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TOPIC HIGHLIGHT

2016 Gastrointestinal Endoscopy: Global view

Video capsule endoscopy in inflammatory bowel disease

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Abstract

Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel, which hitherto had been relatively inaccessible to direct visualisation. VCE has been shown to play a role in monitoring the activity of small bowel Crohn's disease and can be used to assess the response to anti-inflammatory treatment in Crohn's disease. For those patients with Crohn's disease who have undergone an intestinal resection, VCE has been assessed as a tool to detect post-operative recurrence. VCE may also aid in the reclassification of patients with a diagnosis of Inflammatory Bowel Disease Unclassified to Crohn's disease. The evolution of colon capsule endoscopy (CCE) has expanded the application of this technology further. The use of CCE to assess the activity of ulcerative colitis has been described. This advance in capsule technology has also fuelled interest in its potential role as a minimally invasive tool to assess the whole of GI tract opening the possibility of its use for the panenteric assessment of Crohn's disease. VCE is a safe procedure. However, the risk of a retained capsule is higher in patients with suspected or confirmed Crohn's disease compared with patients having VCE examination for other indications. A retained video capsule is rare after successful passage of a patency capsule which may be utilised to pre-screen patients undergoing VCE. This paper describes the use of VCE in the assessment of inflammatory bowel disease.

Key words: Video capsule endoscopy; Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Patency capsule

Core tip: Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel. Prior to the development of this technology, the small bowel had been relatively inaccessible to direct visualisation. In the setting of Crohn's disease, VCE has been shown to play a role in monitoring disease activity and response to treatment. The evolution of colon capsule endoscopy has expanded the application of this technology in inflammatory bowel disease (IBD). This paper describes

the use of VCE in the assessment of IBD.

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INTRODUCTION

Since its development over a decade ago, small bowel video capsule endoscopy (VCE) has evolved to become an important tool for studying the small bowel. VCE directly visualises the mucosal surface of the small bowel that is relatively inaccessible to gastroscopy and ileocolonoscopy, and does so in a minimally invasive manner. Its position in the investigation of gastrointestinal conditions varies according to the condition and is complementary to other investigations of the small bowel.

Among patients undergoing VCE, the assessment of known Crohn's disease or the investigation of suspected Crohn's disease, is often cited as the second most common indication for VCE[1]. The development of colon capsule endoscopy (CCE) has further expanded the potential applications of capsule technology to include the assessment of colonic inflammatory bowel disease (IBD).

In this article, the role of VCE in the diagnosis and assessment of IBD will be reviewed.

TECHNOLOGY

The first small bowel VCE system, M2A, later rebranded as PillCam SB, was developed by Given Imaging Limited (Yokneam, Israel) and was approved for use in 2001. Since then several other VCE systems, sharing a similar component set-up, have been developed (MiroCam, Intromedic, Seoul, South Korea; Endocapsule, Olympus Optical Co, Tokyo, Japan; OMOM capsule, Jinshan Science and Technology Group, Chongqing, China)[2]. In each system, the capsule is ingested and images are transmitted from the capsule to a sensing system attached to a data recorder, upon which real-time images may be viewed if required. Data are later transferred from the recorder to a computer for subsequent review of the images. A further system, CapsoCam, differs from the other VCE devices. It obtains 360° images and information is stored within the capsule itself[2]. The capsule is retrieved after it has been expelled and the information is downloaded wirelessly.

VCE FEATURES OF SMALL BOWEL CROHN'S DISEASE: MAKING THE DIAGNOSIS

The mucosal features of small bowel Crohn's disease that may be seen at capsule endoscopy include erythema, aphthous ulceration, loss of villi, villous oedema, mucosal fissures and strictures[3]. These findings are not specific to Crohn's disease, however, and may be seen in patients with other types of small bowel enteropathy.

There is, therefore, a potential risk for misinterpretation of inflammatory lesions seen at VCE. A non-selective approach to investigating patients may be associated with both a low yield from VCE examination and also may risk over-interpretation of small bowel findings[4,5]. Histological confirmation may be thought of as the gold standard when diagnosing Crohn's disease. However, this may be difficult to achieve in patients in whom the mucosal changes are located in an area that is difficult to access endoscopically. The clinical context in which inflammatory lesions are seen within the small bowel is therefore an important factor for clinicians interpreting VCE findings.

Non-steroidal anti-inflammatory drug (NSAID)-associated enteropathy is, for example, the commonest mimic of Crohn's disease of the small bowel and, for this reason, patients undergoing VCE assessment are advised to avoid taking NSAIDs for 4 wk prior to the procedure[2]. Despite this, surreptitious intake of NSAIDs has been reported in 13.6% of patients attending for VCE[6].

