Evaluation of Crohn's disease recurrence in patients with ileocolic anastomosis: value of computed tomography enterography with water enema

Poster No.: B-0197
Congress: ECR 2013
Type: Scientific Paper
Authors: F. Paparo, M. Revelli, C. Puppo, I. Garello, L. Bacigalupo, L.-P. Rollandi, R. Piccazzo, A. Garlaschi, G. A. Rollandi; Genoa/IT
Keywords: Gastrointestinal tract, CT, Contrast agent-oral, Endoscopy, Barium enema
DOI: 10.1594/ecr2013/B-0197

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Purpose

Ileocolic resection with ileocolic anastomosis may be necessary in Crohn's disease (CD) patients that do not respond to conservative medical treatment. Postoperative recurrence is a feature of CD, which is observed in up to 70% of cases [1]. Several factors have been advocated as predictors of early symptomatic CD anastomotic recurrence, in particular the distribution of inflammatory lesions (CD location) prior to surgery, disease behavior (i.e. inflammatory, stricturing, penetrating [2]), and patient's smoking status [3]. The type of ileocolic anastomosis (stapled side-to-side vs hand-sewn end-to-end anastomoses) has been proposed as a potential risk factor, but results on this issue are controversial [4-6]. Some Authors suggest that wide-lumen stapled end-to-end technique may reduce the risk of obstruction of the anastomosis because of a wider anastomotic lumen [6]. The neoterminal ileum is the most frequent site of CD recurrence, but the prevalence of recurrent inflammatory lesions in other gastrointestinal segments distinct from the ileocolic anastomosis has received little attention. Currently, optical colonoscopy with retrograde ileoscopy represents the gold standard technique for the assessment of anastomotic recurrence after surgery, but the procedure is invasive and carries the risk of colonic perforation. Moreover, anastomotic stenosis can hinder the progression of the endoscope such that a complete evaluation of the anastomotic site, including the neoterminal ileum, is not possible in up to one-third of patients [7]. To overcome the limitations of endoscopy, different non-invasive radiological techniques have been employed to evaluate the postoperative recurrence of CD, including small bowel enteroclysis and small bowel follow-through [8], small intestine contrast ultrasonography (SICUS) [9], CT-enteroclysis and enterography [10, 11] and MR-enteroclysis [12]. CT-enterography with water enema (CTe-WE) [13] is an original CT technique which can produce an effective simultaneous distension of both small and large bowel, providing a complete phenotypic characterization of CD, including disease distribution, behavior and extraintestinal manifestations. Our retrospective study had three main objectives: the primary objective was to determine the diagnostic value of CTe-WE in the evaluation of the surgical anastomosis in CD patients who had previously undergone ileocolic resection; the second objective was to determine the prevalence of synchronous inflammatory lesions (SILs) involving gastrointestinal segments distinct from the anastomotic site; the third objective was to verify the presence of a significant association between the type of ileocolic anastomosis (i.e. side-to-side, end-to-side or end-to-end) and the behavior of CD recurrence (i.e. inflammatory, stricturing, penetrating).
Methods and Materials

This was a retrospective, single-center, institutional review board approved study. CD patients treated by ileocolic resection and ileocolic anastomosis were identified by performing a search in our single-institution radiology database for the association of the keywords "Crohn's disease" and "anastomotic recurrence" in all CTe-WE examinations from January 2007 through December 2011.

