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REVIEW

Gold Nanoparticles in Bladder Cancer Applications: A Paradigm Shift from Diagnostic Tools to Integrated Theranostic Platforms

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Background: Bladder cancer, particularly non-muscle-invasive bladder cancer (NMIBC), poses significant clinical challenges due to its high recurrence rate. Traditional diagnostic approaches such as cystoscopy and urine cytology have limitations, including invasiveness and insufficient sensitivity. Gold nanoparticles (AuNPs) offer unique opportunities to address these challenges with their surface plasmon resonance effect, biocompatibility, and ease of functionalization.

Methods: Through critical review of recent literature, this paper outlines the application principles, achievements, and mechanisms of AuNPs in bladder cancer, including in vitro diagnostics, multimodal molecular imaging, photothermal therapy, targeted drug delivery, radiotherapy sensitization, and tumor immune microenvironment remodeling.

Main Findings: AuNPs are driving a paradigm shift in bladder cancer management. In diagnostics, AuNP-based biosensors enable ultra-sensitive detection of urinary biomarkers. In imaging, they serve as effective contrast agents for enhanced visualization. For therapy, AuNP-mediated photothermal therapy enables precise tumor ablation, and as drug carriers, they help overcome chemoresistance. Additionally, AuNPs demonstrate potential in remodeling the immunosuppressive microenvironment through modulation of signaling pathways and tumor-associated macrophages.

Conclusion: Gold nanoparticles are transforming bladder cancer toward precision, minimally invasive, and personalized treatment models. However, it is important to acknowledge that most current findings remain in the preclinical stage, and significant translational barriers—particularly long-term biosafety and standardized production—must be addressed before widespread clinical adoption.

Keywords: gold nanoparticles, bladder cancer, non-invasive diagnosis, drug delivery, tumor microenvironment, nanomedicine

Introduction

Bladder cancer ranks as the tenth most common malignancy worldwide, with over 570,000 new cases and more than 210,000 deaths annually.[1] Among these, NMIBC accounts for 70–80% of initial diagnoses. Although transurethral resection of bladder tumor (TURBT) combined with postoperative intravesical chemotherapy or immunotherapy can achieve favorable outcomes, 50–70% of patients experience recurrence within five years, with 10–30% progressing to muscle-invasive bladder cancer (MIBC).[2] This "recurrence-treatment-recurrence" cycle consumes substantial medical resources and imposes significant physical and psychological burdens on patients. Traditional cystoscopy combined with urine cytology remains the gold standard for bladder cancer diagnosis and monitoring. However, cystoscopy is invasive, costly, and may cause complications, while urine cytology exhibits low sensitivity, particularly for low-grade bladder cancer.[3] Therefore, developing non-invasive, highly sensitive diagnostic methods and efficient, specific therapeutic strategies has become a critical need in bladder cancer research.

In this context, gold nanoparticles (AuNPs) have shown tremendous potential. As a prominent member of the metal nanoparticle family, AuNPs offer a versatile platform compared to other metallic systems due to their superior stability and tunable surface chemistry.[4–6] Their application in oncology has paved the way for more complex nanomedicines,

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though their safety profile requires rigorous evaluation across different physiological environments.[7,8] Owing to their unique physicochemical properties such as surface plasmon resonance (SPR), high surface-to-volume ratio, ease of functionalization, and excellent biocompatibility, have shown tremendous potential in biomedical applications.[9–14] In bladder cancer management, AuNPs have evolved from initially serving solely as diagnostic tools to multifunctional platforms integrating diagnosis, treatment, and immunomodulation, providing innovative approaches to address key challenges in bladder cancer management. António et al comprehensively summarized gold nanoparticle-based urine biodetection methods, emphasizing their potential for non-invasive diagnosis.[15]

However, existing reviews primarily focus on specific application areas, lacking a systematic description of AuNPs' "role evolution" in bladder cancer theranostics. This article systematically reviews recent advances in AuNP applications in bladder cancer diagnosis and treatment, aiming to highlight the development trend of AuNPs transitioning from single applications to integrated theranostic platforms and the underlying driving mechanisms. We will explore how AuNPs overcome limitations of traditional therapeutic approaches through multiple mechanisms, including enhancing diagnostic sensitivity, improving therapeutic targeting, modulating the tumor microenvironment, and overcoming treatment resistance. Additionally, this paper provides in-depth analysis of current translational challenges and future directions, offering a reference for the clinical translation of AuNPs in bladder cancer.

