

Endoscopic Recurrence or Anastomotic Wound Healing Phenomenon after Ileocolic Resection for Crohn's Disease: The Challenges of Accurate Endoscopic Scoring

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Abstract

Background and Aims: Adequate endoscopic scoring in Crohn's disease [CD] is crucial, as it dictates the need for initiating postoperative medical therapy and is utilized as an outcome parameter in clinical trials. Here we aimed to observe anastomotic wound healing in relation to endoscopic scoring of both inverted and everted stapled lines in side-to-side anastomoses.

Methods: Two prospective patient cohorts were included: ileocolic resection [ICR] for CD, and right-sided colon resection for colorectal cancer [CRC]. Videos taken during colonoscopy 6 months postoperatively were evaluated. The Simplified Endoscopic Activity Score for Crohn's Disease and modified Rutgeerts score were determined. The primary outcome was the presence of ulcerations in CD patients on both the inverted and the everted stapled lines. Secondary outcomes were the presence of anastomotic ulcerations in CRC patients and the number of cases having ulcerations exclusively at the inverted stapled line.

Results: Of the 82 patients included in the CD cohort, ulcerations were present in 63/82 [76.8%] at the inverted- vs 1/71 [1.4%] at the everted stapled line. Likewise in the CRC cohort, ulcerations were present in 4/6 [67.7%] at the inverted vs 0/6 [0%] at the everted stapled line. In total, 27% of the 63 patients in the CD cohort had ulcerations exclusively on the inverted stapled line.

Conclusion: Inverted stapled lines heal with ulcerations, whereas everted stapled lines heal without any ulcerations, in both CD and non-CD patients. The abnormalities at the inverted stapled line might interfere with endoscopic scoring of recurrence, with potentially an impact on patients' quality of life and on healthcare costs if postoperative treatment is initiated incorrectly.

Key Words: Crohn's disease, ileocolic resection, endoscopic recurrence, anastomotic wound healing

1. Background

In colorectal surgery, the anastomotic healing process is influenced by, among others, the type and configuration of the anastomosis. A histopathological difference in anastomotic healing exists in different types of anastomoses [e.g. inverted stapled, everted stapled or hand sewn]. When comparing anastomoses in terms of anastomotic healing, several attempts have been made to reach a consensus on identifying the optimal anastomosis. So far, most available studies have been conducted in animals.^{1–5}

In patients undergoing ileocecal resection [ICR] with a side-to-side stapled anastomosis, both inverted and everted stapled lines are present within the same patient. The longitudinal stapled line, of both the isoperistaltic and the

anisoperistaltic side-to-side anastomoses, is an inverted stapled line, while the cross-stapled line is everted [Figure 1]. The different adaptations of the cut bowel ends determine the type of wound healing. Direct mucosa–mucosa adaptation in an everted anastomosis will result in primary wound healing. The open cut ends of the stapled anastomoses are exposed to the peritoneum [Figure 1]. In serosa–serosa adaptation of the longitudinal stapled line, there is a ridge of the two cut ends of the bowel – joined by the staplers – that is exposed to the bowel lumen [Figure 1], which involves a process in which the mucosa needs to re-epithelialize over the stapled line.⁶ This phenomenon has, to our knowledge, never prospectively been studied in Crohn's disease [CD] patients.

