Clinically Significant Small Bowel Crohn's Disease Might Only be Detected by Capsule Endoscopy

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Background: In Crohn's disease (CD) a small bowel study—in addition to colonoscopy—is considered necessary for diagnosis/staging. In this study we re-examined the role of capsule endoscopy (CE), colonoscopy, imaging tests [magnetic resonance enterography/computed tomographic enterography (MRE/CTE)], and inflammatory markers [fecal lactoferrin and C-reactive protein (FL/CRP)] in CD patients who had undergone intestinal resection and in those who never had surgery.

Methods: In this retrospective study 43 consecutive patients underwent CE because of staging/symptoms unexplained by colonoscopy/imaging. We compared colonoscopy, imaging, and FL/CRP with CE and evaluated the impact of the latter on clinical management and outcomes.

Results: In patients who never had surgery imaging was negative with a positive CE in 8/15 (53%) of cases. Colonoscopy was insufficient for disease staging in 10/20 (50%) cases. CRP and FL were normal with a positive CE in 35% and 28% of cases, respectively. CE findings changed the management in 6/20 (30%) of cases, with 83% showing clinical/biochemical improvement after up to 15 months of follow-up. In postoperative patients CE was positive with negative imaging in 6/8 (75%) cases. Colonoscopy was insufficient for disease staging in 13/22 (59%) cases. CRP and FL were normal in 42% and 31.8% of patients with positive CE. In these patients CE findings changed the management in 12/23 (52%) cases with 83% of them showing clinical/biochemical improvement after up to 18 months of follow-up.

Conclusions: Omitting CE from diagnostic/staging algorithms in CD tends to underdiagnose clinically significant small bowel lesions, thus impacting on patients' management and outcomes.

Key Words: capsule endoscopy, Crohn's disease, colonoscopy, magnetic resonance enterography, computed tomographic enterography, postoperative recurrence, Rutgeerts score.

INTRODUCTION

Diagnosing and staging Crohn's disease (CD) is of paramount importance before planning management and therapy.[1] Disease staging includes information on location, extent, and severity – key elements of disease burden that is in turn the main determinant of medical therapy.[2] Currently, disease location in CD is mostly evaluated by ileocolonoscopy – which appears capable of correctly diagnosing ≥90% of cases.[3] However, since the disease can also involve the entire digestive tract, an imaging study of the small bowel should also be performed. Imaging techniques commonly used to diagnose CD of the small bowel are the traditional small bowel enteroclysis (SBE) and small bowel follow through (SBFT), computed tomographic enterography (CTE), and magnetic resonance enterography (MRE). Less frequently used is the small intestine contrast ultrasonography (SICUS), since it requires a high degree of individual expertise.[4, 5] Due to the absence of ionizing radiations, the capability of differentiating inflammation from fibrosis similar to that of CTE, a possible superiority in defining penetrating disease and a sensitivity as high as SBE in identifying intestinal strictures, MRE is considered the gold standard to identify and define small bowel CD.[6] Furthermore, MRE is considered the best predictor of findings at surgery.[7]

Capsule endoscopy (CE) is a noninvasive imaging technique that has been used in the initial diagnosis of CD in cases of high suspicion despite a negative endoscopy/imaging test. Although the sensitivity of CE for small bowel lesions appears superimposable or superior to that of CTE and MRE, it has been considered less specific, especially for initial CD diagnosis[8] due to its lack of tissue collection capabilities. Furthermore, a suspicion of small bowel stricture—a frequent complication of CD[9] — is a contraindication and often a deterrent to perform CE. Indeed, recent guidelines do not include CE among the techniques considered useful to diagnose CD before or after surgery.[6, 10] Thus, as of today MRE is usually considered the gold standard for initial small bowel CD diagnosis/staging.[6]

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After "curative" resection CD relapse [or postoperative recurrence (POR)] is believed to take place immediately proximally to the anastomosis. Since surgery most often involves the terminal ileum and the right colon, the anastomosis and the neoterminal ileum can be easily reached by colonoscopy, which is considered the best test to diagnose endoscopic recurrence. In this context, mucosal inflammation has been traditionally evaluated by the Rutgeerts score- which is considered a strong predictor of clinical recurrence.[11]

In this retrospective study we have reexamined the role of CE and the other imaging tests in diagnosing small bowel disease in CD patients who have undergone intestinal resection and in those who never had surgery. We reviewed the clinical records of 43 consecutive CD patients who had undergone CE and colonoscopy and/or imaging studies and/or blood/stool markers of inflammation in our institution in the past 2 years because of a specific clinical indication. We compared the different diagnostic tools with each other and evaluated the impact of these findings on the patients' clinical management and outcomes.

