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MINIREVIEWS

Nanotechnology in diagnosis and therapy of gastrointestinal cancer

Meng Liang, Li-Dan Li, Liang Li, Shuo Li

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Abstract

Advances in nanotechnology have opened new frontiers in the diagnosis and treatment of cancer. Nanoparticle-based technology improves the precision of tumor diagnosis when combined with imaging, as well as the accuracy of drug target delivery, with fewer side effects. Optimized nanosystems have demonstrated advantages in many fields, including enhanced specificity of detection, reduced toxicity of drugs, enhanced effect of contrast agents, and advanced diagnosis and therapy of gastrointestinal (GI) cancers. In this review, we summarize the current nanotechnologies in diagnosis and treatment of GI cancers. The development of nanotechnology will lead to personalized approaches for early diagnosis and treatment of GI cancers.

Key Words: Nanodevices; Nanoparticles; Gastrointestinal cancer; Diagnosis; Therapeutics

Core Tip: The aim of this review is to summarize nanotechnologies in gastrointestinal (GI) cancer diagnosis and therapy. Nanodevices have the advantages of enhancing the specificity of detection and reducing toxicity of drugs in diagnosis and treatment of GI cancers.

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INTRODUCTION

Gastrointestinal (GI) cancer is a type of cancer that affects the GI tract and other organs in the digestive system. GI cancers are malignant tumors with both high morbidity and mortality. According to the 2020 World Cancer Report from World Health Organization International Agency for Research on Cancer (IARC), in terms of worldwide cancer morbidity, colorectal, gastric, liver, and esophageal cancers occupy the third, fifth, sixth, and eight places, respectively. Global mortality of colorectal, liver, gastric, esophageal, and pancreatic cancers are 0.94, 0.83, 0.77, 0.54, and 0.47 million, respectively[1]. The clinical manifestations still lack specificity, although GI cancers have mainly symptoms such as inappetence, abdominal distension, abdominal pain, diarrhea, emaciation, *etc*[2]. GI cancers have the worst prognosis of all cancers and have some of the lowest overall 5-year survival rates, with only gastric cancer above 10%[3]. It is particularly important to develop high-accuracy diagnostic approaches and effective drugs for treatment.

Nanotechnology is receiving attention in many fields of chemistry, engineering, biology, and medicine. Nanoparticle (NP)-based technology has significant biocompatibility and programmability, which offers opportunities in therapeutic and diagnostic applications, especially in cancer. NPs are well used in many areas, such as drug and gene delivery, photothermal therapy, recognition, and imaging agents[4,5].

Great histocompatibility and adjustable property have given NPs a boost. Varying pH, pressure, and bacterial content in the GI tract can regulate NPs characteristics, making the GI tract an attractive target for nanotechnological applications[6]. In GI cancers, NPs have been used for identification of biomarkers, for detection of sentinel lymph nodes (SLNs), for detection of GI tumor microenvironment, and as biologically targeted contrast agents for magnetic resonance imaging (MRI)[7]. Advanced imaging approach is the gold standard for cancer diagnosis. Current imaging techniques used in cancer diagnosis include MRI, computed tomography (CT), positron emission tomography (PET), single-photon emission CT, and ultrasound. Imaging results can give accurate diagnosis and staging. Apart from diagnostic approaches, there are many types of NPs that are being used as drug delivery systems and novel therapeutic agents. These applications improve current techniques not only for early diagnosis and accurate staging of GI cancers but also for treatment approaches.

OVERIEW OF NANOTECHNOLOGY IN GI CANCERS

Characteristics and advantages of nanodevices

Nanodevices refer to materials with at least one of the three dimensions in the nanometer range (1-100 nm)[8]. Nanodevices for diagnosis and treatment are now being used throughout oncology due to nanotechnological developments. Nanodevices can offer many possibilities as vectors or as nanodrugs under varying conditions such as pH, transit time, pressure, and bacterial content. Most nanodevices are biocompatible and nontoxic, with high specificity and sensitivity, which have wide applications in precise diagnosis. Moreover, nanotechnology has become one of the most promising cancer treatment strategies. The nanodevices have therapeutic properties and good drug loading capacity, are bound to ligands to achieve high affinity and specificity for target cells, load multiple drugs to achieve collaborative cancer treatment. and avoid conventional drug-resistance mechanisms[9,10].

