

# **Defunctioning ileostomy during ileocolic resections for Crohn's disease; is there an impact on surgical recurrence in the long-term?**

## **INTRODUCTION**

Long-term recurrence rates after surgery for ileocaecal Crohn's disease (CD) are high with reports varying from 10-40% [1, 2, 3, 4, ###]. Known risk factors are young age, perianal disease, penetrating disease, family history of Crohn's and smoking. Only the latter is a well-recognized risk factor through literature, with more diverse supporting evidence for the other factors [5, 6].

There has been renewed interest in technical surgical factors influencing disease recurrence, including extended mesenteric resection and novel anastomotic techniques [5, 7].

Faecal diversion has previously been demonstrated to reduce disease activity in Crohn's colitis and perianal disease [8, 9]. Rutgeerts et al reported on 5 patients who had a temporary diverting ileostomy proximal to an ileocolic anastomosis following ileocaecal resection for Crohn's disease [10]. At 6 months none of the five patients had any evidence of endoscopic or histological Crohn's activity. In contrast 53 of 75 patients undergoing ileocolic resection with primary anastomosis had endoscopic evidence of recurrent disease. Furthermore, of the five patients with a defunctioning ileostomy, when the ileostomy was reversed, all five had evidence of endoscopic recurrence within 6 months. Similarly, Nugent et al reported a 3% recurrence following colectomy and ileostomy for Crohn's colitis compared to a 67% recurrence following ileocolic anastomosis [11].

The primary aim of this study was to assess whether the use of a defunctioning ileostomy following surgical resection of primary ileocaecal CD had an influence on surgical recurrence rates. A secondary aim was to identify predictors of surgical recurrence.

## METHODS

All patients who underwent a primary ileocolic resection (ICR) for histopathological confirmed CD between 2000-2012 in three university teaching hospitals were identified from a prospectively maintained databases. Patients undergoing surgery for recurrent disease and patients having simultaneous procedures (e.g. stricturoplasty or multiple resections) were excluded. As a cut-off point for inclusion regarding date of primary ICR we chose 2012, with the intention to have at least 5 years of follow-up.

Patient demographics, duration of CD, pathology reports and Montreal classification of disease were recorded [12]. Montreal classification was based on endoscopy reports, radiology, clinical notes and pathology results. Smoking history, presence of perianal disease (defined as previous anal abscess/fistula/stricture or surgery for anal disease) and a family history of Crohn's disease were recorded. Medical therapy at latest follow-up was recorded. Patients classified in our "smokers group" were those who continued smoking up to last follow-up or those who were still smoking at time of their surgical recurrence.

Details of surgical treatment including the need for a temporary ileostomy were recorded. When a planned "two-stage procedure" was performed, defunctioning was performed with an end ileostomy. In case of defunctioning because of an anastomotic leak, a proximal diverting loop-ileostomy was performed (Check surgical details two-stage (loop vs end) with Linköping and St Mark's).

Patients were categorized as:

- one-stage (resection and primary anastomosis)
- two-stage (resection and ileostomy).

Patients who had a resection and primary anastomosis who developed a leak requiring ileostomy formation were analyzed separately.

Surgical recurrence was the primary endpoint and defined as subsequent surgery for CD (second ICR, small bowel resection (SBR), stricturoplasty (SP) or colectomy).

Time to surgical recurrence was measured from time of restoration of gastrointestinal continuity, being closure of ileostomy in the two-stage group. Patients with less than 12 months follow-up were excluded.

### *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, an unpaired t-test was used when dealing with normally distributed data and Mann-Whitney U test when dealing with non-normal distributed data. Chi square test or Fishers exact 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 was done using R statistical software.

## RESULTS

### *Demographics study population*

A total of 382 patients underwent ICR for CD, 186 (49%) male, age 36.6 +/- 14.3. Pre-operative details are shown in Table 1.

Median follow-up time for the whole group was 104.5 months (IQR 76.0 – 136.4). Medical prophylaxis after primary ICR was recorded in 53.2% (anti-TNF in 14 patients). Concerning the 85 smokers at time of ICR (23%), 48 patients were classified as our “smoking group”, 28 as quitters, and for 9 patients there was no smoking info available at follow-up. Median time till restoration of GIC in the two-stage group was 9.1 months (IQR 5.4 – 12.2).

Smoking behavior was not significantly associated with perianal disease, nor with penetrating disease ( $p=0.25$ ,  $p=0.71$ ). Borderline non-significance was noticed for the associating between penetrating disease behavior and perianal disease ( $p=0.06$ ).

