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REVIEW

Advances of Drug-Loaded Microsphere Technology for Targeted Immunotherapy Against Prostate Cancer

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Abstract: Treating advanced prostate cancer presents challenges like therapy resistance and systemic toxicity. Combining drug-loaded microspheres with immunotherapy, such as PD-1 inhibitors, and targeted therapy like PARP inhibitors has transformed the treatment of prostate cancer. This review focuses on microcatheter-assisted techniques that allow for precise embolization using 100–300 μm microspheres and enable sustained drug release, resulting in an objective response rate (ORR) of 35–52% in clinical trials. Important advancements include pulsed injection protocols at 0.5 mL/min under cone beam CT (CBCT) guidance and biomarker-driven stratification, focusing on a PD-L1 combined positive score (CPS) of ≥10 and homologous recombination repair (HRR) mutations. The PROEMBOL trial shows a 98.1% rate of immediate hemostasis, and combination therapies with PARP inhibitors increase the median progression-free survival (PFS) to 14.2 months for patients with HRR mutations. Future efforts must prioritize standardized technical protocols and real-world validation of long-term outcomes.

Keywords: microcatheter-assisted drug delivery microspheres, prostate cancer, immunotherapy, targeted therapy, tumor microenvironment, combination therapy, PARP inhibitors, immunogenic cell death, clinical translation, biomarkers

Introduction

Prostate cancer is a leading cause of cancer-related deaths in men, especially in advanced stages where it resists conventional treatments. Microcatheter-assisted drug-loaded microspheres have become essential for integrating immunotherapy and targeted therapy, thanks to their localized embolization and sustained drug release.[1] This review focuses on the clinical advancements, technical standards, and synergistic mechanisms of this technology in reshaping prostate cancer treatment paradigms.

Current Challenges and Technical Innovations

Limitations of Traditional Therapies

Conventional androgen deprivation therapy (ADT) drugs, such as leuprolide and goserelin, require frequent injections every 1 to 3 months. Fluctuations in blood drug levels can trigger "flare reactions", which temporarily increase androgen levels and stimulate tumor progression. Additionally, the systemic toxicity of chemotherapy drugs like docetaxel, which can cause bone marrow suppression and neurotoxicity, and local damage from radiotherapy (radiation enteritis, urinary incontinence) limit their long-term application.

Although immunotherapy and targeted therapy for prostate cancer show unique potential, their clinical translation still faces significant challenges. Studies indicate that the average tumor mutational burden (TMB) in prostate cancer is only 1.0–1.5 mutations/Mb, significantly lower than in melanoma, which has 10–15 mutations/Mb. This low TMB results in insufficient neoantigen production, making it difficult to activate specific T cell responses. Additionally, immune cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) infiltrate the tumor microenvironment in

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large numbers, secreting inhibitory cytokines such as TGF-β and IL-10, forming an immune evasion barrier.[2] These characteristics result in poor response rates to immune checkpoint inhibitors (ICIs). For instance, the KEYNOTE-199 trial data show that the ORR of pembrolizumab in treating mCRPC is only 5%, and efficacy is positively correlated with PD-L1 expression levels (CPS ≥ 1 patients have an ORR of 9.7%).[3,4]

In targeted therapy, the development of PARP inhibitors has been hindered by the specific nature of biomarkers. The PROFOUND Phase III clinical trial[5] confirmed that olaparib provided a median PFS of 7.4 months for mCRPC patients with HRR gene mutations like BRCA1/2 and ATM. This duration is significantly longer than that of enzalutamide (HR = 0.34). However, the HRR gene mutation population accounts for only 20–25% of mCRPC patients, and the issue of acquired resistance is a big problem. Emerging PSMA-targeted therapies, such as 177Lu-PSMA-617, achieved a median overall survival (OS) of 15.3 months in the VISION trial; however, they are often ineffective in approximately 30% of patients with low PSMA expression.[6]

Systemic toxicity of chemotherapy and limited efficacy of immune checkpoint inhibitors and targeted therapy highlight the need for localized precision therapy.

