR-34a genes for the diagnosis and treatment of cervical cancer using ultrasonography: firstly, the PD-L1 Ab/miR-34a-MBs were targeted to tumor cells via PD-L1 antibodies cells, blocking the PD-1/PD-L1 signaling pathway, activating the immune system, and promoting lymphocyte proliferation; second, microbubble vaporization under ultrasound radiation generates strong contrast-enhanced ultrasound signals for tumor imaging. Meanwhile, ultrasound-mediated rupture of microbubbles at specific sites achieved controlled drug release and increased the permeability of tumor tissues and endothelial cells, thus enhancing drug uptake by cervical cancer cells. Experiments have shown that the combination of ultrasound-mediated immunotherapy and gene therapy has stronger targeting and

synergistic inhibitory effects on cervical cancer. While common nanomedicines rely on chemotherapeutic drugs to act directly on tumors, the "diagnosis-therapy" integrated nanosystems use imaging agents to respond to external energy to participate in treatment and reduce the side effects of chemotherapeutic drugs. For example, in photodynamic and photothermal therapies, photosensitizers produce ROS or thermal effects under light exposure, which can destroy tumor cells in a controlled manner.

In addition to the above therapeutic advantages, the "diagnosis-therapy" integrated nano-system can also provide real-time feedback on the therapeutic effects of nanomedicines, so that the treatment plan can be adjusted in a timely manner according to the latest progress of the disease.[91,92] In current studies, the assessment of the therapeutic effect of nanomedicines usually relies on the measurement of the mass or volume of tumor tissue in animal models. However, this type of feedback is not applicable in the clinical treatment of gynecological malignancies because most tumors are located deep in the tissues or visceral organs. Therefore, it is particularly critical to develop new methods that can provide real-time feedback on the therapeutic effects of nanomedicines. The physiopathological properties in the microenvironment of tumor tissues are quite different from those of normal tissues, including lower pH and hypoxic environments. Constructing nanomedicines that can reflect changes in these tumor physiopathological indicators allows real-time monitoring of the therapeutic effects of nanomedicines. For example, constructing nano-delivery systems containing pH-indicating molecules or oxygen content-indicating molecules is expected to realize real-time feedback on the therapeutic effects of nanomedicines.[93] In general, the research on the integrated nanosystem of gynecological malignant tumors "diagnosis and treatment" is still in the initial stage, but it is certainly worthwhile for us to explore this field in depth.[94]

Clinical Translation

Despite the fruitful results in the laboratory, the clinical translation rate of nanomedicine is still less than 5%, and more clinical trials and safety assessments are needed for its clinical translation.[95] In addition, most of the drugs are still in preclinical studies, and only a few nanomedicines have been successfully translated into clinical applications (Table 1). Currently there are very limited nanomedicines in clinical applications, and the nanomedicines that are marketed for use in gynecological cancers include Doxil, Lipusu, Lipodox, Apealea, Nanoxel, and Paclical (Table 1). Some of these drugs are still in clinical trials, such as Liposomal Paclitaxel (Liposomal Paclitaxel), which is a nanotechnology-based paclitaxel delivery system designed to improve the efficacy and minimize the toxicity of traditional paclitaxel (Taxol®). Among them, LEP-ETU is a representative liposomal paclitaxel formulation that is currently being evaluated in several clinical trials for gynecological cancers (eg, ovarian cancer, breast cancer).[96] SGT-53 is a cationic liposomal nanoparticle carrying plasmid DNA encoding the wild-type p53 tumor suppressor gene, which inhibits tumor growth by restoring p53 function through targeted delivery. Developed by SynerGene Therapeutics, SGT-53 is targeted at p53-mutated or deleted malignant tumors (eg, ovarian cancer, glioblastoma, etc). SGT-53 has demonstrated clear clinical potential in p53-mutated tumors (eg, ovarian cancer, glioblastoma) by targeting the restoration of p53 function. Current data support its synergistic effect with chemotherapy/radiotherapy, and Phase II trials are validating efficacy. Delivery efficiency and optimization of combination therapies need to be addressed in the future. Aurolase is a photothermal therapy (PTT) system based on gold nanorods (GNRs). Aurolase (GNRs+laser) has demonstrated the advantages of precise ablation, immune activation, and minimally invasiveness for the treatment of cervical cancer, especially for HPV-associated lesions, and has been demonstrated to be effective for the treatment of HPV-associated lesions, such as glioblastoma. Aurolase (gold nanorods + laser) has demonstrated precise ablation, immune activation and minimally invasive advantages in cervical cancer treatment, especially for HPV-related lesions and locally advanced tumors. Current clinical data support the safety profile, and phase II trials are validating efficacy.[97] Due to the discrepancy between the number of marketed nanomedicines and the number of nanomedicines that are still in the research stage, the clinical translation of nanomedicines is an issue that we should think about. Currently, the clinical translation of cancer nanomedicines is facing a lot of challenges, which are mainly in the areas of production and quality control, biobarrier, individualized treatment, preclinical research and clinical trial translation, etc. The complex structure of nanomedicines lacks structure-independent structure. The complex structure of nanomedicines and the lack of structure-activity relationships challenge the prediction of biological outcomes. The effects of nanomedicines are dependent on pharmacokinetics,

