Role of capsule endoscopy in small bowel management

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2019

Document Version:
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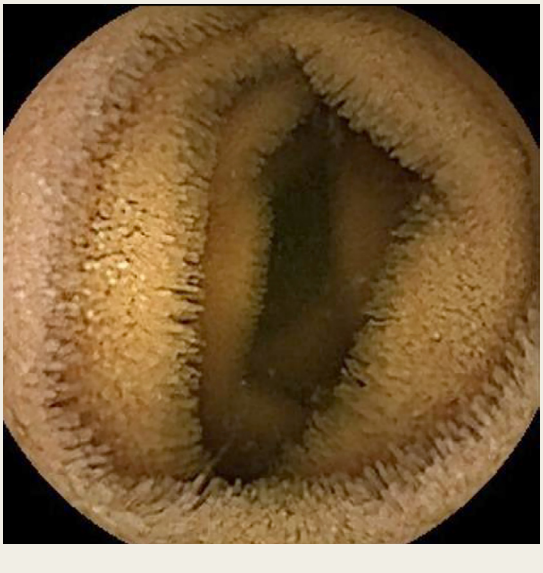

Role of capsule endoscopy in small bowel management

Artur Németh

LUND
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DOCTORAL DISSERTATION
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To be defended at Lilla Aulan, Jan Waldenströms gata 1,

Skåne University Hospital Malmö.

Date March 29, 2019 and time 9.00 am.

Faculty opponent
Docent Hans Strid

Organization	Document name
LUND UNIVERSITY	DOCTORAL DISSERTATION
Faculty of Medicine Department of Clinical Sciences, Malmö	Date of issue March 29, 2019
Author: Artur Németh, MD	Sponsoring organization

Title and subtitle

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Abstract

The small bowel is difficult to reach and to examine endoscopically. Video capsule endoscopy (VCE) using a wireless imaging technology was introduced 2000. VCE is an ingestible capsule camera that takes photographs during its passage throughout the gastrointestinal tract. The diagnosis of small bowel Crohn's disease is among the prime indications for VCE, as one third of patients with Crohn's disease have only small bowel involvement. The aim of this thesis is to increase the knowledge and critically evaluate the use of VCE and its capability to diagnose small bowel Crohn's disease and to explore the most concerning complication of VCE - capsule retention. Specific aims were to explore the risk of capsule retention, to evaluate the clinical impact and the value of the patency capsule test on the risk of capsule retention, to describe the clinical impact of VCE in patients with established Crohn's disease and to examine the impact and safety of VCE performed in children. The usefulness and risk of VCE was evaluated in different clinical situations. The studies were performed using three different models of small bowel capsule endoscopes. Patency capsule examinations were performed using a first or a second generation patency capsule.

The studies demonstrate that capsule retention is a rare complication of VCE. Moreover, a majority of patients with capsule retention can be safely and effectively managed with endoscopic intervention instead of surgery. The results suggest that routine nonselective administration of the patency capsule before VCE in patients with established Crohn's disease is not likely to reduce the risk of video capsule retention. VCE provides meaningful results leading to therapeutic changes in more than 50% of patients with established Crohn's disease. VCE is a safe method and often leads to a definitive diagnosis and has a significant impact on the clinical management of pediatric patients with Crohn's disease. Taken together, VCE has a high capability to diagnose small bowel Crohn's disease and is a very safe method to investigate the small bowel mucosa. The few cases with capsule retention can be mostly managed with endoscopic intervention.

Key words: Capsule endoscopy, Crohn's disease, patency capsule, small bowel, capsule retention

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN and key title 1652-8220 Lund University, Faculty of Medicine Doctoral Dissertation Series 2019:26		ISBN 978-91-7619-755-4
Recipient's notes	Number of pages 114	Price
	Security classification	

Signature  Date 2019-01-23

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Cover photo by Artur Németh

Department of Clinical Sciences Malmö
Lund University, Faculty of Medicine Doctoral Dissertation Series 2019:26

ISBN 978-91-7619-755-4
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2019

MADE IN SWEDEN

To my family

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Abbreviations

ASA	Acetylsalicylic acid
AUC	Area under the curve
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
CTE	Computed tomographic enterography
DBE	Double-balloon enteroscopy
ELISA	Enzyme-linked immunosorbent assay
FCP	Fecal calprotectin
GI	Gastrointestinal
LS	Lewis score
MRE	Magnetic resonance enterography
NSAID	Non-steroidal anti-inflammatory drug
RF	Radio frequency
RFID	Radio frequency identification
OR	Odds ratio
QB	Quantum Blue Rapid test
ROC	Receiver operating characteristic
SD	Standard deviation
TNF	Tumor necrosis factor
VCE	Video capsule endoscopy

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. All papers were reprinted with permission from the publishers.

I. **Nemeth A**, Wurm Johansson G, Nielsen J, Thorlacius H, Toth E. Capsule retention related to small bowel capsule endoscopy: a large European single-center 10-year clinical experience. United European Gastroenterology Journal. 2017; 5(5):677-686.

II. **Nemeth A***, Kopylov U*, Koulaouzidis A, Wurm Johansson G, Thorlacius H, Amre D, Eliakim R, Seidman EG, Toth E. Use of patency capsule in patients with established Crohn's disease. Endoscopy. 2016; 48(4):373-9.

III. Kopylov U, **Nemeth A**, Koulaouzidis A, Makins R, Wild G, Afif W, Bitton A, Wurm Johansson G, Bessissow T, Eliakim R, Toth E, Seidman EG. Clinical impact and safety of small bowel capsule endoscopy in patients with established Crohn's disease: Clinical impact, safety, and correlation with inflammatory biomarkers. Inflammatory Bowel Diseases. 2015; 21(1):93-100.

IV. **Nemeth A**, Agardh D, Wurm Johansson G, Thorlacius H, Toth E. Video capsule endoscopy in pediatric patients with Crohn's disease: a single-center experience of 180 procedures. Therapeutic Advances in Gastroenterology 2018; 11:1756284818758929.

*These authors contributed equally

Introduction

Although gastroenterology has a relatively short history, it has witnessed dramatic technical revolutions in the last decades. The development of flexible endoscopy has completely changed routine clinical practice as well as research in gastroenterology (Tytgat et al., 2000). Endoscopy has provided visual access, direct tissue sampling and therapeutic interventions in the upper and lower gastrointestinal (GI) tract.

The small bowel is located in the middle of the GI tract, which assists in the digestion and absorption of ingested food. The small bowel is the most difficult part of the GI to evaluate due to its length of 4-6 meters. A complete small bowel evaluation was previously possible only with radiological methods, such as barium examination, computed tomography (CT) and magnetic resonance imaging or with intraoperative endoscopy. Developments in both radiological and endoscopic methods have resulted in improved diagnostic options for patients with small bowel diseases, including obscure GI bleeding, celiac, polyposis syndromes and Crohn's disease.

The inflammatory bowel diseases, Crohn's disease and ulcerative colitis, are chronic idiopathic disorders causing inflammation of the GI tract (Baumgart et al., 2007). The incidence of inflammatory bowel disease has stabilized in the western countries, but the prevalence remains high (Ng et al., 2018). However, the prevalence of inflammatory bowel disease in Sweden seems to be increasing in the last years (Büsch et al., 2014). Crohn's disease can affect any part of the GI tract but commonly involves the small bowel. Early and accurate evaluation of the small bowel mucosa is essential for initiating correct treatment of patients with Crohn's disease (Gomollón et al., 2017). While radiology has improved extremely during the last decade and CT and magnetic resonance imaging have become more available they still cannot visualize superficial lesions of the small intestinal mucosa (Jensen et al., 2017).

Video capsule endoscopy (VCE) represents a revolutionary advance in noninvasive imaging of the digestive tract, particularly the small bowel where it facilitates

diagnosis of diseases that are often not detectable with other modalities. VCE appears particularly useful in patients, including children, who have symptoms and signs suggestive of Crohn's disease, when conventional diagnostic modalities remain negative (Maaser et al., 2018).

My intention with this thesis, which is based on more than 15 years' experience in gastroenterology and more than 6000 performed video capsule endoscopic examinations, is to increase the knowledge and critically evaluate the use of small bowel VCE and its capability to diagnose small bowel Crohn's disease and to explore the most concerning complication of VCE - capsule retention. VCE was first introduced in Sweden at the Endoscopy Unit, Skåne University Hospital Malmö and it has been used during the last eighteen years, in order to improve the diagnostic value of small bowel endoscopy.

Background

GI endoscopy has made great improvements over the past century (Thorlacius et al., 2017), and endoscopists have mastered advanced flexible endoscopy in the upper and the lower GI tract. At the same time endoscopic evaluation of the small bowel has remained a unique challenge for decades. VCE is a non-invasive and easy investigation using wireless technology enabling complete visualization of the small bowel mucosa. Since its introduction in 2000 (Iddan et al., 2000), VCE has developed at an explosive pace. The ability to examine of the entire small bowel has shined light into the "black box" of the GI tract.

Technology

The first capsule was constructed by Given Imaging with dimensions of 11x26 mm. The latest small bowel capsule of this company (PillCam SB3, Medtronic, Yoqneam, Israel) was released in 2013. It weighs only 3g and has a broad mucosal coverage due to its field of view being 156 degrees. When the video capsule is activated, it emits a strobe light from light-emitting diodes at the rate of 2-6 flashes per second. Meanwhile, the image that reaches the complementary metal oxide semiconductor chip camera through the optical dome window and lens is delivered by an application-specific integrated circuit to a radio transmitter, which transmits the images to an antenna array (Keuchel et al., 2006). Advanced optics and automatic light control afford optimal image quality and illumination (Figure 1).

In the last 15 years some other companies have developed similar capsules. The types of VCE on the market vary according to manufacturer. The VCE system (PillCam SB; Endocapsule, Olympus Optical Co, Tokyo, Japan; MiroCam, IntroMedic, Seoul, Korea; OMOM capsule, Jinshan Science and Technology Group, Chongqing, China) consists of three main modules: a capsule endoscope; a detecting system with a data recorder, and a portable computer workstation with software for image review and interpretation.

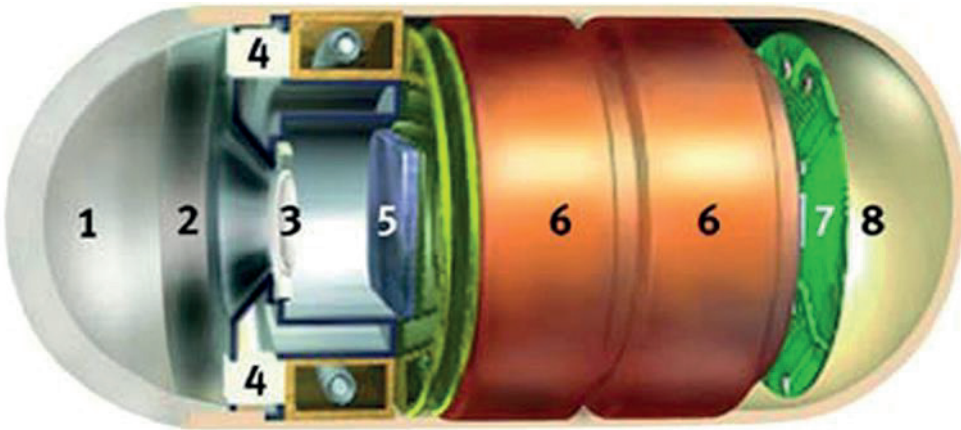

Figure 1. Inside of the video capsule (Pillcam). 1. Optical dome 2. Lens holder 3. Lens 4. Illuminating Light Emitting Diodes 5. Complementary Metal Oxide Semiconductor Imager 6. Battery 7. Applications Specific Intergrated Circuit transmitter 8. Antenna. (Illustration from Given Imaging Ltd.)

MiroCam technology uses the capsule itself to generate an electrical field and the human body as a conductive medium for data transmission in so-called "human body communication" (Rondonotti et al., 2018). All these systems allow real-time review of images during VCE examinations. These capsules do not store any data and are powered by two silver oxide batteries.

The CapsoCam (CapsoVision, Cupertino, California, USA) stores all images on a microchip in the capsule and is designed to offer a 360°panoramic view with wire-free technology. This capsule system has no data transmission therefore the patients have to collect the capsule after expulsion in the stool and then send it back to the endoscopy unit (Pennazio et al., 2015). All capsules are disposable products. Depending on the manufacturer, the battery life of the small bowel capsules varies between 11-15 hours (Table 1).

A capsule endoscope for the colon, as well as for the esophagus has been manufactured (PillCam Colon2, PillCam ESO2, Medtronic) and a pan-enteric PillCam Crohn´s capsule (Medtronic) has been developed and evaluated (Eliakim et al., 2018).

Table 1. Specifications of available small bowel capsule endoscopes.

Capsule endoscope	Pillcam SB3	MiroCam MC 1600	Endocapsule EC-S10	OMOM capsule 2	Capso Cam Plus
Company	Medtronic	Intromedic	Olympus	Jinshan	Capso Vision
					
Size (mm)	26x11	25x11	26x11	25x11	31x11
Weight (g)	3.4	3.2	3.3	4.5	4
Battery life (h)	11.5	11	12	12	15
Field of view (°)	156	170	160	157	360
Frame rate	2-6	3	2	2-4	12-20
Image transmission	RF	Human body communication	RF	RF	None*

*Onboard flash memory

Procedure and evaluation

The first manufacturer of capsule endoscopes did not recommend laxative use before VCE (Given Imaging ltd., 2013). The only recommended requirements were a low-fiber diet on the day before the procedure with clear liquids only in the evening and a 12-hour fast before the procedure. The novel clinical guideline recommends that patients ingest a purgative (2 L of polyethylene glycol) prior VCE for better visualization (Rondonotti et al., 2018). However, a current meta-analysis of adult studies demonstrated that laxatives do not improve diagnostic yield or completion rate in VCE, although small bowel visualization is improved. That meta-analysis concluded that use of laxatives might be beneficial in patients likely to have subtle findings (Yung et al., 2017a).

The reduction of gas bubbles in the small bowel improves quality of VCE. The novel clinical guideline recommends administration of antifoaming agents before capsule ingestion (Rondonotti et al., 2018).

The patient´s data should be entered into the computer before initializing of the recorder. The leads are fixed to the abdomen and the belt with the recorder is strapped by the endoscopy nurse (Figure 2). After swallowing the capsule, patients are allowed clear liquids after 2 hours and solid food after 4 hours. If the patient cannot swallow the capsule it can be placed endoscopically in the duodenum. The real time viewer can be used one hour after swallowing the capsule to detect slow

gastric transit time. If the capsule remains in the stomach, gastroscopy can be performed to move the capsule into the duodenum by use a polypectomy snare.

