Videocapsule Endoscopy

Fiction becoming fact

Bas van Tuyl

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Fiction becoming fact

Videocapsule endoscopie
Van fictie tot feit

Proefschrift

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"…..vague unavailing half-knowledge is often the forerunner of fruitful discovery" (H.S. Williams, A history of science)

Voor Carla

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Clinical application of videocapsule endoscopy

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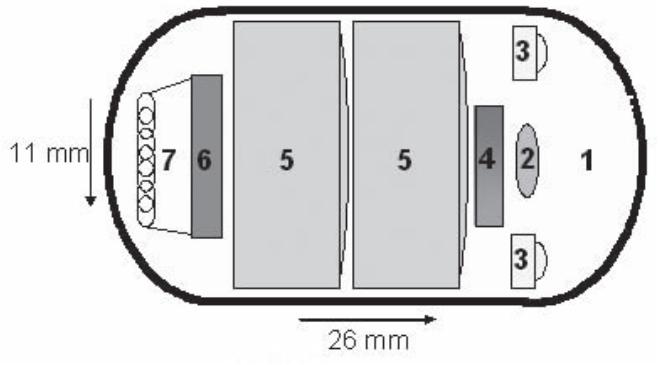
Introduction

After a long period of development, which stretched back as far as the eighties, a swallowable wireless intestinal video capsule became available in 1999 (Given M2A™, Yoqneam, Israel; 1). The first reports of human application came from the group of Swain et al (2, 3). Since then many papers on the subject have been published. The introduction of this thesis gives an overview of the technique of videocapsule endoscopy, the applicability and limitations compared to other diagnostic modalities and finally discusses future developments of this technique.

Technical aspects

The capsule has a diameter of 11 mm and a length of 26 mm and contains six light emitting diodes, a lens, a color camera chip and two batteries (***Figure 1***). The color camera chip can operate at very low levels of illumination and has a wide viewing angle. In the rear dome of the capsule a transmitter and an antenna are located. The capsule obtains two images per second. When the capsule is swallowed by an individual, it is propelled by peristalsis through the human gut. For optimal visualization, the capsule is routinely swallowed after an overnight fast. Four hours after ingestion of the capsule a light meal and a drink are allowed. The capsule is disposable and finally passes with the stools. During the procedure patients can move around freely.

Figure 1 *Videocapsule and its components: 1. lenshood, 2. lens, 3. LED, 4. videochip, 5. battery, 6. transmitter, 7. antenna. (for colour figure see page 142)*



The signals emitted by the capsule during gut passage are captured by eight aerials which are attached to the abdominal wall according to anatomical landmarks (***Figure 2***). The strength of the signal received by the individual aerials allows the correlation between specific video images and anatomical location. The aerials are connected to a recording device. The recorder and its battery are worn in a belt around the waist (***Figure 3***).

Figure 2 *The set of aerials receiving the videocapsule signal and the advised positions on the abdominal wall. (for colour figure see page 142)*

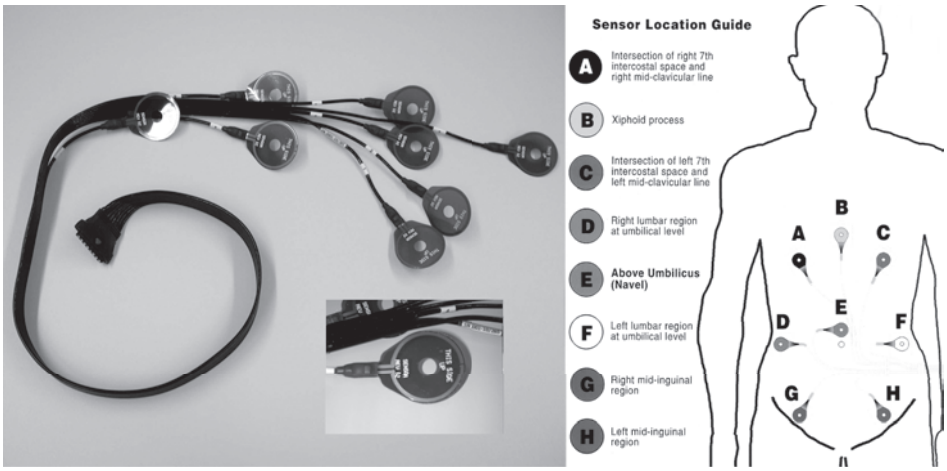
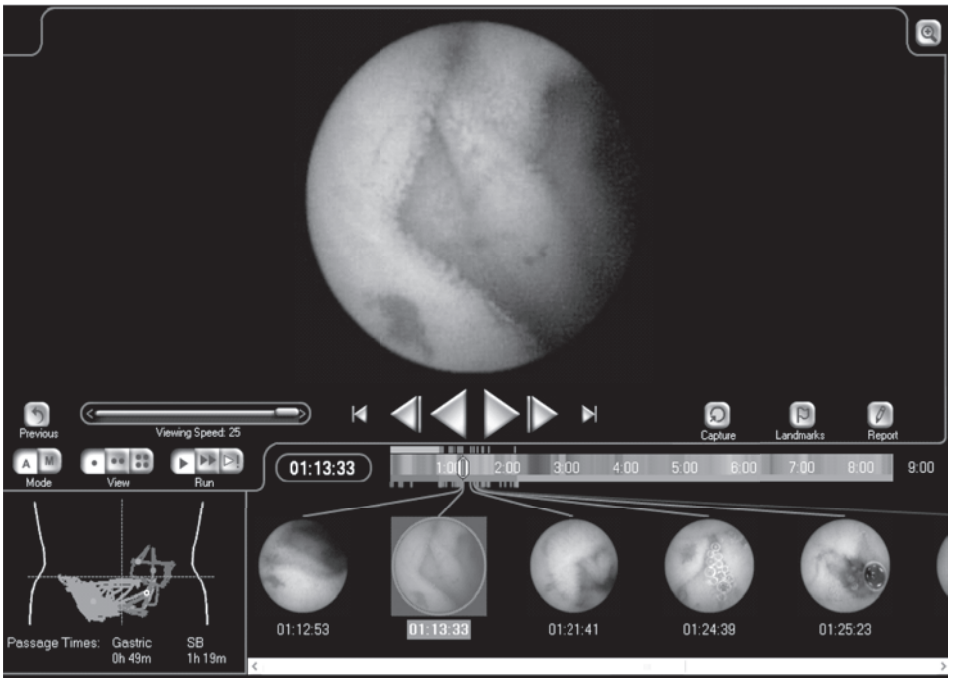


Figure 3 *The belt with the recorder worn around the waist. (for colour figures see page 143)*

At the end of the procedure the data can be downloaded to a work station. This takes about 2 hours. The pictures taken by the capsule are integrated into a video file which can be viewed at a variable number of images per second (***Figure 4***). Best results are obtained in a darkened environment because this enhances contrast and visibility of small mucosal abnormalities. Images of abnormalities can be selected and stored in a separate file. Recently, an algorithm was developed for automatic detection of predefined abnormalities like blood. This software aims to select images with positive

Figure 4 *The screen of the working station for review of the VCE. (for colour figure see page 143)*



findings and reduce the time needed for analysis. The data on the accuracy and clinical value of this new tool are sparse but demonstrate a sensitivity of 25 to 37% in the detection of relevant abnormalities which were found by the observer (4, 5).
Review of the capsule endoscopy images initially took about 90-120 minutes. In our experience the learning curve comprises about ten investigations. The viewing time will probably be reduced with increasing experience. Interobserver agreement has already been assessed and appears to be high (6).

Practical aspects

Indications

The major accepted indication for VCE is obscure gastrointestinal bleeding. VCE is now considered a first line diagnostic tool in the analysis of obscure gastrointestinal bleeding after the performance of a gastroduodenoscopy and colonoscopy without abnormalities. Suspected small intestinal Crohn's disease is another accepted

indication for VCE. It can be valuable in the analysis of unexplained abdominal complaints in known IBD patients but also in patients presenting with abdominal pain, diarrhoea combined with weight loss and elevation of inflammatory parameters. In the near future the potential indications will increase as a result of ongoing research concerning VCE.

Contra-indications

Formally video capsule endoscopy is contra-indicated in patients with a pacemaker or other implanted electronic medical device, although some recent papers reported the use of VCE in patients with pacemakers without any problems (7-9).
Prior small intestinal surgery and known intestinal strictures preclude capsule endoscopy. It is however not routinely advised to perform small bowel enteroclysis for exclusion of intestinal strictures. A new diagnostic tool is the patency capsule, which is a capsule composed of lactose which disintegrates 60-100 hours after ingestion. If this capsule does not lead to obstruction, VCE can also be performed without any problem (10-12). Although the capsule should pass strictures without any problem after disintegration, the patency capsule could not pass a stricture in three patients leading to surgery in two patients in the study of Delvaux et al (12). Further research is needed to establish the value of the patency capsule in routine clinical care.
Prior gastric surgery like Billroth II resection implies the risk of the capsule entering the afferent loop. This can be prevented by the endoscopic introduction of the videocapsule using a Roth net or a specialized VCE delivery system. The capsule is then introduced in the efferent loop under endoscopic view. This technique can also be used in case of swallowing difficulty in patients with neurological diseases or when passage through the esophagus and stomach is problematic, like in motility disorders (13-15).
VCE is now also considered safe in pediatric patients above the age of 10 years although the experience is limited (16). Incidentally VCE has been performed in younger children after endoscopic positioning of the capsule under anaesthesia (17).

Preparation

The day before the examination, patients are advised to use a liquid diet, followed by an overnight fast. The optimal regimen for preparation has not been determined yet. Some studies suggest a better visualization of the small intestinal mucosa after bowel cleansing (18-20). It has been reported that the transit of the capsule is delayed after bowel cleansing implying the risk of an incomplete examination (21, 22). Some studies therefore evaluated the effect of prokinetic medication on the gastric and small intestinal transit time. The transit times were generally reduced after administration of metoclopramide or erythromycin (23-26). In one study the use of erythromycin is associated with reduced small bowel visualization (24). Because of the heterogeneity

of the studies it is not clear in which way bowel preparation should be performed. Further studies are needed to determine the quantity of bowel preparation required to obtain a good mucosal visualization and maintain patient satisfaction at a high level.

Obstruction caused by video capsule

With a diameter of 11 mm the capsule may obstruct the small bowel in case of strictures, inflammation or tumors. Only few authors mention obstruction necessitating surgery (27-29). Bowel obstruction by the capsule does not necessarily cause symptoms because the liquid small intestinal content may still pass the capsule although one case of symptomatic obstruction of the patency capsule has been described (30). Because the long term exposure of the capsule to small intestinal content can lead to its disintegration it has to be removed (31).
The manufacturer of the capsule reports a 0.5% obstruction rate, whereas recent published data show a 1.9% obstruction rate (32). Capsule impaction seems to be more prevalent in patients taking large amounts of NSAID's. This may be related to chronic intestinal inflammation with stricture formation (33). Since there may be either a positive or a negative publication bias, exact figures remain unclear. It appears important to address this potential side-effect when a patient is informed about the procedure and to perform a careful interview concerning medical history and symptoms suggestive for intestinal stenosis.
In case of retention of the capsule in stomach or colon an endoscopic procedure with snare retrieval usually solves the problem. In case of retention of the capsule in the small intestine, surgery generally reveals major anatomical abnormalities like strictures or tumours which would probably have lead to surgery in the near future (34). With the advent of double balloon enteroscopy an impacted capsule can also be retrieved from the small intestine endoscopically with the possibility of interventions like dilation or tissue sampling in the same procedure (35-37).

Results of videocapsule endoscopy

Gastric and small intestinal transit times

Most studies on VCE report gastric and small intestinal transit times. The relevance of these data may be questioned. Gastric transit times are measured in the fasting state and have no clinical relevance. Small intestinal transit time is a mixture of fasting and postprandial propulsion speed since patients take a drink and a light meal 4 hours after ingestion of the capsule. In cases with known or suspected delayed gastric emptying, further information is needed prior to capsule endoscopy as the investigation is useless if the capsule is retained in the stomach. The small intestinal transit time is not relevant although temporary abnormalities in the small intestinal transit times may be

associated with anatomical abnormalities like tumours or strictures (38).
The most important fact concerning the gastrointestinal transit is the percentage of capsules reaching the cecum during the procedure, which varies between 50 and 87% in various studies (39-43).

Diagnostic yield of capsule endoscopy in unexplained gastrointestinal bleeding

Most studies on diagnostic yield of capsule endoscopy comprise patients with obscure occult/overt gastrointestinal bleeding (OGIB). Combined data from several studies report a diagnostic yield of 42-85% (39, 40, 42, 44-49). This is very high because all patients were examined extensively by other means before capsule endoscopy was applied. Diagnostic yield is however not always clearly defined. In the initial studies all abnormalities that were found in the small intestine were considered positive in the assessment of diagnostic yield. Many studies did not state whether these lesions were considered a potential or definite lesion responsible for hemorrhage. This probably caused bias in assessing diagnostic yield as demonstrated by the decrease of the diagnostic yield from about 70% in the initial studies to about 50% in more recent studies.
In an excellent study of Costamagna et al. findings were classified as diagnostic, suspicious or negative (44). Findings were considered diagnostic if the observed finding could explain the signs or symptoms of the patient and helped plan further management or were confirmed by other modalities. Findings were considered suspicious if an observed finding failed to explain the signs or symptoms of the patient, thus necessitating further investigations to evaluate its clinical relevance. When no abnormality was detected or if the procedure was inadequate due to the presence of intestinal contents it was considered negative. The use of this definition is recommended in future papers, although follow-up investigation will be the best way to determine whether VCE findings were indeed relevant.

Diagnostic yield in suspected small intestinal Crohn's disease

Videocapsule endoscopy is promising in suspected small intestinal Crohn's disease, with diagnostic yields varying between 44 and 77% (50-55). In patients with suspected Crohn's disease findings considered positive in the assessment of diagnostic yield were erosions, ulcers and strictures not explained by NSAID use. Voderholzer et al. recently suggested the presence of more than 10 erosions or aphtoid ulcers to be diagnostic of Crohn's disease (56). The variability in diagnostic yield can be explained by differences in indications for VCE. Capsule endoscopy appears to have a role in patients with abdominal pain, diarrhea and weight loss leading to the suspicion of small intestinal Crohn's disease but also in the management of known Crohn's disease (52).
The relevance of newly diagnosed Crohn's disease is clear but also in known Crohn's

disease it is often important to discriminate between symptoms caused by inflammatory bowel disease and irritable bowel disease. The findings of VCE can influence the decision to start medication or to evaluate the effect of treatment which might lead to a change in medication. VCE can also be of value in the differentiation between Crohn's disease and ulcerative colitis in patients with an indeterminate colitis (46, 52).

Diagnostic yield of capsule endoscopy versus radiological small bowel examination

Several studies tried to compare the diagnostic yield of capsule endoscopy with radiological small bowel examination by conventional, Computed Tomography (CT)- or Magnetic Resonance (MR)-enteroclysis (44, 57-60). Conventional enteroclysis in patients with OGIB has a diagnostic yield of about 21% whereas CT enteroclysis has been reported to have a diagnostic yield of 36% (60, 61). Capsule endoscopy has a considerably higher yield. This is not surprising since enteroclysis will not detect very flat or mucosal abnormalities. Although newer techniques like MR enteroclysis probably have a better diagnostic yield, a recent comparison of VCE and MR enteroclysis demonstrated the superiority of VCE in the detection of polyps smaller than 1 cm (62). A potential flaw in the comparison is the fact that previously in most studies on capsule endoscopy patients with suspected or known intestinal strictures were excluded in order to prevent impaction of the capsule. In the future, the need to perform enteroclysis prior to capsule endoscopy will probably disappear because patients with capsule obstruction are generally asymptomatic and the capsule can withstand the influence of intestinal secretions for several months. Beside this, patients with a stenosis which cannot be passed by the capsule will probably need surgery soon, resulting in a definite diagnosis (34). To perform a serious comparison of enteroclysis and VCE, studies are needed in which patients with suspected or known intestinal strictures are not excluded, but are considered as "positive yield" for enteroclysis.

Diagnostic yield of capsule endoscopy versus push enteroscopy

Until the advent of video capsule endoscopy, push enteroscopy was the method of choice to visualize the mucosa of the upper part of the small intestine. Diagnostic yield of push enteroscopy varies widely with the indication. Several studies indicate that for OGIB, the yield is between 26% and 47% (63, 64). The diagnostic yield of capsule endoscopy is superior to push enteroscopy (6, 65-69). No true comparison between both methods is possible since the capsule examines the whole small bowel whereas push enteroscopy examines only the upper part. In the study from Appleyard et al. studying the detection of beads attached to canine small bowel wall, VCE was superior to push enteroscopy (70). This study showed that the superior diagnostic yield of capsule endoscopy was caused by detection of beads in the distal small intestine. The difference in diagnostic yield between push enteroscopy and VCE may disappear

when the results of VCE are compared with intra-operative enteroscopy, which offers visualization of the complete small intestine. One study reported a sensitivity and specificity of 95% and 75% for VCE using intraoperative enteroscopy as the gold standard (71). This is however very invasive and carries a higher risk of complications. A serious advantage of push enteroscopy over capsule endoscopy is that when abnormalities are found, biopsies can be taken and therapeutic interventions can be carried out.

VCE and double balloon enteroscopy

Double balloon enteroscopy (DBE) is a new technique for a complete endoscopic examination of the small bowel (72-76). By the sequential insufflation and desufflation of a balloon on the tip of an endoscope and a balloon on the tip of its overtube the endoscope can be entered through the small bowel. Sometimes both oral and anal introduction are needed for a complete examination. VCE findings can determine whether the procedure should be started by the anal or oral introduction. A recent study by Gay et al. demonstrated that anal introduction was indicated if the capsule transit time from ingestion to arrival at the lesion was more than 75 % of the total time from ingestion to arrival at the cecum (77). During this procedure the tip of the endoscope can be steered, the mucosa can be rinsed and air can be insufflated which offers a potential advantage to the visualization by VCE. Beside this DBE offers the possibility for interventions like taking biopsies, coagulation and dilation. Data on comparison of DBE and VCE are sparse but suggest a superior diagnostic yield of DBE (78-80). Further studies are needed to determine its place in small bowel investigation.

Clinical impact of capsule endoscopy

As demonstrated by several studies mentioned above, video capsule endoscopy has a considerable diagnostic advantage over push enteroscopy and radiological small intestinal examination. Only few studies address the question whether VCE also has clinical implications (40, 81-83). Some studies, performed in Crohn's disease patients, show a very high clinical impact (46). Probably these studies comprise highly selected patients which had solitary small intestinal or therapy resistant disease. On the other hand, VCE opens a new era of understanding and treating Crohn's disease since small intestinal Crohn's disease without stenosis was previously difficult to diagnose or evaluate.

It is however frequently not clear what "clinical impact" means and the number of patients is generally small. In future studies "clinical impact" should be clearly defined and prospectively examined in larger groups of patients.

Potential emerging fiels of application

The range of potential indications for video capsule endoscopy is still expanding. It is most frequently used for patients with iron deficiency anemia, where upper and lower gastro-intestinal endoscopy did not reveal any abnormalities. Another accepted indication is CD of the small intestine. Many new indications are emerging based on ongoing research.

It is suggested that VCE can be useful in the diagnosis of celiac disease (84, 85). Although this diagnosis is primarily established by laboratory tests and jejunal biopsy, capsule endoscopy can determine the involved area of the small intestine. It is difficult however, to diagnose villous atrophy solely by the macroscopic view. Capsule endoscopy can become particularly valuable in understanding and managing therapy resistant celiac disease and the diagnosis of enteropathy associated T-cell lymphoma (86).

Several investigators reported the use of VCE in screening patients with familiar adenomatous polyps and Peutz-Jeghers polyps which implies possibilities for the detection of other small intestinal tumours like adenocarcinoma and gastrointestinal stromal cell tumours (87-90). This was already illustrated by some case reports describing the detection of solid tumours by VCE (78, 91, 92). Further research should focus on the clinical applicability of VCE in the detection of small intestinal tumours like carcinoid tumours. Previous reports studied the effects of NSAID's on small intestinal mucosa and its prevention by misoprostol (93-95). Another potential indication is graft surveillance after small bowel transplantation for the early detection of rejection (96, 97). Finally, VCE can be used as an important research tool. It offers the possibility to examine the small intestine in a non-invasive way. In this way small intestinal manifestations of systemic diseases can be examined. VCE can be used to examine the involvement of the small intestine in portal hypertension (98, 99). Another systemic disease which can be examined by VCE is Hereditary Hemorrhagic Teleangiectasia which frequently causes vascular abnormalities in the small intestine (100). As it is relatively non-invasive, VCE is an excellent research tool for diseases of the small intestine so new indications will definitely appear.

Conclusions

Video capsule endoscopy is a very promising new diagnostic tool. It is easy to perform and very comfortable for the patient because it is non-invasive and can be performed in the outpatient department. Capsule endoscopy has a diagnostic yield of 42-85% in adequately selected patients which is superior to small bowel X-ray or push enteroscopy. The most important disadvantage of video capsule endoscopy is that no interventions or biopsies are possible. VCE has become an accepted diagnostic tool in the analysis of obscure gastrointestinal bleeding and suspected small intestinal Crohn's disease and new indications are rapidly emerging.

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Aims and outline

This thesis starts with the description of the development, clinical introduction and first results of videocapsule endoscopy (Chapter 1). This new technique has in recent years rapidly gained acceptance as an important diagnostic tool in the analysis of suspected small bowel disease, such as in patients with unexplained gastrointestinal bleeding and patients with small intestinal Crohn's disease. Technical improvements, new indications and evolving insights regarding the appropriate clinical application made videocapsule endoscopy (VCE) a very relevant clinical research topic. In this thesis we address several of the many important questions concerning videocapsule endoscopy.

1. The optimal preparation for VCE was unclear. Initially VCE was routinely performed after a clear liquid diet and an overnight fast. Some studies however showed that bowel preparation improves the quality of the images acquired during this procedure, a finding that was not confirmed by others. We therefore performed a randomised controlled trial comparing regular preparation and preparation with 1 or 2 litres polyethylene glycol solution (Chapter 2).

2. Most early studies leading to the acceptance of videocapsule endoscopy were performed in highly selected patient groups. The widespread application of this technique in clinical practice may affect the diagnostic yield. We assessed the technical feasibility, clinical applicability and diagnostic yield of VCE in 250 unselected patients in a general hospital, with special attention to the relation of abnormalities at VCE and the symptoms of the patient (Chapter 3a).
To illustrate the use of VCE in clinical practice one of these patients was described in a case report (Chapter 3b).

