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Journal of Drug Delivery Science and Technology 95 (2024) 105599

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Nanoparticles in cancer diagnosis and treatment: Progress, challenges, and opportunities

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ARTICLE INFO

Keywords:
Nanoparticles
Cancer treatment
Drug delivery
Nanomedicine
Clinical trials

ABSTRACT

Despite considerable progress in patient care, the global incidence of various cancer types continues to rise. Developing safer and more efficient anti-cancer treatment approaches are of great interest. In recent decades, nanotechnology has emerged as a promising and innovative medical approach for cancer diagnosis and treatment. However, as nanomedicine for cancer advances, it is important to understand and address challenges. Herein, we identify gaps in the current understanding of the effectiveness of nanomedicine on clinical outcomes and provide an outlook for the improved application of nanotechnology in medicine. We discuss the use of different types of nanoparticles for cancer diagnosis and therapy and the impact of the use of nanoparticles on the efficiency of existing anti-cancer treatments, such as chemotherapeutic, anti-angiogenic, immunotherapeutic drugs, and radiotherapy. Additionally, an update on the current status of clinical trials for nanoparticle-based treatments is provided.

1. Introduction

Cancer has been a challenge worldwide due to its significant incidence and high mortality rate. Currently, there are approximately 10 million cancer-related deaths per year and this is estimated to reach 30 million by 2030 [1–3]. Surgery, chemotherapy, and radiotherapy have been widely used as first-line treatment options for patients diagnosed at different stages of cancer. As a common treatment strategy for cancer, most patients receive chemotherapy before or after surgery. Chemotherapeutic agents are intended to eliminate rapidly dividing cancerous cells but also affect normal, fast-replicating cells, such as those in the bone marrow, hair follicles, and gastrointestinal tract. The detrimental impact of chemotherapy on organs and systems occurs through diverse mechanisms, including direct toxicity, liver metabolite-induced indirect toxicity, immune system suppression, reduced oxygen supply, and inflammation. The specific adverse effects and manifestation of damage depend on the organs and systems affected [4]. Due to these side effects, the dose of chemotherapy is often limited, reducing the efficacy of the anti-cancer treatment. Current therapies aiming to alleviate these side effects have adverse effects themselves and, therefore, are inadequate [5–7]. As such, there is a need to decrease the side effects to maintain full-dose chemotherapy. Thus, developing new, improved, safer, and more specific therapies is essential for cancer patients. In recent decades, several approaches have emerged to diversify cancer treatment beyond standard chemotherapy. Advanced technologies, including genomic techniques [8] and innovations in translation and protein processing [9], provide valuable insights into deciphering molecular signatures and identifying novel therapeutic targets. Cancer stem cell models [10] help to develop strategies to understand the heterogeneity of tumors, behavior and resistance of cancer cells to treatment [11]. Precision-engineered nanotechnology drug delivery systems, scrutinized in both *in vitro* and *in vivo* studies, revolutionize therapeutic efficacy, showcasing versatility in diagnostics and targeted interventions [12].

Recent advances in nanomedicine have shown that nanotechnology-based drug delivery has great potential in cancer diagnosis and treatment with reduced side effects [13]. Despite the small size of nanoparticles (NPs) compared to cells, they are sufficiently large to encapsulate numerous small-molecule compounds. Simultaneously, the large surface area of NPs possesses an excellent ability to functionalize with ligands (i.e., small molecules, DNA or RNA strands, and peptides).

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https://doi.org/10.1016/j.jddst.2024.105599
Received 24 July 2023; Received in revised form 13 March 2024; Accepted 16 March 2024
Available online 26 March 2024

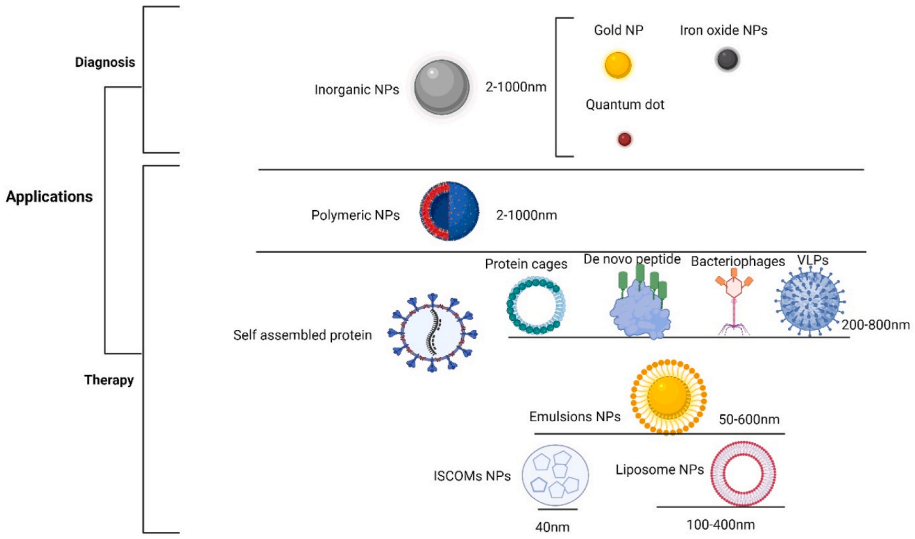

Fig. 1. Summary of different types of nanoparticles (NPs) based on their size and applications.
Abbreviations: ISCOMs, Immune Stimulating Complexes; NPs, nanoparticles; VLPs, Virus-Like Particles.

This modification may include changes in factors such as blood half-life, biodistribution, interactions with the circulatory system and decreased toxicity [14]. NPs, with their versatile characteristics determined by size, shape, and material properties, have become powerful tools in cancer diagnosis and therapy [15]. Fig. 1 presents an overview of diverse NP types categorized based on their applications and size range.

Although several reviews have elaborated on the role of NPs in cancer diagnosis and treatment, the originality of this review lies in critically addressing gaps in the current understanding of nanomedicine's efficacy in clinical outcomes. Specifically, it provides a detailed summary of the diverse applications of NPs and their impact on the efficacy of established anti-cancer modalities, including chemotherapeutic, anti-angiogenic, immunotherapeutic drugs, and radiotherapy. This review presents a forward-looking perspective on the optimal integration of NPs in medical applications, paving the way for future advancements. Furthermore, it provides a comprehensive update on the latest developments in nanotechnology for cancer diagnosis and spotlights the challenges in translating nanotechnology-based diagnostic methods into clinically applicable solutions.

1.1. Progress of NPs in cancer care

Improved and more specific therapies are needed to enhance the efficiency of available standard treatment options, including surgery, chemotherapy, immunotherapy, and radiotherapy, aiming to increase the survival of cancer patients [16]. In this regard, NPs have shown promise in optimizing such treatments. NPs have significant potential in cancer diagnosis and therapy, as they can be tailored to target specific cells and tissues. Moreover, NPs have been evaluated for their potential in targeted drug delivery to the central nervous system (CNS), which is challenging due to the blood-brain barrier (BBB) that limits the transport of therapeutic agents into the brain. NPs can be engineered to cross the BBB and deliver drugs to the brain, offering a promising approach for treating CNS diseases and brain tumors [16–18]. In addition, gold NPs conjugated with the chemotherapeutic drug (doxorubicin; DOX) showed increased accumulation in tumor tissue and improved anti-tumor activity in mice with breast cancer compared to the free drug delivery [19,20].

Nano-particulate drug delivery systems provide high drug stability, sustained release, and low toxicity. Besides, they can boost the concentration of the drugs in the blood, prolong their half-life, and reduce the frequency of drug administration by improving hydrophobic drugs' solubility, stability, and bioavailability [21]. Additionally, nano-encapsulation demonstrates promising potential in drug delivery, achieving therapeutic outcomes equivalent to free drug delivery but with reduced side effects. The enhanced permeation and retention effects of NPs result in a substantial increase in drug accumulation within cancer cells [22]. NPs can also be used in combination with other treatments, such as chemotherapy, immunotherapy, and radiation therapy to improve their efficacy and reduce toxicity. Therefore, while NPs may not be able to eradicate cancer cells on their own, they can play an important role in improving cancer treatment outcomes [23]. Nanotechnology facilitates the early detection of cancer by identifying specific biomarkers through tumor imaging techniques [24]. Additionally, NPs play a pivotal role in improving antigen presentation and T-cell activation, delivering pro-immune and pro-inflammatory agents to tumor microenvironments, thereby enhancing the effectiveness of cancer immunotherapy. Fig. 2 summarizes the applications of different types of NPs in health and biomedical science.

