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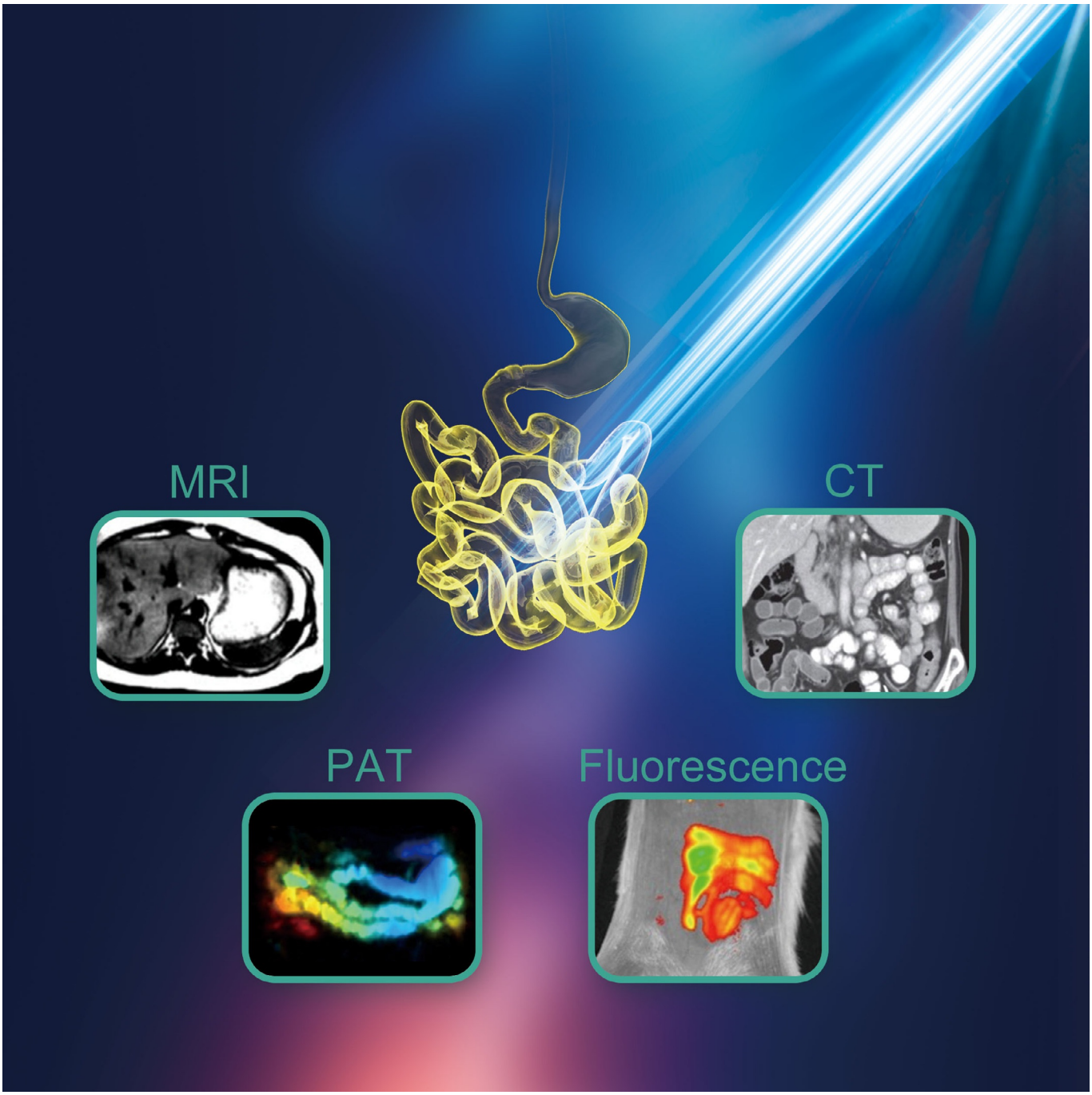
SPECIAL ISSUE

Ingestible Contrast Agents for Gastrointestinal Imaging

Xingyue Yang,[a] Jonathan F. Lovell,*[b] and Yumiao Zhang*[a]



Gastrointestinal (GI) ailments cover a wide variety of diseases involving the esophagus, stomach, small intestine, large intestine, and 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 management. Contrast agents for GI imaging can enhance contrast to distinguish abnormal lesions from normal structures. Computed tomography and magnetic resonance imaging 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, such as barium sulfate, iodine-based agents, gadolinium-based agents, and others, are summarized. Going forward, continued endeavors are being made to develop more emerging contrast agents for other imaging modalities.

1. Introduction

Gastrointestinal (GI) tract diseases are an extremely diverse group of conditions. For example, Crohn's disease and ulcerative colitis affect 1.2 million Americans with growing incidence.[1,2] In the past, endoscopy and fluoroscopy were frontline 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 suboptimal, 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 multimodal 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. Esophageal diseases include gastroesophageal reflux diseases, esophagitis, 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. Some common intestinal diseases are summarized briefly in Figure 1.

