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Nanotechnology for Diagnostic and Treatment of Bladder Cancer

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Abstract

Bladder cancer is one of the ten most common cancers in the world. Unfortunately, conventional strategies for diagnosis and treatment have proven inadequate. Therefore, it is essential to explore new approaches to enhance both diagnosis and treatment. In recent years, nanotechnology has attracted interest in the medical field. Nanoparticles possess excellent physical and chemical properties, presenting significant potential for applications in cancer imaging, biomarker detection, and tracing for diagnosis, as well as targeted delivery for treatment through surface functionalization. Nowadays, a variety of nanoparticles have been developed, including quantum dots, metal nanoparticles, carbon nanotubes and polymers. Due to their unique optical and magnetic properties, certain nanoparticles can be utilized in photothermal therapy and photodynamic therapy for cancer treatment. The integration of conventional approaches with nanotechnology greatly improves the diagnosis and treatment of bladder cancer. In this review, we aim to discuss the applications of nanotechnology and introduce several types of nanoparticles used in the diagnosis and treatment of bladder cancer.

Keywords

Nanotechnology, Bladder Cancer, Diagnosis, Theranostic Nanoparticles

1. Introduction

Globally, bladder cancer ranked as the tenth most common type of cancer and the sixth most prevalent cancer among men in 2020 [1]. The development of the cancer in men is three to four times than in women. The main risk factors of the bladder

cancer are smoking, occupational carcinogen exposure and genetic susceptibility [2]. Patients presenting with gross, painless hematuria are the most common symptoms of bladder cancer, while irritation signs of urinary tract, including urinary frequency, urgency, hesitancy and dysuria, appear less than a third of the patients [3]. Bladder cancer is classified based on the depth of tumor penetration into two categories: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (**Figure 1**). NMIBC accounts for approximately 75% of cases and is characterized by tumors that penetrate the basement membrane, while MIBC, which constitutes about 25% of cases, invades the muscle layer [4]. NMIBC is confined to the mucosa (Ta) or lamina propria (T1) and is further classified into low-grade (indolent) and high-grade (aggressive) categories based on pathological grading. In contrast, muscle-invasive bladder cancer (MIBC) invades the muscularis propria (T2) or beyond (T3/T4), demonstrating a high propensity for metastasis and increased mortality [5]. For NMIBC, it is recommended that patients undergo transurethral resection of bladder tumor (TURBT), followed by intravesical chemotherapy or treatment with Bacillus Calmette Guerin (BCG) [6]. However, within five years, the risk of recurrence for NMIBC can be as high as 70% - 80%, with 10% - 20% of patients progressing to MIBC [7]. For MIBC, as outlined in the guidelines, the standard treatment strategy is radical cystectomy (RC) accompanied by pelvic lymph node dissection. Additionally, it is essential for patients to receive perioperative chemotherapy based on cisplatin [8]. However, this approach does not provide satisfactory outcomes for all patients with bladder cancer. RC is associated with a high complication rate, estimated to be between 30%