NPs play integral roles in various tumor treatment approaches, including immunotherapy, targeted therapy, physical ablation, gene therapy, photodynamic therapy (PDT) [25], and photothermal therapy. The multifunctional nature, minimal adverse reactions, and superior curative effects of NPs distinguish them from traditional tumor therapy methods [26]. In advancing cancer therapeutics, gold nanoclusters (GNCs) combined with chlorine e6 (Ce6) resulted in stable NPs. Integrated into a CD3 antibody (Ab)-enhanced CIK cell-based drug delivery system (Ce6-GNCs-Ab-CIK), these NPs demonstrated enhanced fluorescence, precise tumor targeting, and effective therapy in MGC-803 tumor-bearing mice. The strategic synergy between GNCs-Ce6-Ab NPs and CIK cells highlights the potential of this approach as a versatile cancer theranostic platform, promising targeted imaging and combination therapy [27]. However, poly(dopamine) (PDA) NPs, specifically the PDA-Ce6 nanosphere, exhibit enhanced efficacy against tumor cells in simultaneous photodynamic/photothermal therapy (PDT/PTT). The heightened cellular uptake and increased reactive oxygen species (ROS) production contribute to superior effectiveness. The PDA-Ce6 nanosphere holds promise as a dual-modal phototherapeutic agent, potentially transforming cancer therapy in future clinical applications [28].

Gold NPs, when conjugated with a photosensitizer (chlorine e6), exhibit enhanced effectiveness in photodynamic therapy (PDT) within a mouse tumor model. This improvement is attributed to the heightened accumulation of the treatment in tumors, resulting in a more effective regression of the tumors [29,30]. Similarly, polymeric NPs loaded with a photosensitizer (methylene blue) enhance the efficacy of PDT by improving tumor targeting and reducing side effects in a mouse model of

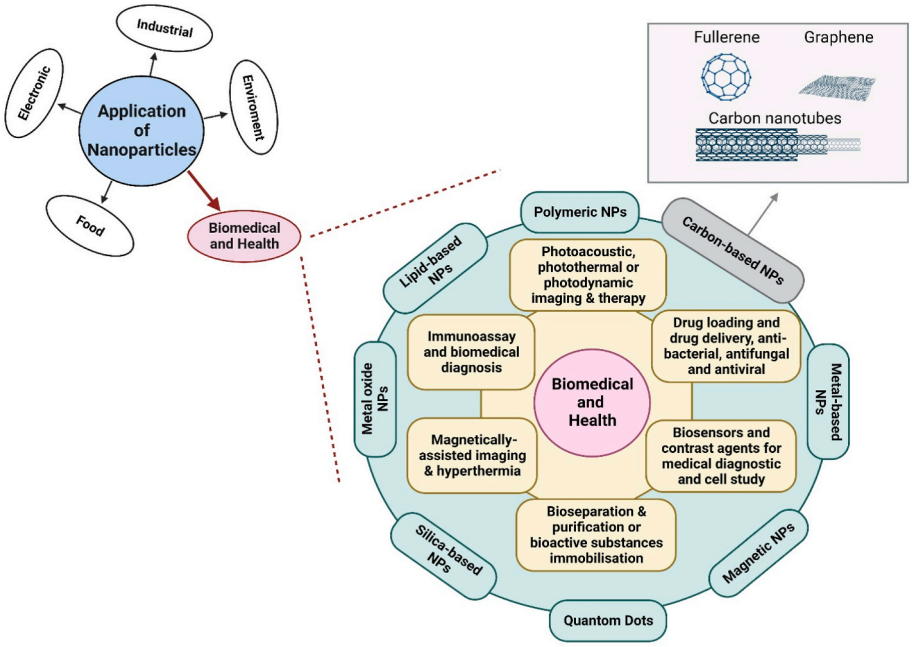

Fig. 2. Application of nanoparticles in biomedicine and health.

colon cancer [31,32]. Iron oxide NPs coated with a cancer-specific antibody are shown to enhance radiation therapy's efficacy in prostate cancer mice [33]. Lipid-based NPs delivering siRNA targeting a cancer gene (Kras) induce tumor regression and prolong survival in a mouse lung cancer model [34].

Liposomes are widely used for delivering chemotherapeutic drugs due to their effective characteristics. In recent years several liposome chemotherapeutic drugs have reached the clinic, and some of them have been approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for different cancer treatments. Conjugation of hydrophilic polymer polyethylene glycol (PEG), also known as polyoxyethylene or polyethylene oxide, to the surface of the liposome phospholipid bilayer, can modify the liposome's surface, which can reduce the interaction of plasma proteins and liposomes by steric hindrance [35,36]. For large unilamellar vesicles (LUVs), of 1, 2-distearoyl-sn-glycerol-3-phosphoethanolamine (DSPE)-PEG2000 achieves maximum biological stability. Alternatively, PEG-block-poly (ε-caprolactone) copolymers at varying molecular weights produce effective stealth lipid nanoparticles, surpassing PEG-phospholipid conjugates in certain cases. Modified liposomes with PEG-block-poly (ε-caprolactone) of 4000 Da demonstrate superior stability, drug loading efficiency, and tumor growth inhibition compared to other formulations. While PEGylation improves circulation, it may hinder liposome binding and uptake by cancer cells [37,38]. Doxil is the first modified PEGylated liposome formulation, which has shown significant selective tumor targeting about 300 times more than free drugs with a dose of 50 mg/m^2. The volume of distribution and clearance is significantly decreased (60-fold and 250-fold, respectively) [39].

Clinical trials have also shown promising results for NP-based therapies. Ongoing clinical investigations explore nanotechnology-based modalities such as chemotherapy, RNA interference (RNAi) therapy, and immunotherapy [40]. So far, some NPs have been approved by the FDA for different types of cancer, including ovarian cancer, non-small-cell lung carcinoma, sarcoma, glioblastoma, pancreatic cancer, leukemia, and multiple myeloma. Examples include Doxil (1995), Abraxane (2005), Oncaspar (2006), Marqibo (2012), Onivyde (2015), Vyxeos (2017), NanoTherm (2010), and Hensify (2019) [41]. In the phase III clinical trial, Abraxane (nanoparticle albumin-bound paclitaxel) showed improved progression-free survival compared to the conventional formulation of paclitaxel (PTX) in patients with metastatic breast cancer [42]. Functionalizing liposomes with various molecules, including antibodies and cell-penetration enhancers, shows promise in preclinical models. Thermosensitive liposomes (TSLs), particularly lyso-thermosensitive liposomal doxorubicin (LTLD) and polymer-modified TSLs, offer enhanced DOX delivery, while phosphatidylglycerol-based TSL (DPPG-TSL) shows potential for clinical translation of Doxil-based drug delivery strategies [43,44]. Lipid-based NPs delivering mRNA-encoding tumor antigens have also shown promising results in clinical trials for cancer immunotherapy [45,46].

In addition to the emergence of nanomedicine advancements in cancer, understanding functional challenges is crucial. The complexity/non-homogeneity of cancer highlights the need for appropriate patient selection to evaluate those who may benefit from NP-based cancer drugs. Despite numerous studies on the pharmacokinetics of NPs, only a limited number have attempted to predict effectiveness using preclinical animal models [47,48]. Transitioning from preclinical and clinical studies to the market is indeed challenging. Nanoparticle-based systems for cancer therapy face limitations such as slow cellular uptake, inconsistent intracellular drug distribution, interactions with or uptake by host immune cells, and challenges in carrying sufficient quantities of drugs or molecules to targeted sites [49]. Despite these challenges, NPs exhibit multifunctionality, fewer adverse reactions, and superior curative effects compared to free drug delivery.

1.2. *Application of NPs in cancer diagnosis*

Early cancer detection is imperative for the successful treatment and management of the disease [50]. There are several strategies available for cancer diagnosis, including physical examination, imaging techniques (such as X-ray, CT, MRI, PET), biopsy, and laboratory tests (such as blood and urine tests) [51]. Current diagnostic approaches have significantly enhanced the accuracy and speed of cancer detection, allowing for timely initiation of treatment and improving patient outcomes. However, there is still a need for more accurate and non-invasive diagnostic methods, as well as the development of personalized approaches that consider the unique characteristics of each patient's cancer [52].