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 has been found that NOD2, or designated CARD15 and IBD1, are susceptibility genes. Since then, a number of other loci have been found to be implicated in IBD, such as IBD5, IL23R, and ATG16.[45–47] In addition, IBD is also associated with enteric flora, and it has been found that "healthy" bacteria or probiotic combinations can improve the conditions of IBD.[48,49]

2.2. Intestinal tumors

Cancers impact the GI tract, including the esophagus, the stomach, and the colorectal region. Small intestine malignant tumors mainly include adenocarcinoma, neuroendocrine tumors, sarcomas, and lymphomas. Adenocarcinoma of the small intestine, accounting for 40% of all the malignant small bowel cancers, mostly stems from the duodenum, jejunum, and ileum. Lymphomas can be classified into three types, im-

[a] X. Yang, Prof. Y. Zhang
School of Chemical Engineering and Technology, Tianjin University
Tianjin 301636 (China)

[b] Prof. J. F. Lovell
Department of Biomedical Engineering
State University of New York at Buffalo
Buffalo, NY 14260 (USA)
E-mail: jflovell@buffalo.edu
yumiaozh@buffalo.edu

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munoproliferative small intestinal disease (IPSID) lymphoma, enteropathy-associated T cell (EATL) lymphoma, and other western-type non-IPSID lymphomas. In addition, celiac disease can contribute to EATL lymphoma, which may be derived from a chronic mucosal inflammatory response induced by exposure to gliadin.[50] Carcinoid tumors can be caused by serotonin and can be further transformed into malignant tumors. The factors below are responsible for 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 the 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 can also induce diarrhea, such as changes in intestinal immune activation, alteration in intestinal permeability, adverse effects of medication, and gut microbiome such as bacterial, fungi, archaea, viruses, and eukaryotes. Bacterial infection, such as, *Campylobacter*, *Shigella* non-typhoidal-*Salmonella*, six subtypes of *Escherichia coli*, and *Clostridium perfringens*, can cause diarrhea symptoms. Rotavirus can cause severe diarrhea in infants and children. However, children with rotavirus infection can be treated with vaccinations.[53] Recently, many studies involving diarrhea treatment have been undertaken. For example, prebiotics can be used to inhibit the growth of potentially harmful bacteria and to increase the growth of bifidobacteria. Probiotics are able to reduce visceral hypersensitivity and to improve psychological symptoms. Furthermore, open-label rifaximin, an antibiotic, significantly helps to improve the symptoms of IBS-D with excellent safety and tolerability.[54] In addition, alosetron treatment is a therapy method for the treatment of severe IBS-D for women.

Xingyue Yang is a Ph.D. student at Tianjin University. She obtained her undergraduate degree from Hebei Normal University of Science and Technology in 2014 and completed her Master's degree at Tianjin University of Science and Technology in 2018.

Jonathan F. Lovell is an Associate Professor of Biomedical Engineering at the State University of New York at Buffalo. He completed his Ph.D. degree at the University of Toronto in Biomedical Engineering. His research interests include developing new imaging contrast agents.

Yumiao Zhang is a professor of Chemical Engineering and Technology at Tianjin University. He completed his Ph.D. degree at the State University of New York at Buffalo. His research interests include molecular imaging and drug delivery.

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 the 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 can be treated with dietary fiber. Alternatively, osmotic laxatives should be used if the response of constipation to fiber therapy is ineffective. In cases of severe constipation for which both fiber and osmotic laxative fail, bisacodyl or senna derivatives and prokinetic medications (e.g., tegaserod or a partial 5-hydroxytryptamine 4-receptor agonist) can be used.[58] Defecatory disorders mostly arise from dysfunction of the pelvic floor or anal sphincter. Defecatory disorders are associated with the transit of large, hard stool, anal fissures or hemorrhoids. 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, which can result in the delay of colonic transit and reduction in intestinal motility and absorption, eventually resulting in constipation. Also, for chronic idiopathic constipation, the relatively unbalanced expression of cyclic guanosine monophosphate (cGMP) signaling components can potentially cause constipation; moreover, overexpression of PDE5 can also cause refractory constipation; it cannot be treated with linaclotide or plecanatide, but PDE5 inhibitors can provide treatment for this type of constipation.[59]