3. Although the diagnostic yield of videocapsule endoscopy is high, most series do not report on the impact of VCE findings on clinical management and outcome. We therefore analysed the direct clinical consequences of VCE findings and the clinical condition of 150 patients one year after the procedure (Chapter 4).

4. Videocapule endoscopy offers the possibility for a complete endoscopic evaluation of the entire small intestine. Neuroendocrine tumours (carcinoids) frequently originate in the small intestine but the primary tumour is usually very difficult to detect. We hypothesised that VCE may enable detection of small intestinal carcinoid tumours. We performed VCE in patients with a metastatic carcinoid tumour and an unknown primary after previous enteroclysis, abdominal CT scanning and nuclear imaging (Chapter 5).

5. Hereditary Hemorrhagic Teleangiectasia is a disease that can lead to gastrointestinal bleeding. These bleeding episodes often originate from the small bowel. Until recently the small intestine was not accessible for easy assessment of the presence of teleangiectasia. Analysis could only be performed using gastroduodenoscopy or ileocolonoscopy, but these invasive techniques only allow visualisation of a small proportion of the small bowel. Videocapsule endoscopy is a potentially useful technique for the analysis of small intestinal teleangiectasia and findings may guide treatment. We investigated the relationship between HHT phenotype, with an emphasis on the occurrence of small intestinal teleangiectasia as assessed by VCE, and the genotype. These data may have implications for the understanding and clinical management of intestinal blood loss in HHT patients (Chapter 6).

This thesis aimed to answer these questions, thus contributing to the knowledge of the clinical applicability of videocapsule endoscopy and its potential indications.

Optimal preparation for videocapsule endoscopy; A prospective, randomized, single blinded study

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Submitted

Abstract

Introduction

Visualization of the small bowel by videocapsule endoscopy (VCE) is frequently disturbed by intestinal contents. Different bowel preparations were studied with controversial results.

Aim

Determine an adequate and tolerable bowel preparation for VCE.

Methods

Ninety patients were randomized for three preparation regimens. Group A underwent VCE after clear liquid diet and overnight fast, group B and C respectively used 1 or 2 litres of polyethylene glycol (PEG) solution before VCE. For each VCE five segments of 10 minutes were selected, at the start of each quartile of the small intestine, and the fifth being the last 10 minutes of the ileum. Mucosal visibility was good if more than 75% of the mucosa could be evaluated. All patients answered a questionnaire regarding procedure tolerability.

Results

PEG solution led to a significant improvement of the mucosal visualisation. Mucosal visibility was good in the terminal ileum in 25%, 52% and 72% in group A, B and C respectively. The diagnostic yield did not change significantly. The use of 2 litres PEG solution was considered more uncomfortable than no or 1 litre of PEG solution.

Conclusion

One litre of PEG solution improves mucosal visualisation without causing discomfort for the patient.

Introduction

Videocapsule endoscopy (VCE) is a non-invasive diagnostic tool to visualise the small intestinal mucosa. It has a high diagnostic yield in patients with obscure gastrointestinal bleeding and suspected Crohn's disease (1-12). Various studies have proven its superiority compared to other diagnostic modalities like push enteroscopy and small bowel enteroclysis (13-21). Preparation for VCE usually consists of a clear liquid diet and an overnight fast. However, this approach does not prevent that VCE is often impaired by the presence of small intestinal contents. Therefore several authors have studied the effect of bowel preparation by means of polyethylene glycol (PEG) or sodium phosphate on small bowel visualisation (22-27). The results of these studies were unfortunately contradictory. Some studies reported that bowel preparation resulted in an improvement of visualisation, whereas others did not find a difference in small bowel visualisation nor diagnostic yield. Furthermore, only one of these studies had a randomized design (28). Other studies were not randomized and generally included small numbers of patients. Moreover, bowel cleansing has been reported to increase small bowel transit time, which in theory may lead to incomplete mucosal visualization (29).
We therefore studied the effect of three different regimens of bowel preparation on mucosal visualization, intestinal transit time and tolerability in a prospective single-blinded randomized study.

Methods

Patients

Ninety consecutive patients who were referred for videocapsule endoscopy for various indications were studied. Patients were randomized using a computer generated list of numbers to one of three preparation regimens by one of the investigators (HO). Group A used the standard regimen consisting of a clear liquid diet for 12 hours on the day before VCE, followed by an overnight fast. Group B received 1 litre PEG solution (Colofort, Ipsen, France) the evening before the examination followed by an overnight fast and group C used 2 litres of PEG solution followed by an overnight fast. For all patients age, gender, body mass index and indication for VCE were registered.

Videocapsule endoscopy

VCE was performed using the Given Imaging M2A wireless capsule (Yoqneam, Israel) as described previously (30). Four hours after swallowing the capsule, a light meal was permitted. At the end of the procedure the data were downloaded to a work station to be viewed as movie file using dedicated software. In all VCE files the first image of the stomach, duodenum and cecum were marked for calculation of gastric and small intestinal transit times.

Findings were classified as diagnostic, probable or negative as described before (31). Findings were considered diagnostic if the observed finding could explain the signs or symptoms of the patient and helped to plan further management, or were confirmed by other modalities. Findings were considered a probable explanation if an observed finding failed to explain the signs or symptoms of the patient, but necessitated further investigations to evaluate its clinical relevance. When no relevant abnormality was detected or if the procedure was inadequate due to the presence of intestinal contents, the procedure was considered negative.

Mucosal visualisation

Each VCE file was reviewed by two independent investigators (ST, MS) without knowledge of the preparation regimen. Both reviewers had previously reviewed at least 100 VCE procedures. Because there is considerable inter-individual variation of small bowel length and transit time, the total small intestinal transit time was divided into quartiles. In this way small intestinal segments of different patients could be compared to each other irrespective of transit time. At the beginning of each quartile and at the end of the small intestine segments of 10 minutes were examined. Mucosal visualisation was classified into six categories depending on the percentage of the mucosal surface which could be visualised in each segment, <5%, 5-24%, 25-49%, 50-74%, 75-95% or >95%. For statistical analysis mucosal visualisation less than 75% was considered as poor visibility and equal to or more than 75% as good visibility.

Patient burden

All patients who underwent VCE answered a questionnaire to assess the impact of the bowel preparation. Patients were asked if they experienced abdominal pain or nausea during bowel preparation and whether the preparation would withhold them to undergo the procedure again. The overall convenience and tolerability of the preparation and the examination were assessed on a numerical scale between 0 and 10, with 10 being no burden at all.

Statistics

Patients were randomised by means of a list with 3 randomly generated numbers. Parametric results were compared by analysis of variance (ANOVA). Non-parametric data were compared by Kruskal Wallis test. Group proportions were compared with Chi-square test or Fisher's exact test where appropriate. Differences between groups and effects in time were analysed by repeated measures ANOVA with post-hoc Bonferroni tests. A $p<0.05$ was considered significant. Interobserver agreement was assessed by Kappa statistics. Statistical analysis was performed with the SPSS program version 14.

Results

Patient data

Ninety patients were analysed (M/F 41/49) with a mean age of 53.6 years (SD 17.8, range 14-86 year). VCE was performed for the analysis of obscure gastrointestinal bleeding in 62 patients (69%), for suspected small intestinal Crohn's disease in 20 patients (22%), and for other reasons in 8 patients (9%; ***Table 1***). No significant differences regarding sex, age and indication for VCE were found between the three groups.

Table 1 *Patient characteristics, indications and diagnostic yield in the three different preparation groups.*

Patient characteristics and VCE results	***Preparation***			
	No PEG	***1 litre PEG***	***2 litre PEG***	***p***
Age (Yrs)	*57 ± 19*	*53 ± 15*	*51 ± 19*	*p=0.49*
Sex (m/f)	*14/16*	*16/14*	*11/19*	*P=0.43*
Indication				*p=0.77*
Obscure GI blood loss	*19 (63%)*	*22 (73%)*	*21 (70%)*	
IBD	*9 (30%)*	*5 (17%)*	*6 (20%)*	
Other	*2 (7%)*	*3 (10%)*	*3 (10%)*	
Diagnosis				*p=0.86*
Definite	*8 (27%)*	*6 (20%)*	*9 (30%)*	
Probable	*12 (40%)*	*14 (47%)*	*10 (33%)*	
No diagnosis	*10 (33%)*	*10 (33%)*	*11 (37%)*	

Gastric and small intestinal transit time of the videocapsule

Gastric transit time was 35±63 min. in group A, 33±52 min. in group B and 29±31 min. in group C (p=0.88). The small intestinal transit time was 277 ±95 min. in group A, 274 ±89 min. in group B and 248±96 min. in group C (p=0.45). The cecum was visualised in 27, 28 and 26 patients in group A, B and C respectively (p=0.69).

Mucosal visualisation

In the first 10 minutes no significant difference was found for the percentage of patients with good mucosal visualisation (p=0.7). In the terminal ileum good visualisation was only achieved in 25% of the patients after standard preparation. After preparation with both 1 and 2 litres of PEG solution mucosal visualisation of the terminal ileum improved to 52% and 72% respectively (p=0.01). In the remainder of the small intestine an improvement in the mucosal visualisation was reported after preparation with a PEG

solution. Mucosal visualisation steadily and significantly declined towards the terminal ileum for all groups (***Figure 1***; p≤0.01).
The visibility curves obtained with 1 and 2 litres of PEG solution differed significantly from the curve obtained with standard preparation (p=0.03 and p<0.01, respectively). No significant difference could be found between the visibility curves for 1 and 2 litres of PEG solution (p=0.47).
Interobserver agreement for mucosal visualisation was high with a kappa of 0.78 (95% C.I. 0.73-0.83).

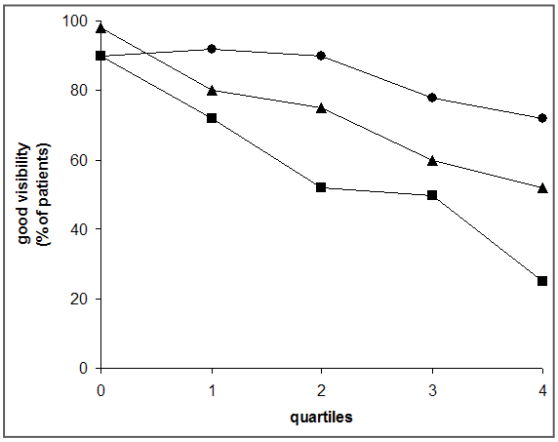

Figure 1 *Proportion of patients with good visualisation of the mucosa per quartile of total small intestinal transit time for the three different preparation regimens (■ Group A, no preparation; ▲ Group B, 1 litre PEG solution; ● Group C, 2 litre PEG solution; Quartile 0: p=0.7; Quartile 1: p=0.02; Quartile 2: p=0.01; Quartile 3: p=0.05; Quartile 4: p=0.01).*

Diagnostic yield of VCE

A definite diagnosis was established in 8 patients (27%) in group A, in 6 patients (20%) in group B and in 9 patients (30%) in group C (p=0.86; ***Table 1***). In patients with obscure gastrointestinal bleeding a definite diagnosis was established in 31%, 18% and 23% in group A, B and C respectively whereas in suspected Crohn's disease a definite diagnosis was established in 11%, 40% and 50% respectively (p=0.58 for group A, B and C; p=0.1 for group A and C).

Tolerability of the procedure

Patients rated the whole procedure with 7.6, 8.3 and 7.5 for group A, B and C respectively (p=0.24). No significant difference was observed for the occurrence of abdominal pain or nausea with the three different preparation regimens. The preparation regimen was rated as 7.8, 7.8 and 6.0 for group A, B and C respectively (p=0.03). Ninety-four percent of the patients were willing to undergo the procedure in the future, irrespective of preparation regimen.

Discussion

VCE has rapidly become an accepted method for the evaluation of patients with suspected small bowel disease. Unfortunately however, the optimal preparation for this procedure is unknown. Although most investigators only prepare patients by a clear liquid diet and an overnight fast, this method appears in our study as well in others to be associated with poor visibility of the terminal ileum in the majority of patients. This is even more important when VCE is used as a diagnostic tool for patients with suspected Crohn's disease.

To improve mucosal visualisation, some authors evaluated different regimens of preparation. A Greek study evaluated 80 patients who were randomized to either regular preparation or 2 litres PEG solution (32). In this study the mucosal visualisation was good in 90% of the patients after bowel preparation compared to 60% after a clear liquid diet and an overnight fast. The diagnostic yield also changed significantly from 30% to 65% after bowel preparation. In a study from Switzerland 61 patients used either regular preparation or 4 litres of PEG solution (33). The overall visibility of the small bowel improved after bowel preparation, but the latter was also associated with a shorter small intestinal transit time. In a small study from Israel 10 patients underwent VCE after standard preparation and 22 patients after sodium phosphate (34). It demonstrated a significant increase of the proportion of patients with adequate mucosal visualisation from 50% to 96%. The effect of bowel preparation on the diagnostic yield was not evaluated in these studies. In contrast to these studies which favour bowel preparation before VCE, a French study did not find any difference on mucosal visibility or diagnostic yield with 2 litres of PEG solution compared to a procedure after an overnight fast (35).

In the present study 90 patients were analysed with three different preparation regimens. In contrast to previous studies mucosal visibility was not assessed at fixed time points after the capsule passed the pylorus but at relative time points by dividing the small bowel in quartiles. In this way mucosal visibility was compared at relatively similar levels of the small intestine. It appeared that the mucosal visualisation per quartile improved significantly after preparation with PEG solution. In the most distal part of the ileum, the use of one and two litres of PEG solution prior to VCE resulted in a better visibility. Despite this, the diagnostic yield did not change after PEG bowel preparation. This might be explained by the fact that after a clear liquid diet and an overnight fast the majority of the small bowel is cleaned adequately or by the fact that in the majority of the patients no definite diagnosis can be established. As the most striking difference is observed in the terminal ileum, it is conceivable that a difference would be found in case of suspected Crohn's disease. This was confirmed by our study in which a definite diagnosis was established more frequently in case of Crohn's disease after bowel preparation with PEG solution. As the indication for VCE might influence the diagnostic yield and transit times, future studies on the effect of bowel preparation should focus on particular indications.

It is not clear whether the preparation regimen influences gastric and small intestinal transit times. This might be an important issue as a delay in transit time might result in an incomplete examination of the small intestine. An Israelian study reported decreased gastric and small intestinal transit times and a Greek study reported an increase of the percentage of complete small bowel examinations after bowel preparation (36-38). Other authors have reported a significant delay of small intestinal transit time or an increase of the gastric transit time after the use of a PEG solution (39, 40). In our study no difference was found for gastric and small intestinal transit times with the three preparation regimens. The proportion of patients in whom the cecum was visualized by VCE also did not change significantly after bowel preparation.

This is the first study which evaluated both mucosal visibility after bowel preparation and the discomfort for the patient. This is an important issue as many people experience the use of a large amount of PEG solution as very uncomfortable. Although the large majority of the patients in this study would undergo the procedure again irrespective of the preparation used, the use of 2 litres of PEG solution was considered to be more uncomfortable than the conventional preparation or 1 litre PEG solution.

The present study supports the use of 1 litre of PEG solution as the preparation of choice for VCE as this leads to an improved mucosal visualisation without causing discomfort for the patient. If VCE is performed with a high a priori suspicion of abnormalities in the distal ileum, like in suspected Crohn's disease, preparation with 2 litres of PEG solution can be considered.

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Results of videocapsule endoscopy in 250 patients with suspected small bowel pathology

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Abstract

Background

We aimed to assess technical feasibility, clinical applicability and diagnostic yield of VCE in a large group of unselected patients.

Methods

VCE was performed with the Given Imaging swallowable capsule. Findings were considered diagnostic if the observed finding could explain the symptomatology of the patient. Findings were considered suspicious if an observed finding failed to completely explain the patient's symptoms.

Results

250 patients were studied. A definite diagnosis was made in 95 patients (38%). Suspicious findings were noted in 80 patients (32%). No diagnosis was obtained in 74 patients (30%). The yield of VCE was higher in patients with suspected Crohn's disease. Mean viewing time decreased significantly from 51±14 min. to 30±7 min. after reviewing 50 procedures.

Conclusions

VCE is an important diagnostic tool but a definite diagnosis is established in only 38% of the patients. The highest diagnostic yield is obtained in patients with suspected Crohn's disease.

Introduction

Until recently, limited access to the small intestine was obtained by ileocolonoscopy or fluoroscopy guided push-enteroscopy. Complete examination of the small intestine was only achieved by an intra-operative enteroscopy. Videocapsule endoscopy is a new, non-invasive diagnostic tool to visualize the entire small intestine. It has revolutionized our ability to visualize the small intestine. Main indications for visualisation of the small intestine are obscure gastrointestinal bleeding (OGIB), suspected small bowel Crohn's disease, and intestinal tumors. Various studies have been performed in highly selected groups of patients. These studies reported a diagnostic yield of 55-85% (1-8). These excellent results are however met by two reservations. First of all, most of these studies came from tertiary referral centers with highly selected patients, a situation that is not met in many centers with the current fast spread of VCE. Secondly, in most of the reported literature, all abnormalities were considered to contribute to the diagnostic yield although it was frequently unclear whether the findings could explain the symptoms.
In many countries VCE has now been implemented in daily practice. It is however considered to be a time consuming procedure. Diagnostic tools, like the suspected blood indicator, might facilitate and accelerate the review process.
In this study we assessed the technical feasibility, clinical applicability and diagnostic yield of VCE in a large group of unselected patients in a general hospital, with special attention to the relation of abnormalities at VCE and the symptoms of the patient.

Methods

Patients and setting

The study was performed in a single, large general hospital. Two hundred and fifty consecutive patients were examined. Data were collected regarding age, sex, use of non-steroidal-anti-inflammatory drugs (NSAID), physical constitution and the symptoms of the patients. Indications were divided in five categories. Patients are classified as occult gastrointestinal (GI) bleeding in case of iron deficiency anaemia in the absence of visible blood and as overt GI bleeding if blood loss has been visualised (9). Both groups together are described as obscure GI bleeding (OGIB). The third group comprised patients with known Crohn's disease (CD) and unexplained symptoms or patients with diarrhoea combined with abdominal pain and laboratory abnormalities suggesting CD. The fourth group were patients with suspicion of a small intestinal tumor. Patients who could not be included in one of these categories were classified as other.
In patients with OGIB, the lowest haemoglobin (Hb) in the year preceding VCE was registered and patients were stratified according to this Hb in categories <5.0, 5.0-7.0

and >7.0 mmol/l. The time delay between the most recent bleeding episode and VCE was registered in case of overt bleeding and categorized as less than 2 weeks or more than 2 weeks.

Videocapsule endoscopy

VCE was performed using the Given Imaging M2A wireless capsule (Yoqneam, Israel). The capsule contains a lens, 6 light-emitting-diodes, batteries, a transmitter and an antenna. The capsule takes 2 pictures per second and the batteries have a lifespan of approximately 8 hours. The patient is prepared for the investigation by a clear liquid diet for twelve hours, preceding an overnight fast. In the morning the patient swallows the capsule which is propelled by intestinal peristalsis. The pictures are transmitted to eight antennas on the abdominal wall in a position depending on several anatomical landmarks. Four hours after swallowing the capsule, a light meal was permitted.
At the end of the procedure the data were downloaded to a work station to be viewed as movie file using dedicated software.

Videocapsule analysis

Each VCE was reviewed by one of four gastroenterologists. Gastric transit time, small intestinal transit time, percentage of capsules reaching the cecum and viewing time were registered. Findings were divided in 15 different categories as shown in ***Table 1***. In case of major findings in more than one category, both findings were registered. Findings were considered diagnostic if the observed finding could explain the symptoms of the patient. Findings were considered suspicious if an observed finding failed to completely explain the symptoms of the patient. In case of multiple findings the most relevant finding determined whether they were considered a definite diagnosis or suspicious findings. If no relevant abnormalities were found and in case of an insufficient investigation, VCE was classified as "no diagnosis"(1). Images were analysed by the suspected blood indicator (SBI) if available. This is an algorithm detecting red pixels suggesting the presence of blood, erythema or inflammation. For every VCE the result of the suspected blood indicator was registered as positive (red pixels detected) or negative (no red pixels detected). Findings of SBI were compared to the VCE findings of the observer. Relevant findings to be detected by SBI were large angiodysplasia, blood, inflammation and erythema. If the SBI detected red pixels and the observer confirmed the presence of abnormalities that should reasonably be detected by SBI, it was considered true positive. In this way performance of SBI was classified as true positive, false positive, true negative or false negative, considering the observer's findings as the gold standard. In case of both false negative and false positive findings in the same patient, the final result was registered as false negative because of the more serious consequence of potentially missing important information.

Table 1 *Diagnostic findings at VCE.*

Findings	*All patients (N=250)*	*Occult GI bleeding (N=150)*	*Overt GI bleeding (N=27)*	*CD (N=57)*
Angiodysplasia, large	*23 (9%)*	*21 (14%)*	*1 (4%)*	*0 (0%)*
Angiodysplasia, small	*36 (14%)*	*29 (19%)*	*4 (15%)*	*0 (0%)*
Aphtoid lesions	*4(2%)*	*3 (2%)*	*0 (0%)*	*0 (0%)*
Blood	*31 (12%)*	*19 (13%)*	*10 (37%)*	*0 (0%)*
Erosion	*32 (13%)*	*21 (14%)*	*4 (15%)*	*5 (9%)*
Ileitis	*18 (7%)*	*5 (3.3%)*	*0 (0%)*	*13 (23%)*
Insufficient	*8 (3%)*	*3 (2%)*	*0 (0%)*	*3 (5%)*
No abnormalities	*50 (20%)*	*31 (21%)*	*2 (7%)*	*11 (19%)*
Other, diagnostic	*5 (2%)*	*3 (2%)*	*0 (0%)*	*1 (2%)*
Other, irrelevant	*24 (10%)*	*16 (11%)*	*0 (0%)*	*7 (12%)*
Other, suspicious	*1 (6%)*	*6 (4%)*	*2 (7%)*	*4 (7%)*
Stomach abnormalities	*15 (6%)*	*7 (5%)*	*5 (19%)*	*0 (0%)*
Tumor	*7 (3%)*	*4 (3%)*	*1 (4%)*	*0 (0%)*
Ulcer	*17 (7%)*	*5 (3%)*	*0 (0%)*	*11 (19%)*
Venectasy	*6 (2%)*	*5 (3%)*	*1 (4%)*	*0 (0%)*

Using these data specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of SBI were assessed.

