Complications and Disease Recurrence After Primary Ileocecal Resection in Pediatric Crohn's Disease: A Multicenter Cohort Analysis

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Background: Studies on the outcome of ileocecal resection in pediatric Crohn's disease (CD) have a limited follow-up and fail to assign predictors of adverse outcomes. Therefore, we aimed to investigate (I) the complication and disease recurrence rates and (II) identify risk factors for these adverse outcomes after ileocecal resection for pediatric CD.

Methods: This is a retrospective cohort analysis of all children (<18 years) that underwent ileocecal resection as first intestinal resection for CD derived from 7 tertiary hospitals in the Netherlands (1990–2015). Risk factors were identified using multivariable analysis.

Results: In total, 122 children were included (52% male; median age 15.5 years [interquartile range 14.0–16.0]). Severe postoperative complications rate was 10%. Colonic disease (odds ratio: 5.6 [95% confidence interval {CI}: 1.3–26.3], $P = 0.024$), microscopically positive resection margins (odds ratio: 10.4 [95% CI: 1.1–100.8] $P = 0.043$), and emergency surgery (odds ratio: 6.8 [95% CI: 1.1–42.2], $P = 0.038$) were risk factors for severe complications. Clinical and surgical recurrence rates after 1, 5 and 10 years were 19%, 49%, 71% and 2%, 12%, 22%, respectively. Female sex (hazard ratio [HR]: 2.1 [95% CI: 1.1–3.8], $P = 0.023$) was a risk factor for clinical recurrence, whereas ileocecal disease (HR: 3.9 [95% CI: 1.2–12.5], $P = 0.024$) and microscopically positive resection margins (HR: 9.6 [95% CI: 1.2–74.5], $P = 0.031$) were risk factors for surgical recurrence. Immediate postoperative therapy reduced the risk of both clinical (HR: 0.3 [95% CI: 0.1–0.6], $P = 0.001$) and surgical (HR: 0.5 [95% CI: 0.1–0.9], $P = 0.035$) recurrence.

Conclusions: Ileocecal resection is an effective and durable treatment of pediatric CD, although postoperative complications occur frequently. Postoperative therapy may be started immediately to prevent disease recurrence.

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Key Words: pediatric, Crohn's disease, surgery, outcomes research

Crohn's disease (CD) is a disabling chronic inflammatory bowel disease that in 7% to 20% of cases already manifests in childhood.[1] The clinical course of pediatric-onset CD is described as more severe with more extensive disease, more aggressive disease behavior, and more periods with active disease compared with adult-onset CD.[2–4] Guidelines on the medical therapy for pediatric CD therefore suggest a different therapeutic and monitoring strategy, including an earlier use of immunomo-

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dulators and biologicals.[5] Despite intensive medical therapy, long-standing refractory inflammation may cause irreversible damage to the bowel wall, resulting in stricturing or penetrating disease,[6] which is best treated by surgical resection. Moreover, growth retardation as a complication of therapy resistant inflammation may also be an indication for surgical resection in pediatric patients with CD.[7]

Historically, a quarter of pediatric-onset CD patients undergo surgical resection within 5 years from diagnosis (25.5%; 95% confidence interval [CI]: 17.50–37.16).[8] Of these, ileocecal resection is the most frequently used surgical procedure in pediatric CD (53.2%), especially for disease confined to the ileocecal region.[9] The main drawback of ileocecal resection is, however, the supposed high postoperative morbidity and disease recurrence rate. A recent study on adults undergoing ileocecal resection for CD demonstrated that up to 9% of patients experienced intra-abdominal septic complications (IASC).[10] Furthermore, in a large population-based cohort of adults with CD, symptomatic disease recurrence was observed in 38% of patients 10 years after primary ileocecal resection.[11] Studies on children and adolescents do, however, not report morbidity and disease recurrence of ileocecal resection alone, but merely on intestinal resections of different extent and location.[12–15] Few studies that do report ileocecal resection in pediatric CD have a limited follow-up and fail to assign predictors for adverse postoperative outcomes.[16–18] As a result, current data on the outcome of ileocecal resection in children and adolescents with CD are limited.

Therefore, the aim of this multicenter study was to investigate complication and disease recurrence rates, identify predictors for these adverse postoperative outcomes, and assess catch-up growth and weight gain after primary ileocecal resection in pediatric patients with CD.

MATERIALS AND METHODS

Patients

In this retrospective cohort study, we aimed to include all consecutive children (aged <18 years) with an established diagnosis of CD according to the revised Porto criteria,[19] who underwent primary ileocecal resection for CD between January 1990 and December 2014 in 1 of 7 tertiary hospitals in the Netherlands. Primary ileocecal resection was defined as ileocecal resection as first surgery for CD without a history of intestinal resection, except for appendectomy. All procedures were performed by pediatric surgeons. Approval from the local Medical Ethics Review Committee was obtained.

