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REPORT ON EMERGING TECHNIQUES IN GASTROINTESTINAL TRACT CANCER

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Abstract: CT DNA Analysis has the potential to overcome challenges for all stages in various types of cancers, including GI Cancers. Immunogenic Cell Death (ICD) arises from the antigenicity of neoantigens derived from dying cancer cells and the adjuvancy of Damage-Associated Molecular Patterns (DAMPs). However , limited data are available regarding the effect of preanalytical variables on CT DNA results. Future studies using blood samples with well documented preanalytical variables are required to address which variables affect the quality of the samples and results of the CT DNA analysis. More sensitive PCR-based technologies have been developed for CT DNA analysis in recent years, such as droplet digital PCR (ddPCR) and beads, emulsions, amplification and magnetic (BEAMing). Activated CD8+ T cells identify cancer cells as "Friend Or Foe" through contact with them. First, preanalytical variables for CT DNA, such as sample collection, handling, transport, processing and storage conditions may affect CT DNA analysis. Gastrointestinal Cancer is one of the leading causes of cancer and third most deadly cancer worldwide.

Index Terms **– CT DNA Analysis,GI Cancers,Immunogenic Cell Death (ICD),Damage-Associated Molecular Patterns (DAMPs),droplet digital PCR (ddPCR) beads,emulsions, amplification and magnetic (BEAMing).**

I. INTRODUCTION

Gastrointestinal cancer is the most common cause of cancer and the third most common cancer type worldwide. Gastrointestinal cancer accounts for 21% of all cancer cases in the United States and 25% of the 4,444 cancer deaths. Despite recent advances in diagnosis and treatment, 4,444 gastric, ductal, and colorectal cancers are the leading cause of 4,444 cancer-related deaths worldwide. The etiology of these cancers remains elusive and available treatment options are limited. Among gastrointestinal cancer deaths, gastric cancer ranks seventh in the United States with 4,444 cases. However, gastric cancer is the leading cause of cancer-related deaths in Japan, China and India. Despite advances in newly developed diagnostic and therapeutic modalities, the prognosis of patients with gastrointestinal cancer remains unsatisfactory. Most gastrointestinal cancer patients are at an advanced stage when is first detected, have a relatively low 5-year survival rate, and can be avoided if detected and treated closer to stage. Currently, traditional approaches such as radio-CT DNA analysis, immunotherapy, and histopathological examination are still widely used .

Circulating tumor DNA analysis (CT DNA analysis / liquid biopsy :

Liquid biopsy has emerged as a promising approach, allowing the detection of small cancerous substances in bodily fluids. Liquid biopsy primarily identifies circulating components such as circulating tumor cells (CTC) , circulating tumor DNA (CTDNA) , extracellular vesicles (EV) , and circulating tumor RNA (CT-RNA) in peripheral blood The purpose is that. With the development of advanced technology, liquid biopsy provides information in less time and has applications in early detection, diagnosis and monitoring of cancer is widely used due to its advantage that detection is mainly based on body fluids such as peripheral blood, urine, milk and cerebrospinal fluid. Compared to the traditional methods, it is very rapid, convenient, inexpensive, less invasive, and overcomes problems such as insufficient tissue sample volume. **[1].**

Limitation of CT DNA analysis :

ct dna analysis has the potential to overcome challenges for all stages in various types of cancers, including gi cancers. immunogenic cell death (icd) arises from the antigenicity of neoantigens derived from dying cancer cells and the adjuvancity of damage-associated molecular patterns (damps). however , limited data are available regarding the effect of preanalytical variables on ct dna results. future studies using blood samples with well documented preanalytical variables are required to address which variables affect the quality of the samples and results of the ct dna analysis. more sensitive pcr-based technologies have been developed for ct dna analysis in recent years, such as droplet digital pcr (ddpcr) and beads, emulsions, amplification and magnetic (beaming). activated cd8+ t cells identify cancer cells as "friend or foe" through contact with them. first, preanalytical variables for ct dna, such as sample collection, handling, transport, processing and storage conditions may affect ct dna analysis. gastrointestinal cancer is one of the leading causes of cancer and third most deadly cancer worldwide [2].

IMMUNOTHERAPY:

The emergence of cancer immunotherapy is currently driven by the application of monoclonal antibodies targeting immune checkpoints such as programmed cell death-1 (PD-1) and cytotoxic T targets cancer revolutionized the therapeutic landscape. Lymphocyte-associated protein. 4 (CTLA-4) releases cellular brakes on T cells. Since the first approval of immune checkpoint inhibitors (ICIs) in melanoma in 2011, ICIs have emerged as a promising treatment option for cancer patients in more than 20 different indications. Within the gastrointestinal cancer range, ICI response rates have not been as high as some immunogenic tumors, but immunotherapy is seen as a potentially curative therapeutic approach supported by numerous clinical studies was done. Accumulating evidence indicates that dynamic interactions between tumors and the immune system can regulate tumor growth and metastasis. A better understanding of the biochemical nature of the tumor antigen and the molecular mechanisms involved in the activation of innate and adaptive immune cells has revolutionized the fields of tumor immunology and immunotherapy . In 1909 Ehrlich postulated the role of immunity in cancer. He demonstrated that the immune system could suppress the growth of carcinomas by recognizing tumor cells as foreign. Tumor cells have evolved multiple mechanisms that directly or indirectly block the activity of effector anti-tumor CD4+ and CD8+ T cells, thereby suppressing local tumor-infiltrating immune responses [3].

