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## Minimally-invasive imaging of the small intestine

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# Chapter 1

General introduction  
and outline of this thesis



The small intestine is one of the most enigmatic organs of the human body. This is in part explained by the fact that the small intestine for long was not accessible for endoscopy, and clinicians often needed to rely on conventional radiologic studies, when making decisions.

It was an interesting coincidence that technical developments in the fields of both endoscopy and radiology almost simultaneously led to techniques that could be used to investigate the small intestine. In endoscopy, the first reliable method for so-called deep flexible enteroscopy, double-balloon endoscopy (DBE), was developed around the same time a method was invented to investigate the small bowel by means of an ingestible capsule, provided with a camera able to transmit images to the outside world – video capsule endoscopy (VCE).<sup>1,2</sup>

In radiology, high-quality magnetic resonance (MR) imaging of the small intestine was for long considered impossible, because of long acquisition times and therefore artefacts associated with respiratory and peristaltic movements. The development of rapid imaging techniques and the possibility to perform sequences in one breath-hold opened the way to small-bowel imaging with MR, with the first papers appearing around the end of the millennium.<sup>3-5</sup>

Soon, these new kids on the block gave rise to a renewed interest in the small intestine. However, flexible deep enteroscopy proved to be invasive, costly and time-consuming, and it became evident that minimally-invasive techniques, like VCE and MR imaging under certain circumstances provided enough information to guide medical therapy. Especially in Crohn's disease, the use of VCE and MR imaging became widespread and, especially the latter, well investigated.<sup>6,7</sup>

In other conditions, such as small-intestinal neoplasms and coeliac disease, less is known on how these new modalities can be used, and many issues regarding the way minimally-invasive techniques could be used to select patients for flexible deep enteroscopy, remain unsettled.<sup>8-10</sup>

This thesis aims to clarify at least some of these issues. However, to be able to appreciate the benefits and drawbacks of minimally-invasive techniques to examine the small intestine, one must be aware of the anatomy and function of the small intestine, as well as of the nature of the most prevalent small-intestinal diseases.

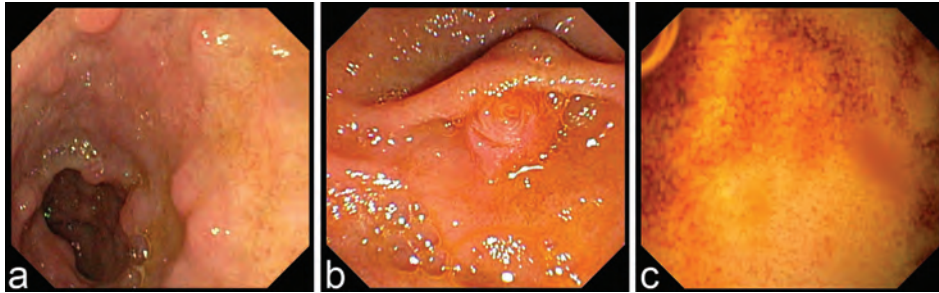
## Anatomy and physiology of the small intestine

### **Anatomy**

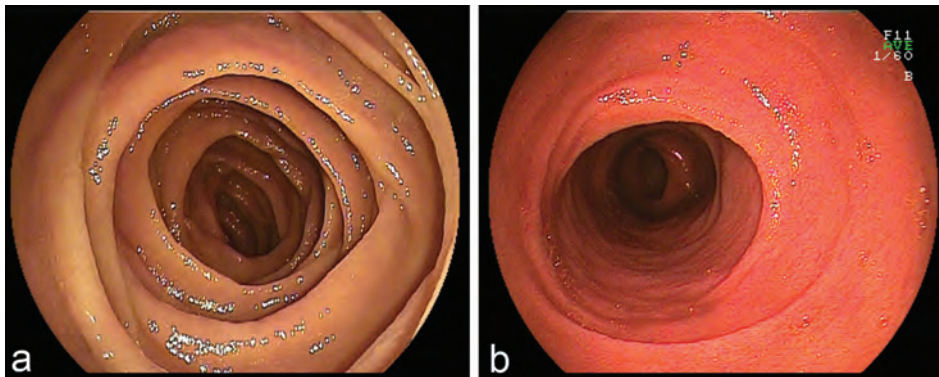
The small bowel is the largest organ of the human body, varying in length between 3 and 9 meters, although this varies with the moment and way of measuring.<sup>11</sup> The first part of the small bowel is the duodenum, which can be divided in the retroperitoneal duodenal bulb, descending part (where the common bile duct and pancreatic duct enter through the ampulla of Vater), horizontal part, and the short, intraperitoneal, ascending part. At the duodenojejunal flexure, which is surrounded by the ligament of Treitz, this part continues as the jejunum. Although it is clear where the jejunum begins, the point