Data Collection

Patients were identified from institutional databases covering all types of surgical procedures. Medical charts were reviewed for the following patient characteristics: age at diagnosis, sex, and disease phenotype according to Paris classification at time diagnosis and ileocecal resection.[20] Preoperative conditions included age at surgery, the use of CD-related medication, and laboratory testing (hemoglobin, serum C-reactive protein, and albumin levels). Preoperative steroid use was defined as use of any steroids within 12 weeks before surgery. Preoperative antitumor necrosis factor alpha (anti-TNFα) use was defined as patients using medication within 12 weeks before surgery, based on anti-TNFα half-life.[21] Surgical variables included type of surgical approach, type of anastomosis, additional surgical procedures, primary stoma rate, operating time, and the pathology report of the resected specimen. Anthropometrics (height, weight, body mass index [BMI], and weight for height with Z-scores) were assessed at the time of diagnosis, at the time of surgery, a year after surgery (within 8–16 months after surgery), and at end of follow-up.[22]

Outcomes

Complications

Complications within 30 days from surgery were distributed using the Clavien–Dindo classification.[23] Severe postoperative complications were defined as a Clavien–Dindo classification grade ≥ III (requiring surgical, endoscopic, or radiological intervention).[23] An IASC was defined as the presence of anastomotic leakage and/or intra-abdominal abscesses. Anastomotic leakage was confirmed if there was any defect at the anastomotic site confirmed on imaging procedures, examination under anesthesia, or by surgical reintervention. Intra-abdominal abscesses were confirmed by percutaneous punctures or imaging procedures. Risk factors for severe complications and IASC were explored.

Disease Recurrence

Clinical recurrence was defined as a Physician Global Assessment of CD activity (inactive, mild, moderate, and severe) from moderate to severe requiring the start of medical treatment or treatment intensification. Surgical recurrence was defined as disease recurrence requiring new resection or strictureplasty for active inflammation or (anastomotic) strictures. Risk factors for clinical and surgical disease recurrence were explored. The influence of postoperative maintenance treatment on clinical and surgical; recurrence was assessed in 2 patient groups: (1) immediate postoperative therapy (initiated within 30 days from surgery), either as prophylactic treatment of disease recurrence or as maintenance therapy (mesalazine, thiopurines, methotrexate, or anti-TNFα agents); (2) delayed therapy started at disease recurrence or patients without any postoperative therapy.

Surveillance endoscopy was not part of routine care after surgery in this pediatric cohort. In those patients who underwent full ileocolonoscopy, endoscopic recurrence at the ileocolonic anastomotic site was defined as a Rutgeerts score of ≥i2.[24]

Anthropometrics

Height for age Z-scores < −1.64 corresponding to < fifth percentile was denoted as the presence of growth failure.[25] Weight

to height instead of BMI was used to assess nutritional status, because length deflection due to chronic illness can flatter BMI, by which nutritional status appears more favorable than it actually is. Weight to height Z-scores below < -2 was defined as chronic malnutrition, according to the Dutch guideline for the detection of somatic causes of abnormal dietary behavior in children.[26] All outcomes were rated by one of the authors (K.D.).

Statistical Analysis

Continuous data with a normal distribution were presented as mean and SD, and paired or unpaired T tests were used. Continuous data with a nonnormal distribution were presented as median and interquartile range, and Mann–Whitney U tests or Wilcoxon signed-rank test were used. Categorical were presented as percentages and Fisher's exact tests were used. Missing data were assumed to be missing at random. Multiple imputation, using a multivariable model, was performed to adjust for missing values.[27] Risk analyses were performed using 5 imputed data sets. Predictive factors for severe complication and IASC were identified by univariate and multivariate logistic regression (expressed as odds ratio [OR] with 95% CI). Predictors for clinical and surgical recurrence were identified by univariable and multivariable Cox regression analysis (expressed as hazard ratio [HR] with 95% CI). In univariable regression, variables with a 2-sided P-value < 0.10 were considered for inclusion in multivariate analysis. All predictors were adjusted for the years of study entry (calculated from January 1991), because of probable changes in patient population and standard treatment that have occurred over a 25-year period. Proportional hazard assumptions of predictive factors in the Cox model were graphically evaluated with log minus log plot. Clinical and surgical recurrences were calculated by means of Kaplan–Meier curves. Statistical analysis was performed using IBM SPSS Statistics 22 for Windows. All statistical tests were 2-sided and assessed at a significance level of 5%.

RESULTS

A total of 122 patients underwent primary ileocecal resection (51.6% male, median age at surgery 15.5 years [interquartile range 14.0–16.0]). The most prevalent indications for ileocecal resection were stenosis of ileocecal area (64.8%), therapy refractory inflammation (27.9%), and intra-abdominal fistulae or abscesses (23.8%). Preoperative imaging was performed in 115 (94.3%) patients (endoscopy 34 [27.9%], computed tomography in 35 [28.7%] patients, ultrasound in 44 [36.4%] patients, magnetic resonance imaging in 50 [41.0%] patients, and abdominal x-ray in 30 [24.6%]) patients. The median time of follow-up after primary ileocecal resection was 48.5 months (18.75–121.00). There was no mortality during follow-up. Table 1 depicts patient characteristics at the time of ileocecal resection and details regarding the surgery.

Postoperative Complications

The overall complication rate, defined as any kind of morbidity within 30 days of primary surgery, was 29.5.% (n = 36) (for Clavien–Dindo classification of complications, see Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B427). Severe complications were reported in 12 patients (9.8%). Risk factors for developing severe complications were colonic disease (OR: 5.75 [95% CI: 1.26–26.31], $P = 0.024$), emergency surgery (OR: 6.84 [95% CI: 1.11–42.21], $P = 0.038$), and microscopically positive resection margin (OR: 10.43 [95% CI: 1.08–100.75], $P = 0.043$) (Table 2). IASCs occurred in 10 patients (8.2%). Colonic disease (OR: 12.91 [95% CI: 1.48–112.56], $P = 0.021$) was a risk factor for developing IASCs (Table 2).

