ORIGINAL CONTRIBUTION

Recurrence of Crohn's Disease After Ileocolic Resection Is Not Affected by Anastomotic Type: Results of a Multicenter, Randomized, Controlled Trial

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PURPOSE: This study attempts to determine whether stapled side-to-side anastomosis, compared with handsewn end-to-end anastomosis, results in decreased recurrence of Crohn's disease following ileocolic resection.

METHODS: Patients with Crohn's disease who underwent an ileocolic resection were randomized to side-to-side anastomosis or end-to-end anastomosis. Colonoscopy was performed at 12 months. The primary outcome was endoscopic recurrence, while the secondary outcome was symptomatic recurrence (defined as symptoms attributable to Crohn's disease and severe enough to warrant treatment, plus endoscopic disease recurrence).

RESULTS: One hundred and thirty-nine subjects were included in the efficacy analysis. After a mean follow-up of 11.9 months, the endoscopic recurrence rate was 42.5 percent in the end-to-end anastomosis group, compared with 37.9 percent in the side-to-side anastomosis group (−4.6 percent difference; 95 percent confidence interval −21.0 to 11.9 percent; $P = 0.55$). The symptomatic recurrence rate was 21.9 percent in the end-to-end anastomosis group, compared with 22.7 percent in the side-to-side anastomosis group (+0.8 percent difference; 95 percent confidence interval −13.2 to 15.3 percent; $P = 0.92$). In multivariate logistic regression analysis, previous resections were predictive of a higher risk of both endoscopic (odds ratio 1.78; 95 percent confidence interval 1.06 to 2.90; $P = 0.028$) and symptomatic (odds ratio 2.0; 95 percent confidence interval 1.14 to 3.60; $P = 0.0016$) recurrence. Compliance with postoperative maintenance therapy was predictive of a lower risk of symptomatic recurrence (odds ratio 0.13, 95 percent confidence interval 0.01 to 0.78; $P = 0.021$).

CONCLUSION: Recurrence rates are similar whether end-to-end anastomosis or side-to-side anastomosis is performed.

KEY WORDS: Crohn's disease; Surgery; Randomized controlled trial; Postoperative recurrence.

Despite recent interest in conservative procedures such as strictureplasty, resection is the procedure of choice for most patients with Crohn's disease requiring surgery. While there are many benefits incurred from surgery, unfortunately there is a propensity of Crohn's disease to recur despite apparent removal of all grossly abnormal bowels. A number of variables have been identified as potentially influencing the risk of recurrent Crohn's disease.[1,2] However, to date there is little evidence that intraoperative strategies are of benefit in decreasing the risk of recurrence.[3–6]

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Recently, there has been interest in the effect of surgical anastomosis on postoperative recurrence rates. Several observations support the hypothesis that anastomosis may play a role in the risk of recurrence. First, the risk of recurrent disease is extremely low in patients with permanent end ileostomies.[7] Second, approximately 90 percent of recurrences occur in the preanastomotic segment of the bowel.[8] Third, recurrence of disease rarely occurs in individuals where the anastomosis is defunctioned, but early changes of disease occur rapidly if feces are infused into the bowel.[9] The mechanism is unknown, but it is postulated that a narrow anastomosis may lead to fecal stasis and increase the likelihood of recurrence of disease. Thus, a wide anastomosis such as a side-to-side anastomosis may lead to a decreased risk of recurrence compared with an end-to-end anastomosis. Several observational studies, however, have shown conflicting results.[10–17]

Thus, the objective of this multicenter, randomized, controlled trial was to compare recurrence rates following stapled side-to-side anastomosis (STSA) with handsewn end-to-end anastomosis (ETEA) in patients with ileocolic resection for Crohn's disease. Operative outcomes and postoperative complications were also compared.

METHODS

Study Population

Patients were accrued from ten Canadian, six American, and one British center. Patients with Crohn's disease limited to the distal ileum and right colon who were scheduled for an elective ileocolic resection were eligible for inclusion. Patients were excluded if they had previously had disease resected at another site of the gastrointestinal tract, required a defunctioning ileostomy, or if medications used to treat Crohn's disease could not be discontinued postoperatively. Patients with an internal fistula who required resection of an otherwise normal segment of bowel were eligible, as were patients with minimal perianal disease that did not require treatment.