Other enteropathies that share similar mucosal appearances to Crohn's disease of the small bowel include small bowel lymphoma, radiation enteropathy, intestinal tuberculosis, Behcet's disease and enteropathy related to human immunodeficiency virus-associated opportunistic infections[7].

A further challenge to the interpretation of VCE findings is the recognition that lesions of the small bowel may be observed in healthy individuals. In a prospective randomised placebo-controlled study examining the incidence of NSAID-induced small bowel injury, 13.8% of healthy volunteers were found to have mucosal erosions at baseline[8]. In addition, it was also observed that 7% of healthy volunteers with a negative initial VCE within the placebo group developed mucosal breaks after a 2-wk period. It would appear therefore that not only do small bowel lesions occur in a significant proportion of healthy subjects, but they may also appear and regress over time.

The International Conference on Capsule Endoscopy (ICCE) have formulated an algorithm to aid in the diagnosis of Crohn's disease[9]. Patients are defined as having suspected Crohn's disease based on several clinical criteria. According to these criteria, a patient is considered to have suspected Crohn's disease if they have chronic diarrhoea, weight loss, abdominal pain or failure to thrive plus one other criterion in the form of extraintestinal symptoms raising a suspicion of Crohn's disease, evidence of elevated inflammatory biomarkers or abnormal imaging suggestive of Crohn's disease.

In a retrospective study of patients undergoing VCE for suspected Crohn's disease, those fulfilling ICCE criteria

Table 1 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Capsule Endoscopy Crohn's Disease Activity Index

A: Inflammation	B: Extent	C: Stricturing	Score for each segment
0 = None 1 = Mild to moderate oedema/hyperaemia/ denudation 2 = Severe oedema/ hyperaemia/denudation 3 = Small ulcer (5 mm) 4 = Moderate ulcer (5-20 mm) 5 = Large ulcer (20 mm)	0 = None 1 = Focal 2 = Patchy 3 = Diffuse	0 = None 1 = Single (passed) 2 = Multiple (passed) 3 = Obstructing	A × B + C

were more likely to be diagnosed with Crohn's disease during follow-up and had a higher burden of inflammation within the small bowel compared to those not fulfilling the ICCE criteria[5]. Twenty-one point four percent (6 of 28 patients) and 60.7% (17 of 28 patients) received a diagnosis of Crohn's disease during follow-up in the group of patients not meeting ICCE criteria and in the group meeting the criteria, respectively ($P < 0.05$).

VCE APPEARANCES IN SMALL BOWEL CROHN'S DISEASE

Scoring systems assessing the inflammatory burden in Crohn's disease

Scoring systems quantifying the burden of small bowel inflammation have been developed in an attempt to refine and standardise the way in which findings at VCE are reported. The two commonest scoring systems used in the literature are the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) and the Lewis score. Both scores quantify the severity and extent of small bowel inflammation.

CECDAI (Table 1)

Three elements of VCE findings contribute to the CECDAI scoring system. The small bowel is divided into two equal segments and a score generated for each segment based on the parameters of inflammation, extent and stricturing. The CECDAI is the sum of the scores for the two segments. Niv *et al*[10] have described the validation of this score in a prospective study.

Lewis score (Table 2)

The Lewis score is a semiquantitative validated scoring system used to assess the burden of small bowel inflammation and is the most commonly used scoring index[11]. The small bowel transit time is divided into three equal parts. Each tertile is scored separately according to the formula: Tertile score = (Villous appearance × Extent × Descriptor) + (Ulcer number × Extent × Descriptor). The score for the most severely affected tertile is added to the stenosis score (Stenosis number × appearance × Traversed score). The final score (Maximum Tertile Score + Stenosis Score) is the Lewis (Table 2)[11]. A score of < 135 correlates with clinically insignificant inflammation, a score of 135-790 correlates with mild inflammation and scores of ⩾ 790 correlate with moderate to severe inflammation.

The Lewis score is a measure of inflammatory activity and does not imply a diagnosis. However, the magnitude of the score may play a role in assessing the likelihood of Crohn's disease accounting for the lesions seen[5,12]. A score of ⩾ 135 was associated with a Crohn's diagnosis in 82.6% of patients undergoing VCE for suspected Crohn's disease. In contrast, only 12.1% of those with a Lewis score of ⩽ 135 received a diagnosis of Crohn's ($P < 0.05$)[5].

In a retrospective study assessing the diagnostic accuracy of the Lewis score in patients with suspected Crohn's disease, 58 patients met the ICCE criteria[12]. Within this group, a Lewis score of ⩾ 135 had a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of Crohn's disease of 89.5%, 78.9%, 73.9% and 91.8%, respectively.

