

Does smoking cessation reduce surgical recurrence after primary ileocolic resection for Crohn's disease?

Running head: Smoking cessation in Crohn's; Category: Inflammatory Bowel Disease

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Abbreviations

CD – Crohn's disease

CI – Confidence interval

ICR – Ileocolic resection

IQR – Interquartile range

FU – Follow-up

SBR – Small bowel resection

SP – Strictureplasty

ABSTRACT

BACKGROUND: Tobacco smoking is known to be a risk factor for recurrence of Crohn's disease after surgical resection.

OBJECTIVE: To assess the effect of smoking cessation on long-term surgical recurrence after primary ileocolic resection for Crohn's disease.

DESIGN: Retrospective review of a prospectively maintained database.

SETTINGS: Patient demographic data, medical and surgical details were combined from two specialist centers. After ethical approval, patients were contacted in case of missing data regarding smoking habit.

PATIENTS: All patients undergoing ileocolic resection between 2000 and 2012 for histologically confirmed Crohn's disease. Those with previous intestinal resection / strictureplasty for Crohn's disease, leak after ileocolic resection or never reversed were excluded.

MAIN OUTCOME MEASURES: The primary endpoint was surgical recurrence measured by Kaplan-Meier survival analysis, and secondary medical therapy at time of follow-up.

RESULTS: Over a 12-year period, 290 patients underwent ileocolic resection. Full smoking data was available for 242/290 (83%). There were 169 non-smokers (70%) (group 1), 42 (17%) active smokers at the time of ileocolic resection who continued smoking up to last follow-up (group 2) and 31 (13%) who quit smoking after ileocolic resection (group 3). Median time of smoking exposure after ileocolic resection for group 3 was 3 years (IQR 0-6) and median follow-up time for the whole group 112 months (9 years) (IQR 84-148). Kaplan-Meier survival analysis showed a significantly higher surgical recurrence rate for group 2

compared to group 3 (16/42 (38%) vs 3/31 (10%), $p=0.02$; risk ratio 3.9 (95% CI 1 - 12)).

Additionally, significantly more patients in group 2 without surgical recurrence received immunomodulatory maintenance therapy compared to group 3 (12/26 (46%) vs 4/28 (14%), $p=0.01$; risk ratio 3.2 (95% CI 1 - 9)).

LIMITATIONS: Retrospective design and small number of included patients.

CONCLUSIONS: Smoking cessation after primary ileocolic resection for Crohn's disease significantly reduces the long-term risk of surgical recurrence and is associated with less use of maintenance therapy.

INTRODUCTION

Surgical resection is required for many patients with ileocolic Crohn's disease (CD) despite improvement in medical management. The major disadvantages of surgery are morbidity and recurrent disease. The risk of recurrent disease requiring further surgery varies in the literature¹⁻³. A recent study from Belgium and Holland reported surgical recurrence rates of 6.5% at 5 years and 19.1% at 10 years⁴.

The link between smoking and CD was first reported by Somerville et al and its deleterious effect on the natural history in the multi-factorial **etiology** of the disease was later confirmed⁵⁻⁷. Smoking has been demonstrated to be a risk factor for recurrence after surgery and to be associated with higher overall disease costs in CD^{8,9}.

Cosnes et al. reported a benefit from smoking cessation, with a 65% lower risk of disease flares in "quitters" compared to those who continued to smoke¹⁰. Similarly, Nunes et al. in a large prospective multicenter study demonstrated a reduction in disease relapses in "quitters" compared to smokers¹¹.

The aim of this study was to assess the impact of smoking cessation on surgical recurrence in a group of patients undergoing first time surgery for ileocolic Crohn's disease.

MATERIALS & METHODS

All patients who underwent a primary ileocolic resection (ICR) without simultaneous small bowel resection (SBR) or strictureplasty (SP) for CD, and who had no previous intestinal resection / SP related to CD were identified from two prospectively maintained databases at two university teaching hospitals, between 2000 and 2012. Those patients who were defunctioned because of a leak after ICR or those who were never reversed were excluded

from our analysis. Patient demographics, duration of CD, pathology reports, Montreal classification of disease and details of surgical treatment, including the need for a temporary ileostomy, were recorded. Perianal disease was defined as previous anal abscess/fistula/stricture or surgery for anal disease. Smoking history was obtained from a prospective databases and notes review. Patients with an absent or incomplete smoking history were contacted for telephone interview to obtain an accurate smoking history. The study was approved by our ethical committee (2011/222-31).