Baseline Information

Prior to surgery, demographic and clinical information was collected, the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ) were completed, and blood work including C-reactive protein was performed. All patients underwent a small bowel examination and colonoscopy within 12 months of surgery to ensure that the disease was confined to the terminal ileum and right colon.

All surgery was performed by colorectal surgeons experienced in the surgical treatment of Crohn's disease. Surgery was performed open or laparoscopically depending on patient factors and surgeon preference. The resection was performed in the usual manner and normal resection margins, where possible, were 2 to 5 cm in length.

Randomization

Eligible patients signed a consent form preoperatively, but randomization was performed intraoperatively once the surgeon had determined that there were no other sites of disease and that either type of anastomosis could be performed safely. Eligible patients were stratified by center. Computer generated randomization was carried out within strata using randomized permuted blocks to ensure balance of the groups. Randomization of patients was performed using a central phone-in randomization service.

Surgical Procedures

In those patients randomized to the ETEA group, the anastomosis was performed either as a single-layer or two-layer anastomosis, depending on the preference of the surgeon, using 2-0 PDS suture material. A Cheatle slit was performed if necessary.

In those patients randomized to the STSA, the anastomosis could be performed in one of two ways. First, enterotomies could be made at the proposed anastomotic sites of the small bowel and colon and then a 100 mm TLC stapler passed through the enterotomies to create a side-to-side anastomosis. Alternately, the bowel could be stapled closed at the appropriate proximal and distal resection margins, and then a corner of the stapled resection line excised and the 100 mm TLC staple passed through the two bowel limbs to construct a side-to-side anastomosis (also known as a functional end-to-end anastomosis). With either method, the anastomosis was completed with another pass of the TLC 100 mm stapler, or a transverse stapler if the surgeon preferred. Prior to the start of the study, all investigators met and agreed upon the surgical details of the operative procedure.

Maintenance Therapy

When the study was initiated per protocol, all subjects were to receive 5-ASA maintenance therapy. However, after only five patients were entered into the study, it was not possible to obtain 5-ASA (Asacol^{R}) because it was not approved for postoperative maintenance therapy. At that time, it was decided that no maintenance therapy would be prescribed. After 72 patients were entered into the trial, there were problems with accrual because some attending physicians felt that some patients required maintenance therapy with azathioprine postoperatively and therefore were not eligible for entry into the trial. At an investigators' meeting in November 2002, it was decided that the inclusion criteria would be expanded so that individuals who otherwise fit the inclusion criteria but were advised to take postoperative azathioprine would be included. However, the decision regarding the need for maintenance therapy had to be made preoperatively, and patients were stratified to an azathioprine

stratum or no maintenance therapy stratum before they were randomized to the two treatment groups.

Follow-Up

Patients were followed in-hospital daily until discharge, then at 6 weeks, and at 3 monthly intervals thereafter until 12 months. At each follow-up, patients answered questions regarding their status, and whether they had taken any medication for their Crohn's disease. Additionally, at 6 weeks and 12 months the CDAI and IBDQ were completed and blood work including C-reactive protein was drawn. Additionally, all subjects had a colonoscopy performed at 12 months. Colonoscopy included visualization of the colon plus neoterminal ileum. During the colonoscopy, photos of the preanastomotic area were taken, and, at the completion of the colonoscopy, the endoscopist completed a form that assessed the bowel for recurrence using a modified Rutgeert's score.[18] If a colonoscopy could not be performed or the neoterminal ileum could not be visualized, then an air contrast barium enema was performed.

If individuals experienced symptoms suggestive of recurrent Crohn's disease prior to the scheduled 12 month colonoscopy, they underwent a colonoscopy and other investigations deemed appropriate by their own gastroenterologist or surgeon to ascertain whether they had recurrent disease. If patients developed symptomatic recurrence, their participation in the study was terminated as they were considered to have reached an end point.