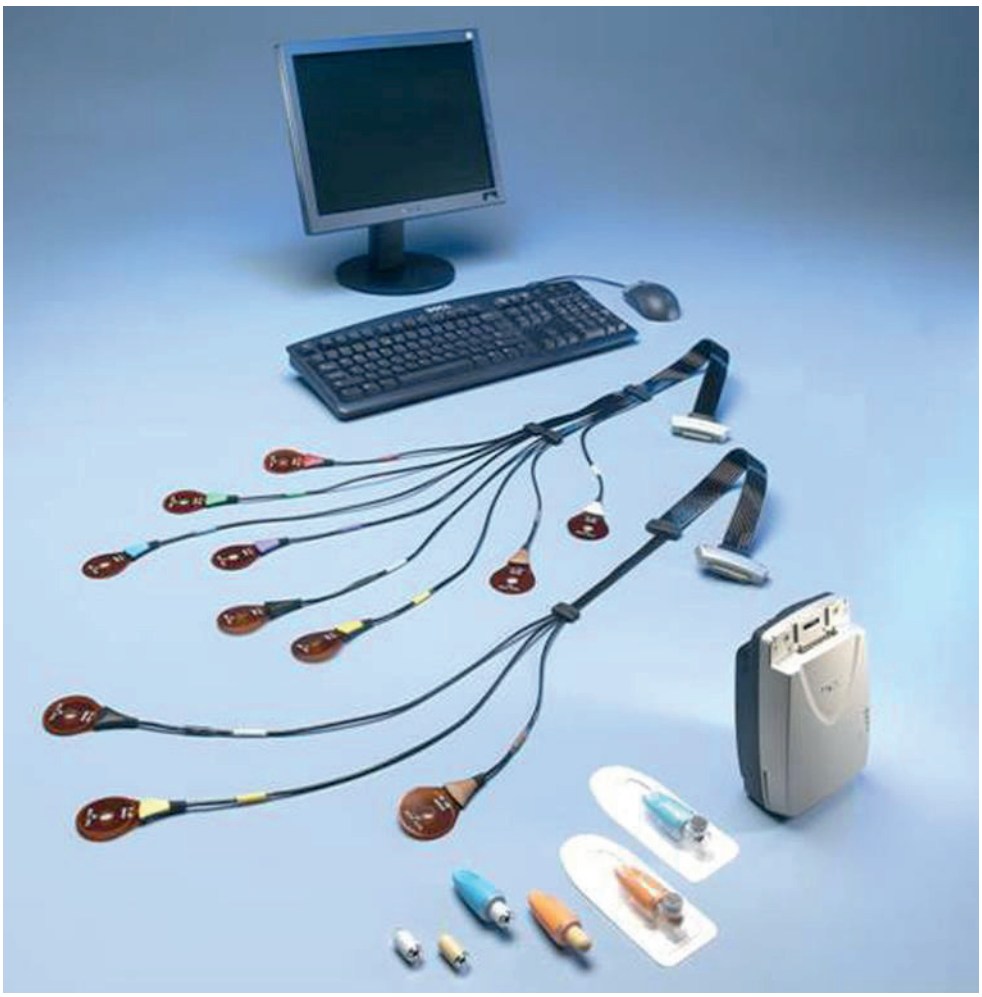

Figure 2. Capsule endoscopy equipment with sensor arrays and data recorder. (Illustration from Given Imaging Ltd.)

Patients may leave the hospital after swallowing the capsule. The ingested capsule passes the intestinal tract due to of peristalsis and leaves the bowel naturally. Images are continuously acquired until battery exhaustion and are registered at a storage device for off-line analysis by a specialist.

Evaluation of the VCE procedure does not require the same technical skills as conventional GI endoscopy (Davison, 2006). Expertise with VCE lies in the ability of an individual to read and interpret the VCE findings. The average VCE reading time varies between 30 and 120 minutes depending on small bowel transit time, the quality of images and the experience of the specialist. The large amount of visual information requires focused attention by the VCE reader since a small bowel lesion may only be visible in just a few or even just a single frame (Rondonotti et al., 2012).

The operating time of the capsules can vary between 8-15 hours depending on the manufacturer. Since images are obtained at 2-20 frames/s, more than 60000 images are produced. The computer unit allows images to be viewed singly or as a video stream. The proprietary reading software of Pillcam SB 3 system contains the Lewis Score (LS) calculator, the Fujinon Intelligent Colour Enhancement, the suspected blood indicator, Quick view, a thumbnail comparisation feature and an improved progress indicator. Other VCE systems have similar functions which may help the reader to analyze the examination.

Complications

The most concerning complication of VCE is capsule retention, defined as the presence of the capsule in the GI tract for at least 2 weeks after ingestion, or when it is indefinitely retained unless directed medical, endoscopic or surgical intervention is initiated (Cave et al., 2005). The incidence of capsule retention varies widely in the literature from 0 to 21%, which might be related to the characteristics of the examined populations or the relatively small numbers of patients used in most of the earlier studies (Sears et al., 2004; Cheifetz et al., 2006; Goldstein et al., 2008). Capsule retention is usually asymptomatic and the capsule can remain in the GI tract without symptoms for several months or even be excreted during follow-up (Bhattari et al., 2013; Stier et al., 2017; Rondonotti et al., 2018). Surgical intervention was the most common approach for removal of retained capsules in early studies (Cheifetz et al., 2006; Li et al., 2008), while more recent reports indicate the possibility of endoscopic treatment methods (Van Weyenberg et al., 2010; Xin et al., 2012).

Capsule aspiration is a rare complication of VCE and a recent systematic literature review reported 0.1% estimated overall aspiration rate (Yung et al., 2017b). Other complications described in the literature such as small bowel perforation and

capsule disintegration are extremely rare and have only been published as case reports (Royall et al., 2014; Pham et al., 2018).

Patency capsule

Known stenosis of the GI tract is a contraindication for performing VCE unless surgery is already scheduled or at least has been considered as an optional treatment modality (Bandorski et al., 2016). Bowel patency can be evaluated by use of radiological small bowel imaging (enteroclysis or barium small bowel follow-through) or by administration of a self-dissolving patency capsule. The patency capsule is a nondiagnostic capsule of the same shape and dimensions as the diagnostic capsule. The cellophane-walled capsule cylinder is filled with lactose and protected by one or two hollow plugs that allow influx of intestinal fluid, which results in dissolution of the lactose (Figure 3a). In addition, the patency capsule has an inner radio frequency identification (RFID) transponder device and barium, which allows its detection by a hand-held scanner (Figure 3b) and/or by plain abdominal radiography (Figure 3c) or CT (Cave et al., 2005).

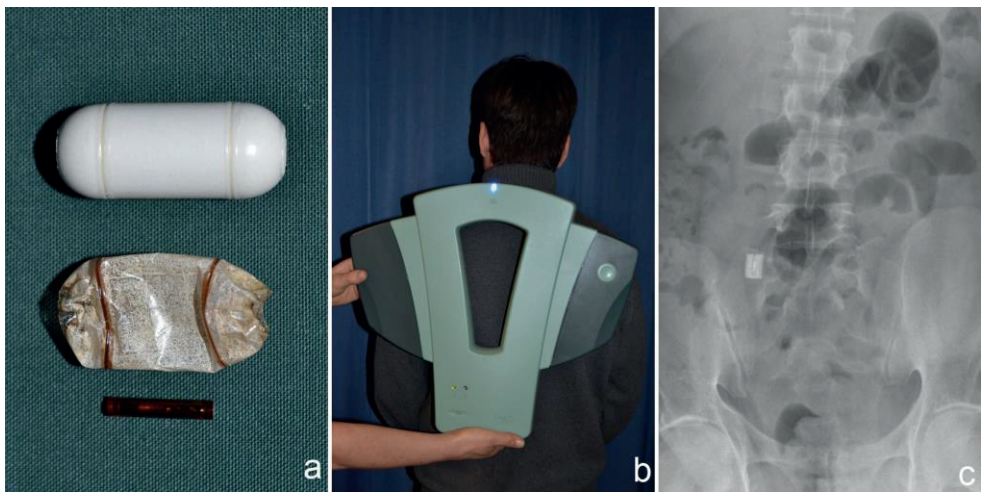

Figure 3. The patency capsule before and after disintegration (a). Methods of locating the patency capsule: Hand-held scanner (b), plain abdominal radiography (c).

The second-generation patency capsule model (Agile) was designed to reduce the incidence of abdominal pain secondary to patency capsule retention; the dissolution time of the Agile patency capsule is shorter (30 vs 40 hours) due to the two timer

plugs instead of one as designed for the first-generation patency capsule, allowing an improved contact with intestinal fluids as well as contraction of both sides minimizing the chance of obstruction (Caunedo-Alvarez et al., 2008). Recently, a third type of patency capsule was introduced without an inner transponder device (Mitselos et al., 2018). This design has the theoretical advantage to eliminate the RFID-transporter impaction. VCE is considered safe to perform following the successful excretion or nondetectability of the ingested patency capsule in a predefined time - 40 hours for the first-generation and 30 hours for the second-generation patency capsule (Postgate et al., 2008). The current guidelines of the European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) suggest that a patency capsule can be used to confirm small bowel patency before performing VCE, if small bowel stenosis is not firmly excluded (Maaser et al., 2018).

Fields of application

The indication for VCE of the small bowel increases steadily. Current recommendations describe the roles of VCE for diagnosis and treatment of small bowel disorders (Pennazio et al., 2015).

Obscure GI bleeding was the first application of video capsule endoscopy and is still one of the most important indications. The most frequent findings in patients with obscure GI bleeding are angiectasias followed by ulcers, tumors and diverticula (Figure 4). Several studies showed that VCE has a significantly higher diagnostic yield compared to other methods, including push enteroscopy, enteroclysis, CT, magnetic resonance imaging and angiography. VCE is recommended as the first-line investigation in obscure GI bleeding. In patients with iron deficiency anemia, VCE is recommended after negative gastroscopy and ileocolonoscopy.

Other indications for VCE are suspected small bowel tumors, inherited polyposis syndromes like familial adenomatous polyposis and Peutz-Jeghers syndrome. The novel clinical guideline suggests the use of VCE for suspected celiac disease in patients unwilling or unable to undergo conventional endoscopy (Pennazio et al., 2015).

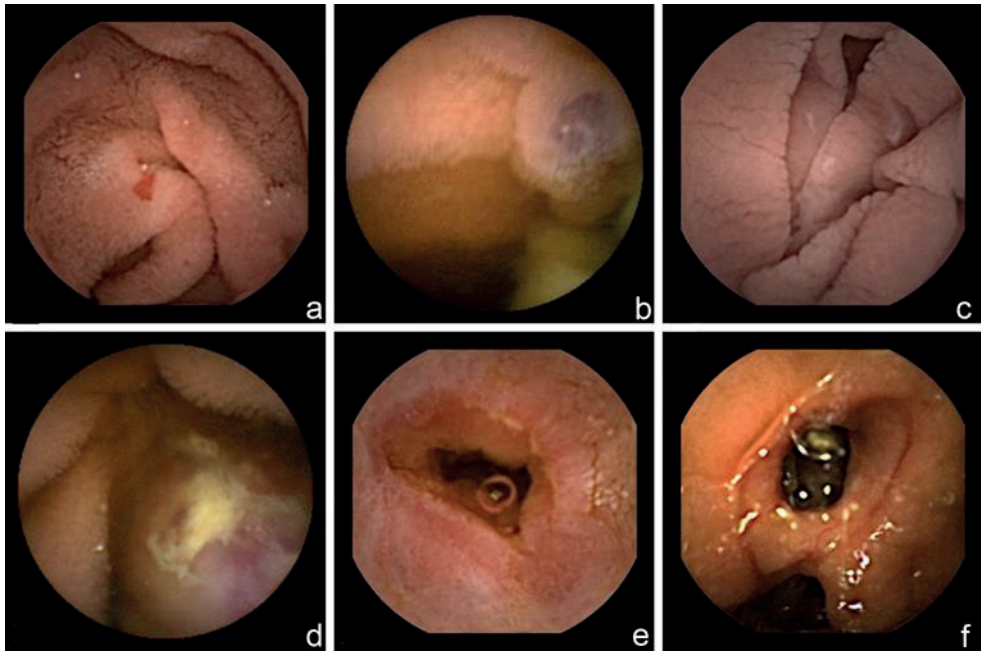

Figure 4. Findings with obscure GI bleeding. Angiectasia (a), venous ectasia (b), villous atrophy (c), tumor (d), NSAID stricture (e), Meckel´s diverticulum (f).

Crohn's disease is among the prime indications for VCE considering that up to two-thirds of patients with Crohn's disease have small bowel involvement (Figure 5). However, the lack of a gold standard for the diagnosis of Crohn's disease hinders precise determination of VCE accuracy for this disorder and “diagnostic yield” for findings consistent with Crohn's disease has often been adopted as a surrogate in the correct clinical perspective (Enns et al., 2017).

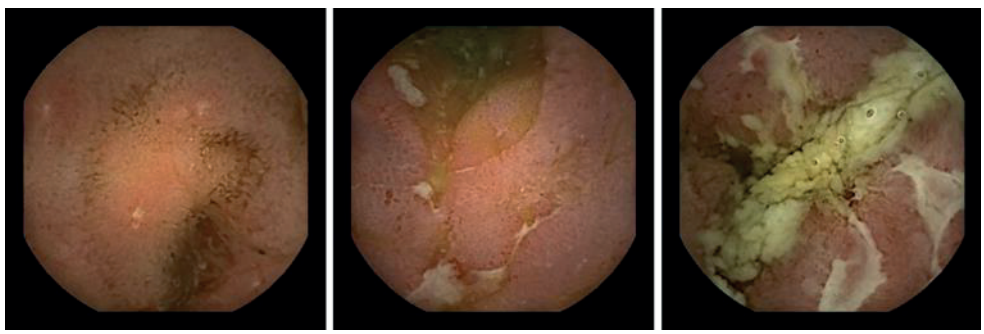

Figure 5. Capsule endoscopy images showing mucosal inflammation and ulcerations consistent with a diagnosis of Crohn's disease.

Known GI obstruction and strictures are generally considered a contraindication for VCE (Enns et al 2017). Relative contraindications are swallowing disorders and pregnancy (Rondonotti et al., 2018).

Crohn's disease

Crohn's disease is a chronic and progressive inflammatory disease of unknown etiology that may affect any part of the gastrointestinal tract. Genetic, environmental and intestinal microbial factors have been reported to play a role in the etiology and pathogenesis of Crohn's disease (Baumgart et al., 2007). Typical presenting symptoms include abdominal pain and diarrhea. Crohn's disease represents a life-long disorder that may occur at any time from early childhood to late adulthood, although generally begin in young adulthood and last throughout life (Cosnes et al., 2011). Intestinal strictures, internal or perianal fistulas or abscesses can appear in patients with Crohn's disease. More than 20% of patients present with perianal lesions and 15%–20% have or have had a fistula (Cosnes et al., 2011). Patients with Crohn's disease may also have extra intestinal manifestations including arthritis, uveitis and aphthous stomatitis, erythema nodosum and pyoderma gangrenosum.

The Montreal classification of Crohn's disease differentiates disease of the ileum, colon, and both ileum and colon. Crohn's disease occurs in these regions in equal proportions of patients (Satsangi et al., 2006). Thus, about two-thirds of the patients have Crohn's disease in the small bowel (Gasche et al, 2000). Crohn’s disease may affect the entire small bowel and can be difficult to diagnose using the traditional methods of evaluation, including colonoscopy with ileoscopy (Rosa et al., 2012; Gomollón et al., 2017). Mucosal features of Crohn's disease are often subtle and normal radiological imaging tests such as magnetic resonance enterography (MRE) cannot entirely exclude small bowel involvement (Maaser et al., 2018).

Early and accurate diagnosis including the evaluation of extension of Crohn's disease in the small bowel is pivotal for initiating correct treatment of patients in a timely manner. Numerous publications compared the diagnostic accuracy of VCE for Crohn's disease with that of other imaging modalities. Its advantage over small bowel follow-through and computed tomographic enterography (CTE) has been frequently confirmed (de Melo et al., 2012; Leighton et al., 2014). VCE and MRE have a similar diagnostic accuracy (Dionisio et al., 2010). MRE is superior to diagnose enteroenteric fistulas and abscesses (Maaser et al., 2018). However, VCE

is more sensitive for detection of elusive mucosal inflammation and for proximal small bowel lesions (Kopylov et al., 2017a). In addition to establishing the diagnosis of Crohn's disease, VCE can also be used for monitoring Crohn's disease (Kopylov et al., 2014).

The small bowel has limited ways to demonstrate injury, the endoscopic appearances of non-steroidal anti-inflammatory drug (NSAID) induced small bowel lesions are endoscopically impossible to differentiate from lesions with other etiologies, such as Crohn's disease (de Melo et al., 2012). The presence of NSAID lesions may be confusing and possibly cause incorrect diagnosis. Novel guidelines recommend that NSAIDs should be stopped at least 1 month before VCE, particularly if the patient is being investigated for the presence of active small bowel Crohn's disease (Pennazio et al., 2015).