VCE IN SUSPECTED CROHN'S DISEASE

The diagnosis of Crohn's disease is made on the basis of a clinical picture that encompasses biomarkers of inflammation, clinical symptoms and targeted investigations[13].

Colonoscopy with ileal intubation is advised as the first line investigation for the diagnosis of Crohn's disease as it will enable the diagnosis of Crohn's disease to be made in the majority of patients. However, 30% of patients will have Crohn's disease restricted to the small bowel that will be beyond the reach of the ileocolonoscope[14]. It is in this group of patients that VCE may useful in establishing a diagnosis of Crohn's disease[2].

The role of VCE in investigating patients in whom Crohn's disease is suspected is complementary to other modes of examination. Cross-sectional small bowel imaging has the advantage of providing information about transmural disease and extra-intestinal features that may include fistulae, collections and significant stricturing disease[3]. However, VCE is able to detect subtle mucosal lesions that may not be detected on small bowel radiological examinations.

In a meta-analysis assessing the yield of VCE *vs* other modalities for changes in keeping with Crohn's disease, VCE performed better than computed tomography enterography (CTE) and small bowel radiography[15]. The incremental yield of VCE examination in patients with suspected or established Crohn's disease compared to CTE and small bowel radiography was 39% ($P < 0.00001$, 95%CI: 27%-50%), and 37% ($P < 0.00001$, 95%CI: 29%-45%), respectively. For magnetic resonance (MR) enterography, VCE for examination of patients with suspected or established Crohn's disease was not demonstrated to be superior to VCE, with a non-significant incremental yield for VCE of 7% ($P = 0.23$,

Table 2 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Lewis score

Parameter		Weightings (Calculated for each tertile)	
Villous appearance	Appearance	Longitudinal extent	Descriptors
	0 = Normal	8 = Short segment	1 = Single
	1 = Oedematous	12 = Long segment	14 = Patchy
		20 = Whole tertile	17 = Diffuse
Ulcer	Number	Longitudinal extent	Descriptors
	0 = None	5 = Short segment	9 = Less than 25% of circumference
	3 = Single	10 = Long segment	12 = 25% to 50% of circumference
	5 = Few	25 = Whole tertile	18 = Greater than 50% of circumference
	10 = Multiple		
Parameter		Weightings (Rated for the whole study)	
Stenosis	Number	Appearance	Passage of capsule past stricture
	0 = None	24 = Ulcerated	7 = Traversed
	14 = Single	2 = Non-ulcerated	10 = Not traversed
	20 = Multiple		

Short segment: ≤ 10% of the tertile; Long segment: 11%-50% of a tertile; Whole tertile: ≥ 50% of the tertile; Few: Two to seven lesions; Multiple: Eight or more ulcers, two or more stenoses.

95%CI: -4%-17%.) However, only four trials assessing VCE and MR enterography were available for inclusion in the meta-analysis and included only a small number of patients. This raises the possibility of a Type Ⅱ error. VCE performed better than the endoscopic modalities of ileocolonoscopy and push enteroscopy with an incremental yield of 22% (P = 0.009, 95%CI: 5%-39%) and 57% (P < 0.00001, 95%CI: 43%-71%). Some caution must be drawn in interpreting these results, however, as the absence of a reference or gold standard for diagnosis may have resulted in a confirmation bias favouring VCE with false positive examinations potentially contributing to the incremental diagnostic yield.

Jensen *et al*[16] addressed the issue of confirmation bias by comparing the diagnostic yield of VCE, MR enterography and CTE with ileocolonoscopy and/or surgery as the gold standard for assessing Crohn's. The authors reported a sensitivity and specificity for Crohn's disease affecting the terminal ileum of 100% and 91% for VCE, 81% and 86% for MR enterography and 76% and 85% by CTE, respectively. VCE was superior to both CT or MR small bowel studies for detecting lesions within the proximal small bowel (P < 0.05).

Leighton *et al*[17] compared the diagnostic yield of VCE *vs* small bowel barium follow-through (SBFT) and ileocolonoscopy in a prospective trial of 80 patients with suspected Crohn's disease. SBFT perfomed less well than the other two modalities. The combination of VCE with ileocolonoscopy detected more inflammatory lesions than the combination of SBFT and ileocolonoscopy [(97.3% and 57.3% of all inflammatory lesions identified, respectively (P < 0.01)]. Among the 25 patients with a final diagnosis of Crohn's disease, based on the physicians' global assessment of the findings of all three modalities, 11 were diagnosed with Crohn's disease on the basis of VCE findings alone, 5 by ileocolonoscopy findings alone but none by SBFT findings alone.