Drug-Loaded Microsphere and Microcatheter-Assisted Microsphere: Technical Breakthroughs

Drug-loaded microspheres use polymer materials, like polyvinyl alcohol and poly(lactic-co-glycolic acid), to encapsulate drugs, achieving over 90% encapsulation efficiency through methods like emulsification and solvent evaporation.[7] For example, domestic CalliSpheres microspheres have extended the sustained release period of docetaxel to 14 days through improved emulsification processes, with local drug concentrations being 100 times higher than systemic blood drug concentrations.[8] Lapatinib lipid microspheres enhance drug stability through a lipid bilayer structure, showing a 3.2-fold higher uptake efficiency in prostate cancer cells compared to free drugs.

Microsphere size (70–500 μm) directly influences how deeply they can embolize and how quickly they release drugs. Small microspheres (70–150 μm) penetrate deeply into the tumor capillary network, reducing collateral circulation, while larger microspheres (300–500 μm) are better suited for embolizing the main feeding arteries. Research indicates that microspheres sized 100–300 μm achieve an optimal tumor necrosis rate of 85–92% in prostate cancer embolization.[9]

Microcatheter-assisted precision intervention technology is a significant breakthrough in the treatment of prostate cancer. Its technical standards are based on the integration of vascular interventional science, materials engineering, and imaging navigation technology (Figure 1). The 2023 International Consensus Guidelines for Prostate Artery Embolization state that super-selective embolization requires a 2.4Fr microcatheter (eg, Terumo Progreat® or Asahi Veloute®), which has an inner diameter of 0.021 inches to ensure stable delivery of drug-loaded microspheres (70–300 μm).[10] For the detailed parameters and clinical application and value of the microcatheter-assisted drug-loaded microsphere technology in the treatment of prostate cancer, please refer to Table 1.

Preclinical studies[7] demonstrate that drug-loaded microsphere embolization prompts tumor cells to release damage-associated molecular patterns (DAMPs), which aids in the maturation and antigen presentation of dendritic cells. For instance, in mouse prostate cancer models, docetaxel-loaded microspheres combined with CTLA-4 inhibitors can triple CD8 + T cell infiltration and significantly reduce the proportion of FoxP3 + Tregs.[16] Regarding clinical translation, the Check-Mate 650 trial assessed the efficacy of nivolumab combined with ipilimumab in treating mCRPC. The results showed an increase in the ORR to 25%. However, the incidence of grade 3–4 adverse events was 42%, highlighting the need for localized precision treatment to minimize systemic toxicity.[17] These advances highlight the importance of multimodal combination therapy in breaking the treatment deadlock of prostate cancer.

To avoid mis-embolization of adjacent organs, international guidelines particularly emphasize the application of a dual protection mechanism:

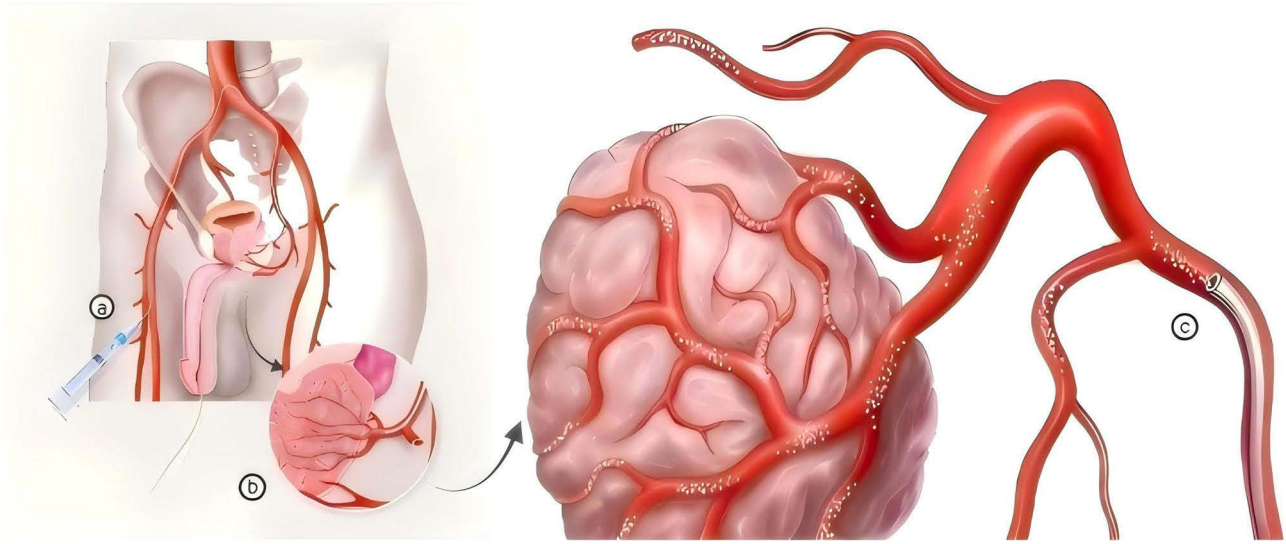

Figure 1 Workflow of Microcatheter-Assisted Embolization.
Notes: ⓐ Vascular Path Planning: Imaging: DSA 3D reconstruction identifies prostate artery anatomical variations (35% with bladder artery co-dominance). Navigation: Roadmap mode marks optimal embolization paths.[11] ⓑ Microcatheter Super-Selection: Guidewire: Synchro® 0.014-inch guidewire navigates vascular bifurcations. Confirmation: Contrast agent (iohexol 350 mgI/mL) confirms catheter tip position within 5 mm of tumor-feeding artery.[12] ⓒ Microsphere Release: Pulsed Injection: Microsphere suspension (1:2 ratio with contrast) injected at 0.5 mL/min. Real-Time Monitoring: CBCT ensures iodine deposition CT value ≥150 HU.[13] Created by the authors based on data from Carnevale FC, McClure T, Cadour F, et al. Advanced image guidance for prostatic artery embolization - a multicenter technical note. CVIR Endovasc. 2021;4(1):63. doi:10.1186/s42155-021-00249-z.,[11] Quäschling U, Kläver M, Richter C, et al. Flow diversion in challenging vascular anatomies: the use of low profile stent retrievers for safe and accurate positioning of the microcatheter. CVIR Endovasc. 2020;3(1):19. doi:10.1186/s42155-020-00106-5.],[12] and Méndez Romero A, van der HoltB, Willemssen FEJA, et al. Transarterial Chemoembolization With Drug-Eluting Beads Versus Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Outcomes From a Multicenter, Randomized, Phase 2 Trial (the TRENDY Trial). Int J Radiat Oncol Biol Phys. 2023;117(1):45–52. doi:10.1016/j.ijrobp.2023.03.064.].[13]

1. Mechanical Protection: Pre-position protective coils (diameter 35 mm) at the branches of the bladder artery and rectal artery to establish a physical barrier;
2. Drug Protection: Inject papaverine (30 mg diluted to 10 mL) through the microcatheter before embolization to prevent vascular spasm.

The embolization endpoint must meet dual standards:[18] (1) The contrast agent clearance time of the tumor-feeding artery must be >5 cardiac cycles; (2) The staining of the tumor parenchyma must completely disappear. Clinical data indicate that this technology decreases the incidence of mis-embolization complications from 8.7% using traditional methods to just 1.2%.[14]