NPs have demonstrated great potential in disparate types of medical tests and screening procedures, such as gold NPs in home pregnancy tests [53,54]. NPs in cancer diagnosis have attracted attention owing to their affordability and versatile capability to detect any type of cancer, capturing cancer biomarkers such as circulating tumor antigens, DNA, various types of cells (such as circulating tumor cells), and exosomes [55,56]. Compared to the existing cancer diagnostic approaches, NP-based assays show better selectivity and sensitivity, giving rise to early detection of cancers and, hence, better prognostic outcomes [57–59]. Cancer biomarkers can be found in tissues, blood, and body fluids, including urine and saliva. The early detection of biomarkers can be limited due to the number of barriers, including their low concentrations in body fluids, timing, and heterogeneity [60]. However, with their ability to perform specific targeting with high sensitivity and selectivity, NPs can improve biosensors for selective diagnostics.

Some common NPs have been used for cancer diagnosis, such as gold NPs (Au NPs), quantum dots (QDs), and magnetic NPs [61]. Au NPs, with their ease of functionalization and biocompatibility, serve as labels in immunoassays and biosensors, amplifying the sensitivity of assays [62]. Au NPs exhibit strong surface-enhanced Raman scattering effects, making them valuable in vibrational spectroscopy-based cancer detection methods [63]. QD NPs demonstrate excellent near-infrared absorption capabilities for effective photoacoustic imaging [64]. Additionally, superparamagnetic iron oxide NPs (SPIONs) play a crucial role in magnetic resonance imaging, providing detailed insights into tissues and tumors [65]. The exploration extends to semiconductor NPs like QDs, which, due to their size-tunable fluorescence, are pivotal in cellular imaging and molecular profiling [66]. Carbon-based NPs, including carbon nanotubes (CNTs) and nanorod arrays, find applications in electrochemical biosensors, leveraging high surface area and excellent electrical conductivity for detecting cancer-related proteins [67]. Organic NPs, such as nanofibers, contribute to fluorescence-based imaging and capturing circulating tumor cells, respectively [68]. Hybrid NPs, particularly those coated with silicon beads, offer a multifunctional platform for cancer detection, carrying imaging agents and allowing surface modifications for specific targeting [69]. These NP cancer detection methods can be evaluated based on protein, micro-RNA, circulating tumor DNA, DNA methylation, and extracellular vesicle detection. Therefore, some proteins such as carcinoembryonic antigen CEA (colon cancer), prostate-specific antigen PSA (prostate cancer), alpha-fetoprotein AFP (liver cancer), and cancer antigen 125 CA-125 (ovarian cancer) are regularly used for cancer detection [70,71]. The specific interactions between antibodies and proteins can be converted to a quantifiable signal, which can be detected. Some studies have developed novel oligonucleotide Au NPs labeled with a fluorophore to transfer cellular nanoflares and agents to detect mRNA in living cells. However, nanoflares can provide a sensitive and effective probe for intracellular mRNA detection with a large signal-to-noise ratio without cytotoxic transfection agents [72]. Table 1 summarizes different available NP types for cancer cell detection, their target specificity, and limitations.

In the last decade, the applications of NPs for cancer diagnosis in the clinic have grown considerably, due to their excellent sensitivity, selectivity, and multi-variation capacity. For instance, some studies have developed a new targeted silica NP with fluorescent cyanine 5.5 surrounded by polyethylene glycol chains attached to cyclo-[Arg-Gly-Asp-Tyr] (cRGDY) peptides (cRGDY-PEG-Cy5.5-C) for lymph node mapping of head and neck cancers, colorectal cancer, breast cancer, and melanoma. The NPs are administered around the tumor site before or during surgery to recognize cancer nodes [88]. Nanochips contribute to the emerging field of precision medicine by identifying specific cancer subtypes and guiding personalized treatment strategies. Nanochips can be functionalized with molecules that specifically bind to cancer-related biomarkers. These biomarkers are substances or indicators present in the

Table 1
Different types of nanoparticles (NPs) for the detection of cancer cells.

Nanoparticle type	Specificity	Cancer	Detection limit	Ref
Quantum dots	PTK7	Leukemia	• Toxicity • Biocompatibility • Expression variability • Cost-effectiveness	[73,74]
Magnetic NPs	EpCAM/Cd3	Colon/liver/lung/breast/leukemia	• False-positive or false-negative results • Cost-effectiveness for large-scale clinical applications	[75–77]
Carbon nanotubes	EpCAM	Liver	• Specificity • Biocompatibility • Reproducibility	[78]
Nanorod arrays		Breast	• Reproducibility • Scalability • Cost-effectiveness for large-scale	[79]
Polymer dots			• Potentially leading to off-target effects or false positives • Reproducibility • Scalability • Cost-effectiveness for large-scale	[80]
Nanofibers			• Detection Sensitivity • Scalability • Integration with imaging technique	[81]
Upconversion NPs (UCNPs)	Her2		• Potential toxicity • Accuracy for different cancer types	[82]
Gold NPs	Her2/Cd2/Cd3	Breast/leukemia	• False positives or misinterpretation of results • Optimizing the sensitivity • Long-term effects and potential accumulation	[83,84]
NP-coated silicon bead	EpCAM/CD146	Breast/colorectal	• Cost and accessibility • Long-term effects • Optimizing sensitivity	[85,86]
PLGA-mPEG	cRGD	Ovary	• Specificity and heterogeneity • Potential toxicity and immunogenicity • Reproducibility • Scalability • Cost-effectiveness	[87]

Abbreviations: cRGD: cyclic arginylglycylaspartic acid; EpCAM: epithelial cell adhesion molecule; Her2: human epidermal growth factor receptor 2; PTK7: protein tyrosine kinase 7; UCNPs: up conversion nanoparticles.

Table 2
Different types of nanoparticles (NPs) used in clinical trials for the detection of cancer.

Nanoparticles	Intention	Phase of study	Type of cancer	Clinicaltrials.gov identifier number
Carbon NPs	Lymph node tracer	Not applicable -Interventional clinical trial	Rectal cancer	NCT03550001
	Lymph node mapping		Cervical cancer	NCT03778268
	Lymph node mapping and tumor localization		Colorectal cancer	NCT03350945
	Lymph node mapping		Endometrial cancer	NCT03778255
Magnetic Iron oxide NPs	Magnetic resonance imaging (MRI)	Early Phase I	Head and neck cancer	NCT01895829
Silica NPs with Fluorescent cRGDYPEG- Cy5.5-C dots	Mapping of nodal metastases/ imaging	Phase I/Phase II	Head and neck cancer/melanoma/breast cancer/colorectal cancer	NCT02106598
Silica NPs with 89Zr-DFO-cRGDYPEG-Cy5-C′ dots	Positron electron tomography (PET)	Phase I	Brain cancer	NCT03465618
Silica nanomolecules with 124I-cRGDY-PEGdots		Not applicable -Interventional clinical trial	Metastatic melanoma/malignant brain cancer	NCT01266096
Nanochip (Immuno-tethered lipoplex NPs)	Monitoring/detection	Not applicable -Interventional clinical trial	Lymphoma	NCT03656835
Nano-sensors	Detection	Completed	Gastric/stomach cancer	NCT01420588

body, often at higher or altered levels in the presence of cancer. Due to their small size and high surface area-to-volume ratio, nanochips can detect even low concentrations of biomarkers, enhancing the sensitivity of cancer diagnosis. Nanochips enable the identification of cancer at its early stages, offering opportunities for timely intervention and improved patient outcomes [89]. Some nanochips are designed for real-time monitoring of biomarkers, allowing for continuous tracking of disease progression and response to treatment. Nanochips can be integrated into minimally invasive diagnostic techniques, such as liquid biopsy, facilitating the detection of cancer-related biomarkers in bodily fluids like blood or urine and reducing the need for invasive procedures [90]. The microfluidic design of these nanochips allows for precise and controlled manipulation of fluids at the nanoscale, optimizing the detection process [91]. By incorporating advanced sensing mechanisms and leveraging the inherent properties of nanomaterials, these chips exhibit remarkable sensitivity, enabling the identification of cancer-related biomarkers at deficient concentrations. Results obtained through cantilever sensor technology are robust in signal response, though they may vary due to laser alignment on the cantilevers [92]. Significant improvements are expected from device and software development progress, particularly for easier handling of cantilever arrays and devices. Eventually, the nano-sensors are anticipated to be more cost-effective than current methods, such as the COBAS test, especially with increased volume production [93]. Thus, nanotechnology has opened new horizons toward more efficient cancer diagnosis, resulting in a higher survival rate for cancer patients [94–96]. Table 2 presents current clinical trials using NPs for the detection of cancer.