Limitation of CT DNA analysis :

CT DNA Analysis has the capacity to conquer disturbing conditions for all degrees in several sorts of cancers, along with GI Cancers. Immunogenic Cell Death (ICD) arises from the antigenicity of neoantigens derived from dying maximum cancers cells and the adjuvancity of Damage-Associated Molecular Patterns (DAMPs). However , restrained records are available regarding the effect of preanalytical variables on CT DNA outcomes. Future studies the use of blood samples with well documented preanalytical variables are required to address which variables have an impact at the high-nice of the samples and outcomes of the CT DNA assessment. More sensitive PCR-based totally definitely generation have been superior for CT DNA assessment in modern years, which incorporates droplet digital PCR (ddPCR) and beads, emulsions, amplification and magnetic (BEAMing). Activated CD8+ T cells identify maximum cancers cells as “Friend Or Foe” through contact with them. First, pre analytical variables for CT DNA, which incorporates sample collection, handling, transport, processing and storage conditions may have an impact on CT DNA assessment. Gastrointestinal Cancer is one of the foremost motives of maximum cancers and third most deadly maximum cancers all over the world.

Application:

CT DNA evaluation has emerged as a capability device for comparing the complex biological tactics concerned in GI cancers, represented with the aid of using intratumorally genomic heterogeneity and clonal evolution, given the confined availability of precision remedy for sufferers with superior GI cancers. CT DNA evaluation has the capability to triumph over demanding situations for all degrees in various styles of cancers, inclusive of GI cancers. [1].Patients with superior stable malignancies, inclusive of GI cancers, and people who had been now no longer formerly dealt with or do now no longer have disease development after anticancer remedy had been screened with the aid of using an NGS- primarily based totally CT DNA assay.[2]

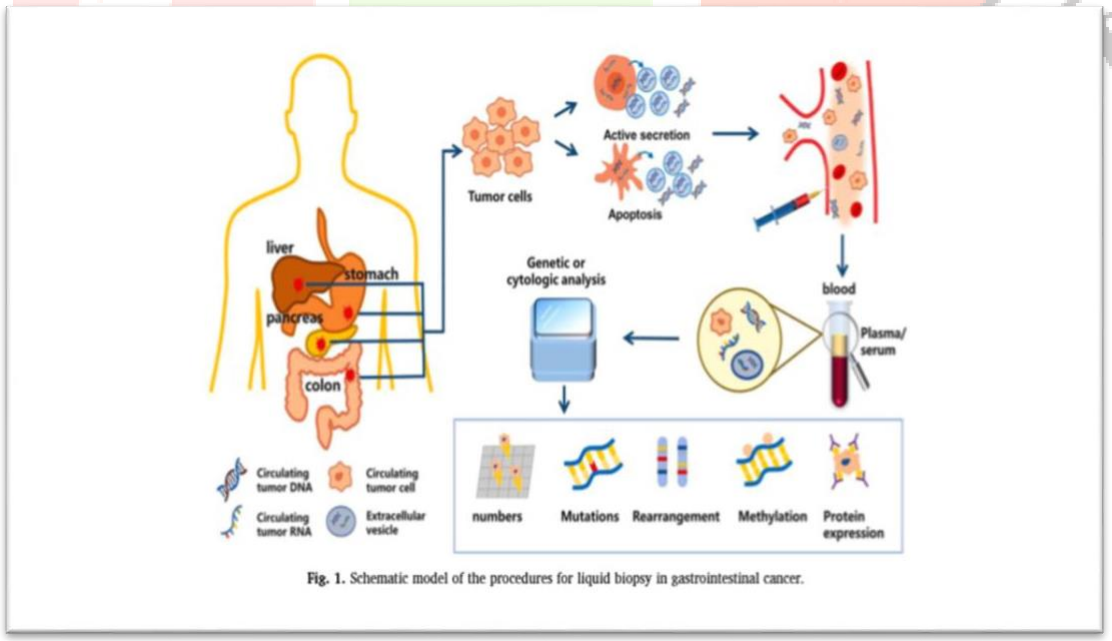

Fig. 1. Schematic model of the procedures for liquid biopsy in gastrointestinal cancer.

Figure 1
Schematic model for procedures of liquid biopsy

Immunotherapeutic strategies:

activation of immune system against cancer derive from active immunotherapeutic strategies, like adoption of cancer vaccines, cytokines, and immune checkpoints inhibitors or from passive immunization mediated by adoptive cellular therapy or monoclonal antibodies.

Some examples of immunotherapy discussed below:

Cellular Immunotherapy:

Adoptive T cell therapies have produced remarkable responses, especially chimeric antigen receptor (CAR)-T therapy in acute lymphocytic leukemia and tumor-infiltrating lymphocyte (TIL) therapy in melanoma. These breakthroughs provided new insights into immunotherapy for GI cancer.

Therapeutic Vaccines:

Therapeutic cancer vaccine is another way to stimulate an anticancer immune response to promote the recognition and eradication of malignant cells. Targets for therapeutic cancer vaccines mainly fall into two categories: tumor-associated antigens and over expressed neoantigens.