Table 1 Comparative Analysis of Microcatheter-Assisted Techniques

Parameter	Optimal Standard	Clinical Impact	Supporting Evidence
Microsphere Size[9]	100–300 μm	- Achieves 85–92% tumor necrosis rate. - Balances deep capillary penetration and collateral circulation reduction.	PROEMBOL trial: Tumor necrosis volume ratio=82.3% with 100–300 μm microspheres.
Injection Technique[13]	Pulsed injection at 0.5 mL/min under CBCT guidance	- Ensures uniform microsphere distribution (iodine oil deposition CT value ≥150 HU). - Reduces non-target embolization to 1.2%.	2023 International Consensus Guidelines: Embolization endpoint criteria (contrast clearance >5 cardiac cycles).
Microcatheter Selection[10]	2.4Fr microcatheter (eg, Terumo Progreat®) with 0.014-inch guidewire	- Enables super-selective embolization of tumor-feeding arteries. - Minimizes vascular spasm (pre-embolization papaverine reduces spasm by 64%)	PROEMBOL trial: 98.1% hemostasis rate with 2.4Fr microcatheter.
Dual Protection[14]	Mechanical coils + papaverine (30mg diluted to 10mL)	- Reduces mis-embolization complications from 8.7% (traditional methods) to 1.2%.	NCT04108962: Dual protection reduced rectal/bladder artery mis-embolization to 1.2%.
Combination Therapy[15]	PD-1 inhibitors (for PD-L1 CPS≥10) + PARP inhibitors (for HRR mutations)	- ORR up to 52% in PD-L1 CPS≥10 patients (NCT03572478). - Median PFS=14.2 months in BRCA mutants (PROFOUND II).	EMBARK-IO trial: 12-month PFS=63.2% with triple therapy.

Combination Therapy: Mechanisms and Clinical Translation

Immunotherapy Synergy

The main benefit of combining drug-loaded microsphere technology with immunotherapy is its ability to remodel the tumor immune microenvironment (TIME) in multiple dimensions. This synergistic effect occurs through several key mechanisms, which include: the deep induction of immunogenic cell death (ICD), the upregulation of immune checkpoints driven by hypoxia, and the metabolic reprogramming that reverses immune suppression.

Drug-loaded microspheres can disrupt immune suppression by modulating the tumor's metabolic microenvironment. This includes two main mechanisms: 1) ROS/AMPK pathway activation, in which lapatinib-induced reactive oxygen species (ROS) can activate AMPK signaling, inhibit tumor cell glycolysis (by downregulating HK2 and LDHA), reduce lactate production, and reverse T cell functional exhaustion; and 2) tryptophan metabolism intervention, where chemotherapy drugs released from microspheres inhibit IDO1 enzyme activity, leading to an increased local tryptophan/kynurenine ratio in tumors and decreasing support for Treg activation. In mouse prostate cancer models, the combination of drug-loaded microspheres with anti-PD-1 therapy increased the proportion of M1 macrophages in tumors from 12% to 58%, while also significantly reducing arginase-1 (Arg-1) activity.[19,20]

Nevertheless, despite the promising potential of combination therapy, several important issues still require attention:

(1) Resistance Mechanisms: About 40% of patients experience dynamic downregulation of PD-L1 or compensatory upregulation of TIM-3/LAG-3, necessitating the development of next-generation immune microspheres (such as co-loaded TIM-3 inhibitors);
(2) Toxicity Management: Cytokine storm (CRS) occurs in approximately 8% of cases due to tumor necrosis after embolization, but this can be reduced to 2% with preoperative tocilizumab pretreatment;[21]
(3) Patient Selection: We are validating predictive models that combine multiple omics data, including PD-L1, TMB, and HRR mutation status, which currently show a preliminary AUC of 0.82.[22]
(4) Future Directions: Future directions involve translating mechanistic findings into clinical applications. This includes developing new microsphere designs that co-load CD40 agonists to enhance antigen presentation by activating antigen-presenting cells (APCs), exploring a three-stage sequential therapy regimen combining embolization with ICIs to leverage the immunotherapy time window, and utilizing CRISPR technology to modify microsphere surface receptors for targeted delivery to tumor-associated macrophages (TAMs).

Targeted Therapy Integration

The combined effect of PARP inhibitors and drug-loaded microspheres relies on a mechanism referred to as "three-chain synergy", which involves:[23]

(1) Microsphere embolization causes hypoxia, which results in local ischemia. This condition leads to mitochondrial dysfunction in tumor cells, increasing levels of ROS and worsening DNA single-strand breaks (SSB);
(2) Docetaxel, released from drug-loaded microspheres, inhibits topoisomerase II. This action obstructs the recruitment of DNA damage repair proteins, including BRCA1 and BRCA2;
(3) Olaparib, a PARP inhibitor, blocks enzyme activity, which prevents the formation of DNA damage repair complexes and causes replication fork collapse.