Statistics

Parametric results were compared by two-sided Student's t-test. Data from multiple groups were compared by analysis of variance. Group proportions were compared with Chi-square test. A $p<0.05$ was considered significant.

Results

Patients

250 patients (M/F 115/135, mean age 54.9 yrs., range 11-85 yrs.) were studied. Obscure gastrointestinal bleeding was the indication in 177 patients (71%) and was divided into occult and overt bleeding (150 and 27 patients respectively). In 57 patients (23%) VCE was performed because of suspected small intestinal Crohn's disease and in 9 patients (4%) for a suspected tumour ***Table 2***.

Table 2 *Indications for VCE*

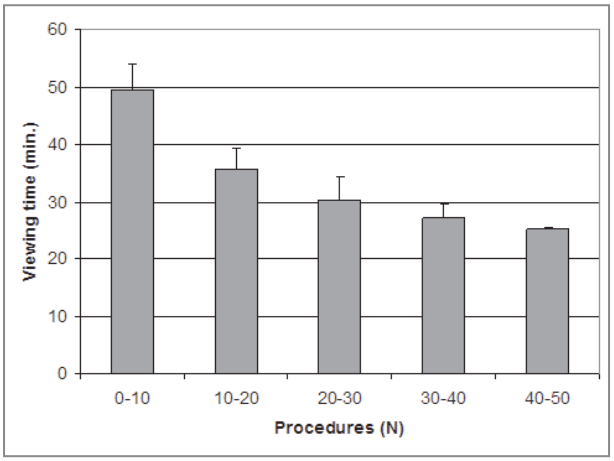
Indication	*N (%)*
Occult GI bleeding	*150 (60)*
Previous overt GI bleeding	*27 (10.8)*
Suspected small intestinal CD	*57 (22.8)*
Tumor	*9 (3.6)*
Other	*7 (2.8)*

VCE findings

VCE was performed without complications in all but two patients. In one patient the capsule was retained in the stomach due to gastroparesis and removed endoscopically. In the other patient the capsule was removed from the cecum by colonoscopy after 6 weeks because of non-passage despite the absence of obstruction. Gastric transit time was 44±71 min. and small intestinal transit time was 254±81 min. No significant difference was found between transit times for the different indications. The complete small bowel was visualized in 189 patients (76%). The mean gastric transit time was 79±127 min. in those patients in whom the small bowel was incompletely visualized, compared to 34±40 min. in patients in whom the capsule visualised the cecum ($p<0.001$).

The viewing time ranged from 5 to 75 min. with a mean of 37±14 min. Mean viewing time for every ten procedures was calculated for all investigators and decreased significantly from 51±14 min. for the first 10 procedures to 30±7 min. for the 50th to 60th procedure ($p<0.001$; ***Figure 1***). Despite the decrease in viewing time, the frequency of a definite or probable diagnosis established at VCE did not change.

Figure 1



Diagnostic findings are shown in ***Table 1***. In 36 patients more than one type of abnormality was found. VCE was considered insufficient in 8 patients (3%) due to retention in the stomach or inadequate visualisation due to intestinal contents. In 14 patients (6%) abnormalities in the stomach were found.
Findings were labelled as definite diagnosis in 95 patients (38%) and as a possible diagnosis in 81 patients (32%). In 74 patients (30%) no diagnosis was established (***Table 3***).
A suspected blood indicator was available in 214 patients. SBI had a positive predictive value of 63% and a negative predictive value of 78%. Specificity and sensitivity were 75% and 68% respectively (***Table 4***).

Table 3 *Establishment of a definite, possible or no diagnosis using VCE.*

	All patients (N=250)	***Occult GI bleeding (N=150)***	***Overt GI bleeding (N=27)***	***CD (N=57)***
Definite	*95 (38%)*	*49 (33%)*	*12 (44%)*	*28 (49%)*
Possible	*81 (32%)*	*55 (37%)*	*14 (52%)*	*8 (14%)*
No diagnosis	*74 (30%)*	*46 (31%)*	*1 (4%)*	*21 (37%)*

Table 4 *Diagnostic performance of SBI.*

	All patients (N=250)	***Occult GI bleeding (N=150)***	***Overt GI bleeding (N=27)***	***CD (N=57)***
Sensitivity	*68%*	*64%*	*57%*	*88%*
Specificity	*75%*	*75%*	*100%*	*73%*
NPV	*78%*	*76%*	*40%*	*92%*
PPV	*63%*	*63%*	*100%*	*61%*

VCE and obscure gastrointestinal bleeding

VCE findings in occult GI bleeding

150 patients (M/F 73/77, mean age 60 yrs., range 11-85 yrs.) with occult GI bleeding were examined by VCE. Mean gastric transit time was 40 min. (SD 56) and mean small intestinal transit time was 250 min. (SD 83). The cecum was reached in 119 patients (79%). These data did not differ significantly from any other group. The major diagnostic findings were angiodysplasia (n=50, 33%), erosions (n=21, 14%) and blood (n=19, 13%). A definite diagnosis was established in 33% and a possible diagnosis in

37% of the patients. In this group, SBI had a PPV of 63% and a NPV of 76%. No relation with the use of NSAID's was found for the presence of ulcers or erosions.

VCE findings in overt GI bleeding

Previous overt GI bleeding was the indication for VCE in 27 patients (M/F 14/13, mean age 66.6 yrs., range 34-84). In 14 (52%) of the 27 patients with overt gastrointestinal bleeding VCE was performed within 2 weeks after first presentation. Mean gastric transit time was 40 min. (SD 68) and mean small intestinal transit time was 267 min. (SD 83). The cecum was reached in 19 patients (70%). The most frequent findings were blood (n=10, 37%), angiodysplasia (n=5, 19%) and abnormalities in the stomach (n=5, 19%). In 12 patients (44%) a definite diagnosis was established which was significantly more than in the occult GI bleeding group (p=0.01). A possible diagnosis was found in 14 patients (52%) and in only 1 patient (4%) no explanation for blood loss was found. The diagnostic yield increased from 39% to 56% if VCE was performed within 2 weeks after bleeding (p=n.s.). In patients with overt bleeding, SBI had a PPV of 100% but a NPV of only 40%.

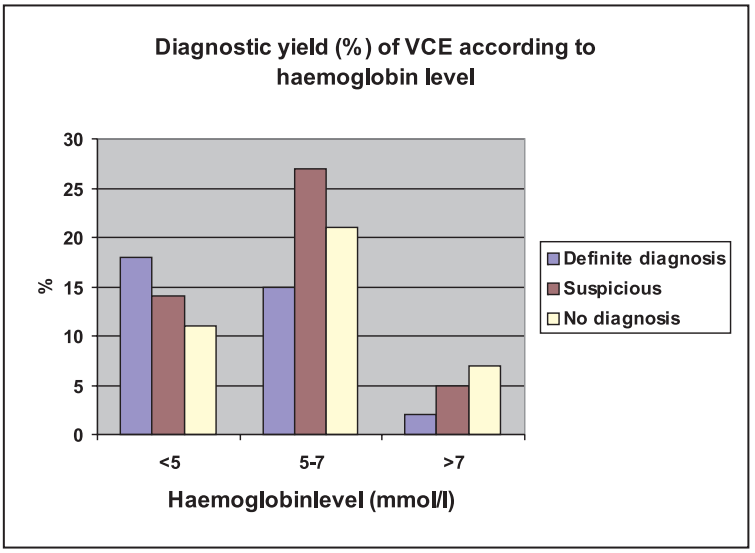
VCE findings and haemoglobin level

Patients with occult GI bleeding had a mean Hb of 5.5 mmol/l (range 2.5-8.7, SD 1.2), whereas patients with overt bleeding had a mean Hb of 4.8 mmol/l (range 2.9-7.7, SD 1.4; p=n.s.). In patients with overt GI bleeding mean hemoglobin level was significantly lower in patients with a definite diagnosis compared to the groups with a possible or no diagnosis (4.1, 5.0 and 6.9 mmol/l respectively, p=0.04).
When the result of VCE in case of OGIB was stratified according to haemoglobin level before VCE (Hb<5.0, 5.0-7.0 and >7.0 mmol/l), a definite diagnosis was found in 42, 24 and 14% respectively (p=0.03; ***Figure 2***). In male patients a definite diagnosis was more frequent than in female patients (42% vs 27%, p=0.02). On the presumption that this difference might be attributed to the confounder of menstrual blood loss in women, two groups were made with an age above or below 50.5 yrs. because at this age 50% of women are post-menopausal(10). In female patients older than 50.5 yrs. a definite diagnosis was found more frequently than in young women (39% vs 21%, p=0.05).

VCE findings in suspected small intestinal Crohn's disease

Suspected small intestinal CD was the indication for VCE in 57 patients (M/F 19/38, mean age 37 yrs., range 19-73 yrs.). This group contained significantly more women (67 vs 50%;p=0.04) and the mean age and Body Mass Index were significantly lower than in the OGIB patients (36.5 vs 61.4 yrs; p=0.05 and 23.7 vs 26.7 kg/m^2; p=0.04 respectively). Average gastric transit time in this group was 52±90 min. and mean small

Figure 2



intestinal transit time was 259±79 min. The cecum was reached in 41 patients (72%). Main diagnostic findings were ileitis (n=13, 23%), ulcers (n=11, 19%) and erosions (n=5, 9%). No correlation with the use of NSAID's could be established. A definite diagnosis was made in 49% of the patients which was significantly more frequent than in case of OGIB (35%, p=0.003). SBI had a PPV of 61% and a NPV of 92% in these patients.

VCE finding in patients with suspected small intestinal tumors

VCE was performed to detect a small intestinal tumor in 9 patients (M/F 5/4, mean age 52.1 yrs., range 24-80 yrs.). Average gastric transit time was 61±61 min. and the small intestinal transit time was 231±98 min. The cecum was reached in 56% of the procedures which was less than in case of OGIB and CD (78% and 73% respectively;p=n.s.). A definite diagnosis was established in 33% of the patients in whom the suspicion of a small intestinal tumor was confirmed by VCE. The cecum was not reached in these three patients but without any complaints of obstruction. One patient had a small intestinal sarcoma, one patient had Peutz Jehger's polyp and one patient had a small intestinal carcinoid tumour. A possible diagnosis was found in 22% and no abnormalities were found in 44%.

Discussion

Videocapsule endoscopy is a new technique and is increasingly used as a diagnostic tool for patients with obscure GI bleeding and suspected small intestinal Crohn's disease. Initial series reported high diagnostic yields varying between 55 and 85% (1-8). These data strongly promote the widespread use of VCE, but some reservations can be made with respect to the fact that most studies came from tertiary referral centers with selected cases. In addition, many series consider all abnormalities at VCE contributing to the diagnostic yield. In the present study 250 unselected patients were analysed who underwent VCE in our hospital for various indications. In our series abnormalities were found in 70% of the patients. This is comparable with previous studies in which the presence of definite and possible diagnosis were taken together (2-4, 6, 8, 11-13). Although our diagnostic yield appears to be high, a definite diagnosis was found in only 38%. The remainder of the abnormalities was insufficient to explain the symptoms of the patient. In our opinion the differentiation of abnormalities depending on the relevance for the explanation of the complaints results in a more realistic but considerably lower diagnostic yield.

In patients with obscure GI bleeding the major findings were angiodysplasia, blood and superficial erosions. In the patient with suspected CD the major findings were ileitis, ulcers and erosions. In our population the presence of erosions, ulcers and ileitis did not have a significant relation with the use of NSAID's. In case of suspected CD a definite diagnosis was made more frequently than in patients with OGIB (49% vs 34%; p=0.003). The higher diagnostic yield of VCE in patients with suspected CD and more frequent clinical implications have been reported previously (4, 11, 14-16).

An important finding in our population was the relation between the haemoglobin level before VCE and the presence of abnormalities in the small intestine. In patients with a haemoglobin level above 7.0 mmol/l, the chance of finding a definite diagnosis was significantly lower than in the other categories. Interestingly a definite diagnosis was established more frequently in men than in women. This difference may in part be related to the confounder of menstrual blood loss contributing to anemia and suspicion of OGIB. In female patients younger than 50.5 years, a definite diagnosis was found in only 12% compared to 31% in women older than 50.5 years.

Although many people consider reviewing VCE a time consuming procedure we observed an initial viewing time of less than one hour for doctors with endoscopic experience. The viewing time is reduced to 30 min. after 50 procedures, which will be acceptable in most endoscopy units. Despite this decrease in viewing time the frequency of a definite diagnosis did not decrease.

Although the presence of the SBI should facilitate the analysis of VCE we showed a sensitivity of 68% and a PPV of only 63%. Although the PPV increased to 100% in the group of patients with overt bleeding, the NPV was only 40% in this group. In patients

with suspected CD the NPV was 92%. No significant differences could be established. In one study in 24 patients (18 patients with OGIB and 6 patients with abdominal pain) the SBI was reported to have a sensitivity of 26% and a PPV of 90% (17).The sensitivity in this study increased to 81% for active bleeding lesions. It was not reported whether there was a difference in the reliability of SBI in patients with OGIB and abdominal pain. This algorithm clearly needs improvement before it can play an important role in improving the review process of VCE.

It is difficult to verify the findings of the videocapsule because a gold standard is still lacking. So far the only way to investigate the small bowel was by push enteroscopy, enteroclysis or intraoperative enteroscopy. VCE has been compared to push enteroscopy (PE) in both animals and humans. PE and VCE performed equally in the detection of beads in the proximal ileum of dogs, but VCE was superior in the detection of the distal beads (18). Several comparative studies have also been performed in humans (19-24). In these studies the diagnostic yield is varying between 19 and 32% for PE and from 65 to 74% for VCE. In only some of these studies the relation of the findings to the symptoms of the patients is described. Although good results of VCE are generally reported, cases have been described in which abnormalities were missed by VCE but were finally found by PE (16).

In several studies VCE and enteroclysis were compared. Enteroclysis has a low diagnostic yield of 3-23% compared to a diagnostic yield of 45-77% for VCE (1, 25-27). One study in CD patients reported an equal result of VCE and enteroclysis of 70% and 67% respectively (14). Some studies also reported comparative studies of VCE and CT enteroclysis. The superiority of VCE was confirmed with a yield of 59-77% as compared to 22-36% for CT enteroclysis (25-29). Until recently intraoperative enteroscopy offered the only possibility for endoscopic investigation of the complete small intestine. VCE findings have been confirmed at intraoperative enteroscopy in 14/16 patients (88%) with OGIB (30).

Recently double balloon enteroscopy has been introduced in which an enteroscope is introduced through the entire small bowel by sequential insufflation and desufflation of balloons on the endoscope and an overtube (31, 32). This technique offers the possibility to investigate the ileum without the need of a laparotomy. Prospective studies comparing double balloon enteroscopy and VCE might result in a fair comparison and a more reliable estimate of the diagnostic accuracy of VCE.

Conclusion

VCE is an excellent technique with minimal risks and side effects. The viewing time decreases to 30 min. after 50 procedures. SBI is not reliable enough to play a role in reviewing VCE. Young female patients with OGIB have a low diagnostic yield which might be attributed to menstrual instead of intestinal blood loss. The diagnostic yield

in patients with OGIB increases when the haemoglobin level is less than 7.0 mmol/l. The diagnostic yield is highest in case of suspected Crohn's disease. Although VCE detects abnormalities in 70% of the patients in unselected group in a large general hospital, the true diagnostic yield of definite findings is considerably lower, in our series 38%. We advocate a differentiation between definite and possible diagnoses in future studies on VCE performance.

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New endoscopic techniques for obscure gastrointestinal bleeding.

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Abstract

We present a case of a postmenopausal woman with a congenital aortic stenosis. She presented with severe iron deficiency anemia. After negative extensive gastrointestinal analysis she was treated for six months with octreotide. After cessation of octreotide, anemia rapidly recurred. A second capsule endoscopy and a double balloon enteroscopy were performed and an intestinal vascular malformation was found. After surgical segment resection the patient had stable normal levels of haemoglobin and no complaints during 14 months follow-up.

Introduction

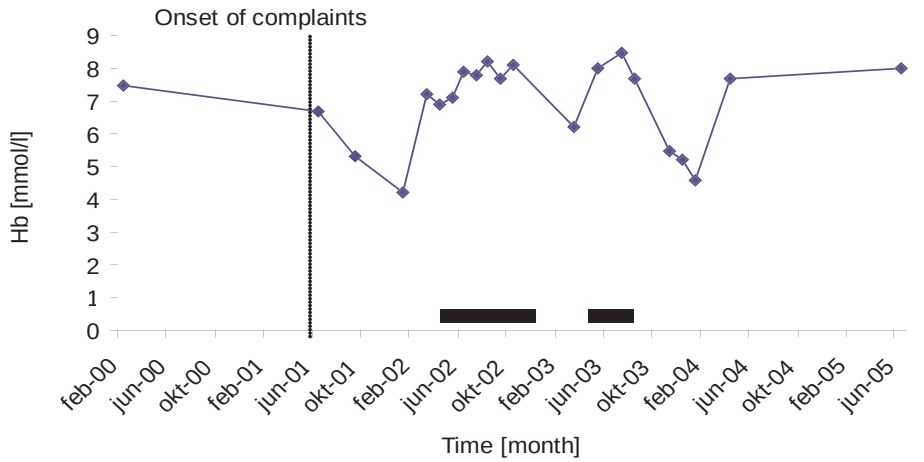
The source of obscure gastrointestinal bleeding is often difficult to locate. The small intestine beyond the ligament of Treitz is the source of bleeding in up to 5% of patients presenting with gastrointestinal bleeding (1). In the small bowel angiodysplasia are the most common cause of obscure bleeding, followed by neoplasm. Until recently, the small bowel was difficult to examine in an effective and patient friendly way. Small bowel enteroclysis can reveal strictures and tumors, but mucosal abnormalities are difficult to detect. Push-enteroscopy allows limited access to the proximal small intestine. Intraoperative enteroscopy allows complete examination of the small bowel but is very invasive. New endoscopic techniques like videocapsule endoscopy (VCE) and double balloon enteroscopy (DBE) now enable complete examination of the small bowel. VCE is a wireless non-invasive imaging technique. After ingestion, a video capsule takes 2 photographs per second during its journey through the small intestine. The main indication is obscure intestinal bleeding which cannot be clarified by esophagogastroduodenoscopy and colonoscopy. VCE can only be used as a diagnostic tool since no interventions are possible with the capsule. Double balloon enteroscopy is a technique in which an enteroscope is introduced from the oral or anal route in the small intestine by sequential inflation and desufflation of two balloons, attached to the enteroscope and an overtube. DBE allows the same interventions as with conventional endoscopy. At present, the best candidates for the procedure appear to be those with obscure bleeding. We present a patient with obscure gastrointestinal bleeding and discuss the application of VCE and DBE.

Case report

A 51-year-old postmenopausal woman presented with iron deficiency anemia. She felt tired and dizzy, but never observed overt blood loss and had no abdominal symptoms. Her medical history showed a congenital aortic stenosis for which an aortoplasty had been performed at the age of 9 years. At the age of 33 years a Bjork Shiley aortic valve prosthesis was implanted and acenocoumarol was started. After mechanical dysfunction, a Sorin valve prosthesis was implanted 6 years later. Laboratory investigation showed a haemoglobin level of 4.2 mmol/l, severe iron deficiency and no signs of haemolytic anemia. Bone marrow evaluation revealed no abnormalities. Colonoscopy, gastroduodenoscopy, small bowel follow through, push enteroscopy and VCE showed no abnormalities. Oral and intravenous iron supplementation only resulted in minor increase of haemoglobin levels. During six months she was treated with octreotide (Sandostatin LAR® 20 mg, Novartis) injections under the presumptive diagnosis of obscure gastrointestinal bleeding. This resulted in a complete normalisation of haemoglobin levels and disappearance of complaints (***Figure 1***). After cessation of octreotide, iron deficiency anaemia rapidly recurred. Gastroscopy and colonoscopy

were repeated, but again revealed no bleeding focus. A second VCE showed a solitary ulcerating angiodysplasia in the middle part of the small bowel (***Figure 2***). DBE was subsequently performed and showed a large submucosal polypoid blue-purple tumour (***Figure 3a***). The lesion was marked at the base by submucosal injection with Indian ink and lipiodol (***Figure 3b***) and a surgical segment resection of 15 centimetres was performed by a mid-line laparotomy. Histopathological examination revealed a large hemangioma-like ectatic vascular conglomerate with variable wall thickness (***Figure 4***). The patient had a quick postoperative recovery and had stable normal levels of haemoglobin and no complaints during 14 months follow-up.