The place of VCE in a diagnostic algorithm for Crohn's disease is not completely clear. If used as a third line investigation after ileocolonoscopy and small bowel imaging, it is not cost-effective[18]. For those in whom Crohn's is suspected, VCE would miss stricturing or penetrating disease which has been reported in 25% of patients at diagnosis[19]. However, as the above studies illustrate, radiological small bowel assessment is inferior to VCE for detecting proximal inflammatory lesions within the small bowel.

VCE IN PATIENTS WITH KNOWN CROHN'S DISEASE

In patients with an established diagnosis of Crohn's disease, VCE has some advantages over other modalities for assessing inflammatory activity. VCE has the potential to identify the presence of active disease that may not be evident from conventional biomarkers, or to identify mucosal lesions that are not visible on radiological imaging. Of patients with Crohn's colitis, 25.6% of patients will also have disease affecting the small bowel[20]. VCE has a role in visualisation of the mucosa beyond the reach of the ileocolonoscope, and is superior to MR and CTE for the detection of small bowel disease[16,21]. This is of prognostic significance, as detection of proximal small bowel disease in patients with Crohn's disease has been associated with poorer clinical outcomes[22,23].

As indicated above, VCE does however, have some limitations compared to cross-sectional imaging of the small bowel for the assessment of small bowel involvement with known Crohn's disease in that only the mucosal surface is visualised. Further, visualisation of the small bowel may be incomplete in up to 25% of patients[24]. However, earlier versions of the video capsule had battery lives that were limited to only 6-8 h. Improvements in the battery life of the most recent iterations of the video capsule would be expected to enable an extended duration of the examination in patients

with the longest transit times. It would be expected that this would translate into a lower rate of incomplete examination.

Correlation of VCE findings with clinical symptoms and biomarkers of inflammation

Clinical symptoms can correlate poorly with the activity of IBD[25]. C-reactive protein (CRP) and faecal calprotectin are inflammatory biomarkers that are frequently used to assess and monitor the activity of IBD. It is recognised that CRP's usefulness as a surrogate marker in IBD can be limited in some patients, however. It is normal in up to 49% of patients with active ulcerative colitis (UC) and in up to 30% of those with Crohn's disease, CRP is not elevated during relapses of disease[26-28].

Several studies have investigated the degree to which findings at VCE correlate with inflammatory biomarkers. Niv *et al*[29] assessed the correlation between laboratory and clinical markers of disease activity and findings at VCE in patients with active Crohn's disease. Forty-three studies were performed in 19 patients. No correlation was demonstrated between the Lewis score and CRP. A similarly poor correlation between the Lewis score and clinical symptoms as assessed by the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ), was reported.

Faecal calprotectin has a stronger correlation with mucosal inflammation than CRP with a reported sensitivity and specificity for the detection of mucosal disease of 70%-100% and 44%-100%, respectively[26]. Its reliability in the assessment of small bowel mucosal inflammation may be less good than for colonic disease[28,30], although some centres have reported an equivalent efficacy for assessing small bowel and colonic inflammation[31].

Koulaouzidis *et al*[32] described the outcome of 70 patients in whom isolated small bowel Crohn's disease was suspected. All patients had undergone a negative ileocolonoscopy and gastroscopy. No patients with a faecal calprotectin value below 100 had active inflammation in keeping with Crohn's disease[32]. In those with a calprotectin of > 200, the diagnostic yield was 65%. The same group reported a moderate correlation between faecal calprotectin and the Lewis score (r = 0.448, P = 0.0014)[33]. When the analysis was restricted to patients with a faecal calprotectin of < 100 a strong correlation was reported (r = 0.68, P = 0.0047). There was no significant correlation between CECDAI and calprotectin (r = 0.245, P = 0.089).

In a multicentre cross-sectional study assessing 187 patients undergoing VCE, significant small bowel inflammation (defined as Lewis score of > 790) correlated poorly with elevation of faecal calprotectin, CRP or a combination of both markers (r = 0.2; P = 0.14)[20]. On the basis of these data, the use of elevated biomarkers as a triage tool would have missed Crohn's in 40% of patients with moderate to severely inflamed small bowel.