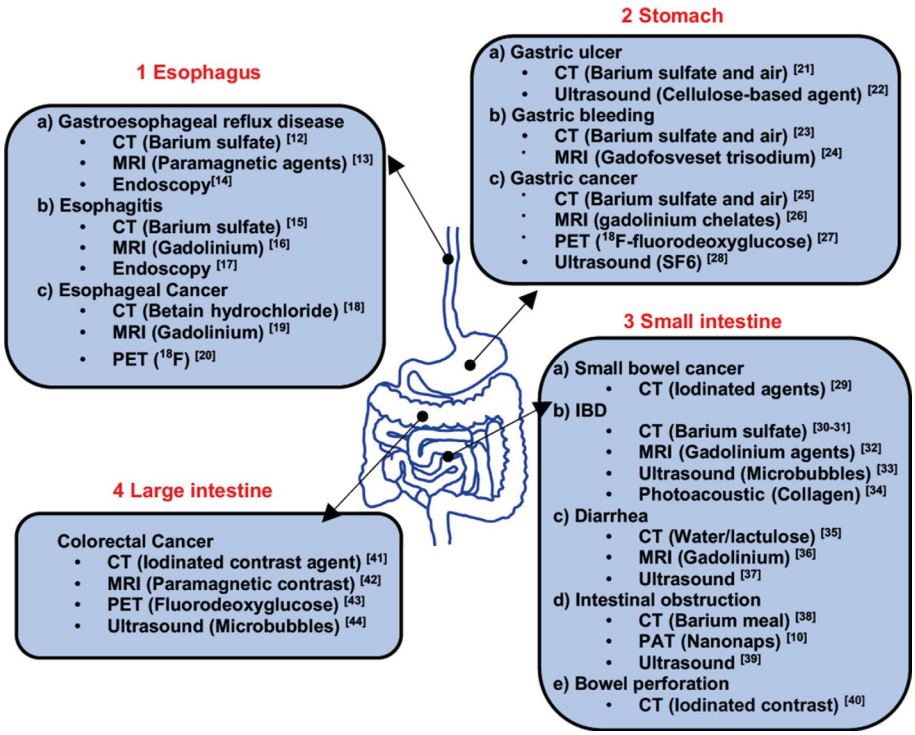

Figure 1. Examples of different imaging modalities for the diagnosis of various GI ailments.

2.5. Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a digestive disorder that causes the 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 (TLESR) is the most common cause, because if the tone of the LES is inhibited, particularly in the postprandial phase, the occurrence of TLESR becomes more frequent, leading to acid reflux. In addition, other factors can also give rise to GERD, such as a reduction in LES pressure, delayed gastric emptying, hiatal hernias, and impaired esophageal clearance.[62,63] The most common symptom of GERD is heartburn, but 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, and it may progress to esophageal adenocarcinoma. Therefore, early detection and timely measurement are important to prevent malignant transformation.[64]

3. Contrast Agents for CT

Computed tomography (CT) or X-ray imaging is used as a standard GI imaging method in many instances. Radiocontrast agents are employed to absorb external X-rays to decrease exposure on the detector, providing contrast for imaging. Typical radiocontrast agents include iodine, barium sulfate, and gadolinium-based compounds. Computed tomography colonography, traditional double-contrast barium enema (DCBE), and colonoscopy are common approaches used to examine colons. Below, some barium-based imaging methods, DCBE, CT colonography, and other imaging methods are briefly summarized.

3.1. Barium-based contrast agents

For imaging of the intestine, one of the imaging approaches is small bowel follow through (SBFT), which uses fluoroscopy and barium- or iodine-based contrast agents to provide non-invasive imaging of bowel diseases, bowel obstruction, polyps, cancers, neoplasm, blood in the stool, and others. Once the contrast agent moves from the stomach into the intestine, X-ray imaging can be used to determine abnormalities. Historically, SBFT has been used as a standard radiologic approach to evaluate active Crohn's disease.[30,31] However, some studies also show 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] However, both methods can only provide indirect and limited information with respect to the state of the bowel; in addition, the effectiveness of these two methods is limited by overlapping bowel loops.[73–75]

A barium swallow test, also known as an 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, and gastric

volvulus. Barium sulfate is commonly used as a contrast agent, as it has higher sensitivity than water-soluble contrast agents such as Gastrografin/diatrizoate. For patients with suspected gastroesophageal reflux disease (GERD), barium esophagram examination is an essential part of the patients' workup process. On the basis of the various symptoms and conditions of a GERD patient, different densities or forms of barium can be selected. A full esophagram 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 can serve as the main means for dysphagia diagnosis, resulting from the dysmotility disorder of GERD. For severe dysphagia, barium swallow must be administered while the patient remains in an upright position, and a total of 250 mL of a low-density barium should be ingested over 45 s before a spot film is taken. If high-density barium cannot coat the esophagus of the patient adequately, fold thickening of the esophagus should be identified to diagnose 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 ingestion is another part before the diagnosis. Administration of a 13 mm barium tablet with water can be used to ensure proper tablet passage. Once tablet passage is impaired, the patient should ingest low-density barium to detect the precise site and cause.[76]