A total of 75 CTe-WEs were obtained, and if one of the selected patients underwent more than one CTe-WE, only the more recent examination was considered for further evaluation, thus resulting in 51 CTe-WEs of CD patients with ileocolic anastomosis. The following clinical and laboratory data were retrieved from the medical records of each patient, when available: 1) age of onset of CD symptoms; 2) time interval between onset of symptoms and surgery; 3) Crohn’s Disease Activity Index (CDAI), C-reactive protein values, and fecal markers of inflammation - faecal calprotectin and lactoferrin - performed within one month of the CTe-WE; 4) clinical indication for the CTe-WE. Surgical records were also reviewed, and ileocolic anastomoses were divided in three main types: "wide-lumen" stapled isoperistaltic side-to-side (functional end-to-end), end-to-side (including both stapled and hand-sewn subtypes), end-to-end (including both stapled and hand-sewn subtypes). Reports of endoscopy studies performed within one month of the CTe-WE examination were analyzed, and Rutgeerts’ scores [14] (0: no lesions; 1: less than 5 aphthous lesions; 2: more than 5 aphthous lesions with normal mucosa between the lesions, or lesions confined to the ileocolonic anastomotic lining (<1 cm); 3: diffuse aphthous ileitis with diffusely inflamed mucosa; 4: diffuse ileal inflammation with larger ulcers, nodules, or narrowing) were considered, when available. When the Rutgeerts’ score was not explicitly written, it was retrieved from the endoscopy report. Mucosal hyperemia and edema of the anastomosis were not considered as signs of recurrence [15].

CTe-WE technique

CTe-WE technique was performed as previously described [13, 16]. Large bowel cleansing was obtained with a low fiber diet for 3 days before the CTe-WE, and oral administration of 2.000 mL of an isotonic non-absorbable electrolyte solution containing polyethylene glycol (Isocolan, Bracco, Milan, Italy) was given the afternoon before examination. At the time of examination, both small and large bowels were distended with neutral enteral contrast material. Small bowel lumen distension was achieved by oral administration of 1.000-2.000 mL of the previously mentioned isotonic solution (Isocolan) 45 min prior to CTE-WE; large bowel lumen was distended by trans-rectal introduction of 2,000 mL of tap water with the patient placed on the CT table. Just before the CT acquisition, bowel hypotonia was obtained with intravenous injection of 2 mL hyoscine-N-butylbromide 20 mg/mL (Buscopan, Boehringer Ingelheim). CT images were acquired with the patient in supine position. Bowel wall enhancement was produced by i.v. injection
of iodinated contrast medium with an iodine concentration ranging between 350 and 370 mg/mL (iobitridol, Xenetix 350, Guerbet, or iopamidol, Iopamiro 370, Bracco). The iodine load was 1.5 mg per kg of body weight. The flow rate was set at 3.2-3 mL/s with an automatic injector and CT acquisition was started in the portal phase 45s after contrast media bolus detection in the upper abdominal aorta, using a bolus-tracking software.

Description of Reading Criteria for CTe-WE Images

CTe-WEs were reviewed in consensus by two gastrointestinal radiologists (M.R. and C.P.) on dedicated workstations, and 1.25-mm thickness reconstructed images were used to obtain Multi Planar Reconstructions (MPR). The distension of the ileal and colonic sides of each anastomosis was qualitatively classified according to a four-point scale (0=absent, 1=incomplete, 2=good, 3=optimal), as previously proposed by Minordi et al [11]. A score of 3 meant that the anastomosis was optimally distended, and the wall was uniformly visualized. A score of 0 meant that the anastomosis was collapsed without any luminal separation and the wall could not be seen. For this purpose axial and multiplanar reformatted images were analyzed. The number of CTe-WEs with a score #2 (i.e. luminal filling adequate for a correct evaluation) was calculated. Obviously, all cases of strictureing CD recurrence may have determined lower scores of distension. Readers had to indicate what side of the ileocolic anastomosis (ileal, colonic or both) was involved by the recurrence.

