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REVIEW

Multifaceted Applications of Nanomaterials in Colorectal Cancer Management: Screening, Diagnostics, and Therapeutics

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Abstract: Colorectal cancer (CRC) is the third most common malignant tumor worldwide. Early detection and treatment of CRC can significantly improve patient survival and quality of life, while advanced-stage patients still face numerous challenges, such as drug resistance and adverse effects. Consequently, researchers are developing more efficient early screening and diagnostic strategies for CRC. Consequently, researchers are actively developing more efficient strategies for diagnosis and refined treatments. This review comprehensively examines the diverse applications of various nanomaterials in CRC management, including screening, diagnostic imaging, surgical guidance, drug delivery, radiotherapy, and modulation of the tumor microenvironment. Firstly, we explored how nanomaterials are revolutionizing CRC screening by enhancing the detection of early-stage tumors. In the realm of diagnostic imaging, nanomaterials are employed to improve the clarity and specificity of imaging modalities, thereby facilitating more accurate diagnoses. The review also examines the use of nanomaterials in surgical guidance, where they aid in the precise identification and removal of tumors, potentially improving surgical outcomes. Furthermore, the review underscores the significance of nanomaterials in drug delivery systems, which enable targeted therapy and reduce systemic side effects. We also discussed the role of nanomaterials in radiosensitization, where they enhance the efficacy of radiotherapy by increasing the sensitivity of tumor cells to radiation. Additionally, the modulation of the tumor immune microenvironment using nanomaterials is highlighted as a promising strategy to induce immune response against cancer cells. Throughout the review, the mechanisms of action of these nanomaterials are meticulously examined, providing insights into how they interact with biological systems to achieve their therapeutic effects. The efficacy of these nanomaterials in overcoming drug resistance is also a focal point, as this is a critical factor in improving the long-term outcomes for CRC patients. In conclusion, while nanomaterials hold great promise for the management of CRC, addressing their biocompatibility and clinical translation challenges is crucial for their safe and effective application in clinical settings.

Keywords: Nanomaterials, Colorectal cancer, Clinical practice, Tumor microenvironment

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, significantly impacting global morbidity and mortality rates. According to the Global Cancer Statistics 2020, CRC ranks as the third most prevalent cancer globally, with over 1.9 million new cases and approximately 935,000 deaths annually.[1] Despite advances in screening and treatment, CRC managing remains a significant clinical challenge. One of the primary challenges is the development of resistance to conventional chemotherapy drugs, which limits their effectiveness over time.[2] Additionally, the side effects associated with chemotherapy and radiotherapy can be severe, impacting the patient's quality of life and limiting the dosage that can be safely administered.[3] Surgical options, while potentially curative in early-stage CRC, are often not viable for patients with advanced or metastatic disease. Furthermore, the heterogeneity of CRC tumors complicates treatment, as different genetic mutations and molecular profiles can influence the tumor's response to therapy.[1]

Nanomaterials have gained significant attention in clinical applications, particularly in cancer treatment. Nanomaterials possess unique properties such as a high surface area to volume ratio, tunable physical and chemical

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characteristics, and the ability to interact with biological systems at the molecular level. Nanomaterials can be classified into several categories based on their composition and structure, including carbon-based nanomaterials (eg, carbon nanotubes, graphene), metal nanoparticles (eg, gold, silver), metal oxide nanoparticles (eg, iron oxide, zinc oxide), and mesoporous silica nanoparticles.[4,5] Each class of nanomaterials has distinct properties that can be leveraged for specific medical applications. These nanomaterials can enhance drug delivery to tumor sites, improve imaging for more accurate diagnosis, and enhance drug efficacy and therapeutic effects compared to standard treatments.[5]

Some nanomaterials have used in the clinical management of CRC, offering enhanced therapeutic efficacy, targeted delivery, and reduced toxicity compared to traditional therapies (Table 1). Liposomal irinotecan (Onivyde®) is a significant example of a clinically approved nanomedicine for CRC treatment. It utilizes a liposomal delivery system to target tumor tissues via the Enhanced Permeability and Retention (EPR) effect, leading to DNA replication inhibition and apoptosis. Another FDA-approved nanoparticle is Ferumoxytol (Feraheme®), a superparamagnetic iron oxide nanoparticle used as an MRI contrast agent to detect lymph node metastasis.[6] Additionally, Guardant360® has been approved for liquid biopsy to detect tumor gene mutations, utilizing nanomaterials for circulating tumor DNA (ctDNA) enrichment.[7] A multitude of promising nanomaterials have already progressed to the clinical validation phase (Table 1). Some nanoparticles are under investigation to enhance chemotherapy efficacy and reduce toxicity. For instance, ASP3082 (NCT05382559) is being evaluated in a Phase 1 trial for its safety and tolerability in patients with advanced solid tumors, particularly those with KRAS G12D mutations. Nanoparticles are also being explored for lymph node mapping and staging in CRC. Carbon nanoparticles are being compared with indocyanine green to improve postoperative lymph node inspection (NCT04759820), and used for identifying metastatic nodes (NCT06783985). These ongoing clinical trials highlight the versatility and potential of nanoparticles in enhancing the precision and efficacy of CRC treatment. In this review, we will summarize the latest research progress on the application of nanotechnology in CRC, demonstrates significant potential in the early screening, diagnosis, treatment, and prognostic evaluation of CRC.

Advancements in Nanomaterial-Based Screening and Diagnosis of CRC

Advancements in Nanomaterial-Based Detection for CRC Screening

In the United States, CRC incidence and mortality have decreased by over 50% in the past 40 years, with screening estimated to account for more than half of this reduction.[9] Colonoscopy has been particularly effective in reducing the risk of left-sided CRC; however, its efficacy for right-sided CRC is less pronounced. The quality of the colonoscopy procedure, including factors such as withdrawal time, plays a critical role in its effectiveness.[10] While there is no universally ideal screening strategy, the best approach is influenced by factors such as economic feasibility and patient adherence. A range of nanomaterials and technologies have been explored for early CRC screening, including carbon nanotubes, dendrimers, gold nanoparticles, fluorescent nanospheres, nanotube arrays, and nanoparticle-based electrochemical sensing platforms (Table 2). These innovations have shown potential in distinguishing between healthy and tumor tissue samples.

Astolfi et al developed a sensor that utilizes gold nanoparticles decorated with tin and titanium oxides to detect volatile organic compounds (VOCs) in the blood of CRC patients. The sensor demonstrated a sensitivity of 80% and a specificity of 70% in differentiating healthy individuals from those with CRC.[24] Similarly, Bhattacharyya employed functionalized titania nanotube arrays (TNAs) as a sensor to detect four VOCs associated with CRC, identifying these VOCs as a potential biomarker signature for CRC screening.[20]

The integration of nanoparticles with endoscopic procedures has further enhanced the efficiency of tumor screening. Zavaleta et al (2013) developed an optical fiber-based Raman spectroscopy device that uses surface-enhanced Raman scattering (SERS) nanoparticles as molecular imaging contrast agents. This technology provides real-time, multiplex functional information during conventional endoscopic procedures, helping endoscopists rapidly distinguish between normal and precancerous tissues, and identifying flat lesions that might otherwise go unnoticed.[17] Additionally, Sakuma et al designed an innovative imaging agent for colonoscopy by immobilizing Peanut Agglutinin (PNA) on fluorescent nanospheres. In an animal model of human CRC in situ, PNA effectively indicated the invasion of implanted cancer cells on the mucosal side. The PNA-immobilized fluorescent nanospheres were able to recognize millimeter-sized tumors on the caecal mucosa with high specificity and affinity.[16]

Table 1 Summary of Nano Structures Used in Clinical Application or Trial for the Treatment and Diagnosis of CRC

