Capsule endoscopy: High negative predictive value in the long term despite a low diagnostic yield in patients with suspected Crohn's disease

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Abstract

Introduction: The role of small bowel capsule endoscopy (SBCE) in Crohn's disease (CD) has expanded with greater understanding of the technology. The ability of SBCE to differentiate CD from other causes of inflammation has been questioned. Longitudinal studies are required to assess the long-term impact and significance of SBCE findings in suspected CD. This study aimed to determine the long-term clinical accuracy of SBCE in patients referred with suspected CD.

Methods: A retrospective review was carried out on SBCE procedures performed for suspected CD since 2010. Only patients with at least 6 months of documented follow up were included. A chart review was undertaken to record SBCE findings/correlate with subsequent diagnosis and outcome.

Results: In all, 95 patients with sufficient follow up were identified. The mean follow up was 13 months (range 8–24). In total, 72 (76%) SBCEs were negative and 23 (24%) positive for CD. Of the 72 negative tests, two patients (3%) were later diagnosed with CD. The negative predictive value is 96%. There was a strong positive correlation between results of WCE and subsequent clinical diagnosis.

Conclusions: SBCE appears capable of safely out-ruling CD, with only 3% of negative SBCE investigations being diagnosed with CD after 15 months.

Keywords

Capsule endoscopy, negative predictive value, suspected Crohn's disease

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Introduction

Crohn's disease (CD) is a debilitating, chronic, relapsing and remitting disease with incidence rates in Europe ranging from 0.7–9.8 per 100,000 people.¹ Over the past two decades attempts have been made at creating a 'phenotypic' classification of disease, designed to help predict disease severity and prognosis from time of diagnosis. These Working Groups have led ultimately to the Montreal Classification² of Crohn's disease, published in 2005. The Montreal Classification makes a number of distinctions from previous classification attempts. Particularly, it mentions the role of newer imaging modalities, such as small bowel capsule endoscopy (SBCE), in changing the perception of the 'spread' of disease in terms of location in the large and small bowel.

The development of SBCE has modified our approach to the diagnosis of gastrointestinal disease. It is a relatively new technique, only being developed

in 2000³ and becoming commercially available in 2001.⁴ The relatively rapid uptake of SBCE as an important clinical tool can be largely ascribed to a number of key factors,⁵ including the absence of an investigation capable of directly viewing the small bowel. The role of SBCE has expanded with greater usage and understanding of the technology.

The superiority of SBCE, when compared with traditional endoscopic or radiological procedures, has been demonstrated in numerous situations, most notably in obscure gastrointestinal bleeding⁶ and both suspected and established CD.^{6,7} SBCE is now an established and

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integral part of the investigation pathway for suspected CD.⁸ Furthermore, changes in management of patients with known CD have been demonstrated based on the results of SBCE.⁹

Despite these advances, the potential lag time between symptom occurrence and diagnosis, which can be as long as 7 years,^{10,11} remains a major issue in suspected CD. The ever-evolving field of CD treatment means any delay in commencement of treatment can be detrimental.¹² Further understanding of the ideal utilization of SBCE in the suspected CD cohort can only be beneficial. As an imaging technique, the ability of SBCE to differentiate CD from other causes of small bowel inflammation has been questioned.¹³ Longitudinal studies are required to assess the long-term impact and significance of SBCE findings in suspected CD.

The aim of this study was to determine the long-term clinical accuracy of capsule endoscopy in patients referred with suspected Crohn's disease.

Methods

Patient selection criteria

As the National Referral Centre for SBCE in Ireland, an extensive database was available for analysis. Patients referred for SBCE between June 2010 and August 2012, for a suspected diagnosis of small bowel Crohn's disease, were identified from the database and included in the study. A retrospective chart review was undertaken of all eligible study candidates. Only patients with a minimum follow up of 6 months available after the procedure were included and data was collected to assess the impact of SBCE findings and to correlate with subsequent clinical diagnosis and outcome. Clinical data collected included patient demographics, past medical history, and presenting symptoms. Previous investigations such as ileo-colonoscopy and/or previous small bowel imaging were documented. A Harvey-Bradshaw index (HBI) was recorded, at baseline and follow up, when available. C-reactive protein (CRP) was also documented at baseline and follow up, where available. Exclusion criteria included any documentation of non-steroidal anti-inflammatory drug (NSAID) use in the 3 months prior to SBCE, any patient with less than 6 months of follow up post procedure, and any patient without a previous colonoscopy. Patients with a known diagnosis of CD prior to SBCE were also excluded from the study.

