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Small bowel capsule endoscopy

Indications, results, and clinical benefit in a University environment

Juliane Flemming, MD[a,b], Silke Cameron, MD, PhD[a,*]

Abstract

Capsule endoscopy (CE) opened a new method for visualization of the small intestine. We here further explore its clinical implications.

We retrospectively analyzed the clinical benefit of CE in view of medical history, diagnostics, and therapy. Our patient collective consisted of 203 patients. CE was investigated in the context of bleeding, anemia, abdominal pain, diarrhea, Crohn's disease, and suspected tumors.

The study collective consisted of 118 male and 85 female patients with a mean age of 58 years (range 8–90 years). Complete bowel transit took place in 82% of the patients. The diagnostic yield in the detection of obscure gastrointestinal bleeding was 80% and for anemia 78%. Mucosal lesions were the most common finding (43%). Unclear abdominal pain had the lowest diagnostic yield (41%). Ensuing therapeutic interventions were mostly medical (66%), and to a minor extent surgical (4.4%) as well as endoscopic (4%).

In conclusion, small intestinal CE is a secure method to clarify small intestinal diseases, especially obscure gastrointestinal bleeding, even in pre-operated patients without stenosis symptoms. Our study emphasizes in a collective of patients with extensive prior diagnostics that due to CE therapeutic measures resulted in 73%.

Abbreviations: BMI = body mass index, CA 19–9 = carbohydrate-antigen 19–9, CEA = carcinoembryonic antigen, Coeff = coefficient, CT = computed tomography, Hb = hemoglobin, MR = magnetic resonance tomography, M2A = mouth to anus, n = number, NSAID = nonsteroidal anti-inflammatory drugs, PET = positron emission tomography, RBC = red blood cell, SB = small bowel, Std err = standard error, var = variation.

Keywords: capsule endoscopy, clinical implications, obscure gastrointestinal bleeding, small bowel

1. Introduction

For a long time, the small bowel was seen as the "black box" of the gastrointestinal tract. The introduction of capsule endoscopy (CE) in the year 2001 opened a new chapter in small-bowel examination.[1–3] It enabled the visualization of abnormalities of the small intestine such as erosions, ulcerations, angiodysplasias, petechiae, venectasias, lymphangiectasias, erythema, edema, changes of the villi, and external constrictions, which are not detectable using tomography. In parallel to CE, push-and-pull endoscopies were introduced; however, they are more invasive and require sedation, with possible complications, including pancreatitis, bleeding, perforations, and sedation-related side effects.[4] In comparison to CE, therapeutic interventions are feasible; however, small lesions can be overlooked[5] in part because of the high magnification of the capsule with 1:8 (65,500 pixel),[6] while the magnification of a conventional video-endoscope can be considered as 1:4 (100,000–300,000 pixel).[7] Therefore, if possible, push-and-pull endoscopies are generally performed after pathologies have been visualized using either CE or computed tomography (CT).

The current European guidelines recommend CE for obscure gastrointestinal bleeding and anemia after negative gastroscopy and colonoscopy.[8] In Crohn's disease, CE can be performed after a nonsuspicious gastroscopy and ileocolonoscopy, and without symptoms of stenosis. In cases of pathological ileocolonoscopy, tomography should be done first. CE can follow, if the result could influence the therapeutic decision. Diagnostic as well as therapeutic options, including surgery for removal of a stricture, need to be discussed with the patient.[9] For tumor suspicion, CE can be done if stenosis symptoms have been excluded.[8] Informed consent has to be obtained before CE.

The outcome of CE can be influenced by appropriate patient selection with careful anamnesis regarding medical history, prior surgery, medical treatment, blood results, stool analysis, and clinical examination as well as bowel preparation.

Although CE is generally only analyzed in view of its indication, we here analyzed CE in view of the patient's status, that is, age, weight, medical history, medication, previous examinations, treatments, and resulting therapeutic measures.

2. Methods

2.1. Study collective and capsule system

Two hundred seven capsule endoscopies were performed in a total of 203 patients between January 2006 and November 2010

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[a] Clinic for Gastroenterology and Gastrointestinal Oncology, University Medicine Göttingen, Göttingen, [b] St. Joseph Hospital, Berlin Tempelhof, Berlin, Germany.

[*] Correspondence: Silke Cameron, Clinic for Gastroenterology and Gastrointestinal Oncology, University Medicine Göttingen, Robert-Koch-Strasse 40, D-37075 Göttingen, Germany (e-mail: silke.cameron@med.uni-goettingen.de).