Aims

General aim

The aim of this thesis was to increase the knowledge and critically evaluate the use of VCE and its capability to diagnose small bowel Crohn's disease and to explore the most concerning complication of VCE - capsule retention.

Specific aims

- To define the incidence, causes, risk factors, management and clinical outcomes of capsule retention (study I).
- To explore the risk of capsule retention in patients with established Crohn's disease (study II).
- To evaluate the clinical impact and the value of the patency capsule test on the risk of capsule retention (study II).
- To describe the clinical impact of VCE in patients with established Crohn's disease (study III).
- To evaluate the diagnostic accuracy of inflammatory biomarkers for prediction of significant small bowel inflammation detected by VCE (study III).
- To examine the impact and safety of VCE performed in children and adolescents being investigated for established and suspected Crohn's disease (study IV).

Methods and patients

Small bowel video capsule endoscopy

VCE were performed using different models of small bowel capsule endoscopes PillCam SB 1/2 (Medtronic, formerly known as Given Imaging Ltd., Yoqneam, Israel), MiroCam (Intromedic Co., Seoul, South Korea) and EndoCapsule (Olympus Co., Tokyo, Japan) in Study I, II and III. The PillCam SB 3 was also used in study II. The procedures were performed only with PillCam SB 1/2/3 capsules in study IV.

Patency capsule

First or second generation patency capsule (Medtronic, formerly known as Given Imaging Ltd.) were used for patency capsule examinations. The patency test was considered negative if the patency capsule was not delectable in the GI tract 40 hours (first-generation capsule) or 30 hours (second-generation capsule) after ingestion (according to the manufacturer's instruction). The elimination of the patency capsule was confirmed using a hand-held scanner, plain abdominal radiography or a combination of the two (Figure 3b-c). Symptomatic retention of the patency capsule was defined as obstructive symptoms, such as abdominal pain or vomiting while the patency capsule was demonstrable in the small bowel.

Preparation and procedure

VCE was usually performed without bowel preparation. The procedure was repeated after 2 liters of polyethylene glycol if the small bowel was poorly visualized on the first examination. Patients swallowed the capsules after 8 hours fast with 200-400 ml of water. After swallowing the capsule, patients were allowed clear liquids after 2 hours and regular diet after 4 hours. The patients were

recommended to perform routine activities during the procedure day. In patients with dysphagia the capsule was placed endoscopically in the duodenum by use of a polypectomy snare, Roth Net retrieval device (US Endoscopy, Mentor, OH, USA) or AdvanCE system (US Endoscopy). In some patients with suspected slow gastric transit time, such as diabetic patients, inward patients and patients with previous slow gastric transit time on VCE, the real time viewer was used 1 hour after swallowing the capsule. If the real time view showed esophageal or gastric mucosa, gastroscopy was performed to place the capsule into the duodenum by use a polypectomy snare. Most of the examinations were performed in outpatient´s settings.

At the end of the procedure, patients returned the data recorder. All VCE studies were read and interpreted by gastroenterologists experienced in VCE. No additional controls were done if the video showed colon mucosa. Plain abdominal radiography was recommended 2 weeks after the investigation if the video did not show capsule passage to the colon and the patient did not detect natural passage of the capsule.

Lewis score

The LS is a validated cumulative scoring system to describe the type, location, and severity of small-bowel inflammatory lesions (Cotter et al., 2015). LS is based on the presence and distribution of villous edema, ulceration, and stenosis. LS was used to grade the mucosal inflammation in study II and III. Normal VCE was defined as LS<135, mild-to-moderate inflammation as 135<LS<790, and moderate-to-severe inflammation as LS>790 (Gralnek et al., 2008).

Study I

Patients and study design

The study included all (2401) consecutive patients undergoing VCE from April 2001 to April 2011 at Skåne University Hospital in Malmö, Sweden (Table 2). This was a single-center retrospective study to evaluate capsule retention. All patients referred for VCE had their medical records reviewed by a gastroenterologist experienced in VCE in order to identify patients with possible VCE contraindications, as suspected small bowel obstruction, known small bowel stricture, pregnancy or dysphagia. Patients with suspected small bowel obstruction

underwent patency capsule test or radiological small bowel examination, such as CTE, MRE, and barium small bowel follow-through. All cases with small bowel patency proceeded with VCE.

Capsule retention

Capsule retention was defined as the presence of the capsule in the GI tract for at least 2 weeks after ingestion, or when it is indefinitely retained unless directed medical, endoscopic or surgical intervention is initiated (Cave et al., 2005). The capsule was removed endoscopically in patients with Kock's reservoir and these cases were not considered as capsule retention. Capsule retention was confirmed using plain abdominal radiography or CT. Patients with confirmed capsule retention underwent further radiological examinations to identify the precise location of the retention or to detect spontaneous but delayed passage of the capsule. Medical, endoscopic or surgical intervention was recommended depending on the location of the capsule and the cause of the retention. We analyzed indications for the examination, site and cause of retention, management, and clinical outcomes in patients with capsule retention.

Study II

Patients and study design

The study cohort included 406 consecutive patients (Table 3) with known Crohn's disease undergoing VCE between June 2005 and December 2013 in three academic referral centers in Malmö (Sweden), Quebec (Canada), and Edinburgh (United Kingdom). This was a retrospective, multicenter, cross-sectional study to examine to use of the patency capsule in patients with established Crohn's disease. Patients who underwent VCE for the initial diagnostic work-up of Crohn's disease were not included in this study.

Patency capsule administration strategy

To identify the optimal policy for administration of the patency capsule in patients with established Crohn's disease two strategies were compared.

1) Nonselective strategy – all patients underwent the patency capsule test before VCE.

2) Selective strategy – patency capsule was used only in patients with obstructive symptoms, or with a history of intestinal obstruction or abdominal surgery (excluding uncomplicated appendectomy and cholecystectomy).

The nonselective strategy was used by the McGill University Health Center (Quebec) and was also utilized by Skåne University Hospital (Malmö) during the period June 2005 to May 2008. The selective strategy was utilized by Skåne University Hospital between January 2010 and December 2013 and was also used in Edinburgh University Hospital.

Patients were excluded from the per-strategy analysis if:

1) The decision to use patency capsule was decided on a radiological imaging or based on previous VCE findings;

2) VCE was performed despite the patency capsule was not eliminated during the patency test.

Study III

Patients and study design

The study cohort included 187 consecutive patients (Table 4) with established Crohn's disease who underwent VCE from January 2008 to October 2013 in 4 academic referral centers in Malmö (Sweden), Quebec (Canada), Cheltenham and Edinburgh (United Kingdom). This was a retrospective, multicenter, cross-sectional study to investigate the clinical effect of VCE in patients with established Crohn's disease. Patients who underwent VCE for the initial diagnostic workup of Crohn's disease were not included. Clinical impact was defined if the patient's Crohn's disease related treatment was changed (escalation or reduction of anti-inflammatory therapy, dose modification, referral for surgery) that was recommended within 3 months after the VCE results.

Inflammatory Biomarkers

Enzyme-linked immunosorbent assay (ELISA) or Quantum Blue Rapid test (QB, Buhlmann Laboratories, Basel, Switzerland) was used to measure fecal calprotectin (FCP). For ELISA, <50 mg/g were considered negative and positive if >200 mg/g. For the rapid test, <30 mg/g were defined negative and positive if >100 mg/g. C-reactive protein (CRP) >5 g/dL was considered as positive.

Study IV

Patients and study design

All consecutive pediatric patients with suspected or known Crohn's disease undergoing VCE from October 2003 to December 2014 at Skåne University Hospital in Malmö, Sweden were included (Table 7). This was a single-center retrospective study to evaluate the clinical effect of VCE in pediatric patients with suspected or established Crohn's disease. The medical records of patients were analyzed by a gastroenterologist experienced in VCE to identify patients with possible GI obstruction. Patients with suspected small bowel stricture underwent patency capsule examination. If the small bowel patency was confirmed, patients continued with VCE. Patients with NSAID treatment within a period of 6 months before VCE were excluded.

Definitions

Patients were identified as having Crohn's disease if they were treated for Crohn's disease on the basis of their symptoms and further objective findings. Patients were categorized as having suspected Crohn's disease if they fulfilled the International Conference on Capsule Endoscopy criteria, or if their referring physician suspected Crohn's disease (Mergener et al., 2007). VCE was defined as consistent with Crohn's disease if the examination showed more than three erosions and ulcerations in the small bowel while three or fewer small bowel lesions was defined as suspected but not diagnostic for Crohn's disease (Tukey et al., 2009).

Ethics

The patients gave written informed consent prior to the examinations. All studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with good clinical practice and local regulations and were approved by the Ethics Committee of Lund University, Sweden (ethic committee approval numbers 582/2006, 412/2016).

Statistics

Study I: Simple logistic regression analysis was used to identify possible association between capsule retention and a number of risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented for dichotomous categorical variables; p-values below 0.05 were considered to be significant. Given the exploratory nature of the study, no correction of significance levels for multiple testing was done.

Study II: The primary exploratory analysis was designed to evaluate the association of clinical and demographic factors with the risk of video capsule retention. Categorical values were compared using the chi-squared test. Continuous variables were compared using the Mann–Whitney–Wilcoxon test. A p-value of <0.05 was considered statistically significant. Due to the exploratory nature of the study, no correction of significance levels for multiple testing was done. ORs and 95% CIs were calculated for dichotomous categorical variables. The strategies for administration of the patency capsule were compared by a univariate analysis and validated by matching the patients from the two groups on the common covariates (sex, age at onset of disease, disease location and behavior, history of abdominal surgery, small-bowel obstruction, and medical therapy) by compiling a propensity score. Matching was carried out using the score for each patient.

Study III: We evaluated correlation of elevated biomarkers (FCP, CRP, and combination) with significant small bowel inflammation (LS >790) on VCE. Sensitivity, specificity, negative predictive value, and positive predictive value as well as Spearman's rank (r) correlation were calculated. R values <0.3 were considered as weak-to-low correlation, 0.3 to 0.49 as low-to-moderate, 0.5 to 0.69 as moderate, and >0.7 as strong correlation. A two-tailed p-value <0.05 was considered to be significant. Receiver operating characteristic (ROC) curve was constructed for correlation of ELISA and FCP with LS >790, and area under the curve (AUC) was calculated. An AUC of 0.6 to 0.7 was considered poor and 0.9 to 1 was defined as excellent correlation.

All analyses were carried out using IBM SPSS (Version 20.0; IBM Corp., Armonk, New York, USA).

Results

Study I

2401 VCE examinations were performed in Skåne University Hospital Malmö between April 2001 and April 2011. Indications for VCE were:

- suspected Crohn's disease (n=980, 41%)
- obscure GI bleeding (n=816, 34%)
- established Crohn´s disease (n=390, 16%)
- miscellaneous (n=215, 9%)

821 (34%) patients underwent patency capsule test and 678 (28%) radiological small bowel imaging were performed to detect small bowel patency. Both tests were used in 38 patients. 268 patients (11%) had undergone previous GI surgery (excluding uncomplicated appendectomy and cholecystectomy).

Capsule retention occurred in 25 patients (1.0%). Only 7 patients (28%) with capsule retention had symptoms of obstruction (dysphagia in 3 cases and abdominal obstructive symptoms in 4 cases). Table 2 shows the details with capsule retention. The risk of capsule retention was significantly increased in patients with:

- older age (OR 1.02; 95% CI 1.00–1.04; p=0.04)
- previous GI surgery (OR 7.64; 95% CI 3.45–16.93, p<0.001)
- known Crohn's disease (OR 2.94; 95% CI 1.29–6.71; p=0.01)
- small bowel radiology before VCE (OR 3.88; 95% CI 1.73–8.67; p=0.001)

The risk of capsule retention was significantly decreased in patients with:

- patency capsule test prior to VCE (OR 0.16; 95% CI 0.04–0.70; p=0.015)
- suspected Crohn's disease (OR 0.36; 95% CI 0.13–0.96; p=0.04)

Table 2. Univariate analysis for development of capsule retention (CR).

Variables	CR (n=25)	No CR (n=2376)	Odds ratio (95% CI) (units)	p-value
Age, y (SD)	54 (19.7)	46 (19.7)	1.02 (1.00-1.04)	0.040
Sex				
Male	15	1033	1.95 (0.87-4.36)	0.104
Female	10	1343		
Previous GI surgery	12	256	7.64 (3.45-16.93)	<0.001
Indication for capsule endoscopy				
Known Crohn's disease	9	381	2.94 (1.29-6.71)	0.010
Suspected Crohn's disease	5	975	0.36 (0.13-0.96)	0.041
Obscure GI bleeding	11	805	1.53 (0.69-3.93)	0.291
Others	0	215	N/A	
Previous small-bowel radiology	15	663	3.88 (1.73-8.67)	0.001
Previous patency capsule	2	819	0.16 (0.04-0.70)	0.015

CR, capsule retention; N/A, not applicable since the logistic regression procedure could not perform the computation

Site and cause of capsule retention

Capsule retention occurred most frequently in the small bowel (Figure 6). The main cause of capsule retention was Crohn's stenosis in the small bowel, which occurred in 12 (48%) patients. Further causes of capsule retention were NSAID-induced webs in the small bowel (3 cases), peptic stricture in the esophagus (2 cases), and pyloric stenosis (2 cases). Uncommon causes of capsule retention were diverticulum in the esophagus, duodenal postoperative stenosis, duplication cyst in the small bowel and colonic metal stent, which occurred in one case each. We observed capsule retention in the esophagus without any macroscopic pathology and one capsule was retained in a normal colon for 37 days.

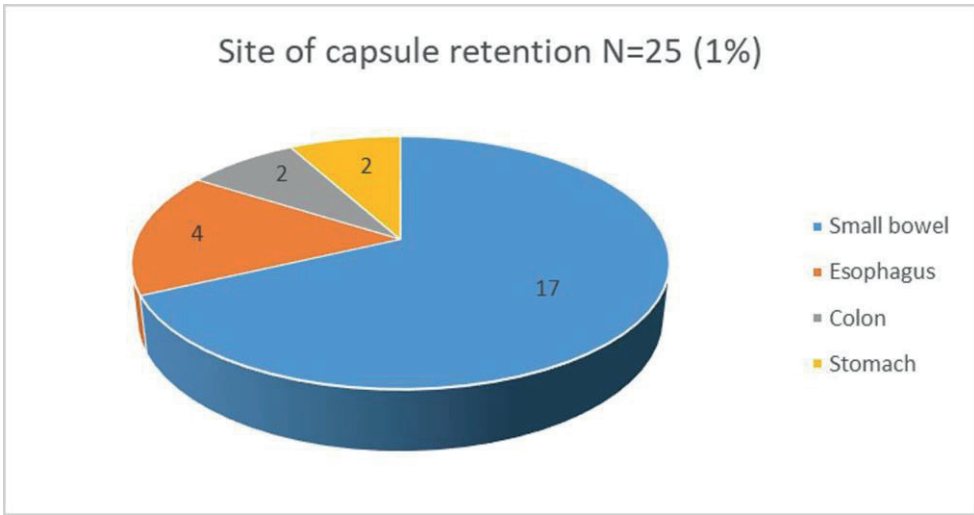

Figure 6. Site of capsule retention.

Previous radiology/patency capsule

We observed that 14 of 17 cases of capsule retention in the small bowel occurred despite previously negative radiological or patency tests. In 12 of these 14 cases radiological imaging did not show any stricture. In one of the two patients who had undergone a patency test before capsule retention the radiological examination incorrectly located the patency capsule in the rectum. VCE was then performed and the video capsule was retained in the small bowel. In the other patient, the patency capsule was eliminated intact after 60 hours instead of the manufacturer's recommendation being 40 hours and a VCE was finally performed resulting in capsule retention.

