

Early Diagnosis and Treatment of Gastrointestinal Cancer by Nanotechnology Applications Review

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Abstract – Propels in nanotechnology have opened new wildernesses in the diagnosis and therapy of malignant growth. Nanoparticle-based innovation works on the accuracy of cancer diagnosis when joined with imaging, as well as the precision of medication target delivery, with less incidental effects. Streamlined nano systems enjoy showed benefits in many fields, including upgraded specificity of detection, diminished toxicity of medications, improved impact of contrast agents, and high level diagnosis and treatment of gastrointestinal (GI) cancers. In this review, we sum up the ongoing nanotechnologies in diagnosis and therapy of GI malignant growths. The improvement of nanotechnology will prompt customized approaches for early diagnosis and therapy of GI malignant growths.

Keywords – Nano devices; Nanoparticles; Gastrointestinal cancer; Diagnosis; Therapeutics.

I. INTRODUCTION

Gastrointestinal (GI) malignant growth is a sort of cancer that influences the GI tract and different organs in the digestive system. GI cancers are malignant growths with both high morbidity and mortality. As per the 2020 World Cancer Report from World Health Organization International Agency for Research on Cancer (IARC), regarding overall malignant growth morbidity, colorectal, gastric, liver, and esophageal tumors possess the third, fifth, 6th, and eight places, respectively. Worldwide mortality of colorectal, liver, gastric, esophageal, and pancreatic malignant growths are 0.94, 0.83, 0.77, 0.54, and 0.47 million, respectively[1]. The clinical manifestations actually need explicitness, albeit GI tumors have symptoms, for example, anorexia, abdominal distension, abdominal pains, diarrhea, emaciation, etc[2]. GI tumors have the most worst visualization of all malignant growths and have the absolute least generally 5-year survival rates, with only gastric cancer above 10%[3]. Growing high-exactness diagnostic methodologies and compelling medications for treatment is especially significant. Nanotechnology is getting consideration in many fields of science, engineering, biology, and medication. Nanoparticle (NP)- based innovation has critical biocompatibility and programmability, which offers open doors in therapeutic and diagnostic applications, particularly in malignant growth. NPs are all around utilized in numerous areas, like medication and gene delivery, photo thermal treatment, recognition, and imaging agents[4,5]. Extraordinary histocompatibility and flexible property have given NPs a lift. Shifting pH, pressure, and bacterial content in the GI tract can control NPs characteristics, making the GI tract an appealing objective for nanotechnological applications[6]. In GI cancers, NPs have been utilized for identification of biomarkers, for location of sentinel lymph nodes (SLNs), for recognition of GI growth micro-environment, and as organically designated contrast agents for magnetic

resonance imaging (MRI)[7]. High level imaging approach is the best quality level for malignant growth finding. Current imaging methods utilized in cancer diagnosis incorporate MRI, computed tomography (CT), positron emission tomography (PET), single photon emission CT, and ultrasound. Imaging results can give precise finding and organizing. Aside from diagnostic methodologies, many types of NPs that are being utilized as medication delivery systems and novel therapeutic agents. These applications further develop current methods not just for early diagnosis and precise staging of GI tumors yet additionally for treatment approaches.