Kopylov *et al*[34] assessed the inflammatory burden in the small bowel in patients with Crohn's disease in clinical remission, defined as those with a CDAI score of < 150. In line with previous observations that the absence of clinical symptoms does not reliably indicate a low inflammatory burden, 44 of 52 (84.6%) patients in clinical remission had significant mucosal inflammation of the small bowel (Lewis score > 135). Of the 21 patients in clinical remission who also had inflammatory biomarkers with a normal range (faecal calprotectin and CRP), 14 (67%) had significant mucosal inflammation of the small bowel (Lewis score > 135). The correlation between faecal calprotectin and the Lewis score was stronger than between CRP and mucosal inflammation (r = 0.39, P = 0.003 *vs* r = 0.28, P = 0.036, respectively). Both biomarkers had a high positive predictive value but low negative predictive value for the presence of moderate to severe inflammation (Lewis score $\geqslant$ 790) (96.2% and 24.1%, respectively, for faecal calprotectin; and 100% and 20.5%, respectively, for CRP).

The reported correlation between the Lewis score and biomarkers of inflammation is therefore variable, with the strongest correlation reported for calprotectin levels < 100[33]. In calculating the Lewis score, only the inflammatory score from the tertile with the most severe inflammation contributes to the final score. This may, in part, explain the variable correlation reported between faecal calprotectin and the Lewis score. That is, mild inflammation in the other two tertiles could reasonably be expected to contribute to an elevation in faecal calprotectin, but would not contribute to an elevation in the overall endoscopic score of inflammation[20]. For Crohn's patients in clinical remission, a stronger correlation between a cumulative Lewis score (using a summation of the individual tertile scores) and faecal calprotectin than the correlation between the conventional Lewis score and faecal calprotectin was demonstrated (r = 0.483, P = 0.001 and r = 0.39, P = 0.003, respectively)[34]. The use of a cumulative score requires further investigation.

Mucosal healing and VCE

Mucosal healing, as demonstrated at colonoscopy, has become established as an important endpoint for treatment in Crohn's disease. It has been associated with improvements in quality of life and in clinically relevant outcomes including rates of hospitalisation, rates of surgery and sustained steroid-free remission[35,36]. Although, there are fewer data on the prognostic significance of small bowel mucosal inflammation as assessed by VCE (see below), it is not unreasonable to infer that an improvement in VCE features of small bowel inflammation would also lead to better outcomes. Mucosal healing and the restoration of mucosal barrier function prevents the translocation of bacteria and the subsequent pathological inflammatory response[37]. It has been observed that in those with Crohn's

affecting both the colon and small bowel, improvement in the mucosal appearances in one section of the gastrointestinal tract may not parallel improvement in other locations[38].

Although a "gold standard" for small bowel mucosal healing in Crohn's disease has not yet been established[39], a Lewis score of < 135 is accepted as representing clinically insignificant inflammation[11]. This has been correlated with a CECDAI score of less than 3.8[33].

VCE findings as a predictor of disease outcome

Long *et al*[40] reported on the outcomes of 86 patients with Crohn's disease undergoing VCE. Severe findings, defined as multiple aphthous ulcers or stenosis, as compared to minimal or no inflammatory change, was associated with the addition of new medication (58.5% *vs* 22.2%, $P < 0.01$), and also with the likelihood of surgery (21.9% *vs* 4.4%, $P = 0.01$) in the 3 mo following the examination. Similarly, in study of 53 patients with Crohn's restricted to the small bowel, moderate-to-severe inflammation (defined as a Lewis score of ⩾ 790) was associated with an increased risk of corticosteroid therapy and hospitalisation during a mean follow-up period of 42 mo [RR = 5 ($P = 0.011$; 95%CI: 1.5-17.8) and 13.7 ($P = 0.028$; 95%CI: 1.3-141.9), respectively][41]. There was a trend towards surgery in patients with a Lewis score ⩾ 790 that was not statistically significant. It appears, therefore, that the severity of inflammation as quantified by the Lewis score may predict a more aggressive course of the disease in patients with Crohn's disease.

Disease location has also been identified as a predictor of disease outcome with proximal disease predicting clinical relapse in a retrospective review of 108 VCE examinations in patients with Crohn's disease[23].

Impact of VCE findings on clinical decisions

As the role of VCE in the assessment of Crohn's disease has expanded, several studies have described the impact of the findings at VCE on clinicians' clinical decisions.

In a retrospective study of small bowel capsule tests performed in 71 patients undergoing VCE for assessment of their Crohn's disease, the findings at VCE led to a change in medical therapy in 38 of 71 patients within 3 mo of the investigation[42]. Similarly, in a study that included 86 patients with Crohn's disease, an alteration in therapy occurred in 62% of patients as a consequence of findings from VCE within the 3 mo after the procedure. In 40%, this took the form of a new anti-inflammatory medication, the most common of which was a corticosteroid[40]. Cotter *et al*[43] reported in a retrospective study of 50 patients that, in the 3-mo period after VCE examination, 44% of patients initiated new IBD medication. the proportion of patients on a thiopurine or biologic increased in their cohort from 4% to 30%.

