Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial

Toer W Stevens, Maria L Haasnoot*, Geert R D'Haens, Christianne J Buskens, E Joline de Groof, Emma J Eshuis, Tjibbe J Gardenbroek, Bregje Mol, Pieter C F Stokkers, Willem A Bemelman†, Cyriel Y Ponsioen†, on behalf of the LIR!C study group‡*

Summary

Background **The LIR!C trial showed that laparoscopic ileocaecal resection is a cost-effective treatment that has similar quality-of-life outcomes to treatment with infliximab, an anti-tumour necrosis factor (TNF) drug. We aimed to compare long-term outcomes of both interventions and identify baseline factors associated with the duration of treatment effect in each group.**

Methods **In this retrospective follow-up study, we collected data from patients who participated in the LIR!C trial, a multicentre randomised controlled trial that compared quality of life after surgical resection versus infliximab in adult patients with non-stricturing and immunomodulator-refractory ileocaecal Crohn's disease. From Jan 1 to May 1, 2018, we collected follow-up data from the time from enrolment in the LIR!C trial until the last visit at either the gastrointestinal surgeon or gastroenterologist. In this study, outcomes of interest were need for surgery or repeat surgery or anti-TNF therapy, duration of treatment effect, and identification of factors associated with the duration of treatment effect. Duration of treatment effect was defined as the time without need for additional Crohn's disease-related treatment (corticosteroids, immunomodulators, biologics, or surgery).**

Findings **We collected long-term follow-up data for 134 (94%) of 143 patients included in the LIR!C trial, of whom 69 were in the resection group and 65 were in the infliximab group. Median follow-up was 63·5 months (IQR 39·0–94·5). In the resection group, 18 (26%) of 69 patients started anti-TNF therapy and none required a second resection. 29 (42%) patients in the resection group did not require additional Crohn's disease-related medication, although 14 (48%) of these patients were given prophylactic immunomodulator therapy. In the infliximab group, 31 (48%) of 65 patients had a Crohn's disease-related resection, and the remaining 34 patients maintained, switched, or escalated their anti-TNF therapy. Duration of treatment effect was similar in both groups, with a median time without additional Crohn's disease-related treatment of 33·0 months (95% CI 15·1–50·9) in the resection group and 34·0 months (0·0–69·3) in the infliximab group (log-rank p=0·52). In both groups, therapy with an immunomodulator, in addition to the allocated treatment, was associated with duration of treatment effect (hazard ratio for resection group 0·34 [95% CI 0·16–0·69] and for infliximab group 0·49 [0·26–0·93]).**

Interpretation **These findings further support laparoscopic ileocaecal resection as a treatment option in patients with Crohn's disease with limited (affected segment ≤40 cm) and predominantly inflammatory terminal ileitis for whom conventional treatment is not successful.**

Funding **None.**

Copyright **© 2020 Elsevier Ltd. All rights reserved.**

Lancet Gastroenterol Hepatol 2020

Published Online June 30, 2020 https://doi.org/10.1016/S2468-1253(20)30117-5

See Online/Comment https://doi.org/10.1016/S2468-1253(20)30234-X

*Joint first authors

†Joint senior authors

‡Study group members are listed in the appendix

Department of Gastroenterology and Hepatology (T W Stevens MD, M L Haasnoot MD, Prof G R D'Haens PhD, E J Eshuis PhD, B Mol MD, Prof C Y Ponsioen PhD) **and Department of Surgery** (C J Buskens PhD, E J de Groof PhD, T J Gardenbroek PhD, Prof W A Bemelman PhD), **Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; and Department of Gastroenterology and Hepatology, OLVG West, Amsterdam, Netherlands** (P C F Stokkers PhD)

Correspondence to: Prof Willem A Bemelman, Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, 1012 WX, Netherlands **w.a.bemelman@amsterdamumc.nl**

See Online for appendix

Introduction

Crohn's disease is a chronic inflammatory bowel disease that has a major effect on quality of life. The effect of different therapeutic strategies on rates of surgery to treat Crohn's disease is a topic of debate. Some studies have shown a clear decrease in the rate of resections in the past few decades.[1,2] A European population-based study did not find a difference in rates of surgery in the first 5 years after diagnosis compared with 20 years ago.[3] Treatment selection depends on several factors such as Crohn's disease activity, location, and behaviour.[4] The selection of the most appropriate treatment for Crohn's disease, including surgery, in the most timely manner is an unmet need in inflammatory bowel disease care and the scientific literature generally offers little guidance on this subject. Crohn's disease is confined to the ileocaecal region in approximately a third of patients with Crohn's disease.[5,6] Ileocaecal resection is the preferred treatment option in the presence of complications such as small bowel obstruction or perforation.[7] In the case of predominantly inflammatory ileocaecal Crohn's disease, patients who do not respond to conventional treatment are usually upscaled to treatment with biologics such as the anti-tumour necrosis factor (TNF) drug infliximab. However, the LIR!C trial[8,9] showed that laparoscopic ileocaecal resection was more cost-effective than

Research in context

Evidence before this study

The LIR!C trial showed that, at 1 year of follow-up, laparoscopic ileocaecal resection is cost-effective and results in similar quality of life as induction and maintenance treatment with the anti-tumour necrosis factor (TNF) drug infliximab in patients with non-stricturing ileocaecal Crohn's disease for whom conventional treatment was unsuccessful.