### *Outcome one-stage versus two-stage ICR*

A one-stage procedure was performed in 305 patients, of which (6 + St Mark's data) had an anastomotic leak requiring a defunctioning ileostomy. 77 patients underwent a planned two-stage procedure. (Add indications two-stage procedure? Sepsis, obstruction, ...). All patients with an ileostomy had the ileostomy reversed. There was no difference in the primary end point of surgical recurrence between the two groups (Figure 1, two-stage (15.6 %) versus one-stage (18 %),  $p=0.61$ ). The two-stage group had a significantly higher proportion of smokers (34% vs 20%) and more patients with penetrating (Montreal B3) disease (52% vs 28%) compared to the one-stage group (Table 2). Details of recurrence are shown in Table 3.

At last follow-up, patients in the two-stage group were less likely to be on anti-TNF / Vedolizumab therapy (67/282 vs 11/76,  $p=0.08$ ).

Of the ### patients who underwent a two-stage procedure because of an anastomotic leak after ICR, surgical recurrence rate was ### (Oxford data: 1/4 , add data Linköping and St Mark's).

#### *Predictors of surgical recurrence*

Smoking at the time of ICR was the only independent variable significantly associated with surgical recurrence (Table 4,  $p=0.01$ ).

There was no correlation between time to ileostomy reversal for the patients in the two-stage group and time to recurrence ( $p=###$ ).

#### *Surgical recurrence in smokers / Montreal B3 disease / perianal disease; one-stage versus two-stage*

For the 48 smokers at time ICR who continued smoking up to last follow-up, surgical recurrence rate was 13/32 (40.6%) for those in the one-stage group and 2/16 (12.5%) for those in the two-stage group ( $p=0.23$ , Figure 2). Surgical recurrence rates for the non-smokers was 35/235 (14.9%) and 7/49 (14.3%) for a one-stage versus two-stage approach.

Of the patients with penetrating disease behavior 32% underwent a two-stage ICR, compared to 15% in the B1/B2 group. For the 125 patients with Montreal B3 disease, surgical recurrence rate was 20/85 (23.5%) in the one-stage group and 4/40 (10.0%) in the two-stage group ( $p=0.09$ , Figure 3). Surgical recurrence rate for the 253 patients in the B1/B2 group was 35/216 (16.2%) in the one-stage group and 8/37 (21.6%) in the two-stage

group. (Patients in the B1/B2 group who underwent a two-stage procedure had a non-significant longer FU compared to those who underwent a one-stage procedure (107 vs 93 months  $p=0.15$ ) and were more likely to be smokers (33% vs 20%  $p=0.09$ ).

For the 81 patients with perianal disease, surgical recurrence rate was 11/63 (17.5%) in the one-stage group and 3/18 (16.7%) in the two-stage group ( $p=0.91$ , Figure 4). Surgical recurrence rate for the 275 patients without perianal disease was 35/220 (15.9%) in the one-stage group and 8/55 (14.5%) in the two-stage group.

For the 17 smokers with penetrating disease behavior, surgical recurrence rate was 0/10 for the 2-stage approach vs 4/7 (57.1%) for the 1-stage approach.

## DISCUSSION

The primary finding of this study was that the use of a temporary ileostomy in the surgical management of ileocaecal CD was not associated with any alteration in the surgical recurrence risk in the long-term.

As previously reported, smoking was significantly associated with an increased risk of surgical recurrence [5, 6]. In this group of patients, other putative risk factors including perianal disease, short time to first surgery and penetrating (B3) disease were not demonstrated to be associated with increased surgical recurrence. These findings emphasise the importance of discussing and supporting smoking cessation with patients at the time of ICR.

Strengths of our study include reasonable large numbers, a homogenous group of patients, good length of follow-up and a “hard” primary end-point of surgical reoperation.

Weaknesses are that the study is retrospective and that the 2 groups (one- and two-stage procedures) differed in key factors including proportion of smokers and penetrating disease.

The precise reason to make a defunctioning ileostomy was also difficult to determine retrospectively and may have been subtly influenced by factors such as smoking and severity of fistulating disease.

An additional difficulty in this study was how should the patients who underwent primary anastomosis but developed a leak requiring ileostomy shortly afterwards be analysed.

Although by “intention to treat” they were in the 1-stage group, because of the leak they became more like the 2-stage group. Fortunately, the numbers with a leak were small (### of ### patients, (###%) ) and the overall findings of the study do not change irrespective of whether these 7 patients are considered as 1- stage, 2-stage or are excluded.

Despite the weaknesses of the study, our study suggests that the use of a defunctioning ileostomy following ICR does not have a clinically significant influence on surgical recurrence. It would obviously be not feasible to address this question in a randomised trial.

The surgical recurrence rate in this study was 17.5% at median follow-up 105 months. This is broadly similar to contemporary reports in the literature [4, ###]. Recommendations regarding medical prophylaxis following surgery for Crohn's remain unclear [13]. The TOPPIC study demonstrated that the use of post-operative 6mercaptoprine was associated with a reduced rate of recurrence (needing escalation medical treatment or surgery), although the effect was most pronounced in smokers [14].