Capsule protocol

SBCE investigations were performed using PillCam SB2 technology (Given Imaging, Yoqneam, Israel)

and analysed with Rapid Reader version 6.5. All procedures followed standard protocol for our unit. All studies were read by experienced gastroenterologists. Capsules were deemed positive if three or more ulcers¹⁴ with concomitant erythema and/or oedema were present. A final diagnosis of CD was made on the specific finding of Crohn's ileitis on SBCE images combined with colonoscopy findings and with either subsequent histological diagnosis or clinical response to therapy.

Statistical analysis

All statistics were performed using SPSS 19. All results are expressed as means. A Pearson's coefficient was used to assess the correlation between variables (>0.7 was considered significant, with a p -value <0.05).

Results

Study population

A total of 625 SBCE procedures were performed during the 2-year time period. Approximately 130 (21%) were performed with suspected CD as the primary indication. In 35 (27%), follow-up data was not available as the subjects were referred from other institutions. Of the 95 (73%) patients, the mean age was 44 years (range 17–69), and 56 (58%) were female. The mean follow up was 13 months (range 8–24). The majority of patients with suspected CD had symptoms of abdominal pain ($n=79$, 83%) and/or diarrhoea ($n=71$, 74%). Table 1 summarizes the characteristics and indications for SBCE.

The majority of patients had an available HBI ($n=59$, 62%) documented prior to SBCE with a mean value of 4 (range 0–13). Every patient had a CRP recorded at baseline with a mean value of 4 mg/l (range 1–30). All patients included in the study had undergone a colonoscopy prior to SBCE. The caecal intubation rate was 95%. All failed colonoscopies had follow-up radiological studies to visualize the right colon. Overall, the terminal ileum was intubated in 60 (63%), although in the subsequent positive SBCE cohort the ileal intubation rate was 80%. This may reflect a higher index of suspicion in the endoscopist in those patients that did actually have Crohn's disease. It is unclear whether this was due to patient symptoms, endoscopist experience, or the clinical suspicion of the endoscopist at the time of the colonoscopy. In total, 16 colonoscopies were reported as macroscopically abnormal, and seven of these had abnormal histology. Furthermore, the majority of patients also had both upper GI endoscopy ($n=55$, 57%) and small bowel imaging prior ($n=78$, 82%) to SBCE investigation.

Table 1. Characteristics and indications for small bowel capsule endoscopy (SBCE) in patients with suspected Crohn's disease

Characteristic	Study population (n = 95)
Age (years)	44 (17–69)
Female	56 (58)
Indication	
Abdominal pain	79 (83)
Diarrhoea	71 (74)
Weight loss	23 (24)
Iron deficiency anaemia	15 (16)
Elevated C-reactive protein	24 (25)
Low B12	25 (26)

Values are mean (range) or n (%).

Table 2. Investigations performed prior to small bowel capsule endoscopy (SBCE)

Investigation	Negative SBCE (n = 72)	Positive SBCE (n = 23)
All radiological investigations	59	19
SBFT		
Normal	44	11
Abnormal	7	2
CT		
Normal	4	3
Abnormal	3	1
MRI		
Normal	4	5
Abnormal	0	0
Upper GI endoscopy	40	15
Colonoscopy	72	23
Caecum intubated	68	23
Ileum intubated	42	18
Ileum macroscopically abnormal	0	7
Colon macroscopically abnormal	9	2
Abnormal histology (colonic)	6	0
Abnormal histology (ileal)	0	1

Values are n.

CT, computed tomography; MRI, magnetic resonance imaging; SBFT, small bowel follow through.

Table 2 summarizes the investigations performed prior to SBCE.

SBCE findings

Negative SBCE. Overall, 72 (76%) SBCE investigations were negative for small bowel CD. Of the 72 negative

tests, 61 (84%) were reported as being entirely normal. Of the 11 (15%) abnormal studies that did not meet the criteria used in the study for small bowel CD of three or more ulcers with erythema and/or oedema, four (36%) went on to have a subsequent negative double balloon pan-enteroscopy (DBE) and biopsy. In total, there were nine (12%) abnormal colonoscopies in this group, with all nine showing colonic inflammation. Abnormal histology (acute or chronic inflammation with no granulomas) was confirmed in six of these colonoscopies. In all, only two (3%) of patients with a negative SBCE were later diagnosed as having CD after a mean 15 months of follow up. Of note, both of these patients' initial SBCE results were negative for small bowel CD. The diagnosis of CD, in both cases, was made following histological confirmation at repeat ileo-colonoscopy 1 year after the SBCE due to persistence of symptoms. The majority (n = 63) were given a diagnosis of functional bowel disease. Three patient's symptoms were attributed to NSAID-induced inflammation, a further three due to post-cholecystectomy diarrhea and three were diagnosed with ulcerative colitis based on both colonoscopy and SBCE findings. Within this cohort, 41 (56%) patients had a HBI recorded of which 30 (73%) were elevated (HBI >3 was considered elevated) with a mean value of 4 mg/l (range 0–10). In all, 17 (23%) patients had an elevated CRP (CRP >5 was considered elevated) with a mean value of 3.7 mg/l (range 1–30). Neither HBI nor CRP was predictive of outcome in this cohort.