Added value of this study

Because Crohn's disease is a relapsing and remitting disease, assessment of outcomes beyond the 1-year endpoint of the LIR!C trial is important. To our knowledge, this is the first study to date to present a long-term comparison between two treatment strategies (anti-TNF *vs* ileocaecal resection). Half of the patients treated with infliximab required surgery and the rest still required treatment with biological therapy. Of the patients who had an ileocaecal resection, almost half did not require additional medical treatment within 5 years.

Implication of all the available evidence

Taking into account the results of the efficacy and cost-effectiveness analyses of the LIR!C trial, the present study indicates that ileocaecal resection for limited (affected segment ≤40 cm) uncomplicated terminal ileitis should no longer be regarded as a complication of the disease, but as a valid treatment option, which compares favourably to anti-TNF treatment.

infliximab therapy, but similar in terms of disease-specific quality of life, for patients with non-stricturing, predominantly inflammatory, ileocaecal Crohn's disease who are refractory to conventional therapy.[8,9] To date, follow-up data on resection versus anti-TNF therapy have been limited to only 1 year. Our aim was to assess the long-term outcomes of patients enrolled in the LIR!C trial and identify baseline factors associated with the duration of the effect of the initial therapeutic strategy.

Methods

Study design and participants

In this retrospective follow-up study, we collected data from patients enrolled in the previously reported LIR!C trial.[8,9] The LIR!C trial was a multicentre, randomised, controlled, clinical trial, that was run in 29 centres in the Netherlands and UK from May 2, 2008, to Oct 14, 2015. Briefly, patients with ileocaecal Crohn's disease were randomly assigned (1:1) to receive laparoscopic ileocaecal resection (hereafter referred to as resection) or infliximab induction and maintenance treatment. Eligible patients were aged 18–80 years with active Crohn's disease affecting the terminal ileum for whom more than 3 months of immunomodulator or glucocorticosteroid therapy, or both, was unsuccessful. Patients with signs of a dominant stricture (eg, prestenotic dilatation), an earlier ileocaecal resection, abscess, an affected ileal segment of longer than 40 cm in length, or an American Society of Anaesthesiologists (ASA) score of III or IV were excluded. The surgical procedure was not defined in the protocol. The resection was done by multi-port or single-port laparoscopy and, for most patients, a stapled side-to-side isoperistaltic anastomotic configuration was made.

We retrospectively collected patient-level, long-term follow-up data by medical chart review and captured it in structured electronic case record forms in Castor EDC. We collected all follow-up data from Jan 1, to May 1, 2018. Follow-up data were obtained for the time from enrolment in the LIR!C trial until the last visit (at the time of data collection) at either the gastrointestinal surgeon or gastroenterologist. We collected data about the first additional therapeutic intervention after randomisation and the need for Crohn's disease-related surgery and anti-TNF therapy in both groups.

For **Castor EDC website** see https://www.castoredc.com/

The study was approved by the medical ethics review committees of the Amsterdam University Medical Centres and all other participating centres. For the present study, a waiver for formal approval and individual patient informed consent was granted by the Medical Ethics Review Committee of the Amsterdam University Medical Centres.

Outcomes

The primary outcome of the LIR!C trial was disease-specific quality of life measured with the Inflammatory Bowel Disease Questionnaire (IBDQ).[10,11] In this study, outcomes of interest were need for surgery or repeat surgery or anti-TNF therapy, duration of treatment effect, and the identification of factors associated with duration of treatment effect. Duration of treatment effect was defined as the time without need for an additional medical treatment or surgery due to a disease flare, treatment intolerance, complications, or a combination of these factors. Additional treatments were defined as the initiation of glucocorticosteroids, immunomodulators, biologics, or the need for a surgical resection. Treatment optimisation with either a dose increase or interval reduction of anti-TNF therapy was not defined as an additional treatment. Notably, although the protocol recommended starting combination therapy with an immunomodulator in the infliximab group, in daily clinical practice the use of a prophylactic immunomodulator in the resection group or concomitant use in the infliximab group was left to the investigator's decision at each participating centre, and was not regarded as additional treatment.[12] Disease flare was defined by the documentation of signs of either clinical, biochemical, radiological, or endoscopic signs of disease at the discretion of the treating physician.

	Resection group (n=69)	Infliximab group (n=65)
Age at randomisation, years	33·4 (13·6)	31·6 (12·9)
Sex		
Male	24 (35%)	19 (29%)
Female	45 (65%)	46 (71%)
Crohn's disease duration, months	12·0 (4·5–37·5)	14·0 (6·0–42·5)
Active smoker*	21 (30%)	30 (46%)
Family history of inflammatory bowel disease	13 (19%)	12 (19%)
Perianal fistula	6 (9%)	12 (19%)
Extraintestinal manifestations	21 (30%)	20 (31%)
Corticosteroid use at baseline	53 (77%)	29 (45%)
Immunomodulator use after randomisation	26 (38%)	38 (59%)
C-reactive protein concentration at baseline, mg/L	10·0 (4·1–24·8)	8·0 (3·0–24·5)
Total follow-up, months	63·0 (33·5–92·0)	65·0 (40·5–96·5)

Data are mean (SD), median (IQR), or n (%). Resection=laparoscopic ileocaecal resection. *Active smoker or previous smoker in year before random assignment to treatment.