where it continues as the ileum is ill-defined: There is a gradual transition from the fold-rich duodenum to the almost fold-less ileum.<sup>11</sup> By convention, the proximal 40% of the intraperitoneal small bowel is called jejunum, and the distal remaining 60% is called ileum.<sup>12</sup> At its end, the ileum is surrounded by a thickened circular muscle layer, and protrudes as the ileocaecal valve into the lumen of caecum. Examples of the normal appearance of various parts of the small bowel as depicted with flexible endoscopy, VCE and MR imaging are shown in *figures 1.1–1.5*.

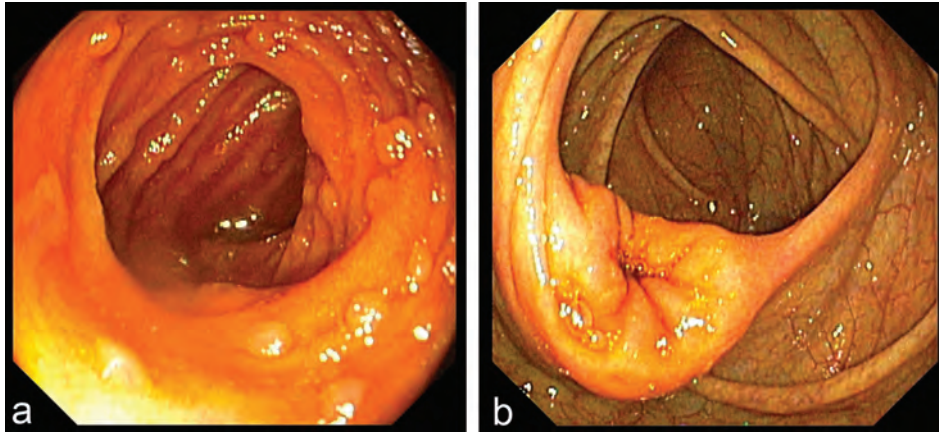
The mucosa and submucosa of the small bowel form circular folds, which are lined by 1 mm long finger-like projections called villi, which are covered with absorptive enterocytes and goblet cells. At the apical cell membrane of each enterocyte are microvilli, which serve to increase the surface of the cell.<sup>13</sup> These villi, in combination with the circular small-bowel folds, result in an overall surface area of approximately 250 square meter.<sup>11</sup> The muscle layer of the small bowel is very thin. The outer layer, the serosa, extends from the peritoneum.<sup>12</sup>



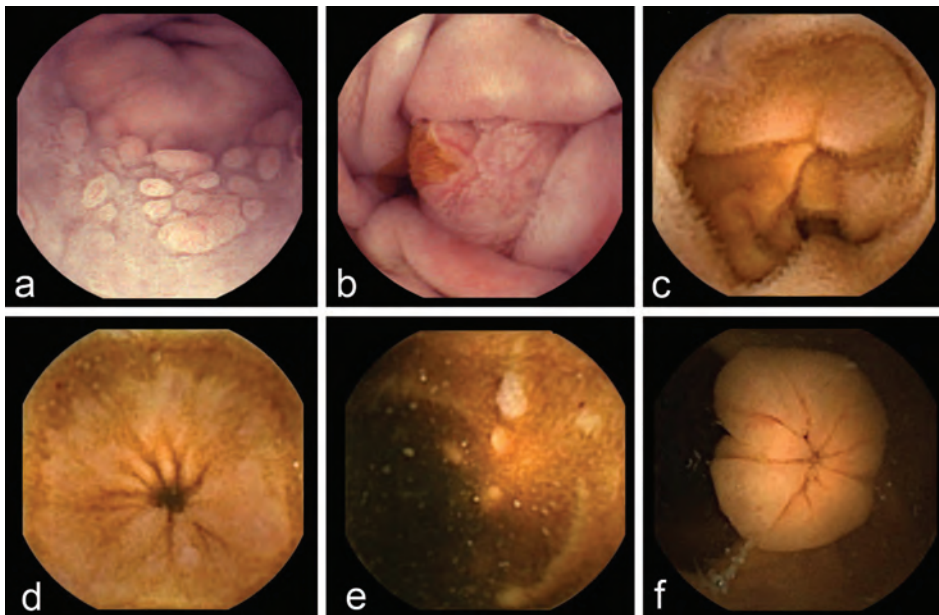
**Figure 1.1:** Flexible endoscopy images of the normal duodenum. (a) Duodenal bulb with Brunner's glands. (b) Descending part of the duodenum with the papilla of Vater. (c) Close-up of duodenal villi.