Nano-Materials	Applications	Mechanisms	Status	Enrollment	Locations	NCT Number
Liposomal Irinotecan (Onivyde®)	Chemotherapy	Enriched in tumor tissue via EPR effect, releasing topoisomerase I	FDA approved			[8]
Ferumoxytol (Feraheme®)	Detects lymph node metastasis	MRI contrast agent, Superparamagnetic iron oxide nanoparticles	FDA approved			[6]
Guardant360®	Liquid biopsy	Nanomaterials for ctDNA enrichment	FDA approved			[7]
Nano Carbon	Lymph node mapping	Lymph node staging, preoperative injection of nano-carbon suspension	Parallel	200	China	ChiCTR1900025127
Carbon Nanoparticles	Surgery	Label lymph nodes to guide surgery and identify metastatic nodes in CRC	Observational	146	China	NCT06783985
Carbon Nanoparticles	Surgery	To improve postoperative lymph node inspection and precise adjuvant therapy	Phase 2/3	298	China	NCT04759820
Nano-carbon Suspension	Surgery	Preoperative injection for lymph node dissection around the inferior mesenteric artery	Observational study	45	China	ChiCTR1900021804
ASP3082	Chemotherapy	Investigating the safety and tolerability of ASP3082 in patients with advanced solid tumors	Phase 1	541		NCT05382559
Cetuximab Nanoparticles	Chemotherapy	To reduce chemotherapy toxicity and enhance drug delivery efficiency.	Phase 1	30	Egypt, Saudi Arabia	NCT03774680
AZD4635	Chemotherapy	AZD4635 in combination with various agents in patients with advanced solid tumors.	Phase 1	313	USA	NCT02740985
CNSI-Fe(II)	Chemotherapy	Carbon nanoparticle-loaded iron (CNSI-Fe (II)) in patients with advanced solid tumors	Phase 1	24	China	NCT06048367
TKM-080301	Chemotherapy	TKM-080301 administered directly into the hepatic artery for tumors	Phase 1	1 (54 estimated)	USA	NCT01437007
MT-302	Chemotherapy	MT-302 in patients with advanced epithelial tumors	Phase 1	48	Australia	NCT05969041
CRLX-101	Neoadjuvant treatment	Combination with capecitabine and radiation therapy as neoadjuvant treatment	Phase 1/2	32	USA	NCT02010567
Nano-crystalline Megestrol	Chemotherapy	First-line treatment for advanced gastric or CRC	RCT	76	China	NCT06830018
Nano-crystalline Megestrol	Chemotherapy	First-line treatment for advanced gastric or CRC with cancer-related fatigue	RCT	76	China	NCT06830018
Nanocurcumin	Metastatic CRC	Adjuvant to XELOX or FOLFOX regimen for the treatment of metastatic CRC	Phase 2	60	Iran	IRCT20200408046990N7

Table 2 Summary of Nano Structures Used for CRC Screening and Diagnosis

Nanomaterial Name	Nano Target or Mechanism	Main Results	Ref
Self-Functionalized nanosensor	DNA methylation signatures of NK cells	CRC-specific methylation signatures identified using Raman spectroscopy; Diagnostic model accurately differentiated CRC patients from normal controls	[11]
CoPt3 nanozyme	Circulating cancer stem cell detection	Detection limit of 3 cells mL^{-1}; Prediction of CRC progression and poor prognosis	[12]
Au Nanocage@Au along with IS-AgMNPs	SERS detection of CRC-related miRNAs	Detection limits: 3.46 aM for miR-21, 6.49 aM for miR-31;	[13]
Au@Fe_3O_4 nanoparticles	Parvimonas micra detection	Limit of detection: 11 CFU/mL	[14]
AIE-Pep nano bioprobe	Fusobacterium nucleatum detection	Limit of detection: 82.97 CFU/mL; significant differentiation between CRC and normal feces	[15]
PNA-immobilized fluorescent nanospheres	Thomsen-Friedenreich antigen targeting	Strong fluorescence observed on cecal mucosa; High affinity and specificity for millimeter-sized tumors	[16]
SERS nanoparticles	Multiplexed molecular imaging	Detection of 326-fM concentrations;	[17]
aSlex-coated dendrimers	Enhanced Capture of Colon Cancer Cells	Maximum capture efficiency of 77.88% within 1 hour;	[18]
Dual-Antibody-Coated Dendrimers	Specific capture and deactivation of CTCs	Enhanced specificity in capturing CTCs in the presence of interfering blood cells	[19]
Nickel-functionalized titania nanotubular arrays	Detection of CRC-related VOCs	Detection of four prominent VOCs (cyclohexane, methylcyclohexane, 1,3-dimethyl-benzene, decanal)	[20]
EGFR-targeted immune magnetic liposomes	Capture of circulating CTCs	Higher capture efficiency compared to EpCAM immunomagnetic beads;	[21]
Gelatin nanoparticle-coated silicon beads	Density-selective capture and release of CTCs	Capture efficiency >80%; purity >85%; release efficiency 94%; viability 92.5%	[22]
Ratiometric fluorescence nanoprobe	Intracellular H_2O_2 evaluation	Effective CTC identification correlation with tumor TNM stage	[23]
Tin, titanium, tantalum, vanadium, and niobium oxide sensors	Detection of CRC exhalations	Sensitivity up to 80%; Specificity 70% with tin and titanium oxide sensors	[24]
Magnetic nanoparticles with ferrocene-labelled PNA	Detection of methylated SEPT9 gene	Detection limit of 0.37%; interference-free measurement	[25]

The SEPT9 gene methylation (mSEPT9) assay is a blood-based test that offers moderate sensitivity (69%) and high specificity (92%) for CRC detection. However, it has limitations, including reduced effectiveness in detecting precancerous lesions and relatively high costs.[26] In response to these challenges, Hanoglu et al developed an electrochemical sensing system based on magnetic nanoparticles, which is capable of selectively quantifying mSEPT9. The system has a limit of detection (LOD) as low as 0.37% and is suitable for point-of-care (POC) applications, enabling rapid, one-step detection.[25]

The identification of bacterial communities associated with CRC, such as Parvimonas micra and Fusobacterium nucleatum, has led to the development of highly specific aptamers. A colorimetric aptasensor using Au@Fe_3O_4 nanoparticles demonstrated high affinity towards P. micra, enabling CRC screening with a detection limit of 11 CFU/mL. Similarly, an aggregation-induced emission nanobioprobe for F. nucleatum showed a LOD of 82.97 CFU/mL, highlighting the potential of these bacteria as biomarkers for noninvasive CRC screening.[14,15]

Advancements in Nanomaterial-Based Detection of Circulating Tumor Biomarkers in CRC

CTC Detections

Circulating biomarkers, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and microRNAs (miRNAs), hold significant promise for the early detection, diagnosis, and prognosis of CRC.[27] In early-stage CRC patients, the number of CTCs in the bloodstream is typically very low, making their detection a critical focus of current research. The development and application of various nanomaterials have greatly enhanced the capture efficiency and analytical accuracy of CTC detection.

Pan et al[23] developed ratiometric nanosensors capable of detecting CTCs by responding to changes in intracellular hydrogen peroxide levels, thus enabling the assessment of CTC activity. These sensors feature dual fluorescence emission peaks, which significantly improve the accuracy and reliability of detection. Additionally, Kuai et al[21] utilized EGFR-targeted immunomagnetic liposomes (EILs) to capture CTCs, demonstrating superior capture efficiency and specificity compared to traditional EpCAM immunomagnetic beads. This approach offers a promising strategy for the diagnosis of CRC.

Antibody-loaded nanoplatforms have shown considerable potential in recognizing tumor cells and biomarkers, addressing the limitations of conventional screening methods.[28] Xie et al[19] found that nanomaterials dual-functionalized with antibodies significantly improved the capture specificity of CTCs. Moreover, the use of multi-Sialyl Lewis X antibodies (aSlex) conjugated to PAMAM dendrimers for the specific binding and capture of colon cancer cells (HT29) demonstrated a concentration-dependent enhancement in capture efficiency.[18] These conjugates of multi-Sialyl Lewis X antibodies with PAMAM dendrimers specifically bind and capture HT29 colon cancer cells, showing a clear increase in capture efficiency with higher concentrations. Huang et al[22] proposed a density gradient centrifugation method using gelatin nanoparticle-coated silica beads for the separation, release, and analysis of CTCs. This method not only improves the efficiency and purity of CTC capture but also preserves the viability of CTCs, thereby enabling subsequent molecular and functional analyses.

Other Biomarkers

In addition to circulating tumor cells (CTCs), other molecular markers have also demonstrated enhanced detection sensitivity through the application of nanomaterials. For instance, a study designed a nanozyme-based pump-free microfluidic chip for capturing and detecting circulating cancer stem cells (CCSCs) in peripheral blood and fecal samples. The use of $CoPt_3$@HA probes for magnetic separation and colorimetric signal transduction enabled a detection limit of 3 cells per milliliter.[12] MicroRNAs (miRNAs) also serve as effective markers for the early detection of CRC. A Surface-Enhanced Raman Scattering (SERS) biosensor was developed using Au nanocage@Au nanoparticles and Ag-coated Fe_3O_4 magnetic nanoparticles. This biosensor achieved detection limits of 3.46 aM for miR-21 and 6.49 aM for miR-31, while also demonstrating high specificity and anti-interference ability.[13]

In conclusion, nanomaterials have shown substantial potential in enhancing the diagnostics of CRC, ranging from the detection of genetic alterations to the identification of microbial biomarkers. However, challenges remain (Table 2). For instance, some technologies may require complex instrumentation or sample preparation procedures. Additionally, the cost-effectiveness and scalability of these methods need further investigation to ensure their practicality in diverse healthcare settings.