Table 1: **Demographic and clinical characteristics of LIR!C trial participants included in follow-up analysis**

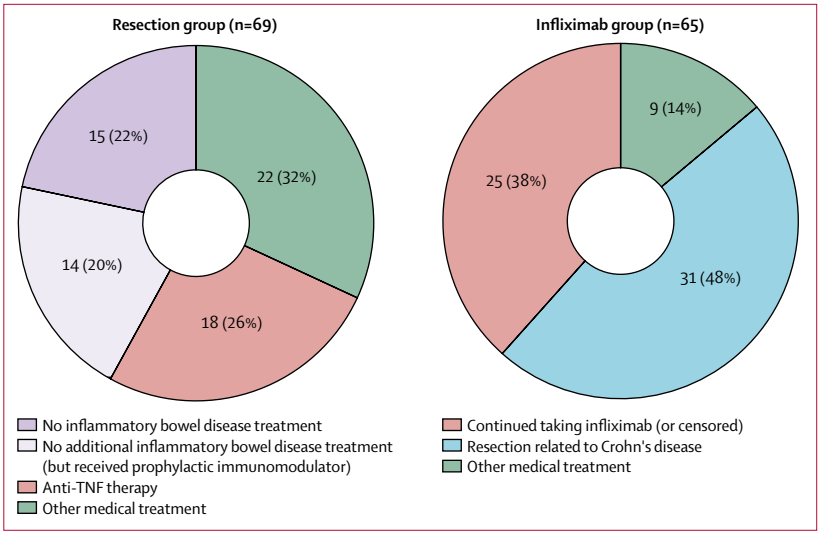

Figure 1: **Need for anti-TNF therapy and surgery in each treatment group**
TNF=tumour necrosis factor.

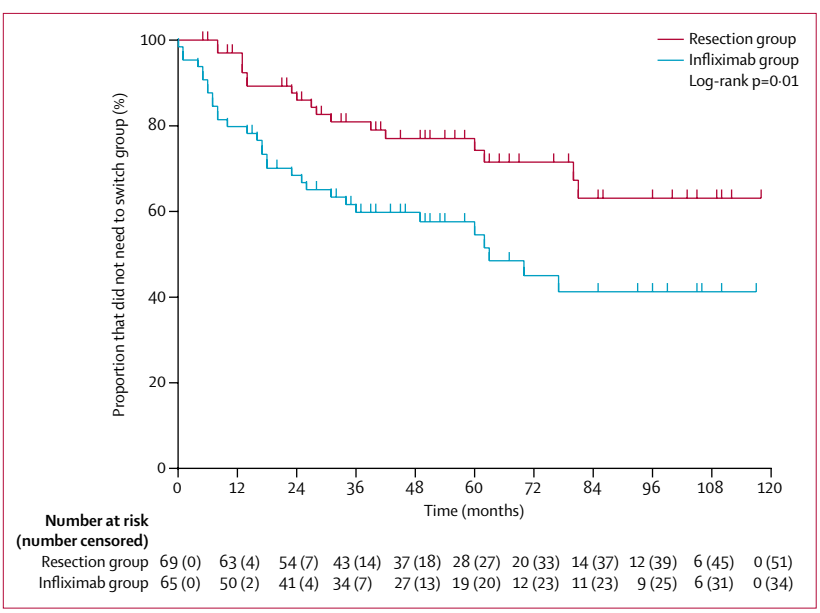

Figure 2: **Time to switching of treatment**
Kaplan-Meier survival curve of the probability of surviving without switching to the treatment of the other group. The log-rank test was used to evaluate differences between the groups.

Statistical analysis

We present normally distributed numerical data as mean (SD), non-normally distributed numerical data as median (IQR), and categorical data as n (%). We assessed normality of the distribution visually with histograms. We used log transformation to transform skewed data to approximate normality. We assessed differences between categorical variables using the χ^2 test using Yates' correction for continuity and between continuous variables using the unpaired *t* test or Mann-Whitney *U* test, depending on distribution. We considered p values of less than 0·05 to be significant.