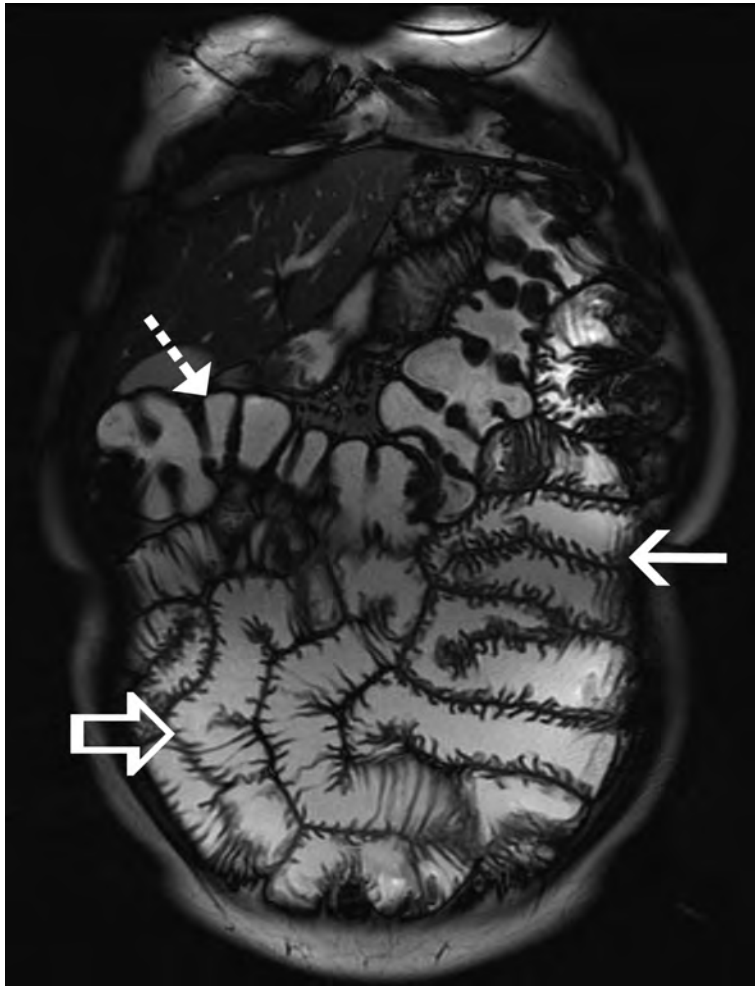
**Figure 1.2:** DBE images of the deep small intestine. (a) Normal morphology of the jejunum. (b) Normal morphology of the ileum.



**Figure 1.3:** Flexible endoscopy images of the ileocaecal region. (a) Terminal ileum with lymphatic tissue appearing as small nodules. (b) The ileocaecal valve seen from the colon.



**Figure 1.4:** VCE images of the normal small intestine. (a) Retrograde view from the duodenal bulb (with Brunner's glands) towards the pylorus. (b) The papilla of Vater excreting bile into the descending part of the duodenum. (c) Jejunum. (d) Ileum. (e) Terminal ileum with lymphatic tissue. (f) Ileocaecal valve seen from the colon.



**Figure 1.5:** Coronal MR enteroclysis image of the normal small intestine depicting the jejunum (arrow), ileum (open arrow), and colon (dashed arrow).