Delayed complications, more than 30 days after primary ileocecal resection, occurred in 6 patients (4.9%). Two patients experienced a delayed wound infection, 2 patients had small bowel obstruction requiring surgical adhesiolysis, 1 patient developed a surgical-related enterocutaneous fistula, and another patient developed an incisional hernia.

Disease Recurrence

Clinical disease recurrence was diagnosed in 18.9%, 49.2%, and 71.0% of patients at 1, 5, and 10 years after primary ileocecal resection, respectively (Fig. 1). Multivariate Cox regression analysis identified female sex (HR: 2.1 [95% CI: 1.1–3.8], $P = 0.023$, Figure 2A) as a risk factor for clinical disease recurrence, whereas immediate postoperative therapy (HR: 0.3 [95% CI: 0.1–0.5], $P = 0.001$, Figure 2B) was associated with a reduced risk of developing clinical disease recurrence (Table 3).

Surgical recurrence was noted in 1.7%, 11.9%, and 22.4% of patients at 1, 5, and 10 years after primary ileocecal resection, respectively (Fig. 1). Disease confined to the ileocecal region (HR: 3.9 [95% CI: 1.2–12.5], $P = 0.024$, Figure 3A) and microscopically positive resection margin (HR: 9.6 [95% CI: 1.2–74.5], $P = 0.030$, Figure 3B) were independent risk factors for surgical recurrence, whereas immediate postoperative therapy (HR: 0.3 [95% CI: 0.1–0.5], $P = 0.001$, Figure 3C) was associated with a reduced risk of developing surgical disease recurrence (Table 3).

Twenty three (19%) patients did not received immediate postoperative therapy, 22 (18%) were treated with mesalazine, 64 (52%) with thiopurines or methotrexate, and 13 (11%) with anti-TNFα agents. In patients who received immediate postoperative therapy with anti-TNFα agents, none subsequently developed surgical recurrence. HRs regarding different types of immediate postoperative therapy for the prevention of disease recurrence, relative to no immediate postoperative therapy, were similar (see Table 2, Supplemental Digital Content 2, http://links.lww.com/IBD/B428).

Full ileocolonoscopy was performed in 59 patients (48%), of which 42 patients (71%) underwent primary postoperative ileocolonoscopy on clinical indication. Endoscopic recurrence at the ileocolonic anastomotic site was noted in 9.0%, 52.0%, and 71.0% of patients at 1, 5, and 10 years after primary ileocecal resection, respectively.

Growth and Weight

Growth failure was present in 22.8%, 21.8%, and 9.6% of patients at the time of diagnosis, surgery, and the last follow-up,

TABLE 1. Demographic and Surgical Characteristics of Pediatric Patients with CD at Time of Ileocecal Resection

	Patients (n = 122)
Male, n (%)	63 (51.6)
Age at surgery (median, IQR)	15.5 (14.0–16.0)
Months since diagnosis (median, IQR)	11 (3.0–31.25)
Smoking, n (%)	7 (8.7)
Age at diagnosis[a] (Paris classification), n (%)	
A1a	9 (7.4)
A1b	113 (92.6)
Disease location[b] (Paris classification), n (%)	
L1	69 (56.6)
L2	0
L3	53 (43.4)
L4a	31 (25.4)
L4b	4 (3.3)
L4ab	35 (28.7)
Disease behavior[c] (Paris classification), n (%)	
B1	26 (21.3)
B2	50 (41.0)
B3	14 (11.5)
B2B3	32 (26.2)
Perianal	24 (19.7)
Medical therapy at surgery, n (%)	
Steriods[d]	65 (54.2)
Anti-TNFα[e]	36 (29.5)
MTX[e]	10 (8.3)
Thiopurines[e]	57 (47.5)
Mesalazine[e]	29 (24.8)
EEN[e]	16 (13.1)
Medical therapy ever used before surgery, n (%)	
Steroids	99 (81.1)
Anti-TNF-α	47 (38.5)
MTX	24 (19.7)
Thiopurines	91 (74.6)
Mesalazine	53 (43.4)
EEN	67 (54.9)
Previous abdominal surgery, n (%)	20 (16.4)
Surgical access, n (%)	
Open	41 (35.0)
Laparoscopy	76 (65.0)
Conversion	10 (13.2)
Operating time (median, min, IQR)	159 (115–119)
Type of anastomosis, n (%)	
End-to-end	87 (74.4)
End-to-side	9 (7.4)
Side-to-side	21 (17.9)
Handsewn	99 (88.4)
Stapled	13 (11.6)
Stoma, n (%)	
Primary end-ileostomy	3 (2.5)
Loop-ileostomy	0
End-ileostomy after leakage	4 (3.3)
Reversal rate	5 (71.4)
Time to reversal stoma (mo, median, IQR)	8.5 (6–13.5)
Additional procedures, n (%)	13 (10.7)
Resection specimen	
Length (median, cm, IQR)	25.0 (19.0–32.0)
Resection margin positivity,[f] n (%)	66 (60.6)
Emergency surgery, n (%)	9 (7.4)
Perioperative blood transfusion, n (%)	4 (3.3)
Length of stay after ICR (d, median, IQR)	8 (6–12)

Variables containing missing data: Medical therapy at surgery, steroids n = 2 (1.6%), MTX n = 2 (1.6%), thiopurines n = 2 (1.6%), mesalazine n = 2 (1.6%), EEN n = 2 (1.6%), access n = 5 (4.1%), operating time n = 19 (15.6%), type of anastomosis (end-to-end/end-to-side/side-to-side) n = 5 (4.1%), type of anastomosis (handsewn/stapled) n = 10 (8.2%), resection specimen (length) n = 3 (2.5%), resection specimen (resection margin positivity) n = 13 (10.7%), and emergency surgery n = 2 (1.6%).