The barium meal is used to image the stomach and small intestine, and it is often performed right after a barium swallow examination. For example, a barium meal can be used to examine the duodenum–biliary reflux (DBR) condition of patients with recurrent common bile duct stones (CBDSs). Prior to investigation, the patient must fast for 6 to 8 h, then receive 3 g aerogenic agent, and subsequently swallow 100 mL sulfate barium. Once the barium meals moves, DBR can be observed in the supine position through fluoroscopy.[77] Another example is the barium suspension method, which involves the use of a 50 mL 200% (*w*/*v*) barium meal to determine the colonic transit time (CTT) for patients with slow-transit constipation (STC). In general, the most popular method for STC measurement is radiopaque markers, and the evaluation of the 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 the location on the transit X-rays through the barium suspension method are clearly visible (Figure 2A). More importantly, the barium suspension method is simple and economical; the barium sulfate contrast agent is easy to acquire, and no other special drugs or equipment is needed.[65] Although bowel obstruction is 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. In the barium meal method, the transit time to the position of the obstruction is rapid; this allows the obstruction to be rapidly and clearly detected and also avoids the problems associated with using roentgenograms alone.[38]

3.2. Double-contrast methods

Double-contrast barium enema is often applied to CT imaging of the colon, and the gas administered orally can help to distend the bowel, which enhances the contrast and allows for better differentiation of 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 enhance the imaging further 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 imaging of the colon and rectum, and it involves the use of two contrast agents to visualize the intestinal structure more easily. DCBM can be used to acquire CT imaging of gastro tumors. An effervescent powder is orally administered to distend the gastro tissue adequately, and butyl scopolamine is intramuscularly injected 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 can be identified. Radiological features can also be clearly seen, including blood clots located in ulcers, arteries in the base of ulcers, and active bleeding during the course of examination.[23] In addition, DCBM can also be used to evaluate gastric tumors, as shown in Figure 2B; here, a double-contrast barium meal has been used to image a submucosal tumor with mucosa coating in a 59-year-old woman with gastrointestinal stromal tumors.[25] Similarly, gadolinium chelate substances have also been intravenously administered to enhance the sensitivity of MRI imaging in the GI tract. This type of double-contrast method has the most benefits for the diagnosis of inflammatory processes of the bowel.[79]

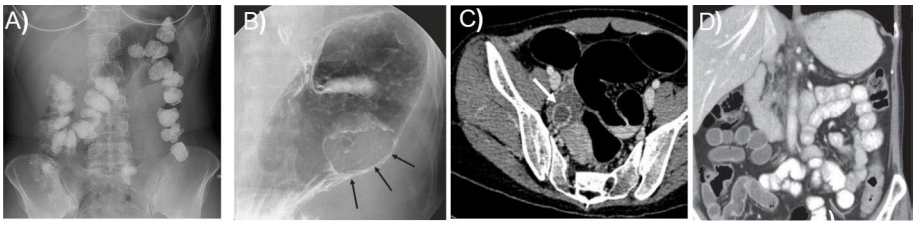

Figure 2. Computed tomography imaging of the GI tract by using different contrast agents. A) Colon visualization following a barium meal.[65] B) A submucosal tumor (arrows) detected by double-contrast barium meal.[25] C) CT colonography following intravenous administration of iohexol provides clear imaging of a corpus luteum cyst.[66] D) Duodenal distension imaged by an iodinated contrast agent, as shown by the bright regions.[67]

3.3. Computed tomographic colonography (CTC)

Computed tomographic colonography (CTC), or colonoscopy, is an emerging radiological technique for imaging of the intestine, mostly the large bowel. It is recommended as a screening test[80,81] and is used for the investigation of patients suspected to have 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 2D and 3D images of the colon and rectum. It can be used to evaluate polyps, diverticulosis, and cancers. During imaging, a small tube for inflation with gas (e.g., carbon dioxide) is inserted into the rectum. an intravenous contrast agent can be used for enhancement to distinguish better between the stool and submerged polyps, as well as flat or accessible polyps that are easily overlooked. For example, to determine if intravenous contrast is necessary for detection of extracolonic findings, iohexol (Omnipaque 350) can be used as an intravenous contrast agent for patients undergoing CTC. Notably, with iohexol intravenously administered, additional extracolonic findings (extracolon cysts) can be found (Figure 2C), even though no increase in the number of patients with significant lesions is observed.[66]

3.4. Iodine as a contrast agent for CT

Bowel cleansing and distention are important for intestinal imaging techniques such as computed tomographic colonography. Fecal tagging by orally administered contrast agents can be used to differentiate fecal material from polyps. Iodinated contrast agents can be used as tagging agents for residual feces in the bowel, and these contrast agents can be classified into nonionic iodinated contrast agents and ionic iodinated contrast agents. Both nonionic and ionic iodinated contrast agents generally have better performance than barium-based contrast agents in terms of the tagging homogeneity of fecal material and the attenuation detection values.[84] Nonionic iodinated contrast agents can be used safely in patients whose gastrointestinal tracts are perforated because of their rapid absorption process.[40] The outstanding features include low risk of dehydration, diarrhea, and good patient compliance. On the other hand, nonionic iodinated contrast agents are more expensive than barium and ionic iodinated contrast agents. Compared to other contrast agents, iodine-based contrast agents are well tolerated and can achieve satisfactory bowel distention and fold visibility (Figure 2D).[67] Aside from their high safety and water solubility, which are similar to those of nonionic contrast agents, the tagging performance of ionic iodinated contrast agents for the bowel is superior to that of nonionic iodinated contrast agents. However, high concentrations of ionic iodinated contrast agents can cause gastrointestinal discomfort, such as nausea, vomiting, cramps, diarrhea, and poor taste; hence, it is recommended to use only small quantities of ionic iodinated contrast agents in fecal tagging for CT of the bowel.[85]