Blinding

Given the nature of the intervention, it was not possible to blind the surgical team to the intervention group. Patients were not informed of the type of anastomosis performed. The colonoscopy was performed at the same center where the surgery was performed, but to minimize observer bias, where possible, a gastroenterologist performed the colonoscopy. An adjudication committee evaluated the outcomes of all subjects based on photos, the procedure report, the score given by the endoscopist, the C-reactive protein, the subject's symptom status, and the CDAI score. Patients were categorized as (1) free of disease, (2) endoscopic recurrence only, (3) symptomatic disease, or (4) inadequate information to assess outcome.

Primary and Secondary Outcome Measures

The primary end point was the presence of endoscopic evidence of recurrence based on a modified Rutgeert's index (Table 1).[18] Only subjects with i2, i3, or i4 disease were considered to have endoscopic evidence of recurrence. Ulceration limited to the anastomotic line was not considered to be recurrence unless there was other evidence of disease, since it is known that ulceration may occur along a staple line and does not represent recurrent disease. Furthermore, only disease proximal to the anastomosis or in the perianastomotic area was considered to be an end point (*i.e.*, colonic disease or disease elsewhere in the small bowel was not considered recurrence).

TABLE 1. Modified Rutgeerts scoring system

Score	*Endoscopic findings*
i 0	No lesions in distal ileum
i 1	<5 aphthous lesions
i 2	>5 aphthous with normal mucosa between the lesions
i 3	Deep aphthous ileitis with diffusely inflamed mucosa
i 4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Symptomatic recurrence was defined as the presence of endoscopic disease (i2, or higher) plus the presence of symptoms attributable to Crohn's disease that were severe enough to require medical or surgical treatment.

In addition, a number of operative outcomes were evaluated. These included time to construct the anastomosis, duration of surgery, postoperative complications, and reoperative rate.

Sample Size

Based on a modified Rutgeert's score, where only individuals with i2, i3, or i4 disease would be considered to have endoscopic evidence of recurrence, it was estimated that 40 percent of subjects having an end-to-end anastomosis would develop endoscopic recurrence at one year. To detect a 20 percent decrease in the endoscopic recurrence rate with a stapled side-to-side anastomosis with 80 percent power and 5 percent significance, a total of 180 patients needed to be recruited. The sample size was adjusted to 200 to allow for a 10 percent loss to follow-up. It was felt that, since endoscopic recurrence rates are higher but less clinically relevant than symptomatic recurrence rates, a 20 percent absolute risk reduction in the endoscopic recurrence rate was clinically significant. It was also felt, however, that a larger trial with symptomatic recurrence as the primary end point would not be feasible.

In fact, accrual was stopped in July 2004, at 171 patients, because accrual had been slow. As a result, the statistical power of the study was reduced to 70 percent power to detect a significant absolute risk difference of 20 percent, or 80 percent power to detect an absolute risk difference of 23 percent.

Analysis of Data

Baseline characteristics are summarized as mean ± standard deviation for continuous variables and percentages for categorical and ordinal data. Differences in baseline characteristics between treatment groups and recurrence status were tested for statistical significance using the Wilcoxon's rank-sum test for continuous and

ordinal variables and the mid-p adjusted Fisher's exact test for categorical data.

Differences in outcomes (symptomatic recurrence, any recurrence, adverse events) between treatment groups were tested using the mid-p adjusted Fisher's exact test, with exact 95 percent confidence intervals [CI] of the estimated treatment differences using StatXact 5.03.

Data from all eligible subjects were included in the analysis comparing operative data and complications. Only subjects who were judged to have an end point (*i.e*, free of disease, endoscopic recurrence, symptomatic recurrence) were included in the analysis for recurrence.

Univariate and multivariate analyses were performed to assess the effect of nine factors which might potentially affect the risk of endoscopic and symptomatic recurrence. These included duration of disease, number of previous resections, smoking status, fistula or abscess present at surgery, type of procedure (laparoscopic or open), length of small bowel affected by Crohn's disease, postoperative azathioprine maintenance therapy, compliance with postoperative azathioprine maintenance therapy, and CDAI at six weeks. For the univariate analyses, differences were tested using either Student's *t*-test or a chi-squared test.