Unique Properties of Gold Nanoparticles and Their Precision Adaptation for Bladder Cancer Management

Core Physicochemical Properties: The Foundation for Multifunctionality

The core physicochemical properties of AuNPs include:

- **Surface Plasmon Resonance (SPR)**: This is fundamental to their optical and photothermal applications. Upon excitation by light at specific wavelengths, AuNPs can efficiently convert photonic energy into thermal energy, providing the physical basis for photothermal therapy (PTT) and photoacoustic imaging (PAI).[16]
- **High Surface-to-Volume Ratio and Ease of Functionalization**: The large surface area makes them ideal "multifunctional linking platforms." Through well-established thiol-gold chemistry, targeting molecules (eg, antibodies, aptamers), therapeutic drugs, or imaging probes can be easily covalently conjugated to their surface, enabling modular and diverse functionality.[17]
- **Controllable Size and Morphology**: By tuning the size and morphology of AuNPs (eg, nanospheres, nanorods, nanostars), their SPR absorption peak can be precisely adjusted to the near-infrared (NIR) window, which offers better tissue penetration for deep tumor imaging and therapy.[18]
- **Excellent Biocompatibility and Stability**: The chemical inertness of gold provides good biocompatibility, while surface modifications (eg, PEGylation) can further prolong their circulation time in vivo and confer targeting or responsiveness to specific microenvironments.[13]

Targeting Strategies Responsive to the Bladder Tumor Microenvironment

AuNPs can be functionally designed to target specific features of the bladder tumor microenvironment:

- **Advantages of Local Drug Delivery**: The intravesical administration environment provides natural advantages for local application and retention of AuNPs, achieving high local drug concentrations while reducing systemic toxicity.[19]
- **Passive and Active Targeting**: The enhanced permeability and retention (EPR) effect in bladder tumor tissues facilitates passive targeting of AuNPs.[20] More importantly, tumor-specific receptor expression (eg, EGFR, folate receptor) provides a molecular basis for active targeting using antibody- or aptamer-modified AuNPs.[21]
- **Microenvironment-Responsive Drug Release**: Through sophisticated chemical design, AuNPs can be engineered as "smart" drug carriers that respond to acidic pH in the tumor microenvironment or specifically overexpressed enzymes (eg, hyaluronidase) to achieve on-demand, precise drug release.[21]

Based on these properties, AuNPs have become ideal carriers for constructing theranostic platforms. They can integrate diagnostic modules (eg, SERS reporters, photoacoustic contrast agents) and therapeutic modules (eg, chemotherapeutics, photothermal conversion agents, radiotherapy sensitizers) into a single nanoparticle. This not only enables "diagnosis-guided treatment" (eg, initiating photothermal therapy after precise lesion localization through imaging) but also allows real-time monitoring of therapeutic effects during treatment and adjustment of treatment regimens based on feedback, ultimately achieving truly personalized precision medicine. These versatile properties are schematically summarized in Figure 1.

Cellular Uptake and Intracellular Trafficking

The biological efficacy of AuNPs depends heavily on their internalization pathways, which typically involve clathrin-mediated endocytosis, caveolae-mediated endocytosis, or macropinocytosis, depending on particle size and surface charge. Once internalized, the ability of AuNPs to achieve endosomal escape—often through the "proton sponge" effect or membrane fusion facilitated by surface modifications—is critical for delivering therapeutic payloads directly to the cytosol or nucleus.[22]

Applications of Gold Nanoparticles in Bladder Cancer Diagnosis: Pursuing Non-Invasiveness and Ultra-Sensitivity

Ultra-Sensitive Detection Platforms Based on Urinary Biomarkers: Revolutionizing Liquid Biopsies

Urine, as the most direct "information source" for bladder cancer, is an ideal sample for non-invasive diagnosis (ie, liquid biopsy). However, urinary biomarkers are present at extremely low concentrations, imposing high demands on detection sensitivity. Leveraging their unique signal amplification mechanisms, such as aggregation-induced color changes, surface-enhanced Raman scattering (SERS) effects, and electrochemical signal enhancement, AuNPs have pushed the detection limits of these biomarkers to new heights.