Patients were divided in three groups;

Group 1 - Non-smokers: those who never smoked or did not smoke at the time of ICR

Group 2 - Smokers: those who were smoking one cigarette or more a day at the time of ICR for at least three months and who continued smoking until last follow-up or surgical recurrence.

Group 3 - Quitters: those who quitted smoking after ICR.

The census point for inclusion regarding date of primary ICR was December 2012, with the intention of having at least 5 years' follow-up.

Surgical recurrence was the primary endpoint, defined as subsequent surgery for CD (ICR, SBR, SP or colectomy). Secondary outcome was the need for maintenance therapy for CD at time of follow-up (FU). Time to surgical recurrence was taken from the time of ICR with anastomosis, to the time of re-operation. For those patients who had a temporary ileostomy, time to recurrence was taken from the time of closure to the time of re-operation. Patients who were never reversed were excluded.

Medical prophylaxis and maintenance therapy related to patients' CD following surgical resection was recorded.

Statistical analysis

For the descriptive analysis, mean \pm standard deviation was used for normally distributed data. For non-normal distributed data, median plus interquartile range (IQR) was used. For comparing numerical data, unpaired t-test and one-way ANOVA test were used when dealing with normally distributed data and Mann-Whitney U test and Kruskal-Wallis test when dealing with non-normal distributed data. Chi square test was applied for comparing proportions from categorical data between groups. A p-value of 0.05 was used as the threshold for assigning significance. Kaplan-Meier survival analysis and odds ratio calculation was done using R statistical software.

RESULTS

Retrospective Cohort

After applying the inclusion criteria, 290 patients were identified. A full smoking history was obtained in 242 (83%), 49% male, age 36 (range 13-78). Preoperative details are shown in Table 1.

Primary anastomosis was performed in 178/242 patients (74%), and 64/242 patients (26%) underwent an ICR with temporary ileostomy. Six patients had an anastomotic leak (2.7%) requiring re-operation and ileostomy formation.

Smoking history

Classified as non-smokers (group 1) were 169 patients (70%), 42 (17%) as smokers (group 2) and 31 (13%) as quitters (group 3) (Table 2). Of group 3, 14 patients (45%) were able to quit within the first year after ICR, 2 patients between one and 3 years after ICR and 15 patients after more than 3 years. Three patients started smoking after their ICR (age of those patients was 14, 15 and 36 years) and were excluded from analysis. Ten patients (3%) died during follow-up, unrelated to CD.

There was no significant difference regarding time of follow-up, demographic data or risk factors for recurrence between the groups (Table 2).

Median time of FU for the whole cohort was 112 (IQR 84-148) months (approximately 9 years).

Surgical recurrence rate at last follow-up

The overall surgical recurrence rate was 47/242 (19%) at 9 years. The highest rate of surgical recurrence was amongst smokers (group 2), which was significantly greater than for the quitters (group 3) ($p=0.02$, Figure 1). The risk ratio until end of follow-up (RR) for surgical recurrence amongst smokers compared to quitters was 3.9 (95% CI 1 - 12) (Table 3). Details of subsequent surgical operations are shown in Table 3.

Eleven out of 16 smokers (69%) at the time of their second intestinal resection continued smoking until the follow-up point and 8 out of those 11 (73%) needed at least a third intestinal resection. Two out of the three patients who started smoking during follow-up had a surgical recurrence.

Maintenance therapy at last follow-up

At follow-up, 117 patients (48%) were taking immunomodulatory medical therapy for CD, of

which 42 (36%) were on anti-TNF therapy or vedolizumab. Of the patients who were free of surgical recurrence at follow-up, those who had quit smoking were significantly less likely to be taking medical therapy compared to smokers (4/28 vs 12/26, $p=0.01$; RR 3.2 (95% CI 1 - 9), Table 3). None of the quitters who were free of surgical recurrence were on biological therapy at time of FU, compared to 4/26 (15%) in group 2.

DISCUSSION

Despite its known negative impact on patients' general health and the introduction of tobacco control policies like the WHO's Framework Convention on Tobacco Control (FCTC) in 2005, the worldwide prevalence of smoking remains high^{12,13}. Consequently, medical caregivers have to deal not infrequently with actively smoking patients at the time of diagnosis or surgery for CD.

