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Ingestible Contrast Agents for Gastrointestinal Imaging

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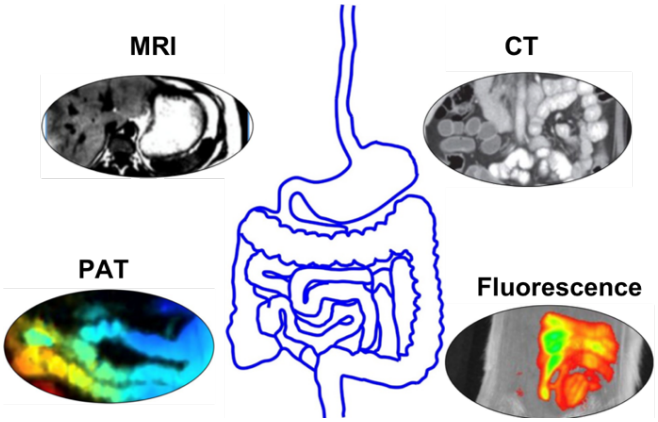
Abstract:

Gastrointestinal (GI) ailments cover a wide variety of diseases involving the esophagus, stomach, small intestine, large intestine or rectum. They bring about many inconveniences in daily life in chronic diseases and can even be life-threatening in acute cases. Rapid and safe detection approaches are essential for early diagnosis and timely managements. Contrast agents of GI imaging could enhance the contrast to distinguish the abnormal lesions from normal structures. CT and MRI are two important diagnostic tools for the evaluation of GI conditions. This review mainly involves several common GI diseases including inflammatory diseases, intestinal tumors, diarrhea, constipation and gastroesophageal reflux diseases. Selected contrast agents are summarized such as barium sulfate, iodine-based agents, gadolinium-based agents and others. Going forward, continued endeavors are being made to develop more emerging contrast agents for other imaging modalities.

Key words: Gastrointestinal diseases; Contrast agents; Bioimaging

Graphic for the Table of Contents



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1. Introduction

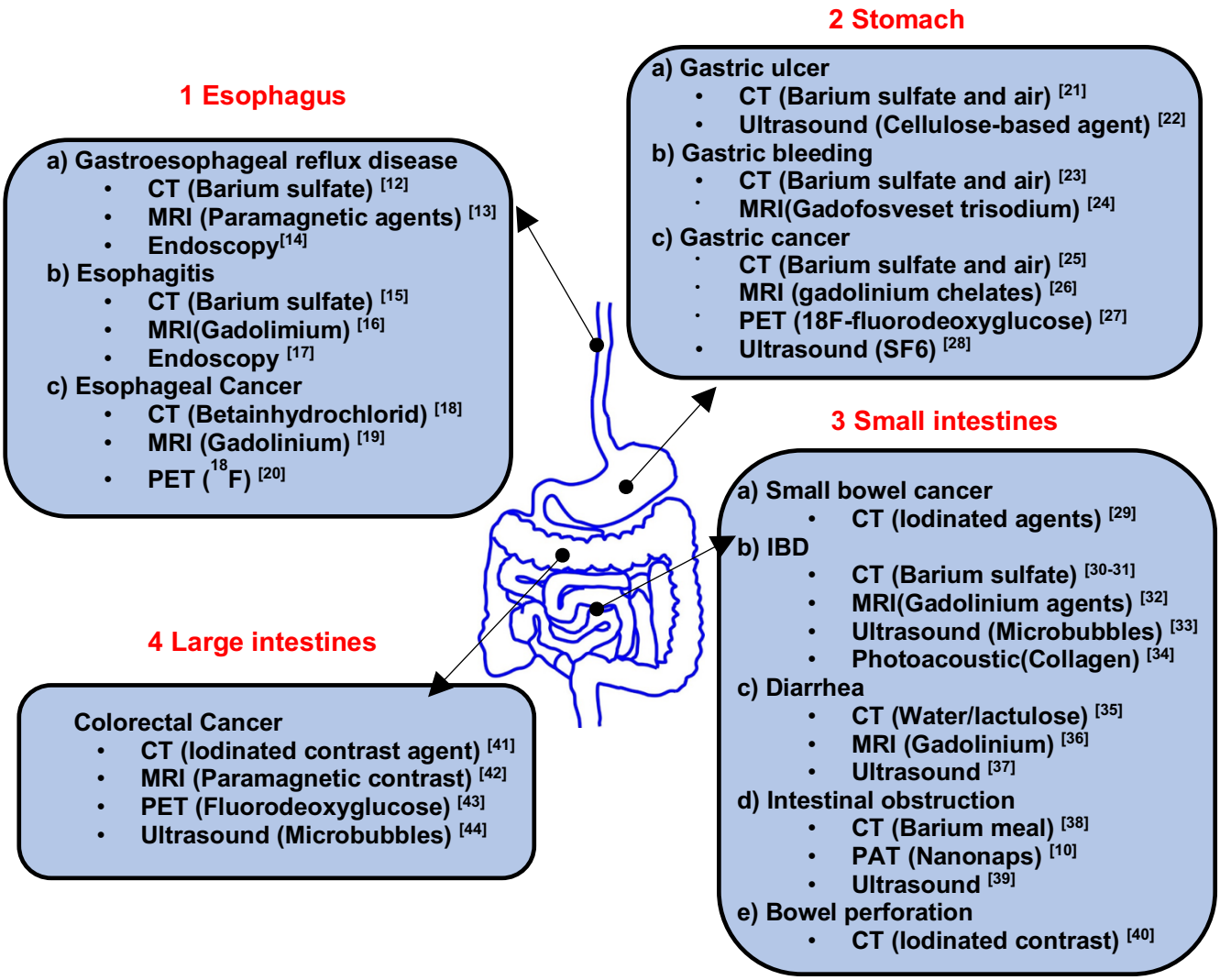
Gastrointestinal (GI) tract diseases are an extremely diverse group of conditions. For example, Crohn's disease (CD) and ulcerative colitis (UC) affect 1.2 million Americans with growing incidence.[1,2] In the past, endoscopy and fluoroscopy were front-line diagnostic tests. However, these techniques are limited to assessing the lumen and mucosal surface and are unable to assess the submucosal layers of the bowel wall. Endoscopy is invasive, which is sub-optimal, particularly if multiple follow-up studies are required over time.[3–6] Other modalities for assessing the bowel wall include cross-sectional imaging techniques such as computed tomography and magnetic resonance imaging. Ultrasound (US) has also demonstrated a limited role. Numerous studies demonstrate the performance of imaging such as magnetic resonance imaging (MRI),[3,7] computed tomography (CT),[8,9] and photoacoustic tomography (PAT).[10] However, anatomic imaging techniques lack functional information. Molecular imaging of the bowel has the potential to provide further functional information that would be useful for guiding management.