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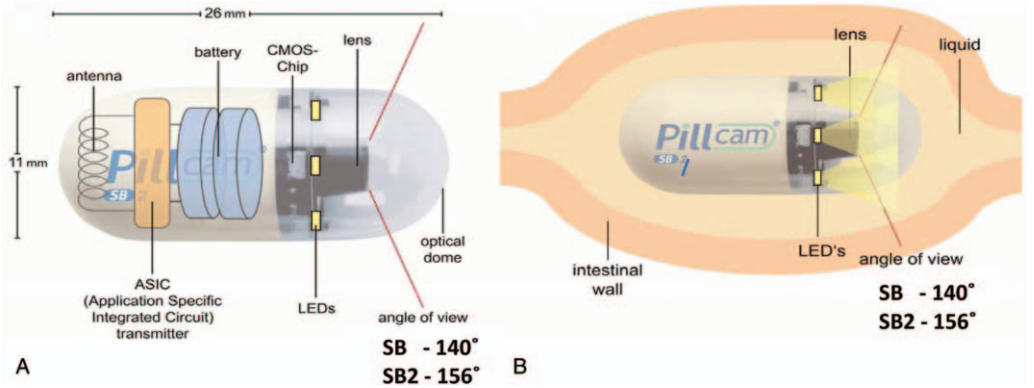

Figure 1. (A) Schematic structure of the capsule, (B) capsule endoscopy in the small bowel. The figure has been modified from[12,13].

at our University. All patients had received a gastroscopy and colonoscopy without findings, which would explain their complaints. As the CE system was upgraded throughout the study, CE was performed 96 times with PillCam SB (former M2A) and 107 times with SB2 capsules (Given Imaging, Yoqneam, Israel). We excluded capsule endoscopies from our analysis where the passage was incomplete and no positive findings were detected in the part passaged.

The PillCam-system consists of 3 components: wireless capsule, data recorder, and work station (a computer with the appropriate software) for the analysis of the pictures. The main difference between the SB and SB2 single use capsules is the angle of view (140° vs 156°), the frames per second (2 vs 4), and the battery life (8 vs 9 hours).[10,11] Technical characteristics are shown in Fig. 1.[12,13]

2.2. Indications and contraindications

In our study collective, indications for CE were obscure gastrointestinal bleeding, anemia, abdominal pain, suspected or known Crohn's disease, diarrhea, surveillance in patients with polyposis syndromes, suspicion of small bowel tumors, and protein-losing enteropathy. Exclusion criteria followed the recommendation for CE, that is, stenosis or suspected stenosis of the gastrointestinal tract and pregnancy. Relative contraindications were dysphagia, gastroparesis, and prior abdominal surgeries. Patients with electromedical implants such as pacemakers or defibrillators received cardiological read-out of their devices after CE. Written informed consent for CE was obtained 1 day before the examination.

2.3. Bowel preparation

The small bowel preparation was similar to the preparation for colonoscopy. The day before CE, patients received a normal breakfast and a broth for lunch. The bowel was cleansed by drinking 2 L of a polyethylene glycol solution with, in between, clear nonalcoholic liquids. The examination followed an overnight fast. The next morning, the capsule was ingested under medical supervision orally (with a glass of water) or endoscopically if oral ingestion was not possible. Patients were allowed to drink clear beverages 2 hours after capsule ingestion and to eat (a low fiber diet) 4 hours later. Capsule read-out was done earliest after 9 to 10 hours. Bowel preparation was considered good (all small intestinal segments were cleansed), fair (several areas with incomplete visualization), and poor or unsuccessful (further analysis could not be done).

2.4. CE evaluation

The CE evaluation time was about 1 to 2.5 hours. It was performed by 1 of 3 medical doctors with more than 10 years of postgraduate education in a University environment, and trained in endoscopy as well as CE. The examiners were aware of the indication for CE. This study is based on these CE evaluation data, and retrospectively analyses the CE results in view of medical records regarding age, sex, weight, indications for the procedure, and medical history (including medication, laboratory test results, prior abdominal surgeries, examinations before and after CE, as well as therapeutic procedures).

2.5. Statistical analysis

All data were collected using the spreadsheet program Microsoft Excel 2007 (Microsoft Office for Windows). The analysis was done using the data-analysis software Statistica 10 (StatSoft, Inc., USA) and the statistical libraries of Python 2.7 (Python Software Foundation). Categorical variables are presented as total numbers and percentages. Quantitative variables are expressed as median. For the analysis of CE-yield, the Chi-squared test was used to evaluate differences for categorical data such as sex and the detection of bleeding. Univariate and multivariate logistic regression analyses were done to analyze continuous data such as age, body mass index (BMI), transit times, and hemoglobin levels. These data were available for 195 patients. Differences of < 0.05 were defined as statistically significant. Dichotomous data were calculated with frequency tables, survival models (Kaplan–Meier), and scatterplots.

3. Results

3.1. Study collective

The study collective consisted of 118 male (58%) and 85 female (42%) patients. The mean age was 58 years (range 8–90 years). The detailed information is given in Tables 1 and 2. Of the 203 capsule endoscopies, 1 was not evaluable because of a technical defect.

3.2. Prior operations

Eighty-one patients (39.9%) had received abdominal surgeries in the past, before CE. Even though abdominal surgery was

Table 1

Patients characteristics (n = 203).

Sex (male/female)	118 (58%)/ 85 (42%)
Median age, y	58, range: 8–90
Hospital treatment	154 (76%) inpatient 48 (23.5%) outpatient 1 (0.5%) unclear
Length of hospital stay, d	$\bar{x}$ = 10.6 d, range:1–47 d 3 patients (1.5%) died
BMI, kg/m^2	
I = <18.5,	I: 15 (7%) patients
II = 18.5–25,	II: 75 (37%) patients
III > 25,	III: 85 (42%) patients
IV = unknown	IV: 28 (14%) patients

considered a relative contraindication, overall, 118 surgical operations of 19 different types were performed. The most common operations included appendectomy, cholecystectomy, partial colectomy, partial small bowel resection, and hysterectomy. A complete list is given in Table 3.