We assessed data regarding the need to switch to the treatment of the other group and the duration of treatment effect using Kaplan-Meier analyses. We defined event-free survival as the time from enrolment in LIR!C until either an event of interest or until the patient was censored (ie, no event until last follow-up visit, loss to follow-up, discontinuation of infliximab electively because of deep remission, in case of a relapse when infliximab was stopped during pregnancy, and withdrawal of consent). If patients had multiple events of interest during follow-up, we only used the first for this analysis. We compared time-to-event data across both study groups using the log-rank test. With regards to duration of treatment effect, to quantify differences between groups and assess the effect of multiple factors we did a Cox proportional hazards regression analysis. The dependent variable was the time until need for additional treatment. We included the following explanatory variables: age at randomisation, Crohn's disease duration, sex, smoking status, family history of inflammatory bowel disease, perianal modifier, extra intestinal manifestations, baseline corticosteroid use, immunomodulator use after randomisation, and baseline C-reactive protein concentrations at baseline. We entered variables that we determined to be significant by univariable analysis into a multivariable model using backward selection. We used a significance level of p=0·2 for entry and of p=0·05 for retention. We express the effect of factors on the duration of treatment effect as hazard ratios (HR) with 95% CIs. We assessed the assumption of proportionality by visually inspecting log-minus-log plots.

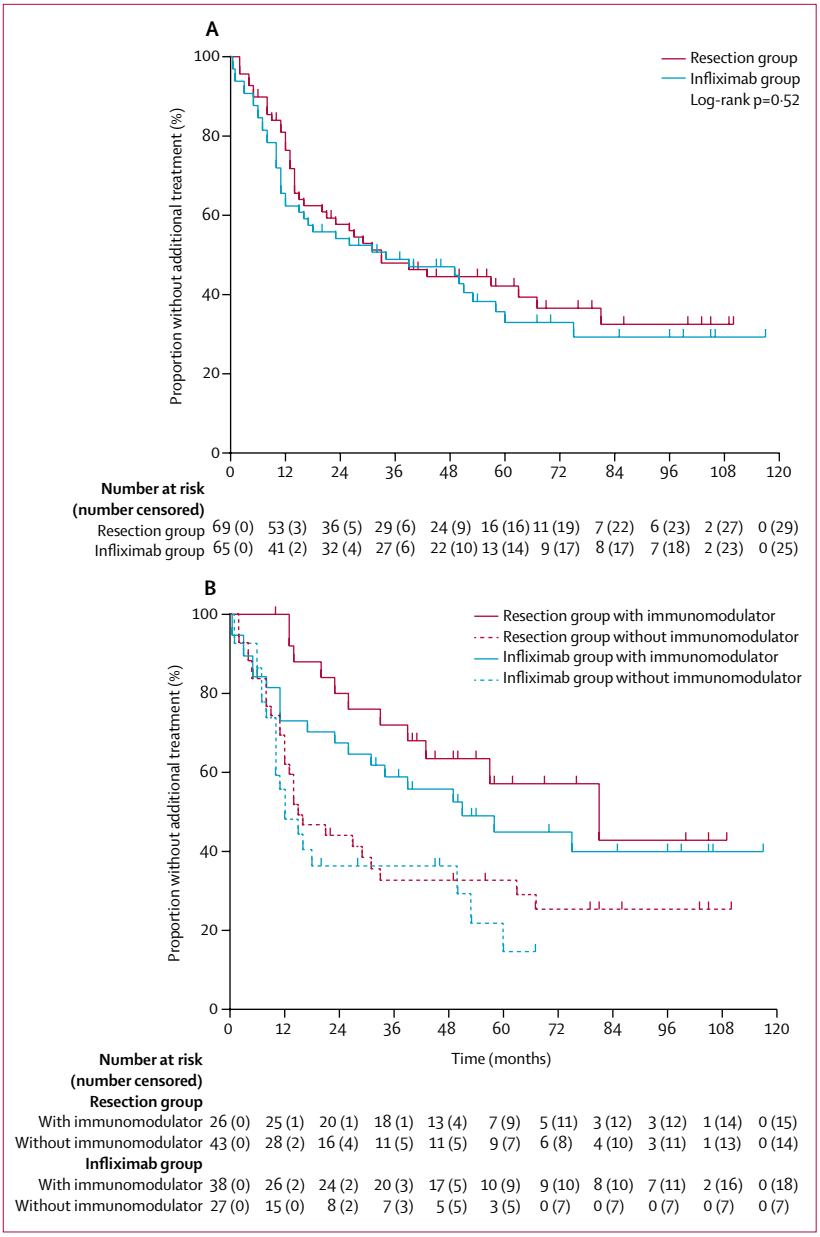

Figure 3: **Duration of treatment effect**
Kaplan-Meier survival curve of the probability of surviving without additional treatment in patients assigned to the resection group or infliximab group overall (A) and with and without additional treatment with an immunomodulator (B). In the Kaplan-Meier plots, the log-rank test was used to evaluate differences between the groups.

Unless we found strong evidence of non-parallelism, we assumed proportionality of hazards. We tested continuous numerical variables for the assumption of linearity by visually inspecting Martingale residuals plots.

We did post-hoc sensitivity analyses, repeating the Kaplan-Meier analysis and Cox proportional hazards regression analyses for duration of treatment effect as a dependent variable. However, in these sensitivity analyses duration of treatment effect was defined by the initiation of additional treatment only due to the onset of a disease flare. Patients that received additional treatment due to intolerance or formation of anti-drug antibodies were censored.