The above-mentioned noninvasive imaging modalities have their own strengths and drawbacks. For example, MRI and CT usually work in a complementary manner. The imaging time involved in CT is short but the sensitivity is low and there is exposure to ionizing radiation, which is concerning, especially in pediatric populations. On the other hand, MRI can provide high spatial resolution but is expensive and time consuming.[11] Molecular imaging is a rapidly emerging field that encompasses various modalities, some of which overlap to form superior multi-modal imaging necessary to diagnose, stage and treat conditions of all forms. Recent developments have consisted of improving and combining modalities resulting in a product with more sophisticated capabilities. Imaging of the GI tract can play a pivotal role in the diagnosis and treatment of these chronic diseases. There are a number of imaging modalities available to image the GI tract such as MRI, US, PAT, positron emission tomography (PET), and single photon emission computed tomography (SPECT).

2 Common intestinal diseases

The gastrointestinal tract is an important organ in the human body and abnormal function causes numerous diseases. Oesophageal diseases include gastroesophageal reflux diseases, oesophagitis and others. Gastric diseases include gastritis, polyric stenosis, gastric antral vascular ectasia and gastric cancers. Intestinal diseases include enterocolitis, inflammatory bowel diseases, intestinal tumors, bowel obstruction, diarrhea and others. Below some common intestinal diseases are summarized briefly (**Table 1**).

Table 1: Examples of different imaging modalities for the diagnosis of various GI ailments



2.1 Inflammatory bowel diseases

Inflammatory bowel disease (IBD) is an idiopathic inflammatory disease that impacts the gastrointestinal tract. The major forms of IBD include Crohn's disease (CD) and Ulcerative colitis (UC). CD is characterized by mucosal inflammation, production of inflammatory mediators and excessive neutrophils with crypts and lamina propria, whereas UC is characterized by macrophage aggregates. These mucosal immune responses are caused by genetic, environmental and other factors. Genetically, it was found that NOD2, or designated CARD15 and IBD1 are susceptibility genes. Since then, a number of other loci were found to be implicated

in IBD such as IBD5, IL23R and ATG16.[45–47] In addition, IBD was also associated with enteric flora and it was found that the "healthy" bacteria or probiotic combinations can improve IBD conditions.[48,49]

2.2 Intestinal tumors

Cancers impact the GI tract, including the esophagus, stomach and colorectal region. Small intestine malignant tumor mainly includes adenocarcinoma, neuroendocrine tumors, sarcomas and lymphomas. Adenocarcinoma of the small intestine, accounting for forty percent of all the malignant small bowel cancers, mostly stems from duodenum, jejunum and ileum. Lymphomas can be classified into three types, immunoproliferative small intestinal disease (IPSID) lymphoma, enteropathy associated T cell (EATL) lymphoma and other western-type non-IPSID lymphomas. In addition, coeliac disease could contribute to EATL lymphoma which may be derived from chronic mucosal inflammatory response induced by gliadin exposure.[50] Carcinoid tumors could be caused by serotonin that can be further transformed into malignant tumor. The factors below are responsible for the malignancy: chromosomal instability, point mutations, dysfunction of tumor suppressor pathways and methylation abnormalities. In addition, gastrointestinal stromal tumors (GISTs) arise from interstitial cells of Cajal, mostly existing in stomach (60%-70%) and small bowel (20%-25%), but there are a small number of GISTs in the duodenum (less than 5%).[51]

2.3 Diarrhea

Diarrhea is a type of irritable bowel syndrome (IBS) and IBS with diarrhea (IBS-D) accounts for about 40% of IBS.[52] The pathogenesis of IBS-D is closely associated with abnormal gut flora, visceral hypersensitivity, dysfunctions in enteral motility, disorder in serotonin secretion, and psychological stressors. In addition, other factors also could induce diarrhea such as change of intestinal immune activation, alteration in intestinal permeability, adverse effects of medication and gut microbiome such as bacterial, fungi, archaea, viruses and eukaryotes. Bacterial infection can cause diarrhea symptoms, for example campylobacter, shigella nontyphoidal-salmonella, six

subtypes of E. coli and clostridium perfringens. Rotavirus can cause severe diarrhea in infant and children. Meanwhile, children with rotavirus infection could be treated with vaccination.[53] Recently, many studies involving diarrhea treatment have been carried out. For example, prebiotics could be used to inhibit the growth of potentially harmful bacteria and increase the growth of bifidobacteria. Probiotics is able to reduce the visceral hypersensitivity and improve the psychological symptoms. Furthermore, open-label rifaximin, an antibiotic has proven to be significantly helpful in improving IBS-D symptoms with excellent safety and tolerability.[54] In addition, alosetron treatment is a therapy method for the treatment of severe IBS-D for women.

