Can Capsule Endoscopy Be Used as a Diagnostic Tool in the Evaluation of Nonbleeding Indications in Daily Clinical Practice? A Prospective Study

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Key Words

Capsule endoscopy · Abdominal pain · Diarrhea · Diagnostic yield

Abstract

Objective: To evaluate the diagnostic yield of capsule endoscopy (CE) and its impact on treatment and outcome in patients without bleeding indications. **Subjects and Methods:** One hundred and sixty-five nonbleeding patients were enrolled in the study. The most common indications for CE were chronic abdominal pain alone (33 patients) or combined with chronic diarrhea (31 patients) and chronic diarrhea alone (30 patients). Among the 165 patients, 129 underwent CE for evaluation of gastrointestinal symptoms and 36 for surveillance or disease staging. **Results:** CE findings were positive, suspicious and negative in 73 (44.2%), 13 (7.9%) and 79 (47.9%) of cases, respectively. The diagnostic yield was highest in patients with refractory celiac disease (10/10, 100%) and suspected Crohn's disease (5/6, 83.3%), followed by patients with chronic abdominal pain and chronic diarrhea (13/31, 41.9%), established Crohn's disease (2/6, 33.3%), chronic diarrhea alone (8/30, 26.7%), chronic abdominal pain alone (8/33, 24.2%) and other indications (3/13, 23.1%) ($p < 0.005$). The CE findings led to a change of medication in 74 (47.7%) patients, surgery in 15 (9.7%), administration of a

strict gluten-free or other special diet in 13 (8.4%) and had other consequences in 11 (6.7%). Management was not modified in 42 (27.1%) patients. Among symptomatic patients ($n = 129$), 29 (22.5%) were lost to follow-up. The remaining 100 patients were followed up for 8.7 ± 4.0 months (range 2–19). Among the latter, resolution or improvement of symptoms was observed in 86 (86%) patients, no change in 11 (11%) and 3 (3%) died. All 86 patients who experienced resolution or improvement of their symptoms had a modification of their management after CE; only 7/11 patients whose symptoms did not change (63.6%) and 2/3 patients who died (66.7%) had a modification of management ($p < 0.001$). **Conclusions:** CE appears to be a useful tool in the evaluation of patients with nonbleeding indications. The outcome of most patients with negative findings was excellent.

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Introduction

Capsule endoscopy (CE) is a valuable tool in the investigation of gastrointestinal bleeding when upper endoscopy and colonoscopy do not reveal any abnormalities [1]. CE can be performed on an outpatient basis, does not require sedation, is noninvasive and allows the examination of the entire length of the small bowel [1]. CE

has also been shown to be useful in other conditions, including Crohn's disease and familial polyposis syndromes [1]. The role of CE in the assessment of other nonbleeding indications and particularly in patients with chronic abdominal pain and/or chronic diarrhea is less clear [2–4]. Moreover, there are limited data on the impact of CE findings on patients' management and outcome [5–7]. In addition, the few existing studies in this area focused on patients with gastrointestinal bleeding [5–7].

The aim of this study was to evaluate the diagnostic yield of CE and its impact on treatment and outcome in patients with a variety of indications other than gastrointestinal-tract bleeding or iron deficiency anemia.

Subjects and Methods

All patients who underwent CE in five hospitals of Northern and Central Greece between January 2008 and January 2010 for indications other than gastrointestinal-tract bleeding or iron deficiency anemia were included in this prospective study. A total of 165 patients (male: 81, female: 84, mean age 45.9 ± 16.7 years, range 14–81) were studied. The indications for CE are shown in table 1. The most common indications were chronic abdominal pain alone, i.e. lasting for at least 3 consecutive months (33 patients), chronic abdominal pain in combination with chronic diarrhea, i.e. lasting for at least 4 consecutive weeks (31 patients), and chronic diarrhea alone (30 patients). Among the 165 patients, 129 underwent CE for the evaluation of gastrointestinal symptoms and 36 for surveillance or disease staging (table 1).