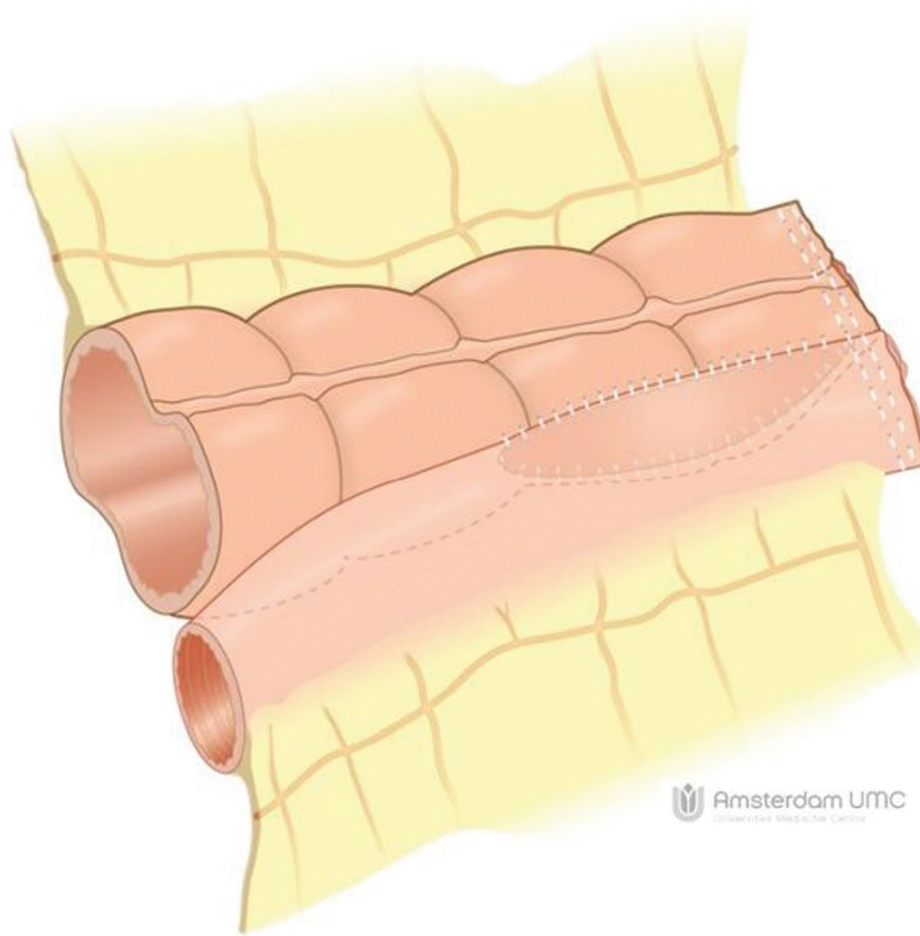


Figure 1. Anisoperistaltic side-to-side anastomosis: A1 = cross stapled line [everted stapled line, mucosa–mucosa adaptation], A2 = longitudinal stapled line [inverted stapled line, serosa–serosa adaptation]. *Red = seromuscular layer, orange = mucosa. Illustration by Van der Zon—Visueel

According to the European Crohn's and Colitis Organisation guidelines, endoscopic assessment of the anastomosis is advised 6 months after ICR for CD to detect recurrence, in order to [re-]initiate timely medical therapy.⁷ In CD patients, the reliability and reproducibility of scoring endoscopic recurrence is therefore critical, as it dictates the diagnosis of 'recurrent disease' with consequences for initiating postoperative medical therapy in daily care, and it is utilized as a primary outcome in clinical trials. Variability or misinterpretation in endoscopic scoring may therefore result in inappropriate therapeutic decisions and study conclusions.^{7,8}

The aim of the present study was to observe anastomotic wound healing in side-to-side anastomoses, wherein both longitudinal and cross-stapled anastomotic lines are present, in two different patient cohorts, in relation to endoscopic scoring.

2. Methods

2.1. Study design and participants

In two cohorts of patients, the ileocolic anastomosis was inspected for ulcerations at the different parts of the anastomosis 6 months after surgery.

The first cohort comprised patients from the previously reported DETECT trial [NCT02010762]. Patients

had established ileal or ileocolic complicated CD. In this multicentre, randomized, placebo-controlled trial, patients were randomized 1:1 to receive vitamin D3 or placebo vials.⁹ At week 26 [6 months] patients underwent a colonoscopy to videotape the anastomosis in order to determine the proportion of patients with significant endoscopic recurrence in the neo-terminal ileum. There was no difference in endoscopic recurrence in the two groups.⁹

For the current study, available videos of the DETECT trial were used to evaluate anastomoses in CD patients. Available data and video recordings were anonymized. None of the patients included in the original study could be identified from the available data. Exclusion criteria for the videos were low quality [faecal contamination, poor quality of the video] and types of anastomoses other than side-to-side stapled anastomoses.