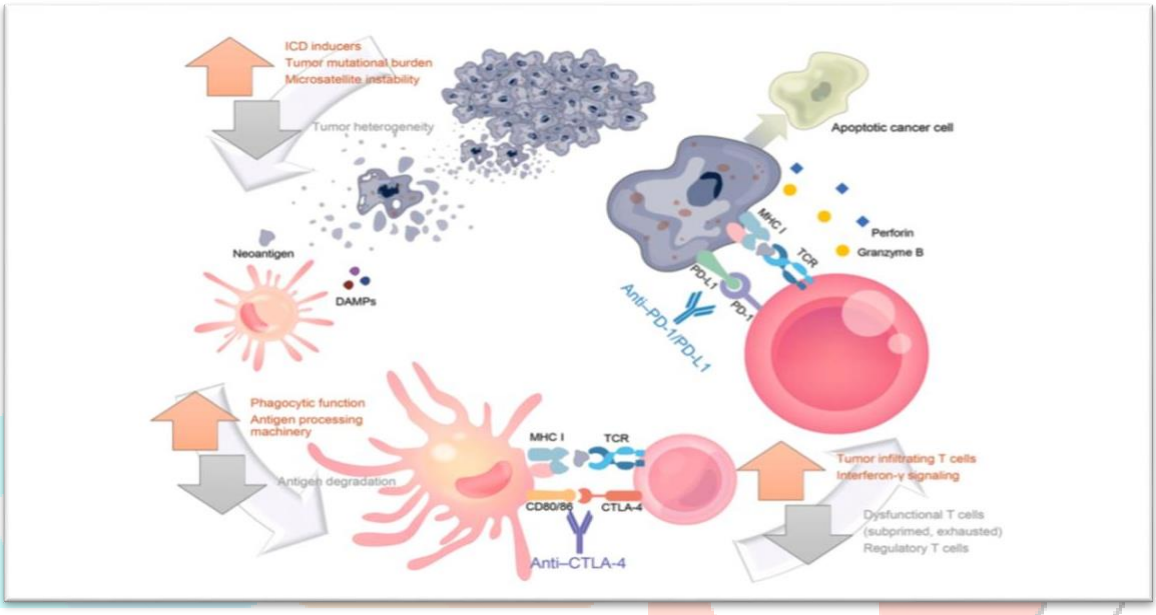

Figure 2

Determinants of responsiveness to immune checkpoint inhibitors in the immune micro environment Immunogenic cell death (ICD) arises from the antigenicity of neo antigens derived from dying cancer cells and the adjuvanticity of damage-associated molecular patterns (DAMPs). This process can be accelerated by ICD inducers, a high tumor mutational burden, and microsatellite instability of the tumor. The ICD-induced products are phagocytosed by dendritic cells (DC)s, and the cancer cell-specific antigens subjected to the antigen-processing machinery are then cross-presented through communication between major histocompatibility complex (MHC) class I of DCs and T cell receptors (TCRs) of effector CD8+ T cells. This process is negatively regulated by cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and anti-CTLA-4 antibodies are used to promote an immune response to cancer cells. Activated CD8+ T cells identify cancer cells as "friend or foe" through contact with them. During this process, if the programmed cell death 1 receptor (PD-1) of T cells interacts with its ligand (PD-L1), which is over expressed in cancer cells, the immune response can be suppressed. When this is blocked using an antibody, the immune response to cancer cells is promoted, perforin and granzyme B secreted from T cells induce cancer cell death, and neo antigens and DAMPs are released once again to form the "cancer-immunity cycle. [4]

DETERMINANTS OF RESPONSIVENESS TO ICIS:

To determine the optimal conditions for CI, it is necessary to closely consider the predictors of responsiveness and resistance mechanisms to ICIs. Numerous studies have examined these topics in terms of the genetic properties of the tumors itself as well as the expression level of immune checkpoints, and the characteristics of immune cells in the TIME. And, recently, even the microbiome has been shown to determine the response to ICIs. However, rather than analysing overly complicated influencing factors, the current CI could be generalized according to the basic concept of AIR through the development of combination strategies thatcan stimulate multiple steps and specifically activate each stage of the CIC. Right tactics of CI Cancer cells and the TIME dynamically change due to cancer progression, the longitudinal status of immune cell conversion, and the adaptive immune signature according to the timing, treatment methods, and order of ICI administration. Therefore, it is necessary to consider how the anticancer immunity from ICIs can be maximized and optimized through our understanding of tumors progression, the treatment design regarding the sequential activation of anticancer immunity, and the treatment combination and order that offers the optimal effect of CI. Right timing of CI Until now, US FDA-approved drugs for CI have mostly been limited to patients with cancer at far-advanced stages or refractory to precedingconventional treatments. These cancer patients may have conditions such as: i) a large tumors burden with heterogeneity, ii) a cancer cell moiety with multidrug resistance, or iii) a TIME altered to a very tumors prone milieu with a devastated immune system after previous high-dose cytotoxic treatments. Eventually, the likelihood of successful ICI treatment may inevitably decrease, which raises the fundamental question of when the appropriate time is to apply ICIs. Therefore, it is necessary to thoroughly analyses the traits of cells in TIME that determine the efficacy of CI and to inspect how the TIME response to anticancer treatments and influences the CIC. [5]

GASTROINTESTINAL ENDOSCOPY:

An endoscopy is a procedure that uses imaging to evaluate the organs and tissues of your body, including gastrointestinal tract. In its 200 years of development history, gastrointestinal endoscopy has gone through the following 4 stages: rigid endoscopy, semi-flexible endoscopy, fibrous endoscopy, and electronic endoscopy and ultrasonic endoscopy. In terms of endoscopic diagnosis and treatment, new technologies such as chromoendoscopy, narrowband imaging, magnifying endoscopy and endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic retrograde cholangiopancreatography (ERCP) are constantly emerging. The emergence of endoscopic ultrasonography (EUS) and natural orifice transluminal endoscopic surgery (NOTES) was a breakthrough from the previous gastrointestinal endoscopy blind area in the biliary and pancreatic system and other nearby organs. The history of gastrointestinal endoscopy is the embodiment of translational medicine in the field of gastroenterology. A series of new digestive endoscopic techniques are used in clinical practice which enabled digestive physicians to make great strides in areas that were previously inaccessible, and ultimately, these advances benefited patients.[6]

