Minimally-invasive imaging of the small intestine

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Chapter 6

Video capsule endoscopy in patients with nonresponsive coeliac disease

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Summary

Goals and Background

Discriminating between patients with nonresponsive but otherwise uncomplicated coeliac disease (CD) and patients with refractory CD (RCD) and/or lymphoma is difficult, especially because many abnormalities encountered in complicated CD are not within reach of conventional oesophagogastroduodenoscopy. We aimed to describe video capsule endoscopy (VCE) findings in patients with CD and persisting or relapsing symptoms despite a gluten-free diet, and to identify VCE findings associated with poor prognosis.

Methods

We retrospectively analysed 48 VCE examinations performed in adult patients with CD because of persisting or relapsing symptoms despite adherence to a gluten-free diet. Patients with either uncomplicated CD or RCD I were considered to have a good prognosis, whereas patients with either RCD II or enteropathy-associated T-cell lymphoma were considered to have a poor prognosis. Multivariate analysis was performed to identify VCE findings independently associated with either good or poor prognosis

Results

Proximal focal erythema (OR 6.7; 95% CI, 1.2–38.7; $p = 0.033$) and absence of progression of the capsule to the distal intestine (OR 16.5; 95% CI, 1.2–224.9; $p = 0.035$) were independently associated with poor prognosis. Of the 28 patients with none of these two features, none died during follow-up, compared to 2 (13.3%) of the 15 patients with one of both features, and 4 (80.0%) of the 5 patients with both features.

Conclusions

VCE is a minimally-invasive endoscopic modality that could be of use in the identification of patients with nonresponsive CD who are at risk of poor prognosis.

Introduction

In patients with coeliac disease (CD) clinical recovery can usually be observed within weeks after the introduction of a gluten-free diet.[1, 2] A minority of patients suffer from recurrent or relapsing symptoms, which usually can be attributed to benign causes such as unintentional gluten ingestion, microscopic colitis, irritable bowel syndrome or lactose intolerance.[3] Some nonresponsive patients may have refractory CD (RCD). This should be considered when patients show persistent or relapsing symptoms and villous atrophy despite adherence to a gluten-free diet and after other causes for persisting or relapsing symptoms have been ruled out.[4-7] RCD can be categorized as type I (RCD I) or type II (RCD II) according to intraepithelial lymphocytes (IELs) immunophenotype, or by differences in clonality of the T-cell receptor (TCR) gene.[3, 8-11] RCD I is characterized by a normal, polyclonal immunophenotype of IELs and in general has a favourable response to nutritional support and immunosuppressive therapy, with a 5-year survival between 80% and 96%.[8, 9, 11] In contrast, RCD II is characterized by the presence of an abnormal population of intracytoplasmic CD3 positive IELs without surface expression of CD3 and CD8, and by monoclonality of the TCR gene.[8, 9, 11] RCD II usually does not respond to immunosuppressive drugs, but may respond to chemotherapy or autologous stem cell transplantation (aSCT).[12, 13] The 5-year survival of patients with RCD II is between 44% and 58%, mainly because of the development of enteropathy-associated T-cell lymphoma (EATL).[8, 9, 11] A small subset of patients present with EATL, before CD has been diagnosed (primary EATL).

Discriminating between patients with nonresponsive but otherwise uncomplicated CD and patients with either RCD I, RCD II or primary EATL is difficult, especially because many abnormalities encountered in complicated CD are not within reach of conventional oesophagogastroduodenoscopy, or need complex, not widely available immunological techniques such as T-cell flowcytometry.[14, 15] Video capsule endoscopy (VCE) has been used to evaluate suspected RCD, but studies using predefined VCE findings to discriminate between uncomplicated CD, the subtypes of RCD and EATL have not been performed.[16-18]

We aimed to describe VCE findings in patients with CD and persisting or relapsing symptoms despite a gluten-free diet. Additionally, we aimed to identify VCE findings discriminating between good prognosis (uncomplicated CD and RCD I) and poor prognosis (RCD II and EATL).

Patients and Methods

Patients

All adult patients with CD who underwent VCE for the evaluation of persisting or relapsing symptoms despite a gluten-free diet (as assessed by a dietician) at our hospital between June 2005 and June 2010 were included in this retrospective analysis. The study group consisted of 48 patients. Capsule examinations were performed in 2005 (n = 8),

2006 (*n* = 12), 2007 (*n* = 9), 2008 (*n* = 7), 2009 (*n* = 7) and 2010 (*n* = 5). Charts were reviewed for demographical data, medication use, results from other endoscopic investigations, results from histopathologic and serologic examinations, indication for VCE and final diagnosis.