Nanomaterial-Enhanced Radiological Examination for CRC Diagnosis

Imaging detections provides detailed anatomical and functional information for tumor. However, it still faces challenges such as insufficient signal intensity and poor specificity. Nanomaterials, with their unique physicochemical properties, hold significant promise in enhancing the diagnostic accuracy of CRC by targeting tumors, boosting signal strength, and improving imaging contrast. Furthermore, they offer potential for real-time treatment monitoring (Table 3).

Nanomaterials can serve as MRI contrast agents to improve tumor imaging quality. For instance, MnO_2-coated nanoparticles, which undergo reduction reactions in the tumor microenvironment, have been successfully applied to achieve T_1-weighted MRI imaging.[38] Additionally, nanomaterials enable multimodal imaging techniques, combining MRI with other imaging modalities such as CT and fluorescence imaging. Fe_3O_4 nanoparticles, for example, have been employed to achieve dual-modal MRI and

Table 3 Advances in the Application of Nanomaterials for Imaging and Surgical Guidance in CRC

Nanomaterials	Application	Target/Mechanism	Research Subject	Main Results	Ref
2D5-IRDye800CW	NIR-II fluorescence-guided surgery	-CEACAM5 targeting; -NIR-II fluorescence signal	Mouse models; human CRC specimens	- Rapid tumor accumulation (15 min); - Detected tumors <2 mm	[29]
Ga-HNI01[30]	PET imaging for detection of primary and metastatic CRC	- CEA targeting; - Synthesized within 10 min, radiochemical purity >98%;	Tumor models; 9 patients with primary and metastatic CRC	-Clear visualization of tumors; -Fast blood clearance; -Detected metastases in liver, lung, pancreas	[31]
Nb41, Nb41-ABD	PET and NIR fluorescence imaging for CRC and lymph node metastasis detection	CEACAM5 targeting	Mouse models	-LNM enrichment; -Tumor-to-normal ratio up to 12.3 (Poly-g-BAT)	[32]
Poly-g-BAT	Real-time tumor detection during surgery	Tumor-selective fluorescent probe	Colorectal tumors; Animal models	- Rapid visualization (3 min after in situ spraying); - Identified minimal premalignant lesions via intravenous injection	[33]
E8-Nb-IR800CW, E8-Nb-PE38	NIR-II fluorescence-guided surgery	CDH17 targeting	CRC cells and tumor models	- Precise tumor removal; - Immunotoxin-induced apoptosis and immunogenic cell death; - Synergistic effects with 5-FU	[34]
Carbon nanoparticles	Enhanced lymph node harvesting during surgery	Lymph node harvesting	Rectal cancer patients	- Higher number of total nodes harvested; - Shorter detection time; - Higher positive LN rate in clinical stage I/II patients	[35]
LH-Fe_3O_4@M	MRI imaging and targeted chemotherapy	Homologous targeting CRC cell membrane	CRC models	- Superior MRI contrast enhancement; - High tumor ablation rate; - No damage to normal tissues	[36]
FE-2PEG	Detection of micrometastases	NIR-II fluorescence-guided surgery	Orthotopic CRC	- PPV 96.57% for peritoneal micrometastases; - PPV 96.07% for micrometastases <3 mm; - successful delineation of tumor-normal tissue boundary	[37]

CT imaging of CRC.[39] Additionally, nanomaterials facilitate molecular-level imaging by targeting tumor-specific molecules. The CEACAM5-targeted probe 2D5-IRDye800CW, which utilizes near-infrared-II (NIR-II) fluorescence, is crucial for real-time surgical guidance. This probe rapidly accumulates in tumors within 15 minutes and can detect tumors smaller than 2 mm[29] Another example is [68Ga]Ga-HNI01, a CEA-targeted PET imaging radiotracer that can be synthesized within 10 minutes and achieves radiochemical purity exceeding 98%. It enables the detection of metastases in the liver, lung, and pancreas with high contrast.[31] Furthermore, a novel nanobody Nb41 has been identified for PET and NIR fluorescence imaging, demonstrating significant accumulation in tumors and lymph node metastases.[32]

The use of nanomaterials in imaging diagnosis offers several advantages, including improved sensitivity and specificity for tumor detection. However, potential off-target effects and toxicity remain concerns, despite no adverse events reported in these studies. It is important to note that these studies are primarily preclinical, and further clinical trials are necessary to validate the safety and efficacy of these nanomaterials in humans.

Advancements in Nanomaterial-Based Therapy for CRC

Nanomaterial-Enhanced Precision Surgery in CRC

Surgery remains the cornerstone of CRC treatment, offering the potential for a cure in localized disease. Complete mesocolic excision and systematic lymph node dissection is critical for optimal outcomes. Recent advances include laparoscopic, robotic, and transanal total mesorectal excision techniques.[40] With the progress of precision medicine and minimally invasive surgical approaches, the unique properties of nanomaterials are playing an increasingly pivotal role in improving surgical navigation, enhancing tumor identification, and optimizing therapeutic outcomes. This section explores the various applications of nanomaterials in CRC surgery (Table 3).

Several studies have shown that preoperative use of carbon nanoparticles (CNs) enhances lymph node detection. A meta-analysis of 1241 patients found that CNs led to an average of 5.21 additional lymph nodes detected per patient (mean difference = 5.21, 95% CI = 4.14–6.29, $p < 0.001$) and a 68% increase in the detection of micro lymph nodes (RR = 1.68, 95% CI = 1.38–2.04, $p < 0.001$). CNs also identified more metastatic lymph nodes (RR = 1.56, 95% CI = 1.40–1.75, $p < 0.001$), although the overall metastatic detection rate was similar between groups. In rectal cancer patients, the CN+ group had a higher number of lymph nodes retrieved at stations 251, 252, and 253, with 54.0% of patients retrieving ≥4 nodes at station 253 (vs 28.3%, $p = 0.004$). The retrieval of ≥4 nodes at station 253 was an independent risk factor for metastasis (odds ratio: 2.40, 95% CI: 1.22–4.74, $p = 0.012$).[41] Another study analyzing 768 patients undergoing radical resection for rectal cancer found that the CNs group had a significantly higher total number of lymph nodes retrieved ($p < 0.001$), a significantly shorter total time for lymph node detection ($p < 0.001$), and a significantly increased percentage of lymph nodes <5mm in size ($p < 0.001$). Among patients with clinical stages I/II, there was a significant difference in positive lymph nodes (21.79% vs 11.95%, $p = 0.029$).[35] These studies indicate that CNs are effective lymphatic tracers in CRC surgery, aiding in determining the extent of surgery and assessing prognosis.[35,42]

Wang et al employed preoperative endoscopic localization of CRC and used carbon nanoparticles for lymph node tracing during laparoscopic surgery. The experimental group demonstrated a higher average number of lymph nodes removed compared to the control group, with a greater proportion of patients in the experimental group achieving ≥12 lymph nodes resected.[43] Additionally, Zinc-gallium-germanate (ZGC) nanoparticles doped with Cr^{3+} and modified with folic acid (ZGC-FA) exhibited strong near-infrared (NIR) luminescence with a signal-to-noise ratio of 23.9 in vivo. In a luciferase-expressing CRC model, 50 minutes after injection, the luminescence signal aligned closely with the tumor boundary (98% overlap), enabling complete tumor resection with minimal healthy tissue removal (2.3%). This improved surgical precision, reduced normal tissue damage, and lowered tumor recurrence, enhancing patient prognosis.[44]

Ma et al utilized a NIR-II organic donor-π-acceptor-π-donor probe, FE-2PEG, for high-resolution in vivo imaging of CRC. This probe exhibited bright fluorescence at 1100 nm and excellent photostability. Under fluorescence-guided surgery (FGS) using NIR-II fluorescence, the probe facilitated the resection of peritoneal micro-metastases with a sensitivity of 94.51%, specificity of 86.59%, a positive predictive value of 96.57%, and a negative predictive value of 79.78%. Notably, even for micro-metastases smaller than 3 mm, the positive predictive value remained as high as 96.07%.[37]

These advancements in CRC surgery underscore the critical role of nanomaterials in enhancing surgical precision. Preoperative use of carbon nanoparticles improves lymph node detection and metastatic identification, aiding in more accurate staging and prognosis. Nanoparticles such as ZGC-FA and NIR-II probes offer superior tumor localization, enabling complete resection with minimal damage to healthy tissue, ultimately improving surgical outcomes and reducing recurrence.

Nanomaterial-Enhanced Radiotherapy in CRC

Radiotherapy plays a crucial role in the treatment of CRC, yet it is limited by challenges such as non-specific tissue damage and suboptimal efficacy. Recent advancements in nanotechnology have introduced innovative strategies to enhance the efficacy of radiotherapy by improving tumor targeting, radiosensitization, and immune modulation (Table 4).