METHODS AND PATIENTS

We reviewed 43 consecutive CD patients followed at our medical center from June 2015 to June 2017. To be included in the study patients had to be >16 years old, have had a CE and a colonoscopy and/or an imaging study performed within 2 months of each other for a specific clinical indication during the study period. Patients with known use of nonsteroidal anti-inflammatory drugs (NSAID's) on a regular basis or with GI diseases other than CD (such as celiac disease, intestinal infections, food allergies) were excluded. Data collected included smoking history, known CD location, disease type, number of surgeries (resections) performed for treatment of CD, and medications. We examined reports, images, and videos from colonoscopy, CE, and CTE/MRE. Relevant laboratory parameters including C-reactive protein [(CRP) in-house assay], fecal lactoferrin (FL), (TechLab, Blacksburg VA)—both also performed within 2 months of CE—and pathology data from endoscopic biopsies or surgical specimen also were reviewed. Finally, we reviewed the impact of CE results on patients' management (ie, initiation of new therapy, dose change of current medications) and clinical outcomes including improvement/resolution of symptoms and improvement/normalization of markers of inflammation after follow-up.

In patients with small bowel lesions at CE and negative imaging tests we defined the imaging tests as discordant after exclusion of other potential causes for the findings— including recent NSAID's use and inaccurate imaging reading. In particular, in all cases of discrepancy the radiology images were carefully reexamined together with the specialist radiologist – who was blinded to the results of the colonoscopy and CE. Lesions present at CE and imaging but significantly different in location, extent, or severity were also defined discordant. Stool FL and CRP were reported discordant when values were within normal range in patients with positive CE findings or elevated in patients with negative CE findings. We did not attempt to correlate disease extent/severity with either FL or CRP values – rather, we only used the standard laboratory upper limit.

Colonoscopy was defined as discordant from CE when insufficient (in and by itself) to properly stage the disease. As defined here, "postsurgical patients" were those with an anastomosis that could be reached by colonoscopy – mostly undergone typical ileocolectomy or ileocecectomy – since the goal was to capture postoperative recurrence. Patients who had intestinal resection in the past but in whom the anastomosis could not be reached by colonoscopy (ie, when it was in the small bowel) were included in the nonsurgical group.

CE was performed with the Pill-Cam SB capsule preceded by the Agile patency capsule (Medtronic, Minneapolis, MN). The passage of the latter had to be verified by the patient or by abdominal x-ray performed 30 hours after the capsule ingestion per manufacturer recommendations.

Statistical Analysis

Presence, extent, and severity of lesions in the small bowel as evaluated by CE, colonoscopy, and/or CTE or MRE are the principal qualitative and quantitative variables in this study. Discordance in findings between CE and the other modalities including colonoscopy, imaging, and inflammatory markers were examined by descriptive analysis. Potential factors that may be associated with discordant findings were evaluated with multivariable regression or Cox regression. Factors taken into consideration included: FL (normal/elevated); CRP (normal/elevated), age (< 40 vs > 40 years), sex, smoking (yes/no/former), disease location, disease type, therapy (yes/no), resection margins (for patients undergone surgery: clear/involved), time to surgery (0–12; 13–24; > 24 months), and Rutgeerts score. Level of significance was interpreted with $\alpha \leq 0.05$ for all analyses.

A power analysis was not conducted since this was a pilot, proof-of-concept study aimed to confirm the hypotheses that: (1) CE might be superior to all the other imaging tools and markers of inflammation in diagnosing small bowel lesions in CD; and (2) that diagnosis of these lesions might impact the medical management of the disease. The study was approved by our Institutional Review Board.

RESULTS

Table 1 shows the demographic and clinical features of the patients included in the study. We enrolled a total of 43 patients, 25 of whom had surgery in the past (23 with an anastomosis that could be reached by colonoscopy – see Methods). The majority were nonsmokers, with the disease known (before performing CE) to be located in most patients in the terminal ileum and being mostly inflammatory (B1) at time of diagnosis according to the Montreal classification.[12] Approximately

TABLE 1: Demographic and Clinical Characteristics of CD Patients

Gender (males – females)	(23 – 20)
Mean age (SD)	40 (14.7)
Smoker (Current, former, never %)	(18, 38, 44)
CD location (%)	
L1: ileal	56
L2: colonic	10
L3: ileocolonic	30
L4: isolated upper digestive	4
CD behavior (%)	
B1: nonstricturing, nonpenetrating	58
B2:stricturing	31
B3: penetrating	11
Surgery yes (once, twice %) – no	25 (88, 12) - 18
Therapy at time of CE (%)	
None	51
5-ASA	5
Steroids	2
Immunomodulators	5
Anti-TNF agents	41

one-half of the patients were not on any therapy at the time the CE was performed with the remaining being mostly on anti-tumor necrosis factor (TNF) agents.

