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CONTROLLED CLINICAL TRIAL

Complications after end-to-end vs. side-to-side anastomosis in ileocecal Crohn's disease—early postoperative results from a randomized controlled multi-center trial (ISRCTN-45665492)

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Abstract
Background Recurrent Crohn's disease activity at the site of anastomosis after ileocecal resection is of great surgical importance. This prospective randomized multi-center trial with an estimated case number of 224 patients was initially planned to investigate whether stapled side-to-side anastomosis, compared to hand-sewn end-to-end anastomosis, results in a decreased recurrence of Crohn's disease following ileocolic resection (primary endpoint). The secondary endpoint was to focus on the early postoperative results comparing both surgical methods. The study was terminated early due to insufficient patient recruitment and because another large study investigated the same question, while our trial was ongoing.

Methods and study design Patients with stenosing ileitis terminalis in Crohn's disease who underwent an ileocolic resection were randomized to side-to-side or end-to-end anastomosis. Due to its early discontinuation, our study only investigated the secondary endpoints, the early postoperative results (complications: bleeding, wound infection, anastomotic leakage, first postoperative stool, duration of hospital stay).

Results From February 2006 until June 2010, 67 patients were enrolled in nine participating centers. The two treatment groups were comparable to their demographic and preoperative data. BMI and Crohn's Disease Activity Index were 22.2 (±4.47) and 200.5 (±73.66), respectively, in the

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side-to-side group compared with 23.3 (±4.99) and 219.6 (±89.03) in the end-to-end group. The duration of surgery was 126.7 (±42.8) min in the side-to-side anastomosis group and 137.4 (±51.9) min in the end-to-end anastomosis group. Two patients in the end-to-end anastomosis group developed an anastomotic leakage (6.5%). Impaired wound healing was found in 13.9% of the side-to-side anastomosis group, while 6.5% of the end-to-end anastomosis group developed this complication. The duration of hospital stay was comparable in both groups with 9.9 (±3.93) and 10.4 (±3.26) days, respectively.

Conclusions Because of the early discontinuation of the study, it is not possible to provide a statement about the perianastomotic recurrence rates regarding the primary endpoint. With regard to the early postoperative outcome, we observed no difference between the two types of anastomosis.

Keywords Randomized controlled trial · Crohn's disease · Ileocecal resection · Side-to-side anastomosis · End-to-end anastomosis

Introduction

Ileocolonic end-to-end anastomoses and side-to-side anastomoses represent safe standard surgical treatments for most patients with Crohn's disease requiring ileocecal resection. Of pivotal clinical importance is the recurrent disease activity at the site of anastomosis after ileocolic resection because up to 93% of all patients develop endoscopically detectable recurrent disease activity [1], 20% of which are symptomatic. Ten to 35% and 20% to 45% of these symptomatic patients require surgery after their initial operation within the first 5 to 10 years, respectively [2]. Within the last years, systematic reviews and meta-analyses have attempted to define risk factors for recurrent postoperative disease activity [3–7]. Among the identified factors, smoking was the strongest predictor of recurrent disease activity [3]. In addition, the indication for the initial operation also influences the risk of developing recurrent disease activity postoperatively. The presence of fistulas or perforations was shown to be associated with a higher rate of complications compared to other indications [4]. The role of the surgical technique used to build the anastomosis in the development of recurrent inflammatory activity has been an issue of constant debate. In a meta-analysis from 2008, which compared hand-sewn end-to-end and stapled side-to-side anastomoses with regard to early postoperative complications in Crohn's disease patients, the authors were unable to show a specific benefit for either technique. Out of the eight studies included in that meta-analysis, only two were prospective randomized trials. One of these prospective randomized trials included 87 patients between 1983 and 1991 [8], while the other investigated 63 patients between 1987 and 1996 [9]. However, both studies failed to achieve a case number that would allow favoring one surgical technique over the other.

In 2009, McLeod et al. published their results from a prospective randomized trial with 170 patients investigating the disease recurrence rate in end-to-end vs. side-to-side anastomoses. This study also revealed that both techniques achieve similar results. In addition, they could not find any difference in early postoperative complication rates particularly anastomotic leak and wound infection rates in both anastomotic techniques [10].