Radiosensitization

Gold nanoparticles (AuNPs) and carbon nanotubes (CNTs), among other nanomaterials, have demonstrated significant radiosensitizing effects in CRC treatment. AuNPs, owing to their unique optical properties, can enhance X-ray absorption, thereby increasing the radiation dose delivered to tumor tissues and improving the overall efficacy of radiotherapy. Additionally, AuNPs generate localized high temperatures upon laser irradiation, enabling a synergistic therapeutic effect in CRC treatment.[66] AuNPs co-loaded with carboplatin in liposomes (LipoGold) have shown notable radiosensitizing effects in HCT116 cells, significantly enhancing tumor cell killing efficiency.[67] Moreover, the combination of 17-AAG with AuNPs and radiation has been shown to significantly inhibit cell viability and induce apoptosis.[68] In addition to AuNPs, CNTs, known for their excellent mechanical strength and thermal conductivity, have gained attention as effective radiosensitizers in radiotherapy. Studies indicate that CNTs can enhance the radiosensitivity of tumor cells, thereby improving the cytotoxic effects of radiotherapy. When combined with chemotherapy agents, CNTs further augment the radiosensitizing effects in CRC, significantly increasing tumor cell apoptosis.[69] Additionally, bismuth disulfide nanoparticles (Bi_2S_3@BSA-MTX NPs) combined with methotrexate have been shown to significantly reduce the survival rate of SW480 cells and exhibit enhanced radiosensitizing effects under X-ray irradiation.[70] The use of X-ray-activated lanthanide-doped scintillators (LNS) combined with a photosensitive NO precursor to generate peroxynitrite in situ. This approach not only enhances radiosensitization but also promotes the polarization of tumor-associated neutrophils (TANs) from an immunosuppressive N_2 phenotype to an anti-tumor N_1 phenotype.[56]

Nanoparticles not only act as radiotherapy sensitizers but also inhibit tumor cell growth by modulating the tumor immune microenvironment. Wang L et al[64] investigated the use of STING agonist cGAMP-loaded nanoparticles (DMPtNPS) in rectal cancer cells. As catalytic radiosensitizers, DMPtNPS facilitate X-ray energy transfer, generate reactive oxygen species, alleviate tumor hypoxia, and enhance radiosensitivity. The study demonstrated that DMPtNPS, when combined with radiotherapy, induced a dual regulatory effect on the immune response. Moreover, cGAMP reversed the negative impact of DMPtNPS and radiotherapy on the tumor immune microenvironment via a type I interferon-dependent pathway, thereby promoting cancer immunotherapy.

The integration of nanomaterials with antitumor drugs and radioactive isotopes has further enhanced tumor suppression and improved nuclear medicine treatments. In mouse models, metal-organic framework (MOF) nanoparticles, such as Hf-DBB-Ru developed by Ni et al,[71] significantly reduced colorectal tumor size through combined radiotherapy and radiosensitization therapy (RDT). Additionally, DuRoss et al,[72] developed targeted nanoparticles that enhanced chemotherapy and radiotherapy effects in CRC mouse models by targeting P-selectin. Similarly, Meng L et al[73] developed manganese dioxide-modified albumin-bound paclitaxel nanoparticles, which improved the hypoxic tumor microenvironment and enhanced both chemotherapy and radiotherapy efficacy in CRC mouse models. The use of MIL-101(Cr)-NH_2 MOFs as carriers for radioactive isotopes has also demonstrated efficient tumor-targeted delivery, improving nuclear medicine treatment.[74] Furthermore, the development of a multifunctional nanoplatform (CCS) that integrates cetuximab for tumor targeting, Ni^{2+}/Mn^{2+}-doped carbon dots for NIR-II photothermal therapy (PTT), chemodynamic therapy (CDT), and photothermal/magnetic resonance/fluorescence imaging (PTI/MRI/FLI). In vitro and in vivo experiments demonstrated that CCS significantly inhibited tumor growth without detectable cytotoxicity.[58]

Overall, nanomaterials enhance the efficacy of radiotherapy in CRC by increasing tumor cell radiosensitivity, amplifying local radiation effects, and synergizing with chemotherapy, ultimately leading to cancer cell death via various mechanisms.

Nanomaterial-Enhanced Precision Chemotherapy in CRC

Chemotherapy plays a vital role in CRC treatment, significantly improving survival rates. In metastatic CRC, sequential use of FOLFOX and FOLFIRI regimens can extend median overall survival to approximately 20 months. The addition of targeted therapies, such as bevacizumab and cetuximab, has further improved outcomes, pushing median survival beyond

Table 4 Advances in the Application of Nanomaterials in Radiotherapy for CRC

Nanomaterials	Activation	Target/Mechanism	Object	Main Results	Ref
HCR NPs	NIR laser, hyperthermia	Co-delivery of IR820 and CLT with HCQ to inhibit autophagy and enhance apoptosis	CRC cells and mouse models	Excellent therapeutic effect both in vitro and in vivo	[45]
AuPB@PDA/Mn	NIR-II light	NIR-II light-activated generation of local hyperthermia and Mn^{2+} ions to enhance immunogenic cell death	Colorectal tumor models	Enhanced infiltration of CD8+ T cells and development of memory CD8+ T cells	[46]
Fe3O4@BSA-CE6	NIR laser, ROS generation	Photodynamic therapy-induced apoptosis and ferroptosis via ROS generation and lipid peroxidation	CRC cells	Synergistic effect of apoptosis and ferroptosis	[47]
IPLPNDs	NIR laser	NIR-activated hyperthermia and ICD-enhanced immunotherapy	Tumor-bearing mice	Tumor size increased by only 56% after 10 days	[48]
PDA/GNS@aPD-L1 NPs	NIR laser, photothermal effect	PD-1/PD-L1 blockade combined with photothermal ablation	Mouse models	Significant tumor growth inhibition and prolonged overall survival	[49]
GSH-triggered ferroptosis nanoplatform	GSH depletion	GSH depletion-induced ferroptosis and chemotherapy sensitization	CRC cells and mouse models	Effective tumor growth inhibition	[50]
BCG@PDA	NIR laser	Photothermal effect combined with BCG-induced immune response	Murine colon cancer model	Significant tumor growth inhibition	[51]
AuSHINRs@TBO	NIR laser	Synergistic photothermal and photodynamic therapies	CRC cells	Cell viability reduced to 39.0%	[52]
Nano-TiO2-coated MCNTs	NIR laser	NIR laser-induced photothermal therapy and regulation of cell apoptosis and cell cycle	CRC cells and mouse models	Superior tumor-killing ability under NIR laser irradiation	[53]
GAMP	NIR laser,	NIR laser-activated photothermal effect and GSH-induced H2S gas release	Colorectal tumors	Significant tumor growth inhibition	[54]
IR-BTGP	NIR-II light	NIR-II fluorescence imaging-guided photothermal therapy	CRC mice model	Tumor inhibition rate of 78.5%	[55]
LNS-*RS* nanoplatform	X-ray	X-ray-activated peroxynitrite ($ONOO^-$) and TANs polarization	Orthotopic CRC	Significant prevention of liver metastasis and recurrence	[56]
L-AuNP@TMT	NIR light	Membrane-targeting and photodynamic properties	CRC mouse models	Effective elimination of CRC without metastasis/recurrence	[57]
CCS	NIR-II laser	Cetuximab-mediated tumor targeting and multimodal imaging-guided synergistic therapy	Colon cancer cells and mouse models	Significant inhibition of tumor growth	[58]

(*Continued*)

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Table 4 (Continued).

Nanomaterials	Activation	Target/Mechanism	Object	Main Results	Ref
SNAP/MOL	X-ray	X-ray-induced ROS generation and NO release to overcome hypoxia	Colorectal and triple-negative breast cancer models	Efficient tumor growth inhibition and reduced metastasis	[59]
AlgNB/MoS_2/5-FU hydrogel	NIR light	NIR-triggered photothermal therapy and 5-FU drug delivery	SW480 cells and CRC models	Remarkable efficacy in tumor regression	[60]
GalNAc-derived photothermal nanotherapeutic	NIR-II laser	Cascade targeting of tumor and intratumoral Fn for enhanced PTT and immunotherapy	CRC cells and mouse models	Enhanced PTT efficacy and augmented immunogenicity	[61]
CCP@HP@M	Ultrasound	Synergistic ROS augmentation and autophagy blockage for enhanced SDT	CRC cells and mouse models	Enhanced SDT efficiency and apoptosis/ferroptosis induction	[62]
NCG	Ultrasound	Sonodynamic therapy and TGF-β inhibition to boost immune response	CRC liver metastasis mouse models	Inhibition of liver metastasis growth	[63]
DMPtNPS@cGAMP	X-ray	Catalytic radiosensitization and STING agonist loading for enhanced iRT	Rectal cancer bilateral tumor models	Durable complete response and enhanced abscopal effect	[64]
Cet-Iri-NPs	NIR laser	EGFR targeting and NIR-triggered chemo-photothermal therapy	SW480 cells and tumor xenograft mice	Promoted tumor-growth suppression effect	[65]

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two years in advanced CRC.[75] However, drug resistance, driven by mechanisms such as reduced drug uptake and enhanced drug efflux, remains a major challenge. To address these issues, novel strategies are being explored to improve drug delivery and efficacy. Nanocarriers, including liposomes, solid lipid nanoparticles, and silica nanoparticles, have shown promise in enhancing the delivery and efficacy of oxaliplatin while minimizing side effects.[76]

Recent Advances in Nanomaterials for Drug Delivery and Chemotherapy Sensitization

Nanotechnology -based drug delivery systems have shown significant potential in improving the therapeutic efficacy of CRC treatments by enhancing drug solubility, stability, bioavailability, and reducing toxic side effects (Table 5).