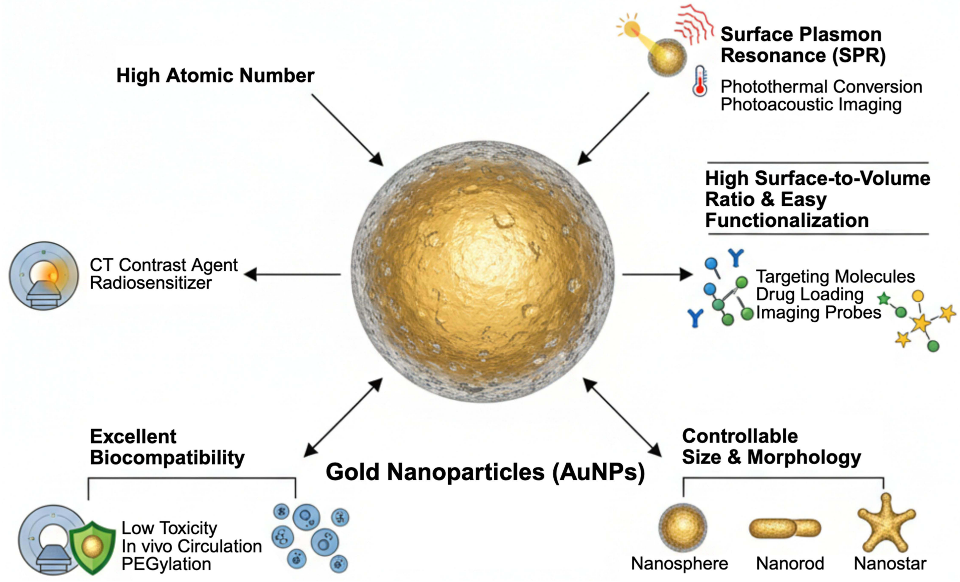

Figure 1 Schematic illustration of the versatile properties of gold nanoparticles (AuNPs) for biomedical applications. Schematic illustration of the versatile properties of gold nanoparticles (AuNPs) for biomedical applications. The central image highlights key characteristics of gold nanoparticles that support integrated bladder cancer theranostics: the unique Surface Plasmon Resonance (SPR) effect enables efficient photothermal conversion for photoacoustic imaging; the High Surface-to-Volume Ratio & Easy Functionalization allow for versatile conjugation of targeting ligands, therapeutic drugs, or imaging probes; Controllable Size & Morphology (eg, nanorods or nanostars) enable optical tuning to the near-infrared window for enhanced tissue penetration; Excellent Biocompatibility, often improved by surface modifications like PEGylation, ensures low toxicity and prolonged circulation; and the High Atomic Number renders AuNPs effective as CT contrast agents and radiosensitizers to enhance radiotherapy efficacy.

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Telomerase Activity Detection: From Laboratory Validation to Clinical Application

Telomerase, as a bladder cancer-specific biomarker, is overexpressed in approximately 85–90% of bladder cancer cases but is barely expressed in normal urothelial tissues, making it an ideal diagnostic target.[23] Researchers have developed various ingenious detection strategies using AuNPs. Wang et al[24] pioneered the combination of strand displacement amplification (SDA) with dynamic light scattering (DLS). Through telomerase extension products triggering SDA reactions, leading to the aggregation of oligonucleotide-modified AuNP probes, telomerase detection could be achieved with only 3 MCF-7 cells, showing a linear range of 5–1000 cells. Li et al[25] further developed a DLS-based method for urinary telomerase activity detection. Telomerase extension products triggered hybridization chain reactions, causing DNA-modified gold nanoparticles to aggregate and increase in hydrodynamic diameter. The detection limit was as low as 4 MCF-7 cells, and it was successfully applied to distinguish urine samples from bladder cancer patients.

Zou et al[26] developed a highly sensitive telomerase activity detection method based on catalytic hairpin assembly-DLS (CHA-DLS), using the change in particle size of AuNP probes as the detection signal: telomerase extension products (TEP) trigger CHA reactions, forming numerous AuNP-H1/H2 nanostructures, resulting in a significant increase in particle size detected by DLS. This technology could detect telomerase activity as low as 6 MCF-7 cells, 10 Huh7 cells, and 35637cells.

Although these DLS-based methods are sensitive, they require sophisticated instruments. To promote point-of-care testing (POCT), Duan et al proposed a more intuitive bidirectional colorimetric strategy based on four detection color states of bifunctional gold nanoparticle probes (blue, purple, red, and precipitation), enabling intuitive judgment of telomerase activity and bladder cancer diagnosis. This method could distinguish normal individuals from bladder cancer patients by the naked eye or UV-Vis spectroscopy, showing great potential for POCT in resource-limited areas.[27] To balance sensitivity and accuracy, Feng et al[28] developed a dual-mode probe based on SERS and colorimetry, providing a more reliable tool for telomerase detection.

Hyaluronidase (HAase) Detection: From Colorimetry to Multi-Modal Sensing

Hyaluronidase (HAase) is highly expressed in various malignancies, and its activity is closely related to bladder cancer grading and progression, making it another highly promising urinary biomarker.[29] Xu et al[30] pioneered the use of electrostatic interactions between positively charged AuNPs and negatively charged hyaluronic acid (HA) to construct a colorimetric detection method. After HAase degraded HA, AuNPs aggregated, producing an intuitive “red-blue” color change. Although this method is simple and straightforward, it is susceptible to interference from complex components in urine.

To further address issues of sensitivity and specificity and enhance performance, researchers have developed more sophisticated sensing strategies. Cheng et al[31] constructed probes based on fluorescence resonance energy transfer (FRET), while Wang, Si, and Chen et al[32–34] turned to SERS technology, designing different Raman reporters and internal references to achieve ultra-sensitive and highly precise quantitative detection of HAase, with detection limits as low as 0.32–0.4 mU/mL. These studies mark the transition of HAase detection from qualitative/semi-quantitative to high-precision quantitative analysis.

Multi-Biomarker Detection Strategies: Enhancing Diagnostic “Resolution”

Given the heterogeneity of bladder cancer, single biomarkers often result in “false positives” or “false negatives,” limiting diagnostic accuracy. Therefore, simultaneous detection of multiple biomarkers using a “combination approach” to enhance diagnostic precision is an inevitable trend. AuNP-based platforms demonstrate significant advantages in multi-biomarker detection due to their ease of functionalization.

Electrochemical immunosensors are particularly favored for their high sensitivity, low cost, and ease of miniaturization. For example, Zhang, Zhou, and Wang et al[35–37] constructed sensors that can simultaneously or separately detect multiple bladder cancer-related protein biomarkers such as CFHR1, NMP22, and NUMA1, with detection limits reaching the astonishing fg/mL level. Li et al utilized SERS technology to achieve simultaneous quantitative detection of FGFR3 and NMP22 by constructing a unique AgAu@Ag core-shell structure substrate.[38] This fully demonstrates the great potential of AuNP platforms in developing high-throughput, high-sensitivity diagnostic tools.