[a]A1a: <10 years; A1b: 10 to 17 years.

[b]L1: distal 1/3 ileum ± limited cecal disease; L2: colonic; L3: ileocolonic; L4a: upper disease proximal to ligament of Treitz; L4b: upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum.

[c]B1: nonstricturing, nonpenetrating; B2: stricturing; B3: penetrating; and B2B3: stricturing and penetrating.

[d]≥ 20 mg per day within 3 months preoperative.

[e]Within 3 months preoperative.

[f]Microscopically positive resection margins.

EEN, exclusive enteral nutrition; ICR, ileocecal resection; IQR, interquartile range; MTX, methotrexate.

respectively. Chronic malnutrition was present in 15.8%, 13.4%, and 3.6% of patients at the time of diagnosis, surgery, and the last follow-up, respectively.

The height for age Z-score, in contrast to the year preceding surgery (mean Δ Z-height score -0.08 [95% CI: −0.20–0.04], $P = 0.180$), improved in the year after surgery, although only in patients younger than 16 years (mean Δ height Z-score 0.33 [95% CI: 0.15–0.51], $P = 0.001$) and not in patients older than 16 years at the time of surgery (mean Δ height Z-score 0.06 [95% CI: −0.05–0.16], $P = 0.264$). The weight to height Z-score, in contrast to the year preceding surgery (mean Δ weight to height Z-score 0.13 [95% CI: −0.74–1.00], $P = 0.764$), improved in the year after surgery in patients with chronic malnutrition (mean Δ weight to height Z-score 1.92 [95% CI: 1.30–2.55; $P < 0.001$), but not in patients without chronic malnutrition (mean Δ weight to height Z-score 0.10 [95% CI: −0.43–0.65; $P = 0.668$). BMI Z-score exhibited similar results similar to weight to height Z-score (data not shown).

TABLE 2. Multivariable Analysis: Severe Complication and Intra-abdominal Septic Complications

	Severe Complications				Intra-abdominal Septic Complications			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex								
Female vs male	0.74 (0.22–2.51)	0.625			0.59 (0.15–2.26)	0.438		
Age at surgery	0.07 (0.83–1.37)	0.743			1.07 (0.69–1.66)	0.752		
Disease duration								
Months	0.99 (0.97–1.02)	0.550			1.00 (0.98–1.03)	0.937		
Disease location[a]								
L3 vs L1	4.62 (1.17–18.22)	0.029	5.75 (1.26–26.31)	0.024[b]	13.21 (1.61–108.34)	0.016	12.91 (1.48–112.56)	0.021[b]
Disease behavior[c]								
B2	0.28 (0.04–1.79)	0.233			1.26 (0.12–12.95)	0.418		
B3 or B2B3	1.10 (0.26–4.74)				2.87 (0.32–25.65)			
Preoperative steroids[d]	1.22 (0.34–4.32)	0.764			1.70 (0.43–6.73)	0.451		
Preoperative anti-TNFα[e]	0.73 (0.20–3.22)	0.701			1.17 (0.28–4.86)	0.828		
Hemoglobin	0.85 (0.41–1.74)	0.653			0.92 (0.44–1.93)	0.835		
Albumin	0.98 (0.89–1.07)	0.641			0.99 (0.90–1.10)	0.844		
CRP	1.00 (0.98–1.01)	0.612			0.99 (0.97–1.02)	0.607		
Emergency surgery	5.73 (1.22–26.93)	0.027	6.84 (1.11–42.21)	0.038[b]	8.23 (1.63–42.33)	0.011	6.38 (0.95–42.75)	0.056
Access								
Open vs laparoscopic	2.56 (0.72–9.10)	0.146			3.68 (0.73–18.73)	0.114		
Type of anastomosis[f]								
End-to-side	0.95 (0.10–9.03)	0.785			2.29 (0.22–23.46)	0.199		
Side-to-side	1.51 (0.36–6.37)				3.32 (0.80–13.81)			
Anastomosis technique								
Stapled vs handsewn	0.67 (0.08–5.78)	0.718			0.91 (0.10–8.18)	0.931		
Resection margin[g]								
Positive vs negative	8.02 (0.99–64.73)	0.051	10.43 (1.08–100.75)	0.043[b]	6.67 (0.81–55.22)	0.078	5.81 (0.63–53.60)	0.120

[a]Paris classification, L1: distal 1/3 ileum ± limited cecal disease; L3: ileocolonic.
[b]Significant multivariate corrected risk factor for postoperative complications, corrected for year of study entry ($P < 0.05$).
[c]Paris classification, categorical variable (reference category B1: nonstricturing, nonpenetrating): B2: stricturing; B3: penetrating; and B2B3: nonstricturing and nonpenetrating.
[d]≥ 20 mg per day within 3 months preoperative.
[e]Within 3 months preoperative.
[f]Categorical variable (reference category: end-to-end).
[g]Microscopically positive resection margins.
CRP, C-reactive protein.

DISCUSSION

In this multicenter study, we determined the postoperative complications and disease recurrence rates, assessed predictors for these adverse outcomes, and evaluated postoperative catch-up growth and weight gain in children and adolescents with CD that underwent primary ileocecal resection.