We did all analyses using the IBM Statistical Package for the Social Sciences (version 24) and visualised figures in Graphpad Prism (version 7). The LIR!C trial was registered at the Dutch Trial Registry (NTR1150).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Long-term follow up data were available for 134 (94%) of 143 patients who were included in the LIR!C trial of whom 69 (51%) had been assigned to the resection group and 65 (49%) had been assigned to the infliximab group. Nine (6%) of 143 patients (four in the resection group and five in the infliximab group) did not undergo the assigned trial intervention and were therefore not included in these follow-up analyses. The main characteristics of the study population are shown in table 1. Overall, median follow-up time was 63·5 months (IQR 39·0–94·5). There were no significant differences between the baseline characteristics of the two treatment groups of the follow-up population.

In the resection group, 18 (26%) of 69 patients started anti-TNF therapy after a median of 25·5 months (IQR 13·0–46·5) months and 29 (42%) did not need any additional Crohn's disease medication, although 14 (48%) of these 29 patients were given prophylactic immunomodulator therapy (figure 1). None of the patients in this group required a second resection related to Crohn's disease. In the infliximab group, 31 (48%) of 65 patients had a resection related to Crohn's disease, after a median of 17·0 months (IQR 6·0–34·0). For all of these patients, surgery was done because of disease activity, which could have included inflammatory activity or fibrostenotic or penetrating complications. Of the remaining patients, 25 (38%) were still taking infliximab at the end of their follow-up period and nine (14%) had switched to another biologic or received immunomodulator or corticosteroid treatment (figure 1). Patients in the resection group were less likely to need infliximab treatment than were patients in the infliximab group to need a resection (log-rank p=0·01; figure 2).

40 (58%) patients in the resection group and 40 (62%) patients in the infliximab group required additional treatment during follow-up. In the resection group, all patients who required additional treatment was due to disease activity (flare). In the infliximab group, 26 (65%) of 40 patients required additional treatment for a disease flare and the remaining 14 (35%) patients were given treatment due to intolerance to infliximab. In six (9%) of 69 patients in the resection group and five (8%) of 65 in the infliximab

group, a disease flare was defined on clinical symptoms alone. In all other cases, objective markers of disease activity were used (appendix p 1). Duration of treatment effect was similar between groups, with a median time without any additional Crohn's disease-related treatment of 33·0 months (95% CI 15·1–50·9) in the resection group and 34·0 months (0·0–69·3) in the infliximab group (log-rank p=0·52; figure 3). Details on the kind of first additional treatment are shown in figure 4. The incidence of additional treatment was 18·6% per person-year in the resection group compared to 20·8% per person-year in the infliximab group. A flow diagram about the number and kinds of treatments initiated over time in each group is shown in the appendix (p 2). Notably, in the resection group, 26 (38%) patients were given prophylactic immunomodulator treatment postoperatively compared with 38 (59%) patients in the infliximab group. The cumulative probability of sustained treatment effect according to treatment groups and prophylactic immunomodulator use is shown in figure 3.

In the resection group, by univariable regression analysis, age at randomisation, immunomodulator use after randomisation, and baseline corticosteroid use were associated with risk of additional treatment (table 2). In the multivariable analysis, both prophylactic immunomodulator use and age at randomisation were independently associated with the risk of additional treatment (table 2). In the infliximab group, by univariable regression analysis, only concomitant therapy with an immunomodulator was associated with the duration of treatment effect (table 3). Therefore no multivariable analysis was done.

In our post-hoc sensitivity analysis, when the analysis was limited to the initiation of additional treatment for Crohn's disease activity and patients who required additional treatment due to intolerance or formation of anti-drug antibodies were censored, the time-to-event distribution changed (figure 5). The risk of additional treatment in the infliximab group decreased, but no significant difference was seen between the resection group and the infliximab group (log-rank p=0·25).

Because the predictive value of potential risk factors might be influenced by the underlying reason for additional treatment (disease activity *vs* intolerance to treatment), we repeated regression analyses focusing on additional treatment due to the onset of a disease flare in the infliximab group (n=26) only. In the univariable regression analysis, concomitant immunomodulator use and baseline C-reactive protein concentration were associated with the need for additional treatment (appendix p 1). In multivariable analysis, none of the variables were independently associated with the risk of additional treatment.