The randomized controlled multi-center trial presented herein was initiated in 2006. The primary endpoint of the study was to compare the endoscopically detectable recurrence rate between hand-sewn end-to-end and stapled side-to-side anastomoses after ileocecal resection in Crohn's disease patients. The secondary endpoints were defined as the early postoperative results comparing both surgical methods. The study was terminated in summer 2010 due to insufficient patient recruitment, a change in the German Crohn's disease treatment guideline 2008 (including azathioprine as a standard medication in the medical prevention of recurrence) and because the large trial with a similar study design by McLeod et al. was published [10].

Due to the early discontinuation of the study, the necessary number of cases in order to reach statistical significance of the primary study endpoint has not been reached. In accordance with the general claim that all data collected within clinical trials should be made accessible, we here descriptively present the secondary endpoints of our study, the early postoperative results from all patients that had been enrolled until termination of the study below.

Patients and methods

Study population

Crohn's patients with ileitis terminalis who underwent elective ileocecal resection were enrolled in nine German surgical centers. All centers constitute the German Advanced Surgical Treatment Study (GAST) Group and have a high level of expertise in surgical treatment of chronic inflammatory bowel disease. The members of the GAST group are shown in Table 1. We also enrolled patients after their first episode of disease recurrence at the site of their neo-terminal ileum after initial ileocecal resection. The indications for ileocecal resection were symptomatic stenosis (terminal ileum), blind-ending fistulas from the terminal ileum with or without formation of abscesses. The exclusion criteria were pregnancy, age under 18 year, and Crohn's disease manifestation at a gastrointestinal site other than the terminal ileum with the exception of perianal fistulas. Also excluded were patients with postoperative indication for the

Table 1 Members of GAST group

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immunosuppressant azathioprine as postoperative recurrence prophylaxis.

Randomization

Randomization using sealed opaque envelopes occurred after an intra-operative check for the safety of both anastomosis techniques. This randomization was performed by a study nurse at each institution. Stratification was performed for each center before the start of the trial. The randomization was prepared as four-block randomization by the organizing center (Charité Berlin) and sent to each participating center in sealed and numbered envelopes. Once the intra-operative randomization was carried out, the operating center immediately informed the organizing institution.

Surgical procedures

All operations were carried out by experienced surgeons with a high level of expertise in colorectal and Crohn's disease surgery. Depending on the patient's wish and the preference of the surgeon, the procedures were either performed laparoscopically or conventionally. If open surgery was performed, median laparotomy or transversal laparotomy represented equivalent alternatives. Conglomerates were dissected, fistulas with blind retroperitoneal endings underwent debridement, while fistulas connecting different parts of the intestinum were sutured. The resections were performed applying a small security margin of 2 cm.

In patients with end-to-end anastomosis, intestinal continuity was re-established after initial resection by classical terminoterminal ileoascendostoma using modified hand-sewn interrupted Gambe suture pattern with bio-degradable polyglactin sutures (strength 4/0) or continuous seromucous self-resorbing monofile sutures, depending on the operator's preference. Patients with side-to-side (stapler) anastomosis received a laterolateral ileoascendostoma with linear cutter 50 mm (e.g., GIA) and linear stapler 30 mm (TA) using standardized techniques in this study (Fig. 1).

Blinding

Given the nature of surgical procedures, it was not possible to blind the surgical team to the intervention group. Patients were not informed of the type of anastomosis performed.

Data collection

The pre-operative data collection included demographic as well as clinical information such as the Crohn's Disease Activity Index (CDAI). All patients underwent a colonoscopy and a radiologic examination (conventional X-ray, CT, MRI) using Sellinck's technique within the last 12 months prior to the surgery. The Crohn-specific pre-operative medication was documented. The surgical technique and the operating time were recorded as well as all postoperative complications and the duration of the hospital stay. In addition, the time of the first postoperative stool was documented.

Sample size

The main outcome parameter used in this study was the postoperative, endoscopically detectable disease recurrence at the site of anastomosis. According to Rutgeerts et al. [11], approximately 73% of all patients with conventional end-to-end anastomosis develop endoscopically detectable disease recurrence within 1 year after surgery. The hypothesis of this study was that side-to-side anastomosis decreases this rate by at least 30% to 43%.

At the end of the study, the disease recurrence rate in both groups should be compared by Fisher's exact test using a significance level of alpha=5%. Using a power of 80%, at least 102 patients per group would be required. Assuming a dropout rate of 10%, 112 patients should be enrolled per group.