The second cohort consisted of patients who had undergone an open or laparoscopic right-sided colonic resection with ileocolic anastomosis for colorectal cancer [CRC]. Patients were excluded if they had left-sided anastomoses and if intra- or postoperative diversion [stoma] was necessary.

Written informed consent was obtained and written as a note in the electronic patient file. Ethical approval with informed consent was obtained from the Medical Ethical Committee of Amsterdam Medical Centre.

2.2. Central reading of endoscopies

In both cohorts, ileocolonoscopy was performed 6 months after surgery and videos of the peri-anastomotic area were recorded. For the current study, all eligible videos of both study cohorts were [again] evaluated and independently [re-]scored by a gastroenterologist [M.D.] and a surgeon [W.B.], both blinded to the study cohort.

The type of anastomosis was extracted from the operative reports or identified from videos by the surgeon [W.B.]. If the inverted longitudinal stapled line was properly assessable, the video was included for analysis. Currently, there is no validated score to evaluate an anastomosis. The Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD] was chosen for this study, as it is a well-known, validated score, which can be applied on individual parts of the anastomosis.¹⁰ The modified Rutgeerts score [mRS] was determined for all anastomoses in both cohorts.^{8,11}

2.3. Outcomes

The primary outcome was the presence of ulcerations in CD patients on separate stapled lines of the anastomosis within the same patient: a cross-stapled line [everted] and longitudinal stapled line [inverted].

Secondary outcomes were [1] the presence of ulcerations in CRC patients on both stapled lines [longitudinal and cross-stapled] of the anastomosis within the same patient; and [2] the number of cases having ulcerations at the inverted stapled anastomosis in the absence of abnormalities in the terminal ileum in both patient cohorts.

2.4. Statistical analysis

All categorical data are presented as the number of cases and percentages, whilst continuous data are shown as either mean \pm standard deviation [range] or as median and interquartile range [IQR], depending on the data distribution. Differences in baseline characteristics and postoperative outcomes, between patients treated with vitamin D and placebo in the CD cohort, were assessed using a chi square test for categorical variables, or in the case of low counts [fewer than five], a Fisher's exact test; for numerical variables, an unpaired *t* test was used. Data were described using the Statistical Package for Social Sciences [SPSS] of IBM Statistics, version 26.0.

3. Results

In total, 99 videos of ileocolonoscopy of 143 patients included in the DETECT trial were available in the CD cohort.⁹ Seventeen videos were excluded, resulting in 82 videos included for analysis [Figure 2]. In all 82 patients the inverted stapled line was properly assessable. In 71 videos the everted stapled line was properly recorded and assessable. In the remaining 11 videos the everted stapled line could not be identified or was too briefly portrayed.

In the CRC cohort, six patients were included. Relevant baseline characteristics of the patients included in this study are shown in Table 1. In the CRC cohort, the median time from surgery until endoscopy was 7 months [range 6.75–7.25].

3.1. Presence of ulcerations on inverted and everted stapled lines

In the CD cohort, ulcerations [SES-CD > 0] were present in 63/82 patients [76.8%] at the inverted stapled lines vs 1/71

