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Non-invasive techniques for assessing postoperative recurrence in Crohn's disease

L. Biancone *, S. Onali, E. Calabrese, C. Petruzziello, F. Zorzi, G. Condino, G.S. Sica, F. Pallone

Departments of Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy

Abstract

Postoperative recurrence after ileo-colonic resection is a feature of Crohn's Disease (CD), almost 73% of patients show endoscopic recurrence at 1 year and 90% at 3 years. After surgical resection for CD, symptoms may be related to the surgical resection itself. Moreover, the development of an early severe endoscopic recurrence within 1 year represents a risk factor for early clinical recurrence. On the basis of these observations, the early detection and assessment of asymptomatic endoscopic recurrence may allow a timely and appropriate treatment of CD patients after ileo-colonic resection. At this purpose, conventional colonoscopy with ileoscopy currently represents the gold standard for assessing CD recurrence, graded according to the Rutgeerts' score. Lesions compatible with CD recurrence can be also detected by conventional radiology, including small bowel follow through and enema, both associated with a high radiation exposure.

Due to the ineluctable course of CD after resection, and to the need of a proper follow up for assessing CD recurrence, several alternative, non invasive techniques have been searched in order to assess the post-operative recurrence, including: faecal alpha 1-antitrypsin clearance, faecal calprotectin, 99Tc-HMPAO scintigraphy, virtual colonoscopy, ultrasonography and, more recently, wireless capsule endoscopy (WCE) and Small Intestine Contrast Ultrasonography (SICUS). Among these, current evidences suggest that in experienced hands, ultrasound examination by SICUS represents a non-invasive technique useful for assessing recurrence in CD patients under regular follow up after surgery. The same findings are suggested for WCE, although the impact risk related to the recurrence or to the surgical anastomosis itself limits the use of this non-invasive technique for assessing CD recurrence after surgery.
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1. Introduction

Postoperative recurrence after ileo-colonic resection is a feature of Crohn's disease (CD). Endoscopic recurrence is indeed observed in almost 73% of CD patients at 1 year and in 90% at 3 years after curative resection [1–4]. The development of CD recurrence as assessed by ileocolonoscopy or radiological examination of the small bowel may occur also in the absence of overt symptoms ("asymptomatic recurrence") [1–4]. The severity of endoscopic lesions in the early postoperative period (within 1 year) has been shown to be predictive of symptomatic and early clinical relapse [4]. Severe endoscopic recurrence is observed in about 30% of patients at 3 months and in 50–90% of patients at 6 months after ileo-colonic resection for CD [5]. In a prospective longitudinal study, approximately 15–40% of CD patients required surgical reintervention at 10 years and up to 50–70% at 20 years after initial resection [5].

Growing evidences support the role of a genetically determined inappropriate mucosal immune response in the pathogenesis of tissue damage in CD [6,7]. Neverthe-

* Address for the correspondence: Livia Biancone, MD, PhD, Cattedra di Gastroenterologia, Dipartimento di Medicina Interna, Università "Tor Vergata" di Roma, Via Montepellier, 1, 00133 Rome, Italy. Tel.: +39.06.72596376; Fax +39.06.20903738.
E-mail address: biancone@med.uniroma2.it

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less, both the etiology and the mechanisms leading to postoperative recurrence remain unknown. Several studies investigated the potential role of risk factors for CD recurrence, but only active smoking, especially in women and the site and prevalent pattern of the lesions (ileocolitis, fistulizing subtype) have been recognized so far [8–10].

As an early development of CD recurrence is predictive of an early clinical relapse, a timely detection of ileal lesions after ileo-colonic resection can lead to an appropriate treatment and possible prevention of symptoms after surgery. Therefore, proper follow up of CD patients after ileo-colonic resection includes the endoscopic assessment of recurrence at 1 year, or every 6 months in case of relapse or severe recurrence [2].

Currently, the gold standard for assessing CD recurrence after ileo-colonic resection includes conventional ileocolonoscopy with the severity of lesions graded according to the Rutgeerts' score [2].

Conventional radiological techniques, including the small bowel follow through or enteroclysis also visualize the presence, extent and prevalent pattern of CD recurrence after ileo-colonic resection, although providing high radiation exposure to the patient.