The overall complication rate of 29.5% in this cohort is in line with earlier reports in adult studies (23%–34%),[28,29] and similar or even lower compared with pediatric studies reporting up to 45% of patients experiencing complications.[14,30] The occurrence of severe complications in this cohort was 9.8%, which is similar to previous reports in adults (11%–13%)[10,29] and lower compared with previous reports in children and adolescents (12%–27%).[30,31]

Clinical disease recurrence was previously reported in 65% of adult patients[32] and in 60% of pediatric patients[12] at 5 years from ileocecal and intestinal resection, respectively. In a pediatric-onset population–based cohort, surgical recurrence was observed in 17% of subjects at 5 years from primary intestinal resection.[13] In this series, clinical and surgical recurrence was observed in 49.2% and 11.9% of subjects at 5 years from resection.

Postoperative complications and disease recurrence are a main point of concern, and identification of and anticipation on predictors is essential to postpone or even to prevent these

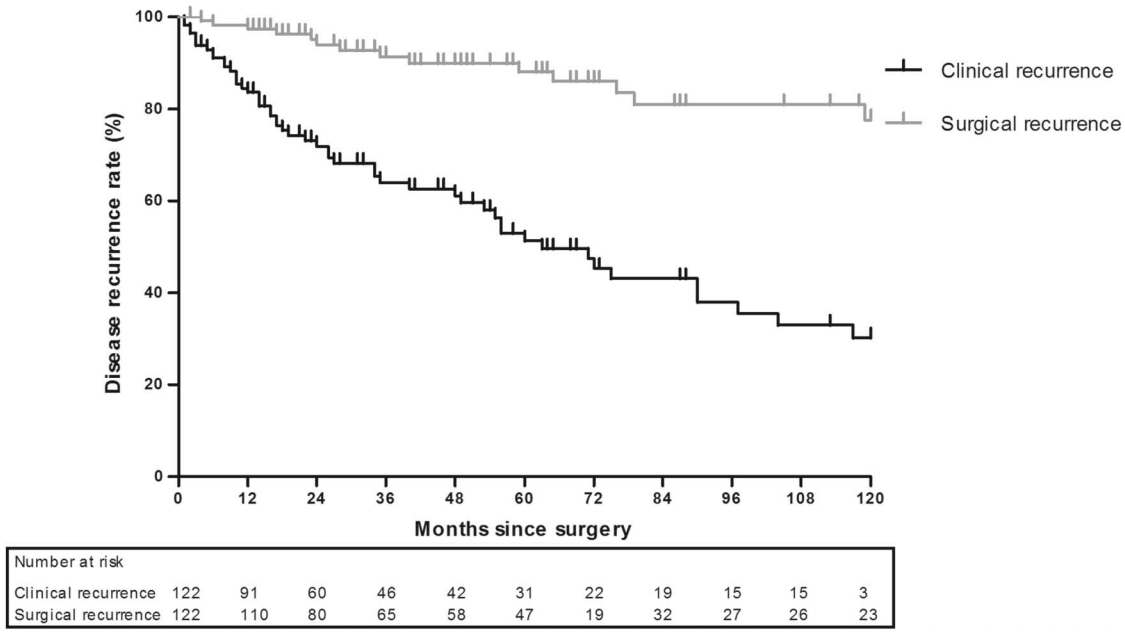

FIGURE 1. Kaplan–Meier clinical and surgical recurrence curves.

adverse outcomes. Numerous patient characteristics, including younger age of disease onset, more severe disease behavior, and duration of disease before surgery has been reported to influence postoperative outcome in few studies in adult patients.[33] None of these characteristics, however, had influence on postoperative complications and disease recurrence in the cohort described here. Yet, we found an association between sex and clinical disease recurrence. Females were more likely to experience earlier clinical recurrence, which was also reported by a study including 428 adult patients with CD who underwent abdominal surgery.[34] The cause of this gender difference remains elusive. Gender differences in smoking behavior, which itself is described to be a risk factor for clinical recurrence, may explain the association between sex and clinical recurrence.[32,35] However in this pediatric cohort, gender differences in smoking behavior were not observed (data not shown). Moreover, as gender difference was only observed in clinical recurrence, which is substantially influenced by clinical symptoms, and not in surgical recurrence, the cause might be in various perception or reporting of symptoms between sexes. Indeed, more severe abdominal pain is reported in females with CD.[36]

A laparoscopic approach has proven to decrease the occurrence of major complications in adults with CD.[37] Unfortunately, no difference was observed between laparoscopic approach and a reduced risk of severe complications or IASC in this cohort, likely related to the low number of cases. Nonetheless, body image and cosmetics are superior when using a laparoscopic instead of an open approach.[38]

Histological inflammation in resection margins has previously been found to increase the risk of IASC.[39] This is consistent with the association between microscopically positive resection margins and severe complications found in this cohort. Related to microscopically positive resection margins, disease outside the ileocecal region was also associated with severe complications and IASC. Histological inflammation at the resection margin, evaluated during the procedure, might be considered in deciding whether to perform a diverting ileostomy in patients with a risk of complications. However, a proper method for the rapid assessment of resection margins remains to be established, as a previous trial found the use of frozen sections to be an inaccurate method of determining histological involvement of resection margins.[40]

In this cohort, microscopically positive resection margin also had a significant impact on the time to surgical recurrence. Previous observational studies reported conflicting results on the influence of microscopically positive resection margin on postoperative disease recurrence.[41,42] In a controlled trial by Fazio et al.,[43] however, no significant difference was reported between patients with and without microscopically positive resection margins. Nevertheless, the presence of myenteric plexitis (i.e., inflammatory infiltrates in the myenteric plexus) at the proximal section margin, which because of inconsistent reporting was not evaluated in this study, seems to predict clinical, endoscopic, and surgical recurrence after ileocecal resection.[44,45] Moreover, plexitis severity has been shown to correlate with severity of endoscopic recurrence.[44] The true importance of microscopically positive resection margins on disease recurrence remains yet to be established.

