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**Nanotechnology for colorectal cancer detection and treatment**

Gogoi P *et al.* Colon cancer and nanotechnology

## **Abstract**

Colorectal cancer (CRC) is the third most diagnosed cancer and the second leading cause of cancer-related mortality in the United States. Across the globe, people in the age group older than 50 are at a higher risk of CRC. Genetic and environmental risk factors play a significant role in the development of CRC. If detected early, CRC is preventable and treatable. Currently, available screening methods and therapies for CRC treatment reduce the incidence rate among the population, but the micrometastasis of cancer may lead to recurrence. Therefore, the challenge is to develop an alternative therapy to overcome this complication. Nanotechnology plays a vital role in cancer treatment and offers targeted chemotherapies directly and selectively to cancer cells, with enhanced therapeutic efficacy. Additionally, nanotechnology elevates the chances of patient survival in comparison to traditional chemotherapies. The potential of nanoparticles includes that they may be used simultaneously for diagnosis and treatment. These exciting properties of nanoparticles have enticed researchers worldwide to unveil their use in early CRC detection and as effective treatment. This review discusses contemporary methods of CRC screening and therapies for CRC treatment, while the primary focus is on the theranostic approach of nanotechnology in CRC treatment and its prospects. In addition, this review aims to provide knowledge on the advancement of nanotechnology in CRC and as a starting point for researchers to think about new therapeutic approaches using nanotechnology.

**Key Words:** Nanoparticles; Colorectal cancer; Carbon nanotubes; Dendrimers; Quantum dots

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**Core Tip:** Colorectal cancer (CRC) is the third most diagnosed cancer and the second leading cause of cancer-related mortality in the United States. Genetic and

environmental risk factors play a significant role in the development of CRC. This review discusses the recent insights into nanotechnology-based methods for screening, detection, and treatment of CRC. This review aims to provide knowledge on the advancement of nanotechnology in CRC and as a starting point for researchers to think about new therapeutic approaches using nanotechnology.

## **INTRODUCTION**

<sup>8</sup>Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the United States, after lung cancer. The mortality rate of a cancer depends on its type and the sex, race, and other social factors of the patient. Death from CRC affects more males than females<sup>[1]</sup>. While it is predicted that more than 1 million individuals will be diagnosed with CRC every year<sup>[2]</sup>, there is a substantial geographical difference in the global distribution of CRC. <sup>6</sup>The countries with the highest incidence rates of CRC are Australia, New Zealand, Canada, the United States, and parts of Europe. The lowest-risk countries include China, India, and parts of Africa and South America<sup>[3]</sup>. Risk factors of CRC are associated with body mass index, smoking cigarettes, red meat consumption, family history of CRC, and irritable bowel disease<sup>[4]</sup>, while <sup>11</sup>published literature also suggests that risk of CRC decreases with physical activity, hormone therapy in postmenopausal women, aspirin/nonsteroidal anti-inflammatory drug use, fruit consumption, and vegetable consumption. Thus, CRC is a disease that the management of our daily habits can prevent. Although a hereditary risk factor is involved with CRC, effective early diagnosis strategies enable earlier initiation of therapy, thereby reducing the cancer's mortality rate.

Recently, nanotechnology has gained global consideration with its great potential for diagnosing and treating CRC. Nanotechnology utilizes nanoparticles (NPs) for <sup>2</sup>specific identification of tumors and cancer biomarkers, biologically targeted contrast agents, drug delivery systems, and novel treatment approaches<sup>[5]</sup>. <sup>2</sup>This review discusses the recent insights into nanotechnology-based methods for screening, detection, and treatment of CRC.