The nanoparticle-drug conjugate CRLX101, administered at 15 mg/m² weekly in neoadjuvant chemotherapy and radiotherapy for locally advanced rectal cancer, achieved a pathological complete response (pCR) rate of 19%, with a notable 33% pCR rate at the weekly dose.[88] Ferritin nanoparticles (Ft NPs) and mucin 1 (MUC1) aptamer-targeted delivery of epirubicin (Epi) to CRC cells resulted in Apt-Epi Ft NPs, with an average size of 37.9 nm and an encapsulation efficiency of 67%. In acidic media, the drug release rate reached 90% within 4 hours, and targeted

Table 5 Summary of Nanomaterial-Based Drug Delivery Systems and Mechanisms in Colorectal Cancer Research

Nanomaterial Name	Drugs Name	Nano Target or Mechanism	Research Subject	Main Results	Ref
$CaCO_3$@Cur@QTX125@HA	Curcumin (Cur), QTX125	Hyaluronic acid (HA) targeting CRC cells	CRC cells and organoid	- Specific inhibitory effects on CRC cell growth - Internalization into PDO models and induced apoptosis of tumor cells	[77]
scFv biofunctionalized nanoparticles	5-Fluorouracil (5-FU)	Anti-CEA single-chain variable fragment (scFv) targeting CEA-expressing CRC cells	CRC cells and donor-isolated macrophages	- Higher cytotoxicity in CEA-expressing cells - No significant impact on metabolic activity or polarization of macrophages	[78]
Nanomicelle	Hemiprotonic phenanthroline-phenanthroline+ (ph-ph+)	Targeting CRC and related bacteria	CRC-related bacteria and CRC cells	- Effective against CRC-related bacteria and inhibits human CRC cell proliferation - Reduces tumor number and volume	[79]
Nano-Twin-Drug (Nir-Ir NPs)	Irinotecan (Ir), Niraparib (Nir)	Inhibition of DNA damage repair and activation of apoptosis	CRC cells	- Effective reversal of irinotecan resistance by inhibiting MRP-1 expression - Enhanced therapeutic effect on CRC without obvious toxicity	[80]
CaO2-N770@MSNs	CaO_2, N770	Targeting colorectal tumor tissues with mitochondrial N770-conjugated mesoporous silica nanoparticles	CRC tissues	- Penetrated dense mucus, inhibited tumor cell growth - Combined with PD-L1 radicate both orthotopic and distant tumors	[81]
Exosome-liposome hybrid nanoparticles	ALKBH5 mRNA	Targeting m^6A modification in CRC cells	CRC cells and tumor models	- Modulated glycolysis and inhibited tumor development	[82]

(*Continued*)

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Table 5 (Continued).

Nanomaterial Name	Drugs Name	Nano Target or Mechanism	Research Subject	Main Results	Ref
Camptothesome-based combination nanotherapeutic regimen	Camptothecin (CPT), Indoximod (IND)	Co-encapsulation of IND and CPT to mitigate IDO1 negative feedback	Tumor-bearing mice	- Drug delivery with higher tumor uptake - Superior in antitumor efficacy without severe systemic toxicities	[83]
Ultrasound-Triggered Nanogel (R-NG)	Oxaliplatin	Charge-reversible nanogel with TiO2 for low-intensity ultrasound (LIU) control	CRC cells	- Enhancing tumor penetration and cellular internalization - Continuously generated ROS, regulating tumor-associated macrophage polarization	[84]
Laser-Activable Murine Ferritin Nanocage (mHFn@MTO)	Mitoxantrone (MTO)	Thermal-responsive mHFn for targeted delivery and laser-controlled release of MTO	CRC cells	- Generating ROS and causing mitochondrial collapse and tumor cell death	[85]
Supramolecular Nanovector (HCCSM)	Camptothecin (CPT), MSA-2	STING agonist MSA-2 for in-situ vaccination immunotherapy	CT26 colorectal tumors	- Induced immunogenic cell death and enhanced antigen cross-presentation through STING	[86]
Diselenide-Bridged Nanovesicles (T-Se-Lip-OSMI)	OSMI-1	Targeting O-GlcNAcylation of Yes-associated protein (YAP)	CRC cells and organoid	- Reduced CRC cell proliferation, migration, and invasion - Targeted delivery and pronounced suppression of tumor growth in vivo	[87]

delivery significantly enhanced Epi's anticancer effects both in vitro and in vivo. scFv biofunctionalized nanoparticles, created by conjugating an anti-CEA single-chain variable fragment (scFv), MFE-23, with PLGA-PEG polymers to deliver 5-fluorouracil (5-FU), achieved a threefold increase in cellular uptake by CEA-expressing CRC cells compared to non-targeted counterparts. The cytotoxicity of 5-FU-loaded nanoparticles was significantly higher in CEA-expressing cells after 24 h and 48 h of treatment, highlighting the specificity and efficacy of this targeted delivery system.[78] Liposome-polymer hybrid nanoparticles (Cet-Iri-NPs), composed of PPG-PEG copolymer, lipid DSPE-PEG-Mal, and lecithin as carriers, were designed for targeted EGFR therapy in CRC. These nanoparticles, loaded with CPT-11 as the chemotherapy agent, indocyanine green (ICG) as the photothermal agent, and cetuximab as the targeting ligand, demonstrated significant photothermal effects. Upon near-infrared (NIR) laser irradiation, Cet-Iri-NPs facilitated faster CPT-11 release, inducing cell death in SW480 cells and inhibiting tumor growth in a xenograft mouse model.[65] A layered double hydroxide (LDH) nanoparticle system, co-loaded with the anticancer drugs 5-fluorouracil (5FU) and albumin-bound paclitaxel (Abraxane, ABX), effectively delivered both drugs to colon cancer cells (HCT-116). This system synergistically induced apoptosis, accumulating efficiently at the tumor site and significantly inhibiting tumor growth after three intravenous injections, without detectable side effects.[89]

Calcium carbonate ($CaCO_3$) nanoparticles loaded with curcumin (Cur) and the HDAC inhibitor QTX125, coated with hyaluronic acid (HA), demonstrated efficient cellular uptake and significant growth inhibition in CRC cells, including patient-derived organoid models. These nanoparticles exhibited a uniform spherical morphology with diameters around 450 nm and a Zeta potential of −8.11 mV.[77] Meanwhile, diselenide-bridged nanovesicles encapsulating OSMI-1, an O-GlcNAc transferase inhibitor, demonstrated superior efficacy in reducing CRC cell proliferation, migration, and

invasion both in vitro and in vivo compared to conventional nanovesicles.[87] pH/cathepsin B sequential responsive nanoparticles (PSRNs) were designed for precise intracellular delivery of PROTACs targeting CDK4/6. Finally, genetically engineered ferritin nanoparticles (mHFn) represent another breakthrough, delivering mitoxantrone (MTO) specifically to tumor tissues for combined chemotherapy and photothermal therapy. Upon irradiation with a 660 nm laser, thermal-sensitive channels on mHFn facilitated efficient MTO release, generating reactive oxygen species and inducing significant tumor cell death.[85]

Collectively, these studies underscore the versatility and potential of nanomaterial-based strategies in overcoming the limitations of traditional chemotherapy. By enhancing cellular uptake, enabling targeted delivery, and modulating the tumor microenvironment, these innovations offer promising avenues for advancing CRC treatment.