Due to these observations, and as approximately two/thirds of CD patients require surgery during the disease course, several attempts have been made in order to provide alternative non-invasive procedures for assessing the postoperative recurrence [1–5].

Several techniques have been investigated and proposed at this purpose, including virtual colonoscopy, 99Tc-HMPAO scintigraphy, faecal alpha 1-antitrypsin clearance (faecal α1AAT-Cl), faecal calprotectin, ultrasonography, small intestine contrast ultrasonography (SICUS) and wireless capsule endoscopy (WCE) [9–13].

2. Computed tomographic colonography

Virtual colonoscopy (VC) is a non-invasive technique providing a three-dimensional view of the inner colonic surface, being proposed as a technique alternative to conventional colonoscopy [11,12]. Although current preliminary observations indicate that VC may be useful for colon cancer screening, few studies investigated the possible usefulness of this non-invasive technique for assessing the post-operative recurrence of CD [13]. In a small series of 16 patients with previous ileo-colonic resection, it was assessed whether VC is comparable to conventional colonoscopy (CC) for assessing the postoperative CD recurrence. At this purpose, recurrence was assessed by CC according to Rutgeerts et al. [2]. VC was performed by using a computed tomography scanner, with images examined by 3 radiologists unaware of the endoscopic findings. Results indicated that CC detected endoscopic recurrence in 15 out of 16 patients, associated with narrowing/stenossi in 11 out of 16. VC showed a 73% sensitivity, 100% specificity, 100% positive predictive value (PPV), 20% negative predictive value (NPV) and 75% accuracy for detecting endoscopic recurrence. False negative findings were detected in patients showing mucosal lesions but no lumen narrowing. However, VC detected a luminal narrowing in 7 out of the 8 patients showing by CC a stricturing recurrence not passed by the endoscope. Results from this small group of patients suggest that although the widespread use of VC in CD is currently not indicated because of possible false-negative findings, this technique may represent an alternative to CC in noncompliant post-surgical patients with a rigid stenosis not allowing passage of the endoscope [13].

Comparable findings have been reported in other few studies investigating the possible role of VC in the assessment of CD lesions [11,12]. Due to the radiation exposure, to the need of bowel preparation, and the not easy feasibility of this technique leading to possible false-negative findings, VC currently does not represent the optimal non-invasive technique alternative to ileocolonoscopy for detecting CD recurrence.

3. Scintigraphy using 99mTc-HMPAO-labeled granulocytes (99Tc-HMPAO scintigraphy)

99Tc-HMPAO scintigraphy has been reported as a non-invasive sensitive technique for detecting intestinal inflammation in CD, providing information regarding the site, extent, and activity of the disease [14,15]. Major limits of this technique include the low specificity due to the high frequency of false positive findings, related to the presence of a "physiological" inflammation of the human

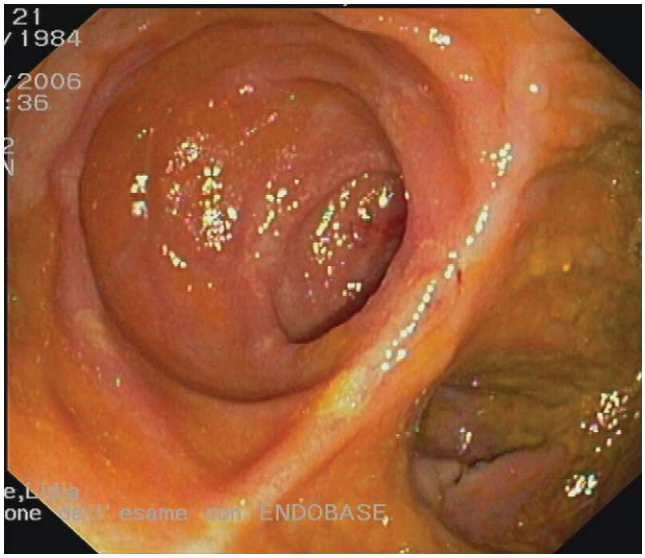

Fig. 1. Endoscopic view of the ileo-colonic anastomosis (side-to-side) from a patient with Crohn's disease, 1 year after ileo-colonic resection. The figure shows a recurrence with deep and apthous ulcers with no lumen narrowing involving the anastomosis and the neo-terminal ileum (Rutgeerts' grade 3).

