



Detecting and Managing Small Bowel Crohn's Disease – Capsule Endoscopy Becoming a First Line Diagnostic Method?

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Abstract

Small bowel endoscopy is crucial for diagnosing small bowel Crohn's disease, and capsule endoscopy is complemented by balloon-assisted enteroscopy to take biopsies and by magnetic resonance imaging to visualize enteral and extra-intestinal involvement. Recently, imaging has also become a key instrument to manage Crohn's disease patients. Treatment control is advised for patients who have undergone bowel resections and is increasingly used to testify treatment success in non-operated patients, too. In this review we present the modern imaging methods to diagnose and to manage Crohn's disease with a special focus on the small bowel. Moreover, current knowledge on the impact of diagnostic methods on the patients' outcome is reported.

Keywords: Small bowel endoscopy; Capsule endoscopy; Crohn's disease

Abbreviations: AZA: Azathioprine; BAE: Balloon Assisted Enteroscopy; CD: Crohn's Disease; CE: Capsule Endoscopy; CT: Computed Tomography; CT-E: CT-Enteroclysis/Enterography; DBE: Double-Balloon Enteroscopy; IBDU: Unclassified type of Inflammatory Bowel Disease; IFX: Infliximab; MR-E: MR- Enteroclysis/Enterography; MRI: Magnetic Resonance Imaging; MTX: Methotrexate; NSAID: Non-steroidal Anti-inflammatory Drugs; SBE: Single-Balloon Enteroscopy; UC: Ulcerative Colitis

Introduction

Crohn's disease (CD) is a chronic inflammatory intestinal disorder that is characterized by episodes when symptoms flare up followed by periods of improvement and clinical remission. The disease is lifelong lasting and frequently manifests in the first decades of life. Clinical symptoms and well-being of the patient is associated to imaging findings of the mucosa and detection of inflammation seems to heavily impact on future prospects of the clinical course of the patient. Ongoing intestinal inflammation- even if subclinical-seems to be responsible for a debilitating course of the disease with involvement of intestinal strictures and/or occurrence of malnutrition due to reduced nutrient uptake. This may lead to a severely reduced quality of life [1]. The small bowel which is involved in at least 2/3 of the patients has a key role in developing dismal outcome and special attention in surveillance of the small bowel of CD patients might therefore be of high importance. Several options are available for imaging the small bowel, but diagnostics should ideally be without objection to repeat them, easily and promptly to apply, and without any side effects. Most of these requirements are satisfied by modern diagnostic and imaging techniques. Recently, also the small bowel has become easier to reach by diagnostic endoscopy, i.e. capsule endoscopy (CE), balloon-assisted enteroscopy (BAE), and spiral enteroscopy. High-quality cross sectional imaging completes diagnostic armamentarium, e.g. with using percutaneous ultrasound and magnetic-resonance imaging (MRI) (Figure 1).

We review the modern imaging methods to diagnose and to manage CD with a special focus on small bowel CD. Moreover, current knowledge on the impact of diagnostic methods on the patients' outcome is reported.

Endoscopic imaging in small bowel Crohn's disease

Video CE is an easy to administer and non-invasive investigation of the small bowel. After the passage of the intestinal tract the images acquired are reviewed by a specialist. Online visualization of the

endoscopic procedure is used to confirm passage progress but not to detect a lesion. To date, four small bowel CE systems are available: PillCam SB2 from Given Imaging, Yoqneam, Israel (<http://www.givenimaging.com/>); EndoCapsule e.g. from Olympus Europe GmbH, Hamburg, Germany, (<http://www.olympuseuropa.com/endoscopy/>); OMOM from Chongqing Jinshan Science, Beijing, China, (<http://www.cqjs.net/>); Miro-Cam from IntroMedic, Seoul, Korea (<http://www.intromedic.com/>). In the USA, only the PillCam SB2 and the Endo Capsule are currently approved by the US Food and Drug