1. Overview of Nanotechnology in GI Tumors

Qualities and benefits of Nano devices allude to materials with something like one of the three aspects in the nano meter range (1-100 nm)[8]. Nano devices for diagnosis and treatment are presently being utilized all through oncology due to nanotechnological advancements. Nano devices can offer numerous conceivable outcomes as vectors or as nano drugs under differing conditions, for example, pH, transit time, pressure, and bacterial content. Most nano devices are biocompatible and non-toxic, with high explicitness and sensitivity, which have wide applications in exact diagnosis. Besides, nanotechnology has become one of the most encouraging cancer treatment procedures. The nano devices have therapeutic properties and great medication loading capacity, are bound to ligands to accomplish high fondness and particularity for target cells, load numerous medications to accomplish collaborative cancer treatment. what's more, keep away from ordinary medication resistance mechanisms[9,10]. The extraordinary properties of nanomaterials empower them to act typically in the complex GI environment. The size, morphology, and surface functionality of the NPs can influence the interactions of medications and the GI tract. Size can impact cell take-up, physical properties, and interactions with biomolecules[8]. The NP diameter ought to be more smaller than the size of the cells so NPs could interact with or be taken up by cells to accomplish their effects in nanomedicine[11]. NP surface attributes can be upgraded for biological reactions. The ζ potential precisely approximates the charge on a NP and is utilized to depict cell-NP interactions[12]. The charge on NPs forestalls their accumulation. The non-specific interactions between the biomolecules and the nano devices are other significant key elements. NPs can be covered with hydrophilic polymers to eliminate the impact of mucosal or GI cells and decrease non-specific interactions[13]. Most nano devices are spherical, and the area to-volume proportion can be portrayed as $3/\text{radius}$. The surface area to-volume proportion increments as the radius diminishes. NPs with high surface area to-volume proportion have more accessible interaction sites, which is significant for drug delivery. Nano drugs can exploit the high surface area to-volume proportion of NPs, which controls the pharmacokinetics[14]. Attributable to the smaller size of NPs, they can be moved effectively through the GI tract and have more uniform circulation and medication release. By utilizing nanomedicine, residence time can be expanded and take-up into mucosal tissues and cells can be improved[15-17]. These benefits give nano devices new applications for the therapy of cancer.

1.1 Utilization of Nanotechnology in GI Cancer

The GI tract is an around 9 m-long muscular tube including the upper and lower regions[18]. The upper GI tract comprises of the mouth, pharynx, throat, stomach, and the initial segment of the small digestive system, while the lower GI tract incorporates different pieces of the small digestive tract and large intestine[19]. The primary elements of the GI tract are processing of food, ingestion of supplements, and discharge of waste products[20]. GI diseases are situated from the throat to the rectum, and the accessory digestive organs like liver, gall bladder and pancreas. The beginning phases of GI cancers are asymptomatic and can be just distinguished by endoscopy and biopsy. GI tumors can be cured through minimal invasive endoscopic surgery or minimally invasive surgery procedure when they are affirmed in the beginning phase. The prognosis is bad in the meddle and late stages and the 5-year survival is $< 30\%$, showing the significance of early diagnosis. There are major diagnostic difficulties in GI cancers[21]: (1) Unable to recognize precisely lesion metastases; (2) hard to recognize malignant and benign lesions; and (3) poor accuracy of early diagnosis. The utilization of NPs is of incredible assistance to the early diagnosis of GI malignant growths. NPs have the qualities of high specificity, sensitivity, and permeability. Nanotechnologies are mostly utilized as contrast media for improved magnetic imaging as of now. For instance, super paramagnetic iron oxide NP (SPION)- based contrast agent for identifying metastases and directing surgical therapy have been completed for both esophageal and gastric tumors in clinical use[22-24]. Feridex has been effectively used to recognize cancer lesions in the liver[25]. One more utilization of nanotechnology in GI malignant growths is drug or gene delivery systems. Nano devices can load drugs at a high focus, which are proficiently delivered to explicit sites with less secondary effects. In the mean time, cationic polymers, for example, chitosan, form complexes with DNA or small interference RNA (siRNA) and may turn into the fundamental type of vectors for gene treatment. Cationic polymers and liposomes are the two most common materials for in vivo siRNA delivery[26]. The polymeric NPs made with

polylactic-co-glycolic acid have utilized for siRNA delivery[27]. Albeit significant advancement has been accomplished, there are still issues connected with nanotechnology in GI cancers: (1) Cytotoxic NPs can change the qualities of the cell membrane and decrease cell adhesion. Recently created NPs have decreased toxicity; however, the issue of toxicity is as yet the principal research focus[28]; (2) NPs might respond with biological macromolecules to create bio toxicity (3) NPs might influence biological metabolic pathways like the respiratory chain. For the future use of nano drug delivery systems or gene treatment, more complete frameworks of pharmacology, pharmacokinetics, and toxicokinetics are required. Nano devices utilized in GI malignant growth incorporate iron oxide NPs, quantum dabs, carbon nanotubes, gold NPs, dendrimers, nano shells, and polymers.