### **Physiology**

The fluid small-bowel content is mixed by segmentation contractions, and is propelled through the small intestine by peristaltic waves. The mixing contractions facilitate contact between the small-bowel content and the secretions of the pancreas (acid-neutralizing bicarbonate, protein and carbohydrate digesting enzymes, and fat hydrolysing enzymes) and the liver (bile for emulsifying large fat particles and aiding absorption of the digested end products).<sup>14, 15</sup>

In addition to the bicarbonate secreted by the pancreas, the duodenal wall is also protected against the acidic juice entering from the stomach, by secretion of bicarbonate-rich mucus by the duodenal Brunner's glands. In the so-called crypts of Lieberkühn, large numbers

of enterocytes secrete and reabsorb large quantities of water and electrolytes to facilitate the absorption of nutrients. In all, almost two litres of fluid is secreted per day by these enterocytes.<sup>16</sup> The enterocytes also contain several peptidases for splitting small peptides into amino acids, and several enzymes for splitting disaccharides into monosaccharides.

In short, all these attributes aid the absorption of water and the digestion and absorption of carbohydrates, fats, proteins, as well as other essential nutrients such as vitamins and iron.

Apart from for the digestion and absorption of nutrients, the small bowel plays an important role in the adaptive response to antigens. The ileum contains large aggregates of lymphoid follicles. The epithelium covering these nodules contains specialized M cells that sample antigens and microorganisms in the intestinal lumen. Antigenic material bound to the apical surface of these cells is translocated to antigen presenting cells and lymphocytes to initiate adaptive responses to the antigens.<sup>13</sup>

## Diseases of the small intestine

It is clear that diseases affecting the small bowel often interfere with its function, and therefore may result in maldigestion and malabsorption, which often result in diarrhoea and/or weight loss. Since the content of the small bowel is fluid, intraluminal obstruction of the small bowel most often becomes symptomatic in a late stage only, when even passage of fluids is impaired.<sup>17</sup> Additionally, the length and location of the small intestine explains why bleeding can present in such various forms: asymptomatic, with anaemia as the only symptom present, as melaena, if blood is partly digested, or as clear rectal blood loss, if bleeding is severe.<sup>18</sup>

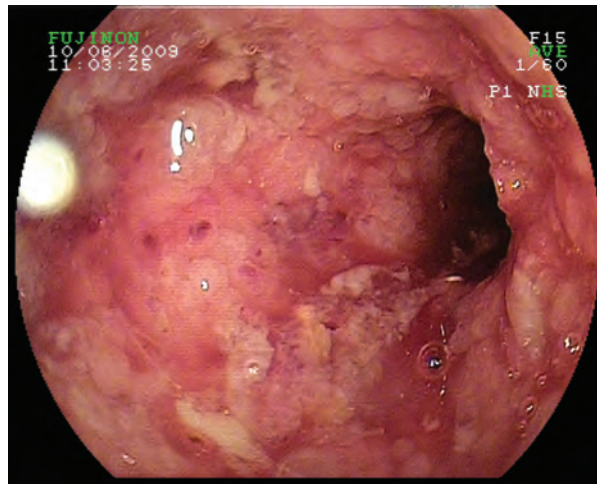
### Crohn's disease

One of the most prevalent conditions affecting the small intestine is Crohn's disease, a chronic inflammatory condition in which a genetic predisposition, the external environment, intestinal microbial flora, and the immune system are all involved. The incidence of Crohn's disease in the Netherlands is estimated to be 6.9/100.000.<sup>19</sup> Crohn's disease results in patchy, transmural inflammation, complicated by stricture or fistula formation. In most patients, the disease is confined to the terminal ileum and colorectum, but involvement of the more proximal small intestine is not unusual (*figure 1.6*).<sup>20</sup> Symptoms include abdominal pain, diarrhoea, fever, weight loss and iron deficiency. There is much evidence on the diagnostic accuracy of ileocolonoscopy and MR imaging.<sup>21, 22</sup> Therapeutic options involve immunosuppressive therapy, including tumour-necrosis-factor- $\alpha$ -antagonists, as well as surgery.<sup>23</sup>