Management of capsule retention

Capsule retention was most frequently managed with endoscopic removal (Figure 7). Gastroscopy were performed in 8 cases and double-balloon endoscopy in 3 cases (Figure 8). 5 (20%) patients needed emergency intervention to manage capsule retention, of which 3 cases were removed by gastroscopy and 2 underwent surgery (Figure 9). No case of capsule retention related death was observed during one-year follow up.

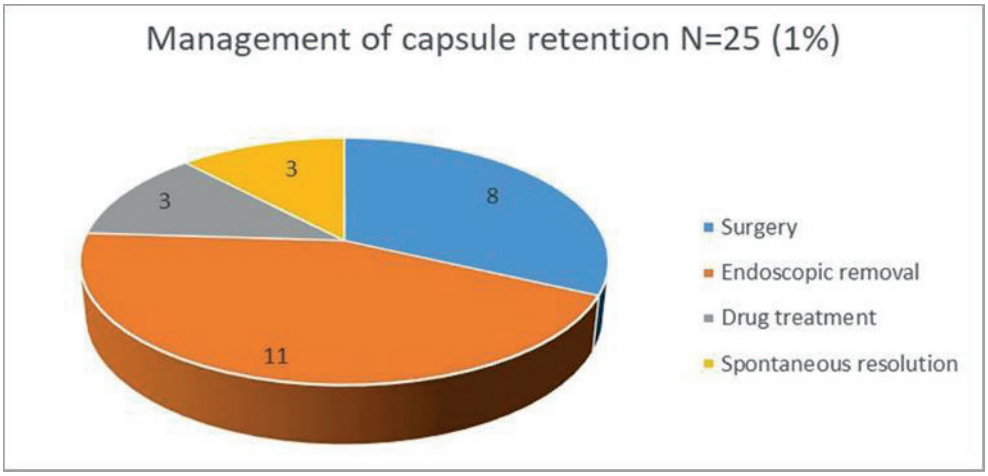

Figure 7. Management of capsule retention.

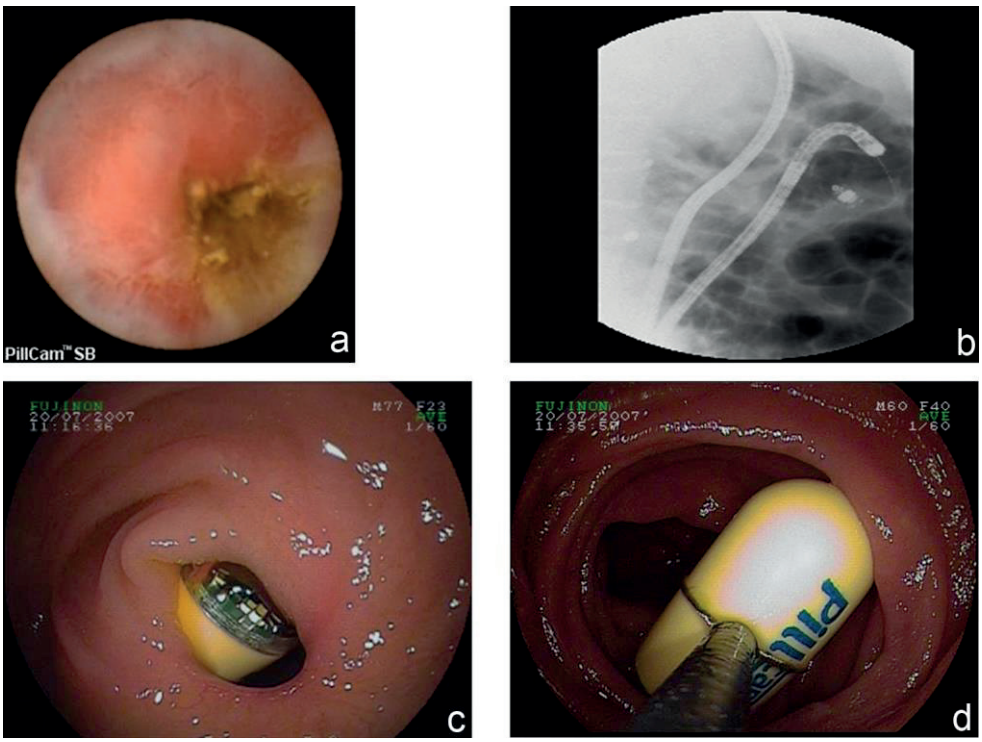

Figure 8. A 73-year-old man with chronic NSAID medication presented with obscure GI bleeding. VCE image shows a stricture in the proximal part of jejunum causing capsule retention (a). Plain abdominal x-ray image during DBE shows the endoscope and the retained capsule in the proximal jejunum (b). DBE image shows the capsule between two small bowel strictures (c). DBE image shows the capsule being retrieved using a snare after balloon dilation of the strictures (d).

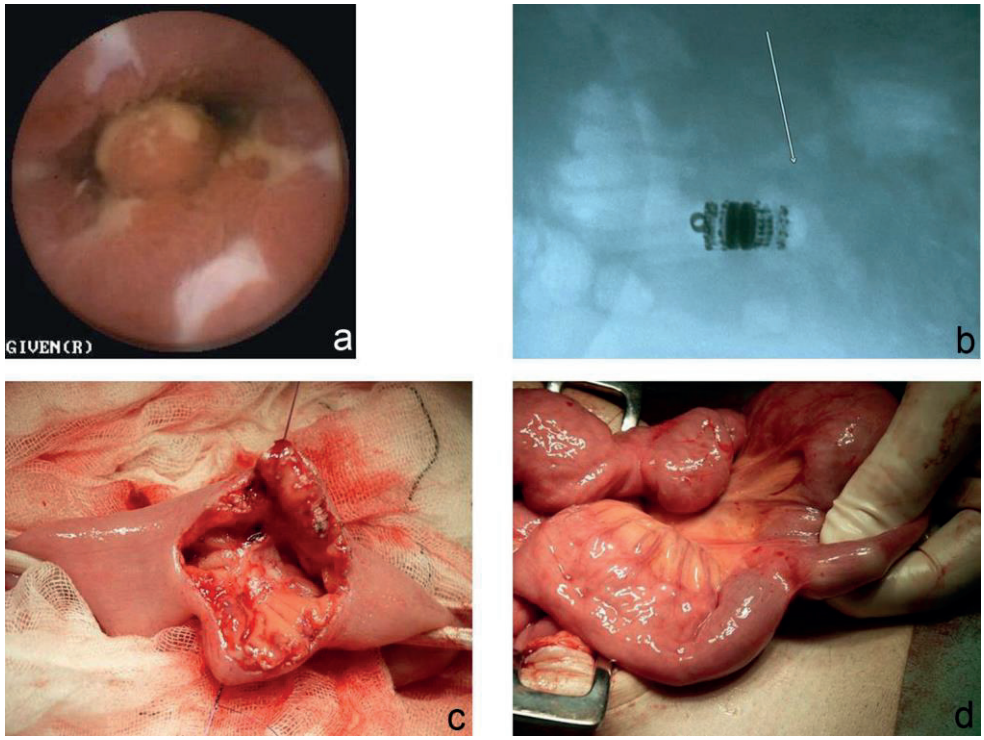

Figure 9. A 44-year-old man with known Crohn's disease who had undergone ileocecal resection presented with suspected disease activity. The patient underwent colonoscopy and small bowel radiology showed normal results. VCE image shows an ulcerated small bowel stricture (a). Plain abdominal x-ray reveals the retained capsule (b). Images showing 4 strictures which were treated by surgery (c and d).

Study II

This study included 406 patients with established Crohn's disease, 354 in Malmö, 41 in Montreal, 11 in Edinburgh. Clinical and demographic characteristics of these patients are described in Table 3. The patency capsule test was performed in 274 patients (67%), and VCE was completed in 343 patients (84%; Figure 10). Pillcam capsule was used in the majority of cases (333/343), while Olympus and MiroCam capsules were used in 5 patients each. Patency capsule test was performed mostly with the second-generation patency capsule (87%), whereas the first-generation model was used in 13 % of the cases. VCE was performed without prior patency capsule testing in 132 patients (33%). In 18 patients, VCE was performed despite a positive patency capsule test. VCE consistent with severe inflammation were detected in 99 patients (29%) and mild-to-moderate inflammation in 134 patients

(39%). Normal small-bowel mucosa was observed in 110 patients (32%). VCE was repeated in four cases due to technical failure or poor visualization.

Table 3. Clinical and demographic characteristic of patients with Crohn's disease who were referred for VCE.

n	406
Sex, male/female, n (%)	223 (55)/183 (45)
Age, mean (SD), years	36 (16)
Age of Crohn's disease onset, mean (SD), years	27 (14)
Duration of disease, mean (SD) years	8 (10)
Disease location, n (%)	
Small bowel	111 (27)
Large bowel	108 (27)
Small and large bowel	187 (46)
Perianal disease, n (%)	40 (10)
Disease phenotype, n (%)	
Luminal	326 (80)
Stricturing	68 (17)
Penetrating	12 (3)
Previous abdominal surgery, n (%)	135 (33)
History of small bowel obstruction, n (%)	85 (21)
Radiological small bowel imaging avilable, n (%)	90 (22)
Small bowel stictures on previous imaging	8 (9)
Diabetes, n (%)	10 (2)
Indication for VCE, n (%)	
Evaluation of disease extent/location	248 (61)
Unexplained symptoms	126 (31)
Elevated biomarkers (clinically quiescent disease)	19 (5)
Anemia/gastrointestinal bleeding	9 (2)
Suspected obstruction	4 (1)
History of small bowel radiation n (%)	1 (0.2)
Patency capsule performed, n (%)	274 (67)
VCE performed, n (%)	343 (84)

Patency capsule retention

The patency capsule test was positive in 81 patients (30%). Patency capsule retention was detected by a hand-held scanner in 72 patients (89%), plain abdominal radiography in 6 patients (7%), and a combination of the two methods in 3 patients (4%). In 6/274 patients (2%), the retention of the patency capsule was symptomatic. In five of these cases (one first-generation capsule, four second-generation capsules), the patency capsule was retained in the terminal ileum, with subsequent obstructive symptoms. Three patients received steroid treatment while the symptoms resolved spontaneously in two cases, and the patency capsule was

eliminated from the small bowel. In one patient, the capsule was retained in the esophagus and it was finally delivered endoscopically into the duodenum. In four of the five patients with symptomatic retention of the patency capsule in the small bowel, following radiological examination verified a significant stenosis in the terminal ileum.

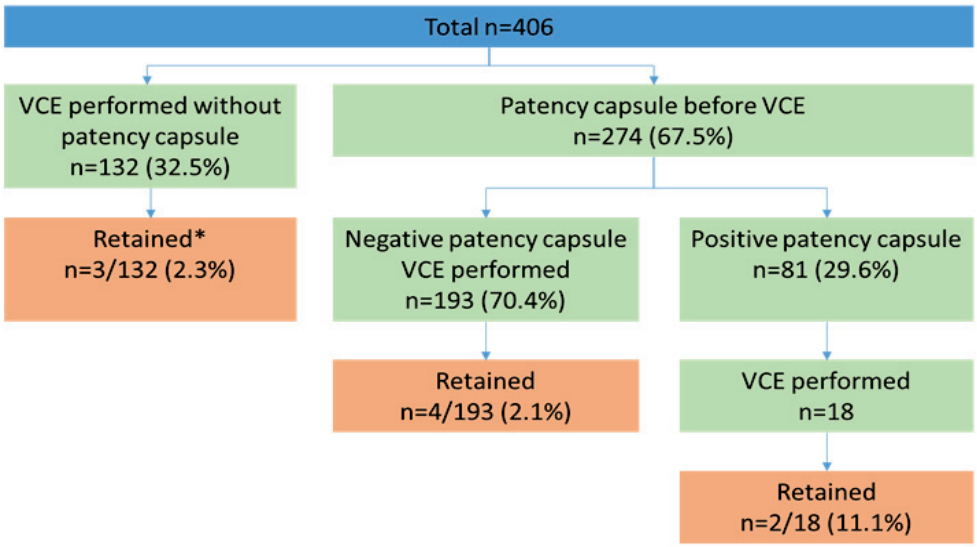

Figure 10. Flow chart of study to investigate the use of a patency capsule to predict the risk of video capsule retention prior to video capsule endoscopy. *In one patient, the capsule was retained in the colon.

Video capsule retention

Video capsule retention in the GI tract occurred in 10/343 patients (3%). Most common side of the retention was the small bowel in 8/343 patients (2.3%), while the capsule was retained in the esophagus and in the colon in one patient each. The retention was resolved following corticosteroid treatment in 4 cases and another 4 patients had surgery. One case of capsule retention resolved without any intervention. In the patient with esophageal retention and dysphagia the capsule was placed into the duodenum endoscopically and the capsule passed the small bowel uneventfully, this case is not mentioned as retention later on.

Effect of the patency capsule test on the risk of small bowel retention

Video capsule retention occurred in 4/193 patients (2%) who had previously excreted the patency capsule. The video capsule retained in the small bowel in two patients (1.5%) who did not undergo patency capsule testing (p=0.70 vs. successful excretion). Capsule retention was observed in 2/18 patients who received VCE

following positive patency test (11%; p=0.01 vs. excretion of the patency capsule). Radiological examination was performed in 52/81 patients after patency capsule retention. The radiological images showed small bowel stenosis in 17/52 patients (33%), significant small-bowel inflammation in 5/52 patients (10%), and normal mucosa in 30/52 patients (58%).

The association between demographic/clinical factors and the risk of small bowel capsule retention was analyzed and only the administration of the video capsule following a positive patency capsule test was significantly associated with a risk of video capsule retention (OR 6.4, 95% CI 1.2–34.1; p=0.01).

Comparison of administration strategies for the patency capsule

The rate of video capsule retention was compared between the selective and the nonselective group to find the optimal administration of the patency capsule. Patients not assigned to one of the two strategies and patients who received VCE despite a positive patency test were excluded from the per-strategy analysis. Video capsule retention occurred in 2/155 patients (1.3%) in the selective arm and in 2/127 in the nonselective arm (1.6%, p=0.99 vs. the selective arm, Figure 11).

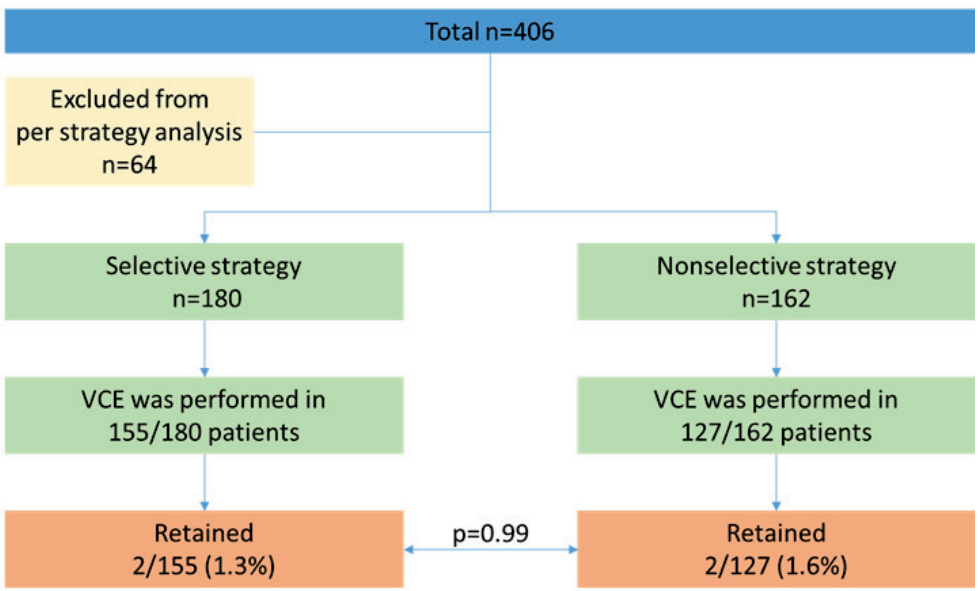

Figure 11. Classification and capsule retention of the included patients by the patency capsule administration strategy. *Patients were excluded from the per-strategy analysis in the following situations: 1) If the decision to administer the patency capsule was based on pre-procedural cross-sectional imaging screening or results of a previous VCE; 2) if a VCE was performed despite a positive patency capsule test; 3) if the patency capsule administration strategy could not be clearly identified.