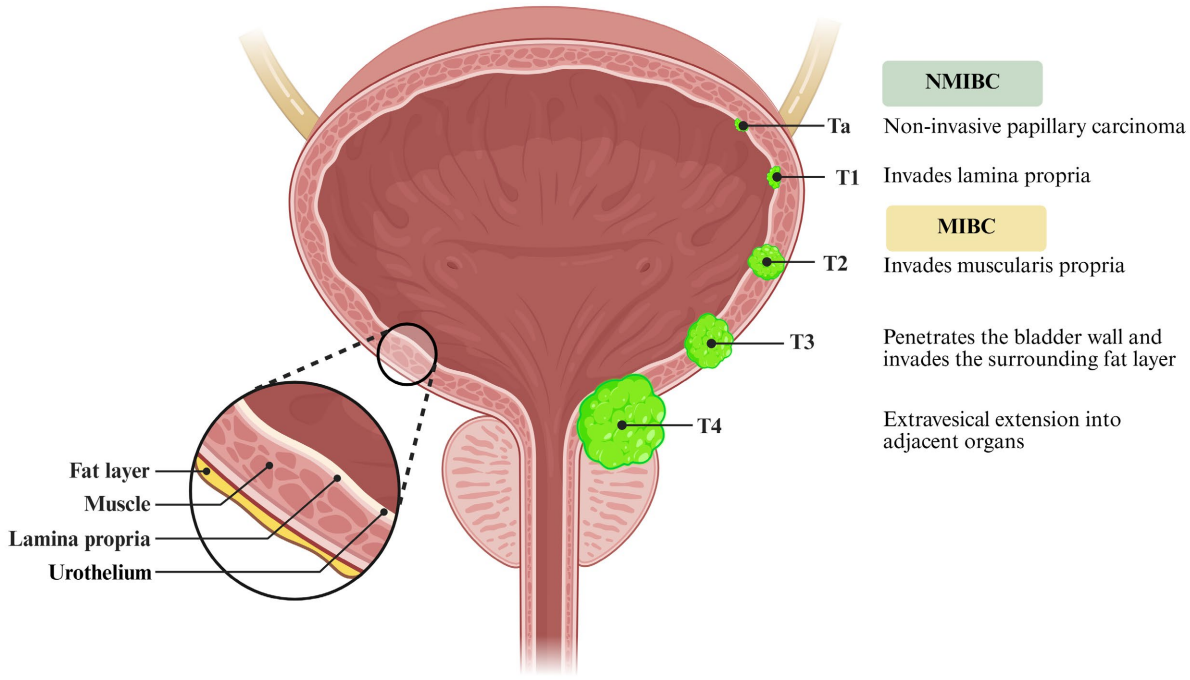

Figure 1. Bladder cancer stages. Created in BioRender (2025) https://biorender.com/oea78s9.

and 70% [9]. The recurrence and metastasis rates in patients with MIBC are approximately 50%, and the 5-year overall survival rate is less than 50%. The majority of patients will experience recurrence and ultimately succumb to metastatic disease, highlighting the urgent need for novel therapies [10]. There was a 77.1% five-year survival rate in US, 95.8% for *in situ* bladder cancer, 69.5% for localized disease and 4.6% for metastatic disease, indicating that the early diagnosis provides many chances [11]. At the same time, the poor detection and diagnosis bring the poor prognosis of the metastatic. It is essential to develop early and accurate diagnosis of bladder cancer. The diagnosis mainly depends on cystoscopy, urinary cytology, computed tomography urography, imaging of the urinary tract and magnetic resonance imaging (MRI) often used for classification of stage [12] [13]. However, the sensitivities of the cystoscopy are insufficient to detect the small or micro lesions, especially for the carcinoma *in situ*. In addition, cystoscopy would bring side effects because of an invasive examination. Urinary cytology is highly sensitive to high-grade tumors but less sensitive in low-grade tumors [14]. Researchers show plenty of interest in biomarkers for diagnosis of bladder cancer, such as BTA and NMP22, but current research and evidence are insufficient to prove that there are biomarkers directly associated with the development of bladder cancer [15] [16].

Nanotechnology overcomes shortcomings of conventional strategies, such as the unsatisfactory biodistribution of drugs, multidrug resistance (MDR) and cancer heterogeneity [17]. It has attracted interest for its potential in detecting biomarkers, cancer cells, and *in vivo* imaging due to its high sensitivity and specificity [18]. With the application of nanotechnology, the efficiency of drug delivery can be significantly enhanced [19]. Nanosized complexes are capable of encapsulating chemotherapy drugs and other novel antitumor agents, including small interfering RNA (siRNA), messenger RNA (mRNA), and targeted molecular agents [20]. Additionally, nanotechnology makes a considerable reduction of the toxicity caused by the non-targeted effect associated with conventional chemotherapy strategy [21]. Nanoparticles (NPs) play an important role in nanotechnology for cancer diagnosis and treatment [22]. Magnetic nanomaterials, metal-based nanomaterials, exosomes, and quantum dots are currently being developed rapidly as various approaches to NPs [23]. NPs can take on various shapes, including nano wreath, nanotriangle, nanorod, nanowires, and spheres [24]-[26]. The use of NPs significantly enhances the efficiency and efficacy of treatments, allowing antitumor drugs to be targeted directly to the intended site rather than being delivered to other vital organs, which can cause side effects. Additionally, the circulation time of drugs is considerably prolonged, resulting in a marked improvement in their half-life [27]. The targeting approach could be categorized into two types: active targeting and passive targeting. Active targeting depends on the interaction between ligands and receptors, which reduces unexpected nonspecific conjugation [28]. Traditional approaches to active targeting include targeting the tumor microenvironment, tumor surface molecules, and targetable molecules within cancer cells [29]. The lat-

ter is associated with the enhanced penetration and retention (EPR) effect. The vascular structure in tumor tissues is often compromised, making it significantly leakier than that in healthy tissues. This allows nanoparticles (NPs) to penetrate and accumulate at the target site, which is the tumor tissue [30]. Most NPs reach the target site, where they are degraded, facilitating the release of drugs encapsulated within the nanoparticles. Additionally, light or temperature can be used for physical stimuli to promote drug release. The tumor microenvironment, including factors such as pH and enzyme, can also influence the efficacy of drug release [31].