Positive SBCE. In all, 23 (24%) SBCEs were positive for small bowel CD. In 14 (60%) patients, the findings were located in the distal small bowel only. A further 8 (34%) had findings in the mid-small bowel with a single study demonstrating changes in the proximal small bowel. A histological diagnosis was sought in nine (39%). No histological confirmation was deemed necessary in the remainder due to factors including previous imaging suggestive of CD. Of note, within the positive SBCE cohorts colonoscopy results, seven (30%) showed evidence of inflamed mucosa, five had ileal inflammation with two showing colonic inflammation. Only one of these had abnormal histology (acute on chronic inflammation). Of the 23 positive SBCE investigations, all with at least 1-year follow up, 20 (87%) have a confirmed clinical or histological diagnosis of CD. During follow up, three (13%) patients were reclassified as not having CD following normal DBE examinations. Two of these patients were diagnosed with NSAID enteritis and one diagnosed with irritable bowel syndrome. Of note, these patients were not started on CD treatment prior to DBE. In all, 18 (90%) of the 20 confirmed cases had an alteration in their management as a result of the SBCE findings.

Table 3. Results of follow-up and longitudinal data

Outcome	Baseline	12-month follow up
Positive SBCE	23	20
Negative SBCE	72	70
Negative predictive value (%)	100	96
Positive predictive value (%)	100	86

Repeat SBCE was not performed at follow-up visit.

In seven (35%) patients, a 5-aminosalicylic acid drug was commenced, seven (35%) were commenced on azathioprine, and three (15%) started adalimumab. One patient underwent surgery for a distal ileal stricture, which was identified by SBCE examination. Of note, this patient passed a patency examination prior to SBCE and the capsule passed the identified stricture spontaneously, although not within the SBCE image time frame. Within this positive SBCE cohort, 15 (65%) patients had a HBI available, of which nine (60%) were elevated with a mean of three (range 0–13). In total, six (26%) patients had an elevated CRP with a mean of 13 mg/l (range 5–26). Neither HBI nor CRP was predictive of outcome in this cohort.

The long-term positive and negative predictive values for SBCE in patients with suspected CD in our cohort were 87 and 96%, respectively. A univariate analysis showed a strongly positive correlation between the results of SBCE and subsequent clinical diagnosis ($r=0.828$, $p<0.01$). However, both HBI ($r=0.183$, $p<0.01$) and CRP (0.149 $p<0.01$) were poorly correlated with the definitive diagnosis. Table 3 summarizes the results of patient follow-up and longitudinal data.

Discussion

The aim of our study was to establish the long-term accuracy of SBCE in patients with suspected CD. Our study is the second largest, to date, assessing the role of SBCE in suspected CD and has the longest follow up for patients with a negative SBCE investigation.¹⁵ The major focus of modern CD medical therapy is disease modification, with resultant reductions in the need for surgery and hospitalization.¹⁶ The potential ‘treatment lag’ due to delayed diagnosis of CD is an important issue, particularly in the era of biological therapy.¹⁷ This potential ‘treatment lag’ between symptom occurrence and diagnosis has been largely in studies assessing cross-sectional imaging. The ability of these modalities to accurately assess mucosal disease is unknown. However, an investigation with the potential to rule out a future diagnosis of CD is invaluable. The long-term negative predictive value of 96% in this study would suggest that SBCE is capable of fulfilling this

role. While meta-analysis data has shown SBCE to be superior to most forms of cross-sectional imaging, magnetic resonance imaging/computed tomography (MRI/CT) is still a useful tool in the diagnostic paradigm of this patient cohort. The relative paucity of MR/CT imaging in our study is largely due to institutional facility constraints. Hence, there is a high volume of capsules performed for suspected Crohn’s disease with a low percentage of concomitant MR/CT cross-sectional imaging in our institution. The majority of patients in our study with negative capsules were diagnosed with functional bowel disease ($n=65$), with a mean follow up of 15 months duration. The authors feel that the robust follow-up time in this study means that a negative capsule endoscopy is likely to be definitive in out ruling a future diagnosis of CD.