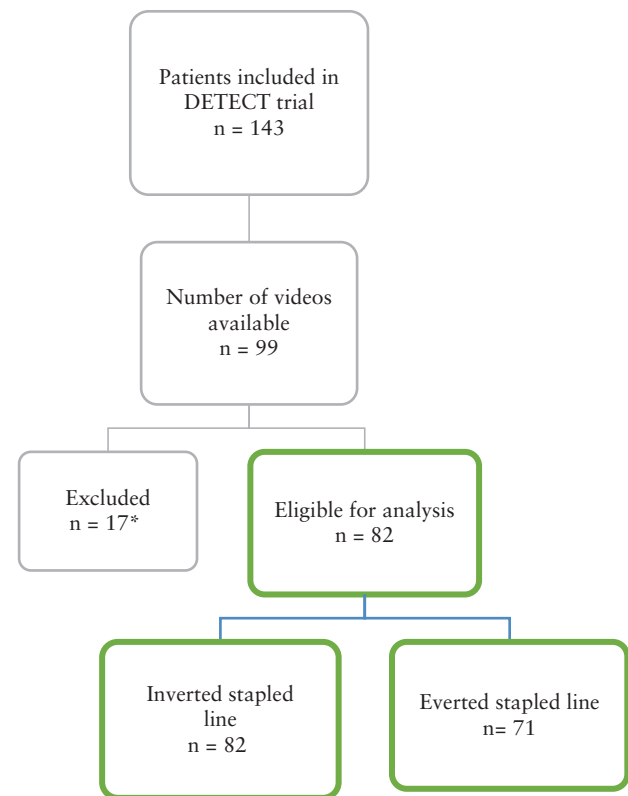


Figure 2. Flow chart study of the Crohn's disease cohort.*Low quality of the recorded video [*n* = 10]; type of anastomosis [*n* = 7].

[1.4%] at the everted stapled lines [Table 2]. The one patient with ulcerations on the everted anastomosis had an SES-CD score of 2 both in the terminal ileum and on the everted anastomosis.

Within the CRC cohort, ulcerations were present in 4/6 [67.7%] at the inverted stapled lines vs 0/6 [0%] at the everted stapled lines within the same patients. In CD patients, ulcerations on the inverted stapled lines were also present between the staples [longitudinal ulcerations] [Figures 3 and 4]; by contrast, in CRC patients ulcerations were solely present on the staples [Figure 5].

3.2. SES-CD inverted stapled anastomosis vs terminal ileum

Of 63 patients in the CD cohort with ulceration on the inverted stapled line, 17 [27.0%] had no ulcerations in the terminal ileum [Figures 3 and 4]. Within the CRC cohort, 4/6 [66.7%] had ulcerations on the inverted stapled line. No patients had ulcerations in the terminal ileum. Two patients showed a single spot of erythema [Table 3].

3.3. Modified Rutgeerts score

In the CD cohort, seven patients [8.5%] had an mRS of i0, six patients [7.3%] i1, 25 patients [30.5%] i2a, 16 patients [19.5%] i2b, 17 patients [20.7%] i3 and 11 patients [13.4%] i4 [Table 3]. Of patients with an mRS of i4, one patient on the initial video had an mRS of i4, while after dilatation the mRS was scored as i2a. This same patient had an SES-CD score of 8 on the inverting anastomosis and an SES-CD of 0 on the terminal ileum.

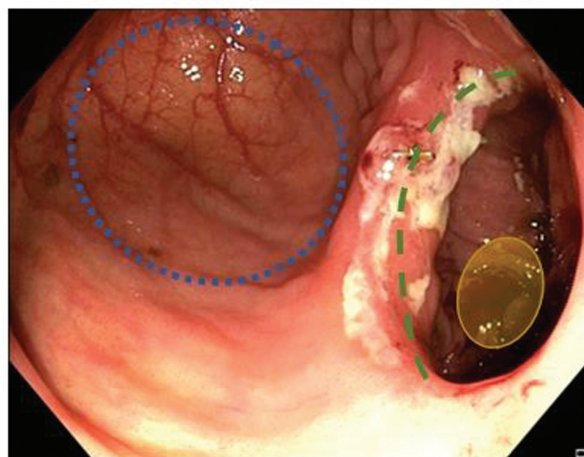
Table 1. Baseline characteristics of the Crohn's disease [CD] cohort and colorectal cancer [CRC] cohort

	CD cohort—Vitamin D [<i>n</i> = 43]	CD cohort—Placebo [<i>n</i> = 39]	CRC cohort [<i>n</i> = 6]
Sex, male, <i>n</i> [%]	21 [48.8]	15 [38.5]	1 [16.7]
Age, years, median [IQR]	34 [27–45]	35 [27–47]	59.7 [12.1]
Type, <i>n</i> [%], side to side	43 [100]	39 [100]	6 [100]
Configuration, <i>n</i> [%]			
Isoperistaltic	19 [44.2]	11 [28.2]	6 [100]
Anisoperistaltic	24 [55.8]	27 [69.2]	0
Unknown	0	1 [2.6]	0
Technique, <i>n</i> [%], stapled			
	43 [100]	39 [100]	6 [100]

Table 2. SES-CD of the inverted and everted stapled lines

	Inverted stapled line [<i>n</i> = 82]	Everted stapled line [<i>n</i> = 71]
SES-CD > 0, <i>n</i> [%]	63 [76.8]	1 [1.4]
SES-CD = 0, <i>n</i> [%]	19 [23.2]	71 [98.6]

SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.