Video capsule endoscopy

We only perform VCE in the absence of signs suggestive of small-intestinal stenosis. VCE examinations were performed using the Pill Cam SB (Given imaging, Yoqneam, Israel). Patient preparation consisted of 2 litres of polyethylene glycol bowel preparation (Klean prep, Norgine, Amsterdam, The Netherlands).[19]

The VCE examinations were de-identified by one of the authors (F. S.) not involved in the readings of the examinations, and were reviewed by a gastroenterologist (S. V. W.) with over five years of experience in VCE reading who was blinded to identification data, all clinical details and final diagnosis. The small intestine was divided in a proximal (first ¼) and a distal part (remaining ¾), based on the small bowel transit time (SBTT). When a small-bowel examination is incomplete, we used transit data from complete examinations and defined the proximal small intestine as the part depicted within two standard deviations of the mean ¼ of the SBTT of complete examinations.

The proximal and distal part of all VCE examinations were reviewed for signs derived from previous publications on VCE or conventional endoscopy in CD, which included: villous atrophy, mosaic pattern, scalloping of folds, mucosal fissures, erosions (defined as flat whitish lesions, with or without an erythematous rim) or ulcers (defined as depressed whitish lesions, with or without surrounding erythema, swelling or raised margins), strictures, and masses.[20-25] The size of erosions and ulcers were classified arbitrary as either small (≤ 5 mm), intermediate (5–10 mm) or large (> 10mm). Additionally, the presence of focal erythema was included, based on previous personal observations of this feature during double-balloon endoscopy (DBE) in patients with suspected RCD.

Additionally, gastric transit time (GTT), SBTT, and the incidence of incomplete small-bowel examinations and capsule retention were recorded.[26] Ulcerative jejunitis was defined as the presence of ≥3 ulcers in the jejunum during enteroscopy.[25]

Histological analysis and T-cell flowcytometry

Small-bowel biopsies were obtained during oesophagogastroduodenoscopy and/or (DBE) within 2 months of VCE and graded according to the Marsh-classification.[27] T-cell flowcytometry was performed according to the method described in detail previously.[10]

Final diagnosis was established at the end of follow-up. Uncomplicated CD was diagnosed if during follow-up clinical symptoms, villous atrophy and positive serology improved without the need for immunosuppressive therapy, or if an alternative explanation for the symptoms had been established. RCD was defined by persistent or recurrent symptoms of malabsorption and villous atrophy despite strict adherence to a gluten-free

diet for at least 6 months in the absence of other causes of nonresponsive treated CD and overt malignancy.[3] Additionally, patients with positive serology (either anti-endomysial antibodies or anti-tissue transglutaminase antibodies) were classified as RCD only after a period of close dietary surveillance or when these patients required additional therapy to control their symptoms.[9] RCD was further classified according to IEL phenotype or clonality of the TCR-gene: RCD I was defined by normal IEL phenotype (less than 20% of the CD103+/CD45+ IELs lacking surface CD3 on flowcytometry) and absence of clonal TCR-rearrangement in duodenal biopsy specimens. RCD II was defined by abnormal IEL phenotype (more than 20% of the CD103+/CD45+ IELs lacking surface CD3 on flowcytometry) and/or by clonal TCR-rearrangement in duodenal biopsy specimens.[10, 28]

The diagnosis of EATL was established according to international criteria.[29] We defined EATL as 'primary' if no previous diagnosis of CD had been established, or as 'secondary' if the patients was known to have CD before the diagnosis of EATL had been made.[11] Patients with primary EATL were not included in this study.

Statistics

For comparison of patient characteristics between the four diagnostic groups we used Pearson's χ^2 test or the two-sided Fishers exact test for categorical variables and ANOVA with post-hoc Bonferroni test for continuous variables. Because of the small number of patients per diagnostic group (either uncomplicated CD, RCD I, RCD II or EATL), we did not perform comparisons of VCE findings according to each of these diagnostic groups.

To identify VCE findings independently associated with a poor prognosis we grouped patients with RCD II and secondary EATL and compared VCE findings in these patients with the findings in grouped patients with either uncomplicated CD or RCD I, using Pearson's χ^2 test or the two-sided Fishers exact test. VCE findings found to be significant in this analysis were included in the multiple logistic regression analysis to determine findings independently associated with RCD II or EATL. The survival period after VCE was calculated with the Kaplan-Meier method. Differences in survival according to the presence of VCE features found to be independently associated with a poor prognosis were analysed with the log-rank test. Odds ratios were calculated with 95% confidence intervals. *P* values < 0.05 were considered to indicate statistical significance.

Results

Study group

A total of 48 patients were included in the analysis (***table 6.1***). A probable cause for the persisting symptoms was found in 17 (77.3%) of the patients with uncomplicated CD: Persisting unintentional exposure to a source of gluten (*n* = 14), lactose intolerance (*n* = 2) and transient small-intestinal invagination (*n* = 1). Twenty-three patients had refractory CD (type I, *n* = 12; type II, *n* = 11). Three patients had secondary EATL.

Table 6.1: Patient characteristics and results of histology and flowcytometry according to diagnosis.