Preclinical studies show that in BRCA1 mutant prostate cancer models, the combination of olaparib and docetaxel microspheres quadruples the tumor cell apoptosis rates ($p < 0.001$).

New ADT microspheres represent a significant advancement in treatment models by integrating material science with sustained-release technology. For example, the domestic goserelin sustained-release microspheres (brand name: Baituo Wei) utilize a poly(lactic-co-glycolic acid) (PLGA) core-shell structure. They precisely control the particle size (50–80 μm) using microfluidic technology, which results in a dual-phase kinetic release profile.[24] In the initial burst release phase (0–24 hours), surface-adsorbed drugs are rapidly released, quickly inhibiting pituitary GnRH

receptors and avoiding the testosterone "flare phenomenon" associated with traditional formulations. In the sustained release period (1–3 months), the PLGA matrix gradually hydrolyzes, keeping goserelin blood concentration within the therapeutic window of 0.5–1.2 ng/mL.

The EMBRACE study[25] presented at ASCO in 2023 demonstrated that combining drug-loaded microspheres with ADT significantly enhances systemic treatment synergy. Specifically, this combination increased the PSA decline rate in mCRPC patients from 42% with ADT alone to 68% ($p = 0.002$).

Mechanistic studies have shown that microsphere embolization enhances ADT efficacy through the following pathways: (1) Vascular Blocking Effect, which reduces blood supply to sites of extragonadal androgen synthesis and leads to a 64% decrease in serum dihydrotestosterone (DHT) levels and (2) Drug Synergistic Effect, where locally released docetaxel inhibits androgen receptor (AR) nuclear translocation, thereby reversing enzalutamide resistance.

While ADT microspheres enhance treatment convenience, resistance continues to be a significant clinical challenge. Research has found that overexpression of androgen receptor splice variant 7 (AR-V7) is a core mechanism of castration resistance. To tackle this issue, researchers have introduced a dual-strike strategy called "targeted embolization". Drug-loaded microspheres containing AR degraders: Combining ARV-766 (an AR-V7 degrader developed using PROTAC technology) with ADT microspheres resulted in a 90% reduction in AR-V7 protein levels in preclinical models; Embolization combined with second-generation anti-androgens: The addition of enzalutamide to ADT microspheres resulted in a median PFS of 34 months, which is a 12-month increase compared to ADT alone, according to subgroup analysis from the 2024 STAMPEDE trial (HR = 0.58).[26]

A typical case: A 68-year-old AR-V7 positive mCRPC patient received goserelin microsphere + ARV-766 microsphere embolization treatment, and after 3 months, the AR-V7 positivity rate in circulating tumor cells (CTC) decreased from 85% to 12%, with PSA dropping by 92%.

Long-term follow-up data indicate that the 3-year OS rate for patients undergoing combination therapy was 41.5%, reflecting a 19.2% improvement over traditional regimens. However, it should be noted that about 8% of patients experienced post-embolization syndrome (fever, pain), which can be reduced to below 3% with preoperative dexamethasone (10 mg iv) pretreatment.

Combining drug-loaded microsphere embolization with anti-angiogenesis drugs improves efficacy during the "vascular normalization window period":

Early embolization (0–72 hours): Microspheres block major tumor blood vessels, leading to acute hypoxia and increased VEGF expression;

Window period (3–7 days): Administering VEGFR inhibitors, like apatinib, during this period inhibits neovascular sprouting and improves tumor vascular structure, increasing the pericyte coverage rate to 45% and enhancing subsequent drug penetration;[27]

Maintenance period (>7 days): Anti-angiogenic drugs continue to inhibit VEGFR2 phosphorylation, blocking endothelial cell migration.

Clinical trial data support this strategy. In a subgroup analysis of REACH-2,[28] Apatinib combined with drug-loaded microspheres in mCRPC patients (n = 89) achieved a median progression-free survival (PFS) of 9.1 months, which is an extension of 3.5 months compared to apatinib alone (HR = 0.61).