2.4 Constipation

There is no clear definition of constipation but it could be defined as the condition of evacuating stool spontaneously less than three times per week or incapability of evacuating stool completely.[55,56] Constipation can be divided into three major types: normal-transit constipation, slow-transit constipation and disorders of defecatory.[57] Typical symptoms of constipation include the presence of hard stools or frequent sense of difficulty in evacuation. These can occur in normal-transit and slow-transit constipation and they could be treated with dietary fiber. Alternatively, osmotic laxatives should be used when the response of constipation to fiber therapy is ineffective. For cases of severe constipation when both fiber and osmotic laxative fail, bisacodyl or senna derivatives and prokinetic medications (e.g. tegaserod or a partial 5-hydroxytryptamine 4-receptor agonist) could be used.[58] Defecatory disorders mostly arises from the dysfunction of pelvic floor or anal sphincter. Defecatory disorders are associated with the transit of large, hard stool or anal fissure or hemorrhoid. The corresponding methods of treating defecatory disorders focus on biofeedback that can promote the entry of stool into the rectum.[58] Other causes of constipation include opioid use that can result in the delay of colonic transit, reduction of intestinal motility and absorption, eventually forming constipation. Also, for chronic idiopathic constipation, the relatively unbalanced expression of cyclic guanosine monophosphate (cGMP) signaling

components can potentially cause constipation; meanwhile, the overexpression PDE5 can cause refractory constipation as well, which could not be treated with linaclotide or plecanatide, but PDE5 inhibitors can provide treatment for this type of constipation.[59]

2.5 Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a digestive disorder that causes stomach contents to reflux back into the esophagus.[60] GERD affects tens of millions of people worldwide and the prevalence in North America is estimated to be 18-28%.[61] The cause of GERD is the abnormal development of the lower esophageal sphincter (LES). Transient lower esophageal sphincter relaxation (TLESRs) is the most common cause, because of the moments of LES tone inhibition, particularly in postprandial phase, the occurrence of TLESRs becomes more frequent, leading to acid reflux. In addition, other factors can also give rise to GERD such as the reduction of LES pressure, delayed gastric emptying, hiatal hernias as well as impaired esophageal clearance.[62,63] The most common symptom of GERD is heartburn and other symptoms include bloating, belching, nausea, and vomiting. If GERD is left untreated, complications may occur such as esophagitis and Barrett's esophagus. Severe esophagitis can cause narrowing of the esophagus, erosions, ulcerations and dangerous GI bleeding. Chronic esophagitis may induce dysphagia. Another complication of GERD, Barrett's esophagus is caused by the persistent acid reflux condition, also referred to as intestinal metaplasia of the esophagus, which may progress to esophageal adenocarcinoma. Therefore, early detection and timely measurement are important to prevent malignant transformation.[64]

3.1 Contrast agents for CT

Computed tomography (CT) or X-ray imaging are used as a standard GI imaging method in many instances. Radiocontrast agents are employed to absorb external X-rays for the decrease exposure on the detector, providing contrast for imaging. Typical radiocontrast agents include

iodine, barium sulfate and gadolinium-based compounds. Computed tomography colonography (CT colonography), traditional double contrast barium enema (DCBE) and colonoscopy are common approaches used to examine colons. Below we will briefly summarize some barium-based imaging methods, DCBE, and CT colonography and others.

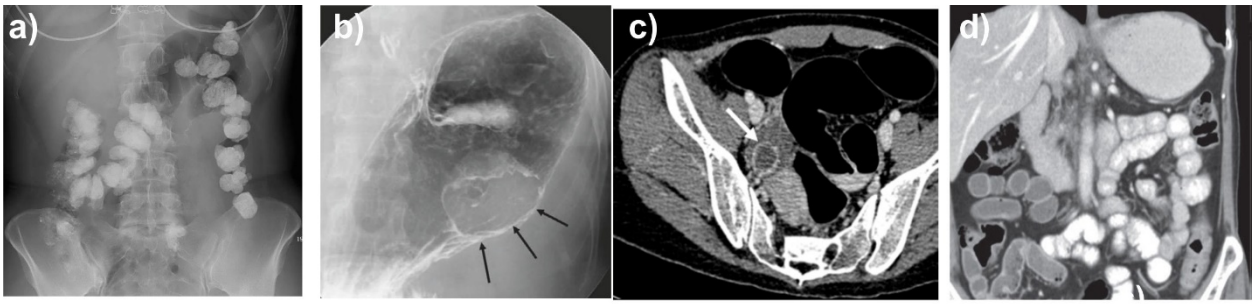


Figure 1 Computed tomography imaging of GI using different contrast agents. a) Colon visualization following a barium meal.[65] **b)** A submucosal tumor (arrows) detected by double-contrast barium meal.[25] **c)** CT colonography following intravenous administration of iohexol provides clear imaging of a corpus luteum cyst.[66] **d)** Duodenal distension was imaged by an iodinated contrast agent as shown by the bright regions.[67]

3.1.1 Barium-based contrast agents

For the imaging of intestine, one of the imaging approaches is small bowel follow through (SBFT) that uses fluoroscopy and barium-based (or iodine based) contrast agents to provide non-invasive imaging of bowel diseases, bowel obstruction, polyps, cancers, neoplasm, blood in the stool and others. When the contrast agents move from the stomach into intestine, X-ray imaging is used to determine abnormalities. Historically, SBFT has been used as a standard radiologic approach for the evaluation of active Crohn diseases.[30,31] However, some studies also shows that SBFT is not completely accurate.[68–70] For example, enteroclysis is shown to be more accurate than SBFT for the detection of early mucosal lesions.[71,72] But they both can only provide indirect and limited information with respect to the state of the bowel, in addition, the effectiveness of these two methods also are limited by the overlapping bowel loops.[73–75]