Parameter	Uncomplicated CD (*n* = 22)	RCD I (*n* = 12)	RCD II (*n* = 11)	Enteropathy-associated T-cell lymphoma (*n* = 3)
Female	19 (86.4)	9 (75.0)	6 (65.5%)	2 (66.7)
Age (y), mean ± SD	48.7 (18.5)	61.9 (9.8)	63.0 (9.8)	63.7 (1.7)
Age at diagnosis (y), mean ± SD	42.4 (18.6)	48.6 (13.4)	55.5 (15.5)	60.3 (3.7)
Duration of gluten-free diet (m), mean ± SD	75 (102)	147 (147)	98 (89)	40 (29)
NSAID use	1 (4.5)	3 (25.0)	1 (9.1)	0 (0.0)
Medication for coeliac disease while undergoing VCE				
None	22 (100.0)	3 (25.0)	3 (27.3)	1 (33.3)
Steroids	0 (0.0)	5 (41.7)	3 (27.3)	2 (66.7)
Immunomodulative therapy	0 (0.0)	4(33.3)	1 (9.1)	0 (0.0)
Cladribine	0 (0.0)	0 (0.0)	4 (36.4)	0 (0.0)
Duration of follow-up (months), mean ± SD	25.7 (23.2)	26.7 (23.8)	24.4 (16.5)	2.5 (0.5)
Death during follow-up	0 (0.0)	1 (8.3)	2 (18.2)	3 (100.0)
Positive anti-endomysial antibodies	14 (63.6)	1 (8.3)	3 (27.3)	0 (0.0)
Marsh-classification*				
Marsh 0	7 (31.8)	0 (0.0)	0 (0.0)	0 (0.0)
Marsh I	4 (18.2)	4 (33.3)	1 (9.1)	0 (0.0)
Marsh II	0 (0.0)	1 (8.3)	1 (9.1)	0 (0.0)
Marsh III A	1 (4.5)	7 (58.3)	5 (45.5)	0 (0.0)
Marsh III B	4 (18.2)	0 (0.0)	3 (27.3)	1 (33.3)
Marsh III C	5 (22.7)	0 (0.0)	1 (9.1)	2 (66.7)
Flowcytometry				
Not performed	10 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)
< 20% abnormal IELs	12 (54.5)	12 (100.0)	0 (0.0)	0 (0.0)
≥ 20% abnormal IELs	0 (0.0)	0 (0.0)	11 (100.0)	3 (100.0)
Double-balloon endoscopy performed	3 (13.6)	4 (33.3)	11 (100.0)	3 (100.0)

Note: Unless otherwise indicated, numbers indicate number of patients, with percentages between parentheses. NSAID = non-steroidal anti-inflammatory drug; IEL: intraepithelial lymphocyte.
* within 2 months of VCE. Note that all patients with RCD had Marsh III when the refractory state was established.

Video capsule endoscopy: indications and technical data

GTT and SBTT did not differ significantly between the four diagnostic groups. Because the small bowel transit time could not be calculated in 10 studies, we could not define the proximal intestine for these studies. We therefore defined the proximal small intestine for incomplete examinations based on transit time data of the 38 complete studies: The mean (SD) length of the proximal small intestine (defined as the part depicted in the first ¼ of the SBTT) of the 38 complete examinations was 70 (25) minutes, we defined the

proximal small intestine for incomplete examinations as the part depicted within two standard deviations of the mean ¼ of the SBTT of complete studies. This resulted in an estimated end of the proximal small bowel at 120 minutes after passage of the pylorus. Abnormalities or nonprogression before 120 minutes were considered to have occurred in the proximal small intestine, whereas abnormalities or nonprogression after 120 minutes were considered to have occurred in the distal small intestine.

Video capsule endoscopy: findings according to diagnosis

Table 6.2 shows the findings of VCE according to location and final diagnosis. Examples of the lesions depicted are shown in ***figure 6.1–6.6***. We found no clear relation between the size or number of erosions or ulcers and final diagnosis (***table 6.3***). Two patients (uncomplicated CD: $n = 1$; RCD I: $n = 1$) fulfilled the endoscopic definition of ulcerative jejunitis.

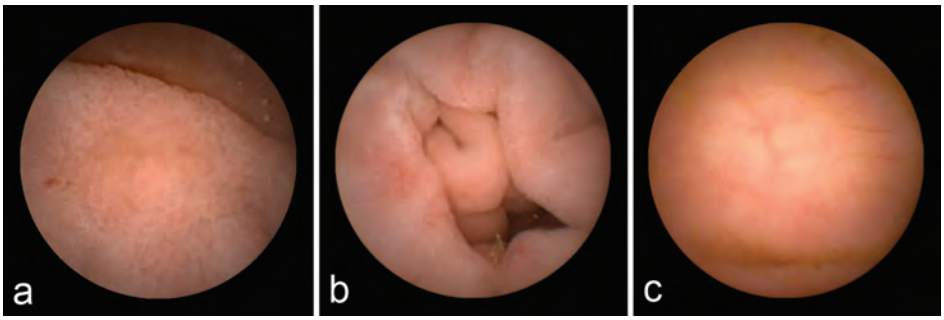

Figure 6.1: Video capsule endoscopy images show examples of abnormalities of small-intestinal villi. (a) Partial villous atrophy in a 43-year-old woman with RCD I. (b) Partial villous atrophy in a 36-year-old female with uncomplicated CD. (c) Total villous atrophy in a 53-year-old woman with RCD II.