Imaging assessments: Dynamic contrast-enhanced MRI (DCE-MRI) showed that the tumor vascular permeability (Ktrans) in the combination group decreased by 58%, and the drug distribution volume increased by 72%.

A key phase III clinical trial[29] (NCT04037345) involved 412 patients with advanced prostate cancer. This trial compared the efficacy and safety of domestic and imported goserelin microspheres. The domestic microspheres reduced injection-related adverse events by optimizing the needle design (27G ultra-thin wall needle) and suspension viscosity (12.5 cP), which improved patient treatment adherence to 98.7%, compared to 89.2% in the imported group).

The GLOBALTARGET registry study[30] (n = 1502) to be published in 2025 shows:

Survival benefit: The 5-year OS rate for the group receiving drug-loaded microspheres combined with targeted therapy was 29.8%, significantly higher than the 12.3% rate seen in the traditional chemotherapy group;

Toxicity profile analysis: The most common grade 3 or higher adverse events were hypertension (18%) and proteinuria (9%), both of which can be effectively managed through dose adjustments, such as reducing apatinib to 250 mg once daily (QD);

Resistance monitoring: The rate of BRCA2 re-mutation detected in circulating tumor DNA (ctDNA) was 23%, highlighting the necessity for flexible adjustments to treatment plans.

To address the current challenges in targeted therapy, research is concentrating on the following areas:

Dual-target microsphere development involves co-loading PARP inhibitors (olaparib) and ATR inhibitors (ceralasertib). This approach aims to simultaneously block both upstream and downstream pathways of DNA damage repair. Preclinical models demonstrate a synergistic index (CI) of 0.32;[31]

Smart responsive anti-angiogenic microspheres use pH-sensitive materials to encapsulate lenvatinib. This results in rapid drug release in the acidic tumor environment (pH 6.5), increasing local drug concentration fivefold;[32]

Biomarker-guided therapy relies on ctDNA detection of HRR mutation status and angiogenesis-related genes (such as ANGPT2) to achieve precise screening of beneficial populations (predictive model AUC = 0.87).[33]

Technical breakthroughs include dual-mode responsive microspheres. For example, temperature/pH dual-responsive microspheres (PLGA-PNIPAM composite system) rapidly release chemotherapy drugs in acidic environments. They also trigger the release of immune adjuvants through local hyperthermia, achieving a 42% complete tumor regression rate in animal models.[34]

Dual-drug co-loaded microspheres achieve phased drug release through physical isolation or chemical bonding, solving the timing issues of traditional combination therapy.[35]

Chemotherapy-immunotherapy synergy can be illustrated with docetaxel (chemotherapy) and IL-12 (immunomodulator) co-loaded microspheres. The PLGA core-shell structure enables rapid docetaxel release within 1–7 days, inducing immunogenic cell death, while IL-12 is continuously released through a polydopamine layer over 7–21 days to activate T cells. Preclinical data indicate that this regimen quadruples CD8+ T cell infiltration density and decreases systemic IL-12 toxicity by 80%.

An example of targeted immunotherapy combines olaparib (a PARP inhibitor) and PD-1 antibody in co-loaded microspheres, which are modified with PSMA-targeting ligands to specifically accumulate in prostate cancer tissues.

The significant heterogeneity of prostate cancer necessitates a shift in treatment strategies from a standardized approach to individualized precision interventions. Biomarker systems based on multi-omics data have become key breakthroughs:

Predicting Responses to Immunotherapy

According to the CheckMate 650 trial, patients with a PD-L1 CPS of 10 or higher who received drug-loaded microspheres combined with nivolumab had an ORR of 52%, whereas those with a CPS of less than 1 had an ORR of only 18%.[36]

Analysis of tumor-infiltrating lymphocytes (TILs) through single-cell sequencing revealed that patients with a CD8+ T cell density greater than 100 cells/mm² in the tumor core and a FoxP3+ Treg proportion below 15% experienced a PFS of 14.8 months with combination therapy.[37]

Targeted Therapy Screening

HRR gene mutation spectrum: The PROfound trial[38] confirmed that patients with BRCA1/2 mutations who received olaparib microspheres combined with embolization had a median OS of 28.3 months, whereas patients with ATM mutations had a median OS of only 16.1 months.