4. 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 the GI tract can enhance the contrast of the bowel and pancreas and, especially, the bowel wall. An ideal intraluminal contrast agent for GI imaging needs to meet the following criteria: 1) it should have good patient compliance; for example, it needs to be palatable, needs to be easy to administer, and needs not stimulate peristalsis; 2) the contrast agent must not be absorbable systematically or diffuse into the adjacent tissues or organs, and ideally, it should be able to be excreted from the GI tract in a timely manner; 3) the enhancement characteristics of the agent need to be unchanged, and homogenous marking of the GI tract during passage is preferred; 4) high sensitivity, high specificity, a safety profile, and low cost are desired.[97] In general, intraluminal MRI contrast agents for gastrointestinal imaging can be classified into positive contrast agents and negative contrast agents.[98,99] Positive contrast agents contribute to the signal for the bowel lumen, whereas negative contrast agents reduce the signal associated with the 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] and barium sulfate.[88] To obtain optimal MRI, intraluminal contrast agents should display high T_1-weighted signal intensity and low T_2-weighted signal intensity. Also, biphasic agents can show positive and negative effects for signal intensity; some representative biphasic agents include clay suspensions, paramagnetic chelates, and manganese chloride. Some foodstuff agents have also been used as intraluminal imaging agents because of their advantages, which include low cost, miscibility, and positive enhancement effects in both the T_1- and T_2-weighted images. In addition, some natural products such as green tea and blueberries may be used for enhancement of the GI tract, because they contain high concentrations of manganese.[91,105] In addition, miscible agents or immiscible agents are used to mix or replace the bowel contents. Some representative examples are noted below and in Table 1.

4.1. Gadolinium-based agents

Gadolinium-based contrast agents are likely the most commonly used compounds for MRI contrast enhancement. They can be administered orally for GI tract scans or intravascularly for most other scans. Many gadolinium-containing contrast agents are commercially available, including gadoterate, gadodiamide, gadobenate, gadoteirtol, gadofosveset, godopentetate, gadoversetamide, gadobutrol, and gadoxetate. Also, there are many oral contrast agents that have been developed for GI imaging. For example, gado-based contrast agents have been 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, a gadolinium chelate was intravenously adminis-

Table 1. 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	exposure to radiation
MRI	gadolinium agents,[32] barium sulfate,[88,89] water,[90] natural contrast agents[91,92]	minimal radiation noninvasive, high resolution	time consuming
PET	^{18}F,[27,43] ^{64}Cu[10,93]	high sensitivity, high specificity, high resolution	high cost
ultrasound	microbubbles[94]	noninvasive, low cost, high safety profile	poor sensitivity
fluorescence	ICG,[95] red chlorophyll,[96] pheophytin[93]	high sensitivity, easy operation	susceptible to interference, very poor penetration depth
photoacoustic	naphthalocyanines,[10] pheophytin[93]	noninvasive, high resolution	restricted penetration depth

tered as a bolus with a dose of 0.1 mmol per kg body weight. In that study, poly(ethylene glycol) (PEG) solution (CE-PEG-MRI) was orally given for small bowel distention; 75 children with suspected CD participated in the study. In all CD patients, increased wall thickness and parietal contrast enhancement were observed. In addition, gadolinium-enhanced MRI can also be used to differentiate active CD from ulcerative colitis (Figure 3 A).

Similarly, cystic fibrosis (CF) can 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, MRI was applied to monitor the pathologic condition of CF in 25 patients.[108] In this study, Fe_3O_4 and gadopentetate dimeglumine (GD-DTPA, 0.2 mmol per kg body weight) were used as contrast agents. MRI findings showed that wall thickening of the terminal ileum and ascending colon was found in 22 patients; nine of them showed hyperintensity of the bowel wall on T_2-weighted sequences. Furthermore, wall enhancement was observed in 13 patients after intravenous administration of gadolinium on T_1-weighted fat-suppressed sequences. Then, a therapeutic adjustment over 3 months was carried out, and therapeutic adjustment with pathologic improvement was clearly seen by MRI.