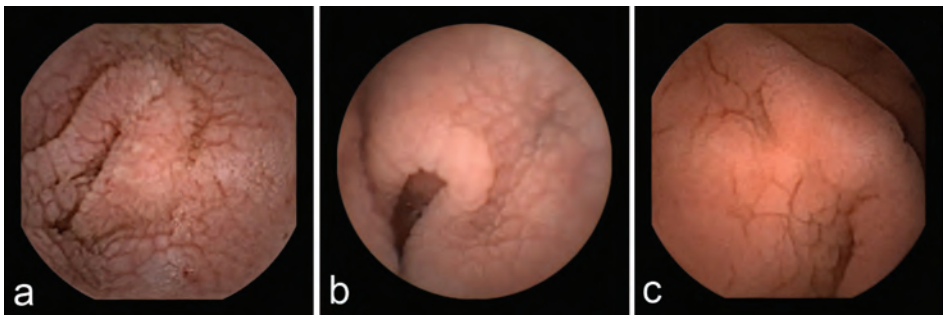

Figure 6.2: Video capsule endoscopy images show examples of mucosal mosaic pattern. (a) Mucosal mosaic pattern in a 37-year old female with uncomplicated CD I. (b) Mucosal mosaic pattern in a 65-year-old woman with RCD II. (c) Mucosal mosaic pattern in a 53-year-old female with RCD I.

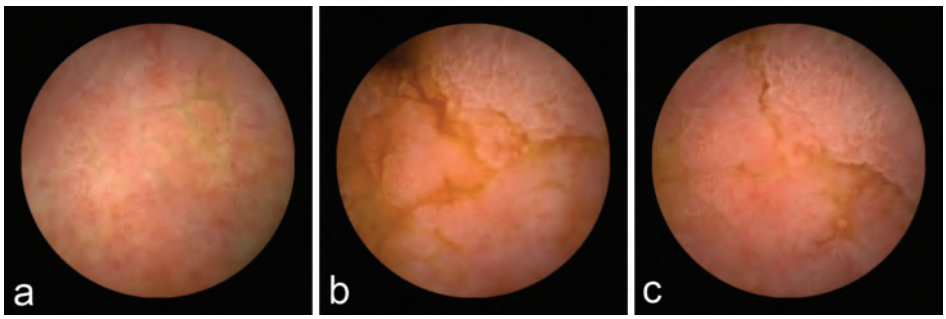

Figure 6.3: Video capsule endoscopy images show examples of mucosal fissures in a 52-year-old man with RCD II**.** (a) Distal duodenum. (b) Proximal jejunum. (c) Proximal jejunum.

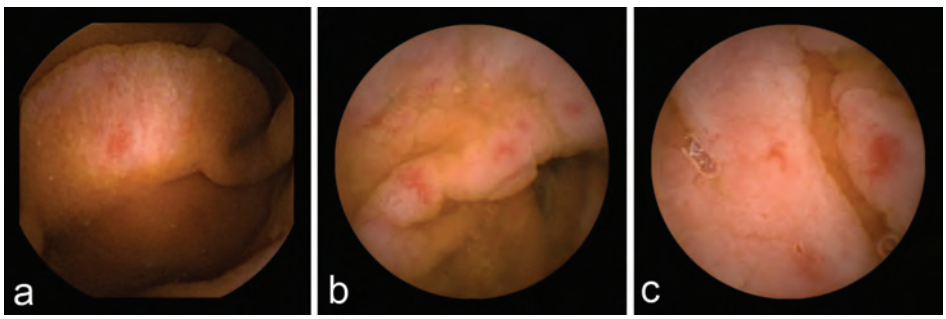

Figure 6.4: Video capsule endoscopy images show examples of mucosal erythema. (a) Proximal jejunum of 65-year-old woman with RCD II. (b & c) Proximal jejunum of a 56-year-old man with RCD II.

Comparisons according to prognosis

We compared patients with an increased risk of poor prognosis (RCD II or secondary EATL) with patients without this increased risk (uncomplicated CD or RCD I) (***table 6.4***). The following parameters were included in the multivariate analysis: proximal nodularity, proximal fissures, proximal erythema, proximal erosions and/or ulcers, proximal strictures and absence of progression to the distal small intestine. Because distal small intestinal findings could not be examined in all patients, these were not included in the multivariate analysis. In the multivariate analysis, the presence of proximal focal erythema (OR 6.7; 95% CI, 1.2–38.7; p = 0.033) and absence of progression of the capsule to the distal intestine (OR 16.5; 95% CI, 1.2–224.9; p = 0.035) were independently associated with an increased risk of poor prognosis.