Nanotechnology-Enhanced Therapies for CRC: Overcoming Resistance and Enhancing Efficacy

Chemotherapy's lack of specificity for cancer cells often results in severe systemic toxicity, limiting its effectiveness. Targeted therapy, as a selective drug delivery system (SDDS), offers a promising strategy to reduce side effects. DNA nanocrosses (Holliday junctions, or HJ) have been used to target doxorubicin (Dox) delivery to colon cancer cells, significantly enhancing antitumor effects in vivo without increasing toxicity.[90] Additionally, embedding superparamagnetic Fe_3O_4 nanoparticles (~10 nm) into chitosan polyelectrolyte complexes (PECs) enables efficient irinotecan (IRT) delivery to tumors under magnetic guidance, overcoming chemotherapy's toxic side effects.[91]

Oxaliplatin resistance, a major obstacle in CRC treatment, contributes to recurrence and metastasis. Colorectal cancer cells secrete high levels of hyaluronic acid (HA), which mediates resistance to chemotherapy. The degradation product of HA, hyaluronic acid oligosaccharide (oHA), can reverse this resistance. OHA-loaded oxaliplatin liposome nanoparticles (oHA-Lipid-Oxa), synthesized via the thin-film hydration method, exhibit excellent tissue compatibility and targeting ability. These nanoparticles significantly suppress tumor growth, increase lymphocyte and macrophage infiltration, and do so without causing significant weight loss in mice. This suggests that oHA-Lipid-Oxa enhances oxaliplatin sensitivity while minimizing adverse effects.[92] Furthermore, a nanodiamond platform enables oral chemotherapy combined with photothermal therapy, improving drug accumulation in tumor tissues and enhancing therapeutic efficacy through near-infrared laser-responsive drug release.[93]

In summary, the integration of nanotechnology into CRC treatment has led to significant advances in targeted drug delivery, overcoming chemotherapy resistance, and improving therapeutic outcomes with fewer side effects.

Nanomedicines Target Cancer Stem Cells to Control Tumor Growth

Cancer stem cells (CSCs) are a subpopulation of tumor cells that contribute to chemotherapy resistance, tumor recurrence, and metastasis, making them key targets for effective therapeutic interventions. Nanomaterials, through precise targeting and controlled drug release, can enhance chemotherapeutic efficacy while minimizing damage to normal cells. Magnetothermal therapy (MHT) combined with local chemotherapy effectively suppresses colorectal CSCs. Iron oxide nanocubes, used as heat mediators for MHT, are coated with a thermoresponsive polymer (TR-Cubes) and loaded with doxorubicin (TR-DOXO) or oxaliplatin. Cells exposed to both chemotherapy agents and MHT show reduced colony formation, and tumor growth is undetectable in exposed mouse models.[94]

Nanomaterials Targeting the Tumor Microenvironment for CRC Treatment

Tumor immune microenvironment (TIME) plays a crucial role in tumor progression and therapeutic response, with immunosuppressive elements often hindering effective treatment. Nanomaterials offer significant advantages by specifically targeting and modulating the TIME to enhance antitumor immunity, overcoming limitations of traditional therapies. Some nanomedicines induce reactive oxygen species (ROS) production, kill tumor cells, stimulate the release of immunogenic cells, enhance T-cell infiltration, and reverse immunosuppression (Table 6).

Targeting Immune Checkpoints and Signaling Pathways

In a liver metastasis mouse model, the combination of nanomedicine (NCG) and anti-PD-L1 inhibited the growth of colon cancer liver metastasis. NCG contains the transforming growth factor-β receptor inhibitor galunisertib (Gal) and the photosensitizer chlorin e6 (Ce_6) generates ROS under ultrasound irradiation, leading to tumor immunogenic cell death and the release of immunostimulatory signals. This also induces M1-like polarization of tumor-associated

Table 6 Advances in the Application of Nanomaterials for Modulating Tumor Microenvironments in CRC

Nanomaterials		Mechanisms	Main Results	Ref
R848 and PPa co-assembled	Self-immolated nanoadjuvants	Accumulate at tumor site, dissociate in acidic endosomes, induce immunogenic cell death, activate DCs, recruit cytotoxic T cells	Synergistic in situ vaccination immunotherapy with immune checkpoint blockade induces sustained immunological memory	[95]
FA_IL/CCL nanotherapeutics	CD46-specific CAR T cells	Suppress proliferation and liver metastasis, potentiate immune efficacy of CD46-CAR T cells	Robust antitumor activity in PDX xenograft model	[96]
LR-S-CD/CpG@LNP		Photothermal and photodynamic properties induce immunogenic cell death, stimulate maturation of dendritic cells	Suppress growth of orthotopic colorectal tumors and their liver metastases	[97]
E@L-P/ICG	Photosensitive bacterial system	Photothermal effect triggers self-rupture, release adjuvants and antigens, stimulate generation of high endothelial vessels	Form tertiary lymphoid structures, enhance adaptive immune responses	[98]
si/F@RL	Targeted cationic liposome	Inhibit CD47 immune checkpoint expression, promote M1-like TAMs polarization and phagocytosis	Strong synergistic anticancer effect, inhibit tumor growth and metastasis	[99]
PA-WSe_2 and LA-WS_2	Functional nanosheet immune switches	Bidirectionally polarize macrophages in tumor and inflammatory microenvironments	Effective immunotherapy for CRC and sepsis	[100]
Cu_2xO@MnO_2@GOx@HA	Tumor-microenvironment-mediated second NIL activation multifunctional cascade nanoenzyme	Target in situ cancer starvation/chemodynamic therapy/photothermal therapy, induce immunogenic cell death	Realize PTT, CDT starvation therapy, and immunotherapy	[101]
CuGI	Metal-phenolic networks	Redirect metabolic pathway, induce oxidative and proteotoxic stresses, induce apoptosis and cuproptosis	Effectively suppress colorectal tumor growth, synergistically potentiate therapeutic efficacy	[102]
pOEG-b-D-SH@NP	Dendronized-polymer-functionalized metal-phenolic nanomedicine	Inhibit cellular oxidative phosphorylation and glycolysis, induce energy depletion and necroptosis	Potently suppress cancer growth and peritoneal intestinal metastasis in mouse models	[103]
Nano-IFNγ/Zole	Bisphosphonate-mineralized nano-IFNγ	Metabolically remodel TAMs, reduce lysosomal acidification, activate TFEB, accelerate reprogramming of TAMs from M2 to M1	Suppress tumor recurrence after incomplete radiofrequency ablation	[104]
Gel-NPs@GA	Injectable gambogic acid-loaded nanocomposite hydrogel	Reshape immunosuppressive tumor microenvironment, promote maturation of DCs, increase T cell infiltration	Significantly inhibit tumor growth in CT26 mice model	[105]
C5-PE38	GRP78 nanobody-directed immunotoxin	Induce ER stress, apoptosis, and immunogenic cell death, activate STING pathway	Antitumor efficacy against CRC models, enhance innate and adaptive immune response	[106]
NP-PROTACs	Self-assembled PROTACs	Dual degradation of β-catenin and STAT3, enhance CD103+ DC infiltration and T-cell cytotoxicity	Synergistic antitumor effect compared to single-target treatment	[107]

(*Continued*)

Table 6 (Continued).

Nanomaterials		Mechanisms	Main Results	Ref
CuS/MnO_2/diAMP nanoparticles		Preferentially activate antitumor inflammatory signaling via STING/IRF7/CXCL10 axis, alleviate protumor cytokines	Rebuild tumor milieus, inhibit tumor growth, alleviate T-cell exhaustion	[108]
DMPtNPS@cGAMP	STING agonist-loaded nanoparticles	Promote positive regulation of type I interferon-dependent radioimmunotherapy	Durable complete response at primary site, enhanced abscopal effect at distant site	[64]
Light-activatable oxygen self-supplying chemo-photothermal nanoplatform		Produce hydrogen peroxide, release oxygen under laser-triggered photothermal effect, induce ferroptosis	Excellent anti-tumor efficacy in chemo-resistant cell lines and nude mice xenograft models	[109]
P127-MLL@Gins	Magnetic natural lipid nanoparticles	Promote apoptosis/ferroptosis through oxidative stress and magneto-thermal effect, activate antitumor immunity	Significantly increase beneficial bacteria, reduce harmful bacteria, increase lipid oxidation metabolites	[110]
CCJD-FA	Copper-based nanoreactor	Generate H2O2 under acidic condition, induce cuproptosis, inhibit intracellular glycolysis and ATP generation	Sensitize cancer cells to cuproptosis, evoke systemic immune responses	[111]
BSA-Cu SAN	Protein-supported copper single-atom nanozyme	Generate ROS, deplete GSH, destroy pathogen-tumor symbionts, induce cancer cell apoptosis	Relieve ROS resistance of CRC, efficiently scavenge F. nucleatum in situ	[112]
CKPP	Copper-based bio-coordination nanoparticle	Amplify ROS production, regulate cellular metabolism, induce pyroptosis and cuproptosis	Remarkable anticancer effect, tumor inhibition rate of 96.3%	[113]
Cu2O@Au	H_2O_2 self-supplied and GSH-depletion therapeutic nanocomposites	Consume endogenous H_2S, generate H_2O_2, induce ferroptosis, promote dendritic cell maturation and T-cell infiltration	Enhance antitumor efficacy of PD-L1 antibody	[114]
FexMoyS-PEG nanoparticles		Produce ROS, deplete GSH, induce ferroptosis, suppress glycolysis	Significantly inhibit tumor growth, especially when combined with NIR light therapy	[115]
OLP/PP nanoassembly		pH-responsive drug release in acidic tumor microenvironment, eliminate intratumoral Fusobacterium nucleatum	Overcome chemoresistance, significantly inhibit tumor growth	[116]
UIRN	Inulin-based nanoparticle	Increase intra-tumoral concentration and accumulation time of REG, induce polarization of tumor-associated macrophages toward M1-type	Efficiently control tumor progression, exhibit adjuvant effects to chemotherapy and immunotherapy agents	[117]
SeNVs@NE-IL32-EcN	Nano-selenium probiotic complexes	Enhance CD8+ T cell-mediated immune responses, overcome immunotherapy resistance	Improve proliferation and activity of CD8+ T cells, reduce tumor progression	[118]

(*Continued*)

Table 6 (Continued).