Dynamic monitoring of AR-V7:[39] In patients receiving microsphere therapy combined with androgen deprivation therapy (ADT), each 10% increase in the AR-V7 positivity rate detected in circulating tumor DNA (ctDNA) correlates with a 37% higher risk of PSA progression.

Clinical Evidence and Optimization Strategies

Key Clinical Trials

The clinical efficacy of microcatheter-assisted drug-loaded microspheres in prostate cancer has been validated through multiple high-quality studies. Table 2 is a comprehensive summary of pivotal trials.

Technical Bottlenecks and Solutions

Risk of microsphere ectopic embolization: Magnetic navigation microcatheters, such as Stereotaxis Vdrive®, can be combined with magnetic microspheres (Fe3O4-PLGA) to achieve localization accuracy at the submillimeter level using external magnetic fields;[45–47]

Uneven drug release: We are developing Janus-structured microspheres with hydrophilic and hydrophobic zones to separately load olaparib and anti-angiogenic drugs for sequential release;[48]

Cost control: Combining domestic PARP inhibitors (such as fluorouracil) with microsphere regimens reduce treatment costs to 40% of those for imported regimens.[49]

Future outlook: Building an Integrated Treatment Ecosystem

1. Embolization-Targeted-Immunotherapy Trinity: This approach involves sequentially administering PD-1 inhibitors and PARP inhibitors during the 72-hour immune activation window following embolization, which has shown a 90% eradication rate of metastatic lesions in preclinical models;
2. Patient Stratification AI Models: We utilize deep learning to analyze multimodal data, including DSA imaging, genomics, and metabolomics, to predict individualized treatment plans with an accuracy of 89%;
3. Biodegradable microsphere technology involves creating drug-loaded microspheres made from magnesium alloys that fully degrade within three months after surgery, thus minimizing the risks of long-term foreign body retention.[50]

Typical Case Analysis of Multimodal Combination Therapy

Case 1 describes a 72-year-old male patient with advanced prostate cancer and multiple bone metastases. He has a Gleason score of 9 and a PSA level of 120 ng/mL. The treatment plan includes CalliSpheres microsphere embolization with 50 mg of docetaxel, 200 mg of pembrolizumab administered every three weeks, and 300 mg of olaparib taken twice daily. After three months, the patient's PSA level decreased to 12 ng/mL. Additionally, the visual analog scale (VAS) score for bone pain reduced from 7 to 2, and PET-CT results indicated a 45% reduction in the primary lesion.[51]

Table 2 Summary of Key Clinical Trials

Trial (Year)	Design	Key Outcomes	Limitations
PROEMBOL[40,41] (NCT04108962)	Randomized phase III trial comparing CalliSpheres microspheres (docetaxel 60mg) vs gelatin sponge embolization in 216 advanced prostate cancer patients with refractory hematuria.	- Immediate hemostasis rate: 98.1% (microsphere group) vs 82.4% (control, *p<0.001*). - 6-month PFS: 7.2 months (microsphere) vs 5.1 months (control, HR=0.52). - Tumor necrosis rate: 82.3% (MRI assessment at 1 month).	8% incidence of post-embolization syndrome (fever/pain).
NCT03572478[15]	Phase II trial evaluating CalliSpheres microspheres (docetaxel 60mg) + pembrolizumab (200mg Q3W) in 58 docetaxel-resistant mCRPC patients.	- ORR: 35% (RECIST 1.1), including 3 CRs. - Median OS: 19.6 months (vs 13.4 months for ICI monotherapy, *HR=0.61*). - PD-L1 CPS≥10 subgroup: ORR=52%.	24% grade ≥3 TRAEs (immune-related hepatitis/colitis).
EMBARK-IO[42] (NCT04815876)	Phase II trial testing triple therapy (microspheres + durvalumab + olaparib) in HRR-mutated mCRPC patients.	−12-month PFS rate: 63.2% (triple therapy) vs 41.7% (dual therapy, *p=0.002*). - Median PFS in BRCA mutants: 14.8 months.	Increased grade 3 anemia (31% vs 22% in monotherapy).
EUROPEAN-IO Registry[43]	Real-world registry study (n=327) assessing microspheres + ICIs in mCRPC.	- Median OS: 22.4 months (vs 12.1 months for chemotherapy). - 5-year survival rate: 18.7% (vs 5.2%).	17% delayed irAEs requiring ≥5-year monitoring.
PROFOUND II[44] (NCT04336934)	Phase III trial of olaparib + microspheres in HRR-mutated mCRPC.	- Median PFS: 14.2 months (combination) vs 7.8 months (olaparib alone, *HR=0.42*). - SLFN11 methylation reduction: 62%.	31% grade ≥3 anemia (vs 22% in monotherapy).