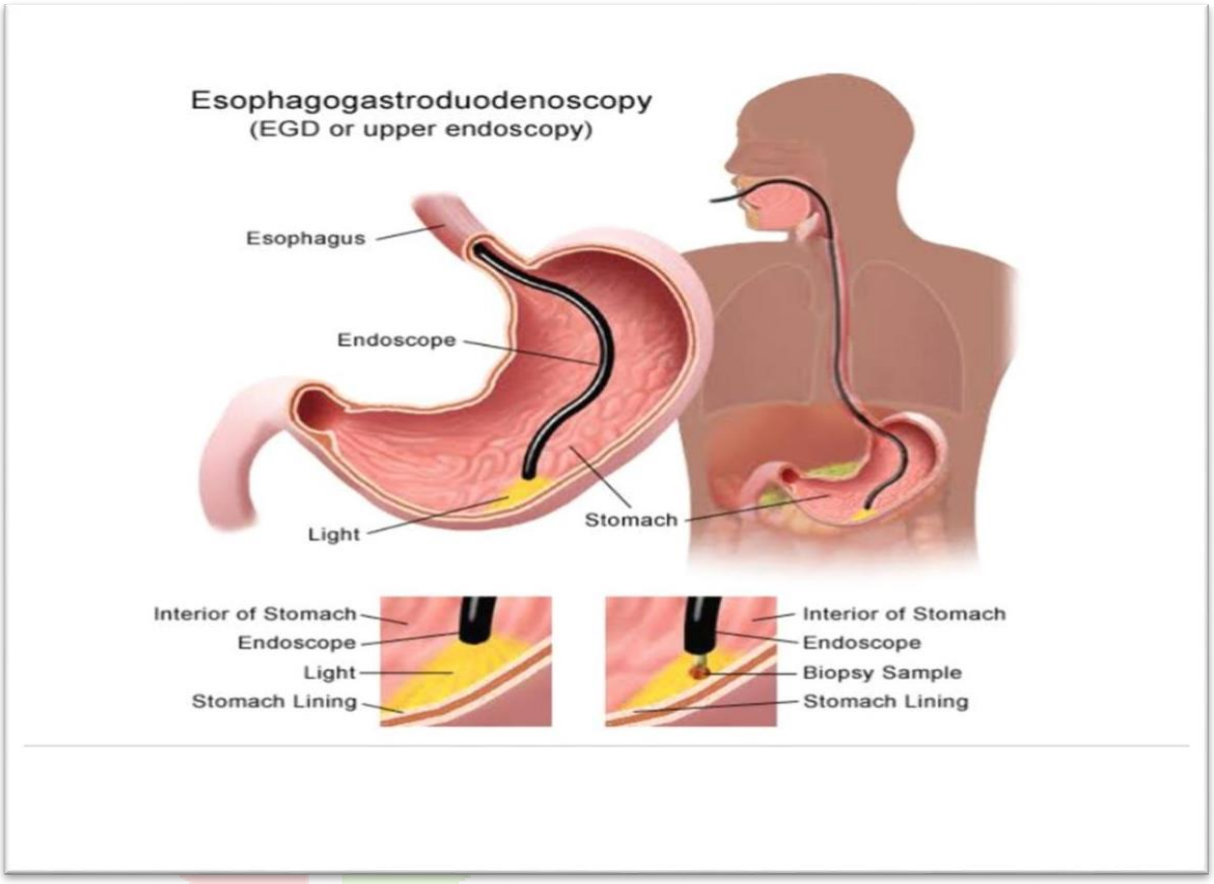

Figure 3

Artificial intelligence (AI) helps in early diagnosis of gastrointestinal cancer

Although gastroenterologists have become increasingly aware of early cancer screening in recent years, data show that the diagnosis rate of early gastric cancer is only 10% in China, far lower than that of early gastric cancer diagnosis rates in Japan (70%) and Korea (50%). The main reasons for this phenomenon include China's huge population base, shortage of endoscopic physicians, lack of advanced equipment, and the inadequacy of early diagnosis skills and experience by endoscopic physicians. The emergence of artificial intelligence (AI) and its successful application in medical imaging and pathology provide a new way to solve the problems. The application of dual-lens 3D endoscope in soft endoscope is limited by the space occupation of optical equipment and soft structure. While the emergence of single-lens 3D devices well solved this problem. 3D imaging systems form both left and right eye images by a computer algorithm and image processing, thereby creating a binocular parallax image to realize stereoscopic vision and providing spatial vision for more accurate visualization of lesions. The implementation of AI in gastrointestinal tract early cancer screening powerfully decreased the omission diagnostic rate and improved the detection efficiency, especially for low-grade digestive endoscopic physician. [7]

CAPSULE ENDOSCOPY: FILL THE DEFICIENCY OF TRADITIONAL ENDOSCOPY :

For a long time, the small intestine has been a restricted area with regards to gastrointestinalendoscopy. As a result, a number of obscure gastrointestinal bleeding (OGIB) issues rely on

Table 1. Comparison Between Currently Available Capsule Endoscopy Systems

Capsule endoscopy	PillCam SB3® Given Imaging	MiroCam® Intromedic Company	EndoCapsule® Olympus Japan	OMOM® Jinshan Science and Technology
				
Size (mm)				
Length	26.2	24.5	26.0	27.9
Diameter	11.4	10.8	11.0	13.0
Weight (g)	3.00	3.25–4.70	3.50	6.00
Battery life (hr)	8 or longer (max. 15)	12	8 or longer	6–8 or longer
Resolution	340×340 30% better than SB2	320×320	512×512	640×480
Frames per second (fps)	2 or 2–6	3	3	2
Field of view (°)	156	170	145	140
Communication	Radio frequency communication	Human body communication	Radio frequency communication	Radio frequency communication