1.3. Application of NPs in chemotherapeutic drug delivery

Drug resistance poses a significant challenge in cancer treatment, impeding the effectiveness of various therapies and contributing to cancer progression. Mechanisms of drug resistance encompass the overexpression of efflux transporters (such as P-glycoprotein), defective apoptotic pathways, and hypoxic tumor microenvironments [97]. The dysfunction of apoptotic pathways often results from disruptions in key proteins like Bcl-2 and nuclear factor kappa B (NF-kB). Bcl-2, extensively studied as an anti-apoptotic protein, is markedly overexpressed in numerous cancer types playing a pivotal role in drug resistance and making it a promising target for overcoming this challenge [98]. Emerging evidence supports the utilization of NPs to co-deliver Bcl-2-targeted small interfering RNA (siRNA) alongside chemotherapeutic agents, presenting an innovative approach to counteract drug resistance in cancer [99].

NPs exhibit the ability to encapsulate chemotherapeutic drugs, allowing them to bypass efflux transporters such as P-glycoprotein [100]. Additionally, NPs can be designed to encapsulate both efflux pump inhibitors and chemotherapeutic drugs, suppressing the expression and function of efflux transporters and thereby enhancing the effectiveness of chemotherapy. Incorporating drugs into nanoparticles for combination therapies involving chemotherapy requires careful consideration of drug loading, primarily involving non-covalent interactions, covalent interactions, and molecular bonding [101,102]. The nano drug delivery system targets a variety of critical signaling pathways within the body, offering a multifaceted approach to combating cancer. These pathways include methanol oxidation reaction, lysosomal apoptosis, PD-1/PD-L1, Nrf-2-Keap1, NF-kB, mTOR/Maf-1/PTEN, cGAS-STING, HER2, DNA repair, JAK2/STAT3, JNK apoptotic, Fas apoptosis, EGFR/ERK, P53/PRC1, and EGFR/PI3K/Akt-mediated pathways [103–107].

The targeting mechanisms in cancer therapies can be broadly categorized into two domains: passive targeting and active targeting. Passive targeting capitalizes on the abnormal vascular characteristics of tumor tissues, utilizing the enhanced permeability and retention (EPR) effect. This approach ensures precise and effective therapeutic interventions by allowing NPs to accumulate within tumors through neovascularization and inadequate lymphatic drainage associated with cancer. The interplay between NP size, vascular permeability, and the tumor microenvironment refines passive targeting, offering valuable insights for advancing targeted drug delivery strategies [108–111]. In contrast, active targeting directly engages with cancer cells through specific interactions between ligands on the surface of NPs and molecules excessively expressed on the cancer cell surface. This selective targeting enables NPs to differentiate between cancer cells and healthy cells, enhancing the delivery of chemotherapy drugs specifically to cancer cells while minimizing damage to healthy tissues and, therefore, reducing the side effects of chemotherapy [112]. Strategies such as transferrin-conjugated NPs, folate-receptor targeting, and epidermal growth factor receptor (EGFR) targeting have been employed in combination with chemotherapy drugs, showcasing the potential of active targeting in cancer treatment [113]. Passive accumulation of NPs in tumors and active targeting of cancer cells are shown in Fig. 3, illustrating nanocarrier-mediated delivery of diverse cancer treatments.

A novel therapeutic platform that utilizes chitosan as a matrix for stabilization provides a higher efficacy photothermal therapy for delivering the anti-neoplastic agent, DOX, to specific sites [114]. The hybrid NPs constructed by loading DOX into reduced graphene oxide with high efficiency and coating it with chitosan stabilized using tripolyphosphate TPP were shown to be effective in targeting PC-3 cancer cells, with cytotoxicity exceeding 65%. The hybrid NPs also efficiently converted energy to heat using near-infrared laser light irradiation at 808 nm, most likely due to graphene oxide, and demonstrated the ability to intracellularly deliver DOX to PC-3 cells. The *in vitro* drug release

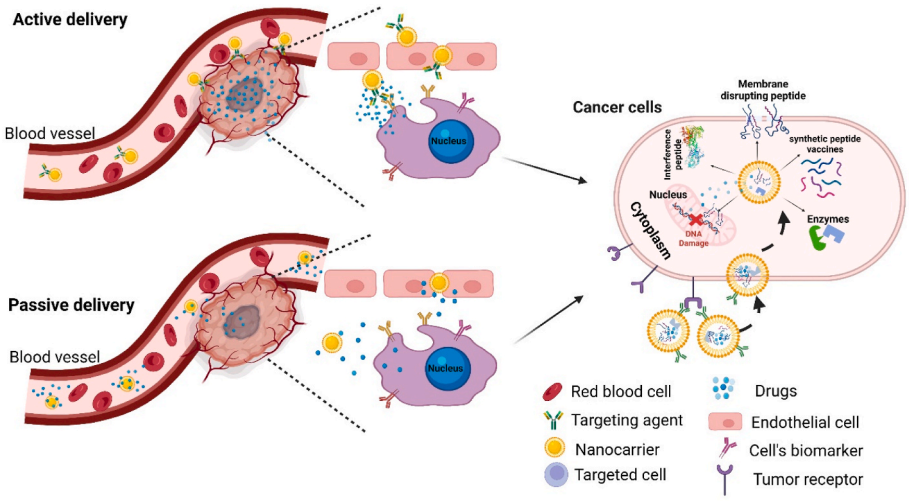

Fig. 3. Graphical illustration demonstrating passive and active nanocarrier-based drug delivery to cancer cells. The nanocarrier selectively accumulates in the tumor site via passive targeting (enhanced permeability and retention effect) and actively targets cancer cells through receptor-ligand interactions. The nanocarrier loaded with synthetic peptide vaccines, enzymes, drugs, and interference peptides releases these treatments inside the cancer cells, offering highly effective targeted therapy.

studies showed that the formulation can hold the drug for a long time and can be used for sustained delivery. The developed graphene-based drug delivery tool offers a feasible and viable approach for the treatment of prostate cancer by delivering DOX photothermally in a clinically translatable mode [115].

Dacarbazine is a commonly used FDA-approved chemotherapeutic drug with a short half-life and poor solubility [116]. Dacarbazine can be encapsulated into lipid NPs, which improves its half-life and delivery efficiency and decreases toxicity in melanoma skin cancer treatment [117]. Paclitaxel-loaded NPs, in combination with the anti-angiogenic

Table 3
Different NPs used to deliver chemotherapeutic drugs in human clinical trials.