Nanotechnology has shown considerable advantages in the diagnosis and treatment of bladder cancer, and numerous nanomedicines have been approved for clinical trials related to this disease. However, their clinical translation still encounters several challenges. For instance, the heterogeneity of the tumor microenvironment results in limited targeting efficiency of nanomedicines. Additionally, the long-term accumulation of metal-based nanomaterials may induce toxicity, while the complement-activating effects of liposomes heighten the risk of immunogenicity. Furthermore, the difficulty in maintaining batch consistency of nanoparticles complicates the scaling up of production.

This review discusses recent advancements in the application of nanotechnology for bladder cancer, emphasizing various types of nanoparticles utilized in the diagnosis and treatment of this disease (**Figure 2**). The advantages and disadvantages of different kinds of nanoparticle applications are also discussed. Furthermore, the current status of clinical applications and the challenges encountered are presented, providing insights for the development of improved nanomedicine-based diagnostic and therapeutic systems for bladder cancer.

2. Nanotechnology in Diagnosis of Bladder Cancer

Cystoscopy and bladder biopsy are the common methods for bladder cancer diagnosis. However, these strategies are invasive and are possible for missed diagnosis for microtumors; another approach depends on urinary cytology, but it is less sensitive for low-grade tumors and often interfered by other factors [14]. Hence, it is necessary to find out a more sensitive and less invasive approach for diagnosis. With the development of nanotechnology, combined with conventional approaches could develop a greater effect in imaging, biomarker detection and tracing for bladder cancer.

2.1. Imaging

Nowadays, the diagnosis in clinical cases mainly depends on magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound, which are restricted by the clinical stage and types of the cancer. In the past decades, the application of nanotechnology in cancer imaging attracts the interest. Due to excellent physical and optical properties, good biocompatibility and high atomic number, the nanoparticles play a more and more important role in the cancer imaging. Quantum

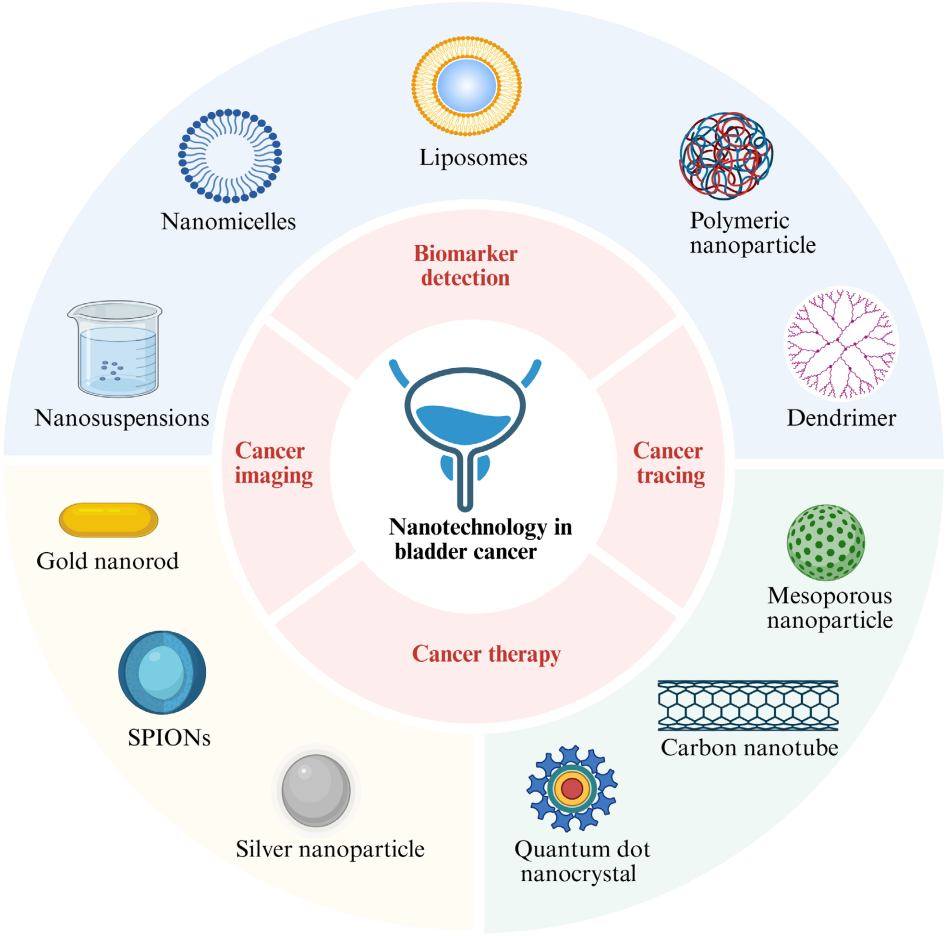

Figure 2. Schematic diagram of the application of nanotechnology for the diagnosis and treatment of bladder cancer. Created in BioRender (2025) https://biorender.com/xj7eiqe.

dots, gold nanoparticles and other magnetic nanoparticles are proved to be suitable for imaging [32].