A multivariate logistic regression analysis was then performed. Variable subsets were determined by comparing all combinations of variables and selecting the final model on the basis of the lowest Akaike Information Criterion (AIC) that has been shown to optimize the overall predictive ability of the model. The variables included smoking status, postoperative azathioprine maintenance therapy, type of procedure, indication for surgery, and number of previous resections. For these analyses, a *P* Value of less than 0.05 was considered to be statistically significant.

Ethics

The study was approved by the Ethics Review Committee or Internal Review Board at all participating institutions. A Data Safety and Monitoring Committee reviewed all complications. The trial was registered with Current Controlled Trials (#ISRCTN72500766).

RESULTS

Between January, 2001 and July, 2004, 171 patients were recruited from 17 sites. One patient was excluded because he had a terminal ileal resection rather than an ileocolic resection, leaving 170 patients available for analysis of postoperative complications and surgical outcomes. The characteristics of these patients and surgical information are shown in Table 2. The patients were similar with respect to all baseline characteristics. In the ETEA group, 81 (94 percent) had the anastomosis performed with 2–0 PDS while another suture material was used in the other 5 (6 percent). The anastomosis was performed in 1 layer in 60 (70 percent) patients and in 2 layers in 26 (30 percent) patients. In the STSA group, 49 (58 percent) had a side-to-side anastomosis and 35 (42 percent) had a functional end-to-end anastomosis. The end of the bowel was stapled using the TLC stapler in 68 (81 percent) patients and with a transverse stapler in the remainder. Twelve (14 percent) patients in the ETEA and fourteen (17 percent) patients in the STSA group had additional procedures.

TABLE 2. Characteristics and operative data of subjects included in the assessment of surgical outcomes (n = 170)

	STSA *N = 84*	*ETEA* *N = 86*
Males: females	30:54	32:54
Mean age (in years)	40.3	38.2
Current smoker	26 (31%)	32 (37%)
Mean weight (in kg)	71.4	69.1
Mean number of previous resections	0.51	0.38
Subjects with no previous resections	53 (63%)	59 (69%)
Procedure type:		
Open	49 (58%)	45 (52%)
Laparoscopic-assisted	25 (30%)	28 (33%)
Laparoscopic-converted	10 (12%)	13 (15%)
Fistula/abscess present	28 (33%)	27 (31%)
Anastomotic type:		
Handsewn: one layer		60 (70%)
two layers		26 (30%)
Stapled: side-to-side	49 (58%)	
Functional end-to-end	35 (42%)	
Other procedures performed	14 (17%)	12 (14%)
Mean length of small bowel involved with CD (in cm)	16.5	19.8
Associated surgical procedures		
Repair/resection of colon	6	2
Repair/resection of SB fistula	3	5
Repair of bladder fistula	3	3
Cholecystectomy	2	1
Bilateral salpingoophorectomy	1	1
Repair of ventral hernia	2	1

Surgical outcome information is shown in Table 3. The mean duration of surgery (113 *vs.* 138 minutes; $P = 0.0009$) and mean time to complete the anastomosis (15 *vs.* 31 minutes; $P < 0.0001$) were significantly shorter in the STSA group. However, there was no difference in the median postoperative stay (six days in each group). There were no significant differences in other outcomes including overall complication rates (24 percent of patients in the ETEA group *vs.* 20 percent of patients in the STSA group; $P = 0.79$), leak rates (7 percent in ETEA group *vs.* 7 percent in the STSA group; $P = 0.86$) and reoperative rates (7 percent in the ETEA *vs.* 7 percent STSA group; $P = 0.86$). In both groups, all reoperations were performed because of an anastomotic leak and/or an intra-abdominal abscess.