Table 2 shows the results for CD patients who either did not undergo surgery or had an intestinal resection (n = 2) leading to an anastomosis that could not be reached by colonoscopy (ie, in the small bowel–see Methods). CE and colonoscopy were performed in all these patients (n = 20). Imaging, stool FL, and CRP were performed in 15/20, 18/20, and 17/20, respectively. The large majority of these patients underwent CE for disease staging or restaging after negative colonoscopy and imaging tests in the presence of symptoms suggestive of active disease. In this group of patients imaging was discordant with CE in 8/15 cases (53.3%) with MRE discordant in 6/8 cases and CTE discordant in 2/8 cases. Colonoscopy would have been insufficient to stage the disease in 10/20 cases (50%). FL values were discordant with CE in 7/18 cases (38.8%) and CRP in 8/17 cases (47%). In 2 cases both FL and CRP were elevated in the presence of a negative CE and colonoscopy. However, biopsies of the terminal ileum in these patients showed inflammation. Hence lactoferrin and CRP were normal in the presence of a positive CE in 28% and 35% of cases, respectively. Overall in this group performing CE led to a change in clinical management in 6/20 cases (30%) – with all 6 patients starting biologics because of the clinical symptoms and significant lesions found in the small bowel on CE. Of these patients 5/6 (83%) had an improvement/resolution of symptoms and of the markers of inflammation (if initially elevated) after a follow-up time of 3 months to 15 months (Table 2). The sixth patient—after initially agreeing to start infliximab—refused treatment.

Table 3 shows the results for CD patients who underwent resection resulting in an anastomosis that could be reached by colonoscopy. In this group, CE was performed in all patients (n = 23) whereas colonoscopy was performed in 22/23, imaging in 8/23, FL in 22/23, and CRP in 19/23. Most patients underwent CE after negative colonoscopy and/or imaging tests in the presence of symptoms suggestive of active disease/relapse. In postoperative patients imaging was discordant with CE in 6/8 (75%) cases – (3/3 CTE and 3/5 MRE). Colonoscopy by itself (using the traditional Rutgeerts score) would have missed significant lesions in 13/22 cases (59%). Figure 1 illustrates images representative of the results of CE and colonoscopy (neoterminal ileum) in individual CD patients in this group. FL was discordant with CE in 7/22 cases (31.8%), whereas CRP was discordant in 8/19 cases (42%). Overall using CE in postoperative patients changed the disease management in 12/23 cases (52%). In most cases a biologic was initiated or the dose of the medication was increased. In these patients therapy resulted in improvement of symptoms and markers of inflammation (if initially elevated) in 10/12 (83%) cases after a follow-up time of 6 months to 18 months (Table 3). In 1 patient subjective symptom improvement was not associated with normalization of inflammatory markers. One additional patient died of unrelated causes.

We next evaluated potential factors (as listed in "Methods") that may be associated with findings discordant with CE. However, no significant associations were found on multivariable regression.

DISCUSSION

By contrast with ulcerative colitis (UC) – which only affects the colon – CD can also affect the upper GI tract and the small bowel. The latter is difficult to explore – which is one of the reasons why CD diagnosis is often delayed compared to UC.[13]

It has been known for some time[14] that in CD, CE can detect small bowel lesions otherwise undetected by other imaging techniques and that postoperative lesions can be present in the small bowel proximally to the reach of the colonoscope.[15–17] However, as of now CE is mostly used in known or suspected CD patients in whom the clinical features are not explained by colonoscopy or imaging studies.[10] Indeed, at the present time MRE is considered the gold standard for initial small bowel CD diagnosis/staging.[6] In postoperative CD—since resection is supposed to completely remove the diseased intestine and since most often it involves the terminal ileum and the right colon—the colonoscope can easily reach the anastomosis and the neoterminal ileum (the only sites were relapse is believed to take place). Hence ileocolonoscopy is considered the best diagnostic test to diagnose postoperative