2.1.1. Quantum Dots

Quantum dots (QDs) are semiconductors in the size of 2 - 10 nm, which are in core-shell construct with specific optical and magnetic properties. Thus, quantum dots have the great potential in the detection of cancer [33] [34]. Pan *et al.* investigated the biodistribution and toxicity of quantum dots when administered intravesically. CD47 is overexpressed on the surface of most cancer cells including bladder cancer, thus the study utilized the quantum dots conjugated with anti-CD47 to distinguish cancer cells from normal urothelium. ICP-MS shows that there is no obvious accumulation of anti-CD47-QD except in bladder. 7 days after injection, no acute toxicity is observed from the result of histology and organs weight [35] [36]. Another study utilized quantum dots as a fluorescent label for cancer imaging non-invasively. They conjugated prostate stem cell antigen (PSCA) monoclonal antibody with quantum dots. The QD-PSCA probe has a specific target to EJ cell lines which overexpress PSCA and emit stable and long-term fluorescence [37].

2.1.2. Superparamagnetic Iron Oxide Nanoparticles

Superparamagnetic iron oxide nanoparticles (SPIONs) consist of an iron oxide core and a functionalized shell designed to enhance stability and biocompatibility. When modified with antibodies, SPIONs can specifically target tumor sites, making them suitable as contrast agents in MRI and other imaging modalities [38]. One study utilized SPIO-R11, a SPION modified with a cell-penetrating peptide (CPP) for targeted delivery. The T24 cell lines present demonstrated a high uptake of SPION-R11, which resulted in a 73% reduction in T2 relaxation time during MRI, indicating the potential of contrast agents in cancer diagnosis [39]. Triantafyllou *et al.* developed an ultrasmall SPION (USPIO) to detect metastases of lymph nodes in normal size in bladder cancer patients, aiming to improve the N0 staging of bladder cancer. However, it still exists certain false negative report due to various factors [40].

2.2. Detection of Biomarkers

Numbers of research focus on biomarkers with high sensitivity and specificity via non-invasive approach. Urine samples are suitable for the sources of biomarkers. Nowadays biomarkers approved by FDA include NMP22, bladder tumor antigen (BTA), ImmunoCyt/Ucyt+ and UroVysion, while non-FDA approved biomarkers contain Survivin, CxBladder, Cytokeratin fragment 21.1 and there are also other biomarkers still in the study [41].

Immunosensors have high specificity in detection of interaction between antigen and target antibody. Electrochemical immunosensors turn the biological reaction into electrochemical reaction so that we could utilize them to detect the specific proteins or molecules expressing in bladder cancer cells [42]. With excellent electrocatalytic activity and biocompatibility, Noble metal nanoparticles, especially polymetallic nanomaterials, are suitable for the platform of label free immunosensor. Jia and his team designed a gold platinum nanostructure and the surface is conjugated with NMP22 antigen, thus an immunosensor is produced. The current response induced by immune reaction is in negative correlation with the concentration of NMP22 from 0.01 ng/mL to 10 ng/mL. The detection limit is 3.33 pg/mL. It also presents good sensibility and stability in the detection of urine samples [43]. Ma *et al.* developed an electrochemical immunosensor with reduced graphene oxide-tetraethylene pentamine (rGO-TEPA) and trimetallic Au-Pd-Pt nanoparticles to detect NMP22. It presents a low detection limit and high sensitivity to NMP22 in urine samples [44]. Another study used Al_2O_3 nanoprobe combined with galectin-1 antibody to develop an electrochemical immunosensor through positive dielectrophoresis (p-DEP). It could target galectin-1, which is a potential biomarker for bladder cancer. It shows to be available in T24 cell lysate spiked PBS and in human urine samples the immunosensor shows high sensitivity (82.1%) and specificity (80.8%) to the detection of galectin-1 [45].