Figure 1 *Haemoglobin levels. Horizontal solid bars indicate octreotide treatment (Sandostin Lar® 20mg monthly injections).*



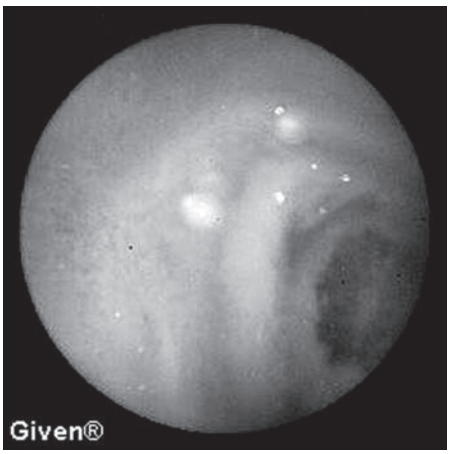


Figure 2 *Images of the second video capsule examination at 2 hours and 9 minutes after ingestion showing a solitary ulcerating angiodysplasia.*
(for colour figure see page 144)

Figure 3 *a) Double balloon enteroscopy showing a polypous angiodysplasia. b) The location is marked with Indian ink and lipiodol. (for colour figures see page 144)*

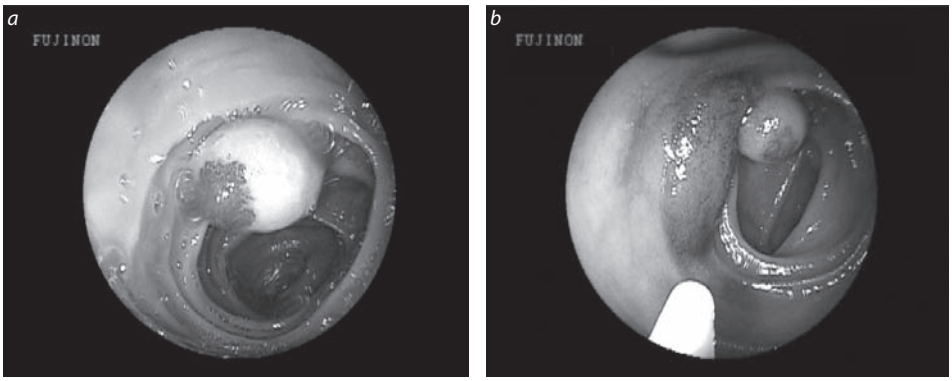
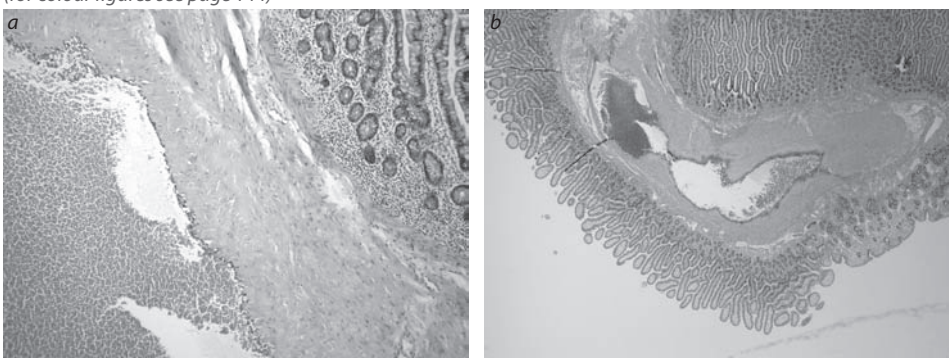


Figure 4 *Histopathological examination showed a large hemangioma-like polypous ectatic vascular conglomerate, partly thin walled partly thick walled. (HE staining, objective 2x en 10x)*
(for colour figures see page 144)



Discussion

Despite examination of the gastrointestinal tract by gastroduodenoscopy and colonoscopy the origin of obscure occult bleeding remains unexplained in 10% of cases (2). Angiodysplasia in the small bowel are the cause of obscure gastrointestinal blood loss in 30-40 percent of these patients (2). These vascular malformations are composed of conglomerates of ectatic, dilated, tortuous thin-walled vessels. Their pathogenesis is uncertain. Associations with chronic mucosal ischemia, as well as with low grade venous obstruction have been suggested and a congenital predisposition has also been considered (3-5). The prevalence of gastrointestinal angiodysplasia in the general population is unknown. Most of these vascular lesion are detected in patients

older than 60 years (3). An association between aortic valve disease and angiodysplasia has been recognized for years (Heyde's syndrome). Evidence is mounting that severe aortic stenosis may cause type 2 acquired von Willebrand's disease. Heyde's syndrome appears to consist of bleeding from previously latent intestinal angiodysplasia as a result of acquired von Willebrand's disease (6, 7). Recently a retrospective analysis of 3.8 million hospital discharges found a significant association between bleeding due to intestinal angiodysplasias and aortic stenosis (7). However, von Willebrand's disease and also its acquired form are very rare and only a positive family history or a typical history of recurrent mucosal bleeding episodes from multiple sites (e.g. epistaxis or bleeding after tonsillectomy) may lead to assessment of von Willebrand factor.

Octreotide, a synthetic somatostatin analogue, is a peptide shown to markedly reduce splanchnic blood flow through specific sub-type receptors (8, 9). In a study of three patients with bleeding due to small intestinal angiodysplasia, octreotide was well tolerated and resulted in a decrease or elimination of the need for transfusions. However it did not result in regression of the angiodysplastic lesions (10). In another study 17 patients were treated with octreotide. Treatment stopped bleeding in ten patients and a transient improvement was observed in another four patients (9, 10). Therefore octreotide may be useful to control bleeding from small bowel angiodysplasia, as was also shown in our patient.

VCE is a new non-invasive imaging technique for the entire small bowel. It provides good visualization of the small intestinal mucosa. The diagnostic yield for obscure bleeding varies between 60 and 92% (2, 11-14) and is now considered an important diagnostic tool in case of normal gastroduodenoscopy and colonoscopy. It is superior to push enteroscopy, small bowel barium follow through and computerized tomography in patients with obscure gastrointestinal bleeding, iron deficiency anemia and Crohn's disease. Diarrhoea, small bowel tumours and coeliac disease may also become important indications (15). A recent study assessed the diagnostic yield of a second VCE with a previous negative evaluation. VCE revealed a definite or suspected source of bleeding in 35% of 20 patients (19). Another study with 24 patients showed a high yield of new findings (75%) on repeat capsule endoscopy (20). A report about false-negative VCE showed reasons for missed lesions like a small intestinal bowel delay of capsule transit greater than fifteen minutes, capsule nonexcretion and dilation of the small bowel without food debris (21). However, none of these factors were identified in our patient. VCE does have certain limitations, there is no possibility for air insufflation, rinsing of tissue, taking biopsies and therapeutic interventions. Due to its patient's friendly nature, VCE will probably be widely used as a "screening tool" whereas DBE will be applied when an abnormality is found by VCE or when severe symptoms are not explained by VCE. DBE allows visualisation of the entire small bowel and offers the possibility to take biopsies and perform therapeutic interventions. Lesions can be marked by submucosal injection of lipiodol or Indian ink (17, 18). Obscure overt

gastrointestinal blood loss is the most important indication for DBE. The exact diagnostic yield and clinical implications still have to be defined. VCE and DBE have an important impact on the diagnostic and therapeutic options for gastrointestinal bleeding. Both are considered essential components of the diagnostic workup of obscure gastrointestinal bleeding (16-18, 22).

Obscure gastrointestinal bleeding gives a high yield of new findings on repeat VCE (20), also DBE appears to surpass other imaging modalities (17), so new pathologic findings will be possible (23). The combination of VCE and DBE is very important for diagnosis and treatment. This case with a large polypous ectatic vascular conglomerate clearly demonstrates the usefulness of repeated VCE and DBE in a patient with obscure gastrointestinal bleeding.

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Clinical consequences of videocapsule endoscopy in gastrointestinal bleeding and Crohn's disease

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Gastrointestinal Endoscopy , in press

Abstract

Background

Videocapsule endoscopy (VCE) has a high diagnostic yield in the analysis of gastrointestinal bleeding and Crohn's disease. Little information is available on the impact of VCE findings on clinical care.

Objective

Assess the impact of VCE findings on clinical management and outcome.

Design

Retrospective descriptive study.

Setting

General hospital.

Patients

VCE was performed in 150 patients for gastrointestinal bleeding (n=97), Crohn's disease (n=36) and miscellaneous reasons (n=17).

Main outcome measurements

Clinical consequences were evaluated using a questionnaire and divided in change of management or unchanged management. Change of medication, endoscopic procedures, surgical procedures, other consequences and avoidance of additional investigations were considered a change of management. For all patients an assessment of the actual clinical condition and the most recent haemoglobin level were registered.

Results

A definite diagnosis was established in 34%, a probable diagnosis in 34% and no diagnosis in 32%. Management was changed in 38% of patients, increasing to 59% if a definite diagnosis was established at VCE. No relation between change of management and clinical improvement or increased haemoglobin level could be established.

Limitations

The start of ethinylestradiol/norethisteron in case of teleangiectasia was considered as a change of management although controversy on the rationale of this treatment exists.
A more detailed and objective evaluation of the clinical condition should be performed to assess the clinical outcome.

Conclusions

VCE findings have serious impact on clinical practice. VCE in particular leads to a change of management in 59% of the patients in whom a definite diagnosis is established.

Introduction

Until recently complete endoscopic examination of the small intestine was only achieved by intra-operative enteroscopy. The only endoscopic access to the small intestine was obtained by ileocolonoscopy or fluoroscopy guided push-enteroscopy. Both approaches offered a limited view of the small intestinal mucosa. Videocapsule endoscopy (VCE) is a new, non-invasive diagnostic tool to visualize the entire small intestine. The system consists of a wireless capsule that can be swallowed and is propelled by peristalsis. It obtains sequential endoscopic images of the small intestine that can be reviewed as a movie.
Main indications for visualisation of the small intestine are gastrointestinal bleeding (GIB), small bowel Crohn's disease, and intestinal tumours. Various studies on the diagnostic yield and clinical applicability of VCE have been performed in highly selected groups of patients. These studies reported a diagnostic yield of 55-85% (1-8). VCE was compared to other diagnostic modalities for the small intestine in a large meta-analyis which demonstrated that VCE is superior to push enteroscopy and enteroclysis in both the analysis of occult gastrointestinal bleeding and suspected small intestinal Crohn's disease (9). This led to the increasing implementation of VCE in clinical practice for the investigation of gastrointestinal blood loss or small intestinal Crohn's disease. Little information is available however on the clinical implications of videocapsule endoscopy. Frequently VCE reveals minor abnormalities of which it is not clear whether they have a causal relation with the patient's symptoms. Even in case of abnormalities at VCE which can reasonably be the cause of the clinical symptoms under investigation, the impact on treatment and outcome is largely unknown. In order to assess the clinical usefulness of VCE not only the diagnostic yield but also the clinical relevance and consequences should be investigated.
In the present study we therefore analysed the direct clinical consequences of VCE findings and the current clinical status of the patients one year after the procedure.

Methods

Patients

For all patients who underwent VCE in the period between January 2002 and January 2005 data were collected regarding age, sex and the indication of VCE. None of the patients previously underwent major gastrointestinal surgery.
The indication of GIB was divided in occult gastrointestinal bleeding in case of iron deficiency anaemia in the absence of visible blood and overt gastrointestinal bleeding if blood loss has been visualised (10). In patients with GIB, the lowest haemoglobin (Hb) in the year preceding VCE was registered. The time delay between the most recent bleeding episode and VCE was registered in case of overt bleeding and categorized

as less than 2 weeks or more than 2 weeks. Patients with Crohn's disease (CD) were categorized in two groups. Patients with known CD were classified as established CD and patients with diarrhoea combined with abdominal pain and laboratory abnormalities suggesting CD were classified as suspected CD. All other indications were classified as other.

Videocapsule endoscopy

VCE was performed using the Given Imaging M2A wireless capsule (Yoqneam, Israel) as described previously (11,12). All images were analysed by one of four experienced gastroenterologists who each had reviewed at least 50 VCE procedures prior to the study. Gastric and small intestinal transit time was calculated and the percentage of complete small bowel evaluations was registered.
Findings were considered a definite diagnosis if the observed finding could explain the symptoms of the patient. Findings were considered suspicious and registered as a probable diagnosis if an observed finding failed to completely explain the symptoms of the patient. In case of multiple findings the most relevant finding determined whether they were considered a definite diagnosis or suspicious findings. If no relevant abnormalities were found and in case of an insufficient investigation, VCE was classified as "no diagnosis" (1).

Questionnaire

One year after VCE a questionnaire was sent to the referring physician. The questionnaire evaluated the impact of VCE findings on clinical care. Clinical consequences were categorized as change or no change of management. Change of medication, endoscopic procedures, surgical procedures, avoidance of additional investigations (e.g. push enteroscopy, CT-enteroclysis or nuclear imaging) and other clinical consequences were considered a change of management. In case of patients referred for VCE by one of the authors the clinical impact was assessed by an independent physician.
The treating physician was asked to judge the present clinical condition of the patient as worse, better or equal as compared to the moment of referral for VCE based on general clinical parameters. If VCE had been performed for gastrointestinal bleeding the haemoglobin level one year after VCE was registered. All referring physicians were asked whether they would refer their patients for VCE for the same indication in the future.
For the assessment of the relation of consequences of VCE findings and clinical outcome consequences were divided in change of treatment or unchanged treatment. The major differences with the assessment of management changes concerned the categories avoiding additional investigation and the performance of endoscopic procedures in IBD patients. These categories were categorized as unchanged treatment as this will

not influence the clinical outcome. The other clinical consequences were considered a change of treatment.

Statistics

Parametric results were compared by two-sided Student's t-test. Data from multiple groups were compared by analysis of variance. Group proportions were compared with Chi-square test or Fisher's exact test where appropriate. A two-sided $p<0.05$ was considered significant.

Results

Questionnaire

One year after the performance of VCE 166 questionnaires were sent to the referring physicians. The response rate was 90.4% (n=150).

Patients

Analysis was performed for 150 patients (M/F 71/79) with a mean age of 54,0 yrs. (SD 19, range 11-83). The indication for VCE was occult gastrointestinal bleeding in 84 patients (56%), overt gastrointestinal bleeding in 13 patients (9%), established CD in 14 patients (9%), suspected CD in 22 patients (15%) and other indications in 17 patients (11%).

Videocapsule endoscopy

A complete small bowel examination was obtained in 115 patients (77%). The mean gastric transit time was 43 min. (SD 75, range 1-480) and the small intestinal transit time was 252 min. (SD 87, range 31-484).
A definite diagnosis was obtained in 51 patients (34%), a probable diagnosis in another 51 patients (34%) and no diagnosis was found in 48 patients (32%; ***Table 1***). In case of gastrointestinal bleeding a definite diagnosis was found in 25 (26%) patients, a probable diagnosis in 40 (41%) patients and no diagnosis in 32 (33%) patients as compared to respectively 20 (56%), 5 (14%) and 11 (31%) patients in case of CD (p=0.01). If overt bleeding was the indication for VCE, a definite diagnosis was found in 5 patients (71%) when VCE was performed within 2 weeks after clinical presentation and in 3 patients (50%) if the delay was more than 2 weeks (p=n.s.).

Table 1 *Diagnosis according to indication for VCE.*

	Definite	*Probable*	*No diagnosis*
Gastrointestinal bleeding	*25 (26%)*	*40 (41%)*	*32 (33%)*
Occult gastrointestinal bleeding	*17 (20%)*	*36 (43%)*	*31 (37%)*
Overt gastrointestinal bleeding	*8 (62%)*	*4 (31%)*	*1 (8%)*
Crohn's disease	*20 (56%)*	*5 (14%)*	*11 (31%)*
Established Crohn's disease	*10 (71%)*	*2 (14%)*	*2 (14%)*
Suspected Crohn's disease	*10 (46%)*	*3 (14%)*	*9 (41%)*
Other	*6 (35%)*	*6 (35%)*	*5 (29%)*

Clinical consequences

VCE findings led to a change of medication in 23 patients (15%), an endoscopic procedure in 15 patients (10%), to surgery in 5 patients (3%), avoided additional investigations in 6 patients (4%) and had other consequences in 8 patients (5%). Unchanged management occurred in 93 patients (62%; ***Table 2***).

Table 2 *Clinical consequences according to indication for VCE.*

	Medication	*Endoscopy*	*Surgery*	*Other*	*Avoiding investigation*	*Change of management*	*Unchanged management*
Total	*23 (15%)*	*15 (10%)*	*5 (3%)*	*8 (5%)*	*6 (4%)*	**57 (38%)**	**93 (62%)**
GI bleeding	*11 (11%)*	*12 (12%)*	*3 (3%)*	*3 (3%)*	*5 (5%)*	**34 (35%)**	**63 (65%)**
Occult bleeding	*10 (12%)*	*8 (10%)*	*1 (1%)*	*2 (2%)*	*5 (6%)*	**26 (31%)**	**58 (69%)**
Overt bleeding	*1 (8%)*	*4 (31%)*	*2 (15%)*	*1 (8%)*	*0 (0%)*	**8 (62%)**	**5 (38%)**
Crohn's disease	*12 (33%)*	*2 (6%)*	*1 (3%)*	*3 (8%)*	*0 (0%)*	**18 (50%)**	**18 (50%)**
Established CD	*3 (21%)*	*1 (7%)*	*1 (7%)*	*1 (7%)*	*0 (0%)*	**6 (43%)**	**8 (57%)**
Suspected CD	*9 (41%)*	*1 (5%)*	*0 (0%)*	*2 (9%)*	*0 (0%)*	**12 (55%)**	**10 (45%)**
Other	*0 (0%)*	*1 (6%)*	*1 (6%)*	*2 (12%)*	*1 (6%)*	**5 (29%)**	**12 (71%)**

Clinical consequences according to indication

In case of gastrointestinal bleeding VCE findings led to a change of medication in 11 patients (11%), a targeted endoscopic procedure in 12 patients (12%) and to surgery in 3 patients (3%; ***Table 2***). VCE resulted in a change of management in 26 patients (31%)

in case of occult GI bleeding and in 8 patients (62%) when VCE was performed for overt GI bleeding (p=0.02). If VCE was performed within two weeks after the manifestation with overt bleeding the effect on management changes did not differ significantly when compared to VCE performed more than 2 weeks after overt bleeding.
In patients with established Crohn's disease medication was changed in response to VCE findings in 3 patients (21%) and in suspected Crohn's disease VCE findings led to a change of medication in 9 patients (41%). No significant difference was found between the occurrence of a change of management between suspected and established CD.

Clinical consequences according to a definite, probable or no diagnosis

In case of a definite diagnosis VCE findings led to a change of medication in 16 patients (31%), to the performance of a targeted endoscopic procedure in 9 patients (18%) and to surgery in 4 patients (8%; ***Table 3***, ***Figure 1***). In case of a probable diagnosis at VCE medication was changed in 5 patients (10%), an endoscopic procedure was performed in 6 patients (12%), a surgical procedure was performed in 1 patient (2%), additional investigations were avoided in 3 patients (6%), and other consequences were reported in 4 patients (8%). A change of management was found in 28 patients (59%) in case of a definite diagnosis at VCE, in 19 patients (37%) if a probable diagnosis was found at VCE, and in 8 patients (17%) if no diagnosis was found (p<0.001).

Table 3 *Clinical consequences according to a definite, probable or no diagnosis.*

	Definite diagnosis	***Probable diagnosis***	***No diagnosis***
Change of management	**30 (59%)**	**19 (37%)**	**8 (17%)**
Change of medication	*16 (31%)*	*5 (10%)*	*2 (4%)*
Endoscopic procedure	*9 (18%)*	*6 (12%)*	*0 (0%)*
Surgery	*4 (8%)*	*1 (2%)*	*0 (0%)*
Other consequences	*1 (2%)*	*4 (8%)*	*3 (6%)*
Avoiding additional investigation	*0 (0%)*	*3 (6%)*	*3 (6%)*
Unchanged management	**21 (41%)**	**32 (64%)**	**40 (83%)**

Clinical consequences and completeness of VCE examination

In 115 patients (77%) the complete small bowel was examined. A definite diagnosis was established in 37 (32%) of those 115 patients, and the findings led to management changes in 41 patients (36%; ***Table 4***). In 35 patients (23%) the small bowel could not be completely visualized. In this group of patients VCE yielded a definite diagnosis in 14 patients (40%) and clinical management was changed in 16 patients (46%). The frequency of management changes did not differ significantly in relation to the (in)completeness of VCE examination.

Figure 1 *Clinical consequences in case of definite, probable or no diagnosis at VCE.*

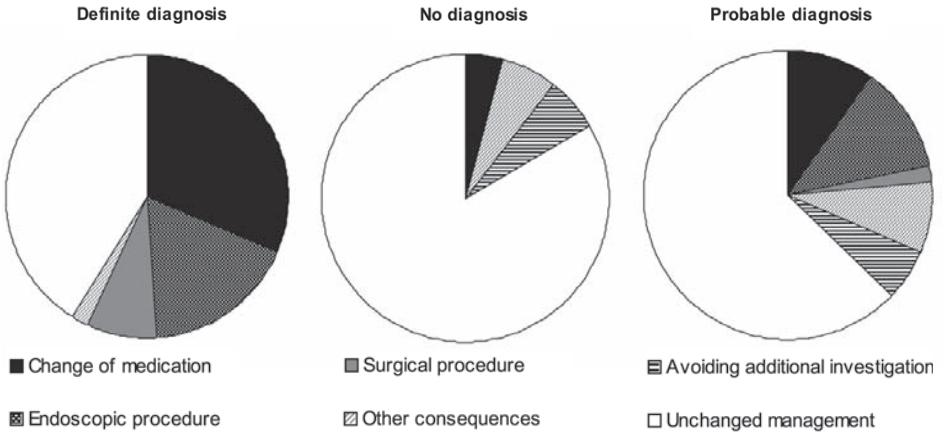

Table 4 *Clinical consequences according to completeness of VCE examination.*

	Complete	*Incomplete*
Change of management	**41 (36%)**	**16 (46%)**
Change of medication	*18 (16%)*	*5 (14%)*
Endoscopic procedure	*11 (10%)*	*4 (11%)*
Surgery	*3 (3%)*	*2 (6%)*
Other consequences	*4 (4%)*	*3 (9%)*
Avoiding additional investigation	*5 (4%)*	*2 (6%)*
Unchanged management	**74 (64%)**	**19 (54%)**

Clinical condition and haemoglobin level one year after VCE

Information regarding the clinical condition at one year follow-up was available in 143 (95%) patients. At that time, 74 patients (52%) were in a better condition (***Table 5***). In case of a change of management the condition of 31 patients (57%) improved whereas in case of unchanged management the clinical condition improved in 43 patients (48%; p=n.s.).

Table 5 *Clinical condition one year after VCE.*

	Total	*Changed treatment*	*Unchanged treatment*
Improved	*74 (52%)*	*31 (57%)*	*43 (48%)*
Unchanged	*55 (38%)*	*18 (33%)*	*37 (42%)*
Deteriorated	*8 (6%)*	*5 (9%)*	*3 (3%)*
Died	*6 (4%)*	*0 (0%)*	*6 (7%)*

When VCE established a definite diagnosis there was a non-significant trend to an improved clinical condition one year after the procedure in 30 patients (65%) compared to 23 patients (45%) and 21 patients (46%) respectively if a probable diagnosis or no diagnosis was found (p=0.08).
The mean haemoglobin level one year after VCE was 8.2 mmol/l (SD 1.10, range 4.9-10.8) in patients with an improved clinical condition and 7.5 mmol/l (SD 1.26, range 4.7-7) in the other patients (p<0.01). The mean haemoglobin level increased from 5.4 ±1.2 mmol/l to 7.7±1.3 mmol/l during the follow-up period (p<0.001). In case of a change of management the mean haemoglobin level increased from 5.4±1.0 to 7.3±1.1 mmol/l but in case of unchanged management an increase of the mean haemoglobin level from 5.4±1.3 to 8.0±1.3 mmol/l was also registered (p=n.s. for comparison between both groups).
All referring physicians would perform a VCE for the same indication in the future regardless whether VCE lead to clinical consequences.