1.2 Nanodevices Utilized in GI Malignant Growths

Nanotechnologies have the qualities of high sensitivity, specificity, and permeability and have been applied essentially for the recognition of tumors and imaging of the GI tract in X-ray based clinical applications. Nanotechnology-based drug delivery is of significance in future clinical therapy, particularly for malignant growth treatment. Attributable to high biocompatibility, nanomaterials show great application for expanding helpful viability. Numerous NPs have potential for loading different medications to accomplish explicit focusing on and controlled drug release[29] (Tables 1 and 2).

Table 1 Summary of types of nano devices 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] |
| Ds | Passive and active targeting; imaging through tunable autofluorescence; multiple treatment opportunities | Excellent PLQY; high photo stability 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 micro-environment 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: Photo luminescent quantum yield.

Table 2: Examples of nano devices currently under investigation for gastrointestinal cancer

| NP type | GI cancer | Application | Ref. |
|------------------|---|--|------------|
| SPION | Colorectal; gastric | Lymph node staging, detection of small metastatic lymph nodes.; liver;magnetic NP-based biosensors for detection of biomarkers; companion diagnostics, evaluate accumulation and predict treatment efficacy of nano medical cancer therapy | [35,64,71] |
| QDs | Colorectal; 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; gastric; esophageal | liver; pancreatic; Photo thermal 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] |
| Nano shell | 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.

1.2.1 Iron oxide Np

Iron oxide NPs have a place with the ferrimagnetic class of magnetic materials, which show the one of a kind property of super paramagnetism[30]. Widder et al[31] first proposed they can be utilized in biological applications. SPION-based X-ray turned into a revolution in the field of diagnostics[32,33]. They can be utilized as contrast agent in MRI to abbreviate the relaxation time of encompassing protons. SPIONs with a core size < 4 nm are known as ultra small super paramagnetic iron oxide (USPIO) NPs, which are another kind of nano molecular contrast agent in imaging of the rectum[34], lymph nodes[35], liver[36]. By utilizing USPIO and MRI, lymph nodes can be imaged in patients with rectal cancer[34]. Lymph node disease might cause poor prognosis in rectal cancer. Preoperative exact MRI determination of lymph node disease and other adverse elements gives a reference to radiotherapy and chemotherapy, which can decrease the risk of relapse[37]. Ferucarbotran and ferumoxide are two types of SPIONs under clinical investigation[38,39]. In spite of the fact that SPION MRI contrast agent has high security, they have been displayed to have a few adverse occasions in clinical use, like hypotension, lumbar pain, and paresthesia in 2%-10% of patients[39]. Iron Imaging: MRI contrast, lymph nodes ; antigen/receptor ligand, magnetic targeting on; different treatment potential simplicity; minimal expense; high reproducibility Adverse effects in clinical use: Hypotension, lumbar pain and paresthesia [63, 64] QDs passive and active focusing on; imaging through tunable autofluorescence; various treatment opportunities Fantastic PLQY; high photo stability and biocompatibility; extreme fast synthesis toxicity [65] Carbon passive and active focusing on; treatment: therapeutic delivery; imaging: Visible, infrared Lightweight, chemically and thermally steady; high tensile and conductivity; high resolution and great penetration into the tissue adverse effects in clinical use: Inflammation, fibrosis [66] Gold Imaging contrast, fluorescence, optical properties; numerous treatment valuable open doors Changed optical properties; high biocompatibility adverse events in clinical use: Nephrotoxicity [67]

Polymers Detached focusing on; antigen/receptor ligand focusing on; cancer micro-environment-dependant drug release High thermal stability, biocompatibility; great biodegradability and controlled drug release ability inhibition of bacterial growth toxicity [69, 70] NP: Nanoparticle; MRI: Magnetic resonance imaging; QDs: Quantum dot; PLQY: Photo luminescent quantum yield. SPION Colorectal; liver; gastric Lymph node staging, detection of small metastatic lymph nodes.; magnetic NP-based biosensors for detection of biomarkers; companion diagnostics, assess accumulation and predict therapy adequacy of nano medical cancer treatment [35,64,71] QDs Colorectal; liver; gastric Malignant growth focusing on and imaging; NIR-QD for synchronous perception of SLNs; multicolor QD tests for diagnosis of malignant tumors [41,72-74] Carbon nanotubes Colorectal; liver Location of lymph nodes and node metastasis; tumor localization [49, 52] Gold NPs Colorectal; liver; gastric; pancreatic; esophageal Photo thermal impact; hyperthermia and cellular destruction; X-beam and CT contrast agent; designated drug delivery [75-80] Dendrimers Pancreatic; colorectal Doal focusing on imaging; designated drugs delivery and gene treatment; boron neutron capture treatment. [60,81,82] Nanoshell Gastric contrast agents; designated drugs delivery and gene treatment [42,77] Polymers Colorectal; gastric; pancreatic; esophageal Controlled drug delivery systems [83-85] NIR-QD: Near to infrared-quantum dot; SLN: Sentinel lymph nodes; NP: Nanoparticle; SPION: superparamagnetic iron oxide NP; CT: Computed tomography.