Gold nanoparticles show great potential in the detection of biomarkers due to its physical and optical properties and their SPR effect. Eissa *et al.* utilized gold

nanoparticles to detect unamplified hepatoma upregulated protein RNA (HURP RNA). HURP RNA, as a new potential biomarker, shows good sensitivity and specificity in bladder cancer patients (78.7% and 94% respectively) in another unpublished study from Eissa's team. The result shows to be more effective in the diagnosis of bladder cancer in early stage with high sensitivity and specificity [46]. There are studies focusing on hyaluronidase (HAase) as a biomarker for bladder cancer. A fluorescence resonance energy transfer (FRET) gold nanoprobe functionalized by HA has high specificity in HA detection in urine samples of bladder cancer patients [47]. Gold nanoparticles with positive charge could interact with the negative charge HA, inducing the generate of gold aggregates, thus form the color shift from red to blue. It is more effective and sensitive than zymography for the detection [48].

2.3. Tracing

Nanomaterials could be used to trace cancer cells for long-term monitoring of bladder cancer. Lien *et al.* treated BFTC905 cell lines with the fluorescent and magnetic nanodiamond (FMND), which is a potential carbon nanomaterial. Both filial and parental generation of BFTC905 cells could be traced due to magnetic and fluorescent properties of FMND [49]. Alifu *et al.* developed a BPN-BBTD nanoparticle in the application of NIR-II emissive theragnostic system. NIR-II light shows the potential in cancer diagnosis and therapy due to good penetration to the tumor site. Forty-eight hours after the injection of BPN-BBTD and NIR-II fluorescence imaging at 785 nm in UMUC3 tumor-bearing mice, a strong fluorescence signal was observed at both subcutaneous and orthotopic bladder tumor sites. The fluorescence signal maintains visible after 32 days, which means that the nanoprobe could provide a long-term tracing of cancer cells [50] [51].

3. Nanomaterials and Their Application in Cancer Therapy

3.1. Liposome

Liposomes are nanosized particles in the shape of sphere with lipid bilayer membrane that is consist of amphiphilic phospholipids. The amphiphilic phospholipids in the aqueous condition could assemble into vesicles with lipid bilayer or multilayer so that the liposomes are able to envelop both lipophobic and hydrophilic drugs in the lipid bilayer [52] [53]. The membrane and the size of liposomes impact on the efficiency of the encapsulation and the circulation time [54]. The delivery system of liposomes mainly relies on the passive targeting mentioned above, which is associated with the tumor blood vessel structure [55]. To improve the targeting capability, it is often used of the conjugation of antigens, antibodies, ligands or enzymes to combine with molecules overexpressing on the cancer cells. Enveloped drugs could be released to target site triggered by pH, light, X-ray, enzyme or the temperature [52]. Liposomes could load different types of drugs, reduce the toxicity caused by off-target effect and prolong the circulation time [56].

Conventional chemotherapy drug doxorubicin is often treated with PEGylation

to prolong the circulation time. However, it is hard to increase the clinical passive targeting efficiency due to several causes [57]. To overcome these shortcomings, Mikhail *et al.* developed a thermosensitive liposome to entrap doxorubicin, combined with loco-regional hyperthermia (HT) for drug delivery to bladder *in vivo* on tumor beard porcine. Compared with the group treated with doxorubicin intravenous, the mean concentration of doxorubicin increases at 9.7 ± 0.67 μg/g and 1.2 ± 0.39 μg/g, respectively in the urothelium and muscular layer [58]. Brummelhuis *et al.* also used the thermosensitive liposome (DPPG-TSL-DOX) for the delivery to AY-27 cell bearing rat *in vivo*. At the dose of 2 mg/kg DOX, the experiment group treated with iv. DPPG2-TSL-DOX combined with HT at day 5 and 8 shows higher complete tumor response (70%) according to the results of histopathological evaluation, compared with control group without treatment and groups treated with iv. or DPPG-TSL DOX without HT [59]. Marian and co-workers developed a pH-sensitive liposome to deliver therapeutic protein to the epithelium. At the environment in specific pH below 6.5, liposomes are stimulated and induce the adhesion to epithelium [60]. Bacille calmette guerin (BCG) is applied for intermediate-risk NMIBC and high-risk MIBC, through presenting antigens and innate and adaptive immune responses after the internalization of BCG into the urothelium [61]. However, the insolubility in the aqueous and organic solvents limit the effectiveness. A research study designed liposomes functionalized with folic acid and the Pep-1 peptide. Folic acid receptor is overexpressed in the tumor cells, which could be used to design for the target. Pep-1 peptide, a cell-penetrating peptide, enhances the intracellular delivery of drugs. Dual targeting liposome performs enhanced uptake by 5637 and MBT2 cell lines and excellent antitumor effect [62] [63]. The above results indicate that liposomes modified in different approaches are able to present great efficacy in drug delivery.