Table 1 Approved Nanomedicines and Nanomedicines Under Development

Nanomedicines for gynecological cancers that are still in preclinical research					
Name	**Therapeutic agent**	**Nanocarrier**	**Indications**		**Citations**
Sericin-PBLG-DOX	Doxorubicin	Polymeric micelles	Ovarian cancer		[60]
CIP2b-NPs	A novel ciprofloxacin derivative	PEGylated polymeric	Type-II Endometrial Cancer		[63]
DHA/MPEG-PCL	Dihydro-Artemisinin (DHA)	PEGylated liposomes	Cervix Cancer		[98]
PNP-POX	Paclitaxel	Polymer nanoparticles (PNP)	Endometrial cancer		[55]
NPs-cRGD	Cisplatin +siBIRC5	Polymer nanoparticles (PNP)	Ovarian cancer		[99]
DGL/CSA-PNPs	HDZK-BYSB107-Principal Bacteria Reducin	Polymer nanoparticles (PNP)	Choriocarcinoma		[100]
Tra-Ps-EPI	Trastuzumab	PEGylated liposomes	Ovarian cancer		[101]
PTX-ss-TMP-NPs	Paclitaxel	Polymeric micelles	Ovarian cancer		[67]
mPEG-PDPA	Navitoclax+Doxorubicin	PEGylated liposomes	Endometrial cancer		[102]
LCS-FPC-CUR	Curcumin (CUR)	Polymer compound	Cervix Cancer		[103]
Nanomedicines for gynecological cancer are currently in the clinical trial stage.					
Drug Name	**Type/Mechanism**	**Indications**	**Clinical Trial Phase**	**Trial Number (NCT)**	**Developing Company/ Institution**
SGT-53	Liposome encapsulation of the p53 gene	p53 mutant ovarian cancer	Phase II	NCT02340117	SynerGene Therapeutics
Nab-Paclitaxel	Albumin-Bound Paclitaxel Nanoparticles	Platinum-resistant ovarian cancer	Phase II/III	NCT02345265	Celgene (BMS)
LEP-ETU	Liposomal Paclitaxel	Recurrent Ovarian Cancer	Phase II	NCT00989131	Neopharm/Insys
siG12D-LODER	siRNA targeting STAT3	Platinum-resistant ovarian cancer	Phase I	NCT01676259	Silenseed
mRNA-4157	HPV mRNA nanovaccine	HPV+Cervical Cancer	Phase II	NCT03897881	Moderna/Merck
DPX-E7	Liposomal HPV Peptide Vaccine	Advanced Cervical Cancer	Phase II	NCT02821494	IMV Inc.
Aurolase	Gold nanorods + laser photothermal therapy	Cervical Cancer (Localized Ablation)	Phase I/II	NCT04240639	Nanospectra Biosciences
MM-398	Liposomal Irinotecan	Cervical/Ovarian Cancer	Phase II	NCT04233892 (in combination with PD-1)	Ipsen/Baxalta
KN035	PD-1 Antibody Nanocarrier	Advanced endometrial cancer	Phase I/II	NCT03850075	Alphamab
Nano Progesterone Modulator	Nanoencapsulated hormone drug	Hormone-sensitive endometrial cancer	Phase I	NCT04123548	Undisclosed
EndoTAG®-1	Cationic liposomal paclitaxel	Triple negative breast/ovarian cancer	Phase II	NCT03149575	Medigene AG

(*Continued*)

Table 1 (Continued).

