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# Early ileal resection in Crohn's disease is not associated with severe long-term outcomes: The ERIC study

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## Summary

**Background:** Early complicated Crohn's disease (CD) may require ileal resection as first-line treatment.

**Aim:** To evaluate the long-term outcomes of patients who underwent early ileal resection.

**Methods:** We conducted a retrospective study in two inflammatory bowel diseases (IBD) referral centres, including patients with ileocaecal resection and segmental ileal resection within 5 years of CD diagnosis. Early resection was defined as within 6 months of diagnosis, intermediate resection between 6 months and 2 years, and late resection between 2 and 5 years. The primary outcome was the cumulative risk of a second ileal surgery. Secondary outcomes included the use of postoperative treatments and morphological recurrence after initial surgery (Rutgeerts score  $\geq 2$ , or recurrence on imaging).

**Results:** Among 393 patients who underwent ileal resection within 5 years of diagnosis, 130, 128 and 135, respectively, had early, intermediate and late resection. The cumulative risk of second surgery at 10 years was not significantly different in the early resection group (25.0% [95% CI 17.4–35.2]), than the intermediate (16.8% [95% CI 10.5–26.2];  $p=0.17$ ) or late resection group (22.7% [95% CI 15.1–33.3];  $p=0.83$ ). The early resection group required fewer postoperative treatments than the late resection group with median survivals without treatments of 3.7 and 0.9 years, respectively ( $p=0.002$ ). Patients who had early resection had significantly less morphological recurrence than the late resection group ( $p=0.02$ ).

**Conclusion:** Early ileal resection in CD is not associated with a higher risk of a second resection. It may be associated with reduced use of medical treatments and fewer morphological recurrences.

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## 1 | INTRODUCTION

Crohn's disease (CD) is a lifelong inflammatory disease affecting an increasing number of patients worldwide.<sup>1,2</sup> All segments of the gastrointestinal tract can be affected. The disease is limited to the terminal ileum in about one-third of the patients at diagnosis with a non-stricturing and non-penetrating disease for most of them.<sup>3</sup> However, about 20% of patients have a complicated disease at diagnosis that may lead to early surgery. To note, nearly 80% of patients with CD will undergo surgery during their life.<sup>4</sup>

In the advanced therapies' era, surgery is often seen as a treatment of last resort for diseases that are complicated or refractory to medical treatment.<sup>5</sup> Though, data from the randomised clinical trial LIR!C, showed the non-inferiority of ileocaecal resection compared to anti-TNFs in terms of quality of life at 1 year follow-up, in non-complicated ileal limited CD.<sup>6-8</sup> The long-term follow-up of individuals in the surgery group revealed no re-resection, whereas in the infliximab group, half of the patients required surgery secondarily. Those data suggest that surgery could be a viable treatment option for a subgroup of patients. However, the LIR!C trial only focused on short ileal non-complicated diseases in patients who were naïve to biologics.

More recently, in a Danish nationwide cohort, Agrawal et al. showed that patients who underwent ileocaecal resection within 1 year of diagnosis had improved outcomes compared to patients treated with anti-TNF.<sup>9</sup> In this study, the primary surgery group was associated with a reduced risk of systemic corticosteroid exposure and CD-related surgery. These results corroborate those of the LIR!C study, suggesting that early surgery could be an equally effective or even superior treatment compared to anti-TNFs, based on the evaluated outcomes.

Only a limited number of studies evaluated the effect of time elapsed from diagnosis to surgery on long-term outcomes of CD.<sup>10-13</sup> Some of them were population-based studies from Northern Europe or the United States with no or minimal data on disease behaviour or location. Those studies did not focus on ileal-limited diseases and could not discriminate ileocaecal resection from other bowel resections. Also, the impact of the time elapsed between diagnosis and surgery on postoperative recurrence and treatment requirements remains unclear. Whereas early complicated CD requiring surgery shortly after diagnosis may represent a particular group of patients with potentially more severe disease, long-term outcomes have been poorly investigated.

Our study aimed to evaluate the long-term outcomes of patients with CD requiring early ileal resection.

## 2 | METHODS

### 2.1 | Study population

We included all patients with CD who underwent ileocaecal or segmental ileal resection within 5 years following diagnosis and followed in Saint-Antoine Hospital between 2001 and 2015 and in Beaujon Hospital between 2007 and 2015. Exclusion criteria included: aged

under 18 at the time of diagnosis, patients without follow-up after the first operation, that is, patients without at least one outpatient visit or hospitalisation, patients with intestinal cancer or tuberculosis on pathological examination of the intestinal resection.