As shown in Figure 1, of the 170 subjects, 9 (3 in the ETEA and 6 in the STSA groups) were lost to follow-up after a mean follow-up of 1.3 ± 2.7 weeks and 22 (10 in

TABLE 3. Comparison of surgical outcomes

	STSA (n = 84)	*ETEA (n = 86)*
Mean time to complete anastomosis (in minutes)*	15	31
Median time to complete anastomosis	10 (7–15)	26 (20–34)
Mean duration of operation (in minutes)*	113	138
Reported to have difficulties with anastomosis	1 (1%)	6 (7%)
Reported to have difficulties with procedure	12 (14%)	10 (12%)
Mean postoperative hospital stay*	8.3	6.8
Median postoperative hospital stay	6 (5–8)	6 (4–8)
Patients experiencing any complication	19 (23%)	21 (24%)
Mean # complications/patient	0.24	0.27
Surgical complications		
wound infection	9 (11%)	8 (9%)
prolonged ileus/SBO	2 (2%)	4 (5%)
intra-abdominal abscess	1 (1%)	1 (1%)
anastomotic leak	6 (7%)	6 (7%)
other	2 (2%)	4 (5%)
Reoperation	6 (7%)	6 (7%)

*$P < 0.05$.

the ETEA and 12 in the STSA groups) refused follow-up investigations despite being followed for a mean of 11.2 ± 1.9 months. None of these 30 patients had symptoms suggestive of recurrent disease. This left 139 subjects who were included in the analysis of primary end points. The characteristics of these patients are shown in Table 4.

Sixteen patients (22 percent) in the ETEA group and eleven patients (16 percent) in the STSA group were on prednisone preoperatively and tapered off the prednisone, on average, four weeks postoperatively. Three patients

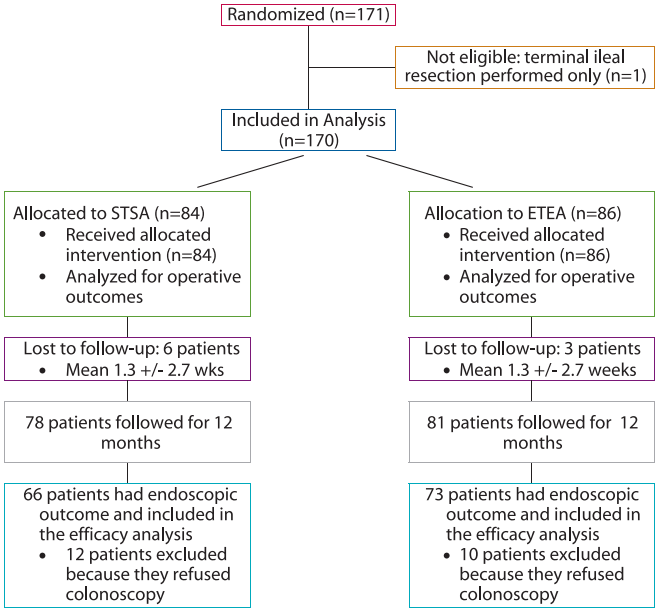

FIGURE 1. CONSORT diagram.

TABLE 4. Characteristics of patients included in the primary analysis (recurrence of disease) (n= 139)

	STSA (n = 66)	*ETEA (n = 73)*
Males:females	26:42	27:46
Mean age (in years)	40.3+/-12.9	38.2+/-13.7
Mean duration of disease (in years)	11.6	9.9
Mean number of previous resections	0.53	0.37
Subjects with no previous resections	40 (61%)	51 (70%)
Current smoker	19 (29%)	24 (33%)
Mean CDAI preoperatively	183	206
Mean IBDQ preoperatively	131	136
Colonoscopy		
performed prior to study	63 (95%)	66 (90%)
performed within 1 year of study	64 (97%)	67 (92%)
SBE		
performed prior to study	61 (92%)	68 (93%)
performed within 1 year of study	65 (98%)	73 (100%)
Open or laparoscopic converted procedure*	49 (74%)	49 (67%)
Fistula/abscess found at surgery	23 (35%)	24 (33%)
Mean length of SB involved with CD (in cm)	16.7	20.1 .
Randomized to postoperative azathioprine maintenance therapy	9 (14%)	14 (19%)
Compliant with postoperative azathioprine maintenance therapy	7/9 (78%)	10/14 (71%)
Mean CDAI at 6 weeks postoperatively	146	128

(4 percent) in the ETEA and two patients (3 percent) in the STSA group received Asacol and remained on Asacol maintenance therapy for the duration of the study. Of 23 patients in the postoperative azathioprine maintenance treatment stratum, 14 (19 percent) were randomized to the ETEA and 9 (13 percent) to the STSA group. Ten of fourteen (71 percent) and seven of nine (78 percent) patients, respectively, were compliant with azathioprine maintenance therapy. Compliance was determined by interviewing patients at three monthly intervals and was based on patient reporting.