## CRC CAUSES AND STAGES

The growth of CRC incidence worldwide is related to genetic and environmental risk factors, in addition to sex, age, ethnicity, gut microbiota, and socioeconomic factors<sup>[6]</sup>. Environmental risk factors include obesity, a sedentary lifestyle, poor diet, alcohol addiction, long-term smoking<sup>[7]</sup>, and genetic factors due to inherited mutations or familial CRC<sup>[8]</sup>. Diet significantly impacts the microbiome environment and the risk of CRC development. Consumption of high-fiber diets and diet supplementation with polyunsaturated fatty acids, polyphenols, and probiotics could potentially reduce the risk of CRC<sup>[9]</sup>. About 70% of CRC cases are sporadically seen among patients over age 50, due mainly to dietary and environmental factors<sup>[10]</sup>. In addition, a family history of CRC and a personal history of chronic inflammatory bowel disease, type 2 diabetes, or genetic diseases like familial adenomatous polyposis or Lynch syndrome are related to augmented risk<sup>[11]</sup>. Acquisition of genetic and epigenetic mutations in specific oncogenes and tumor suppressor genes in normal epithelial cells leads to the sequential transformation of the normal colorectal epithelial cell into adenocarcinoma<sup>[12]</sup>. Chromosomal instability, microsatellite instability, and CpG island methylator phenotype are primary pathways influencing development of CRC<sup>[13]</sup>.

The stages of CRC determine the survival rate. Around 90% of CRCs are stage I, while 10% of the cases are diagnosed with stage IV metastasis, implying that early diagnosis leads to high chances of survival<sup>[14]</sup>. The tumor stage determines whether the therapy is beneficial and how successful the treatment might be against CRC<sup>[15]</sup>. The stages of CRC range from stage 0 to IV depending on the progression of cancer across the layers of the colon and rectum, effect on lymph nodes or nearby tissues, or its metastasis to distant organs (Table 1)<sup>[16]</sup>. Out of all the stages, stage IV CRC is not often curable, but it can be managed based on the cancer's growth and spread<sup>[17]</sup>. The sequential steps in CRC carcinogenesis are presented in Figure 1.

## CURRENTLY AVAILABLE METHODS OF CRC DETECTION

The United States Preventive Services Task Force recommends colorectal screening for adults aged 45 to 75. Several techniques are used to detect polyps or CRC, but colonoscopy is a must to confirm the screening process and other screening tests. The most used methods for screening CRC are stool test, flexible sigmoidoscopy, colonoscopy, computed tomography colonography, and double-contrast barium enema<sup>[17-27]</sup> in Table 2. Detection of DNA biomarkers is a promising technique for CRC screening. Stool-based DNA markers are convenient and easy to use. For early detection of CRC, biomarkers such as *ITG4* methylation, *SFRP2* methylation, miR-21, miR-92a, and miR-135b, as well as Cologuard<sup>®</sup> (Exact Sciences Corp., Madison, WI, United States), can be used. For malignancy detection, biomarkers such as *SFRP2* methylation, *VIM* methylation, *TFPI* methylation, miR-21, miR-92a, and miR-223 can be used<sup>[29]</sup>.

Clinical trials reported that sigmoidoscopy<sup>[30]</sup> and colonoscopy<sup>[31]</sup> reduce the chances of incidence and mortality of CRC. Sigmoidoscopy has a sensitivity and specificity of 92%-97% for the detection of polyps and expanded CRC and can be used to diagnose and treat CRC in patients who are ineligible for surgery (according to the severity of the tumor or comorbidities)<sup>[29]</sup>. The mentioned screening techniques detect either abnormal blood, antibodies, hemoglobin, DNA markers in the stool, or any polyps in the colon or rectum wall. Besides this, circulating tumor cell (CTC) detection-based diagnostic technology is also available, including CellSerch<sup>®</sup> assay (Janssen Diagnostics, LLC, South Raritan, NJ, United States), followed by faster and more efficient diagnostic systems like MagSweeper (Illumina, San Diego, CA, United States), Cynvenio (Cynvenio Biosystems Inc., Westlake Village, CA, United States), IsoFlux (Fluxion Biosciences, Alameda, CA, United States), VerIFAS<sup>t</sup>, AdnaGen, and magnetic sifters<sup>[5]</sup>. Most current screening methods of CRC are costly and not accessible at the point of care. Therefore, developing a more sensitive, fast, low-cost, and specific screening test for CRC is essential.

## **CURRENTLY AVAILABLE THERAPIES FOR CRC TREATMENT**

CRC care entails a multidisciplinary approach as the treatment options depend on factors such as the patient's age, comorbidities, overall health, type and stage of cancer, possible side effects of treatment regimens, *etc*<sup>[32]</sup>. Based on these characteristics and risk factors, patients are grouped into the following four categories for treatment guidance: (1) Group 0, no metastatic disease or relapse; (2) Group 1, potentially resectable metastatic disease; (3) Group 2, disseminated unresectable disease; and (4) Group 3, unresectable disease and unavailability of intensive or sequential treatment.