The unique properties of nanomaterials enable them to behave normally in the complex GI environment. The size, morphology, and surface functionalization of the NPs can affect the interactions of drugs and the GI tract. Size can influence cellular uptake, physical properties, and interactions with biomolecules[8]. The NP diameter should be smaller than the size of the cells so that NPs could interact with or be taken up by cells to achieve their effects in nanomedicine[11]. NP surface characteristics can be optimized for biological responses. The ζ potential accurately approximates the charge on an NP and is used to describe cell-NP interactions[12]. The charge on NPs prevents their aggregation.

The nonspecific interactions between the biomolecules and the nanodevices are other important key factors. NPs can be coated with hydrophilic polymers to remove the influence of mucosal or GI cells and reduce nonspecific interactions[13]. Most nanodevices are spherical, and the surface area-to-volume ratio can be described as 3/radius. The surface area-to-volume ratio increases as the radius decreases. NPs with high surface area-to-volume ratio have more available interaction sites, which is important for drug delivery. Nanodrugs can take advantage of the high surface area-to-volume ratio of NPs, which helps regulate the pharmacokinetics[14].

Owing to the smaller size of NPs, they can be transported easily through the GI tract and have more uniform distribution and drug release. By using nanomedicine, residence time can be increased and uptake into mucosal tissues and cells can be improved[15-17]. These advantages give nanodevices new applications for the treatment of cancer.

Application of nanotechnology in GI cancers

The GI tract is an approximately 9 m-long muscular tube including the upper and lower regions[18]. The upper GI tract consists of the mouth, pharynx, esophagus, stomach, and the first part of the small intestine, while the lower GI tract includes the other parts of the small intestine and large intestine[19]. The main functions of the GI tract are digestion of food, absorption of nutrients, and excretion of waste products[20].

GI cancers are located from the esophagus to the rectum, and the accessory digestive organs such as liver, gall bladder and pancreas. The early stages of GI cancers are asymptomatic and can be only detected by endoscopy and biopsy. GI cancers can be cured through minimally invasive endoscopic treatment or minimally invasive surgery when they are confirmed in the early stage. The prognosis is bad in the middle and late stages and the 5-year survival is < 30%, showing the importance of early diagnosis. There are major diagnostic challenges in GI cancers[21]: (1) Unable to identify accurately lesions metastases; (2) difficult to distinguish malignant and benign lesions; and (3) poor accuracy of early diagnosis. The application of NPs is of great help to the early diagnosis of GI cancers. NPs have the characteristics of high sensitivity, specificity, and permeability. Nanotechnologies are mainly used as contrast media for enhanced magnetic imaging currently. For example, superparamagnetic iron oxide NP (SPION)-based contrast agent for detecting metastases and directing surgical treatment have been completed for both esophageal and gastric cancers in clinical use[22-24]. Feridex has been successfully used to detect tumor lesions in the liver[25].

Another application of nanotechnology in GI cancers is drug or gene delivery systems. Nanodevices can load drugs at a high concentration, which are efficiently delivered to specific sites with fewer side effects. Meanwhile, cationic polymers, such as chitosan, form complexes with DNA or small interference RNA (siRNA) and may become the main type of vectors for gene therapy. Liposomes and cationic polymers are the two most common materials for *in vivo* siRNA delivery[26]. The polymeric NPs made with poly lactic-co-glycolic acid have used for siRNA delivery[27].

Although significant progress has been achieved, there are still issues related to nanotechnology in GI cancers: (1) Cytotoxic NPs can change the characteristics of the cell membrane and reduce cell adhesion. Newly developed NPs have reduced toxicity; however, the problem of toxicity is still the main research focus[28]; (2) NPs may react with biological macromolecules to produce biotoxicity; and (3) NPs may affect biological metabolic pathways such as the respiratory chain. For the future application of nanodrug delivery systems or gene therapy, more complete systems of pharmacology, pharmacokinetics, and toxicokinetics are needed.

Nanodevices used in GI cancer include iron oxide NPs, quantum dots, carbon nanotubes, gold NPs, dendrimers, nanoshells, and polymers. In this review, we summarize the applications of the nanodevices in GI cancer diagnosis and therapy (Figure 1).

NANODEVICES USED IN GI CANCERS

Nanotechnologies have the characteristics of high sensitivity, specificity, and permeability and have been applied primarily for the detection of tumors and imaging of the GI tract in MRI-based clinical applications. Nanotechnology-based drug delivery is of importance in future medical treatment, especially for cancer therapy. Owing to high biocompatibility, nanomaterials show excellent application for increasing therapeutic efficacy. Many NPs have potential for loading various drugs in order to achieve specific targeting and controlled drug release[29] (Tables 1 and 2, Figure 2).