There is an increasing trend towards early (6-12 month) colonoscopy with a decision regarding medical prophylaxis based on the endoscopic findings[###]. Surgical technique has not previously been thought to have a major influence on disease recurrence although recent data on the extent of mesenteric resection, histological plexitis at the bowel resection margins and novel anastomotic techniques (Kono-S) may change this [5, 7, 15, 16].

In our study, a striking difference in surgical recurrence rates was observed between the one- and two-stage approaches in smokers with B3 penetrating disease. Of 10 patients in this group with a two-stage approach, none had a surgical recurrence compared to recurrence in 4 of 7 who had a one-stage approach. Although the numbers are small and it is statistically dubious to "over-analyse" subgroups, the finding is striking. Smokers with fistulating disease would generally be considered to be a high-risk group for recurrent disease. Whilst our finding may be just due to chance, it is intriguing to postulate that in patients with a very high risk of recurrent disease, a temporary ileostomy, perhaps by



modifying the gut bacterial flora may have an influence of disease behaviour. Further studies are necessary to assess this further.

The significance of faecal diversion in CD was first mentioned by Ginzburg in 1939, just a few years after the original description of the disease [17]. Truelove and colleagues observed that faecal diversion with a double-barrelled ileostomy was of no value in ulcerative colitis but tended to be helpful in Crohn's colitis [18]. It is now established that faecal diversion by ileostomy or colostomy is associated with reduced disease activity in Crohn's colitis and severe perianal disease [8, 9]

The mechanism by which faecal diversion reduces disease activity is uncertain. Luminal factors larger than 0.22 microns (Harper et al Gut 1985) and changes in bacterial flora have been implicated (Neut et al Gut 1989, Spivak et al IBD 2006) [19, 20, 21].

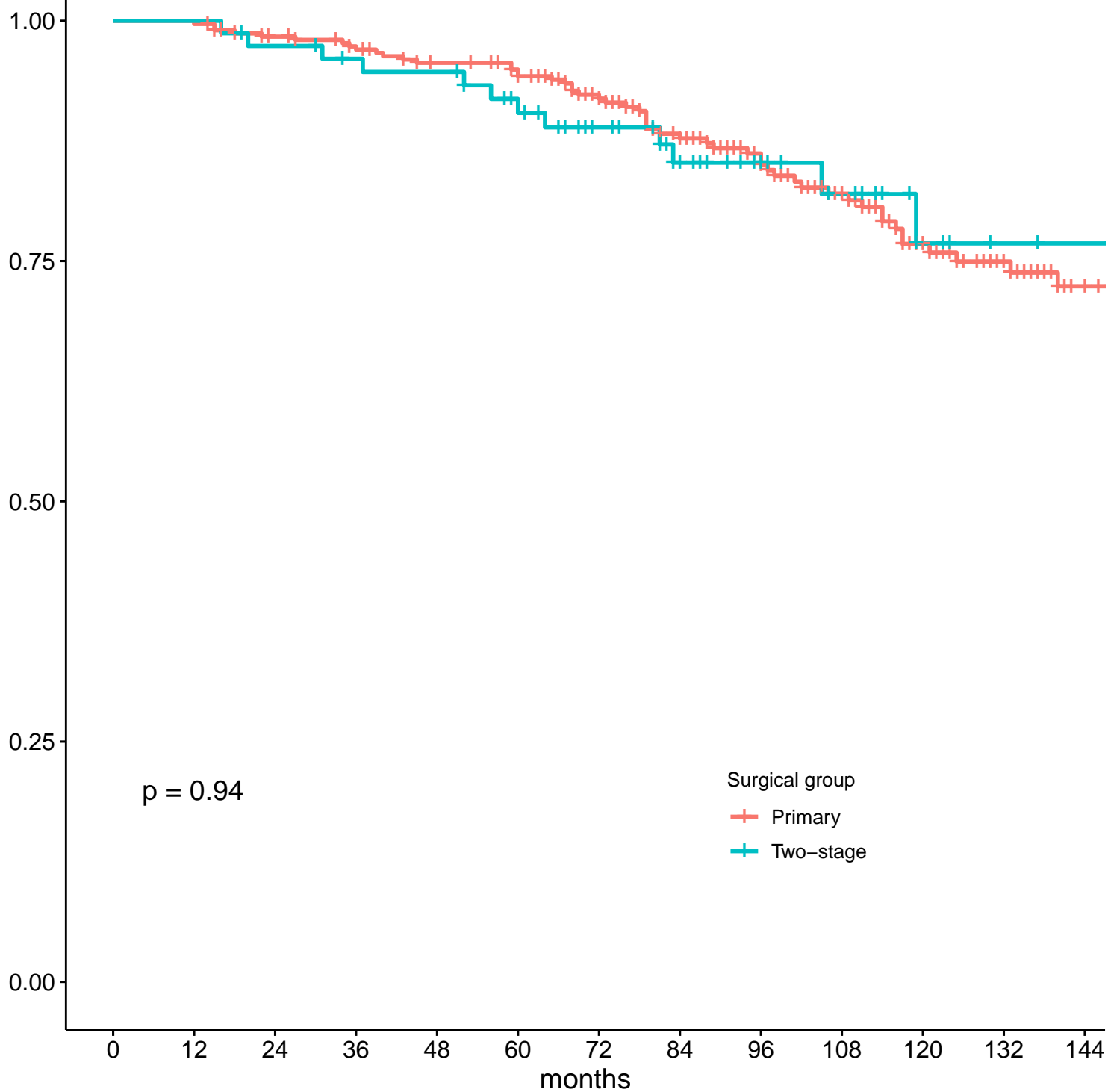
In conclusion this study has demonstrated that a temporary ileostomy at the time of ICR for primary ileocaecal CD does not have a significant influence on long-term surgical recurrence. Future studies might address the impact of a temporary stoma in very high-risk groups. Smoking has once again been confirmed as an independent predictors of disease recurrence.