Figure 3

Indications	Contraindications
Obscure gastrointestinal bleeding	Absolute contraindications
Iron deficiency anemia	Clinical or radiographic evidence of relevant bowel obstruction
CD	Extensive and acute CD of the small bowel with obstruction
Small bowel tumors	Intestinal pseudo-obstruction
NSAID-induced enteropathy	Relative contraindications
Portal hypertensive enteropathy	Cardiac pacemakers or other implanted electromedical devices
Celiac disease	Dysphagia
Inherited polyposis syndromes	Previous abdominal or pelvic surgery
Unexplained chronic abdominal pain	Pregnancy
	Extensive intestinal diverticulosis

Figure 4

intervention angiography or surgical probe to confirm the diagnosis. The advent of capsule endoscopy largely solved the technical barriers. First endoscopy introduced 15 years ago. Gavriel Iddan invented wireless capsule endoscopy in mid 1990s. [6]

Capsule endoscopy uses a small wireless camera to take pictures of the digestive tract. The camera is housed in a small capsule shaped like a pill. Since CE was first used in the small intestine, it has been used in the esophagus, stomach, and colon. The main indications for small intestinal CE are gastrointestinal bleeding of unknown cause, iron deficiency anemia of unknown cause, suspected Crohn's disease, small bowel tumors, non-steroidal anti-inflammatory drugs Enteropathy, portal hypertensive enteropathy , and celiac disease. It may be used for colonoscopy and colorectal cancer prevention. Most small bowel tumors are discovered during investigations of unknown gastrointestinal bleeding or iron deficiency anemia. [7]

Colonography:

colon cancer is his third most commonly diagnosed cancer and his second leading cause of cancer death in both men and women in the United States. According to current estimates, about 5.9% of the population will develop colorectal cancer in their lifetime. Excluding lung cancer deaths, colorectal cancer is the leading cause of cancer deaths in men and women combined. CT colonography is an imaging test that uses a computer program to combine multiple helical CT scans to create a two- or three-

dimensional image of a patient's inside the colon. These images can also be rotated for different views and combined to provide a complete view of the colon that can be 'fly-through'. The term "virtual colonoscopy" was coined in 1994 by Wake and his Forest University researchers, who described the procedure as a simulation of a conventional colonoscopy. Although other terms such as CT pneumonotomy and CT colonography have been used, "CT colonography" has become an accepted medical term and "virtual colonoscopy" is often used as a common general term.

Procedure:

Experts in the field have developed the following basic principles for performing CT colonography.Colon cleansing is required prior to testing. Most clinicians recommend a 48-hour low-residue diet and over-the-counter phosphosoda and bisacodyl supplements. This formulation leaves less fluid in the intestine compared to polyethylene glycol electrolyte solutions. As with colonoscopy, the success of the procedure depends on the integrity of this wash. This means that CT colonography technology currently does not eliminate the need for bowel preparation, one of the barriers to colonoscopy that patients often cite. The colon is blown with room air through the rectal tube to the maximum level that the patient can tolerate. Being able to replace carbon dioxide can reduce patient discomfort, but increases the complexity and cost of the procedure. Spiral CT scans are typically performed in one breath-hold using 5 mm collimation and 2-3 mm reconstruction interval. Patients are placed both supine and prone to redistribute gas to segments of the colon that may have collapsed. Newer multi-detector CT scanners can scan faster (less than 15 seconds, resulting in shorter breath-hold times) and use finer reconstruction intervals and collimation to obtain finer anatomical detail. I can. Data from CT scans are displayed as 2D and/or 3D images. Although not universally, 2D images are commonly used for lesion identification on computer workstations. If suspicious areas are detected, the 3D view can be used for further investigation. CT data are processed on the same workstation with dedicated software to acquire 3D views. The resulting virtual environment and intraluminal “fly-through” allows the physician to view the entire colon relatively quickly. Helical This is an advantage because the CT technology creates so many layers that the reader requires computational post-processing to efficiently analyze all the data. The 3D "virtual reality" environment also allows you to view the hidden surfaces of folds and bends from different angles.

Benefits/indications for CT colonography

1. CT colonography offers the advantage of potentially identifying colorectal cancers that cannot be adequately evaluated or identified with conventional endoscopy. B. Located near the Austral Folds complex. He also has the ability to visualize the colon next to closed and excess loops. And in many situations, completing a colonoscopy after a failed or incomplete colonoscopy is the treatment of choice. It also gives you options. Small hyperplastic polyps are unlikely to quickly become cancerous, so removal may be of little benefit.
2. It implies regular re-evaluation for monitoring, and CT colonography can be identified as an appropriate method for monitoring these patients. In the future, if CT colonography proves useful as a screening test, it will serve as a roadmap for endoscopy, along with therapeutic colonoscopy, to indicate the number and location of polyps to be removed.

Limitations of CT Colonography

Many limitations of CT colonography have been identified, including problems specific to CT colonography and problems common to other imaging studies of the colon. This can lead to unnecessary repeat colonoscopy. Main causes of false positives: 1 flight aborted.