After a mean follow-up of 11.9 months, the endoscopic recurrence rate was 42.5 percent (31/73) in the ETEA group compared with 37.9 percent (25/66) in the STSA group (−4.6 percent difference; 95 percent CI −21.0 to 11.9 percent; $P = 0.55$). The symptomatic recurrence rate was 21.9 percent in the ETEA group compared with 22.7 percent in the STSA group (+0.8 percent difference; 95 percent CI −13.2 to 15.3 percent; $P = 0.92$).

After excluding patients who received azathioprine maintenance therapy, the endoscopic recurrence rates were 42.4 percent (25/59) in the ETEA group compared with 42.1 percent (24/57) in the STSA group (+0.3 percent difference; 95 percent CI −17.7 percent to 18.2 percent).

Risk Factors for Recurrent Disease

This planned secondary analysis included 83 patients who did not develop a recurrence and 56 who developed an

endoscopic recurrence. Thirty-one of the latter had symptomatic disease. Nine factors that might potentially affect the risk of endoscopic recurrence and symptomatic recurrence were assessed. These included length of time since diagnosis, number of previous resections, smoking status, fistula or abscess present at surgery; type of procedure (laparoscopic or open), length of small bowel affected by Crohn's disease, postoperative azathioprine maintenance therapy, compliance with postoperative azathioprine maintenance therapy, and CDAI at six weeks. The results of the univariate analysis are shown in Table 5.

A multivariate logistic regression analysis was then performed. For both outcomes (endoscopic and symptomatic recurrences), the number of previous resections was found to be statistically significant: individuals who had had one or more previous resections were found to have a higher risk of endoscopic recurrence (1.78; 95 percent CI 1.06 to 2.90; $P = 0.028$) and symptomatic recurrence (2.00; 95 percent CI 1.14 to 3.60; $P = 0.0016$). In patients who were compliant with taking postoperative azathioprine maintenance therapy, both the risk of endoscopic (odds ratio [OR] 0.394; 95 percent CI 0.120 to 1.134; $P = 0.087$) and symptomatic recurrence were reduced, although only the reduction in symptomatic recurrence reached statistical significance (OR 0.13; 95 percent CI 0.01 to 0.78; $P = 0.021$).

DISCUSSION

Although surgery is very effective in treating complications and improving quality of life of patients with Crohn's disease, the benefits are minimized by the propensity of the disease to recur early and frequently. Over 90 percent of postoperative recurrences occur in the preanastomotic area, leading investigators to believe that the anastomosis may play some role in the development of recurrence.[8] Furthermore, previous studies have shown that the fecal stream plays a role. D'Haens and colleagues[9] performed a study in three patients who had an ileocolic resection and proximal defunctioning ileostomy. At the time of the study, there was no evidence of disease in the ileum distal to the ileostomy. Following infusion of intestinal luminal contents into the excluded ileal lumen, there was microscopic evidence of inflammation in the ileum of all three patients within seven days of the infusion. Although there was no endoscopic evidence of inflammation in these patients, others have observed endoscopic changes in the neoileum as early as six weeks after surgery.[19]