Exosomal microRNA Detection: Opening a New Chapter in Liquid Biopsy

MicroRNAs (miRNAs) carried by exosomes are considered "messengers" reflecting tumor status, representing a cutting-edge direction in liquid biopsy. However, exosomal miRNAs in plasma or urine are present in extremely minute quantities, making their precise capture and signal amplification major technical challenges. Zhang et al[39] ingeniously combined inorganic nanoscintillators with DNAzyme walkers to detect miRNAs at the femtomolar level. Meanwhile, Liyanage, Hati, and colleagues[40,41] utilized the unique localized surface plasmon resonance (LSPR) effects of structures like gold triangular nanoprisms to further push detection sensitivity to the attomolar level and successfully distinguished between early and late-stage bladder cancer patients. In addition to pursuing ultimate sensitivity, developing detection methods suitable for different scenarios is also crucial. Lin et al developed pH-responsive DNA nanoswitches for SPR platform detection;[42] Nossier[43] and Mollasalehi et al[44] focused on developing amplification-free, user-friendly colorimetric or cross-linking-free hybridization techniques, thereby paving the way for point-of-care testing (POCT); Masterson et al combined SERS and plasmon-enhanced fluorescence (PEF) to develop a multimodal analysis method, effectively reducing false positives and false negatives and demonstrating high stability in clinical applications.[45] These diverse studies collectively promote the clinical translation of exosomal miRNAs as bladder cancer biomarkers. A comparison of the major AuNP-based urinary biomarker detection methods discussed in this section is provided in Table 1.

Other Biomarker Detection Methods

In addition to the above biomarkers, AuNP-based detection methods have also been used for various other bladder cancer-related molecules. These include rapid colorimetric detection of total gelatinases (MMP-2/9) activity[46] and HURP RNA;[47] competitive amperometric immunosensor detection of p53 protein;[48] nanobody-coupled gold nanoparticle cluster

Table 1 Comparison of Major Urinary Biomarker Detection Methods for Bladder Cancer Based on Gold Nanoparticles

Detection Biomarker	Detection Method (Core Technology)	Sensitivity (Detection Limit/Sample Requirement)	Selectivity/Specificity Advantages	Clinical Application Potential and Limitations	Ref.
Telomerase	Dynamic Light Scattering (DLS)	4-6 cells	Strong specificity based on enzyme activity	High (POCT potential), but DLS equipment requires skilled operators	[24–27]
	Colorimetric/Dual-Mode	Visible to naked eye	Intuitive and fast	Extremely high (point-of-care), suitable for resource-limited areas	[27, 28]
Hyaluronidase	Colorimetry	~10 mU/mL	Intuitive "red-blue" color change	Moderate, susceptible to interference from urine components	[30]
	Surface-Enhanced Raman Scattering	0.32–0.4 mU/mL	Strong specificity from "fingerprint" Raman signals	High (high-precision quantitative), requires sophisticated technology	[32–34]
Multi-biomarkers	Electrochemical Immunosensing	fg/mL level	High sensitivity with multi-channel signal differentiation	High (screening), but equipment complex	[35–37]
Exosomal microRNAs	Localized Surface Plasmon Resonance	Attomolar level	Stable LSPR signal, anti-interference	Extremely high (cutting edge of liquid biopsy), technically challenging	[40, 41]
	SERS/Plasmon-Enhanced Fluorescence	Single molecule level	Complementary dual-mode, reduces false positives	Extremely high, excellent clinical stability	[45]
	pH-responsive DNA switches/Non-crosslinking hybridization	-	Simple operation, no amplification needed	Moderate (POCT direction), sensitivity needs improvement	[42–44]

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detection of survivin protein;[49] and direct detection of long non-coding RNA UCA1 based on nanoprobe hybridization technology.[50] Similarly, Jazayeri et al[51] developed a colorimetric method based on antibody-conjugated AuNPs that can rapidly and non-invasively detect survivin protein in urine, showing potential in cancer grading (especially distinguishing low-grade from high-grade), providing new tools for early diagnosis and prognosis of bladder cancer. These studies collectively enrich the "toolbox" for non-invasive bladder cancer diagnosis (Figure 2A).

Epigenetic Biomarker Detection: DNA Methylation

Emerging research highlights urinary DNA methylation as a highly effective biomarker for early detection and recurrence monitoring. AuNP-based platforms are now being engineered for the ultrasensitive detection of these epigenetic markers. For instance, plasmonic biosensors utilizing functionalized AuNPs can capture methylated DNA fragments with high specificity, offering a non-invasive "liquid biopsy" tool that significantly enhances diagnostic resolution.[52]

Enhanced Imaging Diagnosis

CT/MR Dual-Modal Contrast Agents: High-Resolution Bladder Imaging

The high atomic number of AuNPs makes them excellent CT contrast agents, outperforming the clinically used iohexol.[53] To combine the high resolution of CT with the excellent soft tissue contrast of magnetic resonance imaging (MRI), Wen