Of the 28 patients with none of these two features, none died during follow-up, compared to 2 (13.3%) of the 15 patients with one of both features, and 4 (80.0%) of the 5 patients with both features (***figure 6.7***). Nonprogression was observed in one patient with RCD I, who had a short web like stricture, possibly caused by non-steroidal anti-

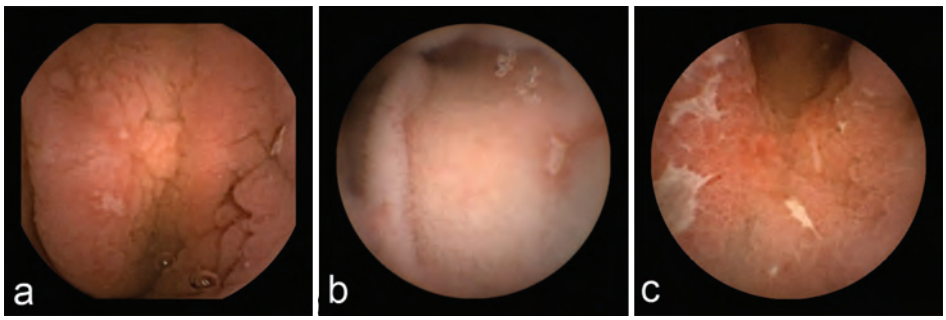

Figure 6.5: Video capsule endoscopy images show examples erosion and ulcers. (a) Small erosion in the proximal jejunum of a 41-year-old woman with uncomplicated CD. (b) Small isolated ulcer in the proximal jejunum of a 74-year-old man with RCD II. (c) Multiple ulcers in the proximal jejunum of a 67-year-old man with RCD I. This patient fulfilled the endoscopic criteria for ulcerative jejunitis.

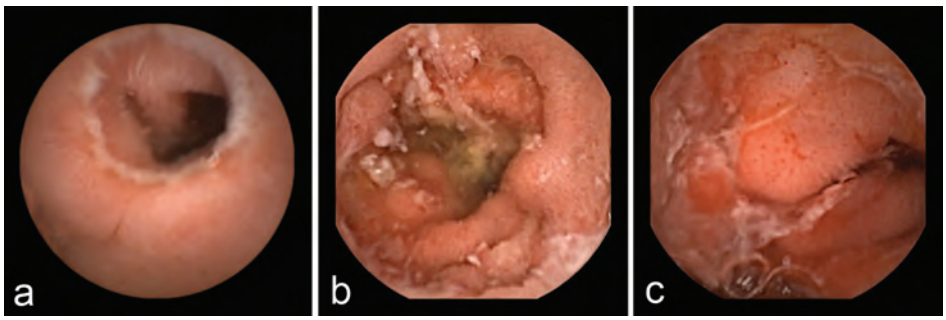

Figure 6.6: Video capsule endoscopy images show examples of small-intestinal strictures. (a) Short, web-like stricture in the jejunum of a 59-year-old woman with RCD I, probably caused by NSAIDs. (b) Diffuse narrowing of the lumen of the proximal jejunum a 64-year-old woman with RCD II.

inflammatory drug (NSAID) use, in 2 patients with RCD II, who both had ulcerative strictures, and in all patients with EATL, of whom 2 had stricturing EATL. In one patient with EATL, no apparent cause for nonprogression was established.

Discussion

Establishing a cause for nonresponsive CD has important prognostic and therapeutic consequences. In general, exclusion of malignancy as cause of nonresponsive CD is required in patients with severe symptoms and can be performed using cross-sectional imaging, ^{18}F-fluorodeoxyglucose positron emission tomography, and/or DBE.[3, 15] Subclassification of RCD using lymphocyte phenotyping is a time-consuming procedure that is only available in a limited number of centres.[10] Because of this complex diagnostic pathway, we investigated VCE, which is widely available and well tolerated modality.

Table 6.2: Comparison of indications for VCE, complete small-bowel visualisation, capsule retention, capsule transit times and findings according to final diagnosis.