Discussion

Many studies have described the clinical applicability of VCE but were mainly focussing on the diagnostic yield. Due to the widely reported high diagnostic yield VCE has now been accepted as a routine clinical investigation in gastrointestinal bleeding and is also increasingly used in small intestinal Crohn's disease. Diagnostic yield may be overestimated because of the presence of minor abnormalities of the small intestinal mucosa which have no relevance for the underlying disease. In more recent papers this was overcome by classifying the abnormalities found at VCE either as a definite diagnosis or a probable diagnosis depending on the chance that the lesions that were found had a causal relation with the clinical problem (1, 4, 13-16).The main question remaining is whether the findings at VCE have an impact on the management and the clinical outcome of the patients who underwent the procedure.
In the present study the consequences of VCE were divided in two categories. A change of medication, the performance of a targeted endoscopic or surgical procedure, avoidance of additional procedures, and other consequences were considered a change of management. In case of change of medication this also included the start of ethinylestradiol/norethisteron (Neocon®), which might lead to an overestimation of the major clinical consequences as there is controversy on the rationale for this treatment of anaemia due to bleeding angiodysplasia (17,18). In all other cases the result of VCE was classified as unchanged management, keeping in mind that the results of VCE may have been helpful in minimizing the differential diagnostic possibilities, which may also have reassured the patient or physician.
In the entire group of patients, VCE led to a change of management in 38% of cases. In case of patients with a definite diagnosis at VCE, findings had major clinical

consequences in 59% of patients. In case of a probable diagnosis or no diagnosis, major clinical consequences occurred in 37% and 17% of patients respectively. The fact that management changes occurred in the absence of a diagnosis at VCE can be explained by the avoidance of push enteroscopy and stopping mesalazine which was previously started for suspected small bowel CD. These results are in accordance with a study by Saurin et al who reported major clinical consequences in 61% of the patients if VCE revealed highly relevant lesions and 23% in case of minor abnormalities (14).

Most studies reported more frequent changes in clinical management. Some small studies reported VCE guided management changes in 67-100% of patients (15,19, 20). The largest series so far report on 96 patients who underwent VCE mainly for GIB resulting in a definite diagnosis in 42%. This resulted in a change of management in 83% of patients and in case of a probable diagnosis management was changed in 35% (21). In this study management changes were endoscopic, surgical or medical treatment, the latter including estrogen therapy and discontinuation of NSAID's. The lower proportion of management changes in the present study is probably related to less strict selection of patients as we present the largest population in a general hospital with a one year follow-up.

In case of GIB change of management occurs more frequently in case of overt gastrointestinal bleeding as compared to occult bleeding (62% vs 31%, p=0.02).

VCE has a diagnostic yield of 40-72% in CD (4, 23-28). In a study of 50 patients with known or suspected CD a definite diagnosis was found in 40% of patients with clinical improvement in 17/20 (85%) patients after a change of treatment. A German study reported the presence of a definite diagnosis in 25/41 patients (61%). In 40% of these patients therapy was changed leading to a subsequent clinical improvement (28). This is in accordance with our results which showed a diagnostic yield of 56% and a change in management in 50% of patients.

We corroborated the finding that VCE performed for small intestinal CD led to more frequent major clinical consequences than in case of gastrointestinal bleeding although this difference did not reach statistical significance in our study.

A complete examination of the small bowel is considered an important advantage of VCE when compared to other techniques. Surprisingly we did not find significant differences with respect to diagnostic yield and clinical consequences between complete and incomplete VCE examination. This could either be due to a type II error or by the fact that even an incomplete VCE still visualizes the major part of the small bowel. Only in case of small intestinal Crohn's disease major clinical consequences were found more frequently in this study in case of a complete small bowel examination which might be associated with the predominant location of abnormalities in the distal ileum in CD.

Although the establishment of a definite diagnosis by VCE led to major clinical consequences in 59% of the patients there was only a nonsignificant trend towards

clinical improvement. The mean haemoglobin level increased during the year following VCE but this occurred irrespective of a change of treatment. Although a more favourable outcome has been reported for patients in whom VCE yields a definite diagnosis this could not be confirmed in our population (14, 19-21). This might be due to the fact that the assessment of clinical condition is rather subjective and registered one year after the performance of VCE. In future studies a more detailed definition of the clinical outcome should be used.

In one study only endoscopic procedures, surgical procedures, cessation of non-steroidal anti-inflammatory drugs and the start of CD directed therapy were considered as a change of management(13). If we apply the same criteria to our population, 34 (23%) patients would be defined as having been subject to treatment changes after VCE. This led to clinical improvement in 67% of them as compared to 42% in case of unchanged treatment ($p=0.06$). This improvement in clinical condition was however not accompanied by a significant change in the haemoglobin level one year after VCE. The application of more strict criteria therefore does not change our observation that treatment changes did not lead to a significant improvement of clinical condition one year after VCE, although a trend towards significance was observed.

To our knowledge this is the largest study on the clinical implications of VCE. It demonstrates that VCE has a high clinical impact with a change of management in 38% of patients overall, and in 59% when VCE yields a definite diagnosis in particular. Besides the potential impact on clinical management VCE can be useful for the exclusion of major abnormalities of the small intestine. Further studies are mandatory to assess the exact clinical role of VCE for several indications with an emphasis on the timing of VCE as a diagnostic tool and a more objective and precise assessment of the long term clinical outcome.

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5

Detection of small bowel neuroendocrine tumours by videocapsule endoscopy

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Abstract

Objectives

Carcinoid tumours are the most common gastrointestinal neuroendocrine tumours (NET). They often originate in the small intestine. The primary tumour is often difficult to locate, and resection in an early phase is recommended to prevent complications. This study evaluated the value of videocapsule endoscopy (VCE) in the detection of small intestinal primary carcinoid tumours.

Design

Prospective descriptive study.

Setting

Tertiary referral centre.

Patients

Twenty consecutive patients (M/F 13/7; 60.5±9.3 yrs.) with metastatic NET of unknown primary.

Interventions

All patients underwent CT-scanning, enteroclysis, nuclear imaging and VCE of the small bowel.

Results

CT-scan and enteroclysis did not detect a primary small intestinal carcinoid tumour. Nuclear imaging demonstrated abnormalities in the abdominal area in 13 patients but was unable to relate this to an intestinal localisation in any patient. VCE revealed a small intestinal tumour in 9 patients. Three other patients showed external compression and erosions. At surgery, five patients had a small intestinal carcinoid tumour and in 2 patients a small intestinal ischemic segment was present.

Limitations

The number of false positive VCE findings is not clear because not all patients underwent surgery. The absence of abnormalities at VCE in patients with abnormalities at nuclear imaging might be related to the presence of carcinoid tumour restricted to the mesenterium or to a false negative VCE.

Conclusions

VCE has a high diagnostic yield of 45% for identification of primary small intestinal carcinoid tumours. Although nuclear imaging had a comparable diagnostic yield it could not differentiate between intestinal and mesenterial localisation of the carcinoid tumour. We suggest VCE as diagnostic procedure of first choice in the search for primary intestinal carcinoid tumours.

Introduction

Neuroendocrine tumours (NET) most frequently (75%) arise in the appendix and terminal ileum (1-3). They are usually submucosal tumours with a diameter of 0.5 to 1.0 cm, and occur in up to 30% of patients at multiple sites in the small bowel. Most patients have metastases in the loco-regional mesenteric lymph nodes and liver. Early detection and resection of the primary tumour is indicated, even in patients with metastatic disease, to prevent complications such as small bowel obstruction, bleeding, and mesenteric ischemia on the basis of mesenteric fibrosis (2, 4). However, the diagnosis and localisation of small intestinal tumours is difficult with currently available techniques. Small bowel follow-through and enteroclysis rarely allow the detection of endoluminal tumours smaller than 1.5 to 2 cm (5). Multi detector computed tomography (CT) with intravenous contrast may show clearly enhancing submucosal lesions, but large series are lacking to report its sensitivity. CT is very accurate in detecting mesenteric masses and liver metastases (6, 7). Magnetic resonance imaging (MRI) enteroclysis is a rapidly evolving technique. A recent study showed positive imaging of small bowel carcinoids in 8 of 12 patients (8). Carcinoids appear on MRI either as a mass that enhances with gadolinium, or as a diffuse thickening of the bowel wall. MRI enables adequate detection of mesenteric masses and liver metastases.
With In^{111}-pentetreotide scintigraphy primary carcinoid tumours and (liver) metastases are detected with a sensitivity of 75% and a specificity of 100%, comparable to I^{131}-metaiodobenzylguanidine (MIBG) scanning (12). The poor spatial resolution of nuclear imaging makes it difficult to distinguish a primary intestinal tumour and an extra-intestinal tumour mass.
Endoscopy of the complete small intestine has for long remained difficult. Double-balloon enteroscopy and peroperative enteroscopy give access to the entire small bowel but are demanding techniques (13-14). Video capsule endoscopy is a non-invasive method to visualize the entire small bowel. It has been shown to be useful in detecting a wide range of small bowel diseases like bleeding foci, Crohn's disease and solid tumours. VCE has been shown to be superior to small bowel follow-through and enteroclysis in detecting small lesions (15).

In the present study we aimed to assess the value of video capsule endoscopy for detection of the primary small intestinal tumour in patients with mestastatic carcinoid disease.

Methods

Patients

Twenty consecutive patients (M/F 13/7, mean age 60.5, range 44 to 77 years) with metastatic carcinoid tumour diagnosed by histology or cytology were examined. All patients were analysed by enteroclysis, CT-scan of the abdomen, nuclear imaging by In^{111} pentetreotide scintigraphy and/or I^{131} MIBG scintigraphy. One patient (no. 7) also underwent ileocolonoscopy demonstrating a multifocal carcinoid tumour in the distal ileum. Because carcinoid tumours are frequently present at multiple sites of the small intestine, VCE was performed for a complete small bowel evaluation. In addition, a VCE was performed in all patients as part of routine clinical care.

Laboratory measurements

5-hydroxyindole-3-acetic acid (5HIAA) was measured using an enzyme ligand immunosorbent assay (DRG Instruments GmbH, Germany) in 24 hrs urine collected in bottles with 6N HCl as preservative (16). Normal values were 5-40 µmol/day. Chromogranin A concentrations were measured in serum using a sandwich radio-immunoassay (CIS Biointernational, France). Normal values were 10-100 µg/l (17).

CT-scan

CT scans were performed using a Philips AVE Expander, single-slice-scanner, until 2004. A slice-thickness of 7 mm and table-speed of 10mm per rotation were used with a reconstruction interval of 5mm. From 2004 a Siemens Sensation open, 20 slice-scanner was used with a slice-thickness of 5mm, table-speed 5mm per rotation (1 second) and a reconstruction interval of 1,5mm. Intravenous contrast (Omnipaque 300, Amersham health, USA) was given in a quantity depending on body weight.

Radionuclide imaging

The patients received 37 MBq (1 mCi) of I^{131}-MIBG by intravenous injection over 5 minutes. Total body imaging was performed after 24, 48 and 72 h. For somatostatin receptor imaging, 110 MBq (3 mCi) In^{111}-pentetreotide (Octreoscan, Mallinckrodt, USA) was administered intravenously. Total body imaging was performed at 24 h (18).

Enteroclysis

Under fluoroscopy a naso-enteral tube (Bilbao-Dotter Hypotonic Duodenography Set, Cook, USA) was positioned distal in the duodenum or proximal jejunum. The examination was performed using fluoroscopy and digital spot filming during infusion

of 600cc Micropaque 100% suspension diluted with 300cc water, until the colon was reached (15-60 minutes).

Videocapsule endoscopy

VCE was performed using the Given Imaging M2A wireless capsule (Yoqneam, Israel) as described previously (19). Patients were prepared for the investigation by a clear liquid diet for twelve hours, preceding an overnight fast. Four hours after swallowing the capsule, a light meal was permitted.
All VCE procedures were reviewed by two experienced endoscopists (S.v.T. and M.S.) who previously performed at least 150 VCE procedures each. The presence of ulceration, submucosal masses and evidence of external compression were considered to be suggestive for the presence of a carcinoid tumour.

Statistics

The diagnostic yields of each method were compared with Chi-square test or Fisher's exact test where appropriate. A two-sided $p<0.05$ was considered significant.

Results

Twenty patients with a metastasized carcinoid tumour and unknown primary were analysed. Eight patients had metastatic lesions in the liver, 7 patients had both liver and mesenteric lesions. In 4 patients only mesenteric abnormalities were present. One patient had a multifocal carcinoid tumour in the distal small intestine at ileocolonoscopy. Diagnosis was confirmed by liver biopsy in 14 patients, by cytological examination of the mesenterium in two patients, by mesenteric lymph node excision biopsy in one patient and by ileal biopsies in one patient. In two patients the initial diagnosis was made after CT scan and analysis of 5-HIAA level. In these patients the diagnosis was confirmed histologically after resection of the small intestinal tumour.

5-HIAA and chromogranin A level

The mean 5-HIAA level (determined in 15 patients) was 848 (SD 372, range 29 to 1354) µmol/day. Chromogranin A was determined in 3 patients with a mean value of 273 µg/l (SD 212, range 74 to 499).

Enteroclysis

All patients underwent enteroclysis. No small intestinal lesions were observed in any patient. In one patient retraction of the small intestine due to mesenterial lesions was seen (***Table 1***).

Table 1: *Results of diagnostic procedures, interventions and pathological examination. (np: not performed, nuclear imaging of the abdomen: liver not included).*

Patient	CT			Octreotide Scintigraphy		MIBG Scintigraphy		Enteroclysis	Videocapsule endoscopy	Intervention	Pathology
	Intestine	Mesenteric	Liver	Abdomen	Liver	Abdomen	Liver				
1	-	+	-	+	+	+	+	-	Distal erosion	Distal ileum resection	Carcinoid tumour
2	-	+	+	+	+	+	+	-	-	-	-
3	+	+	+	+	+	-	-	-	-	-	-
4	-	-	+	+	+	-	+	-	-	-	-
5	-	-	+	-	+	-	-	-	-	-	-
6	-	-	+	+	+	+	+	-	-	-	-
7	-	-	+	-	+	-	+	-	Distal multifocal tumour	-	-
8	-	-	-	-	-	np	np	-	Distal multifocal tumour	Laparotomy, 3 m. multifocal carcinoid tumour, no resection	-
9	-	-	+	-	+	-	-	-	Midileal tumour	-	-
10	-	-	+	-	+	-	-	-	Distal tumour	Distal ileum resection, hemihepatectomy	Carcinoid tumour
11	-	+	+	+	+	-	-	-	Proximal multifocal tumour	Segmental ileum resection, radiofrequency ablation liver metastases	Carcinoid tumour
12	-	+	-	+	-	+	-	-	Distal tumour	-	-

Table 1 – *Continued* –

Patient	CT			Octreotide Scintigraphy		MIBG Scintigraphy		Enteroclysis	Videocapsule endoscopy	Intervention	Pathology
	Intestine	Mesenteric	Liver	Abdomen	Liver	Abdomen	Liver				
13	-	+	+	+	+	+	+	-	Multifocal midleal tumour	Segmental ileum resection	Multifocal carcinoid tumour
14	-	+	-	+	-	np	np	-	External compression	Resection ischemic segment	Intestinal ischemia, carcinoid tumour
15	-	-	+	+	+	-	+	-	-	-	-
16	-	+	+	+	+	+	+	-	-	-	-
17	-	+	-	+	-	np	np	-	External compression, (stasis of capsule)	Resection ischemic segment	Intestinal ischemia, carcinoid tumour
18	-	-	+	-	+	np	np	-	Distal tumour	-	-
19	-	+	+	+	+	+	+	-	-	-	-
20	-	+	+	-	+	-	+	-	Midileal tumour	-	-

Abdominal CT and nuclear imaging

In 13/20 (65%) and 7/16 (44%) patients an abdominal hotspot (liver not included) was found at pentetreotide and MIBG-scintigraphy respectively. In 10/13 (77%) patients with positive findings at pentetreotide scintigraphy a mesenterial lesion was found and 1 had an abnormality in the cecal region at CT scanning. Positive findings at MIBG scintigraphy were related to mesenteric lesions in 6/7 patients. Pentetreotide scintigraphy showed the presence of liver metastases in 16/20 (80%) patients, which was confirmed by CT-scanning in 15 patients. MIBG scintigraphy demonstrated liver metastases in 10/16 (63%) patients which were confirmed by CT scanning in 9 patients.

Videocapsule endoscopy

All patients underwent videocapsule endoscopy. The capsule was introduced endoscopically in one patient because of swallowing difficulties. In two other patients VCE was repeated with endoscopic positioning beyond the pylorus because the capsule remained in the stomach for 7 hours at the first examination. One of these patients had external compression of the small intestine at VCE. When excluding the two patients in whom the capsule remained in the stomach on first investigation, the mean gastric transit time was 17±17 min. The mean small intestinal transit time in all patients was 283±116 min. The cecum was visualised in 13 patients (65%) and in all patients the capsule was expelled naturally. VCE demonstrated abnormalities in the small intestine in 12 patients. One or more submucosal tumours were seen in 9 patients (***Figure 1A-C***), external compression in 2 patients (***Figure 1D***) and mucosal erosion in one patient. The diagnostic yield did not change when the cecum was not visualised.

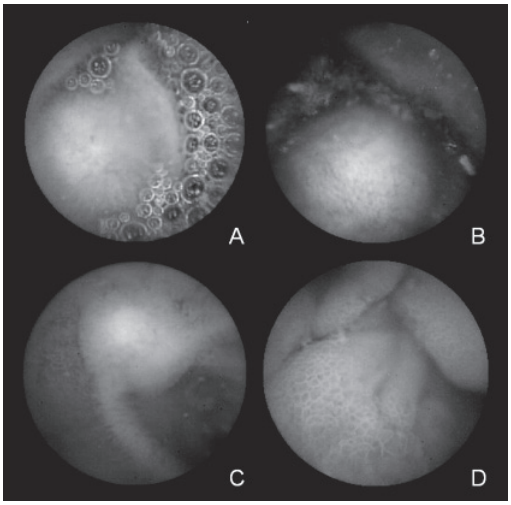
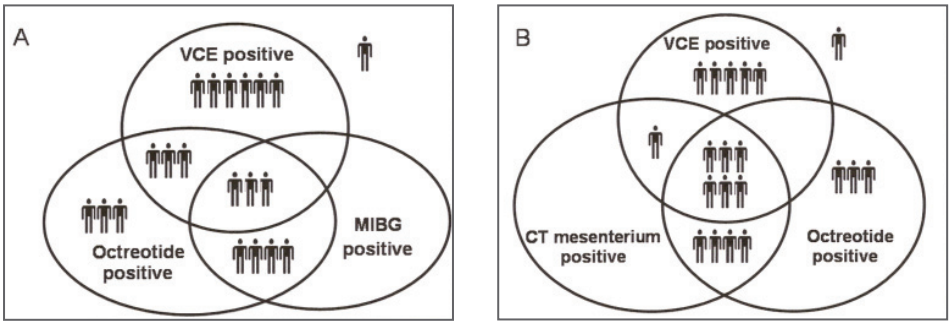


Figure 1 *Submucosal mass in the ileum, finally diagnosed as a small intestinal carcinoid tumour in three different patients (A, B, C). Ischemic small intestinal segment due to external compression by a mesenteric carcinoid tumour (D).*
(for colour figure see page 145)

VCE and other diagnostic procedures

Eight patients had no abnormalities at VCE. Four of these patients had a mesenteric location of the carcinoid tumour at CT-scan and in one patient an aspecific enhancement of the distal small bowel wall was seen. Nuclear imaging of the VCE-negative patients demonstrated the presence of an abdominal hotspot (liver not included) in 7/8 patients (88%) at pentetreotide scintigraphy and in 4/8 patients (50%) at MIBG scintigraphy. All patients with a positive VCE had a normal enteroclysis. The diagnostic yield of VCE was significantly higher than that of enteroclysis ($p< 0.001$).
Twelve patients had abnormalities at VCE suggesting the presence of a primary small intestinal carcinoid tumour location. Five of these patients (42%) had a normal CT and the other patients had only mesenteric abnormalities. In 2/7 (29%) patients with mesenteric abnormalities at CT, external compression was found at VCE. The diagnostic yield of VCE was significantly higher than that of CT ($p< 0.001$).
Pentetreotide scintigraphy was negative in 6/12 (50%) of the VCE-positive patients. In 8/12 patients also a MIBG scintigraphy was performed which was only positive in 3 patients. The diagnostic yield of VCE as compared to MIBG and pentetreotide scintigraphy did not differ significantly ($p=0.3$ and $p=0.1$ respectively). In 5/12 (42%) patients with a positive VCE both CT and nuclear imaging were normal. The findings of VCE, CT and nuclear imaging are plotted in a Venn-diagram (***Figure 2***).

Figure 2 *Venn diagrams showing the distribution of VCE and scintigraphic findings (A) and VCE and CT findings (B).*



VCE and surgery

Seven patients with positive findings at VCE (58%) underwent surgery 2.1 months (range 1-4) after VCE. In one patient a multifocal ileal carcinoid tumour was found over a length of 3 metres, as suggested by VCE. Resection was not performed because of the length of the segment. In this patient ileocolonoscopy with biopsy sampling

confirmed the presence of a multifocal carcinoid tumour in the distal ileum. In two patients a resection was performed of a segment of small intestine which was ischemic due to external compression by a mesenteric carcinoid tumour. One patient died postoperatively due to severe ischemia of the small intestine (patient 14). In four patients a segment of small intestine was resected in which a primary small intestinal carcinoid tumour was found at histopathologic examination. Two of these patients also underwent additional treatment for liver metastases by radiofrequency ablation or hemihepatectomy during the same procedure. In all patients who underwent surgery the findings of VCE were confirmed. Three patients will be scheduled for surgery, the other patients are managed medically.

Discussion

Videocapsule endoscopy is a new diagnostic technique which allows non-invasive visualization of the small intestine. In various series of selected patients with suspicion of small bowel disease the diagnostic yield varied between 55 and 69% (19). The main indications for VCE are obscure gastrointestinal bleeding and suspected Crohn's disease of the small bowel. Some abstracts and case-reports have reported the successful use of VCE to detect small intestinal tumours (20-25). In one abstract a small series of seven patients with a metastatic carcinoid tumour was studied. VCE diagnosed a primary tumour in 5 patients (71%). One patient underwent surgery which confirmed the VCE findings (25).

Intestinal carcinoid tumours are generally smaller than 1 cm. and difficult to detect. At initial presentation, many patients already have metastatic lesions in the liver or mesentery. The presence of a small intestinal carcinoid tumour frequently leads to abdominal complications like intestinal ischemia, bleeding or obstruction. Makridis et al described 138 patients with small intestinal carcinoid tumours leading to abdominal surgery for abdominal complaints in 51 of them (4). Because of the high risk of abdominal complications, resection of the primary tumour is advocated by experts even in metastatic disease for palliative purpose (2).