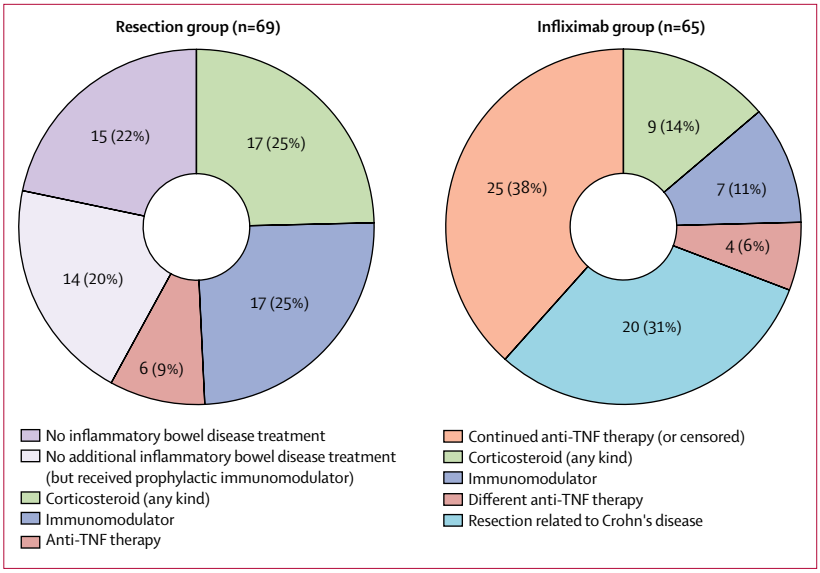

Figure 4: **First additional Crohn's disease-related treatment, by group**
Proportions might add up to more than 100% due to rounding. TNF=tumour necrosis factor.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age at randomisation	1·03 (1·01–1·05)	0·005	1·04 (1·02–1·06)	0·001
Male sex	1·40 (0·74–2·65)	0·306	..	..
Active smoker	1·10 (0·57–2·10)	0·786	..	..
Crohn's disease duration*	0·93 (0·54–1·59)	0·796	..	..
Prophylactic immunomodulator treatment	0·39 (0·20–0·79)	0·009	0·34 (0·16–0·69)	0·003
Positive family history inflammatory bowel disease	0·89 (0·39–2·03)	0·788	..	..
Baseline corticosteroid use	1·84 (0·81–4·19)	0·145	..	..
Extra-intestinal manifestations	1·10 (0·57–2·14)	0·770	..	..
Presence of perianal modifier	0·96 (0·34–2·70)	0·941	..	..
Baseline C-reactive protein concentration*	1·30 (0·66–2·54)	0·449	..	..

*Variables were log transformed to approximate normality.

Table 2: **Baseline factors associated with duration of treatment effect in the laparoscopic ileocaecal resection group**

Discussion

With a median follow-up time of more than 5 years, this long-term observational study of the LIR!C cohort showed that 74% of patients who initially had an ileocaecal resection did not need additional biological treatment, 42% did not need any additional treatment for disease flares, and none required a second resection. Conversely, 48% of patients in the infliximab group had a Crohn's disease-related resection, while the other 52% either maintained anti-TNF therapy or their drug therapy was switched or escalated. taking into account both the cost-effectiveness of resection compared with infliximab and the primary efficacy analysis reported previously,[8,9] these follow-up results further support the use of a laparoscopic ileocaecal resection in patients with Crohn's

	Univariable analysis	
	Hazard ratio (95% CI)	p value
Age at randomisation	1·00 (0·97–1·02)	0·859
Male sex	0·97 (0·49–1·91)	0·923
Active smoker	1·08 (0·58–2·01)	0·814
Crohn's disease duration*	0·81 (0·47–1·39)	0·441
Concomitant immunomodulator treatment	0·49 (0·26–0·93)	0·028
Positive family history inflammatory bowel disease	0·96 (0·42–2·18)	0·925
Baseline corticosteroid use	1·32 (0·71–2·46)	0·384
Extra intestinal manifestations	0·90 (0·53–2·06)	0·897
Presence of perianal modifier	0·59 (0·23–1·51)	0·269
Baseline C-reactive protein concentration*	1·22 (0·63–2·34)	0·558

*Variables were log transformed to approximate normality.

Table 3: **Baseline factors associated with the duration of treatment effect in the infliximab group**

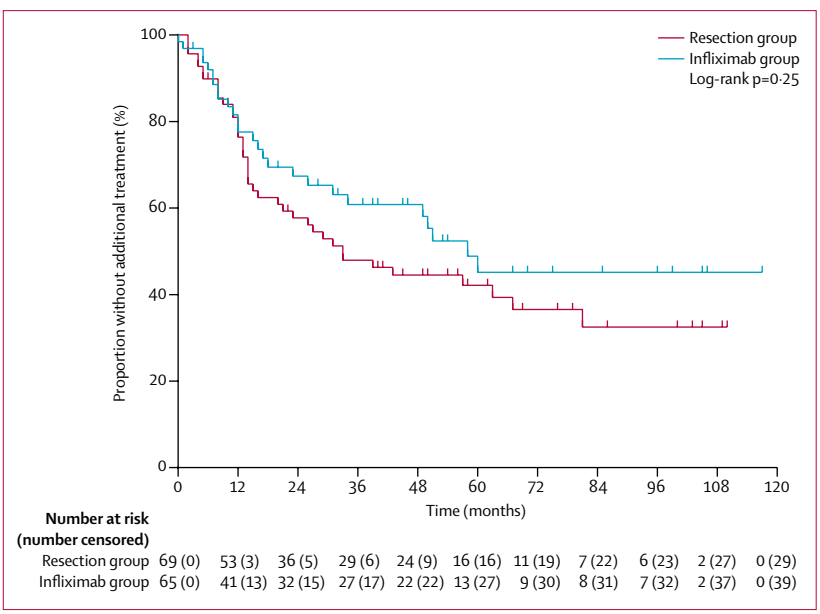

Figure 5: **Duration of treatment effect only considering first disease flare**
Kaplan-Meier survival curve of the probability of surviving without additional treatment because of disease flare (ie, all therapeutic interventions due to intolerance to treatment were censored). The log-rank test was used to evaluate differences between the groups.

disease with limited (affected segment ≤40 cm) ileocaecal disease for whom conventional medical treatment has been unsuccessful.