- [1] Higgins CS, Allen RN. Crohn's disease of the distal ileum. *Gut* 1980;21:933-40
- [2] Kim NK, Senagore AJ, Luchtefeld MA, MacKeigan JM, Mazier WP, Belknap K, et al. Long-term outcome after ileocecal resection for crohn's disease. *Am Surg* 1997;63:627-633
- [3] Cullen G, O'Toole A, Keegan D, et al. Long-term clinical results of ileocaecal resection for Crohn's disease. *Inflamm Bowel Dis*. 2007;13:1369-1373
- [4] 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(12):1713-1722
- [5] Coffey JC, Kiernan MG, Sahebally SM, et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis* 2018; doi:10.1093/ecco-jcc/jjx187
- [6] Unkart JT, Anderson L, Li E, et al. Risk factors for surgical recurrence after ileocolic resection for Crohn's disease. *Dis Colon Rectum* 2008; 51(8) :1211-6
- [7] Kono T, Fichera A, Maeda K, et al. Kono-S anastomosis for surgical prophylaxis of Anastomotic recurrence in Crohn's disease: an international multicenter study. *J Gastrointest Surg* 2016;20(4):783-90
- [8] Singh S, Ding NS, Mathis KL, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. *Aliment Pharmacol Ther* 2015; 42(7):783-92
- [9] Marti-Gallostra et al 2017
- [10] Rutgeerts P, Geboes K, Peeters M et al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 1991;338:771-4
- [11] Nugent FW, Veidenheimer MC, Meissner WA, Haggitt RC. Prognosis after colonic resection for Crohn's disease of the colon. *Gastroenterology* 1973; 65(3):398-402
- [12] Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749-53

- [13] Schlusser AT, Cherng NB, Alavi K. Current trends and challenges in the postoperative medical management of Crohn's disease: A systematic review. *Am J Surg* 2017;214(5):931-937
- [14] Mowat C, Arnott I, Cahill A, Smith M, Ahmad T, Subramanian S, Travis S, et al. Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicenter, double-blind, randomized controlled trial. *Lancet Gastroenterol Hepatol* 2016;1(4):273-282
- [15] Ferrante M, De Hertogh G, Hlavaty T, et al. The value of myenteric plexitis to predict early postoperative Crohn's disease recurrence. *Gastroenterology* 2006; 130(6):1595-606
- [16] Misteli H, Koh CE, Wang LM, et al. Myenteric plexitis at the proximal resection margin is a predictive marker for surgical recurrence of ileocaecal Crohn's disease. *Colorectal Dis* 2015; 17(4):304-10
- [17] Ginzburg L, Colp R, Sussman M. Ileostomy with exclusion. *Ann Surg* 1939;110:648-58
- [18] Truelove SC, Ellis H, Webster CU. Place of double-barrelled ileostomy in ulcerative colitis and Crohn's disease of the colon: a preliminary report. *Br Med J* 1965; 1(5428):150-3
- [19] Harper PH, Lee EC, Kettlewell MG, et al. Role of the faecal stream in the maintenance of Crohn's colitis. *Gut* 1985; 26(3):279-84
- [20] Neut C, Colombel JF, Guillemot F, et al. Impaired bacterial flora in human excluded colon. *Gut* 1989; 30(8):1094-8
- [21] Spivak J, Landers CJ, Vasilias EA, et al. Antibodies to I2 predict clinical response to fecal diversion in Crohn's disease. *Inflamm Bowel Dis* 2006; 12(12):1122-30