3.2. Carbon Nanotubes

Carbon nanotubes (CNTs) are the members of the fullerene. CNTs could be classified into two groups, single walled CNTs (SWNTs) and multi-walled CNTs (MWNTs), based on their structure [64]. With the good strength, electrical and thermal conductivity, CNTs possess great potential in the medical fields [65]. CNTs possess a high specific surface area and aspect ratio, which makes it easier to functionalize the nanoparticles and to load drugs via covalent and non-covalent bonds [66] [67]. Because of their needle-like structure, CNTs could penetrate the membrane and be taken up by cells more easily [68]. CNTs, as nanoparticles, present the EPR effect, thus CNT could accumulate in the tumor tissues more than in other healthy tissues. In addition, CNTs have a strong absorption in the near infrared (NIR) region and this provides the prospect that CNT could be applied for photothermal therapy [69]. Virani *et al.* have designed a SWNT conjugated with annexin V (AV), which is capable of targeting phosphatidylserine (PS) that is overexpressed on the surface of tumor cells and tumor vasculature. Consequently, SWNT-AV can specifically target tumor sites and achieve high accumulation. Mice bearing with orthotopic

MB49 murine bladder cancer in the experimental group were treated with SWNT intravesically and subsequently irradiated under 30 s NIR light at an intensity of 50 J·cm^{-2} and 1.67 W·cm^{-2}. This treatment produced sufficient heat to induce ablation of the cancer cells. Twenty-four hours after treatment, the tumors were no longer visible on the bladder wall, and the healthy tissues remained undamaged. The cure rate after 116 days reached 50% [70]. CNTs are substances characterized by low solubility and dispersibility. To address these limitations, it is necessary to functionalize their surfaces to enhance their physical and biochemical properties. Common functionalization methods include PEGylation, the use of antibodies, RGD peptides, and epidermal growth factor (EGF), which are often employed to improve biocompatibility and biodegradability [71]. Pirarubicin and epirubicin are widely used chemotherapy agents. Suo *et al.* conjugated PEG-functionalized SWNT with pirarubicin, namely SWNT-THP. They evaluated the antitumor efficacy of SWNT-THP in comparison to THP alone, as well as the toxicity associated with SWNT in both *in vivo* and *in vitro* studies using BIU87 cell-bearing rats. The SWNT-THP group demonstrated a cancer cell apoptosis rate of 96.85% ± 0.85% *in vivo* and 74.35% ± 2.56% *in vitro*. In contrast, the THP-only group exhibited minimal antitumor effects. In addition, there were no obvious side effects attributed to SWNT, as indicated by observed symptoms and blood biochemistry results [72].

3.3. Polymer

Polymeric nanoparticles possess specific physical and chemical properties, including adjustable structures, low cost, simplicity of synthesis, and the ability to conjugate with functional units. These characteristics have attracted significant interest in the field of drug delivery [73]. The efficiency of drug delivery is closely associated with the nanoparticles' characterization. Factors such as size, surface charge, and hydrophobicity influence circulation time and biocompatibility. Additionally, morphology affects solubility, which directly determines therapy effect. Furthermore, the biological aspects are related to biodistribution and clearance [74]. Nowadays, several types of polymeric nanomaterials have been developed to deliver drugs to tumor sites, including polymer conjugate complexes, polymeric micelles and dendritic polymers. Due to their stability and biocompatibility, poly(lactide-co-glycolide) (PLGA), poly(lactide) (PLA), and poly(caprolactone) (PCL) are commonly used to synthesize nanocomplexes [75]. Martin *et al.* developed a PLGA-NP, modified with chitosan (CH), which facilitates the adhesion of nanoparticles to the bladder urothelium. The NPs containing survivin siRNA demonstrate a 10-fold increase in uptake and binding to the target site compared to unmodified NPs, resulting in a significant antitumor therapeutic effect on UM-UC-3 cells *in vitro* and in tumor-bearing mice *in vivo* [76].

The nuclear factor E2-related factor2 (Nrf2) can influence drug resistance in bladder cancer, and it has been shown that the adaptive responses induced by Nrf2 enhance drug resistance to the pro-oxidant drug cisplatin. Therefore, Nrf2 pre-

sents a potential target for overcoming drug resistance. Leanne and her team introduced positively charged units on the surface of the nanoparticles to facilitate interaction with negatively charged nucleic acids. The guanidine-terminated carbosilane dendrimers loaded with siNrf (siNNrf2-GCD) enhance the sensitivity of cisplatin chemotherapy and downregulate the expression of Nrf2 [77].

3.4. Metal Nanoparticles

Metal nanoparticles are mainly derived from iron, zinc, copper, and other noble metal such as gold and silver. They play an important role nowadays in drug delivery for treatment and tumor tracing or imaging for diagnosis [78]. In this section, we will focus on the application of gold nanoparticles and silver nanoparticles in treatment of bladder cancer.