Iron oxide NPs

Iron oxide NPs belong to the ferrimagnetic class of magnetic materials, which exhibit the unique property of superparamagnetism[30]. Widder *et al*[31] first proposed they can be used in biomedical applications. SPION-based MRI became a revolution in the field of diagnostics[32,33]. They can be used as contrast agent in MRI to shorten the relaxation time of surrounding protons. SPIONs with a core size < 4 nm are known as ultrasmall superparamagnetic iron oxide (USPIO) NPs, which are a new type of nanomolecular contrast agent in imaging of the rectum[34], lymph nodes[35], liver[36], *etc*. By using USPIO and MRI, lymph nodes can be imaged in patients with rectal cancer[34]. Lymph node disease may cause poor prognosis in rectal cancer. Preoperative accurate MRI diagnosis of lymph node disease and other adverse features provides a reference for radiotherapy and chemotherapy, which can reduce the risk of relapse[37]. Ferucarbotran (Resovist®) and ferumoxide (Feridex® or Endorem®) are two types of SPIONs under clinical investigation[38,39]. Although SPION MRI contrast agent has high security, they have been shown to have some adverse events in clinical use, such as hypotension, lumbar pain, and paresthesia in 2%-10% of patients[39].

Table 1 Summary of types of nanodevices and their properties

NP type	Properties	Advantages	Limitations	Ref.
Iron	Imaging: MRI contrast, lymph nodes; antigen/receptor ligand, magnetic targeting; multiple treatment opportunities	Simplicity; low cost; high reproducibility	Adverse events in clinical use: Hypotension, lumbar pain and paresthesia	[63,64]
QDs	Passive and active targeting; imaging through tunable autofluorescence; multiple treatment opportunities	Excellent PLQY; high photostability and biocompatibility; extreme fast synthesis	Toxicity	[65]
Carbon	Passive and active targeting; treatment: Therapeutic cargo delivery; imaging: Visible, infrared	Lightweight, chemically and thermally stable; high tensile strength and conductivity; high resolution and good penetration into the tissue	Adverse events in clinical use: Inflammation, fibrosis	[66]
Gold	Imaging: MRI contrast, fluorescence, optical properties; multiple treatment opportunities	Adjusted optical properties; high biocompatibility	Adverse events in clinical use: Nephrotoxicity	[67]
Polymers	Passive targeting; antigen/receptor ligand targeting; tumor microenvironment-dependent drug release	High thermal stability, biocompatibility; good biodegradability and controlled drug release ability Inhibition of bacterial growth	Toxicity	[69,70]

NP: Nanoparticle; MRI: Magnetic resonance imaging; QDs: Quantum dot; PLQY: Photoluminescent quantum yield.

Table 2 Examples of nanodevices currently under investigation for gastrointestinal cancer

NP type	GI cancer	Application	Ref.
SPION	Colorectal; liver; gastric	Lymph node staging, detection of small metastatic lymph nodes.; magnetic NP-based biosensors for detection of biomarkers; companion diagnostics, evaluate accumulation and predict treatment efficacy of nanomedical cancer therapy	[35,64,71]
QDs	Colorectal; liver; gastric	Cancer targeting and imaging; NIR-QD for simultaneous visualization of SLNs; multicolor QD probes for diagnosis of malignant tumors	[41,72-74]
Carbon nanotubes	Colorectal; liver	Detection of lymph nodes and node metastasis; tumor localization	[49,52]
Gold NPs	Colorectal; liver; gastric; pancreatic; esophageal	Photothermal effect; hyperthermia and cellular destruction; X-ray and CT contrast agents; targeted drug delivery	[75-80]
Dendrimers	Pancreatic; colorectal	Dual targeting imaging; targeted drugs delivery and gene therapy; boron neutron capture therapy.	[60,81,82]
Nanoshell	Gastric	Contrast agents; targeted drugs delivery and gene therapy	[42,77]
Polymers	Colorectal; gastric; pancreatic; esophageal	Controlled drug delivery systems	[83-85]

NIR-QD: Near infrared-quantum dot; SLN: Sentinel lymph node; NP: Nanoparticle; SPION: superparamagnetic iron oxide NP; CT: Computed tomography.