TABLE 2: Colonoscopy, Imaging, CE, and Inflammatory Markers in CD Patients

Pt #	Ileocolonoscopy	Imaging$_a$ (CTE/MRE)	CE	Clinical indication for CE	Lactoferrin/CRP$_b$ (μg/mL / mg/dL)	Discordance with CE	Clinical Impact	Outcome (followup time)
1	Normal	ND	Normal	Initial disease staging	163/3	No	No	
2	Normal	Normal CTE	Normal	Initial disease staging	WNR/WNR	No	No	
3	Normal	Normal MRE	Multiple ulcers distal ileum	Disease re-staging. Abdominal pain and diarrhea	15/WNR	MRE. CRP. Colonoscopy (insufficient staging)	Started biologic (infliximab)	Symptoms improved (3 months)
4	Normal	ND	Normal	Abdominal pain	36/2.6	Lactoferrin. CRP	No	
5	Normal	Normal MRE	Small ulcerations in the proximal small bowel	Therapy monitoring (adalimumab)	WNR/1.25	MRE. Lactoferrin. Colonoscopy (insufficient staging)	No	
6	Normal	Normal MRE	Diffuse ulcerations throughout the small bowel	Disease restaging. Had stopped therapy	WNR/WNR	MRE. Lactoferrin. CRP. Colonoscopy (insufficient staging)	Started biologic (vedolizumab – intolerant to anti-TNF agents)	Symptoms improved but return 2 weeks before infusion. Lactoferrin/CRP: WNR. (8 months)
7	Transverse and descending colon inflammation	Transverse and descending colon inflammation at CTE	Normal	Disease restaging.	165/4.28	No	No	
8	Tiny ulcerations in the terminal ileum	ND	Few tiny ulcerations in the terminal ileum	Abdominal pain	10/WNR	No	No	
9	Essentially normal (one aphthous ulcer terminal ileum)	Normal MRE	Few large ulcerations in the ileum	Disease restaging	94/WNR	MRE. CRP. Colonoscopy (insufficient staging)	Started biologic (certolizumab)	No symptoms. Lactoferrin: 45. CRP: WNR. (3 months)
10	Mild terminal ileum inflammation and friability	Normal CTE	Ulcerations in duodenum, jejunum, and terminal ileum	Abdominal pain and diarrhea	WNR/ND	CTE. Lactoferrin. Colonoscopy (insufficient staging)	Started biologic (adalimumab)	Symptoms improved (3 months)
11	Mild terminal ileum inflammation and friability	Normal MRE	Extensive diffuse ulcerations throughout the small bowel	Initial disease staging – presenting with pain	434/5.11	MRE. Colonoscopy (insufficient staging)	Started biologic (adalimumab)	Symptoms improved-return before injection. Lactoferrin: 9.9. CRP: WNR. (15 months)
12	Pancolitis with superficial ulcerations	Normal MRE	Normal	Disease staging	524/WNR (had colitis)	No	No	

TABLE 2: Continued

Pt #	Ileocolonoscopy	Imaging[a] (CTE/MRE)	CE	Clinical indication for CE	Lactoferrin/CRP[b] (µg/mL / mg/dL)	Discordance with CE	Clinical Impact	Outcome (followup time)
13	Normal	Normal MRE	Normal	Disease restaging. Abdominal pain.	61/0.45	Lactoferrin.CRP.	No	
14	Anorectal disease	Normal MRE	Normal	Disease restaging. Perianal disease	WNR/WNR	No	No	
15	Normal	CTE: Stricturing and skip areas in the distal ileum, no inflammation	Single ulcer and multiple erosions in the distal ileum	Abdominal pain and diarrhea	ND/WNR	CTE (partial). CRP. Colonoscopy (insufficient staging)	No	
16	Normal colonoscopy. Terminal ileum could not be intubated	Terminal ileum inflammation	Deep terminal ileum ulcerations	Abdominal pain	22/1.48	No	No	
17	Normal	ND	Erosions and one ulceration in distal ileum	Abdominal pain	WNR/ND	Lactoferrin. Colonoscopy (insufficient staging)	No	
18	Apthous ulcers in the terminal ileum	ND	Ulcers in distal ileum and proximal small bowel	Initial disease staging	16/WNR	CRP. Colonoscopy (insufficient staging)	No	
19	Normal	Normal MRE	Duodenal erosions	Restaging	ND	No	No	
20	Mild terminal ileum inflammation and friability	Mild terminal ileum inflammation and friability	Ulcerations in the distal ileum and proximal small bowel	Initial disease staging	WNR/WNR	MRE. Lactoferrin. CRP. Colonoscopy (insufficient staging)	Initially agreed to start biologic (adalimumab)	Has later refused treatment

[a]Imaging results are reported relatively to bowel findings
[b]Lactoferrin upper limit: 7.24 µg/mL; CRP upper limit: 0.45 mg/dL.
WNR: within normal range
ND:not done

TABLE 3: Colonoscopy, Imaging, CE and Inflammatory Markers in Postoperative CD Patients