We herein exclusively present the descriptive data analysis of all patients that were enrolled until the discontinuation of the study. The sample size initially intended for statistical analysis could not be achieved.

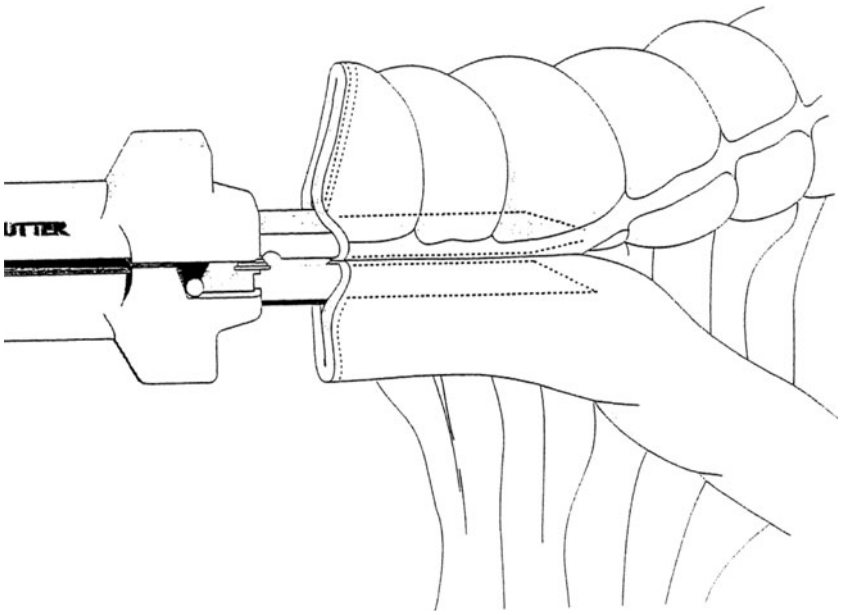


Fig. 1 Side-to-side (stapler) anastomosis

Discontinuation of the study

At the time, this study was initiated, there was no trial published addressing the questions of this investigation using a statistically sufficient sample size. The main outcome parameter for this study was the postoperative endoscopically detectable disease recurrence at the site of anastomosis. A screening of the usual databases did not show any trial investigating the postoperative complications after end-to-end vs. side-to-side anastomosis after ileocecal resection in Crohn's disease.

In 2009, the results from a prospective randomized trial with 139 patients applying a similar study protocol to compare the disease recurrence rates in end-to-end vs. side-to-side anastomoses were published [10]. Among the exclusion criteria of our study was the postoperative use of azathioprine for recurrence prophylaxis. Since the implementation of the German Crohn's disease treatment guideline in 2008, the use of azathioprine became "standard of care" in patients with a complicated disease course, leading to the exclusion of almost all formerly eligible patients.

For these reasons, the trial was discontinued by the organizing center in June 2010. The institutional review boards of all participating institutions were immediately informed of this discontinuation.

Study registration

The trial has been registered at the ISRCTN-Register (www.controlled-trials.com) under the trial number ISRCTN-45665492. Furthermore, the trial was listed in the German journal "Der Chirurg" within the section "surgical multicenter trials enrolling patients in Germany", and in each issue, the current number of enrolled patients was given.

Ethics

The trial was approved by both the institutional review board of the Charité—Universitätsmedizin Berlin as the coordinating center and the local review boards of all participating institutions.