In the present study VCE demonstrated the presence of abnormalities in the small intestine in 12 of 20 patients (60%) who had been examined extensively and appeared to have a metastatic carcinoid tumour but an unknown primary. All patients previously underwent enteroclysis, CT-scan of the abdomen and nuclear imaging and in one patient a colonoscopy was also performed. CT-scan and enteroclysis had not demonstrated evidence of a primary small intestinal tumour. Nuclear imaging frequently showed accumulation of nuclear activity in the intestinal region. Pentetreotide scintigraphy even had a higher diagnostic yield than VCE but without differentiation between intestinal and mesenteric localisation. Performing a resection of a mesenterial mass based on scintigraphy alone is therefore associated with the risk of leaving the primary small intestinal tumour in situ. The fact that 7 patients with

abnormalities at pentetreotid scintigraphy had a normal VCE might be explained by abdominal carcinoid tumour localisation restricted to the mesentery or by a false negative VCE.

VCE has been compared previously to enteroclysis and CT scan of the abdomen in a heterogeneous group of 52 patients. In the majority of patients VCE was performed for obscure gastrointestinal bleeding (15). In patients who underwent enteroclysis (n=40) VCE had a diagnostic yield of 55% compared to 3% at barium study. Twelve patients were analysed by CT with a diagnostic yield of 21% whereas VCE had a diagnostic yield of 63% in these patients. Although the development of multidetector CT-scanning allowing thinner collimation and faster scanning will probably improve it's accuracy, a recent comparison of VCE and CT-enteroclysis also showed that VCE was superior (26). In this study a heterogeneous group of 22 patients was investigated. Only one patient of this group had a metastatic carcinoid tumour with an unknown primary which was neither detected by VCE and CT-enteroclysis.

Combining nuclear imaging and spiral CT-scan by image fusion is a promising new technique. Pfannenberg et al. investigated 54 patients with a suspected or histologically proven neuroendocrine tumour using both nuclear imaging and CT-scan (27). Side by side analysis of CT and nuclear imaging had a diagnostic accuracy of 99% compared to 75 and 84% for spiral CT-scan and nuclear imaging alone respectively.

Experience with MRI in the diagnosis of small bowel tumours is limited. One study demonstrated the presence of a small intestinal carcinoid tumour in 8/12 patients (67%) using abdominal MRI (8). MRI has been compared to VCE in the detection of polyps in 20 patients with Peutz-Jeghers syndrome or familial adenomatous polyposis. In this study VCE and MRI performed similar in the detection of polyps bigger than 15 mm., but for smaller lesions VCE was superior (28). Schulmann et al studied 11 patients with Peutz-Jeghers syndrome using VCE and 4 patients were also studied by MR enteroclysis (29). In one patient the polyps detected by VCE were missed by MR enteroclysis. The yield of MRI may improve with newer MR enteroclysis techniques (30).

Seven patients in our study underwent surgery for suspected small bowel pathology. An excellent correlation was seen between the result of VCE and the findings at surgery. Two patients were suspected to have ischemia due to external compression which was confirmed at laparotomy. In one patient a long segment of multifocal tumour was diagnosed at VCE in the mid-ileum and at laparotomy this segment with carcinoid tumour appeared too long for resection. In the other four patients the location of the tumour was in agreement with the VCE findings. In all resection specimens the presence of a carcinoid tumour was confirmed by histopathologic examination. In patients who underwent surgery, no false-positive results were obtained by VCE. When VCE is negative, repeating the procedure might be considered. A recent study in patients with occult GI bleeding demonstrated the presence of abnormalities in the small intestine in 35% at repeated VCE after a normal initial investigation (31).

Our results strongly suggest that patients with a metastatic carcinoid tumour and an unknown primary tumour should undergo VCE. In patients with a suspected primary tumour at VCE, resection can be performed if the patient is suitable for surgery.

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Assessment of intestinal vascular malformations in patients with hereditary hemorrhagic teleangiectasia and anaemia

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Abstract

Introduction

Hereditary hemorrhagic teleangiectasia (HHT) is an autosomal dominant disorder with mucocutaneous teleangiectasia and visceral arteriovenous malformations. Mutations of endoglin and Activin A receptor like kinase-1 have different phenotypes, HHT1 and HHT2 respectively. The gastrointestinal tract is frequently affected but limited information is available on the relation with genotype.

Aim

Determine whether different genotypes have different phenotypes with respect to intestinal teleangiectasia.

Methods

HHT patients, referred for anaemia, underwent videocapsule endoscopy. Chart review was performed for information on genotype and HHT manifestations.

Results

25 patients were analysed (M/F 14/11, mean age 49±17 yrs.), 14 HHT1, 8 HHT2 and 3 without known mutation. Epistaxis occurred in 96% of patients. Gastroduodenoscopy revealed teleangiectasia in 7/12 (58%) HHT1 and 3/8 (38%) HHT2 patients. VCE found teleangiectasia in all HHT1 and 5/8 (63%) HHT2 patients. In 9/14 HHT1 patients teleangiectasia were large. Teleangiectasia in the colon was restricted to 6/11 (55%) HHT1 patients. Hepatic arteriovenous malformations were present in 1/7 HHT1 and 5/6 HHT2 patients.

Conclusion

Large teleangiectasia in small intestine and colon appear to occur predominantly in HHT1. HAVM is mainly found in HHT2. In HHT patients with unexplained anaemia videocapsule endoscopy should be considered to determine the size and extent of teleangiectasia and exclude other abnormalities.

Introduction

Hereditary hemorrhagic teleangiectasia (HHT) or Rendu Osler Weber's disease is a hereditary autosomal dominant disorder with variable expression. Teleangiectasia are present at characteristic sites like the lips, oral cavity, nose and fingers in about 90% of the patients. Epistaxis frequently is the first manifestation of the disease. The gastrointestinal tract is frequently involved but the exact prevalence of intestinal lesions is not known (1-3). Gastrointestinal haemorrhage is seen in 10-45% of patients (4-6).Other manifestations of HHT are due to visceral arteriovenous malformations which can occur in lungs, liver and brain.

So far, mutations of endoglin (ENG; OMIM 131195) on chromosome 9, of Activin A receptor like kinase-1 (ALK-1; OMIM 601284) on chromosome 12 and MADH4 on chromosome 18 have been demonstrated to be the genetic basis of HHT (7-9).These different genotypes have different phenotypes. The ENG mutation predisposes to the HHT1 phenotype associated with pulmonary and cerebral arteriovenous malformations (PAVM, CAVM; 10). Mutations in the ALK-1 gene, the HHT2 phenotype, are associated with a later onset, a milder phenotype and with hepatic arteriovenous malformations (HAVM; 10,11).MADH4 mutation is associated with the combination of HHT and juvenile polyposis (8).

However, little information is available on the prevalence of gastrointestinal vascular malformations in patients with HHT. Teleangiectasies are located preferentially in the proximal stomach (12-14). Patients above 50 years are more likely to have gastric or duodenal teleangiectasies than patients younger than 50 years (14). Data concerning the involvement of the small intestine in HHT are sparse. Until recently, complete examination of the small intestine could only be achieved by intra-operative enteroscopy. With the advent of videocapsule endoscopy the entire small intestine can be visualised in a non-invasive way (15).

We therefore investigated the relationship between HHT phenotype, with an emphasis on the occurrence of small intestinal teleangiectasia as assessed by VCE, and the genotype. These data may have implications for the understanding and clinical management of intestinal blood loss in HHT patients.

Methods

Patients

Twenty-five patients with known HHT based on the Curaçao criteria were selected because their medical history revealed anaemia insufficiently explained by epistaxis (16). All patients except no. 3, 9 and 20 are a subgroup of the HHT population previously described by Letteboer et al (7, 11). A chart review of HHT manifestations was performed for all patients. Subgroup analysis was performed for genotype, age and gender. The

presence of visceral AVM was established by chest X-ray, abdominal ultrasound, CT-scanning, MRI or angiography. In patients who underwent gastroduodenoscopy, the teleangiectasies were classified depending on the presence in esophagus, stomach or duodenum. For description of teleangiectasia in the duodenum data from gastroduodenoscopy and VCE were used. If a colonoscopy was performed, the presence or absence of teleangiectasia was noted. All patients underwent VCE.

Videocapsule endoscopy

VCE was performed using the Given Imaging M2A wireless capsule (Yoqneam, Israel), as described before (17). In brief, a swallowable capsule is propelled by intestinal peristalsis taking 2 pictures per second of the intestine. Images are transmitted to antennas on the abdominal wall for registration and can be downloaded to a work station.
The VCE images were reviewed by one of four gastroenterologists with extensive experience using this technique, without knowledge of the results of HHT mutation analysis. Vascular malformations were classified for location (stomach, proximal duodenum, small intestine and colon) and for number (none, few (≤5) or multiple (>5)). Because the size of the teleangiectasia cannot be measured adequately at VCE, they were assessed as large or small. This qualification was re-assessed by a second reviewer. In case of large and small teleangiectasia in the same patient, they were classified as large.

Statistics

Parametric results were compared by two-sided Student's t-test. Group proportions were compared with Chi-square test or Fisher's exact test where appropriate. A $p<0.05$ was considered significant.

Results

Patients

Twenty-five patients were analysed (M/F 14/11, mean age 49±17 yrs., range 18-72 yrs.). Fourteen patients carried the ENG mutation (HHT1) and eight patients the ALK-1 mutation (HHT2). In three patients the family mutation was not known (HHTx). No significant difference was found between HHT1 and HHT2 patients concerning age, sex and haemoglobin level (***Table 1***).

Table 1 *Phenotypic differences between HHT1 and HHT2 patients.*

	HHT1	***HHT2***	***p***
N	*14*	*8*	
Age (yrs)	*56±14.9*	*47±13.9*	*n.s.*
Sex (M/F)	*7/7*	*6/2*	*n.s.*
Haemoglobin (mmol/l)	*5.8±0.9*	*5.6±1.6*	*n.s.*
Gastric AVM			
Total	*7/12 (58%)*	*3/5 (60%)*	*n.s.*
Large	*3/12 (25%)*	*1/5 (20%)*	*n.s.*
Small intestinal AVM			
Total	*14/14 (100%)*	*5/8 (63%)*	*0.005*
Large	*9/14 (64%)*	*1/8 (13%)*	*0.02*
Colonic AVM			
Total	*6/11 (55%)*	*0/7(0%)*	*0.03*
Large	*2/11 (18%)*	*0/7 (0%)*	*n.s.*
HAVM	*1/7 (14%)*	*5/6 (83%)*	*0.02*
Epistaxis	*13/14 (93%)*	*7/8 (88%)*	*n.s.*
PAVM	*9/13 (69%)*	*0/8 (0%)*	*0.003*
CAVM	*2/9 (22%)*	*0/8 (0%)*	*n.s*

Arteriovenous malformations of the digestive tract

Teleangiectasia were found in the entire digestive tract in 23/25 patients (92%), at gastroduodenoscopy in 14/21 patients (67%), at VCE in 19/25 (76%) and at colonoscopy in 6/19 patients (32%). All teleangiectasia in the duodenum that were detected by conventional endoscopy were confirmed by VCE.

Upper digestive tract

Twenty one patients underwent a gastroduodenoscopy. This revealed upper gastrointestinal teleangiectasia in 10 (48%) patients. One patient (5%) had a small teleangiectasy in the distal esophagus. Ten patients (48%) had gastric teleangiectasies, 4 of them had large teleangiectasia. Six patients (29%) had duodenal teleangiectasies, three of them had both gastric and duodenal teleangiectasia (***Table 2 & 3***). There were no significant differences in prevalence of lesions between HHT1 and HHT2.

Table 2 *HHT1 manfestations (n.p. not performed)*

N	Sex	Age (yrs.)	Hb (mmol/l)	Epistaxis	PAVM	HAVM	CAVM	Stomach	Ileum	Colon
2	M	26	6,4	+	+	n.p.	-	None	Multiple, small	None
3	F	52	7,1	-	n.p.	n.p.	n.p.	n.p.	Multiple, large	n.p.
4	M	58	5,6	+	+	n.p.	-	None	Multiple, large	None
6	M	57	5,3	+	+	-	-	Multiple, small	Multiple, large	Multiple small
10	F	23	7,4	+	+	-	-	n.p.	Multiple, large	n.p.
13	F	42	5,2	+	+	n.p.	-	None	Multiple, large	Few, small
14	F	18	5,4	+	-	n.p.	+	None	Few, small	Solitary, small
15	M	46	5,8	+	+	-	-	Multiple, large	Multiple, large	None
17	F	52	7,4	+	+	-	-	Few, large	Multiple, large	None
18	M	60	4,7	+	-	n.p.	-	None	Multiple, large	Solitary, large
19	F	51	6,9	+	+	-	n.p.	Few, small	Multiple, small	Solitary, large
21	M	72	4,9	+	-	n.p.	n.p.	Few, small	Multiple, large	None
22	M	34	5,2	+	-	-	+	Few, large	Multiple, small	Few, small
23	F	60	5,6	+	+	+	-	Multiple, small	Few, small	n.p.

Table 3 *HHT2 manifestations (n.p.: not performed)*

N	Sex	Age (yrs.)	Hb (mmol/l)	Epistaxis	PAVM	HAVM	CAVM	Stomach	Ileum	Colon
1	M	72	4,7	+	-	+	n.p.	Multiple, large	Multiple, small	None
7	M	61	3,8	+	-	-	-	None	Multiple, small	None
8	F	43	3,3	+	-	+	-	Few, small	None	None
9	M	71	7,5	+	-	+	n.p.	None	Solitary, small	n.p.
11	M	33	6,5	+	-	+	-	None	None	None
12	M	56	6,7	+	-	n.p.	n.p.	Few, small	Multiple, large	None
16	M	50	7,2	+	-	n.p.	n.p.	None	None	None
24	F	67	5,2	-	-	+	-	None	Few, small	None

Small intestine

All patients underwent videocapsule endoscopy without complications. The average gastric transit time was 25±35 min. and small intestinal transit time was 264±91 min. The cecum was reached in 96%. Small bowel teleangiectasies were found in 19/25 patients (76%). In all HHT1 patients teleangiectasies were present in the small intestine. In 9/14 patients (64%) multiple large teleangiectasies were seen, while the other patients had multiple small teleangiectasies. Teleangiectasies were present in 5/8 of HHT2 patients (63%). Multiple large teleangiectasies were found in 1 patient and few small teleangiectasies were found in 4 patients. The occurrence of teleangiectasia and large teleangiectasia was therefore more frequent in HHT1 than in HHT2 patients (p=0.005 and 0.02 respectively). In 4 patients active bleeding was seen during VCE, three of them were HHT1 patients. In 2 HHTx patients multiple small teleangiectasia were found and in one HHTx patients VCE was without abnormalities.
Six HHT1 patients were younger than 50 years, three of them had large teleangiectasia and the other three had small teleangiectasia. Eight HHT1 patients were older than 50 years and 7/8 (88%) of them had multiple large teleangiectasies and 1 (13%) had multiple small teleangiectasies (p=n.s.). Three HHT2 patients were younger than 50 years and had no abnormalities at VCE, whereas all 5 patients older than 50 years had teleangiectasia (p=0.02). No major abnormalities except teleangiectasia were detected by VCE. In one patient the presence of a polyp in the proximal small intestine was suggested, which could not be confirmed by push enteroscopy. In two other patients superficial erosions in the stomach were found.

Colon

Colonoscopy was performed in 19 patients. Teleangiectasia were found in 6 (32%) patients. Two of them had a solitary large teleangiectasy, one patient a small solitary lesion, and 3 had multiple small teleangiectasies. All six patients with teleangiectasia belonged to the 11 examined HHT1 patients (55%). None of the HHT2 patients had teleangiectasia in the colon (p=0.03).

Liver

HAVM was present in 6 patients. In HHT1 patients 1/7 (14%) had a HAVM and in HHT2 patients 5/6 (83%) had a HAVM (p=0.02). The presence of a HAVM was not known in 7 HHT1 patients and in 2 HHT2 patients. The two HHTx patients who were examined had no HAVM.

HHT manifestations outside the digestive tract

Spontaneous recurrent epistaxis was present in 24/25 patients (96%) and no difference between HHT1 and HHT2 patients was found. PAVM were present in 11 patients (***Table 2 & 3***). In case of HHT1 patients 9/13 (69%) had a PAVM whereas in HHT2 patients no PAVM was found (p=0.003). Two patients with HHTx had a PAVM. In 1 HHT1 patient and in one HHTx patient the presence of a PAVM was not examined.
Eighteen patients were analysed for the presence of a CAVM. CAVM was present in two HHT1 patients and in one patient without a known mutation (p=n.s.).

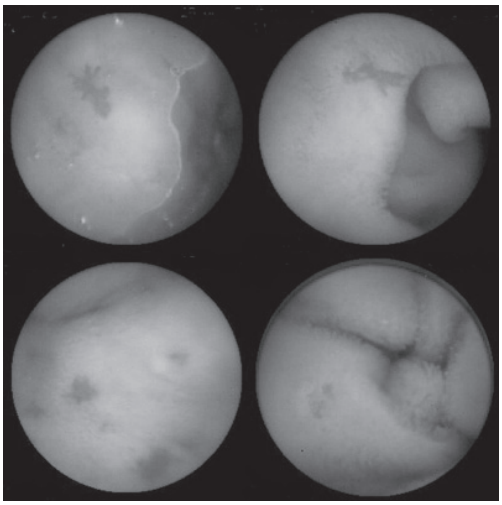

Figure 1 *Small intestinal teleangiectasia detected by VCE in four different HHT patients.*
(for colour figure see page 146)

Discussion

HHT is a relatively rare disorder, but many patients affected by this disease suffer from recurrent occult or overt gastrointestinal bleeding, often leading to anaemia. As a result, these patients may be presented to a gastroenterologist for diagnosis and treatment. Depending on the site of teleangiectasia, treatment with argon plasma coagulation can be considered and in case of diffuse abnormalities treatment with estrogens may be tried (4, 18-21). Longacre et al also described the possibility of treatment with danazol, a weak androgen, or aminocaproic acid which inhibits fibrinolysis (4). There is however, limited information on the distribution of teleangiectasia in the small intestine. The majority of studies examined patients by gastroduodenoscopy and colonoscopy but little information is available on the small intestinal manifestations of HHT as this part of the digestive tract was difficult to examine using endoscopic techniques. The proximal small intestine can be investigated by push enteroscopy, but for the

endoscopic assessment of the entire small intestine until recently an intraoperative enteroscopy was mandatory. This is an invasive procedure. Enteroclysis is not reliable for the detection of superficial mucosal abnormalities like teleangiectasia. VCE is a new and non-invasive technique for endoscopic evaluation of the small intestine.

The presence of teleangiectasia in the small intestine of HHT patients as assessed by VCE has been reported previously in a single study (22). In this study gastroduodenoscopy and VCE were performed in 20 HHT patients without knowledge of the underlying mutation. The prevalence of teleangiectasia was reported to be 56% with a preferential occurrence of teleangiectasia in older patients.

In the present study teleangiectasia of the digestive tract were found in 92% of patients which is much higher as compared to the study of Ingrosso et al. The difference will probably be explained by selection as our study includes only patients with anaemia. Ingrosso et al. describe patients with haemoglobin levels varying between 5.3 and 9.7 mmol/l and report a lower haemoglobin level in patients with teleangiectasia. Although our study also includes colonic teleangiectasia this does not account for the difference because all patients with colonic teleangiectasia also had gastric or small intestinal teleangiectasia. An interesting observation was the absence of teleangiectasia at colonoscopy in HHT2 patients whereas teleangiectasia in the colon were found in 43% of the HHT1 patients. In the small intestine teleangiectasia were found at VCE in all HHT1 patients, with large teleangiectasies in 9/14 (64%). In only one HHT2 patient a large teleangiectasy was found, 4 HHT2 patients had a few small teleangiectasies. Four patients (2, 4, 7 and 24) who were examined in our study had no abnormalities at gastroduodenoscopy and colonoscopy but multiple large teleangiectasia at VCE. The absence of abnormalities at conventional endoscopy in HHT patients therefore does not exclude the presence of large teleangiectasia in the small intestine.

Based on previous reports, the major confounding factor in the gastrointestinal manifestations of HHT is age, because teleangiectasia is more frequent in patients older than 50 years (14). The only other study using VCE for the detection of small intestinal teleangiectasia also reported that patients without teleangiectasia had a mean age of 45 years compared with a mean age of 63 years if teleangiectasia were present (22). These findings are compatible with a study by Plauchu et al describing 324 HHT patients with gastrointestinal bleeding in 15%. Half of the patients were older than 58 years at the initial manifestation of gastrointestinal bleeding as compared to the manifestation of epistaxis in half of the patients before the age of 20 years (23).

So far no consistent difference in the gastrointestinal manifestations of HHT1 and HHT2 could be established (10, 11). In a study comparing 39 HHT1 patients and 16 HHT2 patients, more severe gastrointestinal bleeding was reported in HHT1 patients (24). Berg et al describe data from 49 HHT1 patients and 34 HHT2 patients and found no significant difference for the prevalence of gastrointestinal haemorrhage between both groups. A separate analysis of the prevalence of gastrointestinal bleeding in patients older than 60 years found predominance for HHT2 patients (37% vs. 11%)

although this did not reach statistical significance (10).
Our study found a higher prevalence of large teleangiectasia in HHT1 patients older than 50 years, although this did not reach significance. In HHT2 patients the presence of teleangiectasia was restricted to patients older than 50 years. Despite the significantly higher prevalence of teleangiectasia in the small intestine and colon in HHT1 the level of anaemia was comparable in both genotypes. The question remains to be resolved if teleangiectasia increase in size and number during life. VCE might be a valuable tool to address this issue in a research setting.
It is difficult to determine whether there are true phenotypical differences in the patients of this study between HHT1 and HHT2 with respect to gastrointestinal localisation, because the patients were selected largely on account of anaemia which was insufficiently explained by epistaxis. To confirm the presence of a true phenotypical difference, a systematic investigation in large groups of HHT patients without anaemia should be performed using VCE.
Recently, double balloon enteroscopy (DBE) has been introduced, in which an enteroscope is introduced through the entire small bowel by sequential insufflation and desufflation of balloons on the tip of the endoscope and an overtube (25, 26). This technique allows investigation of the entire small intestine without the need for a laparotomy. It offers the possibility to take biopsies or perform argon plasma coagulation of teleangiectasia. This technique might therefore be of relevance for HHT patients with unexplained blood loss from teleangiectasies identified by VCE because they can be treated by argon plasma coagulation (19, 27, 28). Although solid data are sparse there seems to be a good correlation between images obtained by VCE and conventional endoscopy. A study by Hartmann et al compared the findings of VCE and intraoperative enteroscopy in 47 patients and VCE had a sensitivity of 95% and a specificity of 75%, considering intraoperative enteroscopy as the reference (29). One study prospectively compared the findings of VCE and DBE in 35 patients (30). In this study VCE demonstrated abnormalities of the small intestine in 28 patients that were confirmed in 20 patients (71%). Further comparative studies of VCE and DBE are needed to establish the correlation between both techniques.
In the present study several patients with severe anaemia (patient 8, 11 and 24) showed no or few small intestinal teleangiectasia. Although a negative gastrointestinal endoscopy (gastroduodenoscopy, VCE and colonoscopy) in these patients does not completely exclude an intestinal source of bleeding, it strongly points to epistaxis as the main cause of anaemia. As VCE is now accepted as a diagnostic tool in the analysis of obscure gastrointestinal bleeding it should be considered in case of unexplained anaemia in HHT patients (31, 32). In this way alternative diagnoses can be excluded and in case of large teleangiectasia in the small intestine endoscopic treatment can be considered in case of anaemia requiring chronic iron supplementation or frequent transfusions.