Sufficient distention of the intestine is important for imaging of the gut. In another gadolinium-based contrast agent example, a new distention agent was proposed.[109] A noninvasive distention method involving ispaghula was used for MRI of the intestine. For every dose, 5 mL meglumine gadoterate (0.5 mol L^{-1}) was mixed with ispaghula (0.2 g per kg of body weight). The mixture was orally administered 4 h prior to MRI in ten volunteers. It was shown that the mixture achieved excellent intestinal lumen distension and homogeneous distribution of contrast signal. Furthermore, the intraluminal bowel content was better differentiated from surrounding tissues with fewer artifacts.

4.2. Barium sulfate contrast agent

Barium sulfate is another important contrast agent for MRI of the intestine.[88,89] Barium sulfate in high concentrations and acting as a negative contrast agent can be used to decrease intraluminal signal intensity in T_2-weighted MRI. The bowel wall is able to be detected by MRI by using barium sulfate because of decreased signal intensity of the bowel lumen, which results in an enhancement in bowel wall thickness. As such, barium sulfate, as a negative contrast agent, can be used to visualize inflamed bowel wall and circumambient fat.[110] To assess pediatric CD, magnetic resonance enterography (MRE) is commonly used because of minimal exposure to radiation and the output of excellent images.[106] In one study, barium sulfate with sorbitol (0.1 %) was employed as a contrast agent and was administered orally in 119 children with CD on the MRE scans operated on a present-generation 3 T 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 a contrast agent (Figure 3 B). Furthermore, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelets, and albumin were described to evaluate the active inflammation and erythema. Friability was depicted to evaluate the mild mucosal diseases. The active inflammation of children with CD on MRE showed higher CRP, ESR, and platelets and lower albumin, and all of these were in agreement with the presence of ulcers on endoscopy; however, the MRE data displayed poor agreement

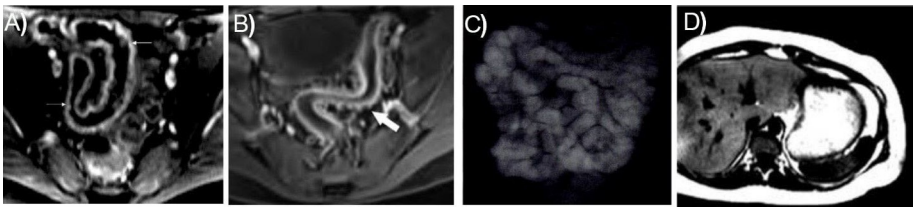

Figure 3. Magnetic resonance imaging by using various contrast agents. A) The parietal enhancement of the distal ileal loop (arrows) is depicted with administration of gadolinium chelate intravenously.[32] B) MR enterography examination with oral administration of barium sulfate displays a smooth enhancement of the wall of the loop of sigmoid (arrow).[99,106] C) Small bowel loops and folds are clearly seen by 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]

with mild mucosal. Hence, MRE with barium sulfate enhancement is able to assess moderate to severe mucosal diseases as well as inflammation of the small bowel and colon in CD patients.

Recently, a mixture of ferumoxsil and barium sulfate was used for fecal tagging in magnetic resonance colonography. The use of intravenous administration of the contrast mixture in the T_1-weighted MRI of the colon enhanced fecal tagging, so that polyps could be clearly seen at a range of over 6 mm with high accuracy with respect to both sensitivity and specificity.[111] Another example involved a comparison of magnetic resonance colonoscopy (MRC) with conventional colonoscopy (CC); here, 200 mL of a contrast mixture (barium sulfate/ferumoxsil) was selected as the fecal tagging agent in MRC and was injected with four meals each day, 2 days prior to MRC. Among all the patients examined, the discomfort rating of MRC was significantly lower than that of CC and the acceptance degree of the experiment by using the contrast mixture for fecal tagging was higher than that for bowel purgation.[112] Although it was earlier found that barium sulfate/ferumoxsil could cause nausea, the degree of discomfort was lower than that for barium sulfate alone, which may be ascribed to the facts that ferumoxsil has a thinner texture and a better taste than barium sulfate.[113] Hence, MRC examination with ferumoxsil/barium sulfate for fecal tagging is preferred over CC.

4.3. Water as a contrast agent

External magnetic fields cause the hydrogen nuclei of water to become polarized; hence, water can be used as a contrast agent for intestinal MRI. MRI of the small bowel to acquire information on bowel obstruction and other various pathologic conditions has been reported.[114,115] However, owing to a lack of a large quantity of intestine fluid, the small bowel lumen cannot be well visualized. In such a case, water can be used as a contrast agent to image the bowel lumen and bowel folds more clearly by using a fast advanced spin echo sequence, a method similar to half-Fourier acquisition single-shot turbo spin echo (HASTE; Figure 3C).[107] Water has also been used as a contrast agent in the MRI evaluation of small bowel obstruction and extraluminal changes in Crohn's disease patients.[90]