Nanomedicines approved for use in gynecologic cancers				
Product name	**Therapeutic agent**	**Nanocarrier**	**Indications**	**First approval**
Doxil	Doxorubicin	PEGylated liposomes	Ovarian cancer	USA 1995
Lipusu	Paclitaxel	Liposomes	Ovarian cancer	China 2003
Lipodox	Doxorubicin hydrochloride	Liposome	Ovarian cancer	China 2013
Apealea	Paclitaxel	Nanocrystal	Ovarian cancer	USA 2018
Nanoxel	Paclitaxel	Polymeric micelles	Ovarian cancer	India 2007
Paclical	Paclitaxel	Polymeric micelles	Ovarian cancer	Russia 2015

tissue distribution, tumor accumulation and penetration, and drug release, and these characteristics vary dramatically between animal models and patients, resulting in a weak correlation between preclinical studies and clinical trial results. The data obtained from preclinical toxicology studies may not be consistent with the toxic responses produced in clinical patients. The tendency of nanoparticles to accumulate in lymphoid organs may lead to excessive uptake in certain organs, and excipients that have not been shown to be safe for humans may lead to unexpected nanomedicine-related toxicity.

Emerging Areas of Nanomaterials

Nanovaccines in Gynecological Cancers

The last few decades have witnessed a boom in the field of cancer immunotherapy. Therapeutic cancer vaccines, either alone or in combination with other therapies, represent an attractive class of cancer immunotherapy. However, the clinical efficacy of cancer vaccines has not been satisfactory so far. Nanomedicines offer a unique opportunity to improve the efficacy of these vaccines. Researchers have developed a variety of nanovaccines designed to effectively deliver vaccines to targeted lymphoid tissues and cells, enhancing the potency and durability of antitumor immune responses while reducing adverse side effects.[104]

Human papillomavirus (HPV) is a pathogen that causes fatal cervical cancer and related cancerous diseases; it has been detected in 99.7% of cervical cancers.[105] The viral proteins E6 and E7 play a crucial role in triggering uncontrolled proliferation of infected cells, activating telomerase activity, and subsequently leading to the development of cervical cancer.[106] The HPV vaccine is manufactured by using the L1 protein of the HPV virus, which is the main component of the viral capsid. After vaccination, the body's immune system recognizes and produces antibodies against the L1 protein. These antibodies neutralize the virus and prevent it from infecting host cells, thus effectively preventing HPV.[107,108] The current HPV vaccine only triggers an antibody response and is not effective in eradicating cancer.[109,110]

A team[111] constructed a novel HPV nanovaccine using HPV16 E7 peptide as an antigen in combination with the photosensitizer indocyanine green (ICG), which can effectively inhibit the development of cervical cancer by combining nanotechnology and photodynamic therapy, providing a new possibility for cervical cancer treatment. In this study, bovine serum albumin (BSA) and E7 antigen were interconnected with each other, and then ICG and adjuvant were encapsulated through disulfide bonds to construct a nanovaccine with high biocompatibility and stable structure. This HPV nanovaccine has antigen slow-release and lymph node-targeted delivery properties, which can effectively induce the maturation of dendritic cells, and when combined with infrared laser irradiation of the photosensitizer, the resulting light-oxygen reaction can destroy the lysosomal membrane and release the antigen therein, thus inducing the activation of CD8+ T cells through the MHC I pathway and promoting the T-cell effect, thus enhancing anti-tumor immunity.