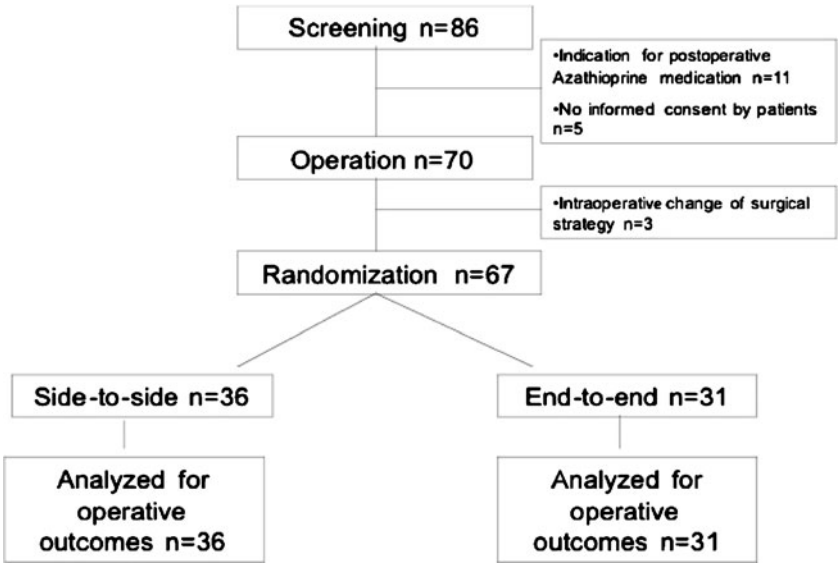
Data analysis

All results are presented in a descriptive manner. Baseline characteristics and intraoperative and postoperative data are given as mean and standard deviation for continuous variables and percentages for categorical and ordinal data.

Results

From February 2006 until the discontinuation of the trial in June 2010, from 86 screened patients, 67 patients were enrolled in the nine participating centers (Fig. 2). The demographic data including the Crohn's disease specific medication at the time of surgery and information regarding the type and duration of the operation are summarized in Table 2. The patients in both groups were similar with respect to all baseline characteristics. In the side-to-side anastomosis group, 18 patients had an open surgery and 18 patients had a laparoscopically assisted approach. Of the 18 patients that underwent open surgery, eight had median laparotomy and ten transversal laparotomy; in the end-to-end anastomosis group, 14 patients had open and 17 laparoscopically assisted surgery. Of the 14 open surgery patients, seven underwent median laparotomy and seven transversal laparotomy. In one case of end-to-end anastomosis, an initial laparoscopic procedure was switched

Fig. 2 Flowchart



to a transversal laparotomy (conversion) due to a massive inflammatory conglomerate tumor. In the side-to-side anastomosis group, the duration of surgery, of 126.7 (±42.8) min, was a bit shorter than in the end-to-end anastomosis group with an average duration of 137.4 (±51.9) min.

Table 3 provides data on the postoperative complications. Five patients (13.9%) in the side-to-side anastomosis group and two (6.5%) patients in the end-to-end anastomosis group developed wound infections. All wound infections occurred after open surgery. Two patients from the side-to-side anastomosis group and both patients with wound infections from the end-to-end anastomosis group had a median laparotomy. Three of the five wound infections in the side-to-side anastomosis group had a transversal laparotomy. With regard to wound infections, one patient from each group required operative wound revision due to deep putrid wound infection. In the end-to-end anastomosis group, two patients developed anastomotic leakage, which, in both cases, became clinically apparent by postoperative day 4 with leucocytosis, meteorism, and peritonism. Both patients underwent a re-do laparotomy and were sutured at the site of the leak. One patient received a protective loop-ileostoma orally of the anastomosis due to putrid peritonitis. In one patient who developed anastomotic leakage, a laparoscopically assisted approach was performed. In both groups, the first postoperative stool was observed by postoperative day 3. In addition, both groups did not differ with regard to duration of hospital stay (Table 3).

Discussion

Recurrence of Crohn's disease is common due to the propensity of the disease to recur early and frequently, also in patients who underwent resective surgery. Despite the fact that resective therapy improves the outcome and quality of life in patients with ileitis terminalis, 88% of this recurrent disease activity is observed in the neo-terminal ileum and the anastomosis [11], which is why the configuration of the anastomosis has long been discussed as one factor influencing the recurrence rate. Several retrospective studies comparing side-to-side anastomosis with various other configurations of the anastomosis revealed ambiguous results [12–20]. All these studies had a different focus, e.g., stapled and hand-sewn anastomoses were compared without considering the configuration of the anastomosis. Only Munoz-Juarez et al. compared stapled side-to-side anastomosis with hand-sewn end-to-end anastomosis in 69 patients. Recurrent disease activity was defined by clinical manifestation of symptom and was reported in 57% after end-to-end anastomosis and in 24% after side-to-side anastomosis [19]. At the time our trial was started in 2006, only two randomized controlled trials comparing the two types of anastomosis were available. One trial, published in 1992, included 86 patients. The recurrence rates reported were 23% and 31% for side-to-side vs. end-to-end anastomosis, respectively. However, this result did not reach statistical significance due to the small sample size [21]. Another randomized controlled trial investigated stapled vs. hand-sewn anastomosis after different intestinal resections using different configurations of the anastomosis. The overall recurrence rate after stapled anastomosis was lower than after hand-sewn anastomosis (18.9% vs. 37.8%). A subgroup analysis that included only patients after ileocecal resection showed a recurrence rate of 9.1% after side-to-side compared to 28.6% after end-to-end anastomosis (n=21) [22]. In 2007, Simillis et al. published their meta-analysis including 661 patients from randomized retrospective trials. This analysis could not identify any differences between the two types of anastomosis and concluded that prospective randomized controlled trial should be performed in order to answer the