**Figure 3.** Isoperistaltic side-to-side stapled anastomosis in the Crohn's disease cohort. Green dotted line: inverted stapled line, with ulcerations; yellow area: terminal ileum; blue dotted line: area where the everted stapled line should be

In the CRC cohort, four out of six patients has an mRS of i2a [Table 3, Figure 5]. Two patients had small irregularities [erythema] in the terminal ileum.

4. Discussion

This study demonstrated a significant difference in wound healing as assessed by endoscopic inspection of the inverted stapled anastomosis compared to the everted stapled anastomosis. Inverted anastomoses show ulcerations and a circular scar long after surgery, regardless of the presence of ulcerations in the terminal ileum. Because these ulcerations were, albeit to a lesser extent, present in the CRC cohort, this must reflect the difference in healing of the inverted staple line vs

the everted staple line, and not necessarily a CD recurrence. The inverted serosa–serosa staple line healed with ulcerations and scarring, whereas the everted stapled anastomosis with mucosa–mucosa adaptation healed without complications, validating our hypothesis. In the CD cohort, for 27% of patients with ulcerations on the inverted staple line, no abnormalities were observed at the terminal ileum or the blind loops.

Adequate scoring of endoscopic Crohn's recurrence is crucial. If a diagnosis of postoperative CD recurrence is made incorrectly, the patient's quality of life may be harmed due to its psychological effect and as a result of [re]initiation of medical therapy with possible side effects. Rivière *et al.* recently suggested an update for a postoperative endoscopic recurrence score, starting by subdividing different parts of the anastomosis and suggesting new terminology.¹² In addition, Hanzel *et al.* proposed the need for the development and validation of a specific endoscopic score for postoperative Crohn's recurrence.¹³ The results of our study support this suggestion.

As early as the 1990s, studies had indicated that anastomotic wound healing in a hand sewn anastomosis, with mucosa–mucosa adaptation, is fundamentally different from the inverted stapled anastomoses with serosa–serosa adaptation, leaving the cut ends exposed to the lumen [Figure 1].^{5,14} Dziki *et al.* described mucosal defects and necrosis at the inverted stapled anastomoses, making it a typical feature of how inverted stapled anastomoses heal. The inverted nature of the anastomosis requires epithelialization over the seromuscular layers, while vascularization is already compromised by the staples holding the bowel ends together. In the stapled [inverted] anastomosis, tissue alignment was worse at 1 month after creating the anastomosis, resulting in less complete wound healing compared to hand sewn anastomoses. The ulcerations can be explained by a combination of secondary wound healing and ischaemia induced by staple compression.⁵ This normal wound healing phenomenon should not be mistaken for CD recurrence. The majority of previous studies investigated histological anastomotic healing shortly after construction of the anastomosis [less than 6 months].^{1–5}

When scored according to the RS, ulcerations at the inverted staple line are scored at least as i2 or even i4 in the case of a stenosis. The RS has therefore been modified to account for wound healing issues at the anastomotic site: a score of i2a describes lesions confined to the ileocolic anastomosis, and i2b moderate lesions on the neo-terminal ileum.⁸ In everyday practice, however, there is a risk of over scoring when scoring endoscopic recurrence due to abnormalities at