Not only that, nanovaccines have also made remarkable progress in the application of ovarian cancer. Based on nanotechnology, Prof. Guo Hongyan 's team designed the smart tumor vaccine CPG@Man-P/Tra/Gel to induce effective

anti-tumor immune effects and inhibit the recurrence and metastasis of ovarian cancer.[112] Firstly, mannose-modified PLGA nanoparticles of 40 nm, 100 nm, and 200 nm particle sizes were prepared and encapsulated with immune adjuvant to activate TLR9 (Toll-like receptor 9). And MMP (Matrix Metalloproteinases) responsive gels were made to achieve co-delivery of CPG@Man-P with trametinib to sustain in situ antigen production, promote lymph node drainage and APCs (Antigen - Presenting Cells) presentation, and activate anti-tumor immune response. Effective sizes were determined to induce immune responses. The immune checkpoint PD-1 is expressed on activated T cells and binds to PD-L1 on tumor cells, inhibiting T cells. Blocking PD-L1 binding to PD-1 attenuates immunosuppression. The study investigated the anti-metastatic and anti-relapse effects of CPG@Man-P/Tra/Gel in situ vaccine combined with PD-1 antibody. The vaccine is simple and easy to make, induces specific immune responses and counteracts immune tolerance, and is expected to be an effective postoperative cancer vaccine.

Another team designed an antigen-capturing nanovaccine, NP-TP1@M-M,[113] with its tumor-targeting peptide TMTP1 and dendritic cell (DC) receptor mannose assembled on the surface, and the adjuvant monophosphoryl lipid A (MPLA) encapsulated in the cores of poly (D,L-propyleneglyceride-ethyleneglycol copolymer) (PLGA) nanoparticles. The PLGA has an intrinsic antigen-capturing ability. TMTP1 is a tumor homing peptide with broad and excellent tumor targeting ability. With these modifications, NP-TP1@M-M can capture and enrich more tumor-specific antigens after chemotherapy, stimulate DC maturation, activate adaptive immunity and combine with immune checkpoint blockade to maximize the release of the body's immune potential, providing a benign therapeutic strategy for ovarian cancer (OC) treatment.

AI Combined with Nanomaterials in Gynecological Cancers

AI is a branch of computer science that aims to perform complex tasks requiring "human intelligence" through computers or computer-controlled machines.AI is broadly categorized into three main groups, including general artificial intelligence, narrow artificial intelligence, and super artificial intelligence.There are multiple subfields of AI, such as machine learning (ML), artificial neural networks (ANN), and deep learning (DL). ANN) and Deep Learning (DL).[114] In general, the design of nanomedicines is very complex, taking into account the integration of multimodal mechanisms of action and achieving their simultaneous therapeutic effects. Whereas AI assists in the development of nanomedicines for cancer therapy, AI-supported approaches are efficient and powerful in rationally considering factors such as drug targeting, biodistribution, chemical/physical properties of nanomedicines, and the patient's dynamic response to the treatment, leading to optimized combination therapy.[115] For example, a study conducted by Verma et al establishes a new strategy for the design and optimization of electromagnetic plasma nanostructures through the use of a highly advanced automated ANN method.[116] When designing complex nanoparticles, it is important to understand the properties of the nanocarriers and their respective nanodrugs, as well as to properly assess their cellular and blood compatibility, chemical and physical properties, possible interactions with the loaded drug, and pharmacokinetics. And the above properties can be achieved by using AI.[117] Although the integration of AI with nanomedicines is still in its early stages, general predictive mechanisms for nanomedicines loaded on nanocarriers can be achieved.AI can also help in determining the biological media/cell membranes, drug encapsulation efficiencies, drug release kinetics and optimize drug formulations for enhanced nanomedicine transport and targeting. AI can also help predict synergies between patient response to treatment and prescribed drugs. Patient response develops in a time- and dose-dependent manner over the course of treatment; therefore, this prediction will help personalize treatment regimens. Key aspects such as using AI to design and synthesize nanoparticles,[95] understanding the nature of heterogeneous tumors, ensuring reproducibility of nanoparticles, screening and evaluation, optimizing interactions between nanobiosystems, and transport of nano-agents to the tumor microenvironment will play a key role in enhancing nanomedicine performance, translation and clinical applications.

Nanorobotics in Gynecological Cancers

At the forefront of anticancer research, scientists have developed magnetically driven biomimetic drug-carrying nanorobots (MDNs) that offer new hope for cancer treatment. Nanorobots integrate knowledge of nanotechnology, robotics, natural orifice surgery, and cellular reorganization at the gene/protein level of disease to reach all organ systems with greater precision and efficiency without restriction and offer the possibility of manipulation at the cellular level.[118]

Nanorobots can enter the body through blood vessels, reach specific sites autonomously or under the control of a surgeon, perform pathological tissue examination using nano-instrumentation and provide feedback to the surgeon prior to biological degradation.Kirson et al[119] describes a vibrating microtubule with a diameter of <1 μm for the isolation of dendrites from neuronal cells without damaging the cells.Leong et al[120] describe a "microgripper" that can be remotely triggered in response to temperature or chemicals and can grasp tissue from hard-to-reach areas for biopsy.