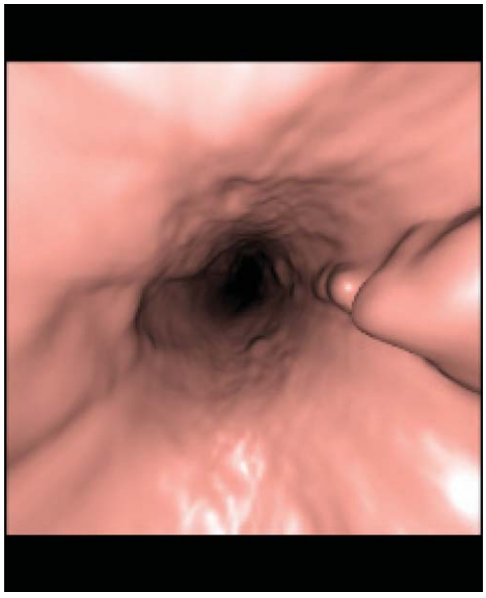

Fig. 2. Virtual colonoscopy from a Crohn's disease patient showing lumen narrowing at the ileo-colonic anastomosis.

intestine, associated with possible migration of labelled leukocytes into the gut lumen. The usefulness of 99Tc-HMPAO scintigraphy in assessing the early postoperative recurrence of CD is unknown. In order to address this issue, in a prospective longitudinal study, 99Tc-HMPAO scintigraphy was performed 6 and 12 months after ileo-cecal resection, with recurrence assessed by colonoscopy within 2 weeks. Results from a limited number of patients indicated that scintigraphic images acquired at 3 hrs show a low specificity in detecting CD recurrence both at 6 and at 12 months, while imaged at 30 minutes show a high sensitivity for detecting CD recurrence in patients under regular follow-up after ileo-colonic resection [16]. As for VC however, 99Tc-HMPAO scintigraphy is not recommended as a non-invasive technique alternative to ileoscolonoscopy for assessing CD recurrence, due to both its highly costly and time-consuming technical requirements and to the high frequency of false-positive findings [16]. This is supported by the few studies addressing this issue [14,15].

4. Faecal alpha 1-antitrypsin clearance (faecal α1AAT-Cl)

Faecal alpha 1-antitrypsin faecal clearance is an indicator of protein loss and increases during active inflammation. Higher values have been reported in patients with CD [17,18]. On the basis of this observation, a prospective longitudinal study evaluated the usefulness of faecal α1-antitrypsin clearance in the early detection of postoperative asymptomatic CD recurrence [19]. At this purpose, these parameters were measured 3, 6 and 12 months after elective ileo-colonic resection in 11 patients with CD, by using small bowel follow through as a gold standard for detecting the recurrence. All patients were prospectively followed for one year. Results from this study showed that at 6 and 12 months alpha 1-antitrypsin clearance was above the upper normal limit in all the 5 patients with recurrence. Results from this small series suggest that fecal alpha 1-antitrypsin clearance is a non invasive, inexpensive, sensitive marker of asymptomatic recurrence in CD patients who are under regular supervision after surgery [19]. The role of fecal alpha 1-antitrypsin clearance in assessing the presence and severity of CD lesions has been suggested by several studies [17,18]. However, the worldwide use of this parameter at this purpose is highly limited by difficulties and unpleasant modalities of measurement as also by its low specificity for diagnosing CD lesions. Therefore, despite promising findings, fecal alpha 1-antitrypsin clearance also currently does not represent a non-invasive parameter used in clinical practice for assessing CD recurrence.