Although MRI has many excellent characteristics for gut imaging, its slow acquisition speed makes imaging of dynamic processes challenging. As such, higher performance gradient subsystems can achieve subsecond imaging acquisition speeds to capture bowel peristalsis. Rapid acquisition with relaxation enhancement (RARE)-based sequences can generate imaging on the basis of the native contrast alone, termed magnetic resonance hydrography.[116] For example, a water contrast medium can solve the limitation of MRI in assessing the luminal small bowel by using rapid and heavily T_2-weighted techniques. In one study, 1–2 L water was administered orally in eight volunteers, and images of the duodenum, jejunum, and ileum were clearly depicted with apparent valvulae conniventes, which provided valuable information to identify the strictures and intraluminal abnormalities of the small bowel.[117] Also, mannitol and locust bean gum and a combination of these two can be used in combination with water for better imaging of the small bowel, as 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]

4.4. Others

Natural contrast agents can be present in the form of fruit juice, pulps, or tea, and they have all been found to have minimal side effects but better palatability than artificial contrast agents.[119] For example, *Euterpe oleracea* (Acai) significantly enhances the contrast of MRI in the GI tract.[92] Another fruit contrast example is blueberry juice, which also enhances contrast if the dosage is adequate, but the application of blueberry juice is limited owing to its high cost and low availability.[91] Moreover, it has been reported that blackberries show excellent performance in enhancing the contrast efficacy in T_1-weighted MRI of the GI tract, because of the content of paramagnetic metals in blackberries. A significant positive contrast of the stomach is clearly seen after injection of 200 g blended blackberries as a contrast agent (Figure 3D).[120] In addition, pineapple juice marked with gadolinium suppresses the signal intensity of the stomach or duodenum.[121] A recent screen of 200 foodstuffs identified roasted barley as a promising photoacoustic contrast agent in mice and humans.[122] Another imaging example is ^{19}F magnetic resonance imaging, and highly selective images of the GI tract can be generated by using perfluorononane on a mouse model. In the study, each mouse was orally gavaged 0.3 mL of perfluorononane after fasting for 1 h. Subsequently, a ^{19}F resonator was used for MRI with prone position. Perfluorononane has been approved as 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. Specifically, its low viscosity and surface tension are significant in the formation of a film that covers the mucosa. In addition, perfluorononane administered in large quantities is well tolerated and safe for delineation of the GI tract. Compared with ^{1}H MRI, ^{19}F MRI better differentiates between contrast agents and proton voids and eliminates the deficiency of ^{1}H MRI by displaying strong positive contrast effects with high spatial resolution.[123,124]

5. 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, intravenous administration of Indocyanine Green (ICG) results in its secretion into bile from the liver; therefore, it can be used as a contrast agent to enable fluorescence imaging of the intestine. Using this approach, intestinal motility can be quantified by dynamic near-IR fluorescence imaging.[95] In addition, red chlorophyll has been used for the noninvasive and dynamic imaging of intestinal motion. Peristaltic and segmental motions are effectively observed in mice, providing a method to monitor motility disorders.[96] Recently, a novel low-temperature surfactant