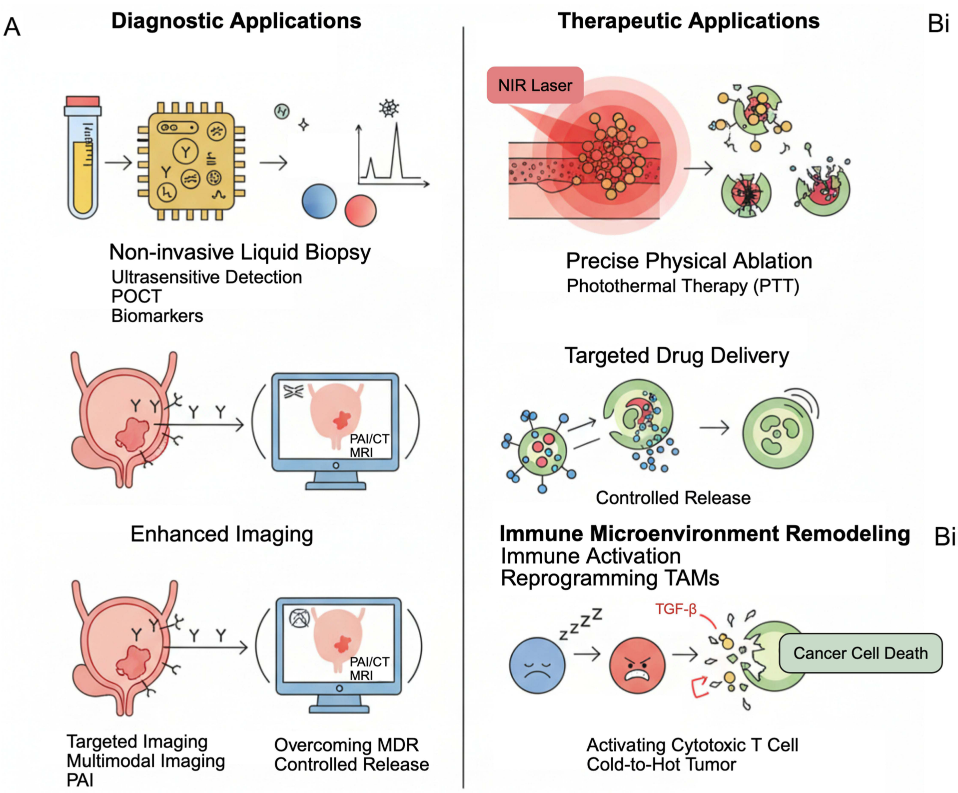

Figure 2 Schematic overview of the dual roles of gold nanoparticles (AuNPs) in cancer theranostics, encompassing diagnostic and therapeutic applications. (**A**) Diagnostic Applications. AuNPs enable advanced cancer diagnosis through two main approaches. Non-invasive Liquid Biopsy: AuNP-based biosensors facilitate ultrasensitive and point-of-care detection of tumor biomarkers in liquid samples (eg, urine), indicated by a colorimetric change or a Surface-Enhanced Raman Scattering (SERS) spectral signal. Enhanced Imaging: Functionalized AuNPs, administered locally, specifically accumulate at the tumor site. This targeted accumulation allows for high-resolution and high-contrast multimodal imaging (eg, Photoacoustic Imaging, CT) to precisely delineate tumor margins. (**Bi**) Therapeutic Applications. AuNPs serve as a multifunctional platform for targeted cancer therapy. Precise Physical Ablation: Upon irradiation with a near-infrared (NIR) laser, AuNPs generate localized hyperthermia, inducing photothermal therapy (PTT) for effective tumor ablation. Targeted Drug Delivery: AuNPs act as nanocarriers to deliver therapeutic agents directly to cancer cells, enabling controlled drug release and overcoming multidrug resistance. (**Bii**) Immune Microenvironment Remodeling: AuNPs can modulate the tumor immune microenvironment by reprogramming tumor-associated macrophages (TAMs) from a pro-tumor M2 phenotype to an anti-tumor M1 phenotype and activating cytotoxic T cells, thereby turning an immunologically "cold" tumor into a "hot" one.

et al[54] developed dendrimer-entrapped gold nanoparticles combined with Gd(III) chelates, successfully achieving CT/MR dual-modal imaging of rat bladders.

Photoacoustic Imaging (PAI): Early Visualization of Tiny Lesions

PAI combines the advantages of optics and ultrasound, and AuNPs are ideal contrast agents for it. Jeon et al[55] showed that transurethral injection of gold nanocages (GNCs) enhanced the photoacoustic signal in rat bladders by approximately 2240%, demonstrating the enormous potential of AuNPs as basic contrast agents. Building on this, Li et al[56] further explored their functional diversity by conjugating different antibodies to gold nanorods with different absorption peaks, successfully achieving simultaneous imaging of multiple targets, breaking through the limitation of traditional PAI being limited to anatomical imaging. The key to advancing this technology to clinical application is the ability to detect tiny lesions. To this end, Alchera and Venegoni et al[57,58] developed gold nanorods (GNRs) targeting integrin α5β1, visualizing tiny lesions smaller than 1 mm in animal models, providing a powerful tool to solve the problem of postoperative minimal residual disease monitoring. Canning et al[59] combined photoacoustic imaging with photothermal therapy, achieving real-time thermal imaging monitoring and dosimetry during the treatment process, showing great potential for theranostics.