The primary objective of Crohn's disease management is to alter the natural disease course, prevent complications, and optimise patient quality of life.[13] Early surgery in ileocaecal Crohn's disease was previously shown to reduce the risk of clinical recurrence when compared with late surgery (HR 0·57, 95% CI 0·35–0·92).[14] Notably, the LIR!C study population consisted of patients with Crohn's disease with predominantly inflammatory terminal ileitis refractory to conventional treatment, who would usually be upscaled to treatment with biologics. The long-term outcome data presented here show that early surgery might help minimise the need for anti-TNF therapy, with 74% of patients in the resection group not needing anti-TNF therapy during follow-up. Furthermore, none of the patients in the resection group needed a second resection. This finding is in contrast with results from a meta-analysis of 11 population-based studies investigating the risk of a second intestinal resection in Crohn's disease, reporting a 5-year risk of second surgery of 24·2% (95% CI 22·3–26·4) pooled for all Montreal classifications of disease.[15] Subsequently, results from a joint effort between our institute (Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands) and the University Hospital of Leuven (Leuven, Belgium), showed a 5-year surgical recurrence rate after primary ileocaecal resection of 6·5%.[16] This observation might be explained by the fact that patients are followed up more intensively after surgery than previously, with systematic endoscopic evaluations and initiation of treatment in the presence of substantial mucosal lesions even in the absence of symptoms. Early surgery and thorough postoperative surveillance seem to pay off in terms of reduction of surgical recurrence. Notably, this observation does not necessarily apply to patients with more extensive terminal ileitis or ileocolonic (L3) disease, since these patients were not part of the study population. Furthermore, the data we present here show that after 5 years of follow-up, and taking into account that 38% of patients were given prophylactic immunomodulator treatment after surgery, a considerable proportion of patients (42%) in the resection group did not have endoscopic or clinical recurrence requiring additional Crohn's disease treatment.

The impact of increasing medical options on surgery rates in Crohn's disease remains a topic of debate. Some studies show a clear decrease while a 2018 report did not observe significant changes compared with 20 years ago.[1–3] Despite widespread availability of biologics, a considerable proportion of patients seem to eventually still require surgery, a postulation that was corroborated in this study. In the infliximab group, 48% of the patients needed to undergo a Crohn's disease-related resection after a median of 17 months. Ideally, patients who would benefit from an ileocaecal resection early in the disease course should be identified early to prevent exposure to ineffective and potentially toxic drugs. Hence, an effective approach might be to identify patients who are unlikely to respond to infliximab upfront, offer an ileocaecal resection as first-line treatment, and reserve treatment with biologics in case postoperative recurrence develops. Unfortunately, the predictive tools for this strategy are lacking and urgently needed.[17]

The duration of treatment effect, defined by the need for additional Crohn's disease-related treatment after the initial assigned treatment, was similar between both

groups. Approximately 60% of patients in both groups required additional treatment. We tried to identify factors associated with the duration of effect. Immunomodulator use in conjunction with both treatment strategies was associated with a reduced risk of requiring additional treatment. Both indications for immunomodulator use (prevention of postoperative recurrence and combination therapy with infliximab) are supported by current guidelines.[4,7] Hence, postoperative prophylaxis with an immunomodulator appears to be an attractive option, although many patients do not tolerate these drugs and risk of malignancy and infections is increased with their use. Prophylactic immunomodulator use is supported by previous research, although the TOPPIC trial only found a beneficial effect of mercaptopurine in preventing postoperative recurrence in active smokers.[18–20] Monitoring for Crohn's disease recurrence with a 6-month endoscopy should prompt treatment escalation if clinically significant mucosal recurrence is present; a strategy that was found to be effective in the Australian POCER trial.[21] For infliximab treatment, combination with an immunomodulator is well established;[22] however, in a sensitivity analysis of the infliximab group focusing on additional treatment due to a Crohn's disease flare only, the beneficial effect of an immunomodulator was no longer significant. This finding is likely due to reduced immunogenicity as the main cause for the beneficial effect of combination therapy.

Inferences coming from our two separate prediction models (the infliximab group and resection group models) should be made with caution. For example, to assess whether the magnitude of protection from addition of an immunomodulator was different between the treatment groups, we repeated the regression analysis for both treatment groups together. In this unified model, in which treatment was fitted in, we found no significant interaction between treatment group and immunomodulator use, suggesting that the protective effect of a prophylactic immunomodulator does not significantly differ between the treatment groups (data not shown). Furthermore, the definition of additional treatment included the initiation of an immunomodulator. Therefore, because patients who received concomitant or prophylactic treatment with an immunomodulator had no risk of receiving an immunomodulator as additional treatment later on, it needs consideration that this might in part influence the observed beneficial effect of adding an immunomodulator to the assigned treatment strategy. However, use of an immunomodulator in conjunction with the allocated treatment strategy did not preclude the initiation of other available therapeutic drugs. Therefore, disease recurrence would have elicited the initiation of additional treatment irrespective of whether an immunomodulator was still an available therapeutic drug.