A barium swallow test, also known as esophagram, is a barium examination of the throat and esophagus. It can be used for the diagnosis of diseases such as esophageal motility disorders, perforations, strictures, hiatal hernias or gastric volvulus. Barium sulfate is commonly used as a contrast agent that can result in higher sensitivity compared to water soluble contrast agents such as Gastrografin/diatrizoate. For patients with suspected gastroesophageal reflux disease (GERD), barium esophagram examination is an essential part of patients' workup process. Based on the various symptoms and conditions of GERD patients, different density or forms of bariums can be selected. A full esophgram examination includes various phases including timed barium swallow, upright phase, motility phase, distension or full-column phase, mucosal relief phase, solid food assessment and gastric findings. In the preoperative examination of barium esophagram, the barium swallow could serve as the main means for dysphagia diagnosis resulting from the dysmotility disorder of GERD. For severe dysphagia, barium swallow must be administered while patients remain upright position, and a total of 250 mL low-density barium should be injected over 45 seconds before the spot film is taken. If high-density barium could not coat the esophagus of patients adequately, the fold thickening of esophagus should be identified to diagnose the esophagitis. In the reflux phase, it is important to keep barium reflux to the cervical esophagus in a continuous, repeated and spontaneous manner. Solid food injection is another part before the diagnosis. Administration of a 13-mm barium tablet with water can be carried out to ensure proper tablet passage. Once the tablet passage is impaired, patients should inject low-density barium to detect the precise site and cause.[76]

The barium meal is used to image the stomach and small intestine, which is often carried out right after a barium swallow examination. For example, a barium meal could be used to examine the duodenum-biliary reflux (DBR) condition of patients with recurrent common bile duct stones (CBDS). Prior to investigation, patients must undergo fasting for 6 to 8 hours and then receive 3 g aerogenic agents, and subsequently swallow 100 mL sulfate barium. When the barium meals

moves, DBR can be observed in the supine position through fluoroscopy.[77] Another example is the barium suspension method that involves using 50 mL 200% (w/v) barium meal used for determination of colonic transit time (CTT) to examine patients with slow-transit constipation (STC). In general, the most popular method for STC measurement is radiopaque markers and the evaluation of CTT is dispensable before surgical treatment of constipation. In comparison with radiopaque markers, the location diagnosed by the suspension method is more accurate. The colonic shape and location on the transit X-rays through barium suspension method could be clearly visible (**Figure 1a**). More importantly, the barium suspension method is simple and economical; the contrast agent of barium sulfate is easy to acquire and no other special drugs or equipment is needed.[65] Although bowel obstruction was generally diagnosed by abdominal roentgenograms, it is difficult to differentiate bowel obstructions from proximal bowels filled with fluid, partial obstruction, bowel strangulation or superior mesenteric artery syndrome. The barium meal method can have rapid transit time to the obstruction position, detecting obstruction more rapidly and clearly, which can also avoid the problems when using roentgenograms alone.[38]

3.1.2 Double contrast methods

Double contrast barium enema is often applied to CT imaging of colon, and the gas administered orally could help to distend the bowel for the contrast enhancement to better differentiate abnormal morphology from normal tissues. [78] Barium is used to outline the colon and rectum, and air is pumped into the rectum and colon to further enhance the imaging by distending the colon. Barium enemas can be used for the diagnosis of inflammatory bowel diseases, diverticulum and intestinal structural changes. Double contrast barium meal (DCBM) is another form of radiocontrast for the imaging of colon and rectum, using two contrast agents to visualize the intestinal structure more easily. DCBM can be used to acquire CT imaging of gastro tumor. An effervescent powder was orally administered to distend gastro tissue adequately. And butyl scopolamine was intramuscularly injected in order to minimize peristaltic activity.[25] Double

contrast barium meal can also be used for examination of acute upper gastrointestinal bleeding. By the double contrast barium meal technique, 70% of the presumed bleeding sites were identified. The radiological features were also clearly seen including blood clot located in the ulcer, an artery in the base of ulcer and active bleeding during the course of the examination.[23] In addition, DCBM can also be used for the evaluation of gastric tumors, as shown in **Figure 1b**; Double contrast barium meal can image a submucosal tumor with mucosa coating in a 59-year-old woman with gastrointestinal stromal tumors.[25] Similarly, gadolinium chelate substances were also intravenously administered to enhance the sensitivity of MRI imaging in GI. This type of double contrast method can have the most benefits for the diagnosis of inflammatory process of the bowel. [79]

3.1.3 Computed tomographic colonography (CTC)

Computed tomographic colonography (CTC), or termed colonoscopy is an emerging radiological technique for the imaging of intestine, mostly of large bowel. It is recommended as a screening test[80,81] and used for the investigation of patients suspected with colorectal cancer.[82] For gut imaging, many studies have compared barium enema, colonography and CT colonography. In general, CTC has higher sensitivity than barium enema and patients mostly prefer it over barium enema.[83] CTC uses X-rays and computers to generate 2-D or 3-D images of the colon and the rectum. It can be used for the evaluation of polyps, diverticulosis and cancers. During imaging, a small tube for inflation with gas (e.g. carbon dioxide) is inserted into the rectum. Intravenous contrast agent could be used for the enhancement to better distinguish between the stool and submerged polyps, as well as flat or assessible polyps that are easy to be overlooked. For example, in order to determine if intravenous contrast is necessary for detection of extracolonic findings, iohexol (Ominipaque^{TM} 350) was used as intravenous contrast agent for the patients undergoing CT colonography (CTC). It was found that with iohexol intravenously administered,

additional extracolonic findings (extracolon cysts) are found (**Figure 1c**), even though no increase in number of patients with significant lesions was observed.[66]