5. Faecal calprotectin

Calprotectin is a Ca-binding antimicrobial protein of granulocytes (60% of cytosolic protein content), monocytes, macrophages, squamous epithelia. As calprotectin resists metabolic degradation, it can be measured in the feces. Faecal calprotectin has been shown to be significantly increased in patients with organic versus nonorganic inflammatory diseases [20]. Higher levels have in particular been observed in inflammatory bowel disease (IBD), colorectal carcinoma and nonsteroidal enteropathy [21]. When considering the role of calprotectin as a predictor of recurrence in asymptomatic CD, a prospective longitudinal study evaluated role of this parameter as a predictive marker of endoscopic recurrence at 1 year [22]. At this purpose, 50 consecutive CD patients with ileo-cecal resection underwent measurement of faecal calprotectin and abdominal ultrasound (US) at 3 months, followed by colonoscopy at 1 year. The sensitivity and specificity of calprotectin and US as predictive markers of recurrence were 26% and 60% vs 75% and 90%, respectively. The authors concluded that at 3 months US is more specific than calprotectin in predicting endoscopic recurrence [22]. However, faecal calprotectin values $>$ 200 mg/L show a higher sensitivity than US, suggesting that calprotectin values $>$ 200 mg may be an indication for colonoscopy in the group of CD patients with negative US to detect early recurrence [22].

6. Transabdominal ultrasonography

Ultrasonography has been proposed for detecting small bowel lesions in patients with suspected or known CD, showing a sensitivity of 67–84% and 81–95%, respectively [23–30]. In a series of 41 patients with CD, ultrasonography showed a low sensitivity (81%) and specificity (86%) and a 83% accuracy in the diagnosis of CD recurrence [31,32].

A good sensitivity (79%) and high specificity (95%) for the diagnosis of post-operative recurrence in CD has been reported by a subsequent study, concluding that bowel ultrasound could replace endoscopy for the diagnosis and grading of recurrence in patients with low compliance for colonoscopy [33].

7. Small intestine contrast ultrasonography (SICUS)

The use of oral contrast (PEG) significantly increases the sensitivity of ultrasonography for assessing small bowel lesions in patients with suspected or known diagnosis of CD (>95%) [34,35]. Suggestions have been provided that SICUS may visualize not only established CD lesions, but also minor changes of the small bowel wall [36]. Parameters detected by SICUS considered compatible with CD lesions related to recurrence include: 1) increased bowel wall thickness (>3 mm) with description of presence/absence of wall layers; 2) "stiff loop", identified by the presence of intestinal loop, with increased wall thickness which is not distended by contrast solution; 3) small bowel dilatation defined as lumen diameter > 2.5 cm; 4) bowel stricture defined as lumen diameter < 1 cm; 5) abnormal motor activity; 6) presence of fistulae; 7) mesenteric enlargement and/or masses; 8) abscesses [34].

SICUS has been shown to be more accurate than TUS for assessing small bowel CD lesions, although the experience of the sonologist significantly affects the accuracy of both techniques, particularly of TUS [34]. However, when comparing TUS with SICUS in terms of detection of small bowel lesions related to CD, when an unexperienced sonologist performs ultrasonography, sensitivity and specificity has been shown to be higher by using SICUS [34].

As detailed below, findings from a prospective longitudinal study in CD patients undergoing elective ileo-colonic resection suggest that SICUS represents an alternative non-invasive techniques for assessing CD recurrence in patients under regular follow-up after ileo-colonic resection [37]. No other studies investigated the possible role of SICUS in assessing the postoperative recurrence of CD.

8. Wireless capsule endoscopy (WCE)

WCE is a diagnostic tool recently used for imaging the entire small bowel. As WCE is able to visualize small bowel lesions, it has been proposed as a new non-invasive technique for detecting lesions related to CD [38–41].

Although several studies recently investigated the role of WCE for the assessment of established lesions related to CD, by our knowledge, only 2 studies evaluated the usefulness of this technique in assessing CD recurrence [37,42].

In the first study, Bourreille et al. [42] compared ileo-colonoscopy and WCE for detecting CD recurrence. At

Fig. 3. Wireless capsule endoscopy shows the presence of lesions compatible with recurrence in the neo-terminal ileum in a patient with ileo-colonic resection for Crohns' disease.