Our study had several limitations, mainly because of its retrospective nature. After 1 year, no structured follow-up or treatment algorithm was applied to the LIR!C trial. Quality-of-life assessments were not available during follow-up. Data collection was focused on the first additional therapeutic intervention and the need for anti-TNF therapy and surgery in both groups. Hence, no specific information was obtained regarding second-line and third-line treatment choices, unless anti-TNF therapy was started or an additional resection was done. Baseline endoscopic and radiological variables were not included in our prediction analyses because data were heterogeneous (coming from 29 hospitals) and detailed information was often missing. Because the measurement of faecal calprotectin concentration was only implemented towards the end of the active recruitment phase of the LIR!C trial (2008–15), calprotectin concentrations could not be included in prediction analyses. Finally, we did not include endoscopic dilatations in the definition of a treatment escalation and data regarding this procedure were not collected.

In summary, with a median of 63·5 months of follow-up data from the LIRIC cohort, this long-term follow-up study supports early surgery as part of a multidisciplinary approach.

Contributors

TWS, MLH, GRD, WAB, and CYP conceived the study. TWS, MLH, EJeG, EJE, TJG, and BM collected the data. TWS and MLH analysed and interpreted the data and drafted the manuscript. GRD, CJB, WAB, and CYP and PCF critically reviewed the data and first drafts of the manuscript. All authors critically reviewed and approved the final manuscript.

Declaration of interests

GRD has served as advisor for AbbVie, Ablynx, Amakem, AM Pharma, Avaxia Biologics, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion Healthcare, Cosmo, Covidien, Ferring, Dr Falk Pharma, Engene, Galapagos, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson and Johnson, Lycera, Mediametrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, Pfizer, Prometheus Laboratories/Nestle, Protagonist, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor and received speaker fees from AbbVie, Ferring, Johnson and Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Shire, Millennium/Takeda, Tillotts, and Vifor outside of the submitted work. WAB reports funding from Vifor and Braun and personal fees from Takeda and Johnson and Johnson outside of the submitted work. CYP reports grants from Takeda and personal fees from Shire and Pliant outside of the submitted work. All other authors declare no competing interests.

References

1 Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut* 2014; **63:** 1607–16.

2 Ma C, Moran GW, Benchimol EI, et al. Surgical rates for Crohn's disease are decreasing: a population-based time trend analysis and validation study. *Am J Gastroenterol* 2017; **112:** 1840–48.

3 Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2018; published online Jan 23. DOI:10.1136/gutjnl-2017-315568.

4 Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. *J Crohns Colitis* 2017; **11:** 3–25.

5 Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101:** 1274–82.

6 de Groof EJ, Rossen NG, van Rhijn BD, et al. Burden of disease and increasing prevalence of inflammatory bowel disease in a population-based cohort in the Netherlands. *Eur J Gastroenterol Hepatol* 2016; **28:** 1065–72.

7 Gionchetti P, Dignass A, Danese S, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: surgical management and special situations. *J Crohns Colitis* 2017; **11:** 135–49.

8 Ponsioen CY, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017; **2:** 785–92.

9 de Groof EJ, Stevens TW, Eshuis EJ, et al. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C Trial. *Gut* 2019; **68:** 1174–80.

10 Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989; **96:** 804–10.

11 Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994; **106:** 287–96.

12 Eshuis EJ, Bemelman WA, van Bodegraven AA, et al. Laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in Crohn's disease: a randomized multicenter trial (LIR!C-trial). *BMC Surg* 2008; **8:** 15.

13 Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015; **110:** 1324–38.

14 Aratari A, Papi C, Leandro G, Viscido A, Capurso L, Caprilli R. Early versus late surgery for ileo-caecal Crohn's disease. *Aliment Pharmacol Ther* 2007; **26:** 1303–12.

15 Frolkis AD, Lipton DS, Fiest KM, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. *Am J Gastroenterol* 2014; **109:** 1739–48.

16 de Buck van Overstraeten A, Eshuis EJ, Vermeire S, et al. Short- and medium-term outcomes following primary ileocaecal resection for Crohn's disease in two specialist centres. *Br J Surg* 2017; **104:** 1713–22.

17 Stevens TW, Matheeuwsen M, Lönnkvist MH, et al. Systematic review: predictive biomarkers of therapeutic response in inflammatory bowel disease-personalised medicine in its infancy. *Aliment Pharmacol Ther* 2018; **48:** 1213–31.

18 Hanauer SB, Korelitz BI, Rutgeerts P, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127:** 723–29.

19 D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. *Gastroenterology* 2008; **135:** 1123–29.

20 Mowat C, Arnott I, Cahill A, et al. Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2016; **1:** 273–82.

21 De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; **385:** 1406–17.

22 Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362:** 1383–95.