Twenty-five patients have had 2 operations, and 5 patients had more than 2 abdominal operations. In none of these cases, capsule retention was observed.

3.3. Known medical conditions

Hepatosplenomegaly was known in 41 patients (20%), liver cirrhosis without ascites in 3 (1.5%), liver cirrhosis with ascites in 8 (3.9%), esophagus varices in 6 (3%), cholecystolithiasis in 16 (7.8%), cholecystitis in 1 (0.5%), pancreatitis in 3 (1.5%), and angina abdominalis in 2 (1%). Diabetes mellitus was known in 29 patients (14.3%).

Tumors with no gastrointestinal primaries included leukemia in 12 patients (5.9%), gynecological tumors in 7 (3.4%), malign melanoma in 4 (1.9%), urological tumors in 3 (1.4%), pulmonal tumors in 2 (1%), and an otho-laryngological tumor in 1 patient (0.5%).

Twenty-eight patients (13.7%) had more than one of the above-mentioned diseases.

3.4. Exams before CE

Before CE was performed, all patients received laboratory tests, including Quick and prothrombin time, blood count, and clinical chemistry (electrolytes, creatinine, liver enzymes, C-reactive protein, and lipase in case of abdominal pain). Furthermore, in all patients, abdominal ultrasonography was performed, as well as gastroscopy and colonoscopy, both mostly with biopsies.

One hundred sixteen patients (57.1%) underwent additional examinations: Patients with anemia had blood tests, including the differential blood count, serum ferritin, folic acid, and vitamin B12. Tumor markers (CEA; CA 19–9 and Chromogranin A) were analyzed in 5 patients (2.5%). Gliadin and transglutaminase antibodies were done in 16 (8%), and hepatitis serology in 16 (8%). Lactulose breath test was performed in 12 (6%), glucose breath test in 3 (1.5%), endoscopic retrograde cholangiopancreatography in 11 (5.5%), enteroclysis in 25 (12.5%), follow-through examination of the gastrointestinal tract in 3 (1.5%), abdominal CT-scan in 28 (14%), and PET examination in 3 (1.5%). Iliac crest puncture was performed in 3 patients (1.5%), otho-laryngological examinations were done in 2 (1%), and gynecological check in 5 (2.5%). The average number of tests before CE was 4.3 examinations per patient.

Table 2

Indications for capsule endoscopy.

Indications	Number of patients (%)
Obscure gastrointestinal bleeding	92 (45.3)
Anemia	23 (11.3)
Abdominal pain	49 (24.1)
Suspicion of Crohn disease	8 (4)
Crohn disease	5 (2.5)
Noninfectious diarrhea	13 (6.4)
Suspected polyps or tumors	11 (5.4)
Protein losing enteropathy	1 (0.5)

3.5. Indications

The patient numbers for each of the studied indications for CE are listed in Tables 1 and 2.

3.6. Capsule ingestion and bowel preparation

One hundred eighty-nine patients (93%) took the capsule orally, 14 (7%) received the capsule endoscopically. Bowel preparation was good in 151 patients (74.7%), fair (several areas with incomplete visualization) in 26 (12.9%), and poor or unsuccessful in 25 (12.4%). One patient was not evaluable because of a technical defect.

3.7. Transit time

Gastric transit time was determinable in 173 patients (85.2%) and for small bowel in 170 (83.7%). The median gastric transit time was 21 minutes (range 1–462) and for the small bowel 245 minutes (range 18–522). There was no significant difference in stomach and small intestinal transit time for diabetic patients (29; 14.3%) and nondiabetic patients (174; 85.7%), neither for patients with a low and high BMI, nor for patients with (157; 77.3%) or without (46; 22.7%) abdominal tract diseases (including Crohn's disease), and patients with (81; 40%) or without (122; 60%) intestinal tract surgeries. However, in

Table 3

Operations performed before CE.

Operations	Number of patients (%)
Appendectomy	27 (13.3%)
Cholecytectomy	24 (11.8%)
Partial or total colectomy	16 (7.8%)
Partial small bowel resection	10 (5%)
Hysterectomy	9 (4.4%)
Partial or total stomach resection	5 (2.5%)
Nephrectomy	5 (2.5%)
Surgical removal of adhesions	5 (2.5%)
Liver transplantation	4 (2%)
Herniotomy	2 (1%)
Fundoplication	2 (1%)
Splenectomy	2 (1%)
Partial pancreas resection	1 (1%)
Implantation of an aortic fabric tube graft	1 (0.5%)
Ovarectomy	1 (0.5%)
Diagnostic laparotomy	1 (0.5%)
Partial liver resection	1 (0.5%)
Adrenalectomy	1 (0.5%)
Urinary bladder surgery	1 (0.5%)