Generic/propitiatory name	Platform	Active pharmaceutical ingredients	Cancer type	Phase	Refs
Liposomal vincristine (Marqibo)	Liposome	Vincristine sulfate	Acute lymphoblastic leukemia	Approved	[122,123]
Liposomal irinotecan (Onivyde)	PEGylated liposome	Irinotecan	Post-gemcitabine metastatic pancreatic cancer	Approved	[124]
DepoCyte	Liposome	Cytarabine	Neoplastic meningitis	Approved	[125]
PEGylated asparaginase (Oncaspar)	Polymer protein conjugate	l-asparaginase	Leukemia	Approved	[126]
Lipusu	Liposome	Paclitaxel, Gemcitabine, Cisplatin	Lung cancer	Approved	[127]
Mifamurtide (Takeda)	Liposome	Mifamurtide sodium	Osteosarcoma	Phase I	[128]
Daunorubicin (Daunoxome)	Liposome	Daunorubicin citrate	Kaposi's sarcoma-associated with HIV	Approved	[129]
Liposomal doxorubicin (Myocet)	Liposome	Doxorubicin	Metastatic breast cancer	Approved	[122]
ATI-1123	Protein-stabilized liposomes	Docetaxel	NSCLC, gastric, pancreatic cancer, and soft tissue sarcoma	Phase I	[130]
Alocrest	Optisomes liposome	Vinorelbine	NSCLC and breast cancers, non-Hodgkin's lymphoma, Hodgkin's disease	Phase I	[131]
Liposomal paclitaxel (EndoTAG-1)	Liposome	Paclitaxel	Pancreatic cancer, liver metastases, breast cancer	Phase II, III	[132–134]
LEP-ETU	Anionic liposomes	Paclitaxel	Metastatic breast cancer	Phase II	[135]
MCC-465	PEGylated liposome	Doxorubicin	Metastatic breast cancer	Phase I	[136]
CPX-351	Bilamellar liposomes	Cytarabine and daunorubicin (5:1)	Stomach cancer	Phase III	[137]
CPX-1	Liposome	Irinotecan HCl:Floxuridine	Acute myeloid leukemia	Phase II	[138]
IHL-305	PEGylated liposome	Irinotecan	Colorectal neoplasms	Phase I	[139]
MM-398 (PEP02)	PEGylated liposomes	Irinotecan	Advanced solid tumors	Phase III	[140]
NanoVNB	PEGylated liposomes	Vinorelbine	Metastatic pancreatic cancer	Phase I	[141]
Nab-rapamycin (ABI-009)	Albumin NPs	Rapamycin	Advanced cancer with mTOR mutations	Phase II	[142,143]
AP5346 (ProLindac)	Polymer	DACH (diaminocyclohexane)	Melanoma, ovarian cancer	Phase II	[144]
ThermoDox	Liposome	Doxorubicin	Hepatocellular carcinoma	Phase III	[145,146]
Lipoplatin	Liposome	Cisplatin	Pancreatic, breast and lung cancer	Phase III	[147,148]
Lipoxal	Liposome	Oxaliplatin	Gastrointestinal cancer	Phase I	[149,150]
MBP426	Liposome	Oxaliplatin + 5-Fluorouracil	Gastrointestinal cancer	Phase I	[151,152]
SPI-77	PEGylated liposome	Cisplatin	Lung cancer	Phase II	[153,154]

Abbreviations: ATI, azaya therapeutics incorporated; LEP-ETU, liposome entrapped paclitaxel easy to use; NSCLC, non-small cell lung cancer; PEG, polyethylene glycol.

molecular inhibitor, BIBF-1120, promoted synthetic lethality specifically in cells with loss of function p53 mutation, resulting in marked inhibition of tumor progression and extended survival in a xenograft model of endometrial cancer [118]. Carboplatin is the second-generation platinum-based chemotherapeutic agent approved by the FDA to treat melanoma. Carboplatin loaded into poly (ε-caprolactone) NPs with a chitosan-β-glycerophosphate gel has been used for intra-tumoral applications [119]. In addition, tamoxifen−gold NP conjugations increase the efficiency of tamoxifen 2.7-fold when used in advanced or metastatic breast cancer patients [120]. Further, titanium dioxide (TiO_2)-based NPs enhanced the chemotherapeutic impacts of 5-fluorouracil in gastric cancer patients by activating the autophagic flux response at 24 h [121]. Table 3 provides an overview of different NPs used for the delivery of chemotherapeutic drugs and their clinical trial status.

1.4. NPs and anti-angiogenic drugs

Blood vessels play a pivotal role in supplying oxygen and nutrients throughout the body. Angiogenesis, the formation of new blood vessels, is essential for processes like pregnancy, tissue growth, and wound healing [155]. However, cancer cells exploit this natural mechanism to foster their own growth and metastasis. In the context of anti-angiogenesis, targeting tumor vasculature emerges as a promising strategy. This multifaceted strategy seeks to either normalize tumor blood vessels, thereby enhancing drug penetration and optimizing blood flow within the tumor microenvironment, or inhibit angiogenesis altogether to cut off the tumor's critical nutrient and oxygen supply [156]. Anti-angiogenic agents primarily focus on disrupting key pathways, molecular mechanisms, receptors, and mediators associated with angiogenesis. The most common pro-angiogenic factors include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiopoietins (Ang), platelet-derived growth factor (PDGF), hypoxia-inducible factor (HIF) and hepatocyte growth factor (HGF) while anti-angiogenic factors include angiostatin and endostatin [157]. Various targeted elements, such as control of regulator of G-protein signaling 5 (Rgs5) [158], regulation of nitric oxide [159], modulation of the integrins family [160], and modulation of the EGFR may play a role in vessel normalization [161]. Additionally, other agents inducing vascular normalization, including certain proteolytic enzymes, exhibit their effects through indirect anti-angiogenic activity [162]. Integrins, crucial cell surface receptors with α and β subunits, are often upregulated in cancer cells, impacting functions like survival and invasion. Selected integrins, such as αvβ6, αvβ3, and a5β1, are overexpressed in specific tumors but not in normal cells, making them potential targets for anti-angiogenic therapy. Notably, αvβ3 and αvβ5 integrins, prevalent in angiogenic endothelial cells, play a key role in tumor-associated angiogenesis. Recognizing their importance, integrins offer promising targets for anti-angiogenic therapy using angiogenesis inhibitors [163,164].

Notably, inhibitors against VEGF, such as bevacizumab (Avastin), Axitinib, Sunitinib, Ranibizumab, and Vatalanib, have shown promise in pre-clinical and human clinical studies. The VEGF family, comprising VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor, interacts with receptors (VEGFR-1, VEGFR-2, VEGFR-3), contributing to processes like endothelial cell migration and metastasis. The VEGF/VEGFR pathway serves as a primary molecular target for the anti-angiogenic activity of NPs, which can inhibit tumor-associated VEGF activity by decreasing VEGFR phosphorylation [165]. By applying nanotechnology, endothelial cells and signaling pathways can be directly targeted with fewer side effects and more specific inhibition of the new blood vessel development [166].

Several NPs have been applied for anti-angiogenic targeting, including silica, carbon, silver, gold, polymeric and lipid NPs [167,168]. Recently carbon-based NPs have attracted much attention in cancer anti-angiogenesis therapy. For example, polyamidoamine dendrimer (PAMAM)-coated carbon nanotubes (CNTs) and polyethyleneimine (PEI) have been shown to effectively deliver microRNAs (miR-503 oligonucleotides) in a mouse model of angiogenesis [169]. Encapsulation of DOX and PTX in NPs made of polylactic acid (PLA) or albumin can improve their efficacy [170]. PLA, as a biodegradable and biocompatible polymer, facilitates sustained drug release at the tumor site. DOX/PTX-loaded PLA NPs have demonstrated notable anti-angiogenic effects by inhibiting the growth of new blood vessels crucial for tumor progression [171]. On the other hand, albumin NPs, leveraging the natural protein albumin, enhance drug stability, solubility, and targeted delivery to the tumor [172]. When loaded with DOX and PTX, these NPs not only improve the bioavailability of the drugs but also interact with endothelial cells, influencing angiogenesis-related signaling pathways. Importantly, the use of NPs can mitigate the systemic toxicity associated with free DOX and PTX by improving their biodistribution and reducing exposure to healthy tissues [173,174]. Dual-targeting peptides with specificity for alpha-V integrins and neuropilin-1 (NRP-1), a VEGF coreceptor, were created. Conjugated to paclitaxel-loaded liposomes, these peptides exhibited enhanced binding and cellular uptake, suppressing tumor growth in lung carcinoma cells (A549) and human umbilical vein endothelial cells (HUVEC). This breakthrough highlights the potential for targeted cancer therapy, especially in the context of VEGF-related pathways [175].