# Surgical-recurrence-free survival

Survival probability



## Number at risk

Surgical group

Primary

305 305 294 287 276 269 226 182 150 122 91 66 44

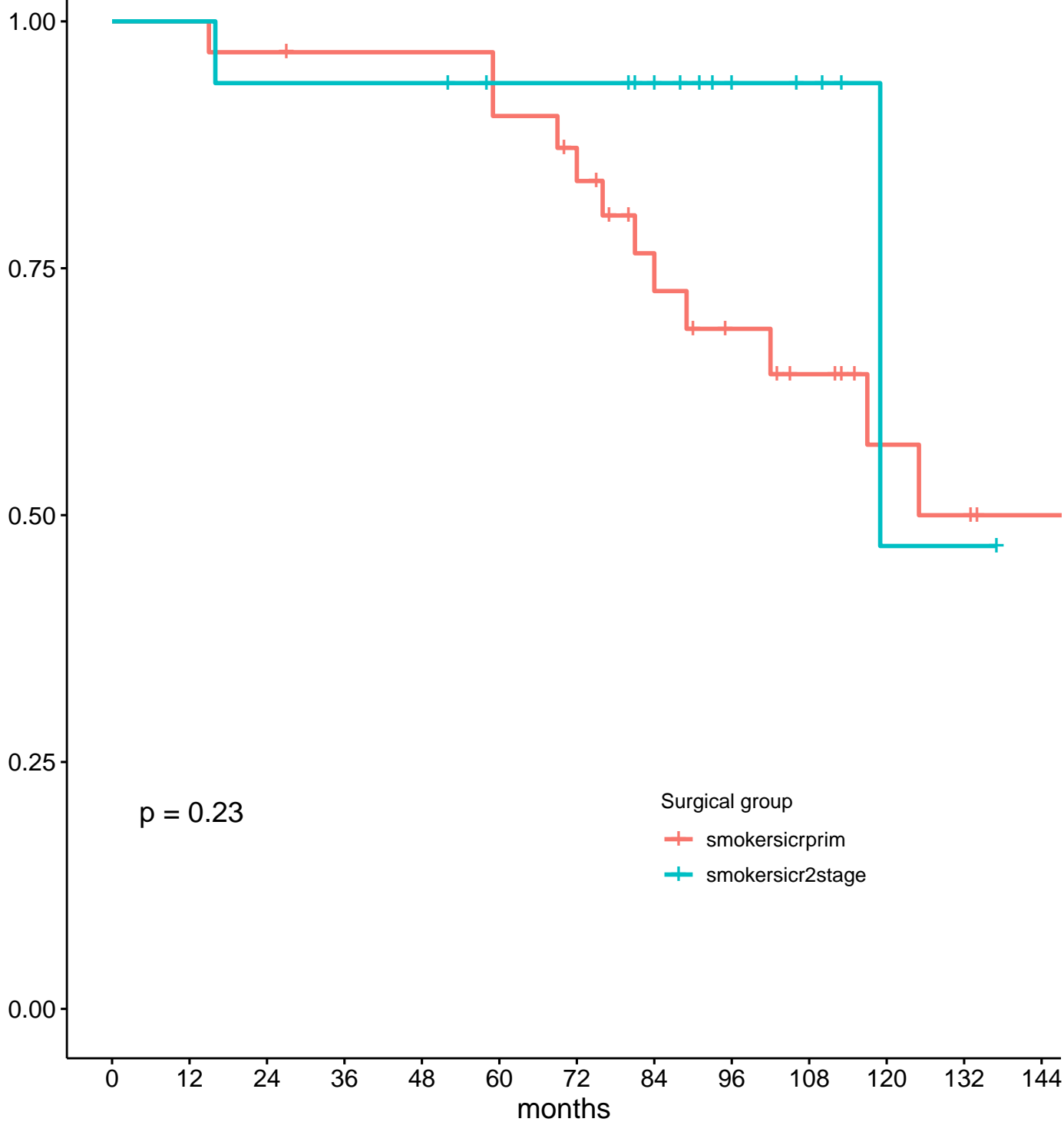
Two-stage

77 77 74 70 69 63 54 42 29 24 13 10 9

months

# Surgical-recurrence-free survival

Survival probability