It has been hypothesized that stasis of stool proximal to the anastomosis may be the reason that most recurrences occur in this location; therefore, a wide side-to-side anastomosis, compared with an end-to-end anastomosis, may lead to a decreased risk of recurrence. However, previous retrospective studies have reported conflicting results likely because of differences in the study objectives and possible biases inherent in retrospective studies.[10–17] Several focused on a comparison between stapled and handsewn anastomosis rather than the configuration of the anastomosis and also included different anastomotic sites. Only one study, by Munoz-Juarez and colleagues, compared patients with stapled side-to-side anastomoses with handsewn end-to-end anastomoses.[10] Sixty-nine patients were included in each group. Recurrent Crohn's disease, based on the presence of symptoms, occurred in 39 (57 percent) in the ETEA group and 16 (24 percent) in the STSA group. The mean follow-up of the two groups was significantly different (70 months *vs.* 46 months). However, the differences remained significant even when analyzed actuarially. It should be noted, however, that it seems that recurrence was based only on symptoms without endoscopic or radiological confirmation. These authors also reported that the ETEA group, compared with the STSA group, had a higher overall complication rate (20 percent *vs.* 7 percent

TABLE 5. Univariate analysis of risk factors affecting recurrence (N = 139)

	No recurrence *n = 83*	*Endoscopic recurrence* *n = 56*	*Symptomatic recurrence* *n = 31*
Mean duration of disease (in years)*	9.5	12.4*	13.8**
Mean # previous resections*	0.34	0.61*	0.71**
Subjects with no previous resection	61 (73%)	30 (54%)	15 (48%)
Current smoker	23 (28%)	20 (36%)	13 (42%)
Fistula/abscess at surgery	28 (34%)	19 (34%)	11 (35%)
Open or laparoscopic converted procedure	56 (67%)	42 (75%)	21 (68%)
Mean length of small bowel involved with CD (in cm)	18	19	15.9
Randomized to postoperative azathioprine maintenance therapy	16 (19%)	5 (9.1%)	2 (6%)
Compliant with postoperative azathioprine maintenance therapy+	16 (19%)	5 (9%)	1 (3%)**
Mean CDAI at 6 weeks postoperatively*	128	150	175**

+ includes 4 patients who took azathioprine *not* per protocol.
*$P < 0.05$ endoscopic recurrence *vs.* no recurrence.
**$P < 0.05$ symptomatic recurrence *vs.* no recurrence.

respectively) and anastomotic leak rate (4.5 percent *vs.* 2.8 percent respectively).

There have been two randomized, controlled trials previously reported that compared anastomotic type. In an underpowered study, Cameron and colleagues reported no difference in recurrence rates between a group of 47 patients having end-to-end anastomoses compared with 39 patients having an end-to-side anastomosis (23 percent *vs.* 31 percent, P = NS).[20] Of interest in this study is that recurrences in the end-to-side group occurred in the preanastomotic area rather than the blind end of the small bowel, giving credence to the suggestion that the anastomosis may be important. A second trial reported by Ikeuchi and colleagues randomized patients to stapled or handsewn anastomosis.[21] In this study, there were variable types of anastomoses performed (*i.e*, ileoileal, ileocolic, colocolic, and ileorectal) as well as anastomotic configurations (functional end-to-end, circular stapled, handsewn end-to-end). Some patients had multiple anastomoses. The outcome was the need for reoperation for recurrent perianastomotic disease. Recurrence overall was lower in the stapled group compared with the handsewn group (18.9 percent *vs.* 37.8 percent respectively). In the subgroup of patients having ileocolic resections, the recurrence rates were 1 of 12 (9.1 percent) in the stapled group compared with 6 of 21 (28.6 percent) in the handsewn group. One concern with this trial is that it is unclear whether patients were truly randomized. Furthermore, in a report published two years earlier, only 3 recurrences in the stapled and 8 in the handsewn group had been detected with a follow-up of up to nine years, whereas two years later there were 7 and 17 recurrences reported respectively in the two groups.[22]

Simillis and colleagues performed a meta-analysis that included both randomized, controlled trials and nonexperimental studies. Eight studies with 661 patients were included in the analysis. These investigators found no significant difference in recurrence rates in patients with end-to-end or side-to-side anastomoses but concluded that "further randomized, controlled trials should be performed for confirmation."[23]

In the current study, only patients who had isolated ileal or ileocolic disease and who required an ileocolic resection were included. Although the objective of the study was to compare end-to-end anastomosis with side-to-side anastomosis, a pragmatic approach to the comparison of the anastomotic types was taken, reasoning that when surgeons perform a side-to-side anastomosis, it is generally performed with a stapler, and if an end-to-end anastomosis, it is generally handsewn. A 100-mm stapler, which is larger than normal, was used to perform the side-to-side anastomosis in order to ensure a wide anastomosis. The technical aspects of the procedure were agreed upon at an investigators' meeting but were otherwise left to the discretion of the surgeon.