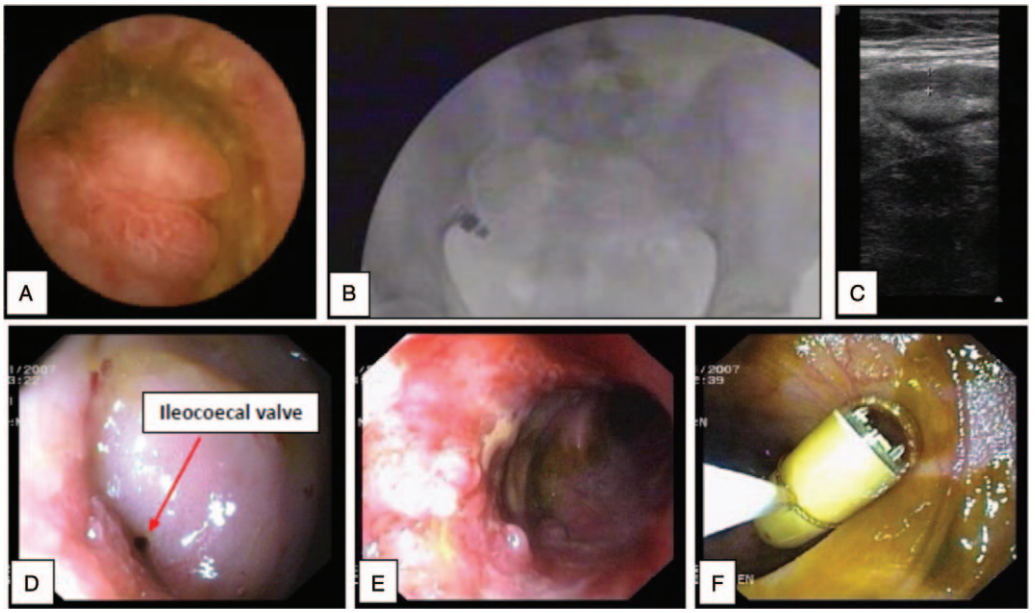

Figure 2. Capsule retention and endoscopic recovery. (A) Capsule image of the lesions in Crohn disease affecting the terminal ileum/ileocoecal valve, (B) X-ray depicting the capsule within the ileal region, (C) ultrasound image with visualization of thickened ileal wall, (D) prominent ileocoecal valve with small opening to the terminal ileum, (E) endoscopic image of the terminal ileum, (F) capsule recovery with polypectomy snare.

patients with Crohn's disease, the median small bowel transit time was prolonged (360 minutes), while the median gastric transit time was unchanged (29 minutes).

3.8. Passage of ileocecal valve and capsule retention

During the battery life of 8 to 9 hours, the capsule reached the cecum (i.e., the complete small bowel was visualized) in 166 patients (82.2%). Of the remaining 36 patients, a positive result from the CE was nevertheless obtained in 29 of the cases. In the remaining 7 incomplete cases, no detection had been made during the time the capsule was operating and it was uncertain whether or not a positive result would have been detected in the segment of the bowel not examined. We have therefore excluded these 7 cases from our analysis of the diagnostic yield.

The complication "capsule retention" occurred in 4 patients (2%). One patient with primary diagnosis of Crohn's disease received an ileocolonoscopy with salvage of the video capsule (Fig. 2). A high-grade stenosis at the ileo-coecal valve was found, and it can be argued that earlier colonoscopy failed to describe the stenosis. In 2 other cases, the retained capsules were mobilized by bowel cleansing. The capsule of the fourth patient (with suspected and then confirmed Crohn's disease) could not be removed by upper and lower endoscopy. He received surgery with partial small bowel resection of the stenosis and capsule recovery.

3.9. Positive findings in CE

In 173 patients (85%), CE revealed the following findings (Table 4). The major positive findings are shown in Fig. 3.

3.9.1. Gastrointestinal bleeding. The diagnostic yield of obscure gastrointestinal bleeding was 80.4% (74/92). Forty-four patients (47.8%) had mucosal lesions. A combination of positive findings (i.e., mucosal lesions, lymphangiectasias, angiodysplasias, and polyps/tumors) was found in 27 (29.3%), and solely vascular changes (venectasias, teleangiectasias) in 3 patients (3%).

Active bleeding was found in 27 patients (13.3%; 10 female and 17 male). The positive findings explained the bleeding in 20 patients (9.9%). Of these, 9 patients had ulcerations (33.3%), 7 erosions (26%), 1 angiodysplasias (3.7%), 1 diverticula (3.7%), 1 polypoid lesions (3.7%), and 1 was iatrogenic (3.7%). Most of these 27 patients with stigmata of active bleeding had received the capsule because of the indication "obscure gastrointestinal bleeding" (n=18, 66.7%). Twelve of these 27 patients had previous abdominal surgeries (44.4%), 10 took anticoagulants (37%), 6 took nonsteroidal anti-inflammatory drugs (NSAIDs) or immunosuppression medication (22%), 5 had diseases of the

Table 4

Findings visualized by CE.