## Number at risk

Surgical group

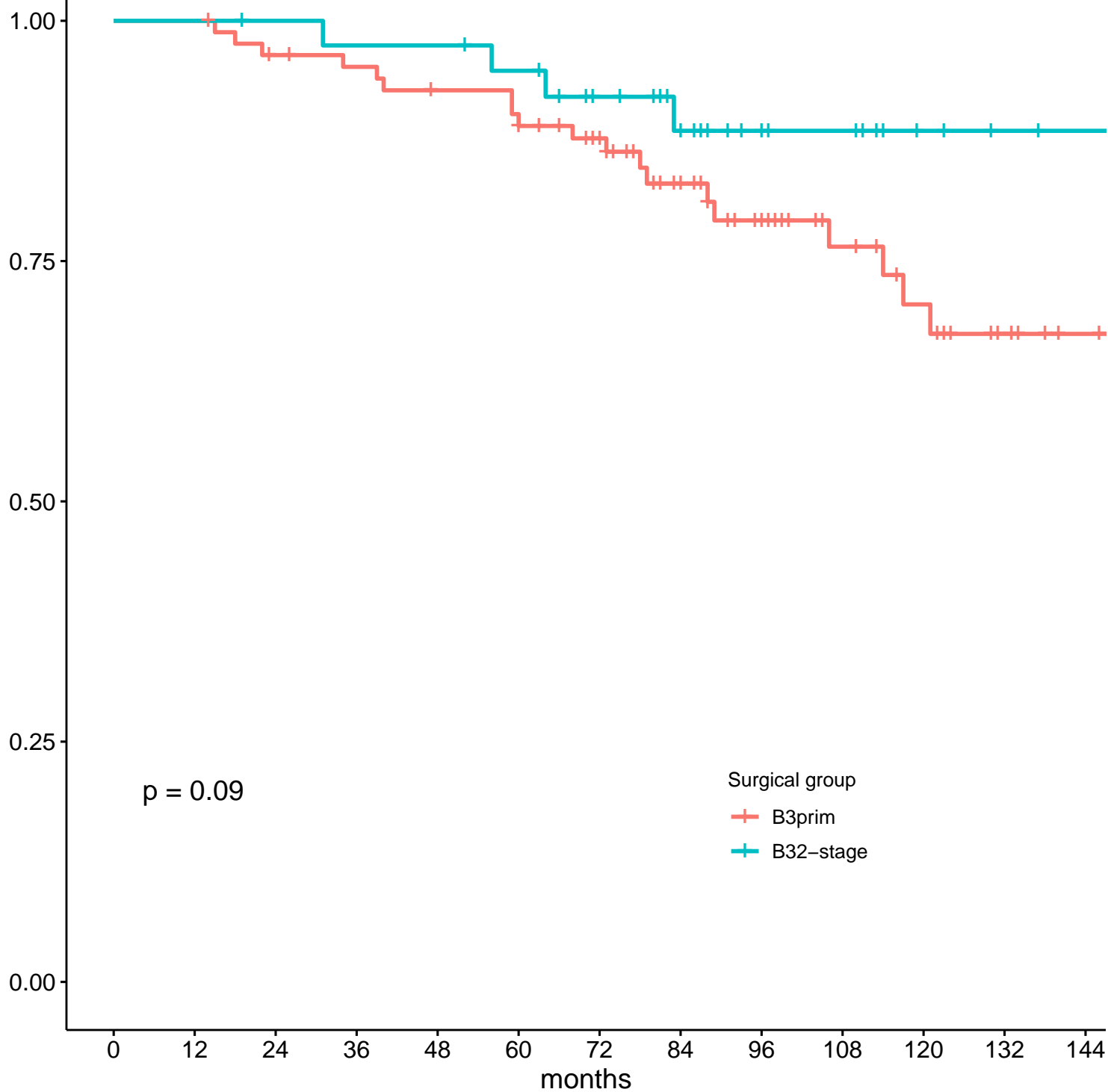
smokersicrprim

smokersicr2stage

months	0	12	24	36	48	60	72	84	96	108	120	132	144
smokersicrprim	32	32	31	30	30	28	26	20	15	12	8	7	5
smokersicr2stage	16	16	15	15	15	13	13	10	6	4	1	1	0