The influence of medical therapy on postoperative outcomes has long been a point of discussion. Preoperative use of anti-TNFα agents is thought to have potential adverse effects on the outcomes of surgery. It is, however, difficult to definitively answer this question, because of confounding of disease severity (more complex disease in the group receiving anti-TNFα), as

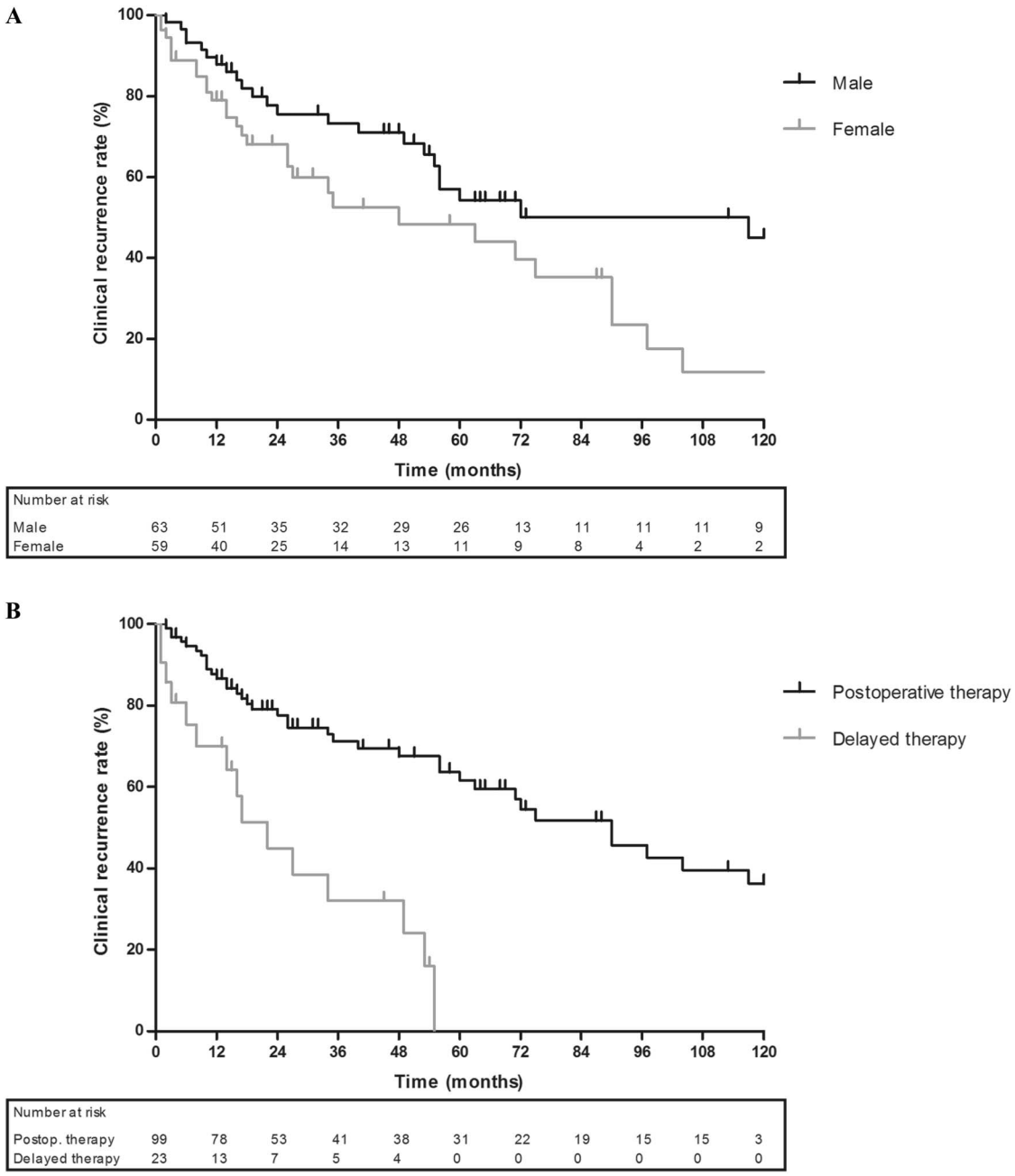

FIGURE 2. Kaplan–Meier clinical recurrence curves. A, female versus male patients; (B) patients with immediate postoperative therapy versus delayed therapy.

randomized studies are lacking. Nonetheless, in a recent meta-analysis, anti-TNFα administration within 3 months of surgery increased the risk for postoperative septic complications (i.e., anastomotic leakage) in adult patients with inflammatory bowel disease.[46] In addition, the height of serum anti-TNFα agents is associated with postoperative complications.[47] In this cohort, in which 29.5% of patients received preoperative anti-TNFα agents, anti-TNFα therapy had no impact on IASC, albeit, IASC were rare.