Surface-Enhanced Raman Scattering (SERS): Achieving Molecular-Level Diagnosis

SERS technology can provide "molecular fingerprint" information of tissues and cells. Jin et al[28] used AuNPs as enhancement substrates to successfully distinguish normal and cancerous bladder tissues. Yang et al[60] used SERS platforms to screen specific membrane receptors for different grades of bladder cancer cells, providing new targets for precise diagnosis and targeted therapy.

Microfluidic Technology and Rapid Diagnostic Platforms

Combining AuNP detection technology with microfluidic chips is an important direction to achieve automated, high-throughput, and point-of-care testing (POCT). Thompson et al[61] developed a 3D-printed modular microfluidic system for AuNP colorimetric detection of HAase. Sun et al[62] combined aptamer biochips with AuNPs, achieving rapid simultaneous detection of bladder cancer-related infection bacteria through electrospray printing technology.

Applications of Gold Nanoparticles in Bladder Cancer Treatment: Advancing Toward Precision Synergy and Immune Remodeling

Gold nanoparticles represent a robust and sophisticated toolkit for the mechanical and thermal eradication of malignant cells, primarily operating through the complementary avenues of photothermal therapy (PTT) and the targeted enhancement of radiographic sensitivity. By functionalizing AuNPs with highly specific ligands—most notably anti-EGFR antibodies or integrin α5β1—researchers have successfully engineered "precision-guided" agents that selectively localize within the complex bladder tumor microenvironment.[63–65] These engineered platforms possess the unique ability to efficiently transform absorbed near-infrared (NIR) light into concentrated hyperthermia, thereby inducing localized cytolysis through thermal stress while effectively minimizing systemic exposure and collateral damage to healthy tissues.

While various gold-based architectures have been explored, empirical evidence suggests that specific morphologies, such as silica-cored gold nanoshells, exhibit a superior capacity for photothermal killing, often requiring a significantly lower particle concentration than other nanostructures to achieve comparable therapeutic outcomes[66] (Figure 2Bi).

One of the most formidable challenges in the clinical implementation of PTT involves the prevention of accidental thermal impairment to the delicate and healthy urothelial lining. To mitigate this risk, recent advancements have introduced armored gold nanostars integrated with real-time photoacoustic thermometry. This integration facilitates meticulous dosimetry control and has resulted in 100% survival rates within preclinical bladder cancer models by allowing clinicians to monitor temperature changes in situ.[59] Furthermore, advanced computational and numerical simulations have elucidated that variables such as the precise anatomical position of the tumor and the specific composition of overlying tissues significantly modulate the overall efficiency of PTT. This underscores the critical necessity for individualized optimization of both laser parameters and nanoparticle dimensions in a patient-specific manner.[67]

Beyond pure thermal ablation, the high atomic number of gold renders these nanoparticles excellent candidates for radiotherapy sensitization. AuNPs tend to accumulate within the tumor-associated stroma, functioning as radiosensitizers that amplify the therapeutic index of X-ray irradiation—a strategy that is particularly vital for developing bladder-preserving protocols in patients with muscle-invasive bladder cancer (MIBC).[68] It is important to note, however, that while AuNPs produce significant sensitizing effects under standard clinical X-ray irradiation, their efficiency is markedly reduced when utilizing proton beam therapy. This distinction is a critical consideration for the design of future clinical trials and the selection of radiation modalities.[69] To further ensure long-term biosafety, the field is increasingly shifting toward the development of renal-clearable, ultra-small AuNPs with diameters of less than 6 nm, which facilitates rapid clearance and minimizes the risk of chronic organ accumulation.[70] Major physical therapy and sensitization strategies are summarized in Table 2.

Strategies for Targeted Drug Delivery and the Mitigation of Chemoresistance

In the realm of pharmacology, AuNPs function as highly versatile nanocarriers designed to circumvent the intrinsic limitations of conventional intravesical chemotherapy, such as poor drug selectivity and the rapid onset of multidrug resistance (MDR). The successful penetration of these carriers often depends on overcoming structural barriers; in this context, the development of molecular tools to assess collagen denaturation has provided essential methodologies for evaluating the physical impediments within the bladder wall that hinder drug diffusion.[76] Beyond their role as passive vehicles, AuNPs themselves can exert direct inhibitory effects on bladder cancer cells by inducing oxidative stress and activating ROS-mediated apoptotic signaling pathways.[77,78]

Targeted delivery via folate receptor-specific or cell membrane-camouflaged AuNPs significantly elevates intracellular drug concentrations while effectively bypassing traditional efflux pump-mediated resistance[71,72] (Figure 2Bi and Table 2). These platforms are also being engineered to combat complex molecular drivers of resistance; for instance, since ac4C modification-mediated DNA damage repair has been identified as a primary engine of cisplatin resistance, future AuNP systems could co-deliver siRNAs or small-molecule inhibitors targeting NAT10 to restore chemosensitivity.[79] Furthermore, AuNPs have proven to be superior scaffolds for Antibody-Drug Conjugates (ADCs). Utilizing AuNPs to deliver HER2-targeting ADCs (such as RC48) can facilitate enhanced tissue penetration and achieve