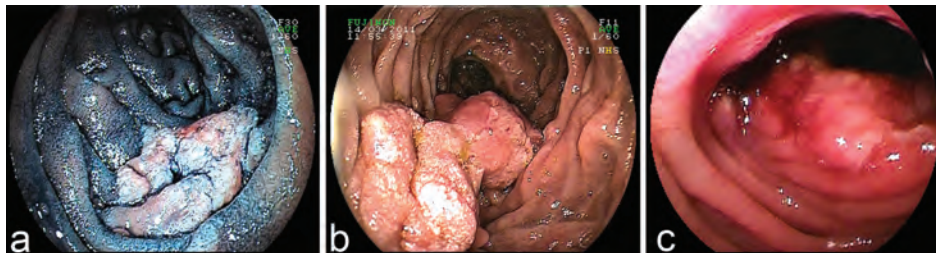
### Neoplasms

Small-bowel neoplasms can be benign or malignant (*figure 1.7*). Benign small-bowel neoplasms include those that occur in polyposis syndromes (such as Peutz-Jeghers syndrome), sporadic adenoma and inflammatory fibroid lesions.<sup>24</sup> Solid malignant small-





**Figure 1.6:** DBE image of Crohn's disease affecting the terminal ileum.



**Figure 1.7:** Examples of small-intestinal neoplasms. (a) DBE image of distal duodenal adenoma after application of indigo carmine. (b) DBE image of ileal hamartoma in a patient with Peutz-Jeghers syndrome. (c) DBE image of primary small-bowel cancer at the duodenojejunal junction.

bowel neoplasms can be primary adenocarcinoma, with an annual age-adjusted incidence of 17 per million, or neuroendocrine tumours or gastrointestinal stromal tumours.<sup>24, 25</sup> Other small-bowel malignancies include lymphoma and metastasis, all of which are very rare.<sup>26, 27</sup> Symptoms may include blood loss or signs of obstruction.

### Bleeding

Usually, midgastrointestinal bleeding (MGIB) is defined as bleeding between the duodenojejunal flexure and ileocaecal valve, and therefore does not include peptic ulcer bleeding from the duodenal bulb.<sup>28</sup> MGIB accounts for only 5% of all cases of gastrointestinal bleeding.<sup>29</sup> Causes include angioectasia (*figure 1.8*), erosions and ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs), tumours and Meckel's diverticula.<sup>30</sup> Bleeding may present as iron-deficiency anaemia, melaena, maroon-coloured stool or rectal blood



**Figure 1.8:** VCE image of an angioectasia in the proximal jejunum.

loss, and may be chronic, acute or intermittent. Therapeutic options include endoscopic clipping or argon plasma coagulation (APC), as well as medical or surgical therapy.<sup>30</sup>

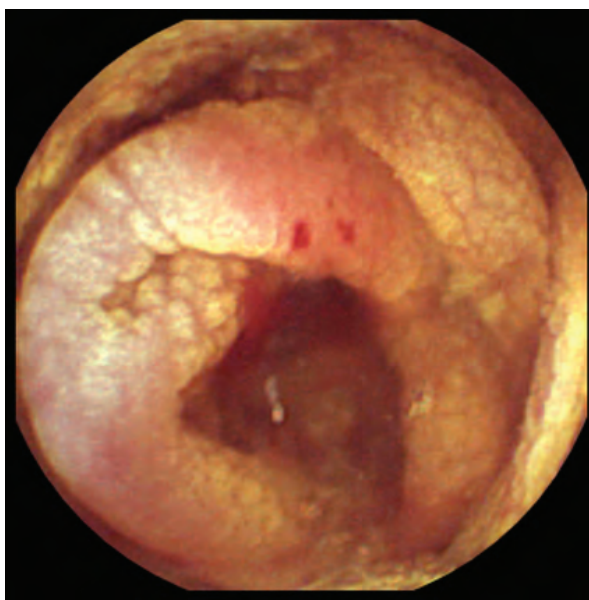
### **Coeliac disease**

Coeliac disease is an immune-mediated enteropathy induced by gluten in susceptible persons, resulting in abdominal pain, diarrhoea and weight loss.<sup>31</sup> The diagnosis can be made by examining biopsy specimens obtained in the duodenum and by serology. Deep enteroscopy is usually not needed. Withdrawal of gluten from the diet results in reversal of symptoms in almost all patients. However, in a small minority of patients so-called refractory coeliac disease occurs. This can lead to persisting symptoms, and may result in jejunal ulcerations (*figure 1.9*) and often lethal small-bowel lymphoma. The diagnosis of this condition requires extensive evaluation of the small intestine.<sup>32</sup>

## **Examination of the small intestine**

When one considers the length of the small bowel, its freedom of movement within the abdomen, and the fact that it is at its proximal end attached to the distal stomach, and at its distal end to the proximal colon, one can imagine why the small intestine for long was considered to be the black box of gastroenterology.