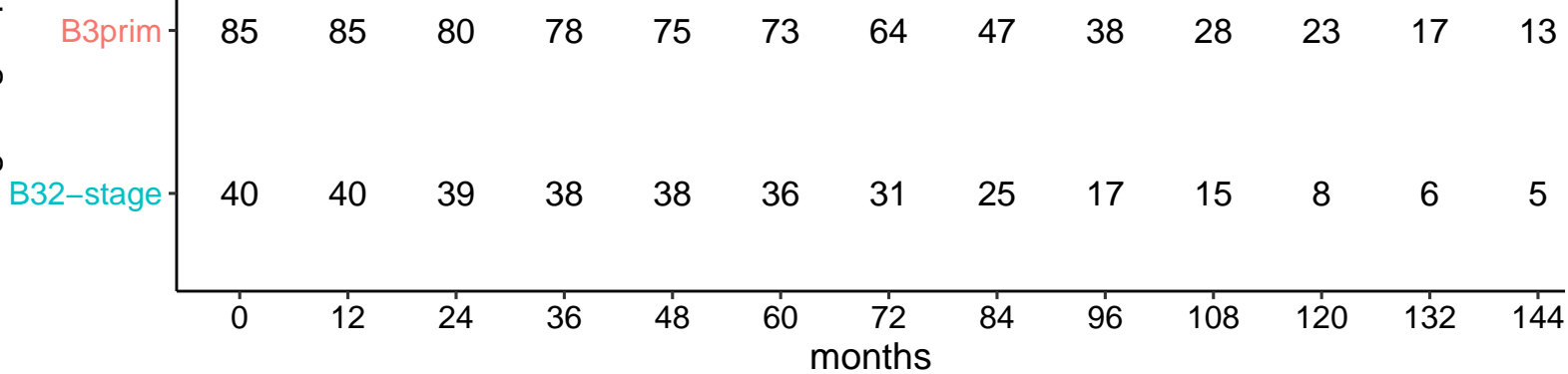
# Surgical-recurrence-free survival

Survival probability



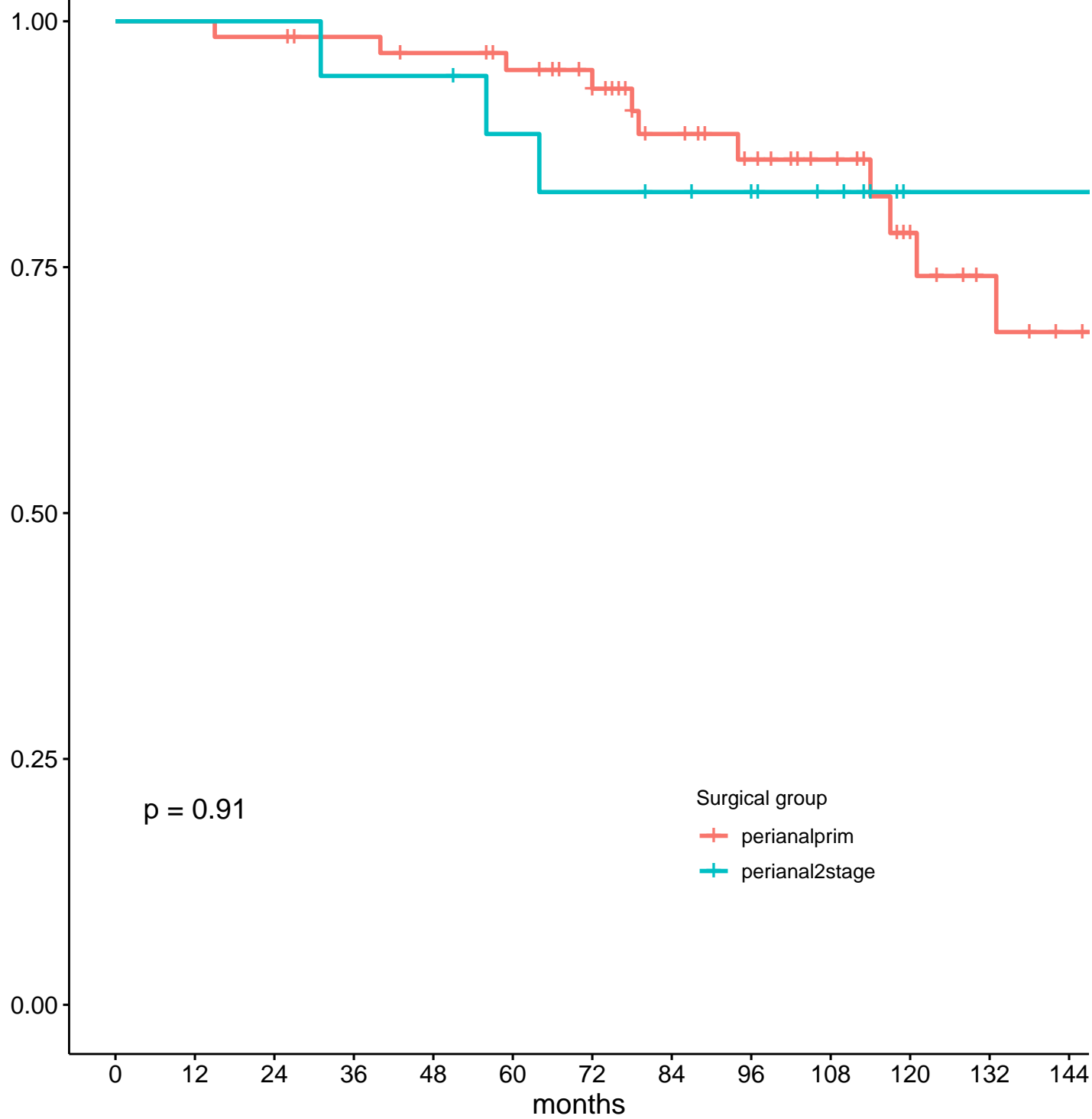
## Number at risk

Surgical group



# Surgical-recurrence-free survival

Survival probability



## Number at risk

Surgical group

perianalprim

perianal2stage

months	0	12	24	36	48	60	72	84	96	108	120	132	144
perianalprim	63	63	62	60	58	55	50	37	32	26	19	13	10
perianal2stage	18	18	18	17	17	15	14	13	12	9	4	4	4