3.1.4 Iodine as contrast for CT

Bowel cleansing and distention are important for intestinal imaging such as computed tomographic colonography. Fecal tagging by orally administered contrast agents can be used for the differentiation of fecal materials from polyps. Iodinated contrast agent can be used as tagging agent of residual feces in bowel and iodinated contrast could be classified into nonionic iodinated contrast and ionic iodinated contrast. Both nonionic and ionic iodinated contrast generally have better performance than barium-based contrast in terms of the tagging homogeneity of feces material and the attenuation detection values.[84] Nonionic iodinated contrast could be used safely for the case of gastrointestinal tract perforation because of its rapid absorption process.[40] The outstanding features include low risk of dehydration, diarrhea and good patient compliance. On the other hand, the cost might be expensive compared with barium and ionic iodinated contrast. Compared to other contrast agents, iodine-based contrast agents are well-tolerated and can achieve satisfactory bowel distention and fold visibility (**Figure 1d**).[67] For Ionic iodinated contrast agents, except for high safety and water solubility that are similar to nonionic contrast, tagging performance for bowel is superior to nonionic ones. However, high concentration of ionic iodinated contrast agents can cause gastrointestinal discomfort such as nausea, vomiting, cramps, diarrhea and poor taste, hence small quantity of ionic iodinated contrast is recommended in fecal tagging of CT bowel.[85]

3.2 Contrast agents for MRI

Compared with other imaging tools, MRI has excellent characteristics such as minimal ionizing radiation, noninvasiveness and high resolution.[86,87] Intraluminal contrast agents of GI can enhance the contrast of bowel and pancreas and especially the bowel wall. An ideal intraluminal

Table 2: Comparison of different imaging modalities and common contrast agents

Imaging modality	Examples of Contrast agents	Advantages	Disadvantages
CT	Barium meal[38,41] DCBM[23] Iodinated agent[85]	High resolution; High acquisition speed; Low cost	Radiation exposure
MRI	Gadolinium agents[32] Barium sulfate [88,89] Water[90] Natural contrast agents[91,92]	Minimal radiation; Noninvasiveness; High resolution	Time consuming
PET	^{18}F[27,43] ^{64}Cu[10,93]	High sensitivity; High specificity; High resolution	High cost
Ultrasound	Microbubbles[94]	Non-invasiveness; Low cost; High safety profile	Poor sensitivity
Fluorescence	ICG[95] Red chlorophyll[96] Pheophytin [93]	High sensitivity; Easy operation;	Susceptive to interference; Very poor penetration depth
Photoacoustic	Naphthalocyanines[10] Pheophytin[93]	Noninvasiveness; High resolution	Restricted penetration depth

contrast agent for GI imaging needs to meet these criteria below: 1) should have good patient compliance, for example, they are palatable, easy for administration and do not stimulate peristalsis. 2) contrast agent must not be absorbable systematically or diffuse into the adjacent tissues or organs and ideally, they are able to excrete from GI tract in a timely manner; 3) the enhancement characteristics of agents need to be unchanged and the homogenous marking of GI is preferred while going through GI tract. 4) High sensitivity, specificity and safety profile but low cost are desired.[97] In general, intraluminal MRI contrast agents for gastrointestinal imaging can be classified into positive contrast agent and negative contrast agents.[98,99] Positive contrast agents can contribute signal to bowel lumen whereas negative contrast agents reduce signal associated with lumen. Positive contrast agents include paramagnetic substances such as

gadopentetate dimeglumine[100] and ferric ammonium citrate[101]. Negative contrast agents include clays (e.g. kaolin[102]), iron oxides[42,103], magnesium sulfate[104], barium sulfate[88]. To obtain optimal MR imaging, intraluminal contrast agent should display high T1-weighted signal intensity and low T2-weighted signal intensity. Also, biphasic agents can show positive and negative effects for signal intensity; some representative biphasic agents are as follows: clay suspensions, paramagnetic chelates and manganese chloride. Some foodstuff agents have also used as intraluminal imaging because of their advantages such as low cost, miscibility and positive enhancement effects on both T1- and T2- weighted images. In addition, some natural products such as green tea and blueberry may be used for the enhancement of GI tract because they contain high manganese concentration[91,105]. In addition, miscible agents or immiscible agents are used to mix or replace the bowel contents. Below some representative examples will be mentioned.

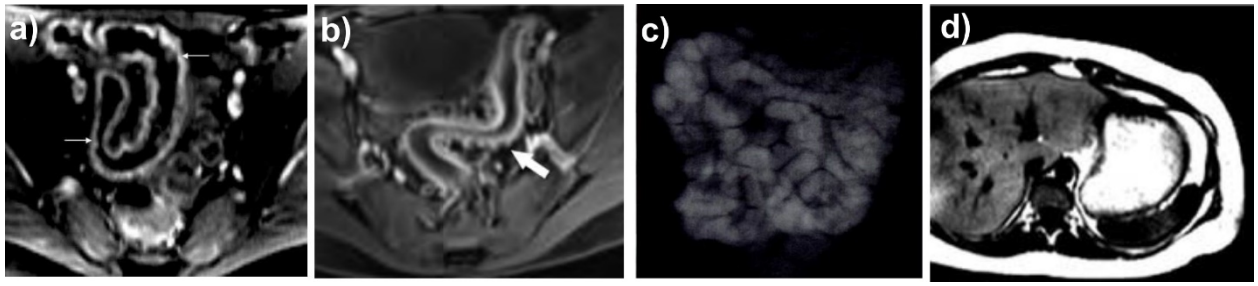


Figure 2: Magnetic resonance imaging using various contrast agents. a) The parietal enhancement of the distal ileal loop (arrows) was depicted with administration of gadolinium chelate intravenously.[32] **b)** MR Enterography examination with oral administration of barium sulfate displayed a smooth enhancement of the wall of loop of sigmoid (arrow).[99][106] **c)** Small-bowel loops and folds were clearly seen using water as a contrast agent.[107] **d)** Imaging of stomach after gavage of blackberry as a positive contrast agent as shown in the bright region.[92]