Postoperative prophylactic medical therapy is also a major point of discussion, because it has the potential to postpone or even to prevent disease recurrence. Mesalazine, thiopurines, and anti-TNFα agents are all considered to be superior to placebo for the prevention of postoperative recurrence.[48] Indeed, we found that patients receiving immediate postoperative therapy were less likely to develop clinical and surgical recurrence, thereby supporting the European Crohn's and Colitis Organisation and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition

TABLE 3. Multivariable Analysis: Clinical and Surgical Recurrence

	Clinical Recurrence				Surgical Recurrence			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex								
Female vs male	1.56 (0.94–2.60)	0.088	2.06 (1.11–3.82)	0.023[a]	0.71 (0.29–1.76)	0.459		
Disease duration								
Months	1.00 (0.97–1.01)	0.295			1.00 (0.99–1.02)	0.963		
Age at diagnosis[b]								
A1a vs A1b	1.50 (0.60–3.77)	0.390			0.73 (0.17–3.18)	0.675		
Disease location[c]								
L1 vs L3/L4	0.815 (0.49–1.36)	0.432			2.90 (1.11–7.58)	0.029	3.86 (1.20–12.45)	0.024[a]
Disease behavior[d]								
B2	1.05 (0.53–2.05)	0.311			0.73 (0.25–2.17)	0.119		
B3 or B2B3	0.68 (0.27–1.29)				0.26 (0.07–1.01)			
Steroids[e]	1.57 (0.74–3.33)	0.237			1.05 (0.31–3.60)	0.943		
anti-TNFα[e]	1.43 (0.84–2.43)	0.183			0.97 (0.34–2.76)	0.942		
Access								
Open vs laparoscopic	0.72 (0.41–1.24)	0.229			1.26 (0.47–3.31)	0.635		
Type of anastomosis[f]								
End-to-side	2.80 (1.14–6.88)	0.013	1.04 (0.44–2.48)	0.720	0.31 (1.14–6.88)	0.445		
Side-to-side	1.78 (0.90–3.53)		0.81 (0.36–1.80)		0.00 (0.00–>99.99)			
Anastomosis technique								
Stapled vs handsewn	1.80 (0.84–3.87)	0.132			0.84 (0.11–6.54)	0.866		
Resection margin[g]								
Positive vs negative	1.25 (0.71–2.19)	0.435			9.53 (1.26–72.38)	0.029	9.61 (1.24–74.51)	0.030[a]
Postoperative therapy[h]	0.26 (0.14–0.48)	<0.001	0.27 (0.13–0.57)	0.001[a]	0.26 (0.11–0.63)	0.003	0.34 (0.13–0.93)	0.035[a]

[a]Significant multivariate corrected risk factor for disease recurrence, corrected for year of study entry ($P < 0.05$).
[b]Paris classification, A1a: < 10 year versus A1b: 10 to 17 year.
[c]Paris classification, L1: distal 1/3 ileum ± limited cecal disease; L3: ileocolonic; and L4: upper gastro intestinal tract disease.
[d]Paris classification, categorical variable (reference category B1: nonstricturing, nonpenetrating): B2: stricturing; B3: penetrating; and B2B3: nonstricturing and nonpenetrating.
[e]Ever used before surgery.
[f]Categorical variable (reference category: end-to-end).
[g]Microscopically positive resection margins.
[h]Immediate postoperative therapy: prophylactic treatment of disease recurrence or maintenance therapy because of extra-ileocolic CD activity.

guidelines to initiate postoperative prophylactic therapy in all patients with surgically induced remission.[5] The postoperative therapy of choice, however, remains to be established. A network meta-analysis demonstrated that anti-TNFα therapy, compared with mesalazine and thiopurines, is most effective in prevention of disease recurrence in adult patients.[49] Comparative studies between postoperative prophylactic therapies in pediatric CD are however lacking. Although we found no differences between various types of postoperative medication for the prevention of clinical or surgical disease recurrence, no conclusion can be drawn regarding the prophylactic treatment of choice, as the rationale behind therapy selection was patient specific (i.e., confounded by indication).

Surprisingly, patients with disease beyond the ileocecal region were less likely to have surgical recurrence compared with patients with disease confined to the ileocecal region. Patients with disease beyond the ileocecal region could have been prone to receive immediate postoperative prophylactic therapy to prevent disease recurrence, over patients with disease confined to the ileocecal region. Also, the association between disease extension and surgical recurrence may have been distorted by a combination of recent improvements in diagnostic workup (i.e., determination of disease extension) and medical therapy. However, correction for all these potential confounders did not reduce the strength of the association between disease location and risk of surgical recurrence. In previous studies including adult patients, a wide variation in risk of postoperative recurrence for disease location was reported.[50] Therefore, disease location cannot reliably predict risk of postoperative recurrence at present.[50]