Depending on the indication for CE, patients had previously undergone diagnostic procedures including colonoscopy, upper endoscopy, small bowel follow-through, computed tomography scan of the abdomen and/or magnetic resonance imaging scan of the abdomen, which were either negative or nondiagnostic. Also, depending on the indication, laboratory tests including inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) were performed.

CE was performed on an outpatient basis, in the morning, after an overnight fast. All patients underwent CE only once. Bowel preparation was performed with 4 liters of polyethylene glycol solution given 15 h before CE. Patients were allowed to drink clear fluids 2 h after capsule ingestion and were instructed to maintain their normal activities during CE. Patients returned to the hospital 8 h after capsule ingestion and then the registration device and the antennae were collected. Five experienced endoscopists who had previously performed more than 200 CE reviewed capsule video recordings. The location of small-bowel lesions was estimated by analyzing the CE transit time between pylorus passage and ileocecal valve. The duodenum was designated to be the small bowel that was visualized during the first 15 min after the capsule exited the pylorus, while the jejunum and ileum were designated to be the small bowel that was visualized after <50% and >50% of small-bowel transit time, respectively. The location of small-bowel lesions was also estimated based on the endoscopic appearance of the small intestinal mucosa (prominent folds and high narrow

Table 1. Indications for CE

Indication	n (%)
Chronic abdominal pain	33 (20.0)
Chronic abdominal pain plus chronic diarrhea	31 (18.8)
Chronic diarrhea	30 (18.2)
Established Crohn's disease	6 (3.6)
Suspected Crohn's disease	6 (3.6)
Refractory celiac disease ¹	10 (6.1)
Cirrhosis – suspected portal enteropathy ²	9 (5.5)
Familial adenomatous polyposis ²	15 (9.1)
Peutz-Jeghers syndrome ²	7 (4.2)
Other	18 (10.9)
Inflammatory bowel disease – unclassified ²	1
Behçet's disease	1
Weight loss	2
Malabsorption syndrome	2
Suspected leishmaniasis	1
Suspected celiac disease	1
Small bowel intussusception	1
Liver metastatic disease of unknown origin	1
Malignant ascites of unknown origin	1
Gastric and duodenal carcinoids ²	1
Fever of unknown origin	2
Episodes of obstructive ileus	1
History of neuroendocrine neoplasm ²	2
Gastric lymphoma ²	1

¹ Persistent symptoms despite patient-reported strict adherence to gluten-free diet. ² Surveillance/staging group.

villi characterize the jejunum whereas fewer folds and shorter villi are observed in the ileum).

In the 129 symptomatic patients, the CE findings were classified as previously described [5, 7]: positive when they allowed a definite or probable explanation for the symptoms of the patient; suspicious when small-intestine lesions were detected but their relationship to the chief complaint was uncertain, and negative when there were no small-intestine abnormalities. In the 36 patients undergoing CE for surveillance or disease staging (e.g. patients with familial polyposis syndromes or with possible portal enteropathy), the CE findings were classified as positive and negative depending on the presence of relevant findings (e.g. polyps or portal enteropathy). The diagnostic yield of CE was defined as the detection of positive findings. Treatment and outcome following CE were recorded.

The study was conducted in accordance with good clinical practice, as set forth by the Helsinki agreements and their later amendments. The study was approved by our hospital's Ethics Committees and informed consent was obtained from all patients.

All data were analyzed using the SPSS (version 17.0; SPSS Inc., Chicago, Ill., USA) statistical package. The χ^2 test was used for comparisons between groups. A p value <0.05 was considered statistically significant.