### ***Surgery***

Surgery is considered the most common treatment for CRC. It demarcates the removal of the tumor clinically during an operation. This is also called surgical resection. Group 0 patients fall under this category. Depending upon the size and location of the tumor, the surgical options include laparoscopic surgery, colostomy, and radiofrequency ablation or cryoablation. Laparoscopic surgery is an effective method that is carried out by passing several scopes into the abdomen *via* smaller incisions, whereas colostomy is a surgical opening for waste removal (into a pouch) by connecting the colon to the abdominal surface. When radiofrequency waves are used to heat or freeze the malignant tumors in the liver and lungs of CRC patients, then it is called radiofrequency ablation or cryoablation, respectively<sup>[33]</sup>.

### ***Radiation therapy***

In radiation therapy, the size of the tumor is reduced, and cancer cells are destroyed using high-energy radiations such as X-rays, radio waves, and protons. This therapy is primarily used in patients at risk of tumor recurrence. Different types of radiation therapies include external-beam, stereotactic, intraoperative, and brachytherapy<sup>[34]</sup>. The difference lies with the dose and the location of the cancer. For instance, external-beam radiation therapy is usually given 5 d a week for several weeks, whereas stereotactic radiation therapy delivers precise radiation to a small area. Stereotactic radiation therapy is given in malignant cancers that spread from the colorectal region to the liver



or lungs. Further, intraoperative radiation therapy and brachytherapy are specialized radiation therapies applicable only in <sup>7</sup> small areas of cancer that cannot be removed by surgery. In intraoperative radiation therapy, a single and high dose of radiation is given, whereas radioactive “seeds” are used and placed inside the body in brachytherapy. Lastly, neoadjuvant therapy shrinks the tumor for easier removal through surgery<sup>[35]</sup>.

### *Therapies using medications*

Medications are given as treatment plans to destroy cancer cells or reduce the tumor size. It can be delivered systemically *via* the bloodstream or directly through intravenous injections, pills, or capsules. Medications include chemotherapy, targeted therapy, and immunotherapy<sup>[36]</sup>. Chemotherapy is generally given to group 1 patients. It is considered a central treatment strategy for all types of cancers. <sup>16</sup> The United States Food and Drug Administration (FDA)-approved drugs to treat CRC are capecitabine (Xeloda®), fluorouracil (5-FU), irinotecan (Camptosar®), oxaliplatin (Eloxatin®), and trifluridine/tipiracil (Lonsurf®). For combined therapies, the combination of 5-FU with leucovorin (folinic acid), or leucovorin and oxaliplatin, or leucovorin and irinotecan, or capecitabine with irinotecan or oxaliplatin are used in group 3 patients for the treatment of CRC<sup>[37]</sup>. Different medications have different mechanistic pathways through which they act upon the cancer cells, *viz.*, inhibition of DNA replication, interference in chromosomal separation in the cell cycle, or cytotoxicity. However, chemotherapy may attack healthy cells. Chemotherapy is often given with radiation therapy to increase the effectiveness of the treatment regimen. A combination of chemotherapy and radiation is known as chemoradiation therapy. Chemoradiation therapy is often given to reduce the risk of colostomy or cancer recurrence.

### *Target therapy*

In targeted therapy, specific genes, proteins, or a niche is targeted to hinder the growth and survival of cancer cells. It limits damage to the healthy cells in group 1 and 2



patients. The targeted therapies for treating CRC include antiangiogenesis therapy and epidermal growth factor receptor inhibitors<sup>[38,39]</sup>. As the name suggests, the role of antiangiogenesis therapy is to stop angiogenesis, *i.e.*, the formation of new blood vessels. In the tumor niche, the nutrients are provided by blood vessels for the growth of tumor cells. However, these antiangiogenesis therapies lead to the starvation of tumor cells. For example, bevacizumab (Avastin®), regorafenib (Stivarga®), ziv-aflibercept (Zaltrap®), and ramucirumab (Cyramza®) are currently used targeted drugs. The FDA approved bevacizumab and chemotherapy as the first-line treatment for CRC in 2004<sup>[40]</sup>.