In the largest of the studies describing the impact of the findings at VCE on disease management data were collected on 187 patients undergoing VCE for assessment of known Crohn's disease[20]. Fifty-two point three percent of patients had their management altered as a consequence of the VCE findings. Initiation or dose-intensification of anti-inflammatory medications was undertaken in 82.5% of patients.

Impact of Crohn's treatment on small bowel inflammation as assessed by VCE

A small number of studies have described the impact of Crohn's treatments on small bowel appearances at VCE[44-46].

In a prospective study of 40 patients treated for a flare of Crohn's disease, VCE was performed at baseline and after at least four weeks of treatment, the choice of which was at the discretion of the treating physician[46]. All patients showed a clinical response. However, of the endoscopic variables assessed, only the number of large ulcers showed a statistically significant improvement after treatment [8.3 ± 1.4 and 5 ± 0.8 (mean ± SEM), before and after treatment, respectively (mean difference 3.3 ± 1.2, 95%CI: 0.8-5.9, $P = 0.01$)]. No patients achieved mucosal healing within the 4-wk period of treatment period examined.

In another small prospective study, 43 patients with active Crohn's were offered VCE assessment, following which they were offered additional treatment. In contrast to the short follow-up period in the previous study, 37 patients underwent a further VCE examination at week 12, and 28 patients underwent VCE at week 52[44,45]. Eighty-four percent received Adalimumab and 16% azathioprine. At initial assessment, 33% had mild disease (CECDAI score < 3.5) and the remainder moderate to severe disease (CECDAI score ⩾ 5.8). At 12 wk, 54% were in clinical remission. None had achieved complete mucosal healing, but the CECDAI had normalised in 27% of patients. Significant reductions in median faecal calprotectin and CRP values were observed. At 12 mo, 42% had complete mucosal healing.

Assessment of post-operative recurrence

Asymptomatic recurrence of Crohn's disease after resection is a common occurrence. Seventy-three percent of patients undergoing ileal resection have endoscopic recurrence in the neoterminal ileum one year after surgery[47]. Eighty percent of patients of these patients were symptom free. Some IBD experts advocate routine endoscopic assessment 6 mo post-operatively and offer a step-up in treatment to those with significant recurrence (Rutgeerts score ⩾ i2)[48].

Conflicting results have been reported in two prospective studies comparing the superiority of VCE or ileocolonoscopy for the detection of recurrent disease in patients who have previously had an ileocolonic resection. However, both studies reported that VCE detected lesions in the small bowel beyond the reach of

the ileocolonoscope in up to two thirds of patients[49,50].

ROLE OF VCE IN THE RECLASSIFICATION OF IBD

The term, Inflammatory Bowel Disease Unclassified (IBDU) is conventionally used to classify patients with an intact colon in whom colonic biopsies are not able to distinguish between UC and Crohn's disease. Following a diagnosis of IBDU approximately 30% of patients will be reclassified as Crohn's disease during follow-up[51]. It is not possible to distinguish between UC and Crohn's disease on histological examination of the resection specimen in up to 15% of patients with colitis undergoing colectomy[52]. These patients are conventionally classified as having indeterminate colitis.

These observations have implications for the monitoring and treatment of IBD in these patients. VCE aid in the reclassification of the diagnosis to Crohn's disease which is of particular relevance, for example, to patients in whom the formation of an ileoanal pouch is being considered as rates of pouch failure are higher in patients with Crohn's disease compared to UC or indeterminate colitis[53].

Mow *et al*[54] described the use of VCE in patients with an established diagnosis of IBD who had previously undergone radiological assessment of the small bowel. Twelve of 21 patients with UC or IBDU were reclassified has having probable Crohn's disease after VCE. In this study, Crohn's disease was defined as the presence of small bowel ulcers that were serpiginous, deep-fissuring, coalescing, linear or nodular. Patients with multiple small or indistinct ulcers could also be classified as having Crohn's disease. Similarly, Mehdizadeh *et al*[55] 2008 reported that 19 of 120 patients with IBDU or UC were found to have VCE findings consistent with Crohn's disease (defined as three or more ulcers in the small bowel). In both these studies, the reclassification of patients as having Crohn's disease was based on the identification of inflammatory lesions within the small bowel. However, it should be noted that a negative VCE examination does not exclude a reclassification of IBDU to Crohn's disease. In a cohort of 30 patients with IBDU, a subsequent diagnosis of Crohn's disease (5 patients) and UC (one patient) was made at ileocolonoscopy after a negative VCE examination[56].