Fortunately, the first 20 cm of the small bowel, the duodenum, is contained in the retroperitoneum, making it relatively easy to intubate its complete length with a conventional



**Figure 1.9:** VCE image of a jejunal ulcer in a patient with refractory coeliac disease.

gastroscope. Additionally, the last 10–20 cm of the small bowel, the terminal ileum, is relatively easy to investigate with a regular colonoscope, once the ileocaecal valve has been passed.

With DBE, the complete small intestine can be visualized with an endoscope, although this usually requires two different sessions. Alternative techniques, such as single-balloon endoscopy (SBE) or spiral enteroscopy seem less effective in achieving complete enteroscopy.<sup>33–36</sup> With flexible enteroscopy it is not only possible to depict lesions, but also to take biopsy specimens for histological analysis, or to perform interventions like haemostasis or polypectomy.<sup>37</sup> However, flexible deep enteroscopy is not widely available, expensive, time consuming and invasive.<sup>24</sup> Therefore, it is not uncommon to perform a less invasive procedure first, to select patients in whom more invasive methods are needed, to obtain a histological diagnosis or to perform an intervention.

Ideally such a diagnostic method should be accurate, with a high positive and negative predicting value, tolerable, and safe. Both MR imaging as VCE might be such modalities: MR imaging, since it provides high-quality imaging of the small bowel including the bowel wall, without the use of ionizing radiation, and VCE, since it only requires the ingestion of a small capsule, which captures high-quality images of the bowel lumen.<sup>5, 38</sup> Detailed information regarding these modalities is provided in chapters 2 and 5.

## Aim of this thesis

This thesis focuses on the use of MR imaging and VCE as minimally-invasive methods to investigate small-intestinal disorders, such as small-bowel neoplasms, refractory coeliac disease and midgastrointestinal bleeding. Additionally, this thesis highlights several aspects of quality in video capsule endoscopy, including safety and complication management, and assessment of bowel preparation.

## Outline of this thesis

The first part of this thesis focuses on MR enteroclysis, a specific MR technique that uses a nasojejunal tube to provide contrast agent to the small bowel in order to achieve optimal bowel distension. **Chapter 2** provides a review on the radiological modalities that can be used to investigate the small bowel. The aim of **chapter 3** is to investigate the diagnostic accuracy of MR enteroclysis in detecting both benign as malignant small-intestinal neoplasms, and to identify MR enteroclysis characteristics capable of enabling discrimination between benign and malignant small-bowel neoplasms. The study described in **chapter 4** investigated the use of MR enteroclysis in patients suspected of having refractory coeliac disease.

The second part of this thesis focuses on VCE. A review on endoscopic methods to investigate the small intestine is provided in **chapter 5**. **Chapter 6** presents data on the use of VCE in patients with coeliac disease who do not respond to gluten-free diet. The results of a study on the use of VCE in patients using anti-thrombotic medication with suspected midgastrointestinal bleeding are presented in **chapter 7**.

Although VCE appears to be a safe method of investigation, there is a risk of capsule retention. **Chapter 8** describes the risk of capsule retention as well as the endoscopic method to retrieve these retained capsules.

As in colonoscopy, the reliability of VCE is related to the quality of bowel preparation. In **chapter 9** a novel, automated method to assess the mucosal visibility in video capsule endoscopy is described.

The third part of this thesis, **chapter 10**, consists of a study performed to compare the diagnostic accuracy of MR enteroclysis and VCE.

**Appendices A1 to A5** show examples of the use of MR enteroclysis and VCE in patients with rare small-intestinal diseases. These examples provide an additional insight in the diagnostic possibilities of both modalities.

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