On the other hand, epidermal growth factor receptor inhibitors such as cetuximab (Erbix®) and panitumumab (Vectibix®) are considered adequate for group 2 patients<sup>[41]</sup>. These drugs are specific for genes like *RAS* and *Raf* and are ineffective in cases with mutations<sup>[42,43]</sup>. Other nonspecific cancerous medications such as larotrectinib (Vitrakvi®) and entrectinib (Rozlytrek®) are also used. These medications act on a specific genetic change called an neurotrophic tyrosine receptor kinase fusion. The currently available treatment methods for CRC and their side effects are detailed<sup>[32-34,36,38,39,43-46]</sup> in Table 3.

## **NANOTECHNOLOGY FOR CRC DIAGNOSIS AND TREATMENT**

NPs were first reported as drug carriers in 1986, and it was shown that they accumulate in tumoral tissues. This passive accumulation of NPs, known as the “enhanced permeability and retention” effect, was one of the turning points of cancer treatment using NPs. Therefore, due to their high specificity, accumulation in tumor sites, and prolonged blood circulation time, NPs are considered promising for cancer therapeutics<sup>[48]</sup> (Figure 2). Various families of organic and inorganic NPs are available today with a vast variety of sizes, structures, and compositions (Figure 3). Some of the common NPs that are used for CRC diagnosis and treatment are listed here.

### ***Iron oxide nanocrystals***

Iron oxide is popular as a diagnostic and therapeutic tool for its use in oncology. The superparamagnetic properties of iron oxide NPs have attracted attention for their biomedical applications, arising due to their biocompatibility and non-toxicity<sup>[49,50]</sup>. The diameter ranges from 1-100 nm with a <sup>1</sup> magnetic core to the iron oxide nanocrystals and a polymer covering containing the various medicinal molecules. These NPs have diverse biological properties due to their relatively small dimension, minimal deposition rate, efficient surface region, and ease of cellular transport. Iron oxide NPs loaded with 5-FU with magnetic hyperthermia effectively reduce tumor growth in heterotopic human colon cancer in mice<sup>[51]</sup>. Epirubicin-5TR1 aptamer-superparamagnetic iron oxide NP (SPION) tertiary complex could efficiently deliver epirubicin to C26 murine colon carcinoma cells and allows tumor detection by magnetic resonance imaging (MRI)<sup>[52]</sup>. Chitosan-coated iron oxide enhanced reactive oxygen species' production in a human colorectal carcinoma cell lines (HCT 116), and cell death was caused *via* caspase 9/3 activation<sup>[53]</sup>.

### ***Quantum dots***

Quantum dots are nanocrystal particles of semiconductors ranging from 2-10 nm, with fluorescence emission affected by particle size. With its optical and chemical advantages, quantum dot-based nanotechnology is a growing platform for cancer research, particularly CRC. Quantum dots are preferred for biomedical imaging due to their high quantum efficiency, photostability, extended excitation wavelengths, and narrow emission band<sup>[54,55]</sup>. Various *in vitro* and *in vivo* studies have used quantum dots as fluorescent markers for cancer, with their *in vivo* use limited to nontargeted or xenograft labeling<sup>[56,57]</sup>. Vascular endothelial growth factor receptor 2 (VEGFR2) is upregulated in CRCs, and QDot655 targeted to VEGFR2 (QD655-VEGFR2) showed its ability to detect VEGFR2-expressing tumors *in vivo*<sup>[58]</sup>.