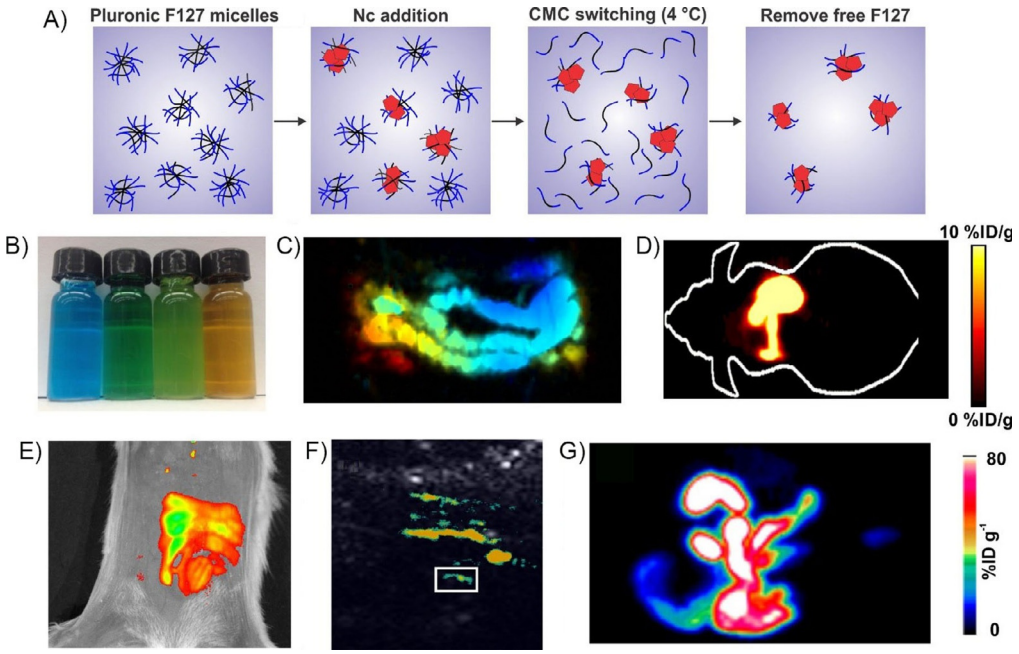

Figure 4. Emerging contrast agent-induced frozen micelles (termed InFroMs or nanonaps) used as a contrast agent for gut imaging.[10,93] A) Schematic illustration of the formation of InFroMs by nanoprecipitation and low-temperature CMC switching process. B) Digital photo of nanonaps with various wavelengths. C) Depth-encoded, 3D photoacoustic images of intestine. D) PET imaging of intestine by using nanonaps as a contrast agent. E) Fluorescence imaging of the intestine by using pheophytin InFroMs as a contrast agent. F) Photoacoustic imaging of the intestine by using pheophytin InFroMs as the contrast agent. G) PET imaging of intestine by using pheophytin InFroMs as contrast agent.

stripping method was developed to generate highly absorbing materials as the first contrast agents for the photoacoustic imaging of the intestine (Figure 4A).[10] The contrast agent is called a nanonap or induced frozen micelles (InFroMs). Nanonap is made from naphthalocyanines encapsulated in pluronic micelles. Because the micellization process of pluronic micelles is temperature sensitive, the excess amount of surfactant can be removed at a low temperature after the excess micelles are turned into unimers. As a result, low-temperature processing generates purified and concentrated nanonaps with tunable wavelengths (Figure 4B), which can provide ideal and strong contrast for photoacoustic imaging of the intestine (Figure 4C). Moreover, ^{64}Cu can be chelated in the center of naphthalocyanines, and nanonaps can also be used as a contrast agent for positron emission tomography (PET) imaging (Figure 4D). Furthermore, by using the low-temperature processing method, pheophytin extracted from the naturally existing dyes in green vegetables can also be encapsulated in pluronic micelles. Pheophytin InFroMs, unlike first-generation nanonap, can also be used as a contrast agent for fluorescence imaging, in addition to photoacoustic imaging and PET (Figure 4E–G).[93] Therefore, InFroMs represent a novel nanoplatform that can be used for multimodal imaging of the intestine.[10] Beyond that, other novel imaging strategies are adding new possibilities to the field of theranostics and molecular imaging.[12–130]

Generally, there are several considerations to be taken into account upon choosing a contrast agent for intestinal imaging. First, it should have superior GI physiological stability. Given the acidic conditions in the stomach and the enzymatic environment of the intestine, an ideal contrast agent should maintain its physiological stability under harsh conditions with minimal systemic absorption. For example, perfluorooctyl bromide was one of the first oral contrast agents approved by the FDA that could rapidly move through the GI tract without systemic absorption.[131] Second, it should have a high safety profile. For example, the introduction of heavy metals into the 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 associated with adverse effects such as nausea, vomiting, diarrhea, and dysentery, which should be avoided.[133] Third, 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 T_1 relaxation time or provide darkened areas by shortening the T_2 relaxation time.[97] Also, for better enhancement, intravenous agents can also be used to improve the sensitivity in the double-contrast method. Fourth, other considerations include wide availability, easy preparation procedure, and low cost. Also, the contrast agent itself should not stimulate peristalsis or be associated with artifacts. Ideally, it should evenly distribute in the GI tract.[119] Compared to other administration routes, ingestible contrast agents have better patient compliance; however, there are also many challenges and limitations upon designing ingestible contrast agents. Besides GI physiological stability, safety is another issue upon using an ingestible contrast agent. For example, some adverse side effects, such as nausea, vomiting, diarrhea, and hypersensitivity reaction, might be induced.[134] Also, after administration of gadopentate dimeglu-

mine or gadodiamide, the accumulation of gadolinium has been observed in cerebral tissues.[135]

The GI tract represents one of the biggest and most complicated organs, and it 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 GI diseases, such as precisely targeting diseased sites, designing smart contrast agents, and multimodal imaging methods. For example, gadolinium acid can be loaded in chitosan nanoparticles and used to target detection of colon mucosa diseases by MRI.[136] Electrospun core–shell fibers have also been designed for sustained release of contrast agents and for the detection of colonic abnormities.[137] Some emerging magnetic nanoparticles such as superparamagnetic nanoparticles enable multiple imaging modalities, including optical coherence tomography, photoacoustic, and ultrasound.[138] Therefore, smart contrast agents for targeting multimodal imaging show promise for the more accurate and comprehensive diagnosis of GI diseases.

6. Conclusion

Biomedical imaging for the evaluation of GI tract diseases remains an important clinical diagnostic service and has attracted much attention over the past decades. MRI contrast agents have gained focus, as there is no ionization radiation involved. CT and CT colonography with barium remain standard approaches. 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 that can be used for multiple imaging techniques. Also, clinical translation of the contrast agents developed in the laboratory are strongly encouraged, as 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.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: bioimaging · contrast agents · imaging techniques · gadolinium · gastrointestinal diseases

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