Quantum dots

Quantum dots (QDs) are inorganic semiconductor NPs with an inorganic element core and a metal shell. The diameter of QDs ranges between 2 and 10 nm. QDs can be used as fluorescent near-infrared (NIR) probes instead of organic dyes. The fluorescence properties of QDs are affected by size and composition[40]. QDs have a variety of applications, such as drug analysis, immuno- and biosensing, and clinical diagnostics and therapeutics. QD-based *in situ* detection can be used to detect macrophage infiltration, tumor microvessel density, and neovascular maturity in gastric cancer. He *et al*[41] have presented the investigation of bioconjugating ability of NIR CdSeTe/ZnS QDs and visible CdSe QDs in immunofluorescent staining for cancer biomarkers in gastric cancer. NIR QDs show higher sensitivity and contrast for the cancer biomarkers in gastric cancer tissues. Peng *et al*[42] reported on a QD-based simultaneous *in situ* detection of infiltrating macrophages, tumor microvessel density, and neovessel maturity in gastric cancer tissues. This approach can yield combined tumor stromal features.

Carbon nanotubes

Carbon nanotubes (CNTs) have advantages in weight, high tensile strength, and conductivity, which make it possible for them to detect cancer cells[43,44]. CNT applications include tissue scaffolding for osteoblast proliferation, drug delivery, and thermal ablation agents[45-47]. CNTs are used to detect colorectal cancer in lymphadenectomy and for cancer prognosis. Single-walled CNTs (SWCNTs) and

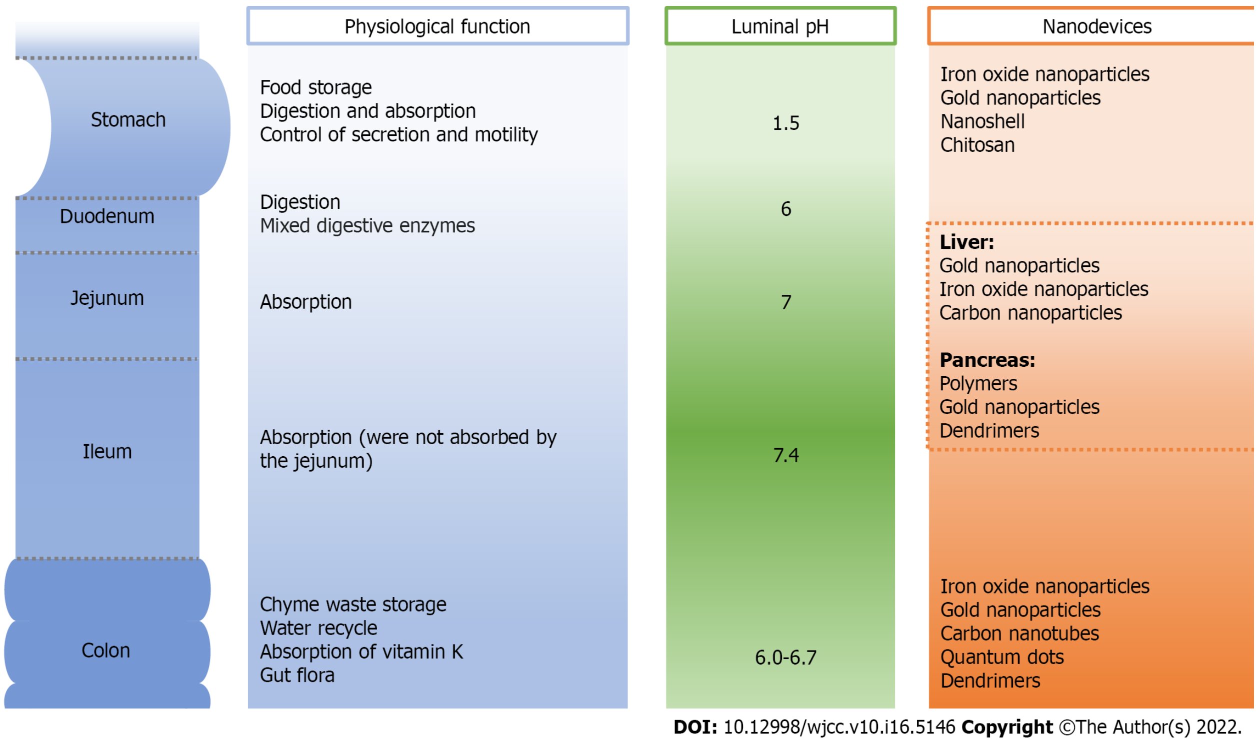

Figure 1 Physiological function in the gastrointestinal tract and representative nanodevices used in gastrointestinal cancers.