### ***Poly (lactic-co-glycolic acid) NPs/nanocells***

Amongst the natural and synthetic polymeric NPs, poly (lactic-co-glycolic acid) (PLGA) has been used for oral drug delivery applications approved by the United States FDA. PLGA NPs are physically and chemically stable, have higher stability in biological fluids, and protect encapsulated drugs from enzymatic degradation. In addition, PLGA NPs can entrap small macromolecules, enhance thermal stability of the molecules, and help in sustained release<sup>[59,60]</sup>. Due to its biodegradability and biocompatibility characteristics and its ability to encapsulate hydrophobic and hydrophilic drugs, PLGA is often used as a drug carrier<sup>[61,62]</sup>. PEGylated-PLGA nanocapsules loaded with docetaxel and SPIONs treated tumor growth in CT26 colon cancer<sup>[63]</sup>. Encapsulated 5-FU into PLGA NPs reduced the proliferation rate of the colon cancer cell line HT-29 by increasing the intracellular concentration of drugs in cancer cells<sup>[64]</sup>. EGF-functionalized PLGA NPs loaded with 5-FU and perfluorocarbons inhibited colon tumor growth<sup>[65]</sup>. The single-step surface-functionalizing technique was used to prepare PLGA/PLA-PEG-FA NPs to incorporate 17-AAG (NP-PEG-FA/17-AAG), which improved the oral bioavailability of 17-AAG and effectively treated ulcerative colitis and associated cancer<sup>[66]</sup>. 5-FU-loaded PHBV/PLGA NPs are a promising nanodrug delivery system for the treatment of colon cancer<sup>[67]</sup>.

### *Dendrimers*

Dendrimers are highly branched spherical molecules having three-dimensional chemical structures, being enormously useful in nanopharmaceuticals due to their biodegradable backbones. The versatility of dendrimers in the delivery of anticancer drugs and theranostic applications in cancer therapy has been well established. Anticancer conjugated dendrimers can deliver the drug intracellularly, bypassing the efflux transporter and improving the bioavailability of loaded molecular cargo. They are also used for delivering diagnostic agents for tumor-targeted imaging<sup>[68,69]</sup>.

The chemotherapeutic approach to treat CRC is not proven to be effective, as only a tiny fraction of the drug reaches the tumor target site at an effective concentration<sup>[70]</sup>. The CTCs are cancer cells that migrate and are primarily responsible for tumor

metastasis. Given the importance of CTCs as an indicator of poor prognosis, several technologies (such as size-based filtration, microfluidics-based, *etc*) were utilized to isolate and capture CTCs from large populations of interfering cells but were not truly successful. Various methods were employed to detect colorectal CTC using dendrimers conjugated with antibodies, such as PAMAM dendrimers conjugated with Sialyl Lewis X antibodies to capture colon cancer HT29 cells<sup>[71]</sup>.

Apart from diagnostic use, dendrimers are also reported for use in anticancer therapy *in vitro*. G4 PAMAM dendrimers conjugated with capecitabine reported decreased tumor size and reduced side effects of capecitabine<sup>[72]</sup>. Gold NPs inside PAMAM dendrimer conjugated with curcumin showed higher cellular uptake, internalization, and cytotoxicity in C26 and HT29 colorectal cells<sup>[73]</sup>. Camptothecin-loaded PEGylated PAMAM dendrimer functionalized with AS1411 (anti-nucleolin aptamers) for site-specific targeting of CRC cells<sup>[74]</sup> and L-lysine dendrimers with polyoxazoline conjugated with SN-38 (the active metabolite of irinotecan) increased efficacy, and it minimized adverse side effects<sup>[75]</sup>. PAMAM G4 dendrimers with oxaliplatin enhanced targeting efficacy towards folic acid receptor-expressing CRC cells *in vitro*<sup>[76]</sup>. Gemcitabine-loaded YIGSR-CMChT/PAMAM dendrimer NPs induced targeted mortality on HCT-116 cancer cells<sup>[48]</sup>.

### ***Carbon nanotubes***

Carbon nanotubes (CNTs) are carbon nanomaterials with multifaceted roles in diagnosis, gene therapy, immunotherapy, and a carrier in the drug delivery system. They have excellent optical properties, thermal conductivity, chemical stability, and functionalization. CNTs are tiny tubular carbon atoms ordered to form a honeycomb nanostructure with exceptional physicochemical properties<sup>[77]</sup>. Based on the sheets of carbon atom numbers, CNTs are divided into single-wall CNTs or multi-wall CNTs. Various researchers have reported the effectiveness of CNT in cancer treatment and diagnosis. CpG-conjugated CNTs elevate the CpG uptake in mouse colon cancer cells and activates nuclear transcription factor-kappa B signals. CpG-CNT conjugation

successfully attenuated local xenograft tumor growth and liver metastasis<sup>[78]</sup>. Fluorescein functionalized single-walled CNT/II-NCC hybrids showed higher intrinsic activity against colon cancer cells (Caco-2) compared to the non-functionalized counterpart<sup>[79]</sup>. Single-wall CNT-conjugated antibody C225 binds to epidermal growth factor receptor-expressed CRC cells *via* receptor-mediated endocytosis<sup>[80]</sup>. Photodynamic therapy enhanced the ability to kill colon cancer cells by single-walled CNT nanobiocomposites<sup>[81]</sup>.