SBCE as an investigation is a safe procedure, the major risk being capsule retention.¹⁸ Within the suspected CD cohort, the risk of retention is 2%.¹⁹ Within our study, 72 (75%) had a patency examination prior to SBCE. There were seven patency capsules still evident on an abdominal X-ray at 28 h post ingestion. These were all deemed to be within the large bowel, by expert radiologists, and were allowed to proceed to SBCE. There were no true SBCE retentions (defined as still present in the small bowel 2 weeks after ingestion) within our cohort. There were 10 (10.5%) failed SBCE procedures defined by failure of the capsule to reach the caecum. This figure would be in keeping with previously reported data.²⁰

In total, 11 (15%) of the negative SBCE cohort had an abnormal capsule. These did not fit the criteria of three or more ulcers with oedema and/or erythema used in our institution during the study time frame. Newer scoring systems, which largely negate intra-observer error, have been developed.²¹ One such scoring system, the Lewis score, in a recent study was shown to increase positive predictive value (PPV), sensitivity, and specificity in the suspected CD cohort.²² As an imaging technique, the ability of SBCE to differentiate CD from other causes of small bowel inflammation has been questioned and the relevance of a robust scoring system certainly becomes apparent from our results. In total, SBCE findings in six patients were eventually attributed to NSAID use. This was despite no documented history of NSAID use in patient notes prior to SBCE. This may reflect a reluctance of patients to divulge this information but it is more likely to represent the fact that they were not asked about NSAID use, which in itself is an important learning point. Unfortunately, it was not feasible to prospectively review all SBCE images in order to attain a Lewis score. This was due to both time constraints due to clinical commitments and the fact that the majority of relevant SBCE images have been archived in an

external database. However, the lack of subsequent false negatives on follow up in our cohort suggests the criteria employed are still a robust way of both diagnosing and, importantly, ruling out CD. In our cohort of patients with suspected disease only, the long-term confirmed diagnostic yield was 21%, which is similar to recently published data from Sheffield.¹⁵ Our data confirms the value of SBCE in the early diagnosis of CD. Similarly, our study confirms the clinical relevance of SBCE findings. In all, SBCE resulted in a change in management in the majority (90%) of positive cases.

Despite encouraging data on diagnostic yield, PPVs reported at 50%²³ have been disappointing. A recent study, using the same criteria for ileitis on SBCE as our own study, demonstrated a PPV of 69%. Our own data substantially increases the PPV to 87%. As such, SBCE is an accurate and sensitive test for Crohn's ileitis.

Our study also highlights the need for the development of a specific biomarker and/or scoring system with the potential to guide towards a diagnosis of CD in this patient cohort. Both HBI ($r=0.183$) and CRP ($r=0.149$) were poorly predictive of outcome in our study. Work has been undertaken into the role of faecal biomarkers as a potential dissociative investigation for organic disorders and functional disorders. Faecal calprotectin and lactoferrin are sensitive for intestinal inflammation but lack specificity for CD.²⁴ Faecal biomarkers, however, have been shown to be more sensitive than CRP in diagnosing CD,²⁵ and may be a useful screening tool prior to SBCE in the future.

The retrospective nature of our study is a limitation, in that referral of patients for SBCE may be biased. It is not clear from our data what percentage of patients referred with symptoms suggestive of CD and negative first-line investigations are routinely referred for SBCE. It could be that symptom severity, the suspicion of the treating clinician, or other variables led to these patients being selected to proceed to SBCE. These factors may affect both the diagnostic yield and positive predictive value. Furthermore, the unvalidated criteria of three or more ulcers with concomitant ulceration/oedema for detecting Crohn's disease on SBCE employed in our study may have had an influence on diagnostic yield and positive predictive value. An argument could also be made that our criteria for performing SBCE may not be strict enough, hence leading to a high negative predictive value. However, currently no validated biomarker capable of categorizing patients with suspected CD into high- or low-risk groups exists in routine clinical practice. SBCE has the best diagnostic yield in comparative studies with other second-line investigations and is a reasonable next step in the diagnostic paradigm for this patient cohort. The high positive predictive value (87%)

negative predictive value (96%), and clinical impact (90%) of SBCE validates this approach.

In summary, CD remains a difficult and challenging entity to manage. The suspected CD patient cohort presents a particularly difficult clinical scenario even after negative initial routine endoscopic investigations. SBCE appears capable of, first and foremost, safely ruling out CD, with only 3% with a negative SBCE being diagnosed with CD after 15 months. Furthermore, the diagnostic yield of 21% and high PPV confirms that it is a useful investigation in patients with suspected CD. Further work on developing biomarkers or clinical scoring systems capable of risk stratifying patients with suspected CD is likely to further enhance and define its future role.

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Conflict of interest

The authors declare that there is no conflict of interest.

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