The following CT signs were considered indicative of CD anastomotic recurrence [10]: mucosal hyper-enhancement of the neoterminal ileum/anastomotic wall compared to that of a presumably normal adjacent bowel loop; parietal stratification, which was defined as bilaminar (hyper-enhancing mucosa with hypoattenuating thickened submucosal layer) or trilaminar (enhanced outer serosal and inner mucosal layers with an interposed hypoattenuating submucosal layer) appearance of the neoterminal ileum/anastomotic wall; preanastomotic ileal wall thickening >3 mm; preanastomotic ileal dilatation, which was considered to be present when the maximal luminal diameter of the preanastomotic ileal loop was >25 mm; perianastomotic comb sign (engorged vasa recta separated more than usual and particularly parallel because of fibrofatty proliferation [13]). The presence of perianastomotic lymphadenopathies, fistulas and abscesses was also recorded. The CT appearance of a perianastomotic fistula was that of an extraenteric tract (hyper-enhancing, iso-enhancing, or hypo-enhancing relative to nearby bowel loops) with or without internal air or fluid [13]. Abscesses were defined as fluid collections with hyper-enhancing rims. The behavior of each CD recurrence (i.e. inflammatory, strictureing, penetrating) was further characterized according to the most evident CT features of the disease. In particular, preanastomotic ileal dilatation associated to anastomotic stenosis were considered CT findings of a strictureing recurrence, while the presence of perianastomotic abscesses and/or fistulas was used to identify a recurrence with penetrating complications. A CTe-WE examination was considered positive for CD recurrence when one or more of the above-mentioned CTe-WE findings were present. CTe-WEs were also analyzed searching for CD lesions involving other gastrointestinal
sites distinct from the ileocolic anastomosis. Only when CD anastomotic recurrence was associated to another gastrointestinal CD-related inflammatory lesion, the latter one was defined SIL (synchronous inflammatory lesion).

A bowel segment was considered to be affected by a SIL when the following CT signs were present: bowel wall thickening (normal thickness of the wall of the small intestine and colon is 1-2 mm and 3 mm, respectively, when the lumen is distended [17]); mucosal hyperenhancement; multilayered appearance of the bowel wall (bilaminar or trilaminar); the comb sign [13]; increased density in the perienteric fat (creeping fat); stricture with prestenotic dilatation (a prestenotic dilatation was considered significant when the small bowel lumen exceeded a 25-mm diameter and the large bowel lumen exceeded a 50-mm diameter); extraenteric complications (fistulas and abscesses). SILs were further characterized according to their location (upper gastrointestinal tract - gastro-duodenal -, small bowel, colon, perianal) and behavior (i.e. inflammatory, stricturing, penetrating).

Reference Standard

The reference standard for determining the real status of the anastomoses was established by the study coordinator (GA. R.) according to the available data of each patient, and it was represented by endoscopy in 30 patients; results of the histopathologic analysis of surgical specimens in 7 patients; Crohn's disease activity index (CDAI) in 5 patients; physical examination and laboratory tests (C-reactive protein [normal values <1 mg/dL], faecal markers of inflammation - faecal calprotectin [normal values >50 mg/L], lactoferrin [positive/negative] -) in the remaining 9 patients. Patients were considered to have recurrent CD when: 1) endoscopy or histopathologic analysis of surgical specimens revealed ulcerations in the neoterminal ileum (Rutgeerts score >1); 2) CDAI was >150 [15]; 3) clinical and laboratory data were consistent with recurrent inflammation (C-reactive protein values >1 mg/dL, fecal calprotectin values >50 mg/L, or positive fecal lactoferrin). CD recurrence was excluded when: 1) endoscopy or histopathologic findings indicated no abnormalities (Rutgeerts score = 0); 2) CDAI was <150; 3) clinical and laboratory data were not coherent with a recurrence.

When perianal disease was detected on CTe-WE images, it was confirmed using MRI and/or fistulography (performed within 2 months of the CTe-WE) as reference standards.