3. Diverticulosis, which causes poorly dilated portions of the colon.
4. Thick or complex Australian folds are misinterpreted as polyps or neoplasms.
5. Metal and Motion Artefacts: X-rays passing through metal hip prostheses, Herrington rod implants, etc. result in metal artefacts (e.g., image streak artefacts) (motion artefacts are caused by breathing deviations or other body movements). . • Unknown ability to detect flat adenomas. Although relatively rare, squamous adenomas are considered more aggressive than typical adenomatous polyps. There are no data on the ability of CT colonoscopy to detect these lesions. However, hyperplastic polyps are flat on the surface of the colon that are softer and swollen than adenomatous polyps and are not immediately visible on CT colonoscopy. This has led to suggestions that this method may be less sensitive in detecting squamous adenomas. • There are no standards for performance, training or scan reading. • CT colonography is not curative. H. Polyps cannot be removed intraoperatively. In a recent study of more than 3,000 US Army veterans (average age 64 years) who underwent colonoscopy, 38% had one or more neoplastic lesions and 8% had progressive lesions (eg, polyps larger than 10 mm). If a polyp is found that needs to be removed, the patient should have a routine colonoscopic polypectomy. However, it is important to note that opinions vary as to whether this is a disadvantage, as most people who undergo screening do not require any diagnostic evaluation or intervention. This may be higher than endoscopy. A cost analysis for this procedure should include the time required to complete the procedure and the time required for the radiologist to interpret the resulting images. Also, you should have regular colonoscopy after every positive test [8].

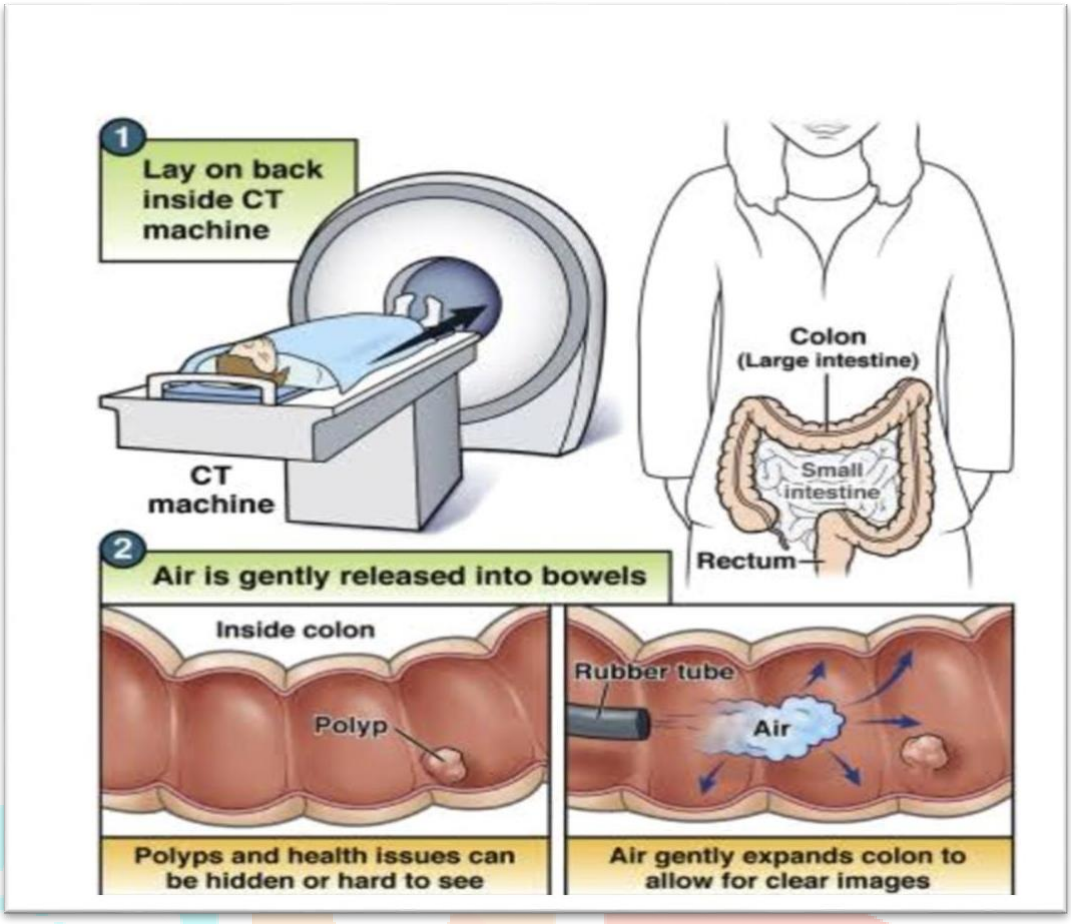

Figure 4

CT colonography

Nanomedicine:

Recent advances in nanotechnology offer new hope for disease detection, prevention, and treatment. Nanomedicine is a rapidly developing field, with targeted therapeutic approaches being developed using nanotechnology based on the pathophysiology of gastrointestinal diseases. Nanoparticulate - vectors, capable of delivering drugs specifically and exclusively to regions of the gastrointestinal tract that are affected over long periods of time, may significantly increase existing side effects and are otherwise effective. These nano scale materials have unique and unusual properties and are now used by interdisciplinary teams of scientists in fields ranging from physics and engineering to biochemistry. Consequently, in parallel with the development of these materials, the field of nanomedicine has developed to exploit some of their new properties.

Tremendous progress has been made in synthesizing a variety of materials that can be used as nanovesicles (carbon, synthetic polymers, polysaccharides, iron, etc.) and techniques to control the shape and length scales of nanomedicine. The discovery of quantum effects (size-dependent properties) that produce nanomaterials with specific emission, absorption, or scattering spectra has broadened the range of potential applications in areas such as imaging and diagnostics. One of the most attractive applications of NMs is in drug delivery systems using NMs as drug carriers. The possibility of targeting single cells represents an innovative tool for medicine .The use of NMs has several advantages: NMs have superior stability, Robustness, and long shelf life. Drugs can be loaded into NPs at high concentrations and NMs can be tricked into avoiding normal digestion processes, thus allowing efficient delivery of drugs to specific sites. The kinetics of drug release can be modulated. Chemically adaptable surfaces can be modified with ligands to affect site-specific drug delivery.