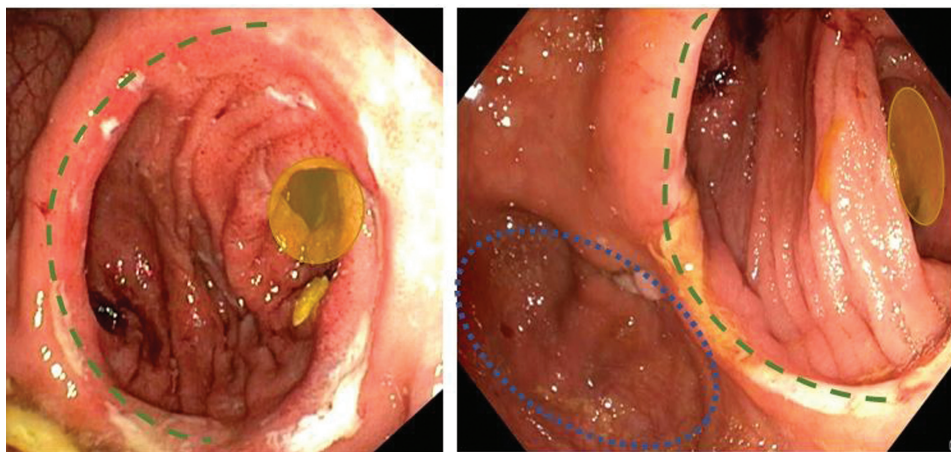


Figure 4. Anisoperistaltic side-to-side stapled anastomosis in the Crohn's disease cohort. Green dotted line: inverted stapled line; yellow area: terminal ileum; blue dotted line: area where the everted stapled line should be

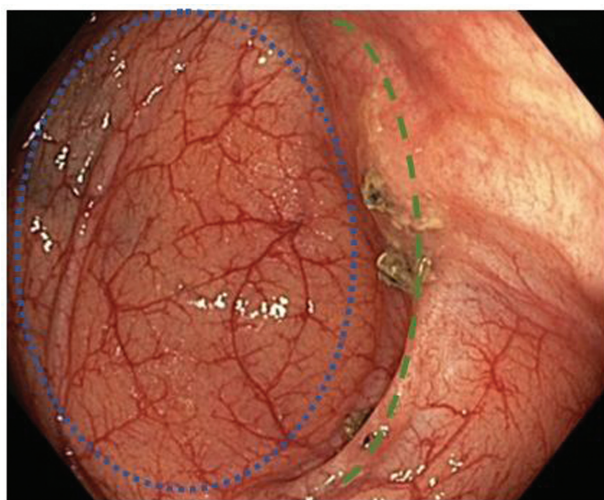


Figure 5. Ulceration on inverted anastomosis in the colorectal cancer cohort. Green dotted line: inverted stapled line; blue dotted line: area where the everted stapled line should be

the inverted staple line, which are essentially caused by secondary wound healing.¹⁵ At the very least, ulcerations could affect endoscopic scoring when comparing, for example, inverted stapled anastomoses and hand sewn anastomoses. Only by scoring the longitudinal and cross staple line separately, within the same patient, can the true nature of the difference be derived.

To date, little attention has been given to a new so-called Kono-S anastomosis, a modified hand sewn side-to-side anastomosis.^{16–18} In a recent study, the Kono-S anastomosis was compared to the inverted side-to-side stapled anastomosis. In that study, endoscopic recurrence was scored as RS ≥ 2 , including ulcers on the anastomotic line as if it was recurrent CD.¹⁸ It comes as no surprise that the stapled side-to-side-anastomosis healing with ulcerations on the anastomotic line had a higher rate of endoscopic recurrence than the hand sewn Kono-S. A study by McLeod *et al.*, a randomized control trial comparing hand sewn end-to-end anastomosis with stapled anastomoses, showed no difference in postoperative endoscopic recurrence rates in both groups. However, they evaluated endoscopic recurrence at 1 year postoperatively.¹⁹ It

Table 3. mRS and SES-CD for CD cohort and CRC cohort

	CD cohort [<i>n</i> = 82]	CRC cohort [<i>n</i> = 6]
Modified Rutgeerts score, <i>n</i> [%]		
i0	7 [8.5]	2 [22.3]
i1	6 [7.3]	0 [0]
i2a	25 [30.5]	4 [67.7]
i2b	16 [19.5]	0 [0]
i3	17 [20.7]	0 [0]
i4	11 [13.4]	0 [0]
SES-CD terminal ileum, <i>n</i> [%]		
Zero	25 [30.5]	6 [100]
> 0	57 [69.5]	0 [0]
SES-CD inverted anastomosis, <i>n</i> [%] [=longitudinal stapled line]		
Zero	19 [23.2]	2 [22.3]
> 0	63 [76.8]	4 [67.7]

mRS, modified Rutgeerts score; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; CD, Crohn's disease; CRC, colorectal cancer.