Pt #	Surgery Type	Time from Surgery (months)	Post op Ileocolono-scopy	Postop Imaging CTE/ MRE[a]	Clinical indication for CE	Postop CE Findings	Post-op lactoferrin/ CRP[b] (µg/ mL / mg/dL)	Discordance with CE	Clinical impact	Outcome (fol-low- up time)
1	Ileocecectomy	2	Rutgeerts score 3	ND	Evaluation of POR	Terminal ileum and midbowel ulcerations	38/1.2	Colonoscopy (insufficient staging)	Started biologic (infliximab)	Lactoferrin/ CRP: WNR (6 months)
2	Ileocolectomy	24	Rutgeerts score 1	ND	Therapy monitoring (adali-mumab)	Duodenal, jejunal and ileal ulcerations	9.8/2.9	Colonoscopy (insufficient staging)	Increased dose of biologic (adalimumab weekly)	Lactoferrin/ CRP: WNR (7 months)
3	Ileocolectomy	18	Rutgeerts score 0	ND	Abdominal pain	Distal ileum ulcerations	76/0.71	Colonoscopy (insufficient staging)	Started biologic (infliximab)	Symptoms resolved. Lactoferrin/ CRP: WNR (12 months)
4	Stoma closure after ileo-colectomy	6	Rutgeerts score 2	ND	Diarrhea	Distal ileum ulcerations	96/<0.40	CRP	No	
5	Extended ile-ocolectomy	10	Rutgeerts score 0	ND	Diarrhea	Distal ileum ulcerations - tiny	WNR/ WNR	Lactoferrin and CRP. Colonoscopy (insufficient staging)	No	
6	Procto-colectomy	132	Rutgeerts score 2	ND	Pain and diarrhea	Extensive ulcerations throughout the small bowel	WNR/WNR	Lactoferrin and CRP. Colonoscopy (insufficient staging)	Started biologic (infliximab)	Symptoms greatly improved. Lactoferrin/ CRP: WNR (7 months)
7	Ileocolectomy	24	Rutgeerts score 0	Normal MRE	Pain and diarrhea	Extensive ulcerations throughout the small bowel	WNR/WNR	Lactoferrin and CRP. MRE. Colonoscopy (insufficient staging)	Increased dose of biologic (weekly adali-mumab) then switched to ustekinumab	Symptoms improved after induc-tion and 1 mainten-ance dose (4 months)
8	Stoma closure after ileo-colectomy	16	Rutgeerts score 3	Normal MRE	Pain and diarrhea	Distal ileum ulcerations	40/0.95	MRE	No	
9	Stoma closure after ileo-colectomy	7	Rutgeerts score 2	ND	Pain and diarrhea	Erosions and ulcerations in jejunum and ileum	WNR/ WNR	Lactoferrin and CRP. Colonoscopy (insufficient staging)	Started biologic (infliximab)	Symptoms improved. Lactoferrin/ CRP: WNR (5 months)
10	Ileocolectomy	7	Rutgeerts score 0	ND	Diarrhea	Extensive ulcerations throughout the small bowel	7.8/1.1	Colonoscopy (insufficient staging)	Started biologic (infliximab)	Symptoms improved. Lactoferrin/ CRP: WNR (7 months)
11	Stoma closure after ileo-colectomy	4	Rutgeerts score 3	ND	Evaluation of POR	Extensive ulcerations throughout the small bowel	58/ND	No	No	
12	Ileocolectomy	24	Rutgeerts score 0	Normal MRE	Therapy monitoring (infliximab)	Normal	WNR/ND	No	No	

TABLE 3: Continued

Pt #	Surgery Type	Time from Surgery (months)	Post op Ileocolono-scopy	Postop Imaging CTE/ MRE[a]	Clinical indication for CE	Postop CE Findings	Post-op lactoferrin/ CRP[b] (μg/ mL / mg/dL)	Discordance with CE	Clinical impact	Outcome (follow- up time)
13	Total colectomy	14	Rutgeerts score 0 – has permanent stoma	ND	Evaluation of POR	Normal	WNR/ WNR	No	No	
14	Stoma closure after ileocolectomy and sigmoid resection	18	Rutgeerts score 4	ND	Therapy monitoring (adalimumab)	Extensive ulcerations throughout the small bowel	87/ WNR	No	No	
15	Ileocolectomy	5	Rutgeerts score 1	Normal CTE	Pain and diarrhea	Distal ileum ulcerations	WNR/ WNR	Lactoferrin and CRP. CTE. Colonoscopy (insufficient staging)	Started biologic (infliximab) Unresponsive. Switched to ustekinumab since did not respond to adalimumab presurgery	Unresponsive. Considering surgery (9 months)
16	Repeat ileal resection	36	Rutgeerts score 3	Normal CTE	Abdominal pain	Ulcerations in neo-TI	ND/WNR	CTE. CRP	No	
17	Ileo-cecectomy	1	ND	ND	Pain and diarrhea	Ulcerations and erosions throughout the small bowel	56/1.7	No	No	
18	Ileocolectomy	12	Rutgeerts score 2	ND	Evaluation of POR	Small ulcerations in neo-TI	WNR/ WNR	No	No	
19	Ileocolectomy	12	Rutgeerts score 1	Normal MRE	Pain and diarrhea	Normal	277/ND	No	No	
20	Ileocecectomy	30	Rutgeerts score 1	ND	Abdominal pain	Deep distal ileum ulcers	WNR/ WNR	Lactoferrin and CRP. Colonoscopy (insufficient staging)	Started biologic (adalimumab). Unresponsive. Switched to infliximab.	Partial symptom response. Interval decreased to 6 weeks (18 months)
21	Ileocolectomy	32	Rutgeerts score 1	Normal MRE	Abdominal pain	Mid- small bowel erosions and ulcerations	27/1.22	MRE. Colonoscopy (insufficient staging)	Started biologic (adalimumab)	Partial symptom response. Lactoferrin: 45. CRP: 1.5 (11 months)
22	Stoma closure after ileocolectomy	10	Rutgeerts score 2	ND	Abdominal pain	Multiple deep ulcers jejunum and ileum	6.9/2.2	Lactoferrin. Colonoscopy (insufficient staging)	Started biologic	Deceased for unrelated causes
23	Ileocolectomy	4	Rutgeerts score 1	Normal CTE	Abdominal pain	Multiple deep ulcers throughout the small bowel	22/ND	CTE. Colonoscopy (insufficient staging)	Started biologic (adalimumab)	Symptoms improved. Lactoferrin: WNR (7 months)