Nanomaterials		Mechanisms	Main Results	Ref
Oxa@HMI	Orally administered hydrogel	Production of ROS, modulation of microbiota and immune responses	Promote chemotherapy efficiency, activate antitumor immune responses	[119]
VA-SAM@BTO	Biomimetic piezoelectric nanomaterial-modified oral microrobots	Targeted catalytic and immunotherapy, disrupt immunosuppressive microenvironment, improve dendritic cell maturation and macrophage M1 polarization	Increase effector T cell proportions, decrease regulatory T cell numbers	[120]

macrophages and disrupts the immunosuppressive barrier of tumor-associated fibroblasts, increasing effector T cell infiltration, reversing tumor immunosuppression, and enhancing the efficacy of anti-PD-L1 antibodies.[63] Additionally, a highly stable cerasomal nano-modulator (DMC@P-Cs) has been developed, effectively accumulating in tumor tissues. It carries the immunotherapeutic adjuvant demethylcantharidin (DMC) in its hydrophilic core. Under ultrasound induction, DMC@P-Cs generates ROS to kill tumor cells and induce immunogenic cell death (ICD), while releasing DMC to downregulate regulatory T cells (Tregs) and enhance antitumor immune responses. The tumor inhibition rate reached 94.73%, with no significant toxic side effects observed.[121] A dual-targeted nano-delivery system (GOx@FeNPs) uses photothermal Fe_3O_4 nanoparticles to release tumor-specific antigens from tumor tissues, stimulating dendritic cell (DC) maturation in the lymph nodes and enhancing CD8+ T cell infiltration into the tumor. Combined with PD-L1, this system achieves a synergistic therapeutic effect, with a tumor suppression rate exceeding 90%.[122]

Ionizable STING-activating nanoadjuvants have been engineered to activate the STING pathway, inducing innate immunity and reshaping the TME. These nanoadjuvants demonstrated robust antitumor effects in mouse models of CRC, shifting the tumor immune landscape from immunosuppressed to tumoricidal.[30] Similarly, STING agonist-loaded nanoparticles (DMPtNPS@cGAMP) have shown the ability to enhance type I interferon-dependent radioimmunotherapy, leading to durable complete responses at the primary site and enhanced abscopal effects at distant sites.[64]

Nanomaterials Modulating the Tumor Microenvironment by Polarizing Immune Cells

CRC tissues that are microsatellite stable/proficient in mismatch repair (MSS/pMMR) are typically considered immunologically "cold", with poor immunogenicity and limited CD8+ T cell infiltration. Nanomaterials that can induce the polarization of immune cells towards a pro-inflammatory phenotype have shown potential in reshaping the TME. One approach utilizes nano-drug delivery of cyclin-dependent kinase (CDK) inhibitors to downregulate phosphorylated retinoblastoma and RNA polymerase II, arresting the G2/M cell cycle. This promotes the release of immunogenic signals, stimulates DC maturation, and enhances CD8+ T cell infiltration. This strategy has shown significant efficacy in activating immune responses in patient-derived xenograft and organoid models of CRC liver metastasis.[123] In another study, inulin-based nanoparticles (UIRN) encapsulating the chemotherapeutic drug regorafenib have demonstrated the ability to increase the intratumoral concentration and accumulation time of the drug, leading to the polarization of tumor-associated macrophages (TAMs) towards the M1-type, which enhances antitumor immunity.[117]

In summary, nanomaterials are emerging as powerful agents to enhance CRC immunotherapy by modulating the tumor immune microenvironment, inducing immunogenic cell death, and synergizing with immune checkpoint inhibitors to achieve high tumor suppression rates. These approaches have demonstrated substantial efficacy in preclinical models, including immunologically cold tumors, offering promising strategies for overcoming treatment resistance and improving patient outcomes.

Nanomaterials Modulating the Tumor Microenvironment by Regulating the Microbiota

Nanomedicines enhance the efficacy of chemotherapeutic drugs by modulating tumor-associated bacteria. Fusobacterium nucleatum (F. nucleatum), prevalent in CRC, is linked to cancer cell proliferation, metastasis, and poor treatment outcomes.