Table 2. CE findings

Indication	Positive findings, n (%)	Suspicious findings, n (%)	Negative findings, n (%)	Total, n (%)
Chronic abdominal pain	8 (24.2)	3 (9.1)	22 (66.7)	33 (100.0)
Chronic abdominal pain plus chronic diarrhea	13 (41.9)	3 (9.7)	15 (48.4)	31 (100.0)
Chronic diarrhea	8 (26.7)	3 (10.0)	19 (63.3)	30 (100.0)
Established Crohn's disease	2 (33.3)	2 (33.3)	2 (33.3)	6 (100.0)
Suspected Crohn's disease	5 (83.3)	0 (0.0)	1 (16.7)	6 (100.0)
Refractory celiac disease	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
Cirrhosis – suspected portal enteropathy	7 (77.8)	0 (0.0)	2 (22.2)	9 (100.0)
Familial adenomatous polyposis	10 (66.7)	0 (0.0)	5 (33.3)	15 (100.0)
Peutz-Jeghers syndrome	7 (100.0)	0 (0.0)	0 (0.0)	7 (100.0)
Other	3 (16.7)	2 (11.1)	13 (72.2)	18 (100.0)

Results

CE findings were positive, suspicious and negative in 73 (44.2%), 13 (7.9%) and 79 (47.9%) of the cases, respectively. Therefore, the diagnostic yield of CE was 44.2%. The rates of positive, suspicious and negative findings for each indication are summarized in table 2. In patients with chronic abdominal pain, positive findings included multiple ileal ulcers suggestive of Crohn's disease (n = 2), jejunal tumor (n = 1), ileal tumor (n = 1), 2 ileal ulcers due to the use of nonsteroidal anti-inflammatory drugs (NSAID, n = 2), jejunal edema and erythema suggestive of ischemia (n = 1) and multiple ileal and jejunal ulcers suggestive of ischemia (n = 1) whereas suspicious findings included 1 small aphthous ileal ulcer (n = 1), multiple ileal nodules (n = 1) and ileal edema (n = 1). In patients with chronic abdominal pain plus chronic diarrhea, positive findings included multiple ileal ulcers suggestive of Crohn's disease (n = 10), jejunal tumor (n = 1) and lymphangiectasia (n = 2) whereas suspicious findings included multiple small ileal ulcers (n = 1), few ileal ulcers (n = 1) and focal jejunal and ileal erythema (n = 1). In patients with chronic diarrhea, positive findings included multiple ileal ulcers suggestive of Crohn's disease (n = 5), multiple jejunal and ileal ulcers due to NSAID use (n = 1), lymphangiectasia (n = 1) and villous atrophy suggestive of celiac disease (n = 1) whereas suspicious findings included ileal polyp (n = 1), jejunal polyp (n = 1) and a small-ileal ulcer (n = 1). All 10 patients with refractory celiac disease had villous atrophy. In the 15 patients with familial adenomatous polyposis, polyps were identified in the duodenum, the jejunum and the ileum in 10, 8 and 9 patients, respectively. All polyps were small (<4 mm) except for 3 duodenal polyps in a single patient, which were >10 mm.

Among the 129 symptomatic patients, the diagnostic yield was highest in patients with refractory celiac disease (10/10, 100%) and lowest in patients with other indications (3/13, 23.1%; $p < 0.005$ between the various indications). In addition, the diagnostic yield was lower in patients with normal laboratory findings (9/57, 15.8%) compared with patients with elevated inflammatory markers (17/29, 58.6%), anemia (1/2, 50.0%) and anemia plus elevated inflammatory markers (10/25, 40.0%; $p < 0.001$). Analysis of symptomatic patients by CE indication showed that the presence of anemia and/or elevated inflammatory markers was associated with a higher diagnostic yield of CE only in patients with suspected Crohn's disease and chronic abdominal pain plus chronic diarrhea ($p < 0.05$ and $p < 0.001$, respectively). Finally, the diagnostic yield of CE was lower in symptomatic patients than in the surveillance/staging group (38.0 vs. 66.7%, respectively; $p < 0.005$).