is expected that ulcerations will disappear at 1 year, compared to 6 months, if the ulcerations are part of a wound healing process. In another study, wound healing was worse in inverted stapled anastomoses compared to hand sewn anastomoses, which potentially influences the study results.⁵

Furthermore, the RS was developed when hand sewn end-to-end anastomosis was the most commonly used technique after ICR.¹¹ Different parts of the recommended anastomosis [stapled side-to-side], for example longitudinal staple line and two cross staple lines [ileal and colonic side], are not included in this prognostic score and therefore might hamper adequate scoring of endoscopic CD recurrence.¹²

Lastly, there has been interest in the interaction of the gut microbiome after intestinal resection and postoperative recurrence.^{20–22} A recent systematic review failed to draw unambiguous conclusions after evaluating studies on gut microbiota profiles, postoperative recurrence and postoperative microbial-based therapies in CD patients.²³ Some studies reported that postoperative treatment with low-dose metronidazole resulted in decreased postoperative endoscopic recurrence.^{24–26} It can

be hypothesized that the inverted stapled anastomosis with an open wound and ischaemia provides an excellent entry point for the microbiome, which might interfere with, and potentially complicate, wound healing and gut immunity.²⁷ Postoperative antibiotics affecting the microbiome might improve the wound healing of these exposed anastomoses. The more extensive ulceration of the stapling line of Crohn's patients compared to CRC patients as seen in this study might reflect a different interaction of the microbiome with the immune system in both groups of patients.

This study had multiple strengths: first, to our knowledge this is the first prospective study observing inverted and everted staple lines within the same patients in a CD cohort. Comparing inverted and everted stapled anastomoses within the same patient results in a decrease of confounding factors. Furthermore, central reading was used to decrease variability in endoscopic scoring. Videos of both cohorts were analysed by the same readers.

A limitation of the study was that 11 videos did not portray the everted stapled line properly. This confirms the importance of making good-quality videos for central reading. The small group of CRC patients could be seen as a limitation. However, this was not a comparative study of wound healing in CD vs CRC patients. The CRC cohort was used as an observational group, as a proof of principle. We examined CRC patients in order to confirm that the anastomotic ulcerations are not unique to CD patients. Therefore, a large patient cohort was not required. Having four out of the six cases [67%] with ulcerations at the inverted stapled anastomosis suggests that ulcerations are a normal wound healing phenomenon for this type of anastomosis and that this is not a unique phenomenon of CD. In addition, postoperative endoscopy was performed at 6 months [against hospital protocol] rather than 12 months. After 1 year the ulcerations might have disappeared if this is a wound healing phenomenon. Since this was an observational study, no sample size calculation was done.

In conclusion, this study has demonstrated that inverted and everted stapled anastomoses have a different type of wound healing and therefore a different appearance 6 months after surgery. This is present in both CD and CRC patients, meaning it is not unique to CD but should be considered as a wound healing phenomenon. This potentially interferes with the classification of postoperative endoscopic recurrence in CD. When scoring recurrence using the RS, it will automatically influence scoring. The RS was modified to overcome this issue. However, due to current suboptimal reproducibility of endoscopic scoring, it might be important to ignore any ulcerations on the longitudinal staple line when scoring endoscopic recurrence in CD.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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All collaborators of the DETECT study [The Effect of Vitamin D3 to Prevent Postoperative Relapse of Crohn's Disease: a Placebo-controlled Randomized Trial] are listed in the Supplementary Appendix.

Author Contributions

Conception and design: EvdDW, MD, WB. Administrative support: none. Illustrations: KAW and van der Zon - Visueel. Provision of study material or patients: Collaborators of DETECT study. Collection and assembly of data: EvdDW, MD, WB. Data analysis and interpretation: EvdDW, MD, CB, WB. Manuscript writing [including critical revision]: EvdDW, MD, GD, JvB, MM, RH, MvdV, CB, WAB, DETECT steering committee. Manuscript final approval: all authors and all collaborators of the DETECT study.

Data Availability

The data that support the findings of this study are available from E.vdD.W., upon reasonable request.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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