3.2.1 Gadolinium-based agents

Gadolinium-based contrast agents are likely the most commonly used compound for MRI contrast enhancement. They can be administered orally for GI tract scans or intravascularly for most other scans. There are many gadolinium-containing contrast agents are commercially available

including gadoterate, gadodiamide, gadobenate, gadoteirtol, gadofosveset, godopentetate, gadoversetamide, gadobutrol, gadoxetate. Also, there are many oral contrast agents that have been developed for GI imaging. For example, gado-based contrast agents were used for the diagnosis of patients with Crohn's disease (CD).[32] To diagnose inflammation of the distal ileum in children with CD and to differentiate them from other inflammatory intestinal diseases, gadolinium chelate was intravenously administered as a bolus with a dose of 0.1 mmol/kg body weight. Polyethylene glycol (PEG) solution (CE-PEG-MRI) was orally given for small bowel distention. Seventy-five children with suspected CD participated in this study. In all CD patients, an increased wall thickness and parietal contrast enhancement were observed. In addition, gadolinium enhanced MRI could also be used to differentiate active CD from ulcerative colitis (**Figure 2a**).

Similarly, cystic fibrosis (CF) could also be diagnosed by the same approach, CF is a disease that is associated with pancreatic enzymes. To evaluate the effect of pancreatic enzymes on CF, MR imaging was applied for monitoring the pathologic condition of CF in twenty-five patients.[108] In this study, Fe_3O_4 and Gadopentetate dimeglumine GD-DTPA (0.2 mmol/kg of body weight) were used as contrast agents. MRI findings showed that a wall thickening of the terminal ileum and ascending colon was found in twenty-two patients; Nine of them showed hyperintensity of bowel wall on T2-weighted sequences; Wall enhancement was observed in 13 patients after intravenous administration of gadolinium on T1-weighted fat-suppressed sequences. Then the therapeutic adjustment over 3 months was carried out and therapeutic adjustment with pathologic improvement could be seen clearly by MRI.

Sufficient distention of the intestine is important for the imaging of gut. In another gadolinium-based contrast agent example, a new distention agent was proposed.[109] A non-invasive distention method using ispaghula was used for MR imaging of intestine. For every dose, 5 mL

meglumine gadoterate (0.5mol/L) was mixed with ispaghula (0.2kg/kg of body weight). The mixture was orally administered four hours prior to MRI in ten volunteers. It was shown that the mixture can achieve excellent intestinal lumen distension, homogeneous distribution of contrast signal. And the intraluminal bowel content can be better differentiated from surrounding tissues with less artefacts.

3.2.2 Barium sulfate contrast agent

Barium sulfate is another important contrast agent for MR imaging of intestine.[88,89] Barium sulfate in high concentration acting as negative contrast agent can be used to decrease intraluminal signal intensity on T2-weighted MRI. The bowel wall is able to be detected by MRI using barium sulfate because of decreased signal intensity of the bowel lumen resulting in the enhancement of bowel wall thickness. As such, barium sulfate, as a negative contrast agent, can be used to visualize inflamed bowel wall and circumambient fat.[110] For assessing pediatric CD, Magnetic resonance enterography (MRE) is commonly used because of minimal radiation exposure and output excellent images.[106] Barium sulfate with sorbitol (0.1%) was employed as contrast agent that is administered orally in 119 children with CD on the MRE scans operated on a present-generation 3-Tesla MRI system. A bottle (450 cm^3) of the contrast mixture was administered 90 min prior to imaging and one more bottle was administered 30 min before imaging. Smooth wall enhancement of the sigmoid loop in patients with chronic CD was observed with barium sulfate orally administered as contrast agent (**Figure 2b**). Furthermore, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelets and albumin were described to evaluate the active inflammation and erythema. Friability were depicted to evaluate the mild mucosal diseases. The active inflammation of children with CD on MRE showed a higher CRP, ESR and platelets and a lower albumin, which is in agreement with the presence of ulcers on endoscopy, however, data of MRE displayed a poor agreement with mild mucosal, hence MRE with barium sulfate

enhancement is able to assess moderate to severe mucosal diseases as well as inflammation of small bowel and colon in CD.

Recently, a mixture of ferumoxsil and barium sulfate was used for fecal tagging in MR colonography. Using intravenous administration of that contrast mixture in T1-weighted MRI of colon could enhance fecal tagging, so that polyp can be clearly seen at the range of over 6 mm with high accuracy with respect to both sensitivity and specificity.[111] Another example was that for the comparison of MR colonoscope (MRC) comparing with conventional colonoscope (CC), 200 mL of a contrast mixture (barium sulfate/ferumoxsil) was selected as fecal tagging agent in MRC and was injected with four meals each day two days prior to MRC. Among all the patients, the discomfort rating of MRC is significantly lower than that of CC and the acceptance degree of experiment using contrast mixture for fecal tagging is higher than that of bowel purgation,[112] although an earlier it was found that barium sulfate/ferumoxsil could cause nausea, the discomfort degree is lower than barium sulfate alone, which may be ascribed to the thinner texture and better taste of ferumoxsil than barium sulfate.[113] Hence, MRC examination with ferumoxsil/barium sulfate for fecal tagging is preferred to CC.

3.2.3 Water as a contrast agent

External magnetic fields cause the hydrogen nuclei of water to become polarized, hence water can be used as contrast agent for intestinal MRI. MR imaging of the small bowel was reported to acquire information on bowel obstruction and other various pathologic conditions[114,115]. However, due to lack of a large quantity of intestine fluid, the small bowel lumen has not been well visualized. In such case, water can be used as a contrast agent to more clearly image the bowel lumen and bowel folds using a fast advanced spin echo sequence, a method similar as half-Fourier acquisition single-shot turbo spin echo (HASTE) (**Figure 2c**).[107] Water was also used as contrast

agent in the MRI evaluation of small bowel obstruction and extraluminal changes in Crohn's diseases.[90]