In a paediatric population, higher rates of reclassification of IBDU and UC to Crohn's disease have been reported, with more than 50% having their diagnosis revised after VCE[57,58].

CCE

The technology

In an extension of the technology that had been developed to examine the small bowel, a wireless capsule endoscopy system has been developed examination the colonic mucosa. CCE uses a capsule that differs slightly from the small bowel capsule. The wider diameter of colon means that the tendency of the capsule to flip around its axis is greater. A second camera was added in order that both ends of the capsule could capture images simultaneously. Advances in battery technology have extended the battery life sufficiently for the capsule to capture images of the entire colon. The most recent version of the CCE, the PillCam COLON 2 (Given Imaging, Yokneam, Israel) has an angle of view of 172°[59].

Standard bowel cleansing regimes used for conventional colonoscopy are insufficient for examination of the colon with CCE. The bowel cleansing regime for CCE includes 4 L polyethylene glycol. During the procedure, further boosters based on sodium phosphate are used in order to enhance the propulsion of the capsule through the small bowel and colon[60].

CCE in Crohn's disease

CCE has been assessed as a tool for assessing colonic inflammation in active Crohn's disease. In a study prospectively following 40 patients with Crohn's disease, all patients underwent colonoscopy and CCE[61]. There was substantial agreement between the Crohn's Disease Endoscopic Index of Severity (CDEIS) scores calculated using both modalities [intraclass correlation coefficient (ICC), 0.65; 95%CI: 0.43-0.80]. There was also a substantial inter-observer agreement for CDEIS scores (ICC, 0.67; 95%CI: 0.35-0.86). Agreement between the two modalities of examination was less good for Simplified Endoscopic Score for Crohn's Disease (SES-CD). However, CCE appeared to systematically underestimate of the severity of disease. The greatest agreement between colonoscopy and CCE was observed in the ileum (ICC, 0.73; 95%CI: 0.54-0.85) with a trend towards poorer agreement towards the distal colon. The sensitivity for the detection of ulcers within the colon was 86%. However, a low specificity for colonic ulceration of 40% indicates that CCE may not be an adequate tool to assess mucosal healing. In common with other studies of CCE, patients found CCE examination to be more tolerable than optical colonoscopy.

Although, CCE was developed as a tool to assess the colonic mucosa, images of the entire GI tract are captured. This has prompted interest in investigating a potential role for CCE's effectiveness in assessing both the large and small bowel[62]. It's potential role as a single minimally invasive tool to assess the entire gastrointestinal (GI) tract in Crohn's is appealing. A small study assessing the efficacy of CCE for panenteric evaluation of Crohn's disease reported the outcomes for 12 patients with Crohn's disease in steroid-free remission[63]. The entire GI tract could be visualised in 10 of the 12 patients. The use of CCE identified isolated SB disease in three patients.

CCE in UC

Several studies have addressed a potential role for CCE

as a minimally invasive investigation for the assessment of the activity of UC. In the largest of the studies, 100 patients with suspected or confirmed UC were assessed with CCE and colonoscopy[64]. CCE was had a sensitivity and specificity for the detection of colonic inflammation of 89% and 75%, respectively. In a prospective study including 26 patients with UC, CCE compared to colonoscopy showed a moderate agreement for assessing extent of disease and a substantial agreement for the assessment of severity of disease (κ = 0.522, P < 0.001 and κ = 0.751, P < 0.001, respectively)[65]. Hosoe *et al*[66] reported a strong correlation between CCE and colonoscopic assessment of the severity of inflammation (average ρ = 0.797).

There are several limitations in the use of CCE to assess UC. UC may only involve the distal colon and an incomplete CCE examination would fail to identify inflammatory pathology in these patients. In common with VCE of the small bowel, the inability to obtain biopsy specimens is a further limitation. Its role in UC would therefore not encompass surveillance for dysplastic change or scenarios in which biopsies to exclude superadded CMV infection are required.

COMPLICATIONS OF VCE

Capsule retention

Capsule retention, defined as the failure of the video capsule to pass through the GI tract after 2 wk, is a significant concern for clinicians who perform capsule endoscopy. It is more common in patients undergoing VCE for suspected or definite Crohn's disease. In a systematic review which included 2538 VCE procedures performed in patients with definite or suspected Crohn's disease, a capsule retention rate of 2.6% was reported in this group, compared to an overall retention rate of 1.4% in 22840 VCE procedures as a whole[24].