Statistical analysis

Descriptive statistics included frequencies and proportions for the binary and semiquantitative data. Quantitative data were expressed as mean ± standard deviation. Sensitivity, specificity, accuracy, positive and negative likelihood ratio, positive and negative predictive values - with corresponding 95% confidence intervals - of CTe-WE in the detection of anastomotic recurrence were calculated. The chi-square test was used to assess the presence of a significant association between the type of surgical ileocolic anastomosis (side-to-side, end-to-side or end-to-end anastomosis) and CD recurrence.
behavior (i.e. inflammatory, stricturing, penetrating). Patients were further divided in two
groups: group A including "wide-lumen" isoperistaltic side-to-side (functional end-to-end)
iloecolic anastomoses; group B including both end-to-side and end-to-end anastomoses. The Fisher's exact test was used to assess the presence of a significant difference in CD recurrence behavior between group A and B.
Results

51 patients were included (26 [51%] male and 25 [49%] female; mean age: 52.88 years ± 13.35; age range: 32-79 years). The mean CD duration in our study cohort was 11.6 ± 6.2 years, with a mean time interval between age of symptom onset and ileocolic resection of 7.2 ± 4.5 years. Ileocolic anastomoses were as follows: 18 (35.3%) stapled side-to-side, 17 (33.3%) end-to-side (7 stapled and 10 hand-sewn), and 16 (31.4%) end-to-end (6 stapled and 10 hand-sewn).

The clinical indication for the CTe-WE was suspected CD anastomotic recurrence with clinical symptoms in 45 patients, and suspected CD anastomotic recurrence without clinical symptoms in the remaining 6 patients.

The degree of distension of the ileal side of the ileocolic anastomosis received a score #2 (on a qualitative 3-point scale) in 38/51 (74.5%) patients, while the colonic side received a score #2 in 46/51 (90.2%) patients (Figure 1).

CTe-WE findings of CD anastomotic recurrence were detected by the two readers in 43 examinations, which included, according to the reference standard, 41 true positive cases and 2 false positive cases (Figure 2). The ileal side of the anastomoses was involved in all cases of anastomotic recurrence.

The remaining 8 CTe-WE examinations included 6 true negatives and 2 false negatives.

With regard to the true positive examinations, isolated anastomotic recurrence (without SILs) was found in the majority of cases (30/41 patients [73.2%]); anastomotic recurrence with a SIL in 11/41 patients (26.8%) (Figure 3).

There were no patients with multiple SILs.

CTe-WE demonstrated a CD recurrence not involving the anastomotic site in only 2/51 patients (3.92%), including one inflammatory ileal recurrence, and one case of perianal fistulizing CD (Figure 4). In both patients colonoscopy was negative for anastomotic recurrence, but CRP values were increased. These two cases were not classified as "SILs" due to the absence of a concomitant anastomotic recurrence.

The chi-square test did not demonstrate a significant association between the type of ileocolic anastomosis and the behavior of CD recurrence (p= 0.2725). Nevertheless, dividing the study cohort in two groups (group A including stapled side-to-side anastomoses and group B including both end-to-side and end-to-end ileocolic anastomoses), the Fisher's exact test revealed a significant lower prevalence of stricturing recurrence in the group A (p= 0.032769) (Figure 5).

The prevalence of both inflammatory (p= 0.176130) and penetrating (p= 0.595635) recurrences was not significantly different between group A and group B.
**Fig. 1:** Sagittal CTe-WE reformatted image showing an end-to-side stapled ileocolic anastomosis with an inflammatory CD recurrence (hyper-enhancement of the mucosal layer) involving the neoterminal ileum. The surgical staples (arrows) indicate the anastomotic site. Legend: is= ileal side; cs= colonic side.

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**Fig. 2:** Curved CTe-WE reformatted image showing an hand-sewn end-to-end ileo-colic anastomosis with two skip lesions (arrows) with a stricturing behavior involving the neoterminal ileum. Legend: cs= colonic side.

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**Fig. 3:** Coronal CTe-WE reformatted image demonstrating a long stricturing SIL (arrows) involving the transverse colon in a patient with concomitant CD anastomotic recurrence.