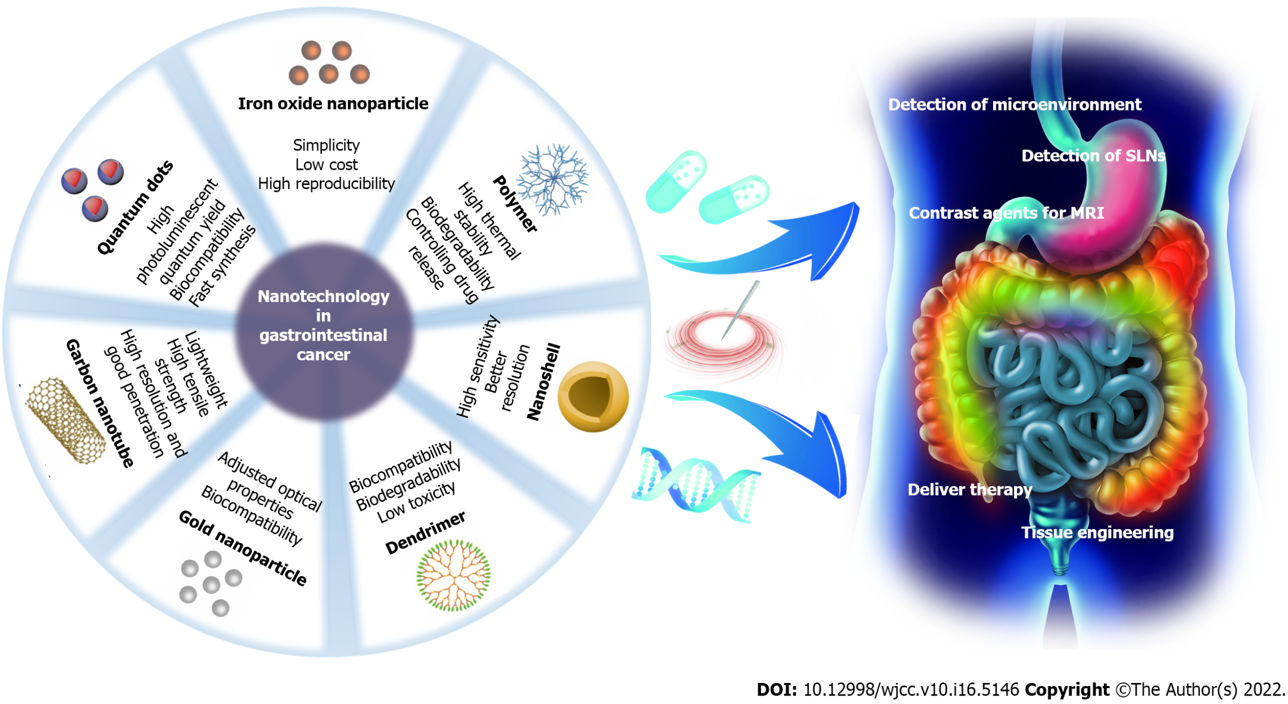

Figure 2 Nanodevices in diagnosis and therapy of gastrointestinal oncology.

multiwalled CNTs are two forms[48]. SWCNTs have a smaller band gap so they are more suitable for fluorescence imaging. They are used as contrast materials in MRI for colorectal carcinoma. Gadolinium-based SWCNTs have high resolution and penetration, and the sensitivity can increase when they are radioisotope-based[49-51]. Activated carbon NP suspensions can enter lymph nodes rapidly after phagocytosis by macrophages. Carbon NPs can be used colorectal laparoscopic surgery, such as tumor localization and lymph node tracking[52].

Gold NPs

Gold NPs work as a new type of photothermal sensor and cancer treatment drug carrier due to their tunable optical properties as well as biocompatibility[53]. Gold NPs can be used in surface enhanced Raman spectroscopy to detect changes such as the amount of nucleic acid and protein in colorectal cancer[54]. Gold nanospheres can be used to diagnose colorectal cancer as a fluorescent dye and contrast agent in CT[55]. In cancer models, small gold nanocages are more absorbed by tumors and have a higher tumor-muscle uptake ratio. The retention and accumulation of gold nanocages in tumors have been determined by PET imaging[56]. Gold nanocages with controllable biochemical properties and radioactive element labeled are used in optical coherence tomography *in vivo*[57]. Gold NPs have also been used as highly sensitive probes for hepatoma detection. Li *et al*[58] used gold NPs conjugated with redox probes on CNTs for a multi-analyte electrochemical immunoassay to detect liver cancer biomarkers.