Pro-angiogenic molecules have various immunosuppressive effects, therefore, anti-angiogenic drugs can stimulate an immune response [157]. Preclinical and clinical studies demonstrate that the effects of anti-angiogenic drugs are transient and do not stop tumor progression and metastatic spread due to evasive and intrinsic resistance to specific angiogenic blockade [176]. Optimizing therapy could involve monitoring VEGF receptor prevalence in initial responses to VEGF/VEGFR-targeted medications. Selective tracers for integrins and VEGF receptors, including some RGD-based tracers in clinical trials, offer potential for molecular visualization [177]. Hence, applying anti-angiogenic drugs by nanotechnology and combining with other therapies such as radiotherapy, chemotherapy, immunotherapy, and phototherapy has the potential to significantly improve anti-tumor efficacy. Researchers investigated the anti-angiogenic properties of bovine serum albumin-capped graphene oxide (BSA−GO) by examining its interaction with VEGF-A165. BSA−GO exhibited remarkable stability and ultra-strong binding affinity to VEGF-A165, surpassing other plasma proteins. *In vitro* and *in vivo* experiments demonstrated that BSA−GO effectively inhibited endothelial cell functions and disrupted angiogenesis, indicating its potential as a therapeutic anti-angiogenic agent through strong VEGF adsorption and activity suppression [178]. The dose-dependent modulation of angiogenesis was demonstrated using reduced graphene oxides and graphene oxides. Low doses increased AKT and VEGF phosphorylation, while high doses triggered anti-angiogenesis [179]. TiO_2 NPs demonstrated anti-angiogenic properties by suppressing the VEGF/VEGFR2/MAPK pathway without hindering the phosphorylation of the PI3K/Akt pathway [180]. This similar mechanism was observed with silicate NPs (SiNPs), where SiNPs inhibited VEGF-induced phosphorylation of VEGFR-2 in human retinal microvascular endothelial cells. This inhibition occurred through the suppression of ERK 1/2 phosphorylation, while AKT phosphorylation remained unaffected [168]. Dual-targeting chemotherapy utilizing fibronectin extra domain B (EDB)-specific peptide-modified PTX-loaded NPs (APT-NP) enhances anti-glioma efficacy. APT-NP selectively targets EDB on glioma neovasculature and cells, improving internalization and cytotoxicity. In endothelial cells, APT-NP enhances PTX-induced apoptosis and inhibits angiogenesis. In vivo, APT-NP achieves specific glioma accumulation, outperforming unmodified nanoparticles and Taxol in xenograft models. This study underscores APTEDB-modified NPs' potential for angiogenesis-targeted dual chemotherapy in anti-glioma therapy [181]. Table 4 presents prevalent polymeric and carbon-based nano-sized targeted drug delivery systems for anti-angiogenic therapeutic strategies [178].

Table 4
Targeted drug delivery systems for anti-angiogenic therapeutic strategies.

Platform	Modification	Therapeutic agent	Reference
Single-wall carbon nanotubes (SWCNTs)	Polyethylenimine (PEI)-SWCNTs conjugations linked with candesartan	VEGF-targeted siRNA (siVEGF)	[178]
PLA	APTEDB peptide functionalized	PTX	[181]
Albumin	Abituzumab (DI17E6)-coupled NPs	DOX	[182]
Multi-walled carbon nanotubes	Polyethyleneimine (PEI) or polyamidoamine dendrimer (PAMAM) functionalized SWCNTs	miR-503 oligonucleotides	[169]
Graphene oxide	Bovine serum albumin-capped	–	[183]
Gelatine	Electrospun gelatin nanofibers	bFGF	[184]

Abbreviations: bFGF, basic fibroblast growth factor; DOX, doxorubicin; PEG, polyethylene glycol; PLA, poly (lactic acid); PTX, paclitaxel; VEGF, vascular endothelial growth factor.

1.5. Application of NPs in immunotherapy/vaccines

Immunotherapy is a novel and promising approach to treating disparate cancers due to its great ability to boost the natural immune system defense. Although immunotherapy has spectacular outcomes for some patients, only a small percentage of patients experience durable responses to these therapies [185,186]. New technologies are required to optimize the delivery of antigens to the immune system for enhanced stimulation of immune cells. More recently, cancer immunotherapies such as chimeric antigen receptor, cell therapy, immune checkpoint blockade therapy, cancer vaccines, and cytokine therapies have been developed and shown promising results in pre-clinical and clinical studies [187]. The main challenge in cancer immunotherapy is the stimulation of $CD8^+$ cytotoxic T-cells, which rely on effective delivery and antigen processing by antigen-presenting cells, namely dendritic cells [188,189]. NPs offer diverse applications in cancer immunotherapy, showcasing innovative strategies to augment the immune system's ability to combat cancer. One approach involves antigen delivery NPs, designed to deliver tumor antigens in the form of peptides or proteins to dendritic cells, thereby promoting a robust immune response [190]. In fact, several NP types, including polylactic-co-glycolic acid (PLGA), gold, iron oxide, and dendrimers have been used [191] (Table 5). Further, the size of the NP is an important parameter that influences their pharmacokinetics, transport, uptake by dendritic cells, and stimulation of cellular immunity [192]. Two other factors that significantly affect the performance of NPs in immunotherapy are the shape and charge of NPs. The shape of NPs can have an unavoidable impact on their circulation and accumulation in the desired site and the NPs' charge may affect the internalization of NPs into cells [193].

Adjuvant delivery NPs, on the other hand, enhance the immune response by delivering immunostimulatory adjuvants, exemplified by polymeric NPs loaded with Toll-like receptor agonists [194]. Cytokine delivery NPs deliver cytokines like IL-2 or INFγ to the tumor microenvironment, inducing local inflammation and recruiting immune cells [195]. Checkpoint inhibitor NPs (often polymeric NPs), featuring anti-PD-L1 or anti-CTLA-4 antibodies, function by blocking inhibitory signals and enhancing T-cell activity. Vaccine NPs carry tumor-specific antigens and adjuvants, eliciting a systemic and durable anti-tumor immune response [196]. Immunomodulatory drug delivery NPs enhance bioavailability at the tumor site, as seen in polymeric NPs with small molecule immunomodulators [197]. Gene delivery NPs deliver genes encoding therapeutic proteins, inducing the expression of immune-activating molecules [198]. Photothermal NPs, featuring photothermal properties like gold nanorods, induce localized hyperthermia, thereby amplifying the immune response [199]. These NP-based strategies offer a nuanced and comprehensive approach to cancer immunotherapy, each tailored to specific aspects of immune activation against cancer. Combining these strategies or integrating them with traditional cancer therapies holds the potential to further optimize treatment outcomes and expand the range of cancers effectively targeted by the immune system. Fig. 4 summarizes diverse NP strategies in cancer immunotherapy.

Nanocarriers, such as PLGA, gold, iron oxide, carbon, and quantum dots, have attracted attention in cancer research due to their characteristic ability to achieve precise targeting, exert minimal cytotoxic effects, and facilitate biodegradation [200,201]. PLGA NPs are common polymeric NPs for pre-clinical and clinical studies for cancer due to their advantages, such as non-toxicity and biodegradability [191,202]. Gold NPs are of great interest for the delivery of proteins and genes [199, 203]. DNA-inorganic hybrid nano vaccines have been shown to stimulate the release of pro-inflammatory cytokines, TNF-α, IL-6, and IL-12, from antigen-presenting cells [204]. In addition, bacterial membrane-coated gold NPs (BM-AuNPs) enhance the production of IL-17, INFγ and stimulate Th1/Th17 responses in immunized mice [205]. Importantly, the size of gold-NPs in the order of 15 and 50 nm results in optimal immune stimulation [206]. Chito6-GNP-DNA (HBsAg) nano complexes, formed by conjugating low molecular weight chitosan to gold nanoparticles, show enhanced DNA binding and stability. A single immunization with these chimeric nanoparticles induces potent antibody and T-cell responses in mice, outperforming the traditional naked DNA-primed HBsAg, which requires four immunizations with a higher DNA dosage. This minimal-DNA approach holds promise for cancer immunotherapy and vaccine development, as evidenced by *in vitro* studies demonstrating the efficient elimination of target cells by HBsAg-specific $CD8^+$ T-cells [207].

Table 5
Use of nanoparticles in immunotherapeutic studies.