Study III

The study included 187 patients with established Crohn's disease. Their clinical and demographic characteristics and the indications for VCE are described in Table 4. The LS was available in 169 of 187 patients. VCE was normal (LS<135) in 28%; VCE findings consistent with mild inflammation were observed in 27% and moderate-to-severe inflammation in 45% of these patients.

Table 4. Demographic and clinical characteristics of patients with established Crohn's disease undergoing VCE.

n	**187**
Sex, male/female, n (%)	75 (40)/112 (60)
Age at VCE, mean (SD), years	36 (15)
Duration of disease, mean (SD) years	7 (8)
Montreal classification	
Age at onset, n (%)	
A1 (<17)	35 (19)
A2 (17-40)	112 (60)
A3 (>40)	40 (21)
Disease location, n (%)	
L1 ileal	71 (38)
L2 colonic	43 (23)
L3 ileocolonic	73 (39)
Disease phenotype, n (%)	
B1 non-stricturing, non-penetrating	149 (80)
B2 stricturing	8 (4)
B3 penetrating	30 (16)
Previous abdominal surgery, n (%)	47 (25)
History of small bowel obstruction, n (%)	85 (21)
Radiological small bowel imaging avilable, n (%)	90 (22)
Small bowel stictures on previous imaging	8 (9)
Diabetes, n (%)	10 (2)
Medications, n (%)	
Anti-TNFs	56 (30)
Thiopurines	58 (31)
5-ASA	57 (31)
Corticosteroids	51 (27)

A change in therapeutic management of Crohn's disease was recommended as a result of VCE findings in 99 of 187 (52%) patients. In patients with no small bowel inflammation (LS<135), a therapeutic change was recommended in 14%, patients with mild inflammation (LS 135–790) in 48% and moderate-to-severe inflammation

(LS>790) in 87%. The recommended change was most often intensification or initiation of anti-inflammatory treatment (Table 5).

Table 5. Therapeutic changes stratified by VCE results in established Crohn's disease.

Change in therapeutic management n=91 (of 187)* *in 8 patients no change despite of recommendation	n	%
Intensification/initiation	75	82
Biologic started	27	30
Biologic dos escalated	4	4
Immunomodulator started	33	36
Surgery	2	2

Disease location and phenotype

VCE showed findings consistent with Crohn's disease in 121 of the 169 patients with available LS. Small bowel findings in all 3 tertiles were demonstrated in 79 (65%) of these cases. VCE detected lesions in the first tertile in 60 patients (50%), whereas distal (third tertile) inflammation was detected in 106 (88%) of these patients. In 11 of 43 (26%) patients diagnosed with colonic Crohn's disease, earlier undetected small bowel Crohn's disease was confirmed by VCE. Ileocolonoscopy (within a year of VCE) was performed in 97 patients. Ileocolonoscopy did not verify small bowel involvement in 45 patients. In 15 of 45 (33%) of these patients, moderate-to-severe SB inflammation was confirmed by VCE (Table 6). Eight patients (4%) were characterized as stricturing disease but VCE confirmed small bowel stricture only in 1 of these patients. Furthermore, small bowel strictures were identified in 7 of 179 (4%) of the patients previously categorized as having a luminal or fistulizing phenotype.

Table 6. Correlation of VCE with ileocolonoscopy findings in established Crohn's disease.

Endoscopy findings	LS<135 n (%)	135<LS<790 n (%)	LS>790 n (%)
Ileitis	4 (13)	11 (37)	15 (50)
Colitis	12 (50)	4 (17)	8 (33)
Ileocolitis	3 (14)	4 (18)	15 (68)
Normal ileocolonoscopy	7 (33)	7 (33)	7 (33)

Correlation with inflammatory biomarkers and safety

FCP was available for 66% of the patients (elevated in 61%) and CRP for 83% (elevated in 48%). Poor correlation with significant small bowel inflammation was detected for elevated FCP (ELISA >200 mg/g, QB >100 mg/g; r=0.164, p=0.07; sensitivity, 70%, specificity, 46%), elevated CRP (r=0.3; p= 0.01; sensitivity, 60%, specificity, 70%), or combination of both indicators (r=0.2; p=0.14). ROC for FCP and CRP was made as a predictor of significant small bowel inflammation. Only

patients with ELISA FCP results were included (n=112). The AUC was 0.63, and with exclusion of patients without known small bowel disease was 0.64 (Figure 12), which corresponds to poor detection accuracy. For CRP, the AUC was 0.66.

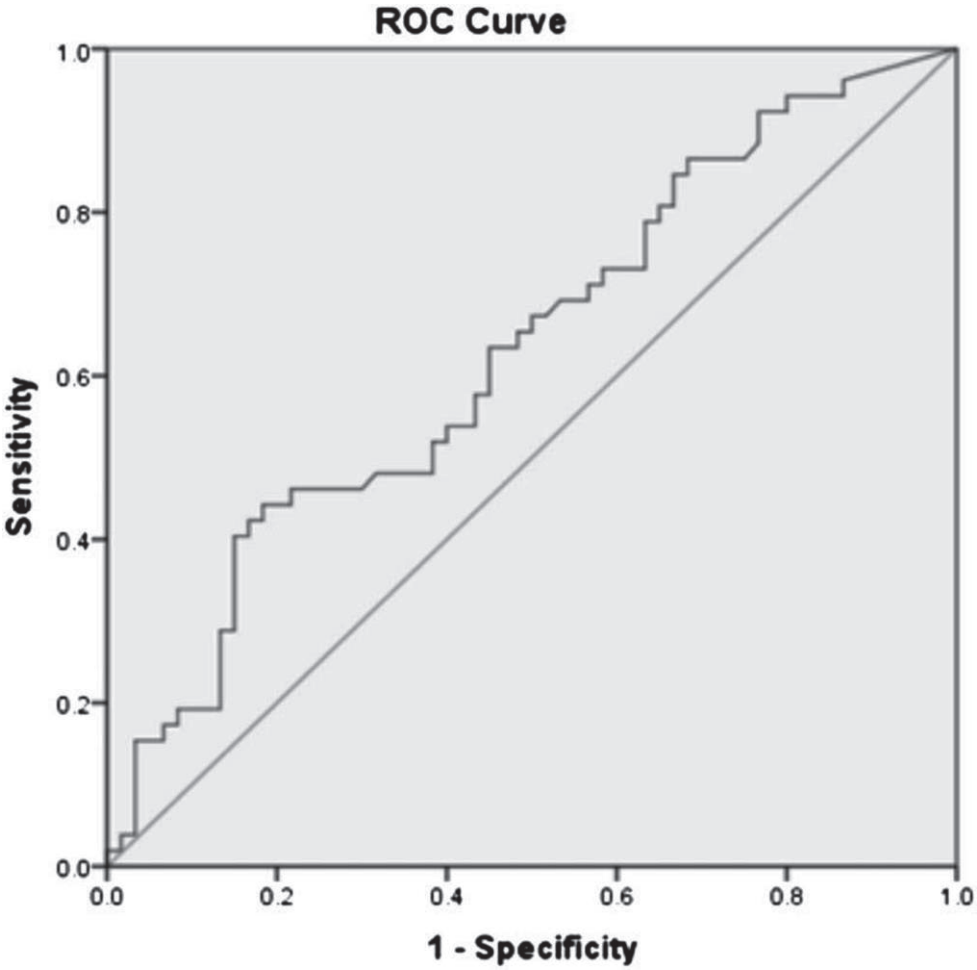

Figure 12. ROC curve analysis of the diagnostic performance of ELISA FCP for detection of significant small bowel inflammation (LS>790) in patients with established Crohn´s disease (AUC=0.64).

Capsule retention in the small bowel occurred in 4 (2%) patients. In 3 cases, the capsule was excreted after corticosteroids, endoscopic capsule extraction was performed in 1 patient. One case of video capsule retention occurred in a patient who had successfully excreted the patency capsule. None of the patients required surgical intervention.

Study IV

A total of 180 VCE examinations which were performed in 169 consecutive patients were included in the study. Patients´ demographic and clinical characteristics are described in Table 5. Twenty-three (13%) patients were younger than 10 years. 86% of patients swallowed the capsule. The median age of patients requiring endoscopic placement of the capsule was 9 years whereas those who could swallow the capsule were on average 14 years old. 30 of 180 (17%) cases were incomplete as the capsule did not reach the colon during the recording time, as shown in Table 7. VCE detected findings consistent with Crohn's disease in 13 (43%) of the 30 incomplete procedures. The capsule showed small bowel mucosa for more than 7 h (range 3–11 h) in incomplete examinations. The majority (67%) of the incomplete studies were performed with the SB1 capsule having only 8 h of recording time, while 27% incomplete procedures were conducted with the SB2 capsule having a maximum of 9 h of battery life. The SB3 capsule, which has 12 h of recording time were used only in 2 of the 30 incomplete cases and these two capsules had been endoscopically placed in the duodenum.

Table 7. Patient characteristics (n=180).

Characteristics	Value
Age and gender	
Median age (range), year	13 (3-18)
Female sex, n (%)	81 (45)
Crohn's disease n (%)	
Suspected	125 (69)
Established	55 (31)
Delivery of capsule n (%)	
Swallowed by the patients	154 (86)
Endoscopic placement	26 (14)
Completeness of VCE n (%)	
Complete	150 (83)
Incomplete	30 (17)

Overall VCE findings in the small bowel (n=180):

- consistent with Crohn's disease: 71 (40%)
- minor changes not diagnostic for Crohn's disease: 17 (9%)
- normal mucosa 92 (51%)

Colonic lesions were seen in 14 (8%) examinations, including 10 cases with normal small bowel mucosa. VCE detected previously unidentified inflammation in the colon in three studies.

VCE small bowel findings in patients with established Crohn's disease (n=55):

- consistent with Crohn's disease: 44 (80%)
- minor changes not diagnostic for Crohn's disease: 1 (2%)
- normal mucosa 10 (18%)

Twenty-nine of the 55 (53%) procedures identified lesions in the jejunum.

VCE small bowel findings in patients with suspected Crohn's disease (n=125):

- consistent with Crohn's disease: 27 (22%)
- minor changes not diagnostic for Crohn's disease: 16 (13%)
- normal mucosa 82 (65%)

The capsule showed lesions consistent with Crohn's disease in the jejunum in 17 of these 125 (14%) cases and earlier unidentified colonic lesions in 3 patients.

Impact on clinical management

A new diagnosis or a change in therapy based on VCE results occurred in 56 (31%) patients. Fifty-three patients had small bowel findings and capsule showed previously unidentified colonic lesion in three patients. We detected 71 cases showing Crohn lesions in the small bowel, and as a result of VCE findings, a change in therapeutic management was recommended in 47 (66%) of these patients. The recommended therapeutic changes based on VCE results are described in detail in Table 8. Surgical intervention was not suggested to any patient.

Table 8. Therapeutic changes stratified by VCE results in pediatric patients with Crohn's disease.

VCE findings (n=180)	Normal or non-specific findings (109)	Consistent with Crohn's disease (71)
Change not recommended n (%)	105 (96)	24 (34)
Change recommended n (%)	4 (4)	47 (66)
Biologicstarted n (%)	0	19 (27)
Immunomodulatory started n (%)	0	14 (20)
Steroids n (%)	4 (4)	7 (10)
Medication decreased n (%)	0	2 (3)
Other (5-ASA, antibiotics) n (%)	0	3 (4)
Patient refused change n (%)	0	2 (3)

Safety

71 patients with suspected small bowel obstruction underwent patency capsule test before VCE.

- In 38 (54%) cases, small bowel patency was confirmed and VCE was performed.
- In 33 (46%) patients, patency capsule test did not demonstrate small bowel patency.
    - In 14/33 (42%) cases, radiological imaging was performed and showed no small bowel stenosis but only 7 of these patients underwent subsequent VCE.
    - In 8/33 (24%) patients the cross-sectional examination confirmed stricture in the small bowel and VCE was not performed.
    - 7/33 (21%) patients without small bowel patency did not undergo further examinations.
    - In 4/33 (12%) patients radiological imaging was not performed, but VCE was offered after repeated evaluation of the symptoms.

Patients requiring endoscopic placement of the capsule and with suspected small bowel stenosis underwent MRE to prove small bowel patency. No small bowel capsule retention was observed. The only complication was a retained capsule within a metallic stent in the sigmoid colon which had been inserted earlier to manage a Crohn stricture. The patient underwent sigmoid resection.

Discussion

Since its introduction in 2000, VCE has been established as the preferred method for visualizing the small bowel mucosa. Generally, VCE is an almost "physiological" endoscopy, the capsule moves passively, driven by bowel peristalsis and evaluates the GI tract without air insufflation (Woods et al., 2011). Patients' tolerability of a diagnostic procedure is essential when choosing between imaging modalities. VCE is widely accepted among patients and it has been proved to be tolerated in several studies (Wiarda et al., 2013; Lahat et al., 2016). Patients' preference is especially important when managing chronic diseases like Crohn's disease as repeated and multiple examinations are needed throughout the patient´s life.

VCE has advantages and weaknesses compared to other diagnostic procedures in the evaluating of the small bowel. VCE is a noninvasive method and majority of patients can be managed as outpatients, which has added to increase its popularity. Several centers perform the examination without laxatives that makes the method uncomplicated for the patient (Macias et al., 2019). One of the major disadvantages of VCE is that its diagnostic accuracy is difficult to determine because there is no single gold standard for the diagnosis of Crohn's disease (Penazzio et al., 2015; Gomollon et al., 2017). Consequently, studies evaluating VCE generally use radiologic small bowel images or endoscopy as a standard for comparison, and assess the incremental diagnostic yield (Enns et al., 2017). In the early years, when obscure GI bleeding was the main indication, VCE had a high diagnostic yield possibly due to case selection and partially to over diagnosing the findings. Since its official introduction the number of peer-reviewed publications on capsule endoscopy has increased continuously and Crohn's disease has become the most important indication (Adler, 2017). VCE has been used in Skåne University Hospital Malmö since April 2001 and more than 6000 procedures have been performed.

Capsule retention

While VCE is a non-invasive method and usually considered to be safe, capsule retention in the digestive tract is a concern, which might cause acute bowel obstruction and require emergency surgery (Baichi et al., 2006; Lin et al, 2007). We evaluated our 10-year clinical experience in study I and observed 1% overall and 0.7% small bowel capsule retention rate. Our study has demonstrated that capsule retention is a rare complication with a good clinical outcome. Majority of the capsule retentions were managed with medical or endoscopic interventions. The patients who underwent surgery had complete resolution of symptoms during the postoperative follow-up period of 1 year and no capsule retention related fatalities were observed.

Several studies have investigated the risk for capsule retention in different clinical materials. Capsule retention rate has been described to vary between 0.9% and 1.4% in previous large single center studies (Li et al., 2008; Van Weyenberg et al., 2010), whereas multicenter investigations reported 0.8% to 2.0% rate of capsule retention (Höög et al., 2012; Fernández-Urien et al., 2015; Soncini et al., 2018). Recently in two large single center studies with a tertiary care population, capsule retention occurred in 0.3% to 1.4% of cases (Al-Bawardy et al., 2015; Han et al., 2017). However, patients with contraindications to VCE, such as known small bowel obstruction or obstructive symptoms did not undergo VCE in these studies. A systematic review on VCE including 227 original papers reported a pooled retention rate of 1.4% (Liao et al., 2010). More recently, a meta-analysis reported a retention rate of 3.6% in suspected IBD and 8.2% in established IBD (Rezapour et al., 2017). Nevertheless, this study did not include several recent publications, which may have increased the pooled rate of capsule retention as the authors excluded studies from the central analysis in which the patency capsule or radiological imaging was used (Kopylov et al., 2017b).