Table 2 Demographic and pre- and intraoperative data

	Side to side (n=36)	End to end (n=31)
m/f	17:19	19:12
Age (years)	39.5 (±12.55)	39.1 (±12.58)
BMI	22.2 (±4.47)	23.2 (±4.99)
CDAI	200.5 (±73.66)	219.6 (±89.03)
Smoker	10 (27.8%)	11 (35.5%)
Prednisolone	19 (52.8%)	15 (48.4%)
Immunosuppressive drug	15 (41.7%)	12 (38.7%)
Mesalazine	8 (22.2%)	8 (25.8%)
No medication	5 (13.9%)	3 (9.7%)
Prednisolone + immunosuppressive	5 (13.9%)	6 (19.3%)
Prednisolone + mesalazine	3 (8.3%)	3 (9.7%)
Prednisolone + mesalazine + immunosuppressive	3 (8.3%)	2 (6.5%)
≥ 2 immunosuppressive drugs	1 (2.8%)	1 (3.2%)
First abdominal surgery	16 (44.4%)	17 (54.8%)
Open	18 (50%)	14 (45.2%)
Laparoscopically assisted	18 (50%)	17 (54.8%)
Conversion	0	1 (5.9%)
Duration of operation (min)	126.7 (±42.8)	137.4 (±51.9)

question if one technique should be favored over the other [6]. In 2009, McLeod et al. published the results from their prospective randomized multi-center trial with 170 patients, out of which 139 were analyzed regarding the endoscopically detectable disease recurrence 11.9 months postoperatively. In the side-to-side group, 37.9% showed recurrent disease activity, while 42.9% in the end-to-end group had endoscopically detectable disease recurrence. Additionally, there was no difference with regard to the rate of symptomatic disease recurrence (22.7% in the end-to-end vs. 21.9% in the side-to-side anastomosis group). The authors concluded that the rate of disease recurrence is independent of the configuration of the anastomosis [10].

However, perianastomotic recurrence is not the only issue when comparing anastomotic techniques. Other short-term outcome data including anastomotic leakage or wound infections are important aspects. Munoz-Juarez et al. reported an overall early postoperative complication rate in patients with end-to-end anastomosis of 20% compared to 7% in the side-to-side anastomosis group. An anastomotic leakage was described in 4.5% in the end-to-end anastomosis vs. 2.8% in the side-to-side anastomosis group [19].

Similis et al. published a meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease [6]. The anastomotic leak rate was significantly higher in the conventional end-to-end anastomosis group (6.7% of 382 patients) compared to the other anastomotic configurations group (259 patients received a side-to-side anastomosis). Only one of the included surveys comparing end-to-end anastomoses vs. side-to-side anastomoses was a prospective randomized controlled trial [8]; the others represented non-randomized, retrospective studies [12–14,19]. Furthermore, overall postoperative complications other than anastomotic leak were decreased in the side-to-side group. The separate analysis of high-quality studies and separate analysis of more recent reports of Simillis et al. showed no significant difference between end-to-end anastomoses and other anastomotic configurations regarding the overall postoperative complications and anastomotic leak. A shorter operating time seems to be one advantage of stapled side-to-side anastomosis [6]. In the prospective randomized controlled trial of McLeod et al., the early postoperative complications did not differ significantly between these groups [10]. They provide an anastomotic leak rate of 7% and a postoperative