Conclusion

HHT frequently affects the digestive tract, resulting in anaemia due to bleeding teleangiectasia. Large teleangiectasia in the small intestine and the colon mainly occurs in HHT1 patients, whereas HAVM is predominantly present in HHT2 patients. This has become more relevant with the emerging possibilities of new endoscopic techniques for the treatment of small intestinal teleangiectasia. In HHT patients with unexplained anaemia videocapsule endoscopy should be considered to determine the size and extent of teleangiectasia and exclude other abnormalities.

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Answers to to the aims of this thesis

1. Initially videocapsule endoscopy was performed after a clear liquid diet and an overnight fast. Some studies showed that bowel preparation improves the quality of the images acquired during this procedure, whereas others did not find any differences. The best way to prepare patients for VCE had not been evaluated systematically.

Based on the data presented in chapter 2, one litre PEG based solution should be used prior to VCE as this significantly increases mucosal visibility without any discomfort for the patient. If special interest exists for the visualisation of the terminal ileum (e.g in case of Crohn's disease), 2 litres of PEG based solution further improves mucosal visualisation.

2. Most early studies leading to the acceptance of videocapsule endoscopy were performed in highly selected patient groups. The widespread application of this technique in clinical practice may have changed the diagnostic yield of capsule endoscopy. It is therefore important to determine the applicability of VCE in a large population of a general hospital.

The diagnostic yield of VCE strongly depends on the definition of the (clinical) relevance of the findings at VCE. The diagnostic yield of VCE regarding clinical relevant findings was 38% overall in our population. In case of unexplained gastrointestinal bleeding, the diagnostic yield was 33%. The severity of the anaemia has a significant relation to the diagnostic yield. In patients with suspected small intestinal Crohn's disease the diagnostic yield rises to 49%.
Although the time to review VCE findings initially was 51 minutes, which might be a barrier for the clinical applicability, this decreases to 30 minutes after reviewing 50 procedures.
Based on the diagnostic yield and the viewing time for an experienced reviewer, we conclude that VCE is a useful technique for clinical application.

3. Although the diagnostic yield of videocapsule endoscopy is high, the important question remains to be resolved whether the findings of this procedure have impact on clinical management and outcome.

One year after the performance of VCE patient management appeared to be changed by its findings in 38% of the patients. This percentage increased to 59% in those cases in whom VCE yielded a definite diagnosis. Despite this impact on clinical management no improvement of the clinical outcome was found.

4. Videocapsule endoscopy offers the possibility for a complete endoscopic evaluation of the entire small intestine. Neuroendocrine tumours (carcinoids) frequently originate in the small intestine but the primary tumour is usually very difficult to detect. VCE may be of important clinical value when searching for the primary tumour.

In the analysis of 20 patients with a metastatic carcinoid tumour with an unknown primary, VCE revealed abnormalities suggestive of a primary intestinal carcinoid tumour in 12 patients (60%). Seven of these patients subsequently underwent surgery which confirmed the diagnosis of a small intestinal carcinoid tumour. Although the diagnostic yield of VCE is comparable to the yield of nuclear imaging techniques, the latter generally cannot discern between an intestinal or a mesenterial tumour location.
VCE therefore appears to be an essential diagnostic tool in the analysis of patients with a metastastatic carcinoid tumour and an unknown primary.

5. Hereditary Hemorrhagic Teleangiectasia is a disease that can lead to gastrointestinal bleeding. These bleeding episodes often originate from the small bowel. Until recently the small intestine was not accessible for easy assessment for the presence of teleangiectasia. Analysis could only be performed using gastroduodenoscopy or ileocolonoscopy. Videocapsule endoscopy is a potentially useful technique for the analysis of small intestinal teleangiectasia and findings may guide treatment.

In the analysis of 25 HHT patients with anaemia, small intestinal teleangiectasia were found in 19 (76%) patients. Small intestinal teleangiectasia were found in all patients carrying the endoglin mutation and in 63% of the patients carrying the ALK-1 mutation. In 4 patients who previously had undergone a diagnostic gastroduodenoscopy and colonoscopy, teleangiectasia had been found in the small intestine.
We conclude that VCE is an essential technique for the assessment of small intestinal teleangiectasia in HHT patients with anaemia. If teleangiectasia are present, VCE findings may guide treatment, for example by argon plasma coagulation at double balloon enteroscopy.

In this thesis we investigated and subsequently demonstrated the clinical feasibility and clinical relevance of video capsule endoscopy. Moreover we demonstrated the application of video capsule endoscopy as a powerful tool to extend the knowledge of small intestinal pathology.

Summary

Chapter 1

The recent introduction of videocapsule endoscopy has provided gastroenterologists a complete and simple endoscopic technique for endoscopic evaluation of the entire small intestine. Previously, the proximal part of the small intestine could be examined using push enteroscopy and the terminal ileum could be evaluated at ileocolonoscopy. Only an intra-operative enteroscopy offered the possibility to examine the entire small intestine. The latter is however a very invasive procedure as a laparotomy is necessary to allow the surgeon to move the small bowel over the endoscope. Videocapsule endoscopy (VCE) is a new technique to examine the small intestine in a non-invasive way. A capsule with a length of 26 mm. and a width of 11 mm. is swallowed by the patient and is propelled by small intestinal peristalsis. It obtains two digital images per second which are transmitted to a data recorder. At the end of the procedure the images are downloaded to a working station where they can be reviewed as a movie.
The first papers on the results of VCE were very promising. The entire small intestine was examined in 85% of the patients and a diagnosis was established in 55-85% of the patients. The diagnostic yield in these first studies could be overestimated by the initial strong case selection, and the clinical relevance of the VCE findings remained unclear. It can be expected that the proportion of patients with clinically relevant VCE findings will be lower when the technique is more widely available. Capsule endoscopy nevertheless appears to be superior to push enteroscopy and radiological examination of the small intestine. Further research is needed on the optimal preparation, clinical consequences of VCE findings and possible other indications for VCE.

Chapter 2

Initially, all patients who underwent VCE used a clear liquid diet on the afternoon before the examination, followed by an overnight fast. Despite this preparation, VCE was frequently disturbed by the presence of small intestinal contents. Although many studies demonstrated that the use of polyethyleneglycol (PEG) containing solutions improved the mucosal visualisation it was unclear how much of this solution should be used for an optimal balance between mucosal visualisation and patient tolerability. Beside this, the effects of bowel preparation on the transit time of the capsule were contradictory, but it was suggested that bowel preparation might lead to rapid propulsion of the capsule, again resulting in reduced luminal visualisation.
Ninety patients were therefore randomly assigned to three groups: regular preparation (a clear liquid diet followed by an overnight fast), 1 litre PEG based solution or 2 litres of PEG solution. The mucosal visualisation was reviewed by two endoscopists who were blinded for the preparation regimen. The tolerability of both the preparation and the procedure was evaluated in all patients.
The regular preparation resulted in a good mucosal visibility of the terminal ileum in

25% of the patients, which improved significantly to 52% and 72% after using 1 and 2 litres of PEG solution respectively. The improvement of mucosal visualisation did not result in an increased diagnostic yield, although a trend towards an increased diagnostic yield was observed in IBD patients. Gastrointestinal transit time was not affected by the preparation regimen. No differences were found regarding the tolerability of the regular preparation or 1 litre PEG based solution, but preparation with 2 litres was experienced as uncomfortable.
These data support the use of 1 litre PEG solution prior to VCE as this significantly increases mucosal visibility without discomfort for the patient. If special interest exists for the visualisation of the terminal ileum, 2 litres of PEG solution can be considered.

Chapter 3

Chapter 3a describes 250 patients who underwent VCE. The indication was occult gastrointestinal bleeding in 150 patients (60%), overt gastrointestinal bleeding in 27 patients (11%) and suspected Crohn's disease in 57 patients (23%). All patients underwent an uncomplicated procedure and in 76% the entire small intestine was visualised. The viewing time was initially 51 minutes but decreased to 30 minutes after reviewing 50 procedures.
VCE findings were classified as a definite diagnosis when the findings were clinically relevant with regard to the indication of the procedure. When it was not clear whether the VCE findings related to the symptoms or laboratory abnormalities of the patient, they were registered as a probable diagnosis. In case of no abnormalities or an insufficient examination, findings were classified as no diagnosis.
A definite diagnosis was established in 38%, a probable diagnosis in 32% and no diagnosis in 30% of the patients. In case of unexplained gastrointestinal bleeding a definite diagnosis was found in 33%. The diagnostic yield increased in case of a more serious anaemia. The most frequent findings in case of unexplained gastrointestinal bleeding were angiodysplasia, erosions and the presence of blood. In case of suspected small intestinal Crohn's disease a definite diagnosis was established in 49% of the patients. In this group the most frequent findings were ileitis, ulcers and erosions.
The suspected blood indicator (SBI) was evaluated for its accuracy by comparing the reviewer's findings and the SBI findings. The positive predictive value of SBI was 63% and the negative predictive value was 78%. This indicator does in its present form therefore not appear to be relevant for daily practice.
Chapter 3b presents one of the patients described in chapter 3a with recurrent iron-deficiency anaemia in whom initial VCE had not revealed any abnormalities. A second VCE demonstrated the presence of an abnormality in the jejunum. This lesion was confirmed by double balloon enteroscopy and appeared to be a large vascular malformation. The lesion was marked using Indian ink and subsequently removed surgically. This case illustrates the usefulness of a repeated VCE procedure and the

complementary value of VCE and double balloon enteroscopy.

Chapter 4

Although the diagnostic yield of VCE appears to be high, little information is available on the clinical consequences of its findings. One year after the performance of VCE in 166 patients, a questionnaire was sent to all referring physicians. This questionnaire evaluated the clinical consequences of VCE findings. Consequences were divided in change of management or unchanged management. Change of medication, the performance of an endoscopic or surgical procedure, avoidance of additional investigation and other clinical consequences were classified as change of management. For all patients the actual clinical condition was compared with their condition at the time of VCE and in case of unexplained gastrointestinal bleeding the most recent haemoglobin level was registered.
Data of 150 patients were analysed. In 97 patients VCE was performed for unexplained gastrointestinal bleeding and in 36 patients for suspected small intestinal Crohn's disease. A definite diagnosis had been established in 34%, a probable diagnosis in 34% and no diagnosis in 32% of the patients. VCE findings resulted in a change of management in 38% of the patients, increasing to 59% if a definite diagnosis was established at VCE. In case of occult and overt gastrointestinal bleeding management was changed in 31% and 62% respectively, whereas in case of suspected Crohn's disease VCE findings a change of management occurred in 50%. No relation could be established between the occurrence of management changes and the clinical condition or haemoglobin level one year after VCE.

Chapter 5

Various studies described that VCE can be useful for the detection of small intestinal polyps or solid tumours. We therefore analysed the clinical applicability of VCE for the detection of small intestinal carcinoid tumours. These tumours frequently originate in the small intestine but are hard to detect due to their small size. Metastatic disease is therefore frequently present at the time of diagnosis. Because small primary tumours can also lead to complications like stenosis or ischemia, resection is advised even in the presence of metastatic disease.
Our study analysed 20 patients with a metastatic carcinoid tumour with an unknown primary. All patients underwent extensive evaluation prior to VCE by means of small bowel follow through, nuclear imaging and CT scanning of the abdomen. Nuclear imaging had been performed using pentetreotide scintigraphy or MIBG scintigraphy and had demonsrtrated abnormalities in respectively 65% and 44% of the patients, but these techniques could not discriminate whether the accumulation of nuclear activity occurred in the mesenterium or in the small intestinal wall. None of the radiological

examinations found abnormalities suggestive for a primary small intestinal tumour.
VCE findings suggested the presence of a primary small intestinal carcinoid tumour in 12 patients. In 9 patients a small intestinal tumour was seen, compression and ischaemia of the small intestinal mucosa was observed in 2 patients and in one patient an area with erosion of the small intestinal mucosa was found. Surgery was performed in 7 of these patients, which confirmed the presence of a small intestinal carcinoid tumour in all 7 patients.
We conclude that VCE is a useful diagnostic tool in patients with a metastatic carcinoid tumour and an unknown primary.

Chapter 6

Hereditary Hemorrhagic Teleangiectasia is a genetic abnormality that causes vascular abnormalities. Teleangiectasia can occur in the mucosa of the nose and entire gastrointestinal mucosa, and arteriovenous malformations can be present in the lungs, liver or brain. The two most frequent mutations leading to HHT are mutation of the endoglin gene (HHT1) and mutation in the Activin-A receptor like kinase-1 (HHT2). HHT1 often has a more serious clinical course than HHT2, and pulmonary vascular abnormalities predominantly occur in HHT 1 patients. Anaemia due to gastrointestinal bleeding frequently occurs in HHT patients when vascular abnormalities are present in the digestive tract. Until recently the presence of teleangiectasia of the small intestine could not be assessed and therefore information on this topic is sparse.
In our study described in chapter 6, 25 HHT (14 HHT1/8 HHT2) patients with anaemia were analysed by VCE. Data regarding HHT manifestations were collected. Small intestinal teleangiectasia were found in all HHT 1 patients, nine of them had large teleangiectasia. Five HHT2 patients (63%) also had teleangiectasia of the small intestine. In the colon teleangiectasia were only found in HHT1 patients. Four patients had previously undergone a gastroduodenoscopy and a colonoscopy without abnormalities, but all four did have teleangiectasia of the small intestine.
Our study demonstrates that VCE is a useful diagnostic tool to assess the presence of small intestinal teleangiectasia in HHT patients with anaemia.

In summary the results of our studies, as described in this thesis, give further support to the clinical applicability of videocapsule endoscopy. We demonstrated that VCE is an endoscopic technique with a considerable diagnostic yield frequently leading to changes in clinical management. It can be used in routine clinical care for patients with obscure gastrointestinal bleeding and suspected small intestinal Crohn's disease. Beside this VCE is a useful diagnostic tool in specific patients with suspected small bowel disease, in particular in those with metastases of unknown primary carcinoids, and in patients with Hereditary Hemorrhagic Teleangiectasia.

Samenvatting

Hoofdstuk 1

De dunne darm was tot voor kort niet makkelijk toegankelijk voor endoscopisch onderzoek. De proximale dunne darm kon onderzocht worden met een push-enteroscopie en het terminale ileum middels een ileocoloscopie. De enige mogelijkheid voor een complete endoscopie van de dunne darm was een operatieve procedure waarbij de chirurg de dunne darm over de scoop schuift (intraoperatieve enteroscopie). Videocapsule endoscopie (VCE) is een techniek waarbij gebruik gemaakt wordt van een capsule van 26 mm lang en 11 mm in diameter die 2 keer per seconde een foto maakt van de dunne darm. De capsule wordt ingeslikt en daarna voortbewogen door de peristaltiek van het darmstelsel. De foto's worden doorgezonden naar een datarecorder waarna ze als een film bekeken kunnen worden.
De eerste resultaten van capsule endoscopie waren zeer veelbelovend. In 85% van de patiënten werd de volledige dunne darm gevisualiseerd en er werd een diagnose gesteld bij 55-85% van de patiënten. Het is belangrijk om daarbij te realiseren dat hierbij in eerste instantie geen rekening werd gehouden met de klinische relevantie van de gevonden afwijkingen en dat initieel sprake was van een sterke selectie van patiënten. Hoewel de klinisch relevante diagnostische opbrengst waarschijnlijk dus lager zal liggen, lijkt VCE wel superieur te zijn ten opzichte van radiologische afbeeldingstechnieken van de dunne darm en push enteroscopie. Nader onderzoek naar de optimale voorbereiding, de werkelijke diagnostische opbrengst, de klinische consequenties en mogelijke andere indicaties voor VCE was noodzakelijk en vormde de aanleiding voor het onderzoek zoals beschreven in dit proefschrift.

Hoofdstuk 2

Bij de eerste studies met de videocapsule gebruikten patiënten daags tevoren een helder vloeibaar dieet en kwamen nuchter naar het ziekenhuis. Al snel bleek dat ondanks deze voorbereiding nog regelmatig sprake was van verontreiniging van dunne darm, welke de beoordeling van de beelden verstoorde. Hoewel verscheidene studies lieten zien dat voorbereiding met polyethyleenglycol-houdende lavagevloeistoffen een betere beoordeling mogelijk zou kunnen maken, bleef onduidelijk wat de optimale hoeveelheid lavage-vloeistof was. Daarnaast waren de effecten van de voorbereiding op de passagesnelheid van de capsule tegenstrijdig.
In hoofdstuk 2 wordt een onderzoek beschreven naar de optimale voorbereiding voor VCE. In dit onderzoek kregen 3 groepen van elk 30 patiënten hetzij de standaard voorbereiding (vloeibaar dieet en nuchter gedurende de nacht), danwel lavage van de dunne darm middels 1 liter Polyethyleenglycol (PEG) of 2 liter PEG. De beoordeelbaarheid van het slijmvlies en de passagesnelheid van de capsule werd beoordeeld door 2 endoscopisten die niet op de hoogte waren van de voorbereiding van individuele patienten. Daarnaast werd alle patiënten na de procedure gevraagd hoe belastend zij de procedure vonden.

Uit dit onderzoek bleek dat voorbereiding met PEG de beoordeelbaarheid van VCE verbeterde. Na de standaard voorbereiding was de mucosa van het distale ileum goed te beoordelen bij 25% van de patiënten. Dit percentage steeg significant naar 52% en 72% na voorbereiding met respectievelijk 1 of 2 liter PEG. De verbetering van de beoordeelbaarheid van de mucosa resulteerde echter niet in een hogere diagnostische opbrengst in de onderzochte patiënten. Een uitzondering hierop vormden de patiënten met verdenking op de ziekte van Crohn. Bij deze patiënten werd na gebruik van 2 liter PEG in 50% van de patiënten een zekere diagnose gesteld terwijl dit in de groep met onbegrepen gastrointestinaal bloedverlies slechts 23% was. De verschillende voorbereidingen hadden geen invloed op de passagesnelheid van de capsule.
Hoewel de mucosa met gebruik van 2 liter PEG het best beoordeelbaar lijkt, werd deze voorbereiding door patiënten wel als belastend ervaren. De standaard voorbereiding en de voorbereiding met 1 liter PEG werden gelijkelijk en hoger gewaardeerd dan de voorbereiding met 2 liter PEG.
Het gebruik van 1 liter PEG resulteert dus in een betere beoordeelbaarheid van de mucosa van de dunne darm zonder dat dit een belasting is voor de patiënt. Wanneer er een hoge verdenking bestaat op pathologie van het terminale ileum kan voorbereiding met 2 liter PEG overwogen worden.

Hoofdstuk 3

In hoofdstuk 3a worden de eerste 250 patiënten beschreven die een VCE ondergingen in ons ziekenhuis. De indicatie voor het onderzoek was onzichtbaar bloedverlies uit het maagdarmkanaal bij 150 patiënten (60%), zichtbaar bloedverlies uit het maagdarmkanaal bij 27 patiënten (11%) en verdenking op de ziekte van Crohn van de dunne darm in 57 patiënten (23%). De procedure verliep bij alle patiënten zonder complicaties en bij 76% van de patiënten werd de volledige dunne darm tijdens de procedure gezien. Hoewel de beoordeling van de VCE beelden aanvankelijk 51 minuten per procedure kostte, nam dit door toenemende ervaring na 50 procedures af tot 30 minuten.
Bij het bepalen van de diagnostische opbrengst van de procedure werd kritisch gekeken naar de relevantie van de gevonden afwijkingen. Afwijkingen werden geclassificeerd als een zekere diagnose wanneer de bevindingen verklarend waren voor het klinische beeld van de patiënt. Wanneer er afwijkingen werden geconstateerd in de dunne darm waarbij twijfel bestond over de relatie met de klachten of laboratoriumafwijkingen van de patiënt, werd dit geregistreerd als een mogelijke diagnose. Wanneer geen afwijkingen werden geconstateerd, de capsule tijdens de gehele procedure in de maag bleef of er teveel verontreiniging was, werd dit geregistreerd als geen diagnose.
In de totale groep patiënten werd een zekere diagnose gesteld bij 38%, een mogelijke diagnose bij 32% en geen diagnose bij 30%. Bij patiënten met onbegrepen bloedverlies uit het maagdarmkanaal werd een zekere diagnose gesteld bij 33%. De diagnostische

opbrengst was hoger naarmate sprake was van een ernstiger anemie. De belangrijkste bevindingen waren angiodysplasiëen, erosies en de aanwezigheid van bloed. Wanneer de verdenking bestond op de ziekte van Crohn van de dunne darm werd een zekere diagnose gesteld bij 49%. Hier waren de belangrijkste bevindingen ileitis, ulcera en erosies.
De software die de aanwezigheid van bloed detecteert werd geëvalueerd op accuratesse door vergelijking van de bevindingen van de software en de beoordelaar. De positief voorspellende waarde van deze software was 63% en de negatief voorspellende waarde was 78%. Vooralsnog lijkt dit algoritme in de huidige vorm slechts een beperkt nut te hebben voor de dagelijkse praktijk.
Hoofdstuk 3b beschrijft een van de patiënten uit hoofdstuk 3a met een langer bestaande recidiverende ijzergebreksanemie waarbij pas bij de tweede VCE een afwijking werd gevonden. Aansluitend werd bij dubbelballon-enteroscopie gezien dat er sprake was van een grote vaatafwijking. Deze werd gemarkeerd en chirurgisch verwijderd. Deze casus onderstreept het nut om in voorkomende gevallen de VCE te herhalen en illustreert de waarde van nieuwe endoscopische technieken zoals VCE en dubbelballon-enteroscopie.