Most of the aforementioned publications defined capsule retention as having the capsule endoscope remain in the digestive tract for a minimum for a minimum of 2 weeks, according the ICCE criteria (Cave et al., 2005). In fact, capsule retention can occur at all levels of the GI tract (Karagiannis et al, 2009; Al-Bawardy et al., 2015); however most of the studies have not described cases of capsule impaction outside the small bowel (Li et al., 2008; Van Weyenberg et al., 2010; Han et al., 2017), or defined capsule retention only inside the small intestine (Höög et al., 2012). In study I, some capsule retentions were detected in the esophagus and in the stomach despite previous negative esophagogastroduodenoscopies in other institutions. Although

more than one third of the retentions seem to be avoidable by correct upper or lower endoscopy our policy was to accept patients for VCE with a previous negative flexible endoscopy performed within 3 months at other institutions. These data indicate that repeated high-quality endoscopy prior to VCE should be considered to reduce the risk of capsule retention.

Novel guidelines recommend observation in cases of asymptomatic capsule retention and medical treatment that may stimulate capsule excretion. If capsule retrieval is indicated device assisted enteroscopy should be performed (Rondonotti et al., 2018). In early capsule studies, capsule retention was largely managed by surgical intervention (Li et al., 2008; Höög et al., 2012; Fernández-Urien et al., 2015), however, later studies have reported a more favorable clinical outcome using endoscopic methods (Van Weyenberg et al., 2010; Xin et al., 2012). We detected a similar strategy in our material; surgery was the method of choice for capsule extraction before 2006, while a majority of capsule retentions were managed endoscopically since double-balloon enteroscopy have been eligible.

Capsule retention can be theoretically prevented by the use of radiological small bowel examinations. While small bowel follow-through and abdominal CT are not suitable to detect small bowel strictures (Rondonotti et al., 2005), specific radiological imaging techniques may prove small bowel patency (Fernández-Urien et al., 2015). Some studies showed high efficacy of the radiological methods (Rozendorn et al., 2016) as other publications described several capsule retentions in patients who underwent negative cross-sectional imaging before VCE (Van Weyenberg et al., 2010). In study I, negative radiological examinations like MRE did not exclude small bowel stenosis and about one fourth of the small bowel capsule retentions occurred after specific cross-sectional imaging had been performed.

Patency capsule

The patency capsule is an important tool for valuation of small bowel patency. Application of a patency capsule may significantly reduce the risk of capsule retention (Spada et al., 2005). As mentioned above, the current guidelines suggest that a patency capsule should be used to confirm small bowel patency before performing VCE, if the patient has higher risk of capsule retention (Rondonotti et al 2018). In study II, the risk of capsule retention in patients with established Crohn's

disease was low (2.3%) and no clinical or demographic factors associated with risk of capsule retention were identified. Previous studies reported that capsule retention occurs more often in patients with known Crohn's disease (Cheifetz et al., 2006; Höög et al., 2012). Importantly, small bowel patency capsule test was not used before capsule administration in these studies. Cross sectional imaging or the patency capsule were systematically performed before VCE in later studies, with subsequent significantly lower retention rates (Esaki et al., 2014; Niv et al., 2014). In study II, the risk of capsule retention was significantly higher in patients who underwent VCE after a positive patency capsule test, unless stenosis was ruled out on subsequent cross-sectional imaging. Notably, use of a video capsule after a positive patency capsule test is not recommended by the manufacturer.

Patency capsule test should be considered in patients with known Crohn's disease if small bowel stenosis is not excluded (Maaser et al., 2018). Nevertheless, it was not known whether routine use of a patency capsule prior VCE to all patients with Crohn's disease reduces the risk of video capsule retention. This question was evaluated in study II by comparing the risk of retention utilizing a selective strategy and a nonselective strategy as mentioned above. The risk of capsule retention was comparable in the two groups. Furthermore, more video capsules and fewer patency capsules were used in the selective group that improved the diagnostic yield and decreased the costs. Consequently, we suppose that the routine administration of a patency capsule to all patients with established Crohn's disease is not necessary. Based on our result we recommend that the use of patency capsule should be limited to patients at high risk of video capsule retention, such as history of abdominal surgery and small bowel obstruction. Since capsule retention is a rare complication, even prospective studies and larger cohorts can be necessary in order to better analyze this patient group.

Previous small studies described complications with a patency capsule as uncommon (Delvaux et al., 2005; Herrerias et al., 2008). Majority of these patients have abdominal pain with rare cases of evident small bowel obstruction. We observed 2.2 % of symptomatic patency capsule retention in our study and none of these patients needed endoscopic or surgical interventions. A subsequent larger study investigated the risk of patency capsule retention in the small bowel and identified only 1.2% patency capsule retention rate in 1615 examinations. Only a single patient required ileocecal resection (Kopylov et al., 2016a). Nevertheless, this minor additional risk should also be incorporated into the evaluation process before patency capsule test.

VCE retention can occur after negative patency capsule test (Postage et al., 2008; Van Weyenberg et al., 2010). In study II, four video capsule retentions were observed in patients who underwent negative patency capsule test. In these cases the patency capsule was localized using plain abdominal film and not by use of the hand-held scanner as it had been performed in the original validation study (Spada et al., 2005). Indeed, there is still uncertainty concerning optimal technique to localize the patency capsule in the bowel lumen. The inaccuracy of the plain abdominal radiography for patency capsule localization was confirmed also in a previous study and dedicated low-radiation CT protocol was suggested. (Assadsangabi et al., 2015).

Crohn's disease

While radiological techniques such as MRE and ultrasound have improved, they mainly visualize the transmural bowel inflammation, have limited sensitivity for superficial lesions and cannot entirely exclude small bowel involvement (Jensen et al., 2017; Maaser et al., 2018). VCE is patient friendly and noninvasive method compared to cross-sectional imaging and allows a complete evaluation of the entire small bowel mucosa with a high sensitivity for minor lesions of Crohn's disease (Greener et al., 2016; Lahat et al., 2017). Our results in study III demonstrate that VCE is associated with a significant clinical impact in patients with established Crohn's disease.

There is a lack of large prospective studies directly comparing the feasibility, sensitivity and specificity of VCE with that of radiological methods in patients with established Crohn's disease (Jensen et al., 2017). A retrospective trial showed that VCE added significant diagnostic information and subsequent impact on the therapy of Crohn's disease (Kalla et al., 2013). At the same time, another retrospective study with established Crohn´s disease found proximal small bowel lesions in the majority of the patients, and the presence of jejunal lesions was an independent risk factor for future clinical relapse (Flamant et al., 2013). Furthermore, in a recent a systematic review, the diagnostic yield of VCE was comparable to MRE and small bowel intestinal contrast ultrasound, and in the proximal small bowel VCE seemed to be superior to the radiological methods (Kopylov et al, 2017a). In study III about 50% of the patients with small bowel Crohn's disease had proximal involvement. Recently, a prospective trial evaluated 50 patients with previous negative CTE/MRE studies for proximal Crohn's disease. VCE detected proximal small bowel

involvement in 14 of these 50 patients (Hansel et al., 2018). Aforementioned studies support the use of VCE in the diagnostic algorithm of Crohn's disease.

There is no gold standard for determining therapeutic success in Crohn´s disease. Clinical scoring systems as the Crohn's disease activity index cannot correctly estimate bowel inflammation (Maaser et al., 2018). However, increasingly clinical experience propose that mucosal healing could modify the natural history of Crohn's disease by decreasing relapse rates, hospitalization days, and risk for surgery (Baert et al., 2010; Colombel et al., 2010; Colombel et al., 2014). Recent clinical trials have shown that VCE can precisely visualize mucosal healing in the small bowel (Niv et al., 2012; Hall et al., 2014). These studies used the capsule endoscopy Crohn's disease activity index to quantify small bowel inflammation (Gal et al., 2008).

In study III, we applied the commonly accepted endoscopic scoring system (LS) in a large cohort of patients with established Crohn's disease. The LS was developed to quantify small bowel inflammatory changes and was validated for the evaluation of small bowel Crohn's disease activity (Cotter et al., 2015). However, LS has certain problems in the monitoring of established Crohn's disease as strictures are strongly weighted components of the LS. Since a known small bowel stricture is a relative contraindication for VCE and confirming functional patency of the small bowel is recommended before using the capsule (Pennazio et al., 2015), there are only few patients with stricturing phenotype that are eligible for VCE. Consequently, in study III, patients with stricturing disease or strictures found on VCE were relatively rare. Furthermore, the LS divides the small bowel into 3 tertiles that are scored independently, and only the tertile with the highest score is used as LS of the procedure. Hence, a patient who has involvement in the entire small bowel may have identical LS to a patient who only has findings in a single tertile. Additionally, the authors reported about a significant overlap in the scores of patients with mild and moderate-to-severe disease (Gralnek et al., 2008). Despite of the abovementioned limitations a novel clinical trial evaluated VCE with LS for assessment of small bowel Crohn´s disease and found the procedure as feasible and valid as ileocolonoscopy (Melmed et al., 2018). Modified LS adjusted for monitoring of Crohn's disease can be used in prospective trials in the future.

Fecal calprotectin is an unspecific marker for bowel inflammation and is frequently used as a screening tool for diagnosis of Crohn's disease, monitoring of mucosal healing and prediction of relapse (Maaser et al., 2018). Elevated CRP, FCP or the combination of both poorly correlated with significant small bowel inflammation in our study. The efficacy of fecal calprotectin for small bowel Crohn's disease has

been debated. Some studies have reported a high sensitivity of fecal calprotectin for small bowel Crohn's disease (Jensen et al., 2011) or found that fecal calprotectin levels <100 mg/kg excluded small bowel Crohn's disease (Koulaouzidis et al., 2011). In a subsequent study, fecal calprotectin had low utility in prediction of small bowel Crohn's disease detected by VCE (Sipponen et al., 2012). In a recent meta-analysis fecal calprotectin >50 mg/kg had a sensitivity and specificity of 83% and 53% for detection of small bowel Crohn's disease (Kopylov et al., 2016b). Interestingly, large differences in fecal calprotectin values from 2 consecutive days has been shown in patients with Crohn's disease (Moum et al., 2010) that indicates that more studies are needed to completely identify the role of fecal calprotectin in this disorder.

Pediatric procedures

VCE has become a valuable and popular diagnostic tool in pediatrics due to the lack of ionizing radiation and potential to visualize the entire small bowel mucosa without anesthesia (Friedlander et al., 2017). Study IV showed that VCE is safe method and has a significant impact on clinical management of pediatric patients with suspected and known Crohn's disease. The earlier published large single-center pediatric cohorts investigated patients up to more than 20 years and they did not analyze the role of VCE in the management of Crohn's disease (Atay et al., 2009; Jensen et al., 2010; Cohen et al., 2012). However more than 50% of pediatric VCEs have been performed in patients with suspected or known Crohn's disease (Oliva et al., 2014). Our study included patients up to 18 years old and we found a 49% detection rate of erosive lesions in the small bowel, which is comparable to previously published data (Thomson et al., 2007; Cohen et al, 2012). Furthermore, a majority (81%) of the small bowel findings were diagnostic for Crohn's disease.

The first concern before pediatric VCE is that not every patient can swallow the capsule. Several devices can be used to place the capsule into the duodenum. Endoscopic placement of the capsule used to be performed under carefully monitored conditions or in general anesthesia to avoid capsule placement in the trachea. Nonetheless, the use of general anesthesia may result in longer small bowel transit time (Oikawa-Kawamoto et al., 2013) which can lead to incomplete procedures. In our study, 42% of the capsules placed endoscopically in the duodenum did not reach the colon during recording time whereas the overall rate of the incomplete procedures (17%) compares well with that in other studies, ranging

from 21% to 23% (Jensen et al., 2010; Nuutinen et al., 2011; Cohen et al., 2012). However, the capsule visualized small bowel mucosa in all incomplete procedures. Remarkably, Crohn's disease was diagnosed more often (43%) in patients with incomplete examinations than those with complete procedures (38%), indicating that incomplete VCE examinations do not decrease the diagnostic yield. In fact, the capsule still spends on average more than 7 h examining small bowel even if not reaching the cecum during recording time that can explain the valuable results of the incomplete procedures.

The use of laxatives has been debated in many years, current guidelines recommend purgative prior to VCE for better visualization (Rondonotti et al., 2018). However, a recent meta-analysis of adult studies showed that laxatives do not improve completion rate or diagnostic yield in VCE, despite better mucosal visualization. The authors suggested that the use of laxatives might be useful in patients likely to have minor findings (Yung et al., 2017a). The use of polyethylene glycol solution and oral simethicone as the preparation of choice for VCE was recommended in a previous prospective pediatric study. This publication showed that despite improvement in small bowel visualization, there was not a significant difference in the overall diagnostic yield between the study arms (Oliva et al., 2014). In study IV, VCE was performed without bowel preparation and small bowel cleanliness grading because Crohn findings in the small bowel are often multiple and missing minor mucosal lesions does not humper diagnostic yield of VCE. Moreover, use of laxatives might increase patient discomfort and decrease compliance in children.

Future perspectives

The first diagnostic video capsule was called “M2A” (mouth to anus) and was introduced in 2001. It was intended to be used as a “whole gut” capsule. However, it turned out that “M2A” was actually best for visualizing the small bowel mucosa. Since then further technical developments have been achieved, such as a magnetically controlled capsule for gastric cancer screening (Zhao et al., 2018), X-ray imaging capsule aiming for colon cancer screening without bowel preparation (Gluck et al., 2016) or Endoluminal Image Analysis which is designed to demonstrate intestinal motor abnormalities in patients with functional bowel disorders (Malagedela et al., 2015).

The capsule might be equipped with more advanced technologies to increase diagnostic yield in the future. Currently, no commercially available capsule is capable of taking biopsies or performing therapeutic interventions. Another important aspect for future success of the current video capsule is automation (Nowak, 2017). A promising project creating a database of VCE images and videos with both graphic and semantic annotations is the KID project, which has been developed specifically for medical decision support systems research (Koulaouzidis et al, 2017). However, incorporating machine learning algorithms into capsule reading is difficult as large amounts of image annotations are required for training. Artificial intelligence could be used to identify abnormalities in the digestive tract as well as classify these findings and their exact location. In a future endoscopic unit, this information could be sent to the endoscopic screen to guide next steps (Nowak, 2017).

Based on the rapid development of wireless endoscopic technology it is great challenge to predict the future progress of VCE. Perhaps, we should follow the Hungarian Nobel Prize winner Dennis Gabor's approach: “The future cannot be predicted, but futures can be invented”.

Conclusions

- Capsule retention is a rare complication of VCE. Careful patient selection in combination with adequate use of patency capsule decreases the risk of capsule retention.
- Majority of patients with capsule retention can be safely and effectively managed with endoscopic intervention instead of surgery.
- Routine nonselective administration of the patency capsule before VCE in patients with established Crohn's disease is not likely to reduce the risk of video capsule retention.
- VCE provides meaningful results leading to therapeutic changes in majority of patients with established Crohn's disease.
- VCE should not be restricted to Crohn's disease patients with positive inflammatory markers because their predictive value for significant small bowel inflammation is limited.
- VCE has a significant clinical impact on the management of children and adolescents with suspected and established Crohn's disease.