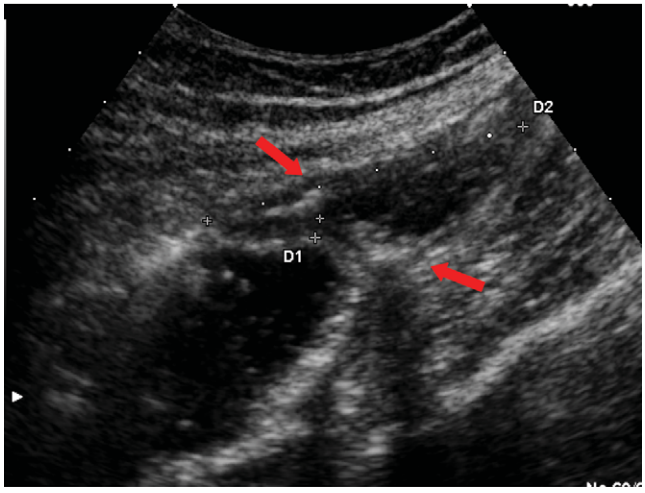

Fig. 4. Peri-anastomotic area of a Crohn's disease patient with ileo-ascending anastomosis, as assessed by SICUS 12 months after surgery. The peri-anastomotic area shows an increased wall thickness (4 mm; n.v. < 3 mm) (arrows), with no stricture or ileal loop dilation.

this purpose, 32 patients with ileo-colonic resection were prospectively enrolled and the results of WCE were interpreted by two independent observers. Results showed that sensitivity of WCE in detecting ileal recurrence was inferior to that of ileocolonoscopy. In contrast, WCE detected lesions outside the scope of ileocolonoscopy in more than two thirds of patients. The authors conclude that currently WCE cannot systematically replace ileocolonoscopy in the regular management of CD patients after surgery.

In a subsequent prospective longitudinal study, the possible usefulness of 2 non-invasive techniques, SICUS and WCE in assessing postoperative recurrence of CD was investigated in patients 1 year after surgery when using ileocolonoscopy as gold standard [37]. At this purpose, 22 patients undergoing ileo-colonic resection for CD were prospectively followed up for 1 year. At 1 year, recurrence

was assessed by SICUS and colonoscopy, followed by WCE. CD recurrence was assessed by colonoscopy. At 1 year, endoscopic recurrence was observed in 21/22 patients. Lesions compatible with recurrence were detected by SICUS in 22/22 patients (1 FP). WCE was not performed in 5 patients due to lumen narrowing. When considering only the 17 patients studied by all the 3 techniques, endoscopic recurrence was detected 16 out of 17 patients, while lesions compatible with recurrence were detected by SICUS in 17/17 (16 TP, 1 FP) and by WCE in 16/17 patients (16 TP, 1 TN). The authors concluded that SICUS and WCE may represent non-invasive techniques for detecting CD recurrence 1 year after ileo-colonic resection [37].

Taken together, despite several studies investigated the possible usefulness of non-invasive techniques for assessing the postoperative recurrence of CD, conventional ileocolonoscopy still represents the gold standard at this purpose. Promising alternative non-invasive techniques include virtual colonoscopy and Small intestine contrast ultrasonography in experienced hands, while the use of wireless capsule endoscopy is not widely recommended to the impact risk limits in all patients with CD, also in those with no overt symptoms.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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Practice points

- Postoperative recurrence is a feature of Crohn's Disease (CD).
- Timely diagnosis of recurrence is required for proper treatment.
- Ileocolonoscopy is the gold standard technique for assessing CD recurrence.
- Small bowel follow through and enema provide a high radiation exposure.
- Alternative non-invasive techniques have been searched.
- Among these, Small Intestine Contrast Ultrasonography (SICUS) is a non-invasive technique useful for assessing recurrence in CD patients under regular follow up.
- Wireless Capsule Endoscopy also is useful at this purpose, although the impact risk limits the use of this non-invasive technique for assessing CD recurrence.

Research agenda

- The usefulness of ultrasonography need to be investigated by multicentric studies assessing the interobserver variation for detecting CD recurrence.
- The clinical relevance of WCE for assessing CD recurrence after small bowel resection needs to be studied in referral centers in order to mimize the impact risk.

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