Finding	Uncomplicated CD (n = 22)	RCD I (n = 12)	RCD II (n = 11)	Enteropathy- associated T-cell lymphoma (n = 3)
Main indication				
Weight loss	2 (9.1)	3 (25.0)	5 (45.5)	2 (66.7)
Diarrhoea	12 (54.5)	7 (58.3)	4 (36.4)	1 (33.3)
Abdominal pain	5 (22.7)	1 (8.3)	2 (18.2)	0 (0.0)
Anaemia	1 (4.5)	1 (8.3)	0 (0.0)	0 (0.0)
Other	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Technical details				
Capsule retention*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Caecum reached within battery-lifetime	20 (90.9)	9 (75.0)	9 (81.8)	0 (0.0)
Gastric transit time (min), mean ± SD	41 ± 46	31 ± 21	45 ± 43	53 ± 30
Small-bowel transit time (min), mean ± SD†	279 ± 83	324 ± 136	281 ± 58	—
Findings proximal small intestine‡				
Abnormal villi	17 (77.3)	9 (25.0)	10 (90.0)	3 (100.0)
Mosaic pattern	5 (22.7)	2 (16.7)	7 (63.6)	2 (66.7)
Fissures	14 (63.6)	6 (50.0)	10 (90.0)	3 (100.0)
Scalloping folds	13 (59.1)	7 (58.3)	9 (81.8)	2 (66.7)
Erythema	2 (9.1)	6 (50.0)	8 (72.7)	3 (100.0)
Erosions and/or ulcers	4 (18.2)	3 (25.0)	7 (63.6)	2 (66.7)
Strictures	0 (0.0)	3 (25.0)	4 (36.4)	1 (33.3)
Mass	0 (0)	1 (8.3)	0 (0.0)	0 (0.0)
Findings distal small intestine§				
Visualized	22 (100.0)	11 (91.7)	9 (81.8)	0 (0.0)
Abnormal villi‖	5 (22.7)	3 (27.3)	6 (66.7)	—
Mosaic pattern‖	1 (4.5)	1 (9.1)	3 (33.3)	—
Fissures‖	4 (18.2)	3 (27.3)	5 (55.6)	—
Scalloping folds‖	4 (18.2)	2 (18.2)	5 (55.6)	—
Erythema‖	3 (13.6)	2 (18.2)	4 (44.4)	—
Erosions and/or ulcers‖	2 (9.1)	2 (18.2)	4 (44.4)	—
Strictures‖	0 (0.0)	1 (9.1)	1 (11.1)	—
Mass‖	0 (0.0)	0 (0.0)	0 (0.0)	—

Note: Unless otherwise indicated, numbers indicate number of patients, with percentages between parentheses.
* Defined as having a capsule endoscope remain in the digestive tract for a minimum of 2 weeks or as the capsule remaining in the bowel lumen unless directed medical, endoscopic, or surgical intervention was instituted.
† Calculated for the 40 studies in which the caecum had been reached during battery-lifetime.
‡ Defined as the part of the small intestine depicted in the last ¾ of the total small-bowel transit time in case of complete examinations. In case of incomplete VCE examinations we defined the proximal small intestine as the part depicted two hours after passage of the pylorus.
§ Defined as the part of the small intestine depicted in the last ¾ of the total small bowel transit time in case of complete examinations. In case of incomplete VCE examinations we defined the proximal small intestine as the part depicted two hours after passage of the pylorus.
‖ Percentage of examinations in which the distal small bowel was depicted.

Table 6.3: Details on erosive and ulcerative lesions diagnosed in the study group.

Video capsule endoscopy findings	Uncomplicated CD (*n* = 22)	RCD I (*n* = 12)	RCD II (*n* = 11)	Enteropathy-associated T-cell lymphoma (*n* = 3)
Number of erosions				
None	18 (81.8)	9 (75.0)	5 (45.5)	1 (33.3)
1–2	3 (13.6)	1 (8.3)	1 (9.1)	1 (33.3)
3–9	0 (0.0)	2 (16.7)	4 (36.4)	0 (0.0)
≥ 10	1 (4.5)	0 (0.0)	1 (9.1)	1 (33.3)
Size of erosions				
5 mm	4 (100.0)	3 (100.0)	6 (100.0)	2 (100.0)
6–9 mm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 mm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of ulcers				
None	20 (90.9)	9 (75.0)	4 (36.4)	1 (33.3)
1–2	1 (4.5)	1 (8.3)	6 (54.5)	0 (0.0)
3–9	1 (4.5)	1 (8.3)	0 (0.0)	1 (33.3)
≥ 10	0 (0.0)	1 (8.3)	1 (9.1)	1 (33.3)
Size of ulcers				
≤ 5 mm	0 (0.0)	0 (0.0.)	0 (0.0)	0 (0.0)
6–9 mm	2 (100.0)	0 (0.0)	7 (100.0)	0 (0.0)
≥ 10 mm	0 (0.0)	3 (100.0)	0 (0.0)	2 (100.0)
Distribution of erosions and ulcers				
Proximal* and distal†	2 (40.0)	2 (66.7)	4 (57.1)	0 (0.0)
Proximal only	3 (60.0)	1 (33.3)	3 (42.9)	2 (100)
Distal only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Numbers indicate number of patients, with percentages between parentheses.
***** Defined as the part of the small intestine depicted in the first ¼ of the total small bowel transit time. In case of incomplete VCE examinations we defined the proximal small intestine as the part depicted within two hours after passage of the pylorus.
† Defined as the part of the small intestine depicted in the last ¾ of the total small bowel transit time in case of complete examinations. In case of incomplete VCE-studies we defined the proximal small intestine as the part depicted two hours after passage of the pylorus.