Material	Therapeutic agent	Target	Function	Size (nm)	Ref.
PLGA-based NPs	AUNP12 anti-PD-1 peptide	Cancer cells	Blockage of PD-1/PD-L1 pathway	400–600	[212]
	Trastuzumb	Human epidermal growth factor 2	HER2 degradation	174 ± 43.9	[213]
	Pam3CSK4 and α-CD40-mAb	CD40	T-cell response	09.8 ± 11.1	[214]
Gold NPs	α-PD-L1	Cancer cells	Imaging and tumor reduction	20	[215]
Iron oxide NPs	Superparamagnetic Fe_3O_4	Dendritic cells and macrophages	Immune cell activation and cytokine production	600–900	[208]
Liposomes	Curdlan and mannan	Cytosol of dendritic cells	Activation of dendritic cells via Th1 cytokine production	100–157	[216]
Micelles	NLG919/IR780	Lymph node	Suppression of cancer cell growth in primary cancers	43 ± 3.2	[217]
Dendrimers	mAbK1/PTX	Cancer cells —mesothelin receptors	Specific binding and anti-tumor activity	–	[218]

Abbreviations: AUNP-12, aurigene nanoparticle-12; Fe3O4, iron oxide; HER2, human epidermal growth factor receptor 2; IR780, near-infrared dye; mAbK1/PTX, monoclonal antibody K1/paclitaxel; NLG919, Navoximod; Pam3CSK4, synthetic triacylated lipopeptide and a TLR2/TLR1 ligand PD-1, programmed cell death protein; PLGA, polylactic-co-glycolic acid; TH1, Type 1 T helper.

Table 6
Nanoparticles (NPs) in cancer radiotherapy.

Nanoparticle type	Cancer	Study	Phase	Trial ID
Ferumoxytol: Iron oxide NPs	Hepatic cancers	SBRT with iron oxide NPs on magnetic resonance imaging on MR-Linac	Phase I	NCT04682847
AGuIX: Polysiloxane Gdchelates	Brain metastases	Radiosensitization /aguix Gadolinium NPs (NANORAD)	Phase I	NCT02820454
	Brain metastases	Radiotherapy	Phase II	NCT03818386
	Brain metastases	Evaluating AGuIX NPs with SRTfor (NANOSTEREO)	Phase II	NCT04094077
	Brain cancer	Combination of AGuIX NPs with radiochemotherapy and temozolomide	Phase II	NCT04881032
	Cervical cancer	AGuIX gadolinium-NPs with chemoradiation and brachytherapy (NANOCOL)	Phase I	NCT03308604
	Brain cancer Brain metastases Melanoma Lung cancer Breast cancer HER2-positive Colorectal cancer Gastrointestinal cancer	SRT with AGuIX gadolinium-based NPs	Phase II	NCT04899908
	Non-small cell lung cancer Advanced pancreatic Adenocarcinoma Unresectable pancreatic cancer Pancreatic ductal adenocarcinoma	NPs with MR-guided SBRT	Phase II	NCT04789486
	Recurrent cancer	Reirradiation and hypofractionated protontherapy	Phase II	NCT04784221
	Liver cancer	Crystalline nanoparticles and stereotactic body radiation cancers	Phase II	NCT02721056
	Prostate cancer	NPs and EBRT or EBRT with brachytherapy	Phase II	NCT02805894
NBTXR3 (PEP503, Hensify): Hafnium oxide NPs	Metastasis from malignant tumor of stomach/cervix/skin/lung/ bladder Squamous cell carcinoma of head and neck	NPs activated by radiotherapy for patients with advanced cancers treated with an anti-PD-1 therapy	Phase I	NCT03589339
	Head and neck cancer	NBTXR3 and radiation therapy	Phase I	NCT01946867
	Head and neck cancer Soft tissue sarcoma	PEP503 (radioenhancer) with radiotherapy and chemotherapy	Phase II	NCT02901483
	Head and neck cancer Recurrent head and neck cancer	Re-irradiation with NBTXR3 in combination with pembrolizumab	Phase II	NCT04834349
	Soft tissue sarcoma Pancreatic cancer	NBTXR3 crystalline NPs and radiation therapy	Phase I	NCT01433068
		NBTXR3 crystalline NPs and radiation therapy NPs activated by radiotherapy	Phase III	NCT02379845
	Soft tissue sarcoma	NBTXR3 crystalline NPs and radiation therapy	Phase I	NCT04484909
	Pancreatic cancer Rectal cancer	NPs activated by radiotherapy PEP503 (radioenhancer) with radiotherapy and chemotherapy	Phase II	NCT02465593
	Lung cancer	NBTXR3 and radiotherapy	Phase I	NCT04505267
	Adenocarcinoma of the esophagus	NBTXR3 activated by radiotherapy	Phase I	NCT04615013

Abbreviations: AGuIX: polysiloxane matrix and gadolinium chelates; EBRT, external beam radiation therapy; MR-Linac, linear accelerator system with an integrated Magnetic resonance imaging, NBTX3: niobium tumor X-ray radio enhance; SBRT, stereotactic body radiotherapy; SRT: stereotactic radiotherapy.

Iron oxide NPs may also be applied as efficient carriers in immunotherapy. Targeted delivery of iron oxide NPs demonstrated immune cell activation and cytokine production. These outcomes corroborated the immunotherapeutic influence of iron oxide NPs in a colon cancer animal model [208]. Photoluminescent carbon dots (CDs) combined with ovalbumin (OVA) acted as potent vaccine adjuvants, enhancing antigen absorption and promoting dendritic cell maturation. The resulting CD-OVA nanocomposite induced key maturation markers (CD80, CD86), elevated TNF-α production, and stimulated splenocyte proliferation. An *In vivo* evaluation demonstrated efficient endocytosis and processing by immune cells, leading to a robust antigen-specific cellular immune response that effectively inhibited B16-OVA melanoma cancer in C57BL/6 mice [209]. Silica and multi-walled carbon nanotubes can stimulate the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome [210]. The use of FDA-approved ferumoxytol iron oxide NPs inhibited tumor growth and prevented liver metastasis by enhancing pro-inflammatory macrophage polarization in various cancer models [211].

1.6. Application of NPs in radiotherapy

Cancer treatment based on radiation is a promising approach to treat primary cancers and improve prognosis following surgical resection [219,220]. The combination of radiotherapy/surgery is the standard protocol for several cancers, including localized prostate cancers with a high risk of recurrence [221,222]. Radiotherapy can also synergistically improve the efficiency of other treatment modalities, such as chemotherapy [223]. Despite the high efficiency of radiotherapy to eliminate residual cancer cells, it can detrimentally influence surrounding healthy cells. Therefore, appropriate control of the administered radiation dose is of great importance to decrease the toxicity of nearby cells and tissues [224,225]. NPs provide unique opportunities for radiotherapy due to having an excellent surface-to-volume ratio, improved cellular uptake, and simplicity of functionalization [226–228]. NPs possess the unique ability to be composed of high-Z elements and serve as radiosensitizers for external ionizing radiation beams. High-Z elements demonstrate significant photoelectric absorption coefficients, resulting in the delivery of an effective radiation dose to surrounding cells [229]. NPs

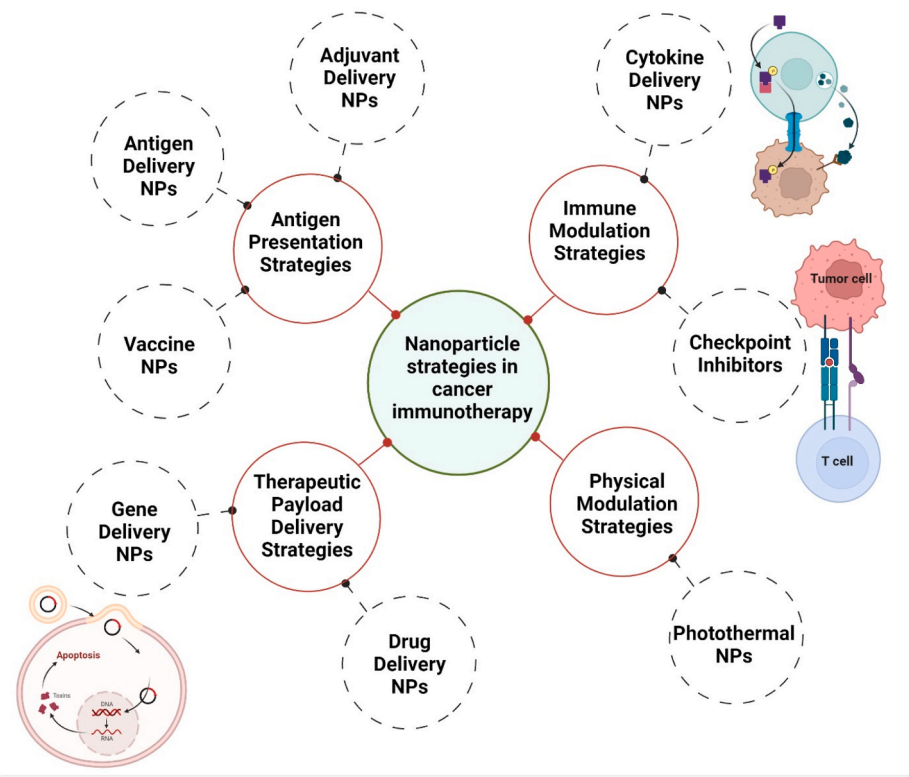

Fig. 4. Summary of diverse nanoparticle strategies in cancer immunotherapy.

possess the unique ability to be composed of high-Z elements and serve as radiosensitizers for external ionizing radiation beams. High-Z elements demonstrate significant photoelectric absorption coefficients, resulting in the delivery of an effective radiation dose to surrounding cells. The increase in dose using high-Z elements is known as the radiosensitization effect. The collision between high-energy photons and high molecular-weight atoms generates Auger electrons, enhancing radiotoxicity within DNA and producing cytotoxic reactive oxygen species [230,231].