### ***Liposomes***

Liposomes are artificial and non-toxic lipid-based vesicular carriers. Historically, liposomes were first introduced as nanocarriers in 1961 as an FDA-approved drug delivery system. It comprises a phospholipid bilayer structure with a small and spherical aqueous core<sup>[82]</sup>. The main characteristic and advantage of NPs is their smaller size, which favors the particle for effective and targeted delivery of the drug used to diagnose and treat the disease<sup>[83]</sup>. Moreover, these particles have minor side effects. Among several NPs, liposomes are primarily used for the delivery system for nucleic acids, proteins, and peptides. Depending on the acting properties of liposomes, there are three types, as follows: (1) Stealth or long-circulating; (2) Active targeting; and (3) Thermo-sensitive/pH-sensitive/magnetic liposomes<sup>[84]</sup>. For example, doxorubicin (Doxil), DaunoXome, and Marqibo® are FDA-approved liposomal drugs, and Thermodox® is a thermo-sensitive liposome used to treat CRC<sup>[85]</sup>.

### ***Silica NPs***

Silica NPs possess a beehive-like porous structure with adjustable sizes of cavities ranging from 50-300 nm and 2-6 nm<sup>[86]</sup>. The advantageous characteristics of silica NPs include a highly porous framework, less toxicity, biocompatibility, pH sensitivity, and easy functionalization<sup>[87]</sup>. It is highly recommended for precise drug delivery for anticancer activity. For instance, a mesoporous silica NP-protamine hybrid system and conjugated hyaluronic acid to silica NPs load more medicine and increase the drug's

efficacy in the tumor niche. For CRC, silica NPs, along with photosensitizer chemicals, are used. The photosensitizers become activated when exposed to light, releasing reactive oxygen molecules to kill the cancer cells<sup>[88]</sup>.

### ***Gold NPs***

Gold NPs are considered the most stable among all noble NPs. They can be nanostructured in the form of cubes, spheres, rods, flowers, branches, wires, pyramids, shells, and cages. With accurate surface coating, the gold NPs are safer, efficient for drug delivery, and specific for cancer targeting<sup>[89]</sup>. Gold NPs enhanced cisplatin delivery efficacy and effectively decompressed CRC vessels<sup>[90]</sup>. Like nanoemulsion, gold NPs can also be conjugated with several molecules, such as antibodies, nucleic acids, proteins, enzymes, and fluorescent dyes. These factors augment the properties of gold NPs, including stability, biocompatibility, and functionalization in the medical field<sup>[91]</sup>.

### ***Nanoemulsion system***

As the name suggests, a nanoemulsion system consists of oil, water, and surfactant, formulating a transparent colloidal solution. It possesses the characteristics of less toxicity, high stability, thermosensitivity, pH-sensitivity, and better efficacy<sup>[82]</sup>. Nowadays, antiangiogenic drugs have been used to target CRC cells. However, these agents cause toxicity and resistance and are affected by barriers. In the tumor niche, vascularized tissue is a barrier that nanoemulsions can easily overcome to target cancer cells<sup>[92]</sup>. Nanoemulsion systems are used to deliver water-insoluble drugs with a hydrophobic core. For effective drug delivery and treatment activity, nanoemulsions are conjugated with different antibodies for selective and specific targeting. Other than antibodies, nanoemulsions are also conjugated with polyethylene glycol. Polyelectrolyte complex micelles and DNA complexes enhance their ability as cancer therapeutics. Tween-80 is a widely accepted and used emulsifier<sup>[93]</sup>.