3.4.1. Gold Nanoparticles

Gold nanoparticles (Au NPs) exhibit unique physical and chemical properties that make them promising candidates for cancer therapy and diagnosis. There are various types and shapes of nanoparticles, including nanorods, nanostars, and nanowreaths [79]-[82]. Through functionalization or conjugation with specific molecules, Au NPs could be effective in drug delivery and cancer therapy mainly depending on photothermal therapy [83].

Au NPs have been extensively studied as drug carriers due to their well-defined optical properties and biocompatibility. Hsu *et al.* developed an Au@TNA@MB nanoparticle, in which methylene blue (MB) serves as the photosensitizer and is adsorbed onto the surface of the Au@TNA nanoparticles. These NPs are modified with folic acid, which is overexpressed in cancer cells. It is investigated that after incubation with T24 cell lines for a specified duration, cells activity decreases significantly, while no significant phototoxicity is observed in SV-HUC-1 cells, which are normal urothelial cells [84].

Au NPs are widely utilized in photothermal therapy (PTT) due to their exceptional optical and electrical properties. The phenomenon of surface plasmon resonance (SPR) enables Au NPs to exhibit high absorption of near-infrared (NIR) light, which can penetrate deeper into tissues than visible light, thereby enhancing the effectiveness of treatment [85]. Yang and his team designed gold nanorods conjugated with anti-EGFR antibody. Epidermal growth factor receptors (EGFRs) are often overexpressed on the luminal surface of bladder cancer cells, making them a potential target for treatment. They employed NIR light irradiation (808 nm) on the externally delivered nanorods and subsequently investigated the effects of photothermal ablation *in vivo* on mice bearing T24 cells. Following treatment, bioluminescence signals and activity significantly decreased compared to mice that treated with only irradiation. These results indicate that gold nanorods are effective in photothermal therapy when combined with NIR light [86]. Another study examined whether the location of bladder cancer influences the effectiveness of photothermal therapy. Researchers accurately implanted cancer cells in different locations along the bladder wall of mice using advanced computer

technology. One group of cells was placed close to the skin, another in the lower half of the bladder, and the third on the side of the bladder. Following photothermal ablation with gold nanorods, the researchers investigated the treatment effects. The results indicated that only the first group, located closest to the skin, exhibited significant cancer damage, while the other groups showed negligible effects. The thermo-physiological responses indicate that the treatment effect also depends on the types of tissue that the irradiation should penetrate. These findings highlight the limitations of gold nanoparticles that must be addressed before they can be used in clinical practice [87]. Au NPs can also serve as radiation enhancers in cancer treatment, improving the effectiveness of radiation therapy and photothermal therapy [88].

3.4.2. Silver Nanoparticles

Silver nanoparticles (AgNPs) exhibit localized surface plasmon resonance (LSPR) similar to that of Au NPs, thus silver NPs could have a strong absorption of NIR light. For this, it is possible for AgNPs to develop photothermal therapy. One study focused on the synthesis of gold-silver nanoparticles coated with polydopamine (Au-Ag@PDA NPs). The polydopamine coating could provide NPs with high biocompatibility, stability and more excellent photothermal effects. The researchers investigated the antitumor effects of these nanoparticles on T24 cell lines *in vitro* and in T24-bearing mice *in vivo*. Under irradiation at 808 nm, the nanoparticles demonstrate significant inhibition of cell proliferation and alternation in cell cycle distribution, particularly in the S phase. In addition, they induce cells apoptosis through a mitochondria pathway. The photothermal effect significantly suppresses cancer growth *in vivo*. It has been shown that AgNPs enhance the generation of reactive oxygen species (ROS), which is reported as another mechanism of antitumor effect [89] [90]. Castiglioni and her team utilized polyvinylpyrrolidone (PVP)-coated silver nanoparticles to assess cytotoxicity in T24 cell lines. AgNPs could induce changes in cell morphology and disrupt the cytoskeleton. Through the production of ROS and activation of ERK1/2 the particles present the toxicity [91].

4. Clinical Application of Nanomaterials in Bladder Cancer

Bladder cancer is associated with high morbidity and mortality rates and is prone to recurrence. Preventing postoperative recurrence is crucial for improving the prognosis of patients with bladder cancer. However, current diagnostic and therapeutic methods demonstrate limited efficacy in clinical practice, highlighting the need for new diagnostic techniques that offer greater specificity and sensitivity, as well as more effective therapeutic agents. Nanomedicine has attracted considerable interest among researchers owing to its modifiable volume and surface area, capabilities for controlled drug release, distinctive magnetic or optical properties, and a comparatively high biosafety profile.