[a]Imaging results are reported relative to bowel findings
[b]Lactoferrin upper limit: 7.24 μg/mL; CRP upper limit: 0.45 mg/dL.
WNR: within normal range; POR: post-operative recurrence.
ND:not done

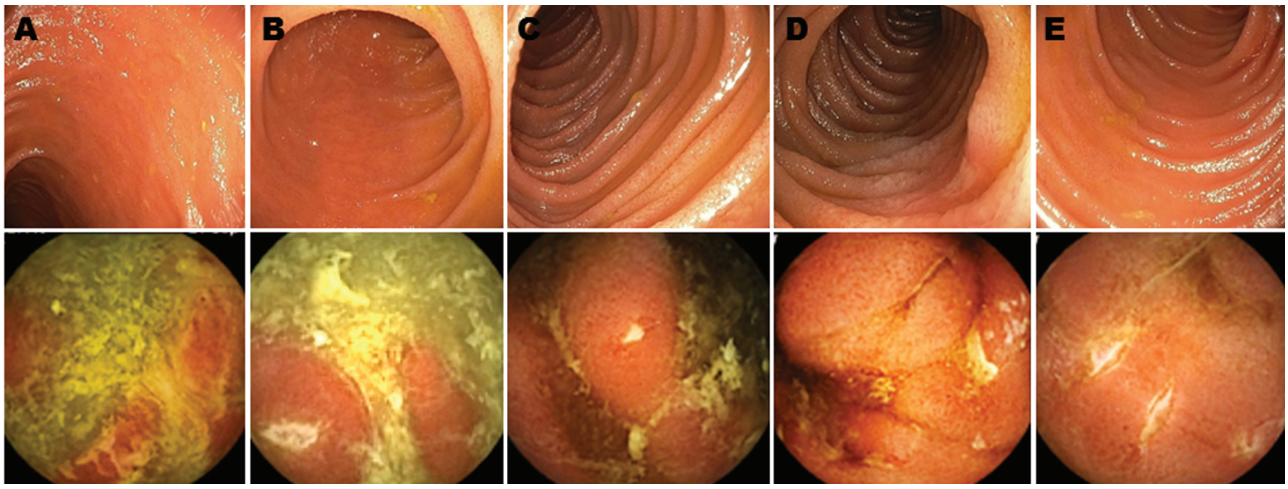

FIGURE 1. Colonoscopy (neo-terminal ileum, upper panels) and capsule endoscopy (lower panels) images in individual post-operative Crohn's disease patients. Rutgeerts scores were 1 (A and E) and 0 (B,C,D) – consistent with endoscopic remission - while capsule endoscopy demonstrated significant disease activity proximally to the reach of the colonoscope.

recurrence. However, it has been well known for a long time that up to 65% of patients operated on for CD have lesions of the small intestine detected by perioperative endoscopy, which were unrecognized by simple radiological imaging tests (small bowel series) before surgery in more than half of the cases.[18–20] Additional studies have shown that CE is more accurate than colonoscopy to diagnose POR[15] – except when lesions are truly limited to the neoterminal ileum.[16] Other studies have found that detection rates for recurrence are essentially similar in patients who have undergone CE, SICUS, and ileocolonoscopy.[21] Finally, another study has reported that MRE and endoscopy are equivalent in predicting clinical recurrence in CD patients after ileocolic resection.[22] To our knowledge, none has compared the yield of CE with MRE for the purpose of diagnosing POR.

In this retrospective study we tested the hypothesis that CE might identify clinically significant lesions otherwise unrecognized by imaging during CD staging or restaging for unexplained symptoms and that in postoperative patients ileocolonoscopy might not be sufficient to diagnose and stage the presence of disease after surgery. In the first group of patients imaging did not identify lesions seen at CE in > 50% of cases and colonoscopy by itself would have been insufficient to stage the disease also in 50% of cases. The inflammatory markers CRP and FL were not elevated in the presence of small bowel lesions identified by CE in 35% and 28% of cases, respectively. These results are very similar to those reported by Vijian et al in a retrospective study so far only published in abstract form.[23] Others have shown that up to 20% of patients with inflammatory findings at CE might have normal levels of fecal markers of inflammation.[24]

Overall, in our study CE led to a change in patient management in 30% of cases. In the large majority (83%) of these patients the initiation of therapy led to improvement in clinical symptoms and normalization of inflammatory markers (if initially elevated).