### ***Other NPs***



In traditional cancer treatments, the therapeutic agents affect the immune system adversely, eliciting several side effects. Nanodrug delivery systems encapsulate the therapeutic agents, followed by targeted drug delivery in the tumor niche, which decreases the side effects. These systems not only lower the toxicity in the body but are highly stable, biocompatible, and efficient [*e.g.*, polypeptide-based copolymers, poly(trimethylene carbonate)-block-poly(L-glutamic acid) derived polymersomes, plitidepsin-unloaded polymersomes, near-infrared fluorescent proteinoid-poly(L-lactic acid), P(EF-proteinoid-poly(L-lactic acid)) random copolymer, proteinoid-proteinoid-poly(L-lactic acid) copolymer, *etc.*]. Several copolymers are effective against CRC cells and do not elicit any side effects. Nanoformulation of curcumin in micelles, nanogels, liposomes, NPs, and cyclodextrins has been documented for treating CRC<sup>[94]</sup>.

### **COMBINED NANOTECHNOLOGY-BASED APPROACHES FOR CRC DETECTION AND TREATMENT**

With the advent of nanotechnology-based approaches, cancer detection and treatment strategies have changed in recent years. However, the <sup>5</sup> clinical applications of nanotechnology-based formulations are limited due to their complex pharmacokinetics. The following are the combinatorial usage of nanotechnology-based approaches in the theranostics of CRC.

#### ***Enhancement of imaging techniques***

Nanotechnology-based contrasting agents are used to enhance the capability of cancer diagnostic imaging modalities such as positron emission tomography (PET), MRI, and other optical imaging techniques. The primary aim of this new technology is to detect the smallest possible number of cancer cells. PET is a powerful tool in diagnosing cancer due to its high sensitivity. A variety of relevant biomarkers are used for molecular and metabolic imaging with PET, such as fluorodeoxyglucose, 9mTc-labeled polyethylene glycol, [18F] DCFPyL, *etc.* Recently, NP-based contrasting agents including 56Fe and 14C conjugated with SPIONs, 99mTc-radiolabeled nanosilica system conjugated with a



trastuzumab half-chain, and MUC1 aptamer conjugated mesoporous silica NP have been used as radiolabeled tracers for PET. PET scan does not provide anatomical information; thus, other modalities such as computed tomography or MRI are used or have been merged with PET. In the case of MRI, SPIONs, gadolinium-encapsulated silicon microparticles, and gadolinium-ion-doped upconversion NPs are mainly used as contrast agents. At the same time, 2-deoxy-d-glucose labeled gold NPs and iodinated gold nanoclusters (AuNCs-BSA-I) are used in computed tomography. The advent of nanotechnology has made advancements in the imaging modalities for early detection of cancer and thus timely treatment for cancer<sup>[95]</sup>.

### ***Combined drug delivery***

The primary functional role of nanotechnology in the cancer field is drug delivery. The issues of multidrug resistance, stability, efficacy, and biocompatibility have been improved by formulating the drug delivery system using NPs. Traditionally, chemotherapy and other therapies have significant side effects, which are also reduced with the implementation of the nanotechnology-based formulation. For instance, 5-FU nanoencapsulation, forming a combinatorial nanomedicine agent with thiolated chitosan, is non-toxic and has enhanced chemotherapeutic efficacy in CRC patients. The use of nanomedicine has also led to a reduction in the dose quantity. In conventional therapy of 5-FU, the dose was much higher and toxic compared to nanoencapsulation of 5-FU<sup>[96]</sup>.

### **CONCLUSION**

There has been significant advancement in the field of nanomedicine over the last decade. Nanotechnology is gaining immense importance because of its highly efficient delivery system. The enormous use of nanomaterials for disease diagnosis and treatment is on-trend currently. The NP-based approaches for colon cancer diagnosis are summarized in Figure 4. The combined therapy with diagnosis, *i.e.*, theranostic application of nanomaterials, makes treatment easier and faster. CRC is mainly

associated with lifestyle, sex, and race, suggesting that certain groups are highly vulnerable. Thus, regular screening of CRC seems to be highly recommended to prevent the occurrence of CRC. Early diagnosis of CRC increases the chances of curing cancer and survival. Theranostic application of nanomaterials against CRC is still in development. Several researchers have already reported the successful treatment of CRC *in vitro* in cancer cell lines and *in vivo* in various CRC model animals. However, new strategies are required to improve the pre-existing therapeutics, and hopefully novel therapeutics using nanomaterials to treat CRC will be available soon for clinical application.

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