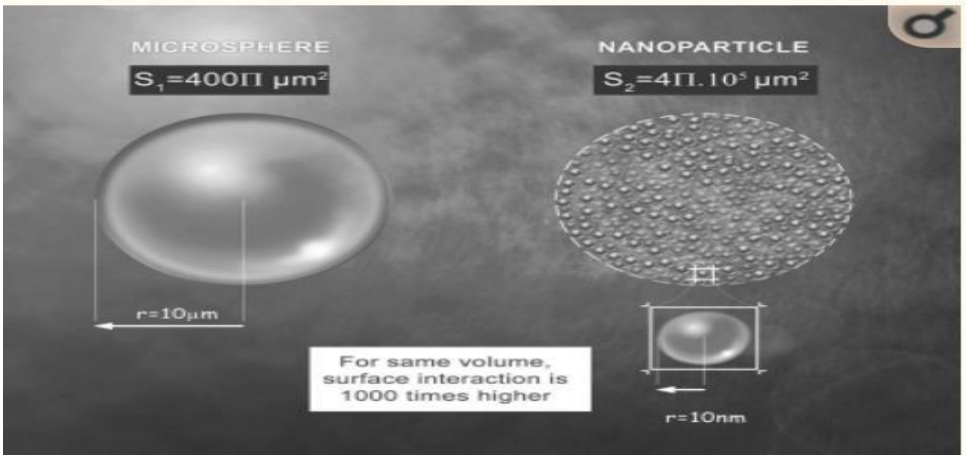

Figure 5

Nanomedicine

CHARACTERISTICS AND TYPES OF NANOMATERIALS USED IN GASTROENTEROLOGY

•The gastrointestinal (GI) tract is an attractive target system for nanotechnology applications . It is the site of therapeutic absorption, and the behaviour of NMs can be regulated during transit through the digestive tract under conditions of varying pH, transit time, pressure, and bacterial content. The distinct features of each part of the digestive tract introduce many challenges to the application of therapeutics to the gut. NM behaviour must be optimized for efficient transit under varying pH, pressure, and enzyme-catalysed degradation to reach the target site. Engineering a nanocarrier that is robust under the range of conditions presented by the gut represents a challenge in and of itself. The properties of the NMs and the interactions with tissues in the gut depend heavily on size, size distribution, morphology, hydrophilic-hydrophobic balance, and surface functionalization of the NM.

NM size.

Size (defined as the diameter of particles over the range from 1 to 1,000 nm) is a key aspect of NMs, since this can influence cellular uptake, physical properties, and interactions with biomolecules. For example, Lamprecht et al. recently characterized the deposition of particles of three sizes, 0.1, 1, and 10 μm, in the gut after oral administration. Interestingly, the authors showed that small particles preferentially deposited in the colon (better bio adhesive properties), with the highest rate of uptake by macrophages in an inflamed colon, relative to the normal intestinal cells. In many cases, the size of a given NM is determined by the procedure used in the synthesis and their chemical composition. For example, 1- to 10-nm particles are typically formed by crystalline iron atoms or micelles of small molecules, whereas larger particles (10–1,000 nm) are typically generated from polymeric materials.

Surface properties.

In all nanomedicine studies, the major challenge is determining how NMs will interact with the mucosa, tissue, or targeted cells. The first stage of oral drug delivery involves the interactions between the NM surface and the mucosa or GI cells. One such parameter that plays an important role in determining these interactions is the electrostatic surface charge of a NM. The zeta potential (accurately approximates the charge on a NP and is used to describe cell- NM interactions. The charge on a NM depends on the polymer used for the NM matrix or can be modulated by adsorbing specific molecules onto the NM surface. The charge displayed on a NM prevents aggregation. Higher (positive or negative) can produce a stronger electrostatic repulsion between NMs, and thus the NM suspension will become more stable.

High surface Area

Nanomedicine can take advantage of the high surface area-to-volume ratio of NMs and the specificity of the digestive system by engineering diversified interaction sites into the NMs. Most NMs are spherical (NPs, micelles, or liposomes) and hence have a surface area-to-volume ratio of 3/r, where r is the radius. As r decreases, the surface area-to-volume ratio increases. A particle with a large surface area has more interaction sites available than a particle with a small surface area, and the rate of an interaction at the surface may, therefore, be higher. This has important implications for drug delivery. It should be noted that the inverse relationship between particle size and surface area-to-volume ratio applies to all geometrical shapes and is not restricted to spheres. For example, the main characteristic of nanotubes (cylindrical NMs) is based on the length-to-diameter ratio, which can reach 28,000,000 in some cases. The lightweight and strong carbon nanotubes are used in bone engineering as structural mimics of bone, collagen, or hydroxyapatite.

STRATEGIES USED IN NP DELIVERY IN THE DIGESTIVE SYSTEM

An unmet need in GI disease treatment is the targeted delivery of drugs to the terminal ileum and colon, two sites that are affected by inflammatory diseases and colon cancer. Four strategies for drug delivery systems in nanomedicine may be enumerated on the basis of the relative constant transit time in the digestive tract, the pH, the enzyme environment, and the ambient pressure.