Hoofdstuk 4

Hoewel de diagnostische waarde van de videocapsule endoscopie hoog lijkt te zijn, is er weinig bekend over de klinische consequenties van de bevindingen. Een jaar na het verrichten van de videocapsule endoscopie werd daarom naar alle verwijzende specialisten een enquête gestuurd. In deze enquête werden de klinische consequenties van de bevindingen bij VCE geëvalueerd. De consequenties werden onderverdeeld in beleidswijziging of onveranderd beleid. Er werd gesproken van gewijzigd beleid wanneer de bevindingen bij VCE leidden tot een verandering van de medicatie, het verrichten van een endoscopische of chirurgische procedure, het vermijden van verdere diagnostiek en overige consequenties. Daarnaast werd voor alle patiënten de huidige klinische situatie vergeleken met de periode waarin de VCE werd verricht en wanneer er sprake was van gastrointestinaal bloedverlies werd het meest recente hemoglobine gehalte geregistreerd.
De gegevens van 150 patiënten werden geanalyseerd. Bij 97 patiënten werd het onderzoek verricht voor onbegrepen gastrointestinaal bloedverlies en bij 36 patiënten wegens de ziekte van Crohn. Een zekere diagnose werd gevonden in 34%, een mogelijke diagnose in 34% en er werd geen diagnose gesteld in 32% van de patiënten. De bevindingen bij VCE leidden tot beleidswijziging in 38% van de patiënten en dit percentage steeg tot 59% wanneer er bij VCE een zekere diagnose kon worden gesteld. Bij patiënten met onbegrepen bloedverlies leidden de bevindingen bij VCE tot een beleidswijziging in 31% en 62% bij respectievelijk occult bloedverlies en manifest

bloedverlies. Wanneer de procedure werd verricht wegens verdenking op M. Crohn van de dunne darm werd het beleid op basis van de bevindingen bij VCE gewijzigd in 50% van de patiënten. Er kon geen relatie worden vastgesteld tussen een verandering in het beleid en de ontwikkeling van de klinische situatie of het hemoglobinegehalte van de patiënt één jaar na VCE.

Hoofdstuk 5

Diverse studies beschreven dat VCE nuttig kan zijn voor de detectie van dunne darm poliepen en tumoren. Dit was reden om een onderzoek te doen naar de waarde van VCE voor de diagnostiek van carcinoid tumoren. Deze tumoren ontstaan vaak in de dunne darm en zijn veelal gemetastaseerd bij het stellen van de diagnose. Ze zijn vaak kleiner dan 1 cm. en daardoor moeilijk te detecteren. Ook kleine afwijkingen kunnen echter aanleiding geven tot stenosering of ischemie, zodat aangeraden wordt om ook in geval van gemetastaseerde ziekte de primaire tumor te verwijderen.
In dit onderzoek werden 20 patiënten geanalyseerd met een gemetastaseerd carcinoid waarvan de primaire tumor onbekend was. Alle patiënten waren eerder onderzocht met dunne-darm-passage-foto, CT-scan en nucleaire technieken zoals octreotide- of MIBG-scintigrafie. Deze nucleaire technieken detecteerden afwijkingen bij respectievelijk 65% en 44% van de patiënten waarbij het niet mogelijk is om te bepalen of de afwijking zich in het mesenterium of in de dunne darm bevindt. De radiologische technieken detecteerden geen enkele primaire tumor in de dunne darm. Tijdens VCE werden bij 12 patiënten afwijkingen gevonden in de dunne darm die suggestief waren voor een primaire tumor van de dunne darm. Bij 9 patiënten was sprake van een tumor in de dunne darm, bij 2 patiënten werd compressie en ischemie van de dunne darm gezien en bij één patiënt bleek sprake van een erosieve afwijking.
Zeven patiënten werden kort hierna geopereerd waarbij in alle gevallen de bevindingen van VCE histologisch werden bevestigd. Deze studie onderstreept de waarde van VCE voor de analyse van patiënten met een gemetastaseerd carcinoid met onbekende primaire tumor.

Hoofdstuk 6

Patiënten met Hereditaire Hemorrhagische Teleangiectasieen (HHT) ontwikkelen op basis van genetische aanleg vaatafwijkingen op diverse plaatsen in het lichaam. Deze kunnen voorkomen in neus, longen, lever, hersenen maar ook in het maagdarmkanaal. De twee belangrijkste mutaties zijn bekend. De mutatie in het endoglin (HHT1) gaat samen met een ernstiger beloop en frequenter voorkomen van vaatafwijkingen in de longen. De mutatie in Activin A receptor-like kinase-1 (HHT2) gaat vaker samen met vaatafwijkingen in de lever.

Bij HHT komt ook vaak een ijzergebreksanaemie voor door bloedverlies uit het maagdarmkanaal. Omdat de dunne darm tot voor kort niet toegankelijk was voor endoscopie is er weinig informatie over het voorkomen van vaatafwijkingen hierin. In dit onderzoek werden van 25 patiënten met HHT en anemie gegevens verzameld over de diverse lokalisaties van vaatanomalieën. Daarnaast ondergingen alle patiënten een VCE. Hierbij werden vaatafwijkingen in de dunne darm gevonden bij alle 14 HHT1 patiënten, bij 9 van hen bleek sprake van grote vaatafwijkingen. Bij 5 van de 8 HHT2 patiënten werden vaatafwijkingen in de dunne darm gevonden. Daarnaast bleek dat vaatafwijkingen in het colon alleen werden gevonden in de HHT 1 groep. Bij 4 patiënten met een normale gastroscopie en coloscopie werden afwijkingen in de dunne darm gevonden bij VCE.
VCE is nuttig bij het bepalen van de uitgebreidheid van de vaatafwijkingen in de dunne darm bij HHT patiënten met een anemie. De afwezigheid van afwijkingen bij gastro- en coloscopie is geen reden om van VCE af te zien.

Samenvattend bieden de resultaten van ons onderzoek, zoals beschreven in dit proefschrift, een onderbouwing voor de veiligheid en klinische toepasbaarheid van videocapsule endoscopie. Wij hebben aangetoond dat videocapsule endoscopie een veilig onderzoek is met een hoge diagnostische opbrengst en vaak belangrijke klinische consequenties. Naast het gebruik in de algemene praktijk voor de analyse van onbegrepen gastrointestinaal bloedverlies en M. Crohn van de dunne darm lijkt er ook een plaats te zijn voor videocapsule endoscopie bij de detectie van primaire carcinoid tumoren en voor het vaststellen van de verspreiding van teleangiectasieen bij patiënten met hereditaire hemorrhagische teleangiectasieen.

List of abbreviations

AVM	Arteriovenous malformation
CAVM	Cerebral arteriovenous malformation
CD	Crohn's disease
CT	Computed Tomography
DBE	Double Balloon Enteroscopy
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
HAVM	Hepatic arteriovenous malformation
Hb	Haemoglobin
HHT	Hereditary Hemorrhagic Teleangiectasia
5HIAA	5-hydroxyindole-3-acetic acid
IBD	Inflammatory Bowel Disease
IOE	Intraoperative enteroscopie
MIBG	Metaiodobenzylguanidine
MR	Magnetic Resonance
NET	Neuroendocrine tumour
NPV	Negative Predictive Value
NSAID	Non Steroid Anti Inflammatory Drug
OGIB	Obscure gastrointestinal bleeding
PAVM	Pulmonary arteriovenous malformation
PE	Push enteroscopy
PPV	Positive Predictive Value
SBI	Suspected Blood Indicator
SD	Standard Deviation
VCE	Videocapsule endoscopy

Colour figures

Chapter 1

Figure 1 *Videocapsule and its components: 1. lenshood, 2. lens, 3. LED, 4. videochip, 5. battery, 6. transmitter, 7. antenna.*

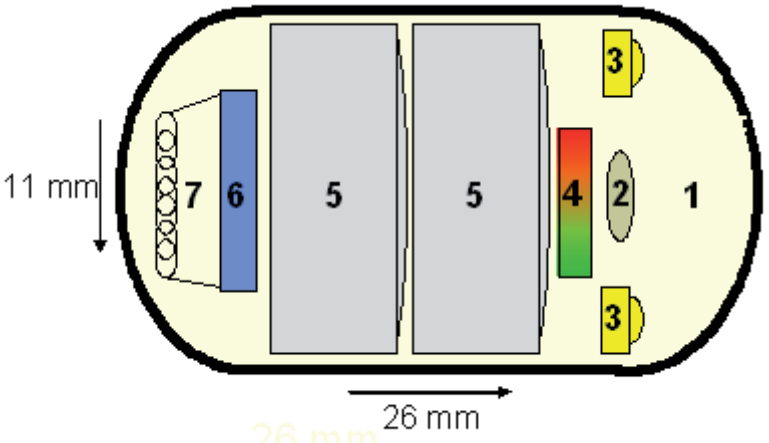


Figure 2 *The set of aerials receiving the videocapsule signal and the advised positions on the abdominal wall.*

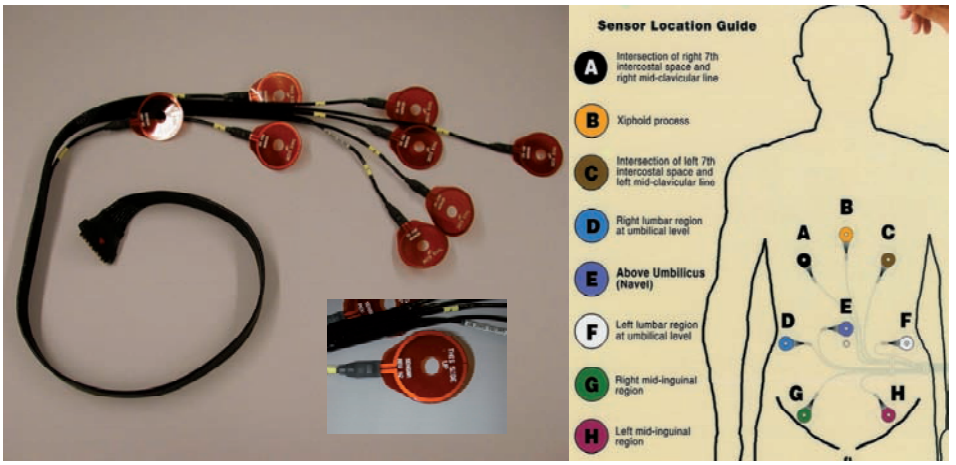


Figure 3 *The belt with the recorder worn around the waist.*

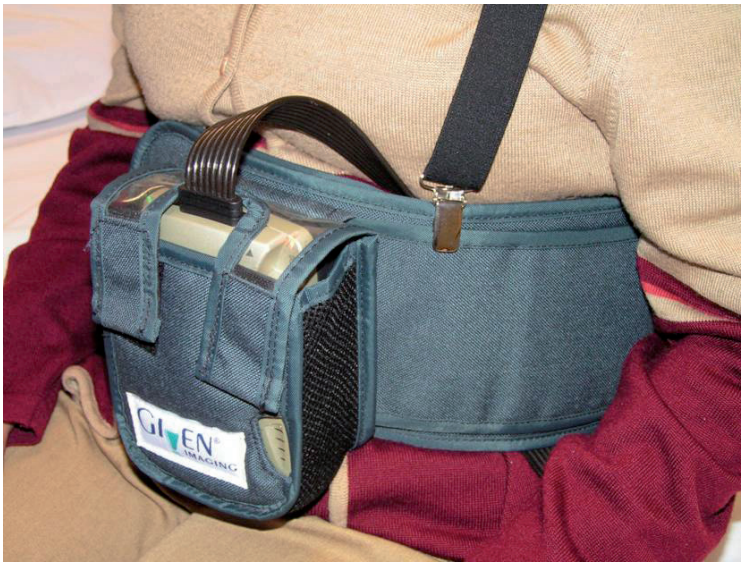
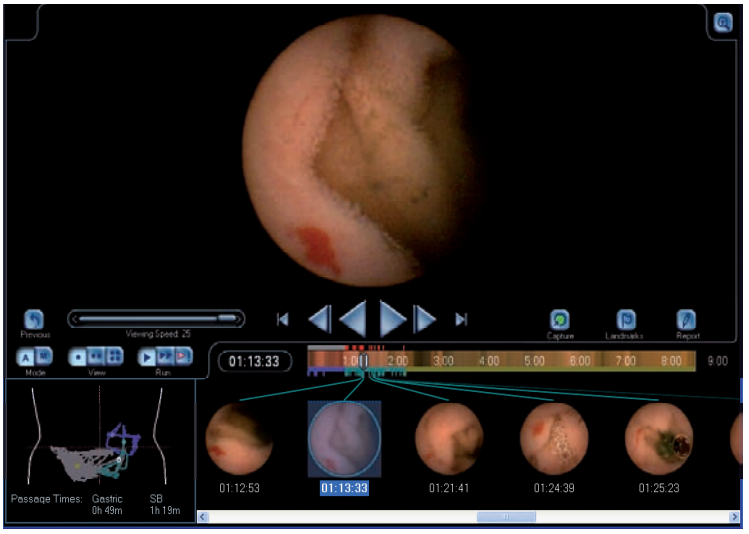


Figure 4 *The screen of the working station for review of the VCE.*



Chapter 3b

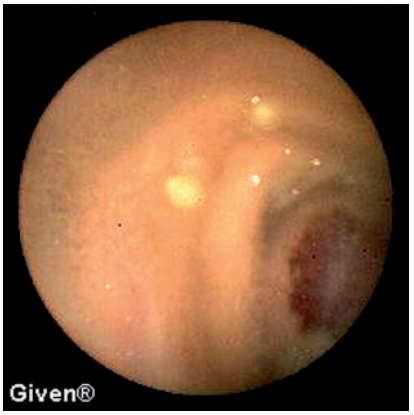


Figure 2 *Images of the second video capsule examination at 2 hours and 9 minutes after ingestion showing a solitary ulcerating angiodysplasia.*

Figure 3 *a) Double balloon enteroscopy showing a polypous angiodysplasia. b) The location is marked with Indian ink and lipiodol.*

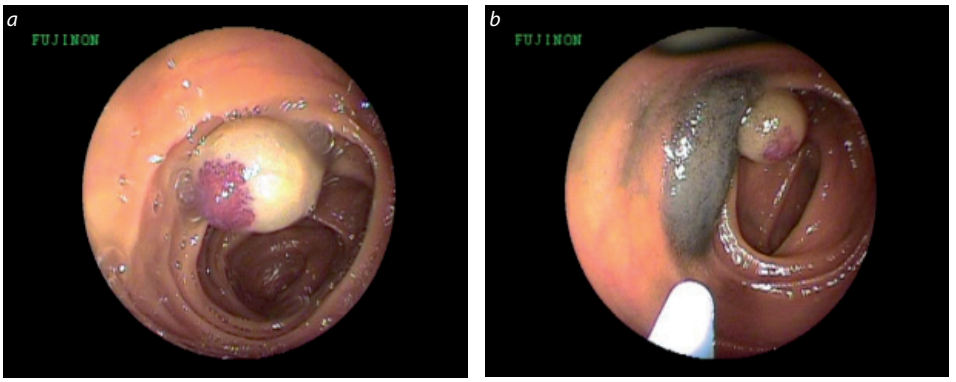
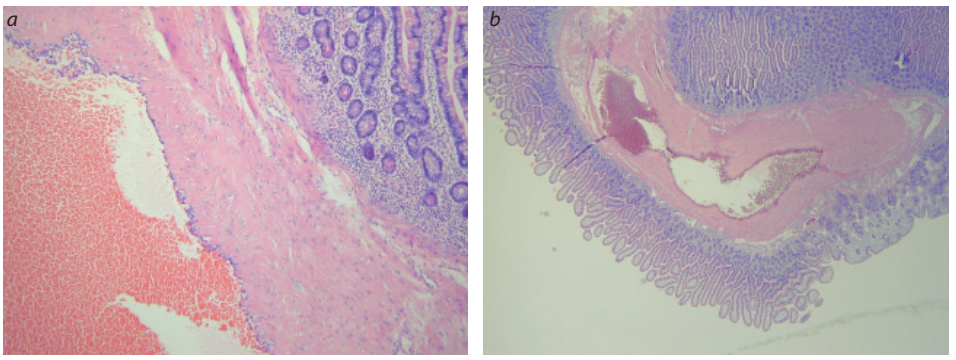
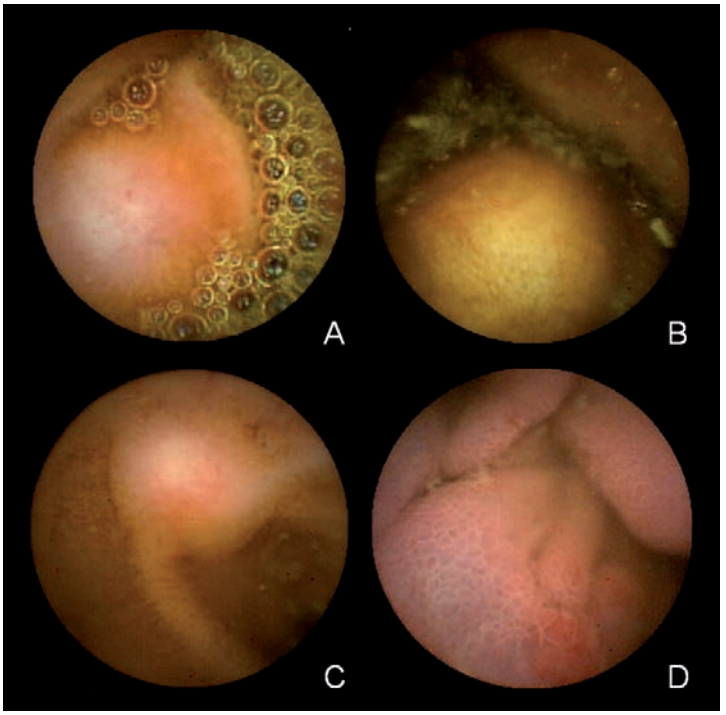


Figure 4 *Histopathological examination showed a large hemangioma-like polypous ectatic vascular conglomerate, partly thin walled partly thick walled. (HE staining, objective 2x en 10x)*



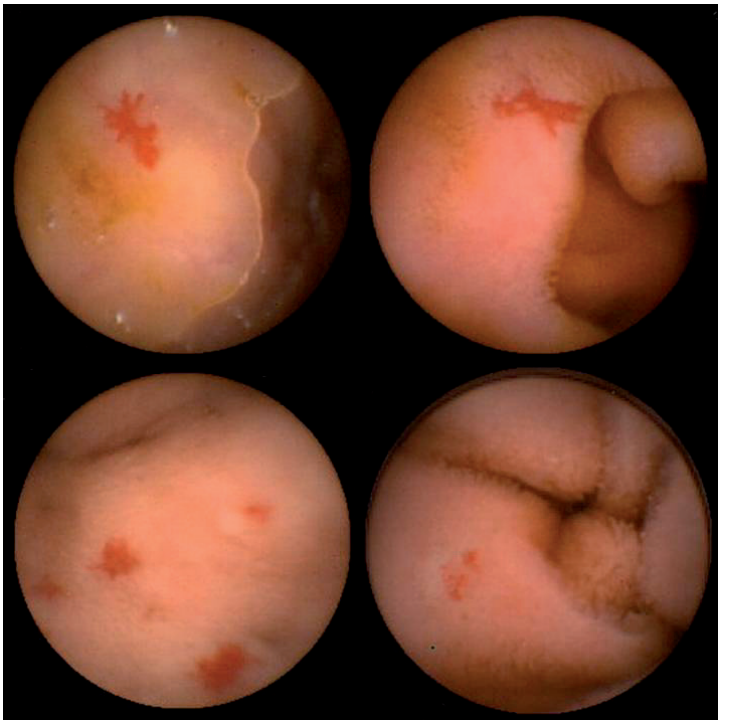
Chapter 5

Figure 1 *Submucosal mass in the ileum, finally diagnosed as a small intestinal carcinoid tumour in three different patients (A, B, C). Ischemic small intestinal segment due to external compression by a mesenteric carcinoid tumour (D).*



Chapter 6

Figure 1 *Small intestinal teleangiectasia detected by VCE in four different HHT patients.*



Dankwoord

Toen ik aan het werk met de videocapsule endoscopie begon, wist ik nog niet wat er op mijn pad zou komen en dat is waarschijnlijk de reden dat dit boekje er nu ligt. Het verschijnen van dit boek was niet gelukt zonder de motivatie en steun van talloze mensen om mij heen. Het noemen van namen impliceert het risico mensen te vergeten. Mocht ik jou vergeten zijn, bedank ik je bij deze.

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De Maatschap Interne geneeskunde en MDL-ziekten van het St. Antonius Ziekenhuis Nieuwegein wil ik bedanken voor de prettige opleidingstijd.

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De endoscopie afdeling van het St. Antonius ziekenhuis: Ik kwam en kom graag op jullie

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Maatschap interne geneeskunde & MDL van het Diakonessenhuis: De "s" is eraf. Dank voor de prettige samenwerking tot nu toe, voorlopig zijn jullie nog niet van me af.

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Curriculum Vitae

Bas van Tuyl werd geboren op 27 januari 1970 te Waalwijk. In 1988 haalde hij zijn VWO diploma aan het Cobbenhagen College te Tilburg. Aansluitend startte hij in 1988 met de studie medische biologie aan de universiteit Utrecht waarvan het doctoraal examen in 1994 werd behaald. In 1992 startte hij daarnaast aan dezelfde universiteit met de studie geneeskunde. Het doctoraalexamen geneeskunde werd behaald in 1995 en gevolgd door het artsexamen in 1997. Na enige tijd gewerkt te hebben als AGNIO in het Eemland Ziekenhuis te Amersfoort werd in 1999 de opleiding interne geneeskunde gestart. Het eerste deel van deze opleiding werd in het UMC Utrecht genoten (Prof. Dr. D.W. Erkelens†) waarna de opleiding werd voorgezet in het St. Antonius Ziekenhuis (Dr. H.C.M. Haanen).

Na bijna drie jaar opleiding tot internist bleek zijn voorliefde voor de maag-darm-leverziekten te sterk. Vanaf 2002 ging hij daarom in hetzelfde ziekenhuis verder met de opleiding tot MDL-arts onder leiding van Dr. R. Timmer. In deze periode werd ook gestart met het onderzoek naar de waarde van de videocapsule endoscopie wat onder leiding van Dr. M.F.J. Stolk en Prof. Dr. E.J. Kuipers resulteerde in dit proefschrift. Per 1 januari 2005 werd hij geregistreerd als MDL-arts en sinds 1 juni 2005 is hij gevestigd als MDL-arts in het Diakonessenhuis Utrecht/Zeist.