We determined three groups of patients according to the time elapsed between diagnosis and surgery. Early ileal resection was defined as ileocaecal or segmental ileal resection within 6 months following CD diagnosis, intermediate resection as a surgery between 6 months and 2 years after CD diagnosis and late resection between 2 and 5-years following CD diagnosis.

Variables were collected in Saint-Antoine Hospital from the SUVIMIC registry<sup>14</sup> (a prospective clinical database of all patients with IBD evaluated by Saint-Antoine Hospital digestive disease medical staff), and in Beaujon Hospital from medical records. The data were collected up to 31 September 2022 (date of last news).

### 2.2 | Outcomes

The primary outcome was the cumulative risk of second ileal surgery defined as ileocolonic anastomosis resection or ileo-ileal anastomosis resection. The secondary outcomes were the survival without postoperative treatments defined as immunosuppressive treatments introduction (thiopurines or methotrexate) or advanced therapies introduction after first resection (anti-TNFs/vedolizumab/ustekinumab or tofacitinib) or a second ileal surgery.

Morphological recurrence was defined as endoscopic and/or imaging recurrence after first surgery. The cumulative risk of morphological recurrence was expressed as the time between the first surgery and the first examination with signs of recurrence on endoscopy or imaging. Endoscopic recurrence corresponded to a Rutgeerts score equal to or greater than i2 assessed with the first endoscopy after first surgery.<sup>15</sup> The modified Rutgeerts score was only available for patients operated after 2010, when it became standard of care.<sup>16</sup> The i2a and i2b subgroups were only used for stratified analysis. An active colonic disease with ulcers, stenosis or fistula were also considered as endoscopic recurrence.<sup>17</sup> Imaging recurrence was defined as the first imaging after surgery showing significant signs of relapse on magnetic resonance imaging (MRI) or computed-tomography scan (CT-scan) according to previous studies and guidelines: on MRI, the presence of ulcers and/or length of diseased segment >20mm and/or luminal narrowing/stenosis and/or upstream dilation were considered as relapse<sup>18,19</sup>; the presence of stenosis/fistula/abscess on CT-scan or on small bowel enteroclysis.<sup>17</sup> Morphological recurrence was assessed independently of all treatments, as were morphological data at 12 months. Occurrence of perianal disease, perianal surgery and endoscopic dilation after first surgery were also collected.

### 2.3 | Statistical analyses

Follow-up began the day after the first surgery and continued until the last outpatient visit or last hospitalisation if there was no second

ileal resection, or until the second ileal resection. Time to outcome was defined as the time between the first operation and an event occurring. Continuous data were presented as medians and interquartile ranges (IQRs) and were compared with Kruskal–Wallis test. Categorical variables were summarised as frequencies with percentages and compared with chi-squared test. Cumulative risk of second surgery or treatments was assessed in the whole cohort. Survival analysis was expressed with Kaplan–Meier survival curves. Log-rank test was performed to compare survival curves. In subgroup analyses, the risk of second surgery was assessed according to ileocaecal resections, the disease behaviour at first surgery, and the calendar year of first surgery. The results were analysed according to the median year of first surgery in our cohort, which was 2009. A sensitivity analysis was conducted by excluding treatments prescribed within 6 months after first surgery to differentiate prophylactic postoperative treatments and those introduced for relapse. Cox regression model was used to determine predictive factors of second ileal resection. Only variables with  $p < 0.20$  in univariate analysis were included in multivariate analysis.  $p < 0.05$  were considered statistically significant. Survival curves expressing the risk of morphologic recurrence were compared using the log-rank test. The study was approved by the Saint-Antoine Hospital ethics committee for both centres (no. 2014-A01788-39). GraphPad Prism (version 10.0.0) was used for the figures and the statistical analysis.

### 3 | RESULTS

#### 3.1 | Study population

Between 1 January 2001 and 31 December 2015, 569 patients underwent a first ileal resection within 5 years following CD diagnosis.

Of these, 393 patients were included in the analysis (Figure 1), including 130 patients in the early resection group, 128 patients in the intermediate resection group and 135 patients in the late resection group. Overall, 318 of 393 patients were included in Saint-Antoine Hospital, and the remaining 75 patients were included in Beaujon Hospital.