1.2.2 Quantum dots

Quantum dots (QDs) are inorganic semiconductor NPs with an inorganic element core and a metal shell. The diameter of QDs ranges somewhere in the range of 2 and 10 nm. QDs can be utilized as fluorescent near infrared (NIR) probes rather than organic dyes. The fluorescence properties of QDs are impacted by size and composition[40]. QDs have various applications, like medication analysis, immune-biosensing, clinical diagnostics and therapeutics. QD-situated in situ detection can be utilized to distinguish macrophage infiltration, tumor micro vessel density, and neovascular development in gastric cancer. He et al[41] have introduced the investigation of bio conjugating capacity of NIR CdSeTe/ZnS QDs and apparent CdSe QDs in immunofluorescent staining for malignant growth biomarkers in gastric cancer. NIR QDs show higher sensitivity and contrast for the malignant growth biomarkers in gastric cancer tissues. Peng et al[42] covered a QD-based concurrent in situ location of penetrating macrophages, growth micro vessel density, and neovessel development in gastric cancer tissues. This approach can yield consolidated growth stromal features.

1.2.3 Carbon Nanotubes

Carbon nanotubes (CNTs) enjoy benefits in weight, high elasticity, and conductivity, which make it workable for them to distinguish cancer cells[43,44]. CNT applications incorporate tissue framework for osteoblast multiplication, drug delivery, and thermal ablation agents[45-47]. CNTs are utilized to distinguish colorectal disease in lymphadenectomy and for malignant growth prognosis. Single-walled CNTs (SWCNTs) and multi walled CNTs are two forms[48]. SWCNTs have a smallest band gap so they are more reasonable for fluorescence imaging. They are utilized as contrast materials in MRI for colorectal carcinoma. Gadolinium based SWCNTs have high goal and penetration, and the sensitivity can increment when they are radioisotope-based[49-51]. Activated carbon NP suspensions can enter lymph nodes quickly after phagocytosis by macrophages. Carbon NPs can be utilized colorectal laparoscopic surgery, for example, tumor localization and lymph node tracking[52].

1.2.4 Gold Nps

Gold NPs function as another kind of photo thermal sensor and cancer treatment drug carrier because of their tunable optical properties as well as biocompatibility[53]. Gold NPs can be utilized in surface enhanced Raman spectroscopy to identify changes, for example, how much nucleic acid and protein in colorectal cancer[54]. Gold nano spheres can be utilized to diagnose colorectal malignant growth as a fluorescent color and contrast agent in CT[55]. In malignant growth models, small gold nano cages are more consumed by cancers and have a higher cancer muscle take-up proportion. The retention and accumulation of gold nano cages in cancers still up in by PET imaging[56]. Gold nano cages with controllable biochemical properties and radioactive component marked are utilized in optical coherence tomography in vivo[57]. Gold NPs have likewise been utilized as exceptionally sensitive probes for hepatoma detection. Li et al[58] utilized gold NPs formed with redox probes on CNTs for a multi-analyte electrochemical immunoassay to distinguish liver disease biomarkers.