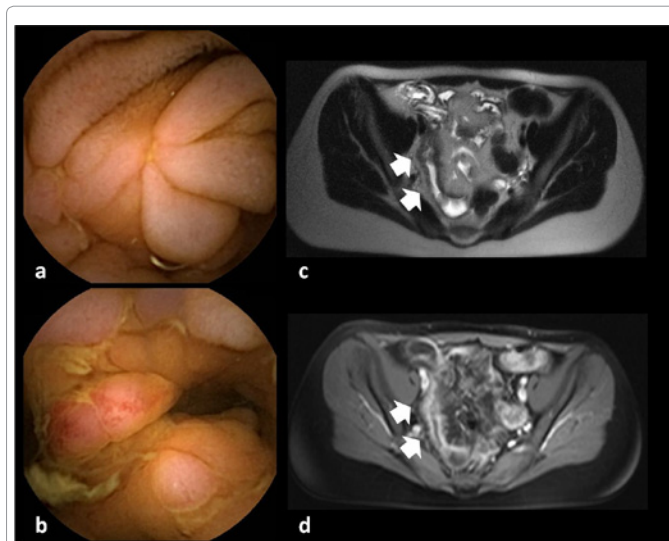


Figure 1: Crohn's disease of the small bowel in capsule endoscopy (CE; a,b) and MRI (c,d). Proximal (a) and distal (b) small bowel Crohn's disease is well detected by CE, and thickening of the small bowel wall is found in T2w (c) and contrast enhancement is seen in GRE sequence (d).

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Administration, in Europe all four systems can be purchased in most countries. For most CE studies in CD patients the PillCam SB 2 capsule has been used, which consists of a CMOS-chip with a resolution of 0.1 mm at a magnification of 1:8. Battery life is 8 h (SB 2) to about 12-16 hours (SB 2L) (Table 1).

For fear of capsule retention CE is usually not used in patients with known intestinal strictures or potential stenosis but administering patency capsule before performing video CE, capsule retention can reliably be prevented [2,3]. The main limitation of the capsule is its inability to take biopsies or to perform interventions, the difficulty with which identified lesions can be accurately localized, and its inability to control its movement.

Balloon-assisted enteroscopy (BAE) involves push-and-pull maneuvers for deep intubation of the small bowel [4] and includes single- and double-balloon enteroscopy techniques (SBE, Olympus, Japan; and DBE, FujiFilm, Japan) [5]. Rate of complete small bowel investigations seems to be more regularly achievable using double-balloon rather than the single-balloon technique whereas the therapeutic impact was similar with SBE and DBE [6-8]. Complications are reported in less than 5% of procedures and include pancreatitis (< 1%), bleeding, and perforation, with the rate of complications increasing in therapeutic interventions [9]. Another enteroscopy technique is the Endo-Ease system (Spirus Medical, Stoughton, MA) that uses a spiral-shaped overtube to advance or withdraw the endoscope with rotatory clockwise and counterclockwise movements of the spiral [10]. Examination time might be reduced, but the insertion depth is minor in comparison with DBE [11,12]. With simple push-enteroscopy even less of the small bowel may be intubated [13]. BAE is used to yield biopsies for histopathological examination in patients with newly detected small bowel lesions with suspicion of CD to exclude neoplastic or infectious disease.

Radiology in imaging small bowel Crohn's disease

Distension of the intestines by use of luminal contrast is essential to improve characterization of the bowel wall. Thereby, either a sonde is inserted into the proximal small bowel (enteroclysis) or the luminal contrast medium is taken orally (enterography). Conventional fluoroscopy (small bowel follow-through and small bowel enteroclysis) is thereby more and more replaced by cross sectional imaging methods.

For both, Computed tomography (CT) and magnetic resonance imaging (MRI), there have been enterography and enteroclysis techniques developed (CT-enterography/CT-enteroclysis; CT-E or MR-enterography/MR-enteroclysis; MR-E). Thereby, oral contrast application (enterography) provides similar quality of the images but improves patient comfort [14-16]. Inflammatory alterations of the small bowel and extraluminal complications such as abscess or fistula are equally well visualized. Lifetime radiation exposure is a concern, particularly in young patients [16] and doses of more than 100 mSv have been observed in some patients. Lack of radiation and excellent soft tissue contrast argue for use of MRI in CD patients and against fluoroscopy or CT [17-19].

Diagnosing small bowel Crohn's disease: endoscopy vs. cross sectional imaging

Sequence of investigations and definition of indications for small bowel endoscopy vs. cross sectional imaging is still under debate [20]. Meta-analysis suggests higher sensitivity and optimal negative predictive value of endoscopic methods in comparison to radiology, but extraintestinal lesions are only detected by radiological imaging [21,22] (Table 2).