Tailored multi-component nanoparticles, such as poly(vinylpyrrolidone)- and selenocysteine-modified Bi2Se3 NPs, show promise in cancer treatment. These nanoparticles excel in near-infrared absorption for targeted photothermal therapy, selectively eliminating cancer cells. Simultaneously, the inclusion of selenocysteine boosts immune function, offering a dual-action approach. This innovative strategy not only enhances the efficacy of radiotherapy by augmenting direct cytotoxic effects but also minimizes associated side effects, presenting a comprehensive solution for advanced cancer treatment [232].

Additionally, the noteworthy optoelectronic characteristics of inorganic NPs, which can be managed via crystal engineering, may present a new approach for combining radiotherapy with other modalities, such as optothermal therapy or theragnostic [232,233]. Table 6 summarizes NP-based targeted cancer radiotherapy.

In the context of radio-enhancement, there is a notable focus on elements with high atomic numbers. Combining photon radiation with heavy NPs induces local radiation hardening and elevates linear energy transfer. Among these elements, gold (Z = 79) has been extensively studied for its potential in radiation therapy due to its biocompatibility [234]. Goserelin-targeted gold nanorods (gAuNRs) effectively delayed tumor growth in mice with prostate cancers. This strategy, coupled with megavoltage radiation therapy, demonstrated significant effects with a lower gold dose compared to prior studies [235,236]. Notably, unconjugated AuNRs, despite higher intratumoral concentration, lacked significant radiosensitization, emphasizing the crucial role of active targeting for enhanced internalization and increased ionization density within cancer cells [237]. However, additional studies are required to assess the optimal dose and timing of nanoparticle administration *in vivo* and the safety and toxicity of gold NPs in living organisms before considering their use as radiosensitizers in clinical settings [238].

The findings of the investigation on intra-tumoral thermotherapy, utilizing magnetic iron-oxide NPs with external beam radiotherapy, for recurrent glioblastoma multiforme indicate a noteworthy improvement in overall survival by integrating thermotherapy with a lower radiotherapy dosage of 30 Gy. This outcome suggests the effectiveness of the administered heat in combination with radiotherapy. Nonetheless, it is essential to note that the study acknowledges the likelihood of selection bias due to the absence of randomization [239]. A combination of iodine NPs with radiotherapy significantly increased the median life of mice with human gliomas grown orthotopically compared to radiotherapy alone [240]. Gadolinium (Z = 64) forms the basis for promising nanoradiosensitizers, creating multifunctional theranostic nanoparticles that integrate therapy and diagnostics. These particles enable precise imaging through computed tomography and magnetic resonance imaging coupled with effective photothermal or radiation therapy. Demonstrating strong efficacy, they achieve potent *in vitro* photothermal cancer cell ablation and highly effective *in vivo* tumor radiotherapy [241].

In ongoing trials, AGuIX (polysiloxane NPs) and NBTXR3/PEP503 (hafnium-based NPs) use gadolinium chelates for radiosensitization and multimodal imaging through MRI and CT before radiation therapy. AGuIX is intravenously administered, while NBTXR3 can be delivered intra-tumorally (IT) or intra-arterially (IA) (refer to NCT01946867 v5 and NCT02721056 v6). The advantage of IT injection enhances tumor biodistribution, optimizing the initial dose impact [242].

1.7. Nanotheranostics in personalized cancer treatment

In recent years, cancer medicine has transformed through theranostics, combining diagnostic and therapeutic capabilities. Nanotheranostics, featuring both imaging and therapeutic agents within a single nanostructure, offer advantages over traditional nanomedicines.

They enable probing of nanocarrier accumulation at the disease site without drugs, allowing patient stratification for nanotherapy. Real-time monitoring and outcome prediction at administration, a high-density load of agents for improved imaging, and on-demand activation by biological stimuli or energy sources highlight their efficacy. Additionally, nanotheranostics can self-report drug release, enhancing precision in cancer treatment [243]. Nanotheranostics revolutionize cancer care by enabling non-invasive assessment of nanocarrier accumulation without therapeutic drugs. This allows personalized interventions based on real-time monitoring and efficient delivery of therapeutic and imaging agents, enhancing sensitivity and efficacy in cancer treatments [243,244]. Compared to molecular agents, nanotheranostics offer advantages like patient stratification and on-command activation. Examples include iron oxide nanocubes for MRI-visible magnetic hyperthermia, nanocarriers with heavy metals for enhanced radiation efficacy, and versatile NPs guiding surgical resection through luminescent or fluorescent signals [245]. Nanocarriers transport persistent luminescence NPs and chemotherapy through passive diffusion. Iron oxide-loaded nanocarriers, guided by MRI, release anti-cancer molecules under high-intensity focused ultrasound stimulation. Clinical demonstrations, like polymeric gadolinium complexes (AGuIX), showcase nanotheranostics' potential to transform cancer treatment. AGuIX's MRI-visible deposition in brain metastases correlates positively with disease regression, illustrating their clinical impact [246]. Versatile nanotheranostics, armed with cancer-targeting moieties, provide crucial insights for surgery and tumor margin visualization. Despite promising strides, challenges in clinical translation persist, with agent composition influencing translatability [247,248].

Optimizing innate theranostic materials for a delicate balance between imaging and therapy is a key to overcoming technical challenges. Strategic regulatory approaches, including repurposing nanomedicines and leveraging artificial intelligence (AI), pave the way for clinical trials [249,250]. In the future of personalized cancer medicine, integrating nanotheranostics into routine practice promises powerful tools for tailored interventions.

2. Conclusion

NPs have shown significant potential in cancer diagnosis and therapy, as they can be tailored to target specific cells and tissues. However, several challenges are associated with the successful translation of NP-based therapies to the clinic. One of the challenges of using NPs for diagnosis is their specificity to target cells. Although NPs can be engineered to target specific cells or tissues, their selectivity and sensitivity to detect cancer at an early stage still require improvement. In drug delivery, achieving optimal pharmacokinetics and biodistribution is a significant challenge. The size, shape, surface charge, and surface chemistry of NPs can affect their interactions with biological systems and their ability to target specific cells or tissues. Additionally, there is a need for more effective methods for controlling the release of drugs from NPs and for optimizing their drug loading and encapsulation efficiency. While promising, animal studies and clinical trials highlight the potential of NP-based therapies. However, further research is imperative to thoroughly examine toxicity, clearance, scalability, regulation, stability, and biodistribution. Investigating the long-term safety and efficacy of NP-based therapies, along with assessing their reproducibility and cost-effectiveness, is crucial. This extensive research is essential to address regulatory challenges and ensure thorough safety and efficacy testing before the clinical approval of NP-based therapies.

CRediT authorship contribution statement

Niloufar Rashidi: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Majid Davidson:** Writing – review & editing, Writing – original draft. **Vasso Apostolopoulos:** Writing – review & editing, Writing – original draft, Supervision. **Kulmira Nurgali:** Writing – review & editing, Writing – original draft, Supervision, Project administration.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors would like to thank the Immunology and Translational Research Group, the Enteric Neuropathy Research Group and the Institute for Health and Sport, Victoria University Australia for their support. N.R. and M.D. are supported by the Victoria University Postgraduate Scholarships.

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