The pathophysiological mechanism linking smoking and CD is still incompletely understood. Alterations in the immune system, gut permeability/motility, intestinal microbiome and bacterial overgrowth may be factors in this complex, multifactorial interaction^{14,15}.

Data regarding the impact of smoking cessation on surgical recurrence in the literature are scarce. This study shows a more than four-fold reduction in the need for a second intestinal resection in the 31 patients who decided to quit smoking after surgery compared to those who continued, in a uniform group of patients over a median FU of more than 9 years (112 months).

A remarkable 73% of patients who continued to smoke after a second resection went on to need a third intestinal resection, although numbers are small (8/11 patients).

Ryan et al observed a similar benefit of smoking cessation, but in a smaller group of 21 patients quitting smoking who were at risk for a second intestinal resection after surgery for CD in a retrospective study. They reported a follow-up rate of just 46% and those who quit

smoking within one year after surgery were classified as “non-smokers”, which makes it difficult to assess the impact of smoking cessation after ICR for CD¹⁶.

The overall surgical recurrence rate in our study of 242 patients derived from prospectively maintained databases was 19% at 9 years (median follow-up 112 months), compared to 18-44% reported in literature^{1, 17-19}.

The lowest surgical recurrence rate was in our “quitters group”, and patients in this group who were free from surgery were significant less likely to be on immunomodulatory maintenance therapy for CD at follow-up. The act of smoking cessation appears to “overcorrect” a dysregulated immunological system, although it may simply reflect increased “health awareness”¹⁴. It is also possible that the lower need for maintenance therapy in the smoking cessation group might reflect a higher threshold to stop this therapy in active smokers. On the other hand, quitters had even less need for maintenance therapy at follow-up than non-smokers, which counteracts possible bias.

Despite an observed overall lack of impact of tailored medical prophylaxis with mercaptopurine after surgery for CD on clinical recurrence in the multicenter randomized Trial of Prevention of Postoperative Crohn’s disease (TOPPIC), there was benefit for the subgroup of smokers²⁰. Nevertheless, most studies addressing this topic are underpowered and use varied drug regimens which makes it difficult to reach a consensus regarding the role of medical prophylaxis after surgery²¹. Furthermore, it has been difficult to demonstrate an impact of surgical technique on long-term recurrence²²⁻²⁴. There may be a benefit a mesenteric resection or performing a complete anti-mesenteric (“Kono-S”) anastomosis, but the jury is still out and none of these techniques were used in our study population^{25,26}.

In the current study 73/242 patients (30%) were smoking at time of primary ICR, in line with previous observations⁸. Despite the complicated course of their CD with a need for intestinal resection, fewer than half (42%) of the smokers were able to quit after resection.

Smoking cessation programs seems to be crucial in improving the outcome of smokers with CD²⁷. Despite discouraging results of active smoking cessation programs reported by Cosnes et al, more recent publications observe high effectiveness of this intervention^{10,28}. Such programs appear to be cost-effective, since patients with CD have an increased motivation to quit²⁹. Challenge for the future seems to target those programs more by identifying high risk patients for failure of smoking cessation³⁰.

Historical concerns that smoking cessation just before abdominal surgery actually increased respiratory or wound complications have not been confirmed^{31,32}.

Our study is limited in that it is retrospective in design, with small numbers of smokers and variation in time after surgery when patients in the smoking cessation group decided to quit. On the other hand, we observed a clear statistical difference between smokers and the “quitters” for our endpoints in a uniform group of patients by applying strict inclusion criteria. Change in medical strategy with regard to biological therapy during the period under study (2000-2012) might have affected the risk of surgical recurrence, but this has been difficult to demonstrate in a randomized controlled trial and patients in our three subgroups would have been similarly influenced³³.

Excluding those patients who were defunctioned because of a leak after ICR could have created bias, but even when those patients were included, the difference between “quitters” and smokers remained significant.

CONCLUSION

This study shows that patients who continue to smoke after ileocolic resection have more than a 5-fold increase in the risk of needing a further resection. For those who continue to smoke after a second resection, three quarters will need a further resection. Active follow-up after

surgery in combination with smoking cessation programs may be the key to success in this group of patients.

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FIGURE LEGENDS

FIGURE 1: Kaplan-Meier curve for our three study groups. P-values regarding relationship three groups; for all three groups $p=0.004$, comparing group 2 vs group 3: $p=0.02$