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Fig. 4: Coronal CTe-WE reconstructed image (A) and the corresponding confirmatory coronal CT-fistulography reconstructed image (B) demonstrate an extrasphincteric fistula (rectocutaneous fistula) (white arrow) tracking into the left ischioanal fossa in a patient with perianal CD but without anastomotic recurrence. Note the rectal enema tube (void arrow in A) through which the neutral contrast material (water) was injected.

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Fig. 5: Curved CTc-WE reformatted image showing an hand-sewn end-to-end ileo-transverse anastomosis with a long stricturing CD recurrence (arrows) involving the neoterminal ileum. Legend: cs= colonic side.

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Conclusion

Currently ileocolonoscopy remains the gold standard technique to evaluate CD recurrence in patients who have undergone ileocolic resection. Nevertheless, endoscopy is an invasive method that frequently needs patient's sedation or anaesthesia. In addition, it may also be incomplete due to modified anatomy and luminal narrowing in correspondence to the anastomotic site, preventing the progression of the endoscope in approximately one-third of cases [3, 9]. In such situations, endoscopy allows for an evaluation limited to the colonic side of the anastomosis. On the other hand, the assessment of the neoterminal ileum is of great clinical value, because CD recurrence mainly involves the ileal side of the ileocolic anastomosis [1], and imaging plays an important role in this concern (Figure 6).

Both CT-enterography and CT-enteroclysis have been used to evaluate CD patients with suspected anastomotic recurrence. In a previous work [11], Minordi et al. have shown that both CT-enterography (performed after oral administration of a solution containing polyethylene glycol) and CT-enteroclysis can provide a complete distension (grade 3 on a 4-point qualitative scale) of the neoterminal ileum and ileocolic anastomosis in a high percentage of patients (92.3% and 80.9%, respectively), and no significant difference (p= 0.1502) has been demonstrated between these two CT techniques. More recently, Soyer et al. used CT-enteroclysis to characterize the status of the ileocolic anastomosis in a cohort of 40 CD patients, finding that it provides an adequate distension and visualization of the anastomotic site in all cases [10]. They demonstrated that severe anastomotic stenosis and anastomotic wall thickening >3 mm are the two most sensitive CT-enteroclysis findings for the diagnosis of abnormal anastomosis (including inflammatory recurrence and fibrostenosis), with sensitivities of 97% and 93%, respectively, while stratification had a specificity of 100%. In a previous work [13], we retrospectively assessed the value of CTe-WE (i.e. CT-enterography performed after the additional trans-rectal administration of a water enema) for a comprehensive phenotypical characterization (i.e. CD location and behavior according to the Montreal classification [3]) of 221 CD patients. In the CTe-WE technique the reflux of water from the cecum through the ileocecal valve into the terminal ileum combines with the orally ingested contrast material, resulting in excellent luminal distension of both sides of the ileocecal area [16].

In the present study, CTe-WE has shown the ability to provide a constantly adequate distension of the colonic side of the ileocolic anastomoses (90.2% of patients with a distension score #2), while the lower percentage of patients with a distension score #2 of the preterminal ileum (74.5%) may be due to the high prevalence of strictureing recurrences (29.27%). Another advantage of CTe-WE over the other CT techniques dedicated to the study of the bowel (i.e. CT-enterography and -enteroclysis) is the simultaneous distension of both small and large intestine, which can be precious to verify the presence of inflammatory lesions in CD patients throughout the whole gastrointestinal
tract [13, 16]. In our study an unexpected high prevalence of SILs was demonstrated (11/41, 26.8%), including 2 colonic SILs that might have been missed by standard CT-enterography. In their study cohort of 34 CD patients Minordi et al. found only one (2.94%) case of an isolated jejunal SIL (without concomitant anastomotic recurrence) and three patients (8.82%) with anastomotic recurrence associated to SILs in the proximal ileum. Soyer et al. [10] did not report the prevalence of SILs in their study group of 40 patients, as they mainly focused on the CT-enterography findings that allow to differentiate between inflammatory CD recurrence and anastomotic fibrostenosis.