Findings	Patients (n=173)
Mucosal lesions (erosions, ulcerations)	131 (75.7%)
Capillary lesions (angiodysplasias, petechiae)	76 (43.9%)
Mucosal changes (erythema, edema, prominent mucosal folds)	70 (40.5%)
Changes of the villi (flat mucosa, coarsened villi)	72 (41.6%)
Venectasias	28 (16.2%)
Lymphangiectasias/lymphocellular infiltrates/lymph follicles	102 (59%)
Small bowel bleeding (erosions, ulcerations, angiodysplasias, polyps)	27 (15.6%)
Crohn's lesions (aphtae, erythema, ulcers)	12 (6.9%)
Polyps	30 (17.3%)
Luminal changes (external constrictions, submucosal and extrinsic protrusions)	29 (16.8%)
Air bubbles (meteorism)	22 (12.7%)
Increased peristalsis (visible contractions or blurred image)	8 (4.6%)
Stomach changes (gastritis, ulcerations, portal hypertensive gastropathy)	26 (15%)
Colonic bleeding (angiodysplasias, ulcerations, teleangiectasias, diverticula, iatrogenic)	7 (4%)

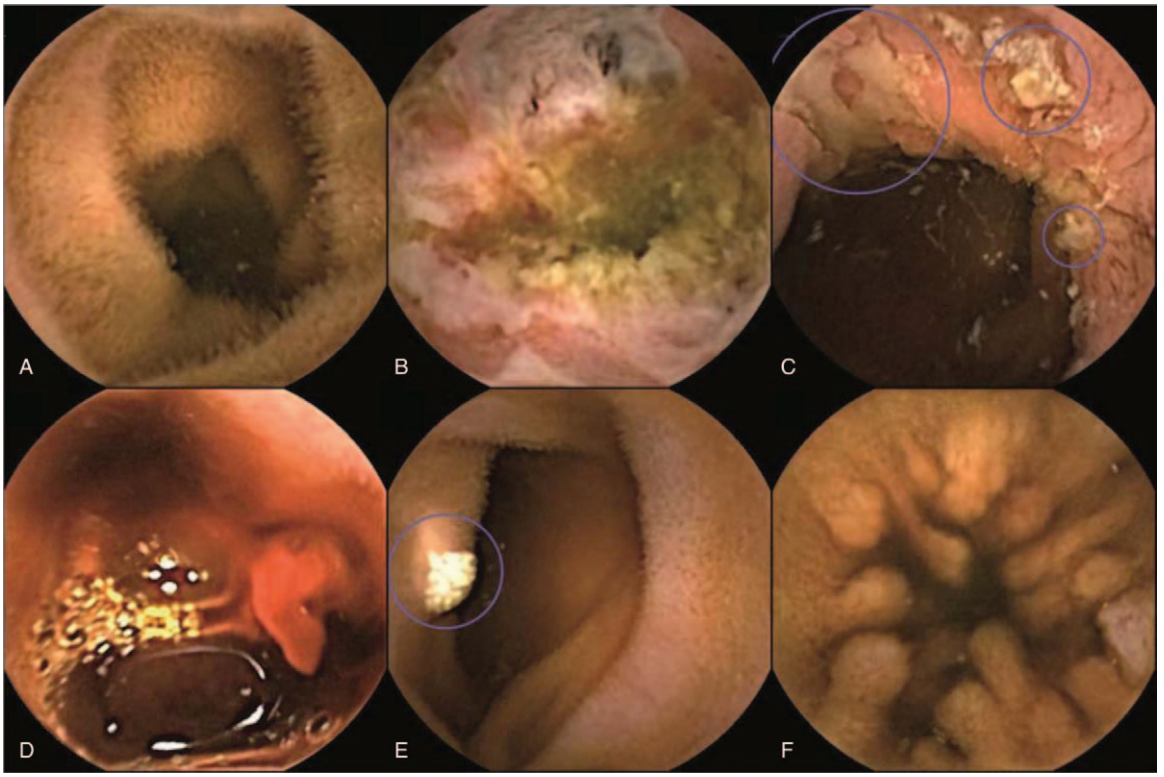

Figure 3. (A) CE images of normal small bowel, (B) NSAID-associated ulcerations limited to the small intestine, (C) ulcerations in a patient with Crohn disease, (D) small bowel bleeding, (E) lymphangiectasia, (F) polyps in familial adenomatous polyposis syndrome. Modified from[13].

abdominal tract (i.e., cholecystitis, cirrhosis, and hepatic duct stenosis), 4 were diabetic (14.8%), and 1 patient was cigarette dependent (3.7%).

3.9.2. Anemia. The rate for positive findings for anemia was 78% (18/23). A combination of positive findings (i.e., erosions, submucosal protrusions, lymphangiectasias, and teleangiectasias) was the most commonly diagnosed (47.8% = 10/23). A singular type of mucosal lesions was seen in 5 patients (21.7%) and vascular changes in 3 (3%).

3.9.3. Abdominal pain. Unclear abdominal pain had the lowest diagnostic yield (41% = 20/49). A combination of pathologies (i.e., aphtae, diverticula, erythema, lesions, polyps, and luminal changes) was found in 10 patients (20.4%), vascular changes in 6 (12.2%), and mucosal lesions in 4 (8%).

3.9.4. Crohn's disease and suspicion of Crohn's disease. CE showed typical lesions of Crohn's disease in 12 of 203 patients (6%). Two of these patients were female and 10 male. Mucosal lesions (erosions, ulcerations) were seen in 10 of 12 patients (83.3%), mucosal changes (such as erythema, and edema) were found in 7 (58%), cystic lymphangiectasias in 5 (41.7%), luminal changes in 4 (33.3%), polyps in 2 (16.7%), and small bowel bleeding in 3 (25%). The mean age was 42 years (range: 17–77 years).