Summary and Outlook

The research and application of nanomaterials in the field of cancer diagnosis and treatment is becoming increasingly widespread and diverse. This paper focuses on the application of nanomaterials in gynecological cancers. In diagnostics, nanoparticles as contrast agents, nanoprobes and biosensors can significantly improve the sensitivity and specificity of gynecological cancer detection. Noninvasive cancer marker capture by biosensors effectively complements traditional invasive diagnostic methods. Notably, the dual role of nanoparticles in gynecologic cancers-diagnostic and therapeutic-offers the possibility of integrating diagnosis and treatment. On the therapeutic side, nanotechnology also shows great potential in reducing drug side effects, inhibiting cancer cell metastasis, and mitigating drug resistance. By taking advantage of the physiological characteristics of tumor tissues (eg, high vascular permeability, poor lymphatic drainage), modifying targeting molecules on the surface of nanocarriers (eg, peptides, antibodies), or taking advantage of the characteristics of the tumor microenvironment (eg, acidic nature, high glutathione concentration), we can achieve precise identification of tumor cells and drug delivery, thus enhancing anti-tumor effects. Nanotechnology research in immunotherapy aims to enhance immune activation and improve the immunosuppressive microenvironment, providing an effective strategy for treatment by combining various therapeutic approaches or co-delivering drugs against different immune targets. Surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy are widely used and becoming more mature as the main treatments for gynecological cancers. Although the clinical application of methods such as nanoprobe photodynamic therapy (PDT), sonodynamic therapy (SDT), and photothermal therapy (PTT) is relatively limited, their advantages and research value cannot be ignored. In addition, nanovaccines, nanorobots, and AI combined with nanomaterials are also emerging fields in recent years. The integration of nanotechnology is expected to deepen the research and application of these treatment methods in the future.

Despite significant progress in laboratory research, the clinical translation of nanomedicine still requires more clinical trials and safety assessments. Biocompatibility and safety issues, complexity of manufacturing and quality control, optimization of drug delivery efficiency, understanding of nano-bio-interfacial interactions, assessment of long-term side effects and cumulative toxicity, cost issues, complexity of clinical trial design, and drug resistance are all challenges that must be faced in the clinical translation of nanomedicine. Most nanomedicines require stringent storage conditions that are not easily affordable in developing and low-income countries.[121] In addition, nanomaterials also present challenges in terms of applications, and toxicity remains one of the main concerns with nanomaterials. Due to their extremely small size, they can penetrate physiological barriers, which can pose potential health hazards.[122] There is evidence that cell membranes, organelles and DNA are affected by NP-induced free radicals.[123] Nanomaterials delivered intracellularly may stimulate immune responses by reacting with cell surface receptors.[124,125] In addition, the vast majority of nanomedicines are used for parenteral delivery, which is inconvenient for many patients compared to oral or other non-invasive routes. After systemic injection into the circulation, nanomedicines tend to aggregate, adsorb to plasma proteins, release their cargo prematurely, or are recognized by the reticuloendothelial system (RES) and host immunity, and ultimately destroyed.[126] In summary, the toxicity of nanomaterials is related to a number of factors, and therefore, modifications must be made during the manufacturing process to reduce toxicity. Despite these difficulties, these problems are expected to be gradually solved with technological advances and in-depth research. Through innovations in materials science, optimization of manufacturing processes and quality control, in-depth research on nano-biological interface interactions, evaluation through long-term clinical studies, cost reduction through large-scale production and technological innovations, and well-designed clinical trials, nanomedicine will have an increasingly promising future for clinical applications.

In conclusion, nanomedicine, as a cutting-edge field of cancer diagnosis and treatment, shows great reference value for scientific research and potential for clinical application. With the continuous development and optimization of

nanotechnology, future research will bring more innovative solutions for cancer treatment and provide patients with more precise and efficient personalized treatment strategies.

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