**TABLE 1:** Preoperative details for total group (N=382)

	<b>Total group (N=382)</b>
Age time ICR (years)	36.6 ± 14.3
Gender male N (%)	186 (48.7)
Perianal involvement N (%)	81 (21.6)
Median time diagnosis CD and ICR (years)	3 (IQR 1-10)
Smokers at time of ICR N (%)	85 (23.0)
Family history N (%)	43 (19.1)
Montreal classification disease behavior N (%)	
- B1	53 (14.0)
- B2	200 (52.9)
- B3	125 (33.1)

**TABLE 2:** Follow-up time, demographic data and risk factors for recurrence for one-stage and two-stage groups

	<b>One-stage (N= 305)</b>	<b>Two-stage (N= 77)</b>	<b>p-value</b>
Median follow-up time (months)	106.0 (IQR 75.9 – 138.1)	93.1 (IQR 80.2 – 122.8)	0.13
Age time ICR (years)	36.6 ± 14.1	36.5 ± 15.1	0.92
Gender male (%)	141 (46.2)	45 (58.4)	0.055
Smokers N (%)	60 (20.3)	25 (33.8)	<b>0.01</b>
Perianal disease N (%)	63 (22.2)	18 (24.7)	0.66
Family history N (%)	29 (17.8)	14 (22.6)	0.41
Median time diagnosis CD and ICR (years)	4 (IQR 1 – 10)	2 (IQR 0 – 7)	0.08
Medical prophylaxis after ICR N (%)	125 (51.7)	42 (58.3)	0.32
<b>MONTREAL CLASSIFICATION</b>			
A1 N (%)	45 (14.8)	11 (14.3)	0.92
A2 N (%)	206 (67.5)	49 (63.6)	0.52
A3 N (%)	54 (17.8)	17 (22.1)	0.38
L1 N (%)	164 (54.3)	45 (58.4)	0.51
L3 N (%)	133 (44.0)	32 (41.6)	0.70
L4+ N (%)	6 (0.02)	2 (3.0)	0.74
B1 N (%)	47 (15.5)	6 (8.0)	0.08
B2 N (%)	169 (55.8)	31 (40.3)	<b>0.01</b>
B3 N (%)	85 (28.1)	40 (51.9)	<b>0.00007</b>



**TABLE 3:** Details surgical recurrence one-stage versus two-stage ICR

	<b>One-stage (N=305)</b>	<b>Two-stage (N=77)</b>	<b>P-value</b>
<b>Surgical recurrence N (%)</b>	55 (18.0)	12 (15.6)	0.61
- Redo ICR	37	9	
- Redo ICR + ileostomy	1	/	
- Twice redo ICR	7	2	
- Three times redo ICR	1	/	
- Ileal resection twice + redo ICR	1	/	
- SBR / SP	5	/	
- Segmental colectomy	1	/	
- Total colectomy	1	1	
- Completion proctocolectomy + SP	1	/	
Median time till (first) surgical recurrence (months)	68.3 (IQR 48.3 – 89.0)	79.0 (IQR 58.9 – 104.0)	0.48
Therapy Crohn's disease at last FU (%)	157/282 (55.7)	40/76 (52.6)	0.64
Need for anti-TNF / Vedo at last FU (%)	67/282 (23.8)	11/76 (14.5)	<b>0.08</b>

**TABLE 4:** risk factors for surgical recurrence (primary group; N = 305)

	Surgical recurrence rate in absence risk factor	Surgical recurrence rate if risk factor / yes / 1	P-value (chi square)
Age time ICR (< 40 years)	15/93 (16.1)	26/149 (17.4)	0.79
Gender (M)	30/161 (18.6)	25/141 (17.7)	0.84
Smoking	35/235 (14.9)	17/60 (28.3)	<b>0.01</b>
Perianal disease	35/220 (15.9)	11/60 (18.3)	0.65
Family history	25/134 (18.7)	7/29 (24.1)	0.50
Diagnosis at time of surgery	39/228 (17.1)	10/61 (16.4)	0.9
Medical prophylaxis after ICR	18/117 (15.4)	18/125 (14.4)	0.83
Penetrating disease behavior (B3)	35/216 (16.2)	20/85 (23.5)	0.14