Despite efforts to minimize the use of medication postoperatively, 12 patients in the ETEA group and 11 patients in the STSA group were prescribed variable medications for variable periods of time by their individual physicians. During the latter part of the trial, because of difficulties accruing patients, the inclusion criteria were amended to permit some patients to receive postoperative azathioprine maintenance therapy. However, we aimed to minimize bias by requiring that the decision to receive maintenance therapy be made prior to randomization, and then stratifying patients accordingly. A similar proportion of patients who received postoperative azathioprine maintenance therapy were allocated to each group and a similar proportion were compliant in taking it. Five patients were allocated to receive Asacol maintenance therapy, all of whom had evaluable end points and two of whom developed endoscopic or symptomatic recurrence.

We chose to use endoscopic recurrence as the primary outcome measure because endoscopic recurrence occurs earlier and more frequently, and there was a concern that a study using clinical recurrence rate would not be feasible unless a larger sample size could be attained. We chose to define endoscopic recurrence using a modification of the Rutgeerts score, considering only patients with "severe" endoscopic disease to have recurrence. In a previous study, we showed that over 65 percent of patients with evidence of severe endoscopic disease would develop symptomatic recurrence within a mean of 28 months.[24] Other studies assessing postoperative maintenance therapy have also used this end point.[25] The endoscopic recurrence rate of 40 percent in the present study is in keeping with previously reported studies. Rutgeerts *et al.*[18] found that 34 percent of patients had i2 or greater in a cohort of 122 patients who had an ileocolic resection and were colonoscoped at one year. In a previous study by our group, the observed endoscopic recurrence rate was 29 percent at one year.[24]

In this study, the symptomatic recurrence rate overall was approximately 20 percent, which is consistent with reported rates. With regard to the endoscopic rates of recurrence between the groups, we observed a difference of 4.6 percent, with 95 percent CI ranging from -21 percent to 11.9 percent. Because the trial ended early, our statistical power was reduced and the minimally significant difference was increased to 23 percent. However, we feel that this does not affect our conclusions, given that the observed difference was only 4.6 percent and not nearly close to the 20 percent hypothesized. Furthermore, the symptomatic recurrence rates, which are of greater clinical relevance, were virtually the same in both groups. Thus, the results of this study do not support the hypothesis that a wide side-to-side anastomosis leads to decreased recurrence of Crohn's disease and therefore, either type of anastomosis can be used. In addition, this

study has shown that both anastomotic techniques are equally safe. There was no difference in complication rates, particularly leak rates and reoperation rates. The leak rates of approximately 7 percent are in keeping with other reports where rates have ranged from 0 to 14 percent.[10,13–15,17,20,22,23] Because of the small number of patients who developed anastomotic leaks, it was not possible to assess what factors might predispose them to a leak. On the other hand, the advantage of the stapled anastomosis is the time saved to perform the anastomosis and the decreased total duration of the operation.

A number of variables suggested by previous authors as predictors of recurrence were examined. Interestingly, smoking status was not predictive of higher recurrence rates despite fairly strong evidence from observational studies that it is associated with a higher risk of recurrence.[26] Only the number of previous resections was found to be associated with a higher risk of recurrence. On the other hand, compliance with postoperative maintenance therapy was associated with a significantly reduced rate of symptomatic recurrence as well as a trend toward a reduced rate of endoscopic recurrence, which is in keeping with a previous randomized, controlled trial.[27]

In conclusion, this study has shown that recurrence rates are similar whether a handsewn end-to-end anastomosis or a stapled side-to-side anastomosis is performed. Both techniques can be performed safely. The advantage of a stapled side-to-side anastomosis is the reduced operative time. Postoperative maintenance therapy with azathioprine appears to be effective in reducing the risk of symptomatic recurrence in this cohort of patients.

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