We found proximal focal erythema and absence of progression of the capsule to the distal small intestine during battery-lifetime were independently associated with the presence of RCD II and EATL, and were also associated with increased mortality. In our opinion, the finding of either one of these features warrants further (endoscopic) small-intestinal evaluation. Disturbances in gastrointestinal motility in patients with CD are well documented. Therefore, reduced motility might have contributed to this observation.[30] The high prevalence of EATL in patients with transit abnormalities during VCE justifies further endoscopic evaluation. None of the patients who underwent VCE

Table 6.4: Comparison of video capsule endoscopy findings between patients with either uncomplicated CD or RCD I, and patients with RCD II or enteropathy-associated T-cell lymphoma.

Video capsule endoscopy findings	Uncomplicated CD or RCD I (*n* = 34)	RCD II or EATL (*n* = 14)	*P* value univariate analysis
Proximal small intestine*			
Abnormal villi	26 (76.5)	13 (92.9)	0.250
Mosaic pattern	7 (20.6)	9 (64.3)	0.006
Fissures	20 (58.8)	13 (92.9)	0.037
Scalloping folds	20 (58.8)	11 (78.6)	0.320
Erythema	8 (23.5)	11 (78.6)	< 0.001
Erosions and/or ulcers	7 (20.6)	9 (64.3)	0.006
Strictures	3 (8.8)	6 (42.9)	0.012
Mass	1 (2.9)	0 (0.0)	1.00
Distal small intestine†			
Visualized	33 (97.1)	9 (64.3)	0.006
Abnormal villi‡	8 (24.2)	6 (66.7)	—
Mosaic pattern‡	2 (6.1)	3 (33.3)	—
Fissures‡	7 (21.2)	5 (55.6)	—
Scalloping folds‡	6 (18.2)	5 (55.6)	—
Erythema‡	5 (15.2)	4 44.4)	—
Erosions and/or ulcers‡	4 (12.1)	4 (44.4)	—
Strictures‡	1 (3.0)	1 (11.1)	—
Mass‡	0 (0.0)	0 (0.0)	—

Note: Unless otherwise indicated, numbers indicate number of patients, with percentages between parentheses. EATL = enteropathy-associated T-cell lymphoma.
* Defined as the part of the small intestine depicted in the first ¼ of the total small bowel transit time. In case of incomplete VCE-studies we defined the proximal small intestine as the part depicted within two hours after passage of the pylorus.
† Defined as the part of the small intestine depicted in the last ¾ of the total small bowel transit time in case of complete studies. In case of incomplete VCE-studies we defined the proximal small intestine as the part depicted two hours after passage of the pylorus.
‡ Percentage of studies in which the distal small bowel was depicted.

for nonresponsive CD had clinical signs suggestive of intestinal stenosis. Patients who have such signs primarily undergo MR enteroclysis in our centre. Without such a policy, we suspect the retention rate would have been much higher than we observed.

Focal erythema has not been identified previously as a feature associated with RCD II or EATL. It is likely that erythema represents ongoing mucosal inflammation.[31-33]. We are aware that qualifications of mucosal colour can be subjective.

It is important to stress that we only included capsule examinations of patients with established CD. Therefore, proximal focal erythema and absence of nonprogression to the distal small intestine are only indicative of a poor prognosis in this selected population.

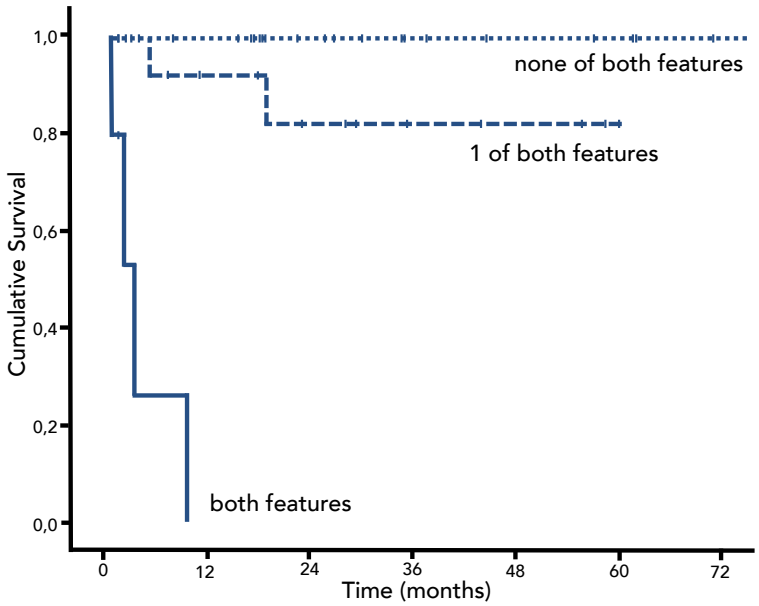

Figure 6.7: Survival by Kaplan-Meier method according to the presence of proximal focal erythema and/or non-progression of the capsule to the distal small intestine. + = censored.