Dendrimers

Dendrimers are three-dimensional, highly branched monodispersed macromolecules. The diameters are usually between 1 and 10 nm. Dendritic macromolecules can perform different functions depending on shape, size, surface function, and branch length[59,60]. Dendrimer NPs acting as functional NPs are utilized for MRI or NIR fluorescence in a single probe for their unique properties such as monodispersity, modifiable surface functionality, and internal cavities. Polyamidoamines (PAMAMs) are a type of dendrimers commonly used for targeted drug delivery. PAMAM dendrimers conjugated to against CD14 or prostate-specific membrane antigen can be used as contrast agents in flow cytometry and confocal microscopy[61]. Gene therapy is a promising strategy for a plethora of diseases including cancer and inflammation. RNA interference is a post-translational gene regulation technology for gene therapy[62]. It can specifically inhibit the gene expression triggered by siRNA, genome origin miRNA, and double-stranded short hairpin RNA[63]. Many nanomaterial-based gene delivery systems have been developed for GI diseases. Polo-like kinase 1 has been formulated in stable nucleic acid lipid particles and used to evaluate patients with GI neuroendocrine tumors[64]. Dendrimers with high transfection efficiency are most commonly used in gene delivery. Heat treatment increases the dendrimer flexibility to enhance the transfection efficiency[65]. The biodegradable polymeric envelope protects and transports siRNA into the cytosol, thereby allowing siRNA to be efficiently transfected *in vivo* for inflammatory bowel disease[66]. The polymeric NPs made with poly lactic-co-glycolic acid are biocompatible and biodegradable polymers with low toxicity, sustained release profiles, and high stability and have emerged as suitable siRNA carriers in metastatic colorectal cancer[67].

Nanoshell

The nanoshell is composed of a metal shell and a nonconductive core. It can adjust the plasmon resonance by changing the relative size of the metal shell and the nonconductive core[68]. Nanoshells can enhance the sensitivity and resolution of traditional contrast agents for *in vivo* imaging of tumors. Nanoshell-based contrast agents have become important in noninvasive imaging and are used in tumor detection and staging[69]. Nanoshells are used to carry molecular conjugates to achieve better functions. Conjugated gold NPs show stronger intensity and emission. Some conjugated gold NPs give greater sensitivity and have been applied successfully to enhance fluorescence[70] and detect gene expression level[71] and mutations[72] in colorectal cancer. The incorporation of iron or iron oxide into nanoshell structures confers some advantages for MRI. Nanoshells conjugated with diarrheagenic bacterial heat-stable peptide enterotoxin ligands have been used for the targeted delivery and ablation of colorectal cancer[73].

Polymers

Polymers can adapt to the variability of conditions along the GI tract, which accelerates the design of controlled drug delivery systems for GI diseases. Polymers have the properties of adjusted size, controlled drug release, and high drug loading capacity[74]. They have wide applications in targeted drug delivery. Chitosan[75], polyethylene oxide[76], hydroxypropyl methylcellulose[77], and hyaluronic acid[78], *etc* are widely used for developing GI cancer drug delivery systems. In addition, liposomes[79], nanopyramids[80], and nanogels[81] are widely used in diagnosis and therapy in GI disorders. Chitosan has been considered as a vehicle for drug delivery in many GI cancers. It can effectively achieve controlled drug release, improve drug stability, reduce adverse drug reactions, and enhance drug bioavailability[82]. In a recent study, norcantharidin conjugated with carboxymethyl chitosan was successful in inducing apoptosis of gastric tumor cells and decreasing systemic toxicity [83]. Nanogels are swollen nanosized networks formed by noncovalent interactions or covalent crosslinking of polymer chains. Nanogels have been regarded as oral drug delivery systems because they are more sensitive to external stimuli than macroscopic gels are[84]. Senanayake *et al*[85] reported a drug conjugated with gemcitabine in cancer chemotherapy, which enables target delivered.

CONCLUSION

In this review, we summarize the current nanotechnologies in diagnosis and treatment of GI cancers. Nanodevices are biocompatible and nontoxic with high specificity and sensitivity. They have diagnostic and therapeutic properties with wide applications in precision medicine. Although there are few applications in clinical research, nanodevices have demonstrated advantages in many fields, including enhanced specificity of detection, reduced drug toxicity, enhanced effect of contrast agents, and improved diagnosis and therapy of GI cancers. Nanodevices will promote the development of personalized therapy for early diagnosis and treatment of GI cancers.

FOOTNOTES

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