Time-Dependent Strategy

This strategy is based on the transit time in the GI tract. In time-dependent release, the drug is released after the outer layer of the drug delivery system is destroyed. Several properties can be used for this purpose, including the degree of swelling of a polysaccharide matrix or the pH change. Dorkoosh et al. used the change in the enteric coating and the concentration or thickness of the layer to modulate the release time profile. With this technique, one can target any part of the intestine or colon. A similar approach was used to target the colon by Laroui et al. in a study of the behaviour of different concentrations of a mixture of two polysaccharides (alginate and chitosan). In this study, a high drug release profile was observed from the NPs in the targeted area. The kinetic of the release was modulated by the osmotic activity of the salt or charged polymers, or the erosion rate of the polymer coating.

pH-Dependent Strategy

The GI tract presents a wide range of pH values: 2–3 in the stomach, 5–6 in the small intestine, and 7 in the colon. NMs that release drugs in a pH-dependent fashion have been commercially developed. Examples include Eudragit poly(meth)acrylate polymers. Those polymers contain acidic or alkaline groups that enable the pH-dependent release of the active ingredient. Polyacrylamide, for example, is a polymer that is highly sensitive to pH. It is stable in acidic pH but degraded in a neutral pH. This characteristic is suitable for drug protection during GI tract transit. Several polysaccharides, such as chitosan, pectin, or alginate, have been developed for delivery purposes by taking advantage of their pH-dependent stability. Microspheres can be made to be pH sensitive as well. Lamprecht et al. showed that pH can be used to modify the release of 5-fluorouracil over time using Eudragit P-4581F microspheres. In this study, the authors showed that a relatively weak change in pH (from 6.8 to 7.4) produced a dramatic effect on the kinetics of drug release from the microspheres. Sensitivity to small pH adjustments is relevant to colonic delivery systems. Other strategies call for the encapsulation of a prodrug that is chemically modified to the active drug in a pH-dependent

manner, or polysaccharides grafted with a drug for cell targeting. The weak changes in pH convert the prodrug from an inactive form to an active form in the targeted area.

Pressure-Dependent Strategy

The strong muscular contractions in the colon serve as a "driving force" to move its contents. faeces must be evacuated, and this organ produces muscular contractions that enable this function. These motions result in intracolonic mechanical pressures that are higher than in other parts of the GI tract. Intestinal pressure-controlled colon delivery capsules (PCDCs) rely on the relatively strong peristaltic waves in the colon for drug release. Such capsules are coated with a water-insoluble polymer, ethyl cellulose. After oral administration, PCDCs act as an ethyl cellulose balloon. The suppository base liquefies at body temperature. In the upper GI tract, PCDCs are not directly subjected to the luminal pressures due to the fluid present in the stomach and small intestine. Reabsorption of water in the colon, however, increases the viscosity of the luminal contents. As a result, increased intestinal pressures directly affect the system via colonic peristalsis. In response to the increased pressure, PCDCs rupture and release the drug in the colon.

Enzyme-Based Strategy

Enzyme-based strategies depend on the colonic bacteria to degrade a NM and release the drug in the colon. Because bacteria are located mainly in the colon, this strategy is a powerful method for delivering drugs to the colon. Specific enzymes are produced only by colonic bacteria and thus only detectable in that area. That characteristic made enzyme-based strategies very interesting and powerful. In that strategy, Laroui et al.have synthesized polylactic acid NPs loaded with anti-inflammatory tripeptide and succeeded in releasing them in the colon by giving it orally encapsulated in a hydrogel. This hydrogel, made with a specific proportion of alginate and chitosan, is specially degraded by the colonic enzymes. Plenty of polysaccharides can be used since they are specifically degraded by colonic bacteria such as amylase/amylopectin and chitosan.

APPLICATION OF NMS IN GASTROENTEROLOGY

Nanomaterials Used as a Theragnostic Special "theragnostic" NMs are currently being designed with the goal of progressing through preclinical development for cancer imaging and therapy. Theragnostic rely on double encapsulation of both therapeutic and diagnostic molecules, within a single carrier. These NMs are designed to assist in both imaging (diagnosis) and therapeutic applications. Implementation of this concept requires the development of key molecules that can respond to stimuli (biological or chemical) within the area targeted for treatment. Several stimuli may be coupled to the system, for example, inflammatory indicators such as pH, elevation of temperature, hypoxia, or specific binding to an inflammatory ligand. To assist in imaging applications, signalling molecules may be encapsulated or conjugated to the carrier. Polymers may be bonded via noncovalent or covalent interactions directly during the nanocarrier synthesis or after synthesis by surface modification reactions. Noncovalent or covalent interactions are selected according to the application and the specificity of the area targeted for treatment. Covalent linkages based on carbonyl, amine, or silane coupling chemistries allow a wide range of functionalities under various pH or oxidative conditions. Hydrophobic, electrostatic, or hydrogen-bonding interactions present alternatives to covalent linkages, if flexibility under chemical conditions is required. Polymers may be selected to include a variety of functional groups and/or hydrophobic sites, leading to a large set of potential linkages between the diagnostic/therapeutic molecule and the nanocarrier. Amide, ester, disulphide, hydrazine, or thioether linkages have been successfully used to enable covalent or hydrophobic interactions (hydrophobic drug loading) or ionic interactions (nucleic acids). As a theragnostic study, Yang et al. demonstrated a promising approach to the treatment of pancreatic cancer. In this study, the author used a urokinase plasminogen activator (uPA) amino-terminal fragment (ATF) peptide as a target ligand with a high binding affinity to uPAR to block the interaction between uPA receptor (uPAR) and its natural ligand, uPA. ATF peptides have been shown to inhibit tumour growth and angiogenesis in several animal tumour models. Yang et al. showed that the ATF-coated NPs were efficiently taken up by cancer cells, thereby increasing their tumour- specific accumulation, both for tumour imaging and for the delivery of therapeutic agents.[9]

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