Table 2 Combined Bladder Cancer Treatment Strategies Mediated by Gold Nanoparticles and Their Synergistic Mechanisms

Combined Treatment Strategy	Nanocarrier/ System	Treatment Module 1	Treatment Module 2	Synergistic Mechanism	Ref.
PTT + Chemotherapy	Cell membrane-coated Au nanorods	Photothermal ablation	β-lapachone (NQO1 enzyme-activated prodrug)	PTT increases membrane permeability, promoting drug uptake; chemotherapy drugs eliminate residual cells after hyperthermia	[71]
	Folate receptor-targeted thermosensitive liposomes	Photothermal effect	Doxorubicin	PTT reverses multidrug resistance, increases intracellular drug concentration	[72]
PTT + Ferroptosis	Zr(Cu)-MOF @Au@DHA	Photothermal ablation	Ferroptosis induction (DHA)	Oxidative stress induced by PTT and ferroptosis core mechanism (lipid peroxidation) have additive effects	[73]
PTT + Immunotherapy	Immunomodulatory intelligent hydrogel	Photothermal ablation	Immunomodulation (inducing systemic immune response)	PTT causes immunogenic cell death, releasing tumor antigens; removes immunosuppressive TAMs, forming "hot tumor"	[74]
Image-guided + PTT + Chemotherapy	$NaYF_4:Yb^{3+},Er^{3+}$/AuNR nanoclusters	Upconversion imaging/ chemotherapy	Photothermal therapy	Image guidance achieves precise positioning and dose control; chemotherapy and PTT synergistically kill cells	[75]

more regulated, responsive drug release within the unique bladder microenvironment compared to traditional systemic administration.[80,81]

Remodeling the Tumor Microenvironment and Enhancing Immunotherapy

AuNPs are undergoing a functional transition from passive tumor killers to active immune activators capable of fundamentally remolding the immunosuppressive "tumor soil". These nanoplatforms can trigger the repolarization of pro-tumor M2-type macrophages into anti-tumor M1-type phenotypes and activate the cGAS-STING signaling pathway to dismantle the mechanisms of local immune evasion[74] (Figure 2Bii). By conjugating particles with tumor-specific antigens or utilizing them to directly neutralize immunosuppressive factors like TGF-β1, clinicians can effectively convert immunologically "cold" tumors into "hot" ones characterized by robust T-cell infiltration.[82,83] The integration of AuNPs with natural plant extracts, such as EGCG or Abies spectabilis, has also demonstrated synergistic anti-tumor effects that far exceed the performance of single components by activating mitochondrial-dependent apoptosis.[84,85] Furthermore, combining AuNPs with ferroptosis-inducing agents like DHA or RSL3 within intelligent hydrogel systems allows for a "divide-and-rule" strategy that promotes immunogenic cell death and fosters durable systemic anti-tumor immunity.[73,74,86,87] Relevant immune synergistic mechanisms are detailed in Table 2.

Towards Theranostic Integration: A Closed-Loop AuNP Platform

The ultimate paradigm shift in bladder cancer management involves the construction of a closed-loop clinical workflow. By utilizing specific molecular targets such as HER2 or FGFR3, functionalized AuNPs enable high-precision patient stratification through ultra-sensitive SERS detection or multimodal imaging techniques.[38,57,60] In this integrated model, therapeutic interventions—such as PTT or targeted chemotherapy—are initiated only after precise lesion localization has been confirmed via imaging. Simultaneously, real-time imaging provides a continuous feedback loop on the patient's therapeutic response, allowing for the dynamic adjustment of treatment regimens based on real-time efficacy.[75] Such a closed-loop system ensures that bladder cancer management moves toward a truly personalized precision medicine model.

From Laboratory to Clinic: Challenges and Future Prospects

Safety and Biocompatibility Considerations

The clinical translation of AuNPs is fundamentally dependent on a comprehensive and rigorous understanding of their biological fate and long-term safety. While ultra-small AuNPs (< 1.9 nm) are primarily excreted via the renal-bladder pathway, existing data suggests that renal impairment can significantly correlate with reduced clearance and increased systemic retention. The biological performance of these particles is governed by their intracellular trafficking—including clathrin-mediated endocytosis—and their subsequent ability to achieve endosomal escape through mechanisms like the "proton sponge" effect. Furthermore, the formation of a protein corona upon contact with biological fluids remains a critical hurdle, as it can mask targeting ligands and alter the intended biodistribution. Designing zwitterionic polymer coatings to create immune-silent surfaces is a promising strategy to evade the mononuclear phagocyte system.[70,88,89]

Large-Scale Production and Quality Control

Transitioning from laboratory-scale synthesis to clinical-grade production involves significant technical and economic hurdles. Established laboratory methods, such as green synthesis or chemical reduction, must be strictly standardized to ensure that every production batch meets rigorous requirements for size uniformity, morphology, and surface ligand density.[90,91] Establishing manufacturing facilities that comply with global Good Manufacturing Practice (GMP) standards represents a major capital investment. Consequently, the development of low-cost, high-stability synthetic routes is an essential prerequisite for the eventual dissemination of AuNP-based diagnostic and therapeutic tools to primary healthcare centers and regions with limited medical infrastructure. Major translational challenges and potential solutions are summarized in Table 3.