Populärvetenskaplig sammanfattning

Traditionellt har man inte kunnat undersöka tunntarmen i detalj utan bara övre delen och nedre delen av mag-tarmkanalen med gastroskopi och koloskopi, respektive. Gastrointestinala sjukdomar, med eller utan tunntarmsengagemang, främst blödning, tumörer och inflammation är vanligt förekommande med signifikant morbiditet, mortalitet och nedsatt livskvalitet för drabbade patienter. Utredning och behandling av dessa patienter involverar både primär- och specialistvård och tar stora sjukvårdsresurser i anspråk.

Trots sedvanlig, omfattande och kostsam utredning med gastroskopi, koloskopi, radiologiska metoder (bariumröntgen, CT/MR, angiografi, scintigrafi) och även kirurgi hos cirka 5-10 % av patienter med blödning, förblir blödningskällan oklar och misstanke om blödningskällans tunntarmslokalisation kvarstår. Diagnostiken av inflammatorisk tunntarmssjukdom (Crohns sjukdom) är ofta fördröjd med flera år räknat från symptomdebuten pga. att tillgängliga undersökningsmetoder är otillförlitliga. Dessutom, är dagens diagnostiska metoder ofta obehagliga för patienter och innebär en inte försumbar risk för komplikationer såsom perforation, blödning, hjärt-lungpåverkan och röntgenstrålning.

Med kapselendoskopi (sväljbar kamera) kan man nu undersöka även tunntarmen i detalj endoskopiskt vilket skulle kunna påverka diagnostik och behandling av patienter med sjukdomar i tunntarmen. Den naturliga peristaltiken gör att den nedsvalda kapseln passerar genom hela tarmsystemet samtidigt som bilder tas och registreras i en bärbar dator. Utrustningen består av tre delar: kapseln, mottagaren (en liten bärbar dator) som patienten bär på sig och ett digitalt system som installerad i en vanlig dator som finns på sjukhuset och där bilderna laddas ner och granskas.

Kapseln är 26 x 11 mm stor och innehåller ett litet TV-chip samt 6 stycken dioder som blinkar 2–4 gånger i sekunden. Kapseln innehåller en liten kamera som tar panoramabilder. Bilderna transmitteras via en radiosignal till antenner arrangerade i ett bälte runt patientens midja. Signalen spelas in på en bärbar dator och laddas ner för en senare utvärdering i form av en högkvalitativ videofilm. Batterierna som driver kapselkameran innehåller silveroxidbatterier som varar upp till 15 timmar.

Mottagaren har kapacitet att lagra mer än 100 000 bilder. Bilderna är förstorade med 8 gånger och kan detektera slemhinneförändringar ned till 1,1 mm. Kapseln är biologiskt inert, miljövänligt och lämnar kroppen med avföringen. Patienter med obstruktiva tarmsymptom undersökas med en testkapsel för att utesluta tunntarmsförträngningar.

Avhandlingens övergripande syfte var att utvärdera betydelsen av kapselendoskopi för hanterandet av patienter med patologi i tunntarmen framförallt med avseende kronisk inflammation men också med avseende på komplikationer såsom kapselretention och sätt att identifiera riskpatienter.

Studie I: Kapselretention

Syftet med den här studien var att undersöka incidensen, orsaker, riskfaktorer, behandlingsmöjligheter och kliniskt resultat med avseende på kapselretention. Journaler på alla patienter som genomgått kapselendoskopi mellan 2001 och 2011 i Malmö har granskats retrospektivt. kapselretention definierades som kvarvarande av kapseln mer än 2 veckor efter intag eller om kapseln krävde medicinsk, endoskopisk eller kirurgisk åtgärd.

2401 konsekutiva kapselendoskopi utfördes under en 10-års period. Indikationer för kapselendoskopi var misstänkt (982) och känd (392) Crohns sjukdom (CS) (1374, 57%), oklar GI-blödning (817, 34%) och övriga indikationer hos 218 (9%) patienter. Tunntarmsstriktur uteslöts hos 1254 (52%) patienter med tunntarmsröntgen (481 patienter) och testkapsel (773 patienter). Kapselretention inträffades i 25 fall (1%) och oftast i tunntarmen (68%). 14 av 25 patienter med kapselretention har genomgått radiologisk tunntarmsundersökning (12/14) alt testkapsel (2/14) före kapselendoskopin. 7 av 25 patienter (28%) hade symtom i samband med kapselretention. I 5 fall behövdes akut undersökning för att hämta ut kapseln, varav tre löstes endoskopiskt och två har genomgått operation. 17 fall kunde hanteras planerat varav 8 endoskopisk, 6 kirurgisk och 3 med medicinsk metod. Tre fall löstes spontant.

Vårt material är som visar att kapselretention är en mycket sällsynt komplikation och associerad med en gynnsam klinisk utgång. De flesta patienter med kapselretention kan hanteras planerat med icke-kirurgiska metoder.

Studie II: Patency kapsel

Syftet med detta arbete var att undersöka hur testkapselns (patency) användning påverkar risken för kapselretention hos patienter med känd Crohns sjukdom.

Samtidigt försökte vi ta reda på om risken för kapselretention kan minskas med att alla patienter genomgår testkapsel innan kapselendoskopin. I en retrospektiv multicentrisk studie deltog 3 endoskopienheter från Malmö, Quebec och Edinburgh. Inkluderades patienter med Crohns sjukdom som genomgått kapselendoskopi mellan 2005 juni och 2013 december. Patency kapsel har använts med 2 olika metoder, non selektiv metod (alla patienter svalde testkapseln) och selektiv metod (endast patienter med misstänkt obstruktion i tunntarmen svalde testkapseln).

406 patientens data analyserades. 132 patienter (32,5%) har genomgått kapselendoskopi utan föregående testkapsel. Testkapsel användes i 274 fall och blev negativ (passerat kroppen) hos 193 patienter. Kapselretention inträffades i 2,3% av patienter som inte har genomgått testkapsel och 2,1% av patienter som har genomgått negativ testkapsel (P=0,9). 18 patienter har genomgått kapselendoskopi trots positiv testkapsel (testkapseln har inte lämnat kroppen) med en retention av 11% (P=0,001). Risken för kapselretention inte minskade om alla patienter genomgått testkapsel före kapselendoskopin.

Vi konkluderade att kapselretention är en liten risk för patienter med känd Crohns sjukdom och risken kan inte minskas med att alla patienter genomgår testkapsel före kapselendoskopin. Samtidigt ökar risken för kapselretention om patienten genomgår kapselendoskopi efter en positiv testkapselundersökning.

Studie III: Kapselendoskopi vid Crohns sjukdom

Syftet med denna kliniska studie var att undersöka kapselendoskopins säkerhet och kliniska betydelse hos patienter med känd Crohns sjukdom. Samtidigt försökte vi utvärdera inflammatoriska biomarkörers diagnostiska värde.

I ett retrospektiv multicentrisk studie analyserades 187 patienter med etablerad Crohns sjukdom i fyra akademiska centra i Sverige, Kanada och Storbritannien under perioden 2008 - 2013. Inflammationen i tunntarmen kvantifierades med Lewis score. C- reaktivt protein och fekal kalprotektin värden blev korrelerad med Lewis score. I studien inkluderas 187 patienter. Svår tunntarmsinflammation hittades i 45% måttlig inflammation i 26,6% och ingen inflammation i 28,4%. Ändring av behandlingen rekommenderades hos 99 (52,3%) patienter. Två patienter (1 %) genomgick kirurgi. Förhöjda inflammatoriska markörer som faces kalprotektin och CRP, eller kombination av båda, var dåligt korrelerade med tecken på Crohns sjukdom i tunntarmen. Kapselretention inträffades i 4 fall (2,1%).

Slutsatsen vi drog var att kapselendoskopi är en säker metod med signifikant terapeutisk effekt hos patienter med känd Crohns sjukdom. Kapselendoskopi bör

inte begränsas till patienter med positiva inflammatoriska markörer eftersom dess prediktiva värde är svagt för sjukdomsaktivitet hos patienter med känd Crohns sjukdom.

Studie IV: Kapselendoskopi hos barn och ungdomar

Syftet med studien var att undersöka kapselenteroskopins säkerhet och kliniska betydelse hos barn och ungdomar med känd eller suspekt Crohns sjukdom. Journaler på alla patienter som genomgått kapselendoskopi mellan 2003 och 2014 i Malmö har granskats retrospektivt.

180 konsekutiva kapselendoskopi utfördes hos 169 patienter. Indikationen var misstänkt Crohns sjukdom i 125 fall och känd Crohns sjukdom i 55 fall. 154 patienter svalde kapseln medan 26 kapsel blev placerad i duodenum med gastroskop. Patency kapsel utfördes i 71 fall för att utesluta tunntarmsobstruktion. Kapselendoskopi visade tecken på Crohns sjukdom i 71 (40%) fall medan 17 (9%) undersökningar visade minimala förändringar som inte var diagnostiska för Crohns sjukdom. Kapseln visade normal tunntarmsslemhinna i 92 (51%) fall. Terapiändringar rekommenderades i 56 (31%) efter kapselendoskopi. Kapselretention inträffade hos en patient.

Vi konkluderade att kapselendoskopi en säker metod hos barn och ungdomar med suspekt och känd Crohns sjukdom. Kapselendoskopi bekräftar ofta diagnosen och har a signifikant betydelse på den kliniska handläggningen.

Acknowledgements

I want to thank all the people who made this work possible. I would like to express my appreciation to:

All the patients who participated in the studies.

Ervin Tóth, my excellent principal supervisor, clinical tutor and friend. He has invited me to Sweden and guided me through this journey and gave me the motivation to continue my research. Especially thanks for his kindness and patience. His enthusiasm and passion have been outstanding and will guide me in the future.

Henrik Thorlacius my brilliant co-supervisor. This thesis would not have been possible without his engagement. He has been an excellent guide providing me a broad education in research and has been always available for discussions and questions. He has been an unending source of inspiration and support.

Uri Kopylov and Anastasios Koulaouzidis, my co-authors, for excellent collaboration and outstanding ideas.

The nurses, assistant nurses and secretaries at the Endoscopy Unit, Skåne University Hospital in Malmö for their kindness, acceptance, helpfulness and creating a home atmosphere.

The management and the colleagues at the Department of Gastroenterology, Surgery and Pediatrics, Skåne University Hospital in Malmö, for creating stimulating working conditions. Especially to my colleagues Gabriele Wurm Johansson and Jörgen Nielsen (Endoscopy Unit), Jan Lillienau, Daniel Klintman and Stefan Lindgren (Department of Gastroenterology), Sara Regnér (Department of Surgery), Daniel Agardh (Deparment of Pediatrics) and Marek Wroblewski (in memoriam, former Department of Medicine).

The management, colleagues, nurses and patients at the 1st Department of Medicine and Gastroenterology, Petz Aladár County and Teaching Hospital in Györ, Hungary, for introducing me in the world of medicine and endoscopy. Special thanks to professor István Rácz and Rózsa Fehér.

Erzsébet Fehér and Éva Pöltz for all selfless help.

Hilda Pattogató and Károly Németh, my loving parents for their support and patience, always believing in me.

My wonderful daughters, Noémi and Rebeka.

My wife, Eszter.

This work was supported by grants for PhD students from Region Skåne and by the Swedish Medical Research Council.

References

Adler SN (2017). The history of time for capsule endoscopy. Ann Transl Med. 5(9):194.

Al-Bawardy B, Locke G, Huprich JE, Fletcher JG, Fidler JL, Barlow JM, et al. (2015). Retained Capsule Endoscopy in a Large Tertiary Care Academic Practice and Radiologic Predictors of Retention. Inflamm Bowel Dis. 21(9):2158-64.

Assadsangabi A, Blakeborough A, Drew K, Lobo AJ, Sidhu R, McAlindon ME (2015). Small bowel patency assessment using the patency device and a novel targeted (limited radiation) computed tomography-based protocol. J Gastroenterol Hepatol. 30(6):984-9.

Atay O, Mahajan L, Kay M, Mohr F, Kaplan B, Wyllie R (2009). Risk of capsule endoscope retention in pediatric patients: a large single-center experience and review of the literature. J Pediatr Gastroenterol Nutr. 49(2):196-201.

Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. (2010). Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 138(2):463-8

Baichi MM, Arifuddin RM, Mantry PS (2006). What we have learned from 5 cases of permanent capsule retention. Gastrointest Endosc. 64(2):283-7.

Bandorski D, Kurniawan N, Baltes P, Hoeltgen R, Hecker M, Stunder D, et al. (2016). Contraindications for video capsule endoscopy. World J Gastroenterol. 22(45):9898-9908.

Baumgart DC, Carding SR (2007). Inflammatory bowel disease: cause and immunobiology. Lancet. 12;369(9573):1627-40.

Bhattarai M, Bansal P, Khan Y (2013). Longest duration of retention of video capsule: A case report and literature review. World J Gastrointest Endosc. 16;(7):352-5.

Büsch K, Ludvigsson JF, Ekström-Smedby K, Ekbom A, Askling J, Neovius M (2014). Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. Aliment Pharmacol Ther. 39(1):57-68.

Caunedo-Alvarez A, Romero-Vazquez J, Herrerias-Gutierrez JM (2008). Patency and Agile capsules. World J Gastroenterol. 14(34):5269-73.

Cave D, Legnani P, de Franchis R, Lewis BS; ICCE (2005). ICCE consensus for capsule retention. Endoscopy. 37(10):1065-7.

Cheifetz AS, Kornbluth AA, Legnani P, Schmelkin I, Brown A, Lichtiger S, et al. (2006). The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 101(10):2218-22.

Cohen SA, Ephrath H, Lewis JD, Klevens A, Bergwerk A, Liu S, et al. (2012). Pediatric capsule endoscopy: review of the small bowel and patency capsules. J Pediatr Gastroenterol Nutr. 54(3):409-13.

Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. (2010). Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 362(15):1383-95.

Colombel JF, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, et al. (2014). Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol. 12(3):414-22.e5.

Cosnes J, Gower-Rousseau C, Seksik P, Cortot A (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 140(6):1785-94.

Cotter J, Dias de Castro F, Magalhães J, Moreira MJ, Rosa B (2015). Validation of the Lewis score for the evaluation of small-bowel Crohn's disease activity. Endoscopy. 47(4):330-5.

Davison C (2006). Reader extender of capsule endoscopy. Tech Gastrointest Endosc. 8(1):188-93

Delvaux M, Ben Soussan E, Laurent V, Lerebours E, Gay G (2005). Clinical evaluation of the use of the M2A patency capsule system before a capsule endoscopy procedure, in patients with known or suspected intestinal stenosis. Endoscopy. 37(9):801-7.

de Melo SW Jr, Di Palma JA (2012). The role of capsule endoscopy in evaluating inflammatory bowel disease. Gastroenterol Clin North Am. 41(2):315-23.

Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, et al. (2010). Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol. 105(6):1240-8.

Eliakim R, Spada C, Lapidus A, Eyal I, Pecere S, Fernández-Urién I, et al. (2018). Evaluation of a new pan-enteric video capsule endoscopy system in patients with suspected or established inflammatory bowel disease - feasibility study. Endosc Int Open. 6(10):E1235-E1246.

Enns RA, Hookey L, Armstrong D, Bernstein CN, Heitman SJ, Teshima C, et al. (2017). Clinical Practice Guidelines for the Use of Video Capsule Endoscopy. Gastroenterology. 152(3):497-514.

Esaki M, Matsumoto T, Watanabe K, Arakawa T, Naito Y, Matsuura M, et al. (2014). Use of capsule endoscopy in patients with Crohn's disease in Japan: a multicenter survey. J Gastroenterol Hepatol. 29(1):96-101.

Fernández-Urién I, Carretero C, González B, Pons V, Caunedo Á, Valle J, Redondo-Cerezo E, et al. (2015). Incidence, clinical outcomes, and therapeutic approaches of capsule endoscopy-related adverse events in a large study population. Rev Esp Enferm Dig. 107(12):745-52.

Flamant M, Trang C, Maillard O, Sacher-Huvelin S, Le Rhun M, Galmiche JP, et al. (2013). The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. Inflamm Bowel Dis. 19(7):1390-6.