Table 3 Postoperative data and complications

	Side to side (n=36)	End to end (n=31)
Complications		
Bleeding postoperative	0	0
Wound infection	5 (13.9%)	2 (6.5%)
Pneumonia	1 (2.8%)	1 (3.2%)
Thrombosis	0	0
Anastomotic leakage	0	2 (6.5%)
Re-operation	1 (2.8%)	3 (9.7%)
First postoperative stool (days)	3.1 (±1.48)	3.07 (±1.03)
Duration of hospital stay (days)	9.9 (±3.93)	10.4 (±3.26)

wound infection rate of 9% vs. 11% (side-to-side vs. end-to-end anastomosis). Other postoperative complications were found in 2% vs. 5% of the patients (side-to-side vs. end-to-end anastomosis). Even in our study we could not find any anastomotic leak after side-to-side-anastomosis whereas in 6.5% of our patients who received an end-to-end anastomosis, an anastomotic leak was described. The wound infection rate in our patient population was increased with 13.9% after side-to-side anastomosis and with 6.5% after end-to-end anastomosis compared to the trial of McLeod et al. Furthermore, due to the lack of statistical power resulting from the early discontinuation of the study, our data are of only descriptive character.

In the trial of McLeod et al., a 100-mm TLC stapler was used to create a side-to-side anastomosis. In our study, the laterolateral ileoascendostoma was carried out using a linear cutter 50 mm (e.g., GIA) and linear stapler 30 mm (TA). Whether this difference has a major influence on the early postoperative outcome could again not be verified due to the early termination of our study although we did not observe any anastomotic leak in the side-to-side group.

In our study population, there is a major difference in gender between the two groups. The end-to-end anastomosis group is clearly biased toward male gender (Table 2; m/f= 19:12). A recently published study in a similar field investigating if gender of the patient may influence perioperative and long-term complications after ileal pouch anal anastomosis could clearly demonstrate that a significantly greater proportion of male patients developed anastomotic separation during the 30 day postoperative period [23]. Conversely, Resegotti et al. in another study analyzing the influence of side-to-side stapled anastomosis on anastomotic leak rates in Crohn's disease surgery could not define gender as a specific risk factor for an anastomotic leakage (anastomotic leak rate: female gender 4.8% vs. male gender 11.2%, $p=0.33$). Our descriptive data with the lack of statistical power cannot provide a statement if gender effects the early postoperative outcome.

The trial presented here was designed as a prospective randomized controlled trial with nine study centers in 2006 and aimed at comparing hand-sewn end-to-end and stapled side-to-side anastomosis in resective ileocecal surgery in Crohn's disease. The primary outcome parameter in this trial was the endoscopically detectable disease recurrence with a planned sample size of 121 patients per group. At the time the trial was started, we did not find any comparable trial in the usual clinical trial databases. One significant difficulty of the study was that postoperative azathioprine prophylaxis was initially defined as an exclusion criterion for this trial. However, in 2008, the German S3 treatment guidelines (*Arbeitsgemeinschaften der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.* and *Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen*) were updated to include a new grade A recommendation for azathioprine prophylaxis in all complicated Crohn's disease cases. Although there is no general recommendation for postoperative pharmacological prophylaxis, in Germany azathioprine use is now based on interdisciplinary consent. Due to this fact, patient enrollment became almost impossible once the new guideline had been implemented.

The trial by McLeod et al., which had a similar study protocol, also defined postoperative azathioprine prophylaxis as an exclusion criterion for their study. Therefore, an investigators' meeting decided to also enroll patients on postoperative azathioprine in 2002 and to stratify additionally with regard to azathioprine treatment. A univariate analysis of this patient population showed a significant benefit with regard to symptomatic disease recurrence for the patients using postoperative azathioprine compliantly [10].

After the results of McLeod et al. were published, in June 2009 we carefully discussed whether we should terminate our trial due to the low patient recruitment and the expectation of similar results. We also considered changing our study protocol by including patients on postoperative azathioprine prophylaxis as in the trial by McLeod et al. However, since new results were not to be expected, we finally decided to terminate the study. Prior to discontinuation, we enrolled 67 of the initially intended 224 patients.

Although this study was discontinued and in accordance with the claim that all data obtained in patient research should be made publicly available, we believe that the descriptive data of this study are of value to clinicians. Although the planned primary outcome of endoscopically detectable disease recurrence 1 year postoperatively could not be investigated, the secondary endpoint of our study, the early postoperative results with regard to anastomotic leakage and wound infection rates, do not differ substantially from those reported by other investigators. Our data suggest that both types of anastomosis after ileocecal resection are equally safe.

Conflicts of interest None.

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