Consensus conferences cling to a diagnostic sequence in suspected CD to first perform ileo-colonoscopy for diagnosis of terminal ileitis and colitis, followed by cross sectional imaging to identify proximal CD or extra-enteric lesions. CE is regarded a final identifier of unexplained symptoms [20,29]. Proximal small bowel CD is best seen with CE, though, and detection of distal small bowel disease is equal sensitive with CTE, MRE, and CE suggests using CE to exclude CD in suspected disease cases: A pooled analysis of the results of 24 CE trails comprising 530 patients found that CE had a low miss rate of 0.5% for small bowel ulcerations, compared to 79% of other modalities (SBFT, push-enteroscopy, or ileo-colonoscopy) [31]. Thus, the diagnosis of CD can possibly most reliably be excluded with a negative CE, even if negative small bowel CE might not completely exclude CD – e.g. of the colon [32]. But, it should be remembered that any diagnostic findings are far from being pathognomonic, and small bowel ulcerations may be compatible with chronic inflammatory, neoplastic, and infectious origin, or might be secondary to NSAID-intake. In a cohort of patients who were suspected to be afflicted with small bowel CD, 37% of 102 patients were initially diagnosed with small bowel ulcerations by CE, but

Capsule	Company	Size (mm)	Frame rate (Images/s)	Field of view	Acquisition time (hours)
PillCam SB 2	Given imaging, Israel	11 x 26	2	156°	8 (SB 2); ca. 12-16 (SB 2L)
EndoCapsule	Olympus, Japan	11 x 26	2	145°	> 8
MiroCam	IntroMedic, Korea	25 x 11	3	-	> 11
OMOM	Chongqing Jinshan Science, China	28 x 13	2 or 1	140°	8

Table 1: Four capsule endoscopes are available at present.

Author	N	Capsule endoscopy		Cross sectional imaging		Statistical significance
Eliakim [23]	2004	CTE	35	77%	20%	p < 0.05
Voderholzer [24]	2005	CTE	41	25/41 (61%)	12/41 (29%)	p=0.004
Hara [25]	2006	CT	17	12/17 (71%)	9/17 (53%)	n.s.
Solem [26]	2008	CTE	28	83%	67%	n.s.
Albert [27]	2005	MRI	52	25/27 (93%)	21/27 (78%)	n.s.
Tillack [51]	2008	MRI	19	18/19 (95%)	18/19 (95%)	n.s.
Böcker [30]	2011	MRI	21	9/21 (43%)	6/21 (29%)	Proximal small bowel
Jensen [14]	2011	MRI and CTE	93	100%	81 % (MRI)	Proximal small bowel
Casciani [52]	2011	MRI	37	10/11 (91%)	76% (CTE) 19/19 (100%)	n.s.

Table 2: Comparison of diagnostic yield or sensitivity in cross sectional imaging techniques and in endoscopy in diagnosing small bowel Crohn's disease; CTE – computed tomography enterography; MRI – magnetic resonance imaging; CE – Capsule endoscopy.

Year	N	Methods	Treatment	Diagnostic modality	% mucosal healing	
D'Haens [44]	1997	19	Cohort study	AZA	Ileocolonoscopy	Complete or partial healing: 11 / 15
D'Haens [45]	1999	30	Multicenter, randomized, double-blind study	IFX	Ileocolonoscopy	IFX: most. Placebo: none.
D'Haens [39]	1999	20	Retrospective study	AZA	Ileocolonoscopy	Complete healing: 12/20
Rutgeerts [46]	2006	99	Subgroup of randomized, double-blind study	IFX, scheduled vs. episodic treatment	Ileocolonoscopy	Responders (w2), scheduled: 50% Episodic: 7% (p = 0.007)
Regueiro [47]	2009	24	Prospective study	IFX, prevention of postoperative recurrence	Ileocolonoscopy, capsule endoscopy	IFX: 84.6% Placebo: 9.1% (p< 0.01)
Schnitzler [43]	2009	214	Retrospective study	IFX, scheduled vs. episodic treatment	Ileocolonoscopy	Scheduled IFX: 76.9% Episodic IFX: 61.0% (p = 0.02)
Colombel [48]	2010	508	Randomized, double-blind study	IFX, AZA, IFX + AZA	Ileocolonoscopy	IFX + AZA: 43.9% IFX: 30.1% (p=0.06) AZA: 16.5% (p<0.05)
Baert [41]	2010	49	Cohort of randomized study	AZA + IFX vs. placebo	Ileocolonoscopy	Maintenance of remission with no therapy: 15/ 17
Laharie [49]	2011	51	Retrospective study	MTX, AZA, or IFX	Ileocolonoscopy	MTX: 11% AZA: 50% (p=0.011 vs. MTX) IFX: 60% (p=0.008)