Friedlander JA, Liu QY, Sahn B, Kooros K, Walsh CM, Kramer RE, et al. (2017). NASPGHAN Capsule Endoscopy Clinical Report. J Pediatr Gastroenterol Nutr. 64(3):485-494.

Gal E, Geller A, Fraser G, Levi Z, Niv Y (2008). Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Dig Dis Sci. 53(7):1933-7.

Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, et al. (2000). A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis. 6(1):8-15.

Given Imaging ltd. (2013). Pillcam SB. Information for health professionals. http://www.givenimaging.com/en-us/Innovative-Solutions/Capsule-Endoscopy/PillcamSB/HCP-resources/pages/What-Your-Patient-Can-Expect.aspx.

Gluck N, Shpak B, Brun R, Rösch T, Arber N, Moshkowitz M (2016). A novel prepless X-ray imaging capsule for colon cancer screening. Gut. 65(3):371-3.

Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG; Investigators (2005). Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol. 3(2):133-41.

Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. (2017). 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 11(1):3-25.

Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS (2008). Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther. 15;27(2):146-54.

Greener T, Klang E, Yablecovitch D, Lahat A, Neuman S, Levhar N, et al. (2016). The Impact of Magnetic Resonance Enterography and Capsule Endoscopy on the Re-classification of Disease in Patients with Known Crohn's Disease: A Prospective Israeli IBD Research Nucleus (IIRN) Study. J Crohns Colitis. 10(5):525-31.

Hall B, Holleran G, Chin JL, Smith S, Ryan B, Mahmud N, et al. (2014). A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. J Crohns Colitis. 8(12):1601-9.

Han Z, Qiao W, Ai X, Li A, Chen Z, Zhang J, et al. (2018). Risk factors for surgery in patients with retention of endoscopic capsule. Scand J Gastroenterol. 53(1):107-113.

Hansel SL, McCurdy JD, Barlow JM, Fidler J, Fletcher JG, Becker B, et al. (2018). Clinical Benefit of Capsule Endoscopy in Crohn's Disease: Impact on Patient Management and Prevalence of Proximal Small Bowel Involvement. Inflamm Bowel Dis. 24(7):1582-1588.

Herrerias JM, Leighton JA, Costamagna G, Infantolino A, Eliakim R, Fischer D, et al. (2008). Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. Gastrointest Endosc. 67(6):902-9.

Höög CM, Bark LÅ, Arkani J, Gorsetman J, Broström O, Sjöqvist U (2012). Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations. Gastroenterol Res Pract. 2012:518718.

Iddan G, Meron G, Glukhovsky A, Swain P (2000). Wireless capsule endoscopy. Nature. 25;405(6785):417.

Jensen MK, Tipnis NA, Bajorunaite R, Sheth MK, Sato TT, Noel RJ (2010). Capsule endoscopy performed across the pediatric age range: indications, incomplete studies, and utility in management of inflammatory bowel disease. Gastrointest Endosc. 72(1):95-102.

Jensen MD, Kjeldsen J, Nathan T (2011). Fecal calprotectin is equally sensitive in Crohn's disease affecting the small bowel and colon. Scand J Gastroenterol. 46(6):694-700.

Jensen MD, Brodersen JB, Kjeldsen J (2017). Capsule endoscopy for the diagnosis and follow up of Crohn's disease: a comprehensive review of current status. Ann Gastroenterol. 30(2):168-178.

Kalla R, McAlindon ME, Drew K, Sidhu R (2013). Clinical utility of capsule endoscopy in patients with Crohn's disease and inflammatory bowel disease unclassified. Eur J Gastroenterol Hepatol. 25(6):706-13.

Karagiannis S, Faiss S, Mavrogiannis C (2009). Capsule retention: a feared complication of wireless capsule endoscopy. Scand J Gastroenterol. 44(10):1158-65.

Keuchel M, Hagenmüller F and Tajiri H (eds.) A Comprehensive Guide and Atlas. Springer 2015

Kopylov U, Seidman EG (2014). Role of capsule endoscopy in inflammatory bowel disease. World J Gastroenterol. 20(5):1155-64.

Kopylov U, Nemeth A, Cebrian A, Wurm Johansson G, Thorlacius H, Fernandez-Urien et al. (2016a). Symptomatic retention of the patency capsule: a multicenter real life case series. Endosc Int Open. 4(9):E964-9.

Kopylov U, Yung DE, Engel T, Avni T, Battat R, Ben-Horin S, et al. (2016b). Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 28(10):1137-44.

Kopylov U, Yung DE, Engel T, Vijayan S, Har-Noy O, Katz L, et al. (2017a). Diagnostic yield of capsule endoscopy versus magnetic resonance enterography and small bowel contrast ultrasound in the evaluation of small bowel Crohn's disease: Systematic review and meta-analysis. Dig Liver Dis. 49(8):854-863.

Kopylov U, Yung DE, Koulaouzidis A, Eliakim R (2017b). Retention rate in small-bowel capsule endoscopy. Gastrointest Endosc. 86(3):573.

Koulaouzidis A, Douglas S, Rogers MA, Arnott ID, Plevris JN (2011). Fecal calprotectin: a selection tool for small bowel capsule endoscopy in suspected IBD with prior negative bi-directional endoscopy. Scand J Gastroenterol. 46(5):561-6.

Koulaouzidis A, Iakovidis DK, Yung DE, Rondonotti E, Kopylov U, Plevris JN, et al. (2017). KID Project: an internet-based digital video atlas of capsule endoscopy for research purposes. Endosc Int Open. 5(6):E477-483.

Lahat A, Kopylov U, Amitai MM, Neuman S, Levhar N, Yablecovitch D, et al. (2016). Magnetic resonance enterography or video capsule endoscopy - what do Crohn's disease patients prefer? Patient Prefer Adherence. 10:1043-50.

Leighton JA, Gralnek IM, Cohen SA, Toth E, Cave DR, Wolf DC, et al. (2014). Capsule endoscopy is superior to small-bowel follow-through and equivalent to

ileocolonoscopy in suspected Crohn's disease. Clin Gastroenterol Hepatol. 12(4):609-15.

Li F, Gurudu SR, De Petris G, Sharma VK, Shiff AD, Heigh RI, et al. (2008). Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. Gastrointest Endosc. 68(1):174-80.

Liao Z, Gao R, Xu C, Li ZS (2010). Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc. 71(2):280-6.

Lin OS, Brandabur JJ, Schembre DB, Soon MS, Kozarek RA (2007). Acute symptomatic small bowel obstruction due to capsule impaction. Gastrointest Endosc. 65(4):725-8.

Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. (2018). ECCO-ESGAR Guideline for Diagnostic Assessment in Inflammatory Bowel Disease. J Crohns Colitis. Aug 23 doi: 10.1093/ecco-jcc/jjy113. [Epub ahead of print].

Macias E, Elosua A, Fernández-Urién I (2019). One more reason to avoid purgatives before capsule endoscopy examinations: Hypokalemia and low completion rates. Saudi J Gastroenterol. Jan 14. doi: 10.4103/sjg.SJG_577_18. [Epub ahead of print]

Malagelada C, Drozdzal M, Seguí S, Mendez S, Vitrià J, Radeva P, et al. (2015). Classification of functional bowel disorders by objective physiological criteria based on endoluminal image analysis. Am J Physiol Gastrointest Liver Physiol. 309(6):G413-9.

Melmed GY, Dubinsky MC, Rubin DT, Fleisher M, Pasha SF, Sakuraba A, et al. (2018). Utility of video capsule endoscopy for longitudinal monitoring of Crohn's disease activity in the small bowel: a prospective study. Gastrointest Endosc. 88(6):947-955.

Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, et al. (2007). Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. Endoscopy. 39(10):895-909.

Mitselos IV, Katsanos K, Tsianos EV, Eliakim R, Christodoulou D (2018). Clinical Use of Patency Capsule: A Comprehensive Review of the Literature. Inflamm Bowel Dis. 24(11):2339-2347.

Moum B, Jahnsen J, Bernklev T (2010). Fecal calprotectin variability in Crohn's disease. Inflamm Bowel Dis. 16(7):1091-2.

Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. (2018). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 390(10114):2769-2778.

Niv E, Fishman S, Kachman H, Arnon R, Dotan I (2014). Sequential capsule endoscopy of the small bowel for follow-up of patients with known Crohn's disease. J Crohns Colitis. 8(12):1616-23.

Nowak T (2017). A global perspective on capsule endoscopy. Ann Transl Med. 5(21):422.

Nuutinen H, Kolho KL, Salminen P, Rintala R, Koskenpato J, Koivusalo A, et al. (2011). Capsule endoscopy in pediatric patients: technique and results in our first 100 consecutive children. Scand J Gastroenterol. 46(9):1138-43.

Niv E, Fishman S, Kachman H, Arnon R, Dotan I (2014). Sequential capsule endoscopy of the small bowel for follow-up of patients with known Crohn's disease. J Crohns Colitis. 8(12):1616-23.

Niv Y, Ilani S, Levi Z, Hershkowitz M, Niv E, Fireman Z, et al. (2012). Validation of the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score): a multicenter prospective study. Endoscopy. 44(1):21-6.

Oikawa-Kawamoto M, Sogo T, Yamaguchi T, Tsunoda T, Kondo T, Komatsu H, et al. (2013). Safety and utility of capsule endoscopy for infants and young children. World J Gastroenterol. 19(45):8342-8.

Oliva S, Cucchiara S, Spada C, Hassan C, Ferrari F, Civitelli F, et al. (2014). Small bowel cleansing for capsule endoscopy in paediatric patients: a prospective randomized single-blind study. Dig Liver Dis. 46(1):51-5.

Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, et al. (2015). Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 47(4):352-76.

Pham T, Miller A, La Paglia D, Cham A (2018). Small Bowel Obstruction with Perforation Secondary to PillCam. Case Rep Gastrointest Med. 2018:9081742.

Postgate AJ, Burling D, Gupta A, Fitzpatrick A, Fraser C (2008). Safety, reliability and limitations of the given patency capsule in patients at risk of capsule retention: a 3-year technical review. Dig Dis Sci. 53(10):2732-8.

Rezapour M, Amadi C, Gerson LB (2017). Retention associated with video capsule endoscopy: systematic review and meta-analysis. Gastrointest Endosc. 85(6):1157-1168.

Rondonotti E, Herrerias JM, Pennazio M, Caunedo A, Mascarenhas-Saraiva M, de Franchis R (2005). Complications, limitations, and failures of capsule endoscopy: a review of 733 cases. Gastrointest Endosc. 62(5):712-6

Rondonotti E, Soncini M, Girelli CM, Russo A, Ballardini G, Bianchi G, et al. (2012). Can we improve the detection rate and interobserver agreement in capsule endoscopy? Dig Liver Dis. 44(12):1006-11.

Rondonotti E, Spada C, Adler S, May A, Despott EJ, Koulaouzidis A, et al. (2018). Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy. 50(4):423-446.

Rosa B, Moreira MJ, Rebelo A, Cotter J (2012). Lewis Score: a useful clinical tool for patients with suspected Crohn's Disease submitted to capsule endoscopy. J Crohns Colitis. 6(6):692-7.

Royall NA, Fiscina CD (2014). Report of video-capsule endoscopy disruption producing episodic small bowel obstruction after prolonged retention. Int J Surg Case Rep. 5(12):1001-4.

Rozendorn N, Klang E, Lahat A, Yablecovitch D, Kopylov U, Eliakim A, et al. (2016). Prediction of patency capsule retention in known Crohn's disease patients by using magnetic resonance imaging. Gastrointest Endosc. 83(1):182-7.

Satsangi J, Silverberg MS, Vermeire S, Colombel JF (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 55(6):749-53.

Sears DM, Avots-Avotins A, Culp K, Gavin MW (2004). Frequency and clinical outcome of capsule retention during capsule endoscopy for GI bleeding of obscure origin. Gastrointest Endosc. 60(5):822-7.

Sipponen T, Haapamäki J, Savilahti E, Alfthan H, Hämäläinen E, Rautiainen H, et al. (2012). Fecal calprotectin and S100A12 have low utility in prediction of small bowel Crohn's disease detected by wireless capsule endoscopy. Scand J Gastroenterol. 47(7):778-84.

Soncini M, Girelli CM, de Franchis R, Rondonotti E; SBCE Lombardia Study Group; On behalf AIGO, SIED and SIGE Lombardia (2018). Small-Bowel Capsule Endoscopy in Clinical Practice: Has Anything Changed Over 13 Years? Dig Dis Sci. May 16. doi: 10.1007/s10620-018-5101-9. [Epub ahead of print]

Spada C, Spera G, Riccioni M, Biancone L, Petruzziello L, Tringali A, et al. (2005). A novel diagnostic tool for detecting functional patency of the small bowel: the Given patency capsule. Endoscopy. 37(9):793-800.

Stier MW, Paramsothy S, Dalal S (2017). Ten-Year Retained Video Capsule With Crohn's-Associated Small-Bowel Adenocarcinoma. Clin Gastroenterol Hepatol. 15(10):A29-A30.

Thomson M, Fritscher-Ravens A, Mylonaki M, Swain P, Eltumi M, Heuschkel R, et al. (2007). Wireless capsule endoscopy in children: a study to assess diagnostic yield in small bowel disease in paediatric patients. J Pediatr Gastroenterol Nutr. 44(2):192-7.

Thorlacius H, Cronstedt J, Toth E (2017). [Endoscopy – an innovative history of optics, mechanics and photography]. Lakartidningen. 42(114):1782 pii: ETFZ. Swedish.

Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC (2009). The utility of capsule endoscopy in patients with suspected Crohn's disease. Am J Gastroenterol. 104(11):2734-9.

Tytgat GN, Classen M, Waye J, Nakazawa S (eds.) Pratice of therapeutic endoscopy. Harcourt Publishers Limited 2000.

Van Weyenberg SJ, Van Turenhout ST, Bouma G, Van Waesberghe JH, Van der Peet DL, Mulder CJ, et al. (2010). Double-balloon endoscopy as the primary method for small-bowel video capsule endoscope retrieval. Gastrointest Endosc. 71(3):535-41.

Wiarda BM, Stolk M, Heine DG, Mensink P, Thieme ME, Kuipers EJ, et al. (2013). Patient burden and patient preference: comparing magnetic resonance enteroclysis, capsule endoscopy and balloon-assisted enteroscopy. J Gastroenterol Hepatol. 28(3):464-71.

Woods SP, Constandinou TG (2011). Towards a micropositioning system for targeted drug delivery in wireless capsule endoscopy. Conf Proc IEEE Eng Med Biol Soc. 2011:7372-5.

Xin L, Liao Z, Du YQ, Jiang YP, Li ZS (2012). Retained capsule endoscopy causing intestinal obstruction - Endoscopic retrieval by retrograde single-balloon enteroscopy. J Interv Gastroenterol. 2(1):15-18.

Yung DE, Rondonotti E, Sykes C, Pennazio M, Plevris JN, Koulaouzidis A (2017a). Systematic review and meta-analysis: is bowel preparation still necessary in small bowel capsule endoscopy? Expert Rev Gastroenterol Hepatol. 11(10):979-993.

Yung DE, Plevris JN, Koulaouzidis A (2017b). Short article: Aspiration of capsule endoscopes: a comprehensive review of the existing literature. Eur J Gastroenterol Hepatol. 29(4):428-434.

Zhao AJ, Qian YY, Sun H, Hou X, Pan J, Liu X, et al. (2018). Screening for gastric cancer with magnetically controlled capsule gastroscopy in asymptomatic individuals. Gastrointest Endosc. 88(3):466-474.

Printed by Media-Tryck, Lund 2019 NORDIC SWAN ECOLABEL 3041 0903

FACULTY OF MEDICINE

Department of Clinical Sciences, Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2019:26
ISBN 978-91-7619-755-4
ISSN 1652-8220