Management details following CE were not available in 10 patients (6.1%). In the remaining 155 patients, management was modified in 113 (79.9%) but not in 42 (27.1%) patients. The modifications were as follows: change of medication in 74 (47.7%) patients, surgery in 15 (9.7%) patients, administration of a strict gluten-free or other special diet in 13 (8.4%) patients and had other consequences in 11 (7.1%) (in 6 patients colonoscopy was repeated, in 3 patients NSAIDs were discontinued, in 1 patient CT of the abdomen was repeated, and in 1 patient serum gastrin levels were determined). The rates of management modification differed significantly according to CE indication ($p < 0.001$) and are shown in table 3. Thirty-seven patients with chronic abdominal pain and/or chronic diarrhea and normal CE findings were considered to have irritable bowel syndrome and were given

Table 3. Rates of management modification by CE indication

Indication	Management modification
Chronic abdominal pain	28 (87.5%)
Chronic abdominal pain plus chronic diarrhea	30 (100.0%)
Chronic diarrhea	23 (88.5%)
Established Crohn's disease	4 (66.7%)
Suspected Crohn's disease	6 (100.0%)
Refractory celiac disease	10 (100.0%)
Cirrhosis – suspected portal enteropathy	0 (0.0%)
Familial adenomatous polyposis	3 (20.0%)
Peutz-Jeghers syndrome	2 (28.6%)
Other	7 (50.0%)

symptomatic medical treatment. Therapy was changed in 7/11 patients with chronic abdominal pain and positive or suspicious CE findings and included a change of medication ($n = 2$), surgery ($n = 3$) and discontinuation of NSAIDs ($n = 2$). Therapy was changed in 16/16 patients with chronic abdominal pain with diarrhea and positive or suspicious CE findings, and included a change of medication ($n = 13$), surgery ($n = 1$) and administration of a diet rich in proteins and medium-chain lipids (in 2 patients with intestinal lymphangiectasia). All 10 patients with refractory celiac disease were instructed to improve their adherence to the gluten-free diet. Management was altered in 51/73 patients with positive CE findings (69.9%), in 10/12 patients with suspicious CE findings (83.3%) and in 52/70 patients with negative CE findings (74.3%; $p = 0.59$). When indications for CE were analyzed separately, there was also no association between CE findings and management modifications.

Among symptomatic patients ($n = 129$), 29 (22.5%) were lost to follow-up. The remaining 100 patients were followed up for 8.7 ± 4.0 months. At the last follow-up visit, resolution or improvement of symptoms was observed in 86 patients (86%), no change in 11 patients (11%) and 3 patients had died (after 2, 4 and 6 months, respectively; 3%). The latter 3 patients underwent CE for the evaluation of liver metastatic disease of unknown origin, malignant ascites of unknown origin and chronic abdominal pain plus chronic diarrhea, respectively. CE did not identify any abnormalities in the first 2 patients and diagnosed the jejunal adenocarcinoma in the third; however, the tumor was inoperable at laparotomy. Patients with chronic diarrhea or refractory celiac disease had the highest rate of symptom resolution (100% in both groups; 20/20 and 10/10, respectively), followed by patients with

chronic abdominal pain and chronic diarrhea (24/26, 92.3%), suspected Crohn's disease (4/5, 80.0%), other indications (6/8, 75.0%), abdominal pain alone (19/26, 73.1%) and established Crohn's disease (3/5, 60.0%; $p < 0.001$ between the various indications). All 86 patients (100%) who experienced resolution or improvement of their symptoms had a modification of their management after CE whereas only 7/11 patients whose symptoms did not change (63.6%) and 2/3 patients who died (66.7%) had a modification of management after CE ($p < 0.001$). Resolution or improvement of symptoms was observed in 44/47 patients with positive CE findings (93.6%), in 9/11 patients with suspicious findings (81.8%) and in 33/42 patients with negative CE findings (78.6%; $p = 0.27$).

CE was generally well tolerated even in adolescents. There was only 1 case of capsule retention in a 68-year-old female who underwent CE for chronic abdominal pain. In this patient, CE revealed multiple nodules in the ileum. Surgery was required for the removal of the capsule and the pathologic examination of the resected part of the small intestine revealed multifocal carcinoid. The pain did not recur after surgery.