The suspicion of Crohn's disease was decisive in 8 patients (4%). In 3 patients with diagnosis of Crohn's disease in the CE, the indication for CE were abdominal pain (2 patients) and obscure gastrointestinal bleeding (1 patient).

Before CE, 5 patients had known Crohn's disease (2.5%), which had been verified histologically by endoscopy in the past. Two of these showed bleeding stigmata and typical lesions for Crohn's disease, and another 2 patients had typical lesions and 1 patient had negative findings.

In 3 patients, where Crohn's disease was diagnosed by CE, capsule retention occurred. One patient with Crohn's disease and stenosis at 150 cm from the ileocecal valve had to be operated for capsule removal and restoration of bowel passage. In the other cases, the capsule was recovered by bowel cleansing (1 case) and endoscopy (1 case) (Fig. 2).

3.9.5. Diarrhea. For diarrhea, we found positive findings in 6 of 13 patients (46%). Five patients (38.5%) had a combination of pathologies (aphtae, mucosal lesions, angiectasias, lymphangiectasias, and villus atrophy).

3.9.6. Suspected tumors. CE was performed for the indication "suspicion of tumor" in 11 patients. In one of these patients, a lymphoma of the small intestine was confirmed. Two other patients with known primary tumors underwent CE because of additional gastrointestinal bleeding. In 1 patient with known melanoma, a bleeding exulcerating metastasis was found. In the other patient, an ulcerative sarcoma metastasis with bleeding stigmata was found.

3.9.7. Rare case. One patient had the rare indication "protein loosing enteropathy." In this case, edematous villi and multiple lymphangiectasias were found, indicating primary intestinal lymphangiectasia (Morbus Waldmann).

3.9.8. Statistical analysis. To investigate whether there was a statistically significant impact regarding the detection rate using the SB2 capsule as against the SB capsule, we performed a categorical Chi-squared contingency analysis for lesion detection (Table 5). The results comparing the diagnostic yield between the 2 types of capsules were not statistically significant ($P = .085$).

Table 5

Categorical Chi-squared contingency table for lesion detection in SB and SB2 capsules.

	SB capsule (M2A)	SB2 capsule
No diagnostic yield	7 (11.44)	17 (12.55)
Diagnostic yield	86 (81.55)	85 (89.44)

Expected numbers are given in brackets.

Table 6

Categorical Chi-squared contingency table for lesion detection in view of cleansing level.

	Good	Fair	Poor
No diagnostic yield	16 (18.34)	3 (2.83)	5 (2.83)
Diagnostic yield	133 (130.66)	20 (20.17)	18 (20.17)

Expected numbers are given in brackets.

We also performed a categorical Chi-squared contingency analysis for the diagnostic yield depending on the cleanliness of the bowel in the evaluable CEs (Table 6). The results did not show any statistically significant differences for the diagnostic yield. Seven capsules with incomplete passage had to be excluded.

Univariate linear regression analysis for the diagnostic yield regarding transit times, hemoglobin levels before (mean 10.8 g/dL) and after (mean 11.9 g/dL) CE, BMI and age did not show significant differences in lesion detection (Table 7). No predictive value for these variables could be identified. As not all variables were available for all patients, the number (n) of patients, which was considered in each of the logistic regressions, is shown.

3.10. Follow-up examinations

Follow-up examinations were performed in 71 patients (35%). Thirteen patients had more than 1 further test. Ultrasonography of the abdomen was done in 5 patients (7%), repeated gastroscopy in 10 (11.9%), and repeated colonoscopy in 17 (24%). In the repeated colonoscopy, 6 patients showed no positive findings. An adenocarcinoma of the colon was assured histologically in 3 patients. Four patients had sigmoid diverticulosis. One patient had bleeding stigmata, but the lesion could not be found. Single-balloon enteroscopy was done in 4 patients (5.6%), endoscopic retrograde cholangiography in 2 (2.8%), enteroclysis in 3 (4.2%), gastrografin enema in 1 (1.4%), abdominal CT-scan in 21 (29.5%), magnetic resonance imaging in 5 (7%), PET examination in 2 (2.8%), and bone scintigraphy in 1 patient (1.4%). The single-balloon enteroscopy was done in 2 patients with bleeding stigmata and in 2 patients with suspicion of tumor. The tumors were assured by biopsy. A lymphoma and a sarcoma were found.

3.11. Medical and surgical treatment

As a result of CE, therapeutic measures were taken in 73% patients (149/203). In 133 of 203 patients (66%), the medication was changed. Forty-seven patients received more than 1 medicament (35%). They included analgesics in 4 patients (3%), antibiotics in 20 (15%), immunosuppressants (steroids/azathioprine) in 11 (8.2%), mesalazine in 9 (6.7%), erythrocytes concentrates in 60 (45%), fresh frozen plasma in 10 (7.5%), proton pump inhibitors in 39 (29%), iron supplements in 10 (7.5%), prokinetics in 14 (10.5%), muscle relaxants in 2 (1.5%), thalidomide in 1 (0.75%), and reduction/pause of anticoagulants in 30 (22.5%).

Nine of 203 patients were operated (4.4%). Four partial small bowel resections were performed, 4 partial colon resections, and 1 gastrectomy. Five of these patients had the indication "obscure gastrointestinal bleeding," 3 "abdominal pain," and 1 patient had the indication "suspicion of Crohn's disease."