Although MRI has many excellent characteristics for gut imaging, slow acquisition speed makes imaging of dynamic processes challenging. As such, higher performance gradient subsystems could achieve sub-second imaging acquisition speeds to capture bowel peristalsis. Rapid acquisition with relaxation enhancement (RARE) based sequences could generate imaging based on the native contrast alone, termed MR hydrography.[116] For example, water contrast medium can solve the MRI limitation in assessing the luminal small bowel using rapidly heavily T2-weighted techniques. 1-2 L water was administered orally in eight volunteers and MRI images of the duodenum, jejunum and ileum were clearly depicted with apparent valvulae conniventes, providing valuable information to identify the strictures and intraluminal abnormalities of small bowel.[117] Also, mannitol and locust bean gum and a combination of these two could be used in combination with water for better imaging of the small bowel, since they can increase distension of the small bowel and decrease water reabsorption. Water contrast has minimal side effects, is inexpensive and enables accurate delineation of bowel loops.[118]

3.2.4 Others

Natural contrast agents can be present in the form of fruit juice, pulps or tea, which have been found to have minimal side effects but better palatability compared with artificial ones.[119] For example, Euterpe Oleracea (Acai) significantly enhanced the contrast of MRI in the GI.[92] Another fruit contrast example is blueberry juice, that can also enhance the contrast when the dosage is adequate, but the application of blueberry is limited due to the high cost and low availability.[91] Moreover, it was reported that blackberry has excellent performance in enhancing contrast efficacy in T1-weighted MRI of GI, because of the content of paramagnetic metal in blackberry. A significant positive contrast of stomach was clearly seen after injection of 200 g blended

blackberry as contrast agent (**Figure 2d**).[120] In addition, it was found that pineapple juice marked with gadolinium could suppress the signal intensity of stomach or duodenum.[121] A recent screen of 200 foodstuffs identified roasted barley as a promising photoacoustic contrast agent in mice and human.[122] Another imaging example is ^{19}F-magnetic resonance imaging that highly selective images of GI tract can be generated using perfluorononan on a mouse model. Each mouse was orally gavaged 0.3 mL of perfluorononane after fasting for 1h. Subsequently, ^{19}F resonator was used for MR imaging with prone position. Perfluorononane has been approved to be an ideal contrast agent with excellent properties such as biochemical inertness, immiscible characteristics with water, high content of fluorine, low viscosity and good surface tension. Especially the low viscosity and surface tension are significant for forming perfluorononane film covering the mucosa. In addition, perfluorononane administered in large quantity is found to be well tolerated and safe for the delineation the GI tract. Compared with ^{1}H-MRI, ^{19}F-MRI could better differentiate between contrast agents and proton voids and eliminate the deficiency of ^{1}H-MRI, displaying strong positive contrast effects with a high spatial resolution.[123,124]

4 Perspectives

Beyond MRI and CT, there are some emerging imaging methods that can achieve great imaging quality (e.g. fluorescence and photoacoustic imaging). For example, ICG was intravenously administered and secreted into bile from liver, therefore, it can be used as contrast agent to enable the fluorescence imaging of intestine. Using this approach, intestinal motility can be quantified by dynamic NIR fluorescence imaging.[95] In addition, red chlorophyll was also used to non-invasively and dynamically image the intestinal motion. Peristaltic and segmental motion could effectively observed in mice, providing a method to monitor motility disorders.[96] Recently, a novel low temperature surfactant stripping method was develop to generate the most absorbing materials as the first contrast agent for photoacoustic imaging of intestine (**Figure 3a**).[10] The contrast agent was termed nanonap or induced frozen micelles (infroms). Nanonap was made by

naphthalocyanines encapsulated in pluronic micelles. Because micellization process of pluronic is temperature sensitive, excess surfactant could be removed at low temperature after excess micelles turn into unimers. As a result, low temperature processing generates purified and concentrated nanonaps with tunable wavelengths (**Figure 3b**), which can provide ideal and strong contrast for photoacoustic imaging of intestine (**Figure 3c**). Moreover, ^{64}Cu can be chelated in the center of naphthalocyanines, nanonaps could be also used for contrast agent for positron emission tomography (PET) imaging (**Figure 3d**). Furthermore, using the low temperature processing method, pheophytin extracted from naturally existing dyes in green vegetables can also be encapsulated in pluronic micelles. Pheophytin informs, unlike the first generation of nanonap, can also be used as contrast agent for fluorescence imaging, besides photoacoustic imaging and PET (**Figure 3e-g**).[93] Therefore, informs represent a novel nanoplatform that can be used for the multimodal imaging of intestine.[10] Beyond that, other novel imaging strategies are also adding new possibilities to field of theranostics and molecular imaging.[125–130]

Generally, there are several considerations when choosing a contrast agent for intestinal imaging: 1 it should have superior GI physiological stability. Given the acidic condition in the stomach and enzymatic environment in intestine, an ideal contrast agent should maintain its physiological stability in the harsh condition with minimal systemic absorption. For example, perfluorooctyl bromide was the first oral contrast agents approved by FDA that can rapidly move through the GI tract without systemic absorption[131]; 2 It should have high safety profile. For example, introduction of heavy metals into body can cause safety concerns, despite the proven track record of barium for gut imaging. It has been shown that oral administration of silver nanoparticles leads to significant accumulation of silver in the liver and kidney.[132] Some contrast agents are found to be associated with adverse effects such as nausea, vomit, diarrhea or dysentery, which should be avoided;[133] 3 It should provide good contrast with high sensitivity and specificity. For example, MRI contrast agents should either greatly enhance the bright areas by shortening the T1

relaxation time or obtain darken areas by shortening of T2 relaxation time. [97] Also, for better enhancement, intravenous agents were also used to improve the sensitivity in the double contrast method. 4 Other considerations include wide availability, easy preparation procedure, low cost. Also the contrast agent itself should not stimulate peristalsis or be associated with artifacts. Ideally it should evenly distribute in GI.[119] Compared to other administration routes, ingestible contrast agents have better patient compliance, however, there are also many challenges and limitations when designing ingestible contrast agents. Besides GI physiological stability, safety is another issue when using ingestible contrast agent. For example, some adversely side effects such as nausea, vomiting, diarrhea and hypersensitivity reaction might be induced. [134] Also, after administration of Gadopentate dimeglumine or Gadodiamide, the accumulation of gadolinium was observed in cerebral tissues. [135]