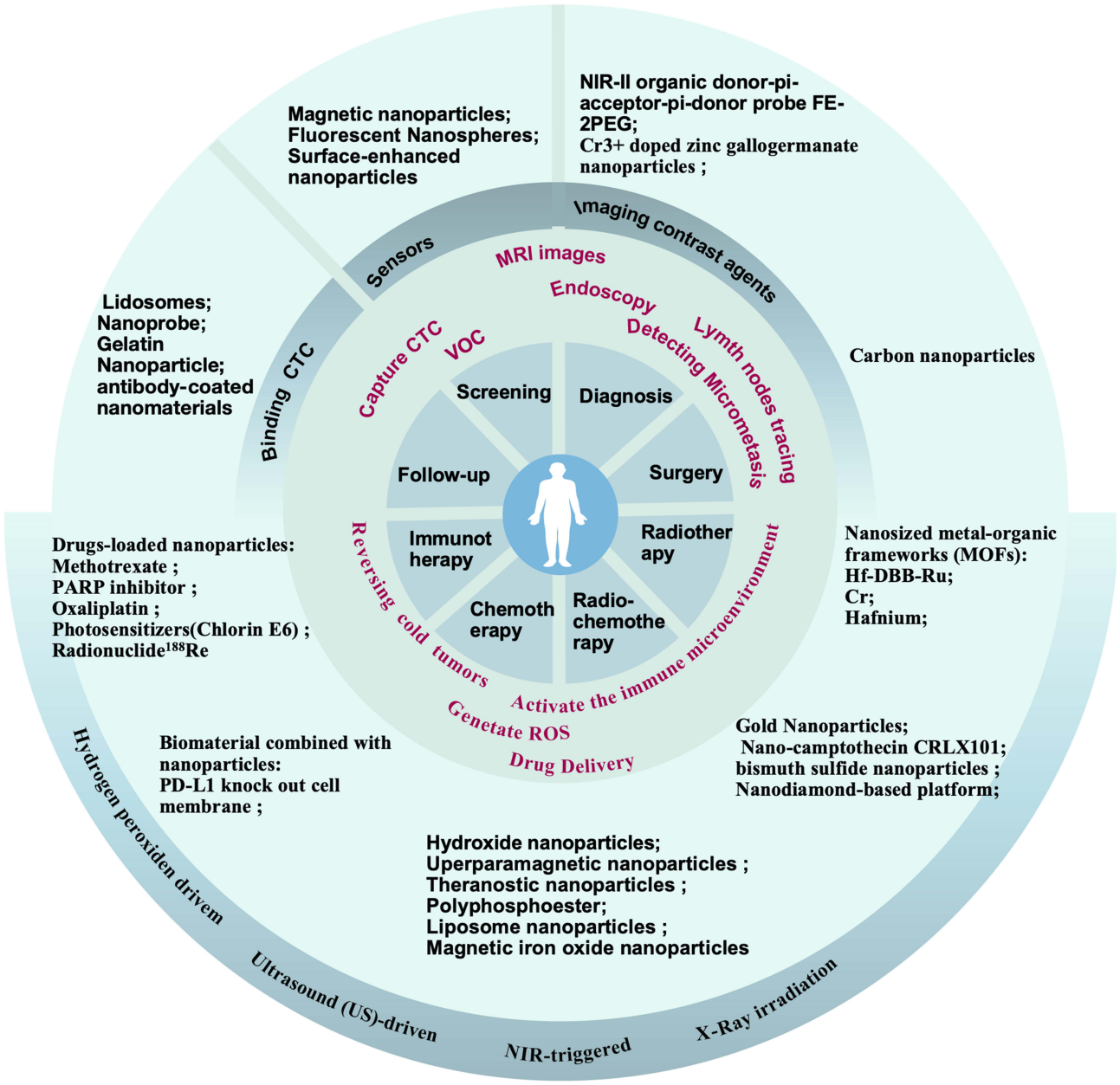

Figure 1 Multifaceted Applications of Nanomaterials in Colorectal Cancer Management. This figure illustrates the diverse roles of nanomaterials in the screening, diagnostics, and therapeutics of colorectal cancer (CRC). Nanomaterials serving as imaging contrast agents have demonstrated significant potential in augmenting the sensitivity and specificity of colorectal cancer detection during endoscopic and magnetic resonance imaging (MRI) procedures. These agents enhance the intraoperative identification of micro-metastatic lesions, thereby facilitating the precise resection of tumor tissue. Moreover, the nanomaterials contribute to the efficient capture of circulating tumor cells within the bloodstream, which is instrumental for patient surveillance, as well as for the early detection and screening of cancer. The drug delivery systems that utilize nanomaterials to efficiently and specifically deliver therapeutic agents to tumor sites remain a focus of research. Upon activation by stimuli such as near-infrared light or ultrasound, these nanocarriers can trigger the release of cytotoxic drugs directly at the tumor site. Additionally, they have the capability to suppress tumor growth through mechanisms that include the induction of reactive oxygen species, modulation of the tumor's immunological microenvironment, and other therapeutic strategies. This multifaceted approach underscores the versatility and promise of nanotechnology in advancing cancer treatment and management.

Incorporating highly immunostimulatory cholesterol-modified CpG oligonucleotides into autologous F. nucleatum membranes using nanovaccines significantly improves chemotherapy responses in F. nucleatum-infected CRC and reduces metastasis.[124] Additionally, phage-guided nanotechnology markedly enhances chemotherapy efficacy in mouse models of CRC by inhibiting tumor-promoting F. nucleatum and boosting the effectiveness of first-line chemotherapeutic agents.[125] Nano-selenium probiotic complexes (SeNVs@NE-IL32-EcN) have been developed to enhance CD8+ T cell-mediated

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immune responses and overcome immunotherapy resistance in CRC. This complex significantly improved the proliferation and activity of CD8+ T cells and reduced tumor progression in humanized mouse models.[118]

Nanomaterials Modulating the TME by Inducing Oxidative Stress and Immunogenic Cell Death

Nanomedicines can eliminate tumor cells by inducing the production of reactive oxygen species (ROS). In photodynamic therapy, photosensitizers are commonly used to generate ROS that target cancer cells. Nanoparticles were constructed via self-assembly of an amphiphilic hyperbranched polyphosphoester containing thioketal units and photosensitizers, synthesized through self-condensing ring-opening polymerization of a novel cyclic phosphate monomer and end-capped with Chlorin e6. These nanoparticles serve as drug carriers, loading camptothecin and maintaining stability in blood circulation. The Chlorin e6 in the nanoparticles effectively generates ROS to kill cancer cells.[126] In another study, nanoparticles delivered to tumor tissues gradually released chemotherapeutic drugs and Mn2+ through glutathione (GSH)-triggered biodegradation. The released chemotherapeutic drugs not only exhibited potent anticancer effects but also enhanced H_2O_2 generation.[38] Moreover, H_2O_2/ultrasound (US)-driven mesoporous manganese oxide (MnOx)-based nanomotors, upon entering the tumor microenvironment, decompose excess H_2O_2 into singlet oxygen via Mn^{2+} mediated Fenton-like reactions, inducing ferroptosis in tumor cells and releasing tumor antigens. This strategy directly kills cancer cells, reverses the immunosuppressive microenvironment, and boosts systemic antitumor immunity, thereby controlling both primary and distant tumors.[127] These nanoformulations induce ROS production and ferroptosis, leading to direct tumor cytotoxicity and stimulating systemic antitumor immunity, thus offering a multifaceted approach to improving chemotherapy outcomes in CRC.

The use of nanomaterials to target the TME in CRC offers several advantages, including enhanced drug delivery, specific targeting of tumor cells, and the ability to modulate the immune response. However, these approaches also face limitations, such as potential toxicity, the need for precise targeting to avoid systemic side effects, and the challenge of translating preclinical success to clinical settings. Future research should focus on optimizing nanomaterial design to minimize toxicity, improve biocompatibility, and enhance therapeutic efficacy.

Conclusions

Nanomaterials, including polymeric nanoparticles, liposomes, micelles, and exosomes, have shown great potential in medicine due to their unique physicochemical properties. The applications of nanomaterials in CRC were summarized in Figure 1. These nanoscale formulations enhance drug solubility, bioavailability, and tumor specificity, potentially overcoming multidrug resistance and reducing toxic side effects.[128] These materials have shown significant potential in enhancing the precision of drug delivery systems, enabling targeted therapies that minimize damage to healthy tissues while maximizing therapeutic efficacy. Given their ability to directly target tumor cells, nanomaterials have also shown considerable promise in tumor radiotherapy, enabling the selective destruction of cancer cells, activation of the immune microenvironment, and enhancement of radiotherapy efficacy. By leveraging tumor organoid technology to identify nanodrugs to which patients are most responsive and to evaluate potential toxicities, we can facilitate the selection of personalized therapeutic agents.

Additionally, the application of nanomaterials in tumor diagnosis and imaging has been steadily increasing. For instance, nanomaterials have demonstrated superior performance in the efficient capture of tumor biomarkers and the detection of minimal metastatic lesions. Nanomaterials offer enhanced efficiency in capturing circulating tumor cells and cell-free tumor DNA (ctDNA), thereby improving the sensitivity of early screening and diagnosis for CRC. Moreover, when combined with colonoscopy and intraoperative imaging, these materials can effectively identify micrometastases and delineate tumor margins from normal tissue, thus optimizing therapeutic strategies.

In addition to improving drug delivery efficiency, researchers are exploring alternative therapeutic approaches. Over the past few years, an increasing number of studies have reported the use of nanomaterials to target and modulate the tumor microenvironment. One strategy involves regulating the internal homeostasis of tumors, such as by altering levels of reactive oxygen species or modulating intratumoral microbiota, to control tumor progression. With the advent of immunotherapy, the tumor immune microenvironment has emerged as a novel therapeutic target. In the past two years,

there has been a notable increase in studies utilizing nanomaterials to modulate immune cells within tumors or to activate tumor immune cells by regulating molecular pathways, thereby enhancing antitumor immune responses.

Moreover, researchers are developing nanomaterials to improve drug administration methods. For instance, oral nanotherapeutics have been designed to overcome gastrointestinal barriers, selectively target tumor cells, and exert therapeutic effects, potentially transforming the chemotherapy experience for patients. The development of these innovative technologies expands the scope of nanomaterial applications and holds promise for advancing cancer treatment strategies.

Challenges in the Clinical Translation of Nanomaterials

However, significant challenges remain in translating nanomedicines from the laboratory to clinical practice. Biocompatibility and potential toxicity are primary concerns for their clinical application. Studies have shown that the size, shape, and surface properties of nanomaterials can influence their distribution, metabolism, and excretion in the body, affecting their safety profiles. Additionally, many nanomaterials are fabricated from heavy metals such as copper (Cu) and gold (Au), and their potential toxic effects on the human body also need to be validated. Therefore, a comprehensive evaluation of the biocompatibility and toxicological properties of nanomaterials is crucial for their safe clinical use.

Another critical challenge is the large-scale production and quality control of nanomaterials. To ensure consistency and efficacy in clinical applications, standardized manufacturing processes and stringent quality control standards must be established. This includes rigorous monitoring of the physicochemical properties of nanomaterials, batch-to-batch consistency, and long-term stability. Additionally, the development of efficient synthesis methods and scalable production technologies is essential to reduce costs and improve yield.

In future studies, establishing standardized manufacturing processes and stringent quality control standards is crucial for ensuring consistency and efficacy in clinical applications. This includes rigorous monitoring of the physicochemical properties of nanomaterials, batch-to-batch consistency, and long-term stability. Additionally, further investigation into the biocompatibility and toxicity profiles of these nanomaterials is necessary to ensure their safety and effectiveness in patients. As nanotechnology continues to advance, it is expected that more nanomaterials will successfully transition into clinical applications, providing patients with safer and more effective therapeutic options.

Highlights

1. Nanomaterials Revolutionize CRC Management: Enhancing Screening, Diagnostics, and Therapeutics.
2. Advanced Nanotechnologies Improve Early Detection and Precision Surgery Outcomes.
3. Nanomaterials enable precise targeting of tumor cells, thereby enhancing the efficacy of radiotherapy and chemotherapy;
4. Nanomaterials specifically target the tumor microenvironment, modulating reactive oxygen species and activating tumor-infiltrating immune cells.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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