Table 3 Major Challenges and Solution Directions for Clinical Translation of Gold Nanoparticles

Translation Challenge	Specific Issues/Current Status	Solution Strategies and Future Directions	Ref.
Safety and Biocompatibility	Unclear long-term in vivo distribution, potential organ accumulation toxicity	Develop small-sized (<6 nm) kidney-clearable AuNPs; in-depth study of protein corona effect, design “immune-silent” surface modifications	[70, 88, 89]
Large-Scale Production and Quality Control	Diverse laboratory synthesis methods, difficult to standardize; high cost of GMP production, lack of quality control standards	Explore green synthesis methods; establish uniform, repeatable synthesis processes; develop automated, high-throughput production and quality control platforms	[90, 91]
Regulatory Pathways and Clinical Studies	Most research still in animal model stage, lack of human data; unclear approval pathways for nanomedicines by regulatory agencies	Conduct multicenter, prospective clinical validation trials; establish evaluation standards under drug-device combination mo strengthen industry-academia-research cooperation to accelerate translation	[57, 59, 91]
Cost-Effectiveness and Popularization	High cost of nanomaterial preparation and functionalization, limiting clinical popularization	Develop low-cost, high-stability synthesis routes; transform detection methods toward POCT for better promotion in primary hospitals	[27, 42–44]

Regulatory Pathways and Clinical Translation Prospects

The current lack of longitudinal human data remains a primary obstacle to the translation process. Regulatory agencies worldwide face challenges in establishing clear evaluation standards for nanomedicines, particularly those operating under a drug-device combination model for theranostic use.[57,59,91] To bridge this gap, there is an urgent need for multi-center, prospective clinical trials designed to empirically validate the superiority of AuNP-based interventions over traditional cystoscopy and conventional intravesical chemotherapy. Addressing these regulatory and clinical gaps through intensive interdisciplinary cooperation will be essential to bring these innovative technologies to the patient’s bedside.[27,42–44]

Conclusion and Future Prospects

Gold nanoparticles exhibit revolutionary potential in bladder cancer management due to their unique surface plasmon resonance effect, ease of functionalization, and excellent biocompatibility. AuNPs have evolved from simple imaging or detection tools into multifunctional theranostic platforms integrating multimodal imaging, targeted delivery, controlled release, and immune modulation. In diagnostics, ultra-sensitive AuNP-based sensing platforms enable femtomolar detection of urinary biomarkers, significantly improving early screening accuracy. In therapy, AuNPs serve as efficient carriers to overcome chemoresistance and achieve precise physical ablation while actively remodeling the tumor immune microenvironment through pathways such as cGAS-STING. This transition from “passive delivery” to “intelligent intervention” is fundamentally reshaping the diagnostic and therapeutic paradigm for bladder cancer.

Future breakthroughs will depend on establishing a new paradigm of “intelligent responsive” and “closed-loop” theranostics. Ideal AuNP platforms should dynamically sense and respond to the tumor microenvironment (eg, low pH or specific enzymes) or external stimuli to achieve precise drug “detonation” and “dual-track” immune regulation. By integrating AuNPs with technologies such as NIR-II window imaging and real-time photoacoustic thermometry, urologists can implement closed-loop management from diagnostic stratification to real-time efficacy monitoring, enhancing controllability and preventing damage to the healthy urothelium. Furthermore, combining AuNPs with CRISPR-Cas9 technology targeting markers like HER2 or FGFR3 offers a theoretically promising strategy for simultaneously repairing oncogenic mutations and eradicating residual cancer cells.

Achieving truly personalized precision medicine requires the deep integration of Artificial Intelligence (AI) with nanomedicine. By analyzing large-scale multi-omics patient data, AI can guide the “tailor-made” optimization of AuNP morphology and ligand density to precisely predict and improve individual treatment responses. Simultaneously, the development of biomimetic platforms—such as exosome-coated or cell-membrane-camouflaged AuNPs—and microbiome-aware systems will further enhance targeting efficiency and reduce immunogenicity. Regarding clinical safety concerns, the exploration of biodegradable or "self-dissolving" gold nanostructures is an essential pathway to eliminate long-term accumulation toxicity and meet the safety requirements of repeated intravesical administrations.

While clinical translation still faces significant challenges in GMP standardization and regulatory approval, the potential of AuNPs in the urinary system extends far beyond bladder cancer, including applications in prostate cancer management and sensitive assessment of acute kidney injury. Beyond oncology, AuNPs show promise in non-cancerous diseases like chemical cystitis and urinary tract infections.[92,93] Cutting-edge explorations such as urease-driven nanomotors further illustrate their potential for complex intravesical interventions.[94,95] Multidisciplinary collaboration among urologists, materials scientists, and AI experts will be the driving force behind turning these research achievements into clinical reality. We firmly believe that as our understanding of nano-bio interface interactions deepens, these "golden seeds" will bear healthy fruits for bladder cancer patients worldwide.

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