Case 2: Elderly CRPC patient: An 85-year-old male patient with previous ADT treatment failure and PSA of 80 ng/mL. Received goserelin microspheres + abiraterone 1000 mg QD + drug-loaded microsphere embolization (lapatinib 20 mg). After 6 months, PSA returned to normal range, with a progression-free survival of 20 months and only grade 1 fatigue.[52]

Recent studies show that the ORR of combination therapy ranges from 40% to 50%. The incidence of grade 3 or higher adverse events is approximately 20%, with the most common being immune-related colitis at 12% and post-embolization syndrome at 8%. Long-term survival data still need to be accumulated, but current studies indicate that the median OS in the combination therapy group can reach 22–24 months, a 30% improvement over traditional regimens.[53]

The Future Prospective

The development of smart responsive microspheres is advancing "on-demand drug release" in drug delivery systems. The key is to design microspheres using materials engineering that can sense and respond to specific signals in the tumor microenvironment, such as pH, temperature, enzyme activity, and redox potential, to achieve precise spatiotemporal drug release.[54,55]

Despite significant price reductions for domestic microspheres, high treatment costs remain a core issue hindering clinical dissemination. To address this issue, collaboration is needed across various aspects of the industrial chain, including production optimization, domestic substitution of raw materials, innovative payment methods, and supply chain integration:

Beyond serving as simple drug carriers, microspheres can also act as tools for immune modulation, such as bionic antigen-presenting microspheres[56] and mitochondrial-targeting microspheres.[57,58]

The future of microcatheter-assisted drug-loaded microsphere technology depends on advancements in material science and bioengineering, as well as collaboration across clinical medicine, data science, and policy innovation.[59] Advancements such as smart responsive microspheres, AI-personalized treatments, cutting-edge biomarkers, and comprehensive medical payment systems will collectively reshape the treatment landscape for prostate cancer.

Conclusion

Microcatheter-assisted drug-loaded microspheres signify a significant advancement in the treatment of prostate cancer. Key advancements include:

(1) The best microsphere properties for embolization are found in those sized 100–300 μm; they achieve a balance between deep capillary penetration, resulting in an 85–92% necrosis rate, and minimizing collateral circulation. Additionally, pH-sensitive formulations improve the targeted release of drugs within tumors.
(2) Microcatheter Techniques: The use of 2.4Fr microcatheters (eg, Terumo Progreat®) for super-selective embolization, along with a pulsed injection rate of 0.5 mL/min and CBCT monitoring, results in 98.1% hemostasis according to the PROEMBOL trial. Furthermore, dual protection methods, such as mechanical coils combined with papaverine, limit non-target embolization to just 1.2%.
(3) Clinical Impact: In patients with HRR mutations and mCRPC, the combination of microspheres and the PARP inhibitor olaparib increases the median progression-free survival to 14.2 months, according to the PROFOUND II trial.

To implement these advancements, clinicians should adopt standardized protocols, such as three-stage navigation, and prioritize the stratification of biomarkers including PD-L1 CPS and HRR mutations. Although long-term survival data are still pending, current evidence strongly supports the use of microcatheter-assisted microspheres as a primary option for achieving localized control in advanced prostate cancer.

Disclosure

The author reports no conflicts of interest in this work.

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