CT has the added value of enabling the examination of the entire bowel wall as well as extra-luminal involvement, which are two well-known limitations of endoscopy [10-13]. In our study, CTe-WE detected 4/41 (9.75%) penetrating anastomotic recurrences (Figure 7) and 3/11 (27.3%) penetrating SILs (excluding perianal disease), that might have been missed by conventional endoscopic studies.

In the work of Minordi et al. [11] CT-enterography and CT-enteroclysis have shown high values of sensitivity, specificity and accuracy in the assessment of CD anastomotic recurrence (96.9%, 100% and 97%, respectively), with only one false-negative CT case and no false-positive cases, using ileocolonoscopy as reference standard. In our work we found two false-positive and two false negative cases, which all had an endoscopic correlation. The false-negative cases were both related to anastomotic recurrence manifesting with only small aphthous lesions (i.e. less than 5, Rutgeerts score = 1), and it is known that CT-enterography may fail in the detection of these tiny mucosal ulcerations due to insufficient spatial resolution (i.e. inferior to that of conventional barium studies [17]). On the other hand false-positive cases were both determined by a slight mucosal hyper-enhancement, which may reflect hyperemia and edema of the anastomotic site, without mucosal ulcerations (Rutgeerts score = 0).

Recent studies have shown that recurrence rates are similar whether end-to-end anastomosis or side-to-side anastomosis is performed [5]. Nevertheless, with regard to the behavior of CD recurrence, we found that end-to-end and end-to-side ileocolic anastomoses are significantly more prone to stricture than wide-lumen stapled side-to-side ileocolic anastomoses (p= 0.032). This result, despite the low number of patients of our study cohort, is supported by other Authors [6], who suggest that the stapled side-to-side technique may reduce the risk of obstruction because of a wider anastomotic lumen.

The major drawback of our study relies on its retrospective design (i.e. systematic search in our institutional radiology database), which may have led to inclusion of patients only when anastomotic recurrence was clinically suspected. This method of inclusion resulted in a relatively high prevalence of abnormal anastomoses (41/51 [80.4%]), and it might have conditioned the overall diagnostic performance of CTe-WE in the detection of CD anastomotic recurrence. A disadvantage of CTE is the radiation exposure, particularly in the setting of a chronic and remitting disease such as Crohn's, which can lead to multiple CT examinations in young patients. Despite the development of new techniques of dose reduction and optimization is overcoming this problem, several authors advocate the use
of MR-enterography/enteroclysis in particular in younger CD patients [18-20]. However, a disadvantage of MRI in the assessment of ileocolic anastomoses is that surgical clips may impair the diagnostic capabilities of this imaging modality in about 10% of cases, due to the presence of metal artifacts [10, 12]. On the other hand, CT is not limited by the presence of surgical clips in correspondence to the anastomotic site, is a less expensive and more available technique and requires shorter examination times.

In conclusion, the value of CTe-WE in the assessment of CD patients who have undergone ileocolic resection relies on its ability to provide a good distension of both sides of the ileocolic anastomosis and to detect SILs throughout the remaining gastrointestinal tract including small bowel segments which are not accessible by conventional endoscopic techniques.
**Fig. 6:** Coronal CTe-WE reformatted image showing an hand-sewn end-to-side ileocolic anastomosis with a stricturing CD recurrence in the neoterminal ileum (solid arrows) manifesting with hyper-enhancement of the mucosal layer with hypoattenuating thickened submucosa and comb sign. Multiple mesenteric lymphadenopathies (void arrows) are well appreciable. Legend: cs= colonic side.

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Fig. 7: Curved CTe-WE reformatted image showing an hand-sewn end-to-end ileocolic anastomosis with penetrating CD recurrence. Void arrows indicate the inflamed neoterminal ileum; solid arrow depicts an extra-enteric fistulous tract connecting the neoterminal ileum to an adjacent small bowel loop. Legend: cs= colonic side.

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