Partial small bowel resection was done in 1 of 4 patients for resection of the stenosis in Crohn's disease and capsule recovery, in 2 patients for metastasis and 1 for adhesions.

Partial colon resection was performed in 2 patients for rectal carcinoma, and in another patient for the resection of an adenocarcinoma in the ascending colon. One patient was operated for perforation after polypectomy. Recurrent bleeding episodes from the stomach in a patient with hypertensive gastropathy led as a last resort to gastrectomy.

4. Discussion

CE has become an important diagnostic tool in small bowel examination over the past 15 years. There is almost no age restriction. Especially in negative colonoscopy, with restriction of the disease to the small intestine and with mucosal involvement only, or sero-muscular involvement not detectable by imaging, CE can prove to be a very useful diagnostic technique. In our study, the age ranged from 8 to 90 years. The median age of 58 years mirrors that of the main indications "obscure gastrointestinal bleeding" and "anemia." Other indications for CE included abdominal pain, Crohn's disease and suspected Crohn's disease, noninfectious diarrhea, suspected polyps or tumors, and rare diseases such as protein losing enteropathy.

There does not seem to be a sex predilection for CE. In our study, similar to Pennazio et al,[14] more men (58%) than women (42%) received CE, while in other studies, more women underwent CE.[15,16]

Table 7

Linear regression analysis for lesion detection regarding univariate parameters.

	Coeff	Std err	95% confidence interval	*P*	n
Transit time small intestine	0.1697	0.123	[−0.071 to 0.410]	.166	184
Transit time stomach	−0.1687	0.161	[−0.484 to 0.147]	.294	182
Hb_before CE	0.0189	0.110	[−0.197 to 0.235]	.864	161
Hb_after CE	−0.0713	0.077	[−0.223 to 0.080]	.356	163
BMI	−0.0478	0.043	[−0.133 to 0.037]	.271	168
Age	0.0085	0.011	[−0.013 to 0.030]	.431	195

(Expected numbers are given in brackets) $P = .085$.

(Expected numbers are given in brackets) $P = .33$.

Diagnostic yield: coeff x(var) + coeff_2; (coeff = Coefficient; var = variation, Std err = Standard error).

BMI = body mass index, CE = capsule endoscopy.

The focus of our study was to analyze not only the outcome of CE itself but also the medical history of the patients as well as diagnostics performed before CE. We further studied the clinical benefit of CE in view of therapeutic consequences.

In our collective, all patients had received laboratory blood tests, as well as ultrasonography of the abdomen, gastroscopy, and colonoscopy before CE. Enteroclysis and follow-through examination of the gastrointestinal tract were performed in 14% of the patients and CT-scan or PET examination in 15% of the patients. Overall, 4 examinations per patient were performed before CE. Forty percent of the patients had abdominal operations in the past.

Probably because of the high standard deviation of gastric and small intestinal transit times, no significant differences were obtained for diabetic and nondiabetic patients, patients with low ($<18.5\,kg/m^2$), and high BMI ($>25\,kg/m^2$), and patients with abdominal tract diseases such as lactose intolerance, fructose intolerance, sigmoid diverticulosis, familial tumor syndromes, colorectal cancer, and lymphoma.

Patients with bowel operations in the past had a shorter transit time (81 minutes) than patients without intestinal tract surgeries (122 minutes). Even though bowel surgery was considered a relative contraindication, no capsule retention was observed in these patients. Patients with Crohn's disease showed a prolonged transit time of about 1 hour, reflecting the risk for capsule retention in this group.

The retention rate in our study was comparable to other studies.[17–19] Crohn's disease has been reported as most common indication resulting in capsule retention (5%), with suspected Crohn's disease leading to capsule retention in 1.4% [ICCE-report (1.5% in our study)].[20] Other studies report even higher retention rates.[9,18]

As a secondary cause for capsule retention, NSAID-enteropathy with mucosal lesions and associated bleeding was described.[19,20] Even if gastroscopy and ileocolonoscopy were normal, mucosal lesions of the small intestine cannot be excluded. In our collective, no retention was observed with gastrointestinal bleeding.

Our results evidence that CE should be applied with strict indication especially in younger patients with abdominal pain. Good anamnesis is not only required to ameliorate the outcome of CE but also to minimize capsule retention. Colonoscopy with ileoscopy, and in selected cases, MR-enteroclysma or patency capsule are possibilities to avoid capsule retention.[21] Furthermore, we could show that especially for the indications "Crohn's disease" and "tumors of the small bowel," the history of the patient enhanced the detection rate. For these indications, CE could also be used as a *negative predictor*.