In the clinical diagnosis and treatment of bladder cancer, the application of nanotechnology is gradually transitioning from laboratory research to clinical

practice (Table 1) [92]. However, this translation process still encounters numerous challenges and opportunities. Currently, the number of nano-formulations that have progressed to clinical trials remains relatively limited, primarily focusing on phase I and phase II studies. This indicates that the efficacy of nanomaterials for bladder cancer patients, as well as their long-term biocompatibility, remains inconclusive. In this discussion, we examine the results derived from available preclinical studies. Foremost among the concerns is safety, which represents one of the most significant barriers to the integration of nanomaterials into clinical applications. Various types of nanomaterials, including liposomes, polymers, carbon-based nanoparticles, and metal-based nanoparticles, have been explored for the diagnosis and treatment of bladder cancer. At the same time, the local and systemic toxicity associated with nanoparticle treatments warrants careful consideration. For instance, the complement-activating effect of liposomes can heighten the risk of immunogenicity, potentially leading to allergy-like reactions in some patients and limiting the feasibility of repeated dosing. Quantum dots can elicit cytotoxic reactions when not adequately surface-coated, resulting in the release of toxic ions. Metallic nanoparticles, including gold and silver, can induce normal cell death and suppress immune responses. Therefore, it is essential to determine the optimal concentration for their therapeutic action to achieve a balance between safety and efficacy, which is critical for clinical applications. Additionally, other potential issues must be addressed, including the metabolism and biodistribution of nanoparticles within the body, as well as strategies to enhance their accumulation

Table 1. Representative nanomedicines in clinical trials for bladder cancer.

Drug	Formulation	Conditions	Sponsor	Phase	NCT Number
Liposomal doxorubicin	Liposome	Solid Tumors	Santa Maria Biotherapeutics	I	NCT02262455
PLZ4-coated paclitaxel-loaded mi-celles (PPM)	Micelles	Non-muscle-invasive Bladder Cancer	VA Office of Research and Development	I	NCT05519241
ONM-100	Micelles	Urothelial Carcinoma	OncoNano Medicine, Inc.	II	NCT03735680
Genexol PM	Micelles	Bladder Cancer	Asan Medical Center	II	NCT01426126
Ferumoxtran-10 (USPIO)	Magnetic Nanoparticles	Bladder Neoplasms	University Health Network, Toronto	I/II	NCT00188695
Ferumoxytol	Magnetic Nanoparticles	Bladder Cancer	National Cancer Institute (NCI)	II	NCT02141490
Nanoparticle camptothecin	Nanoparticle	Urothelial Carcinoma	National Cancer Institute (NCI)	I/II	NCT02769962
NanoDoce®	Nanoparticle	Bladder Cancer	NanOlogy, LLC	I/II	NCT03636256
NC-6004	Nanoparticle	Solid Tumors	NanoCarrier Co., Ltd	I/II	NCT02240238
ABI-009	Nanoparticle	Non-muscle Invasive Bladder Cancer (NMIBC)	Aadi Bioscience, Inc.	I/II	NCT02009332
EP0057	Nanoparticle	Urothelial Carcinoma	National Cancer Institute (NCI)	I/II	NCT02769962

and maximize their therapeutic effects. Furthermore, the challenge of scaling up production must be addressed, as achieving batch-to-batch consistency in the manufacture of polymer nanoparticles is often difficult. Functional modifications further complicate the process and increase production costs. The associated economic barriers are also significant, as the elevated costs of nanotechnology-based treatments make them considerably more expensive than traditional chemotherapy. Finally, to facilitate the translation of nanoparticles into clinical practice, it is imperative that nanoparticle preparation adheres to established standards of quality, control, and production specifications.

5. Conclusion

Bladder cancer is a common malignant tumor of the urinary system. It is essential to enhance diagnosis approaches and treatment strategies due to the unsatisfactory accuracy and high recurrence rate associated with conventional therapy. The integration of nanotechnology, characterized by its excellent penetration, biocompatibility, and specific targeting of tumor sites, significantly improves diagnostic sensitivity. Additionally, targeted drug delivery systems, augmented by nanoparticles and their inherent anti-tumor effects, enhance the effectiveness of treatment. Nowadays, multifunctional nanomaterials play an important role in cancer diagnosis and therapy. The development and application of theragnostic nanomaterials in clinical practice could facilitate the early diagnosis of bladder cancer and improve treatment outcomes and prognosis. Nonetheless, obstacles persist in the translation of nanoparticles into clinical applications. These challenges encompass issues related to the safety of nanomaterials, the need for standardized production processes, and considerations regarding cost. Addressing these factors is essential for enhancing the clinical translation of nanoparticle technologies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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