These findings are rather nonspecific, and should not be translated to more general populations without established CD.

VCE has been investigated in patient with nonresponsive CD previously. Daum and co-workers reported the findings of VCE examinations performed in 14 patients with RCD, subclassified as RCD I or RCD II according to the same diagnostic criteria we used.[17] Interestingly, the VCE examination was incomplete in 4 of the 14 patients which is comparable to the 23.1% incidence of incomplete VCE examinations we observed. Although the only VCE features studied by Daum were villous atrophy, ulcerations and tumour, most abnormalities were encountered in the proximal small bowel, as did we observe in our series.

Culliford and colleagues performed VCE in 47 patients with possible complicated CD, but analysed the results of VCE according to indication, rather than to final diagnosis.[16] In the subgroup of patients with persisting abdominal pain, weight loss and/or diarrhoea, villous atrophy, mosaic pattern, fissures and ulcers were found at comparable rates as in our series. In one patient with a stricture nonprogression to the distal small intestine was observed, but did not lead to capsule retention. Overall, despite the different angle of observation, the conclusion of the study from Culliford and co-workers, that VCE has a high yield in patients with CD that is complicated by persistent symptoms, is confirmed by our series.

Maiden and co-workers studied a group of 19 patients with persisting symptoms despite a gluten-free diet.[18] VCE findings were described in more general terms like mild-moderate and moderate-severe, making comparisons with our results difficult. Additionally,

the main study aim was to correlate VCE findings with the Marsh-classification, and not to correlate VCE findings with a cause for the persisting symptoms. Eight patients had normal small-intestinal histology, so the proportion of patients with potential RCD was most likely lower than in our study.

Recently, Atlas and co-workers described VCE findings in 42 patients with nonresponsive CD and compared them with patients with uncomplicated CD and CD-free controls.[34] No further details were provided regarding the cause for nonresponsive CD. Villous atrophy was present in 31% of the nonresponsive patients and in 47% of patients with uncomplicated CD, demonstrating that this feature is not associated with lack of response. Additionally, erosions or ulcerations were present in 19% of patients with nonresponsive CD, and in 31% of patients with uncomplicated CD, which suggest ulceration is not a specific sign of nonresponsive CD. These findings were confirmed by our study. In contrast, we did not find a clear relation between the use of NSAIDs and erosive or ulcerative lesions in patients with CD.

The finding that distal small-intestinal findings are of limited value in the management of CD was recently described by Collin and co-workers as well.[35] Although capsule results are presented in more general terms than in our study and the interpretation of capsule examinations and the management of patients were not uniformly in this study, it is of great interest that the results of VCE altered the management in 9 of the 33 patients with RCD. A sub-classification of RCD was not made.

We realise that the generalizability of our results is limited by the relatively small number of patients and by the fact that it was performed in a tertiary referral centre, with a very high incidence of RCD. One might argue that peroral DBE, combined with flowcytometry, could be preferred over VCE as the initial investigations in nonresponsive CD. However, most patients with nonresponsive CD will have other causes than RCD II or EATL for their persisting symptoms. Therefore, with such a strategy, many patients with a low a priori risk of having RCD II or EATL will be exposed to expensive, non-widely available invasive examinations to exclude rare complications of CD. If our results are confirmed in larger studies, VCE could be of use to select patients who require more invasive examinations, and to reassure patients with benign causes for persisting symptoms.

The retrospective design of our study very likely resulted in a selection bias in favour of older patients with more severe symptoms, which are the patients with the highest risk of having RCD II or EATL. Because we do not perform VCE in the presence of signs or symptoms suggesting small-bowel stenosis, our findings are only applicable to patients without clear signs of small-intestinal obstruction. Additionally, our study suffers from a verification bias, because DBE was performed in all patients who eventually were diagnosed with RCD II or EATL, but only in 14.6% of patients with uncomplicated CD and 33.3% of the patients with RCD I. Most of the patients with a form of complicated CD were on immunosuppressive or immunomodulating drugs. If fact, VCE examinations were frequently performed because of deterioration despite medical therapy. Although we did not study the effect of medical therapy on mucosal healing, it is likely that intestinal damage is more extensive in patients who had not yet received specific therapy.

Prospective multicentre studies to establish the value of VCE in patients with nonresponsive CD, are needed. Such studies should include measurements of intra- and interobserver agreement of pre-defined features. Because in our, but also in other studies on this subject, almost all relevant findings were observed in the proximal small intestine, future research should include comparisons with push enteroscopy and device-assisted enteroscopy, which have the additional benefit of obtaining biopsy specimens, and therefore might be one-stop-shop-investigations in suspected RCD.

In conclusion, VCE is a minimally-invasive endoscopic modality that could be of use in identifying patients with nonresponsive CD who require urgent and intensive medical treatment.

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