Nonetheless, it has to be kept in mind that unclear abdominal pain had the lowest diagnostic yield (41% = 20/49). In other studies, this was even less with 14.9%.[22]

The indication "non-infectious diarrhea" did also not lead to therapeutically relevant findings in our study. As in the literature, lesions in patients with noninfectious diarrhea were nonspecific and included combinations of mucosal lesions, angiectasias, lymphangiecasias, and villus atrophy.[23]

Overall, most pathologies were mucosal lesions (erosions, ulcerations) (>130 patients), lymphangiectasias (>100), capillary lesions (angiodysplasias, petechiae) (>70), villus changes (>70), mucosal changes (erythema, edema, prominent mucosal folds) (70), polyps (30), small bowel bleeding (>20). The newer SB2 capsule, even though more user-friendly with a larger angle of view, did not significantly affect the diagnostic yield. This is in accordance with previous findings who report a better resolution, sharpness, and homogenous light exposure with the SB2 capsule; however, no significant difference in diagnostic yield was found in these smaller groups of patients.[24,25] To our knowledge, no head-to-head comparison yet exists for the current SB3 capsule. Furthermore, as the diagnostic yield in our study was generally high (87.7%) and bowel preparation was mostly good and fair (87.6%), no further effect by the cleansing level was observed on the diagnostic yield in the evaluable capsules. The high detection rate also explains that we do not find specific positive predictors for the diagnostic yield in view of age, BMI, hemoglobin levels, or transit times.

The most common indications were obscure bleeding and anemia, with almost 57%. The diagnostic yield for obscure gastrointestinal bleeding in our study was calculated to be 80%. In other studies, it was above 60%.[15,22,26] The higher detection rate in our study might be due to a rather long evaluation time with meticulous reporting of the lesions.

In our patient collective, diagnostic and therapeutic consequences resulted in 73%. Follow-up examinations were performed in 35% of the patients. In 4.4% of our patients, surgery was performed. Mostly however (66%), the medication was changed, including analgesics, antibiotics, immunosuppressants, mesalazine, proton pump inhibitors, iron supplements, muscle relaxants, thalidomide as well as reduction or pause of the anticoagulants. The therapeutic yield depends on the indication and CE findings. The literature varies for the indication "obscure gastrointestinal bleeding" between 40% and 88%.[14,27,28] Obscure gastrointestinal bleeding might result from angiodysplasias of the small bowel where therapeutic options are limited. However some attempts exist with anti-angiogenic treatment such as vascular endothelial growth factor-blockers (bevazicumab) and thalidomide.[29] As for tumor detection, resection could mostly be done in 95%.[17]

CE is safe and requires no sedation or radiation. It is less invasive compared with balloon-endoscopies and the rate of complete bowel passage is higher.[30] It has further been shown that in obscure gastrointestinal bleeding, CE might have a higher detection rate for small intestinal lesions than balloon enteroscopies.[31,32] Especially for obscure bleeding, with unsuspicious gastroscopy and colonoscopy, CE should be the first step taken, as other diagnostic tools are more invasive or less sensitive. The same accounts for tumors limited to the lumen, which are more difficult to visualize in conventional imaging techniques. Preceding push-and-pull endoscopies, CE can help to detect the lesion and decide on the procedure with oral or ileocecal access. Until now, CE does not allow interventions; however, prototypes are being tested, which can be steered from the outside for precise medical applications.[33] Furthermore, the applications for capsule evaluation might get better with shortened evaluation times.[34] This is important, especially for the detection of bleeding, where time might be critical.[35] Technical staff is already being trained for the viewing of the capsule video.[36–38] Our data show that precise indication for CE by a gastroenterologist leads to better diagnostic yield, and as a consequence makes treatment decisions possible.

In comparison to radiographic imaging techniques, CE is highly sensitive in the detection of occult arterial and venous bleeding, especially if done during bleeding episodes.[35] Its sensitivity is higher than CT-angiography or magnetic resonance enteroclysis.[39] Nevertheless, blood flow rates for bleeding detection by CE have not yet been described. For the depiction of active hemorrhage by CT angiography, flow rates of 0.3 mL/min have been shown.[40] With direct mesenteric angiography, bleeding was detected at blood flows greater than 0.5 mL/min.[40] For Tc-99m red blood cell (RBC) scintigraphy, bleeding detection rates have been described for flow rates as low as 0.2 mL/min.[41] However, the diagnostic yield of RBC scintigraphy is limited by its low spatial resolution.

5. Conclusion

Small intestinal CE is, with clear indication and good bowel preparation, a secure and meaningful examination method to clarify obscure gastrointestinal bleeding. Specific diseases of the small bowel, for example, Crohn's disease or tumors, can be excluded rather safely. In our heavily pre-diagnosed patients, CE helps to clarify or eliminate an underlying disease. The therapeutic benefit should not be overlooked, as CE led not only to a change of medication in two-thirds of the patients but also to endoscopic and surgical interventions. Timely communication of the result is beneficial.

Author contributions

Conception and design, data acquisition, and interpretation, as well as drafting of the article: J. Flemming and S. Cameron.

Final approval for publication of the current manuscript: J. Flemming and S. Cameron. Accountable for all aspects of the work, and especially ensure the accuracy and integrity of the work: J. Flemming and S. Cameron. This work is part of the doctoral thesis of the first author, J. Flemming.
Conceptualization: S. Cameron.
Data curation: J. Flemming.
Formal analysis: J. Flemming.
Funding acquisition: S. Cameron.
Investigation: J. Flemming, S. Cameron.
Methodology: S. Cameron.
Project administration: S. Cameron.
Software: J. Flemming.
Validation: J. Flemming, S. Cameron.
Visualization: J. Flemming.
Writing – original draft: J. Flemming.
Writing – review & editing: S. Cameron.

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