Table 3: Mucosal healing in terms of immunosuppressive therapy as determined by endoscopic findings. IFX- infliximab, AZA – azathioprine, MTX – methotrexate, CD – Crohn's disease, UC – ulcerative colitis.

only 13% had the diagnosis of CD maintained at one year of follow-up [33]. Even if some features of small bowel lesions might rather suggest CD (irregular and longitudinal ulcerations, multiple locations, cobble stone aspect of the small bowel) than NSAID use (circular ulcerations, webs) or neoplasia (circumscribed lesion), these identifier must be interpreted very cautious before labeling a patient to be affected by CD. In established CD, immediate access to cross sectional imaging (e.g. MRI) is important in many clinical scenarios such as the septic patient, or in ileus, and severe intestinal inflammation, suppurative disease, and conglomerate tumor or fistulae can be detected. Endoscopy is necessary to discriminate inflammatory from chronic, non-inflammatory lesions or strictures. In the unclassified type of inflammatory bowel disease (IBDU) it may be reasonable to screen for small bowel involvement to confirm the diagnosis of CD in some patients. In one study, the diagnosis of IBDU had been revised and changed to CD in 15 % of 120 patients [34,32] but minor findings should not mislead to revise the diagnosis [35]. Postoperatively endoscopic surveillance is recommended [30] and inflammatory lesions are best discriminated from non-inflammatory bowel alterations by use of endoscopy. Hereby, CE might replace ileo-colonoscopy to detect recurrence, as accuracy of CE is similar to conventional colonoscopy in the anastomotic region, but proximal disease is exclusively visualized by CE [36,37].

Outcome in terms of mucosal healing

Endoscopy has been used to detect CD activity in the postoperative situation, i.e. in a high-risk group of patients who were prone to undergo a complicated disease course with high probability to be in need of further surgery. In this patient group, the future course of the disease was best predicted by the severity of the early postoperative lesions, as observed at ileo-colonoscopy [38]. Since then, endoscopic treatment control in the postoperative patient group is well established with endoscopy being the golden standard of surveillance [38]. Endoscopy has increasingly been used to document on mucosal healing in CD patients and in ulcerative colitis, and mucosal healing has more and more been established as an important sign of treatment efficacy and a reliable prognostic marker, table 3. Mucosal healing has been described in CD patients who were on Azathioprine and who experienced complete healing of their colitis that was confirmed by disappearance of the inflammatory infiltrate in histopathologic examination [39]. Mucosal healing as documented by endoscopy after

1 year of treatment has been found to predict reduced subsequent disease activity over the following five years and decreased need for active treatment [40]. Recently, complete mucosal healing was found to be associated with a sustained, steroid-free remission in early-stage Crohn's disease [41]. Thereby, endoscopic monitoring the treatment has been shown ideal to identify those patients that are at high-risk of a dismal outcome: At 3 months from the start of IFX therapy, endoscopic investigations correctly predicted responders of maintenance therapy in active luminal CD [42]. Moreover, mucosal healing was associated with an improved long-term outcome with lesser need for major abdominal surgeries [43] (Table 3).

Today, endoscopic surveillance is used to assess disease activity and mucosal healing in patients with persistent symptoms despite therapy and when treatment discontinuation is considered. Regular, scheduled screening endoscopies are not established. Ileocolonoscopy is the standard procedure in use, even if CE or colon CE could be used to visualize both, the small and the large intestines. Thus, a recent study demonstrated that the findings of CE had a serious impact on clinical practice with a change of management in 50% of the patients with established or suspected CD [50].

Conclusion

Small bowel endoscopy is crucial for diagnosing small bowel CD, and CE is complemented by BAE to take biopsies and by MRI to visualize enteral and extra-intestinal involvement. Recently, imaging has also become a key instrument to manage CD patients. Treatment control is advised for patients who have undergone bowel resections and is increasingly used to testify treatment success in non-operated patients, too. Recent studies have illustrated the higher sensitivity of CE to detect small bowel lesions in comparison to radiology and clinical impact of the findings has been demonstrated. Further studies are needed to evaluate the exact clinical role of small bowel CE, colonic CE, and maybe pan-intestinal CE in the management of CD.

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