In postoperative patients CE identified small bowel lesions mostly unseen by imaging and importantly ileocolonoscopy by itself would not have diagnosed (or would have underestimated) the presence of disease in almost 60% of cases. CRP and FL in postoperative patients were within normal range in 42% and 31.8% of patients with small bowel disease at CE. Overall, in this group of patients CE findings changed the disease management in 50% of cases. In these patients therapy led to symptom improvement and marker level normalization (if initially elevated) in 83% of cases. However, regardless of these positive outcomes it should be pointed out that the presence of inflammation after "curative" surgery for CD is, in and by itself, an indication to start therapy to prevent clinical recurrence.[25] No significant associations were found between patients'/disease features and likelihood of discrepancy between CE and other tests. However, these results might reflect the relatively small sample size of this study. Whether the lesions identified in the small bowel after surgery represent true postoperative relapse[26] or were preexisting surgery as suggested by earlier studies[18] is not clarified by our findings. As shown in this and other studies,[27] the inflammatory markers might be within normal range in the presence of small bowel inflammation and hence they might not always be useful to raise the suspicion of persisting or relapsing disease.[28] Indeed, fecal markers should not replace the need for other tests, but rather serve as a complementary investigation.[29]

Hence, our study shows that current clinical practices and imaging tests tend to underdiagnose small bowel lesions in CD. This might cause a number of issues. First, the presence of inflammation in the small bowel impacts on the disease burden and might call for a therapeutic adjustment. Second, such lesions could be responsible for symptoms often attributed to "irritable bowel syndrome" (IBS) when colonoscopy and imaging tests are

completely normal and the disease is thought to be in remission.[30] By the same token, the lesions could also be responsible for postoperative symptoms, which are usually attributed to a number of unrelated causes (such as short bowel, inflammation caused by surgery, altered anatomy, adhesions, and bile salt diarrhea) – but not to active disease if colonoscopy and imaging tests are "normal". Finally, undetected small bowel lesions might significantly impact the results of clinical trials probing medications to treat or prevent postoperative relapse - since the endpoints often include colonoscopy and are based on the Rutgeerts score.[31]

This is a relatively small, single center, and retrospective study that was not originally designed to test the specific yield of the individual procedures/imaging tests. As such not all the tests were systematically performed in every patient and precisely at the same time. However the time lapse between CE and colonoscopy/imaging/markers was kept to a maximum of 2 months, thus minimizing the chance that lesions seen at CE represented disease progression.

CONCLUSIONS

In summary, CE in CD might add crucial clinical and mechanistic information to our present diagnostic algorithms and might greatly impact on CD clinical management. In addition, it has been recently shown that patients prefer and tolerate CE more than MRE.[32] Whereas preoperative CE should be done with caution (and always after a patency capsule has excluded the presence of strictures), postoperative CE is in principle a low risk technique if done early after surgery and could become the procedure of choice to diagnose POR in CD patients.