In patients with a retained capsule due to a Crohn's inflammatory stricture, a short course of steroids may enable the capsule to pass spontaneously. However, most patients with a retained capsule may require endoscopy or surgery to retrieve the capsule[67]. Surgical retrieval has been reported to be necessary in 53%-100% of cases of capsule retention. In one small study of 12 patients with a retained capsule, of whom 8 had a Crohn's-associated stricture, double balloon enteroscopy avoided the need for surgery in 75% of cases[68].

Strategies to reduce the risk of capsule retention in IBD

Among patients with Crohn's disease undergoing VCE assessment, those thought to be at highest risk of capsule retention include those with extensive small bowel disease, small bowel strictures, previous abdominal surgery and those with a prior history of small bowel obstruction. Conventional small bowel imaging (small bowel barium studies, CTE and MR enterography) or assessment with a patency capsule (PC) (see later) are useful adjuncts to identify small bowel features that may contraindicate the use of VCE.

However, in one study examining the use of PC assessment of the small bowel (see below), the authors assessed the use of selective PC assessment[69]. Those at higher risk of capsule retention were defined as those patients with obstructive symptoms, previous small bowel resection or bowel obstruction, or those deemed to require a PC by the referring clinician. Interestingly, a selective selection strategy *vs* a non-selective strategy did not correlate with the risk of retention of the video capsule.

Small bowel imaging and prediction of capsule retention

Among patients with an established diagnosis of Crohn's disease, CTE or MR enterography may identify stenotic lesions that would contraindicate VCE in 27%-40% of patients[70]. However, capsule retention may still occur if small bowel imaging misses clinically significant stricturing disease. In a retrospective study of 50 patients with a confirmed diagnosis of Crohn's disease, for example, 6% of the patients had capsule retention despite normal cross-sectional small bowel imaging studies and no history of obstructive symptoms[43].

PC

The Agile PC (Given Imaging Limited, Yokneam, Israel) was developed for use as a pre-screening tool to reduce the risk of capsule retention in patients undergoing VCE. The PC is the same size and shape as the video capsule. It consists of a core containing lactose and 10% barium, the latter component rendering the capsule radio-opaque. The core is contained within a cellophane wrapping with hollow wax plugs at each end of the capsule. Enteric fluid pass through the hollow wax plugs and the capsule disintegrates after 30 h[71]. The PC contains a radiofrequency emitter that can be detected by a hand-held scanner. If, after 30 h, the PC is detected, then its position within the GI tract can be assessed radiologically.

Video capsule retention is a rare occurrence after a negative PC test with retention rates of between 0.6% and 2.1% reported after a satisfactory PC assessment[20,69,72].

There are a number of possible explanations for the observation that the video capsule may become retained after a negative PC test. Rapid disintegration of a PC leading to false negative patency test and subsequent VCE retention has been reported[73]. Assadsangabi *et al*[72] utilized low-dose CT scanning to assess the position of the PC. In the single case of video capsule retention that occurred in this study, the PC was seen to have been retained in a dilated, faecalised segment of ileum that had been misinterpreted as a segment of colon[72].

A positive PC test is associated with a significant risk of video capsule retention. The retention rate in 18 patients with established Crohn's disease who underwent a VCE examination after a positive PC test was 11.1% (P = 0.01)[69].

Adverse effects of PC include abdominal discomfort which has been reported to occur in 20% of patients with established Crohn's disease in one series[69]. Surgical intervention for small bowel obstruction secondary to retention of a PC has been reported[71,74,75]. It is thought that this may arise if the PC lodges in such a way that the enteric luminal contents are unable to access the lactose core of the PC.

A retrospective study of 42 patients undergoing PC and radiological assessment demonstrated a similar sensitivity and specificity for both tests for detecting significant small bowel stricturing [sensitivity for patency and radiological tests of 57% and 71%, respectively (P = 1.00) and specificity of 86% and 97%, respectively (P = 0.22)][76].

Current European guidelines advise use of a PC prior to VCE in patients with a confirmed diagnosis disease[2].

Other complications of VCE

The handful of cases of perforation reported in patients undergoing investigation with VCE have largely occurred in patients with capsule retention and an established diagnosis of Crohn's disease[77]. Aspiration of the video capsule occurs rarely, and has been reported in 1 in 800 examinations[78].

CONCLUSION

VCE has evolved into an important complementary tool to investigate the small bowel in patients with suspected or established Crohn's disease. It is a minimally invasive and well tolerated test with a high diagnostic yield. Its place in the monitoring of Crohn's disease and the implications of VCE findings for the treatment of Crohn's disease are becoming better understood. The more recent development of CCE has expanded the potential applications of capsule endoscopy to include assessment of UC and to provide a pan-enteric assessment of patients with Crohn's disease.

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