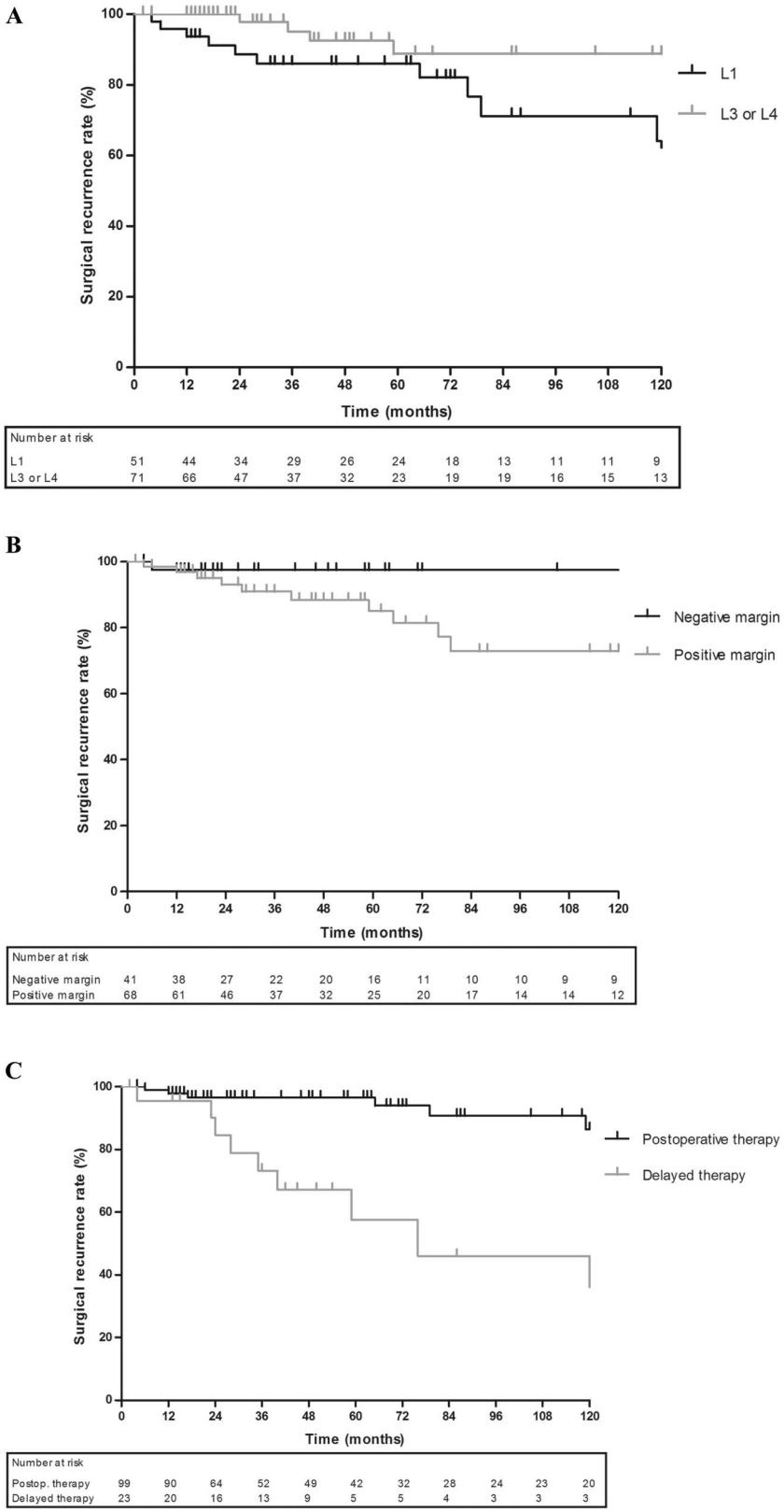

FIGURE 3. Kaplan–Meier surgical recurrence curves. A, patients with disease limited to the ileocecal region (L1) versus ileocolonic (L3) or upper gastro intestinal tract disease (L4); (B) patients with microscopically negative versus positive section margin; and (C) patients with immediate postoperative therapy versus delayed therapy.

Growth retardation can be an indication for intestinal resection in pediatric CD, because chronic persisting inflammation may eventually result in adolescents not achieving their target height.[7] Although most studies show postoperative catch-up growth after intestinal resection,[18,51,52] results have not been univocal.[31] In this study, postoperative catch-up growth was found in patients younger than 16 years in the year after surgery, which was not seen in the year preceding surgery. It must be taken into account that potential influence of periods of expected growth spurt, assessed by Tanner stage, are not taken into account, although reported Z-scores are adjusted for age and sex. Nonetheless, this finding implicates that ileocecal resection should be considered early in patients with growth retardation and high growth potential to increase the chances for catch-up growth. This is in contrast with the enduring notion that surgery is a last resort for children and adolescents with a paucity of medical options left. Concerns regarding surgical recurrence with the probability of multiple resections and finally short bowel syndrome, may have led to delay of surgical resection. Our data demonstrate that the overall need for additional surgical procedures is relatively low, thereby indicating the efficacy of surgery to induce disease remission. Furthermore, ileocecal resection might also be a valuable option in patients with disease located beyond the ileocecal region, because this had no adverse effects on disease recurrence. Nevertheless, these patients should be carefully monitored, because a substantial portion requires additional interventions because of complications.

In contrast to previous studies, the strength of this study are the strict inclusion criteria by selecting only patients with primary ileocecal resection, thereby eliminating potential bias from previous resections, which also seems to be a risk factor for recurrence by itself.[53] Furthermore, to our knowledge, this is the largest cohort of children and adolescents with CD with primary ileocecal resection so far, including 7 academic centers in the Netherlands. Moreover, we think that the cohort presented here is a representative sample of children and adolescents with CD, as national guidelines state that all pediatric patients with inflammatory bowel disease should to be under guidance and treatment of a pediatric gastroenterologist. Limitation of this study is the retrospective character of the data collection, by which postoperative follow-up has not been standardized. Furthermore, in our practice, surveillance ileocolonoscopy is not routinely performed to monitor postoperative disease recurrence in children and adolescents with CD, making data on endoscopic recurrence, which usually precedes clinical symptoms,[24] hard to interpret. Moreover, in the period of inclusion, changes have been made in the management of pediatric CD (i.e., the introduction of anti-TNFα agents). However, in the analysis of predictors for adverse outcomes, the potential influence of changes in management has been teased out.

In conclusion, ileocecal resection is an effective and durable treatment of pediatric CD. Therefore, ileocecal resection should be considered, respective of the substantial chance of postoperative complications, as a valid therapeutic option rather than a failure of medical treatment in children and adolescents with ileocecal CD.

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