1.2.5 Dendrimers

Dendrimers are three-layered, exceptionally spread mono dispersed macromolecules. The diameters are as a rule somewhere in the range of 1 and 10 nm. Dendritic macromolecules can carry out various roles relying upon shape, size, surface capability, and branch length[59,60]. Dendrimer NPs going about as functional NPs are used for MRI or NIR fluorescence in a single probe for their novel properties like monodispersity, modifiable surface functionality, and internal cavities. Polyamidoamines (PAMAMs) are a kind of dendrimers generally utilized for designated drug delivery. PAMAM dendrimers conjugated to against CD14 or prostate-specific layer antigen can be utilized as contrast agent in flow cytometry and confocal microscopy[61]. Gene treatment is a promising system for a plenty of diseases including disease and inflammation. RNA interference is a post-translational gene regulation innovation for gene therapy[62]. It can explicitly restrain the gene expression set off by siRNA, genome origin miRNA, and double stranded short hairpin RNA[63]. Numerous nanomaterial-based gene delivery systems have been created for GI illnesses. Polo-like kinase 1 has been formed in stable nucleic acid lipid particles and used to assess patients with GI neuroendocrine tumors[64]. Dendrimers with high transfection proficiency are most commonly utilized in gene delivery. Heat treatment builds the dendrimer adaptability to improve the transfection efficiency[65]. The biodegradable polymeric envelope protects and transports siRNA into the cytosol, accordingly permitting siRNA to be effectively 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, supported release profiles, and high steadiness and have arisen as appropriate siRNA transporters in metastatic colorectal cancer[67].

1.2.6 Nano shell

The nano shell is made out of a metal shell and a non-conductive core. It can change the plasmon resonance by changing the overall size of the metal shell and the non-conductive core[68]. Nanoshells can improve the sensitivity and goal of conventional contrast agents for in vivo imaging of growths. Well-balanced contrast agent have become significant in non-invasive imaging and are utilized in cancer location and staging[69]. Nanoshells are utilized to convey molecular conjugates to accomplish better capabilities. Conjugated gold NPs show more grounded intensity and emission. A few conjugated gold NPs give more noteworthy sensitivity and have been applied effectively to enhance fluorescence[70] and identify gene expression level[71] and mutations[72] in colorectal malignant growth. The incorporation of iron or iron oxide into nano shell structures gives a few benefits for MRI. Nano shells conjugated with diarrheagenic bacterial heat stable peptide neurotoxin ligands have been utilized for the designated delivery and ablation of colorectal cancer[73].

1.2.6 Polymers

Polymers can adjust to the changeability of conditions along the GI tract, which speeds up the plan of controlled drug delivery systems for GI diseases. Polymers have the properties of changed size, controlled drug delivery, and high medication loading capacity[74]. They have wide applications in designated drug delivery. Chitosan[75], polyethylene oxide[76], hydroxypropyl methylcellulose[77], and hyaluronic acid[78], and so on are broadly utilized for creating GI malignant growth drug delivery systems. Moreover, liposomes[79], nanopyrramids[80], and nanogels[81] are broadly utilized in diagnosis and treatment in GI therapy. Chitosan has been considered as a vehicle for drug delivery in many GI malignant growths. It can actually accomplish controlled drug release, further develop drug steadiness, decrease unfavorable medication responses, and improve drug bioavailability[82]. In a new report, norcantharidin formed with carboxy methyl chitosan was fruitful in prompting apoptosis of gastric cancer cells and diminishing systemic toxicity [83]. Nano gels are enlarged nano sized networks framed by non covalent interactions or covalent cross-linking of polymer chains. Nano gels have been viewed as oral medication delivery systems since they are more sensitive to external stimuli than microscopic gels are[84]. Senanayake et al[85] detailed a medication conjugated with gemcitabine in cancer chemotherapy, which empowers target delivered.

II. CONCLUSION

In this review, we sum up the ongoing nanotechnologies in diagnosis and therapy of GI malignant growths. Nano devices are biocompatible and non-toxic with high specificity and sensitivity. They have diagnostic and therapeutic properties with wide applications in precision medication. In spite of the fact that there are not many applications in clinical research, nano devices enjoy exhibited benefits in many fields, including enhanced specificity of detection, decreased drug toxicity, upgraded impact of contrast agents, and further developed diagnosis and treatment of GI tumors. Nano devices will promote the improvement of personalized treatment for early diagnosis and therapy of GI malignant growths.

III. CONFLICT OF INTEREST

All authors declare no conflicts of interest.

IV. AUTHOR CONTRIBUTION

Authors have equally participated and shared every item of the work.

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