The GI tract represents one of the biggest and most complicated organ, and is associated with numerous diseases. CT and MRI are the most common imaging modalities and there are many potential future directions for the diagnosis of the GI diseases such as precisely targeting diseased sites, designing smart contrast agents and multimodal imaging methods. For example, gadolinium-acid was loaded in chitosan nanoparticles that can be used for targeted detection of colon mucosa diseases by MRI.[136] Electrospun core-shell fibers was also designed for sustained release of contrast agent and for the detection of colonic abnormities.[137] Some emerging magnetic nanoparticles such as superparamagnetic nanoparticles enabled multiple imaging modalities including optical coherence tomography, photoacoustic and ultrasound. [138] Therefore, smart contrast agents for targeting multimodal imaging show promise for the diagnosis of GI diseases more accurately and comprehensively.

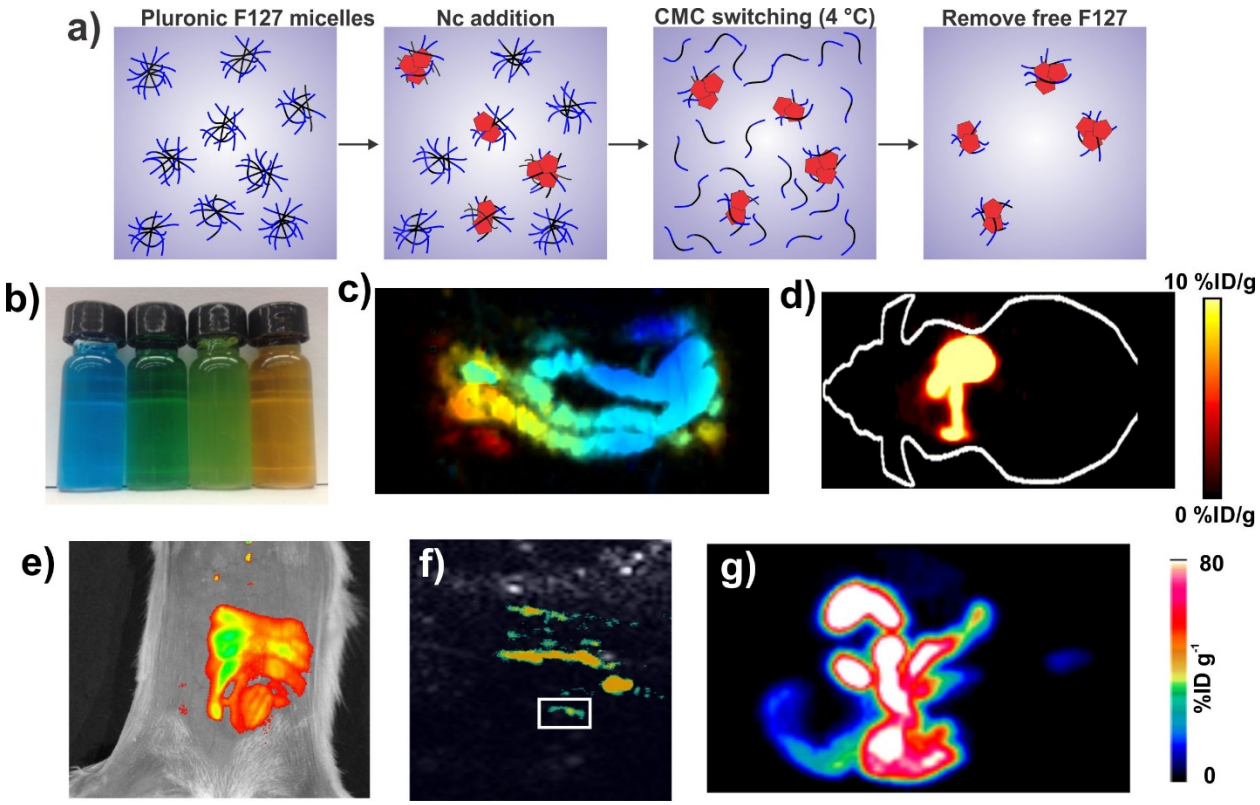


Figure 3: Emerging contrast agent, induced frozen micelles (termed infroms or nanonaps) used as contrast agent for gut imaging.[10,93] **a)** Schematic illustration of formation of infroms by nanoprecipitation and low-temperature CMC switching process; **b)** Digital photo of nanonaps with various wavelengths; **c)** Depth-encoded, 3-D photoacoustic images of intestine; **d)** PET imaging of intestine using nanonaps as contrast agent; **e)** Fluorescence imaging of intestine using pheophytin infroms as contrast agent; **f)** Photoacoustic imaging of intestine using pheophytin infroms as contrast agent; **g)** PET imaging of intestine using pheophytin infroms as contrast agent.

5 Conclusion

Biomedical imaging for the evaluation of GI tract diseases remains an important clinical diagnostic service and has attracted much attention past decades. MRI contrast agents have gained focus since there is no ionization radiation involved. CT and CT colonography with barium remains a standard approach. Future research should be focused on improving the imaging capabilities and targeting efficacy for improved imaging results. More efforts have been directed towards the development of universal contrast agents which can be used for multiple imaging techniques. Also, clinical translation of the contrast agents developed in the laboratory are strongly

encouraged since most of the contrast agents never get translated from bench to clinic. There might be several reasons for this including but not limited to toxicity, complex design and cost effectiveness. Incorporating multiple ligands for multimodal imaging could be a new direction for exploration.

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