Discussion

The role of CE in the evaluation of patients with chronic abdominal pain and/or chronic diarrhea is unclear. Previous studies reported a relatively low diagnostic yield of CE in this setting [2, 4]. However, only one small study assessed the outcome of 16 patients undergoing CE for chronic abdominal pain [8]. The impact of CE on patients with chronic diarrhea alone or in combination with chronic abdominal pain has not been assessed before. In our study, most patients with chronic abdominal pain and/or chronic diarrhea and negative CE findings (78.6%) showed improvement in their symptoms. Therefore, it appears that a normal CE limits the possibility of serious diseases such as Crohn's disease or small intestine tumors being present. Nevertheless, CE is still considered complementary in the evaluation of small-bowel pathology and can miss serious small-intestine pathology. Therefore, if there is a high index of suspicion or if symptoms persist, other imaging techniques should be considered, particularly computed tomography, magnetic resonance enterography and double-balloon enteroscopy [9].

In patients with suspected or established Crohn's disease and inconclusive findings on ileocolonoscopy, CE appears to be the imaging method of choice [1]. In our study, the diagnostic yield of CE was higher in patients

with suspected than in those with established Crohn's disease (83.3 vs. 33.3%, respectively). This might be because the latter patients received treatment and had no findings at the time of CE. Even though CE findings are not very specific in Crohn's disease and we did not confirm these findings in all patients with other imaging modalities, most patients with suggestive CE findings who were given specific treatment for Crohn's disease responded to this treatment. Therefore, the possibility of false-positive CE findings is low but cannot be excluded. In patients with both established and suspected Crohn's disease, the detection of positive small-bowel lesions in CE results in modifications of management in most cases [10–12]. However, only a few small ($n \leq 23$) studies reported outcomes following changes in treatment in established or suspected Crohn's disease and reported an improvement in most patients [10–14]. The small numbers of patients in the existing studies preclude definite conclusions, but it appears that CE-guided treatment leads to symptom resolution in the majority of patients with either established or suspected Crohn's disease.

Our study and previous reports [15–17] suggest that the presence of anemia and elevated markers of inflammation increases the diagnostic yield in patients with chronic abdominal pain and chronic diarrhea or with suspected Crohn's disease. Therefore, better selection of patients with gastrointestinal symptoms will likely improve the cost effectiveness of CE.

Current guidelines recommend that patients with refractory celiac disease should undergo CE [1]. The role of CE in these patients is complementary; when careful history and serological markers rule out noncompliance with gluten-free diet, CE is indicated for identifying complications such as cancer, ulcerative jejunitis or ileitis and other associated conditions such as collagenous sprue [1]. In previous studies in patients with celiac disease and persistent abdominal pain, CE was useful in revealing these complications [18, 19]. In our study, no case of cancer or ulcerative jejunitis or ileitis was detected in the 10 patients with refractory celiac disease. The only CE finding in all these patients was villous atrophy, and implementation of strict gluten-free diet resulted in resolution of symptoms in all of them.

In the present study and in previous cohorts [20–23], CE identified polyps in most patients with familial adenomatous polyps and Peutz-Jeghers syndrome, and the majority of these patients underwent polypectomy. CE is currently considered a first-line examination for the surveillance of patients with Peutz-Jeghers syndrome and is

also indicated in patients with familial adenomatous polyps when duodenal polyps are present [1].

The identification of portal hypertensive enteropathy is potentially important because gastrointestinal bleeding secondary to this condition is associated with high mortality [24]. In previous studies in cirrhotic patients, the prevalence of portal hypertensive enteropathy in CE varied between 63 and 68%, which is similar to our findings (77.8%) [25–27]. In our study and in previous reports, the identification of these lesions did not change patient management [25–27].

CE detected small-intestine tumors in 6.1 and 3.2% of patients with chronic abdominal pain and chronic abdominal pain plus chronic diarrhea, respectively. In another study that included 120 patients who underwent CE for nonbleeding indications, small-intestine tumors were diagnosed in 8.3% [28].

In conclusion, CE appears to be a useful tool in the evaluation of patients with chronic abdominal pain and/or chronic diarrhea. The outcome of most patients with negative findings was excellent. In addition, patients with established and suspected Crohn's disease as well as those with refractory celiac disease also benefit from CE when indicated. Better selection of patients will increase the diagnostic yield and cost effectiveness of CE.

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