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REFERENCES

1. Benevento G, Avellini C, Terrosu G, et al. Diagnosis and assessment of crohn's disease: the present and the future. *Expert Rev Gastroenterol Hepatol*. 2010;4:757–66.
2. Sorrentino D, Nguyen V, Henderson C, et al. Therapeutic drug monitoring and clinical outcomes in immune mediated diseases: the missing link. *Inflamm Bowel Dis*. 2016;22:2527–37.
3. Dorn SD, Abad JF, Panagopoulos G, et al. Clinical characteristics of familial versus sporadic crohn's disease using the vienna classification. *Inflamm Bowel Dis*. 2004;10:201–6.
4. Kohli MD, Maglinte DD. CT enteroclysis in small bowel crohn's disease. *Eur J Radiol*. 2009;69:398–403.
5. Bruining DH, Siddiki HA, Fletcher JG, et al. Benefit of computed tomography enterography in crohn's disease: effects on patient management and physician level of confidence. *Inflamm Bowel Dis*. 2012;18:219–25.
6. Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis*. 2013;7:556–85.
7. Spinelli A, Fiorino G, Bazzi P, et al. Preoperative magnetic resonance enterography in predicting findings and optimizing surgical approach in crohn's disease. *J Gastrointest Surg*. 2014;18:83–90; discussion 90.
8. Leighton JA, Legnani P, Seidman EG. Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. *Inflamm Bowel Dis*. 2007;13:331–7.
9. Wiarda BM, Mensink PB, Heine DG, et al. Small bowel crohn's disease: MR enteroclysis and capsule endoscopy compared to balloon-assisted enteroscopy. *Abdom Imaging*. 2012;37:397–403.
10. Enns RA, Hookey L, Armstrong D, et al. Clinical practice guidelines for the use of video capsule endoscopy. *Gastroenterology*. 2017;152:497–514.
11. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of crohn's disease. *Gastroenterology*. 1990;99:956–63.
12. Satsangi J, Silverberg MS, Vermeire S, et al. The montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749–53.
13. Nguyen VQ, Jiang D, Hoffman SN, et al. Impact of diagnostic delay and associated factors on clinical outcomes in a U.S. inflammatory bowel disease cohort. *Inflamm Bowel Dis*. 2017;23:1825–31.
14. Petruzziello C, Onali S, Calabrese E, et al. Wireless capsule endoscopy and proximal small bowel lesions in crohn's disease. *World J Gastroenterol*. 2010;16:3299–304.
15. Pons Beltrán V, Nos P, Bastida G, et al. Evaluation of postsurgical recurrence in crohn's disease: a new indication for capsule endoscopy? *Gastrointest Endosc*. 2007;66:533–40.
16. Bourreille A, Jarry M, D'Halluin PN, et al. Wireless capsule endoscopy versus ileocolonoscopy for the diagnosis of postoperative recurrence of crohn's disease: a prospective study. *Gut*. 2006;55:978–83.
17. Kopylov U, Yung DE, Engel T, et al. Diagnostic yield of capsule endoscopy versus magnetic resonance enterography and small bowel contrast ultrasound in the evaluation of small bowel crohn's disease: systematic review and meta-analysis. *Dig Liver Dis*. 2017;49:854–63.
18. Lescut D, Vanco D, Bonnière P, et al. Perioperative endoscopy of the whole small bowel in crohn's disease. *Gut*. 1993;34:647–9.
19. Klein O, Colombel JF, Lescut D, et al. Remaining small bowel endoscopic lesions at surgery have no influence on early anastomotic recurrences in crohn's disease. *Am J Gastroenterol*. 1995;90:1949–52.
20. Flamant M, Trang C, Maillard O, et al. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in crohn's disease. *Inflamm Bowel Dis*. 2013;19:1390–6.
21. Biancone L, Calabrese E, Petruzziello C, et al. Wireless capsule endoscopy and small intestine contrast ultrasonography in recurrence of crohn's disease. *Inflamm Bowel Dis*. 2007;13:1256–65.
22. Koilakou S, Sailer J, Peloschek P, et al. Endoscopy and MR enteroclysis: equivalent tools in predicting clinical recurrence in patients with crohn's disease after ileocolic resection. *Inflamm Bowel Dis*. 2010;16:198–203.
23. Vijayan S, Yung DE, Suzuki H, et al. Correlation between small bowel MRI, faecal calprotectin and capsule endoscopy in the investigation of inflammatory bowel disease. *UEG Journal*. 2017;5(S1):A703.
24. Aggarwal V, Day AS, Connor S, et al. Role of capsule endoscopy and fecal biomarkers in small-bowel Crohn's disease to assess remission and predict relapse. *Gastrointest Endosc*. 2017 Sep 22. pii: S0016-5107(17)32273-3. doi: 10.1016/j.gie.2017.09.011. [Epub ahead of print].
25. Sorrentino D. State-of-the-art medical prevention of postoperative recurrence of crohn's disease. *Nat Rev Gastroenterol Hepatol*. 2013;10:413–22.
26. D'Haens GR, Geboes K, Peeters M, et al. Early lesions of recurrent crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*. 1998;114:262–7.
27. Sipponen T, Haapamäki J, Savilahti E, et al. Fecal calprotectin and S100A12 have low utility in prediction of small bowel crohn's disease detected by wireless capsule endoscopy. *Scand J Gastroenterol*. 2012;47:778–84.
28. Wright EK, Kamm MA, De Cruz P, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of crohn's disease after surgery. *Gastroenterology*. 2015;148:938–47.e1.
29. Schoepfer AM, Lewis JD. Serial fecal calprotectin measurements to detect endoscopic recurrence in postoperative crohn's disease: is colonoscopic surveillance no longer needed? *Gastroenterology*. 2015;148:889–92.
30. Morrison G, Van Langenberg DR, Gibson SJ, et al. Chronic pain in inflammatory bowel disease: characteristics and associations of a hospital-based cohort. *Inflamm Bowel Dis*. 2013;19:1210–7.
31. Regueiro M, Feagan BG, Zou B, et al.; PREVENT Study Group. Infliximab reduces endoscopic, but not clinical, recurrence of crohn's disease after ileocolonic resection. *Gastroenterology*. 2016;150:1568–78.
32. Lahat A, Kopylov U, Amitai MM, et al. Magnetic resonance enterography or video capsule endoscopy - what do crohn's disease patients prefer? *Patient Prefer Adherence*. 2016;10:1043–50.