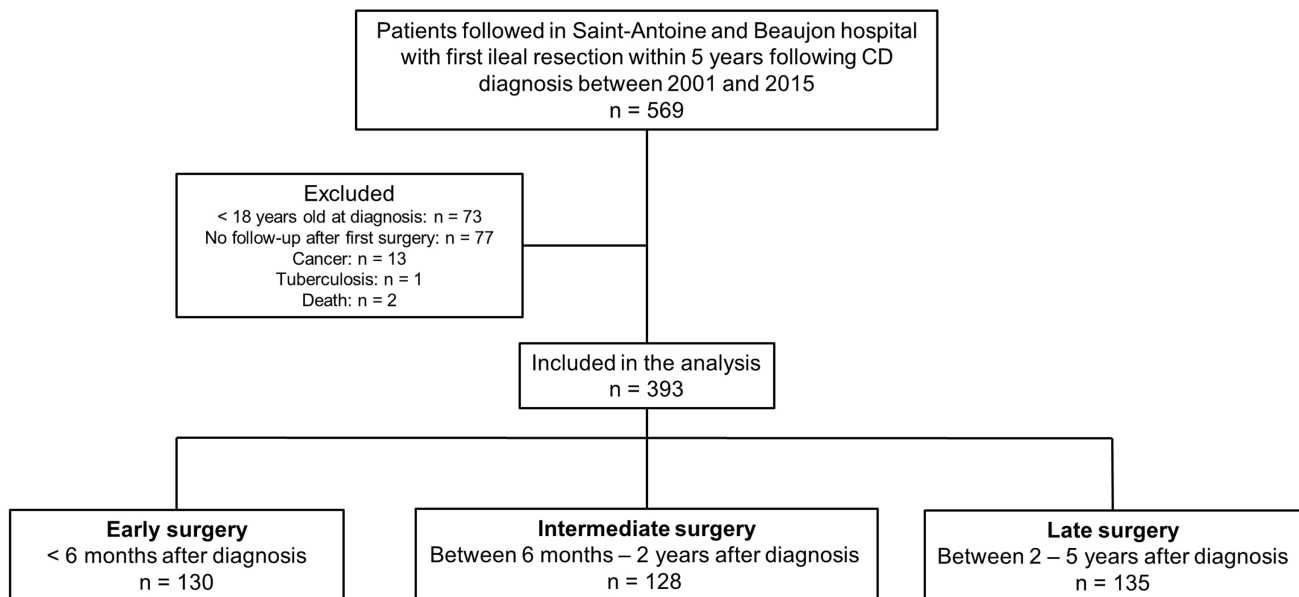
Baseline characteristics are presented in Table 1. There was no statistically significant difference at first surgery in terms of age, sex, disease location, perianal disease, or the year of resection. However, there were significantly more complicated disease at first surgery ( $p = 0.001$ ), more smokers ( $p < 0.001$ ) and a higher rate of segmental ileal resection ( $p = 0.01$ ) in the early resection group. There were more stenoses or fistulas in the early resected group (95%) compared to the late resection group (88%;  $p < 0.001$ ). Regarding treatments exposure before first resection, in the early resection group, 69.2% of the patients had never been exposed to any treatment, whereas only 16.4% and 8.1% were treatment naive in the intermediate and late resection groups, respectively. More patients were previously exposed to anti-TNFs in the late resection group ( $p < 0.001$ ).

Median follow-up after the first surgery was 117 months (IQR: 75–162) in the early resection group, 113 months (IQR: 66–164) in the intermediate resection group and 99 months (IQR: 59–163) in the late resection group. There was no difference in terms of length of follow-up ( $p = 0.81$ ).

#### 3.2 | Main outcome

##### 3.2.1 | Cumulative risk of second resection

In our cohort, 73 of the 393 patients (18.6%) had a second ileal resection. In the early resection group, 27 (20.8%) patients had at least one



**FIGURE 1** Flow chart of the study. CD, Crohn's disease; No follow-up, consultation after first surgery; Cancer, adenocarcinoma, or lymphoma on pathological examination of resected specimens.

TABLE 1 Characteristics at first surgery.

Clinical variables at first surgery	Early resection <6 months (n = 130)	Intermediate 6 months–2 years (n = 128)	Late resection 2–5 years (n = 135)	p-value
Age (years), median (range)	29 (18–88)	30 (19–81)	29 (20–70)	0.57
Female sex (%)	58 (44.6)	68 (53.1)	77 (57.0)	0.12
Disease location (%)				
L1	96 (73.8)	98 (76.6)	88 (65.2)	0.08
L3	34 (26.2)	29 (22.7)	47 (34.8)	
Upper gastrointestinal tract disease (%)	7 (5.4)	8 (6.3)	14 (10.4)	0.25
Behaviour (%)				
B1	10 (7.7)	25 (19.5)	19 (14.1)	0.001
B2	31 (23.8)	44 (34.3)	51 (37.8)	
B3	89 (68.5)	59 (46.1)	65 (48.1)	
Perianal disease (%)	14 (10.8)	11 (8.6)	23 (17.0)	0.09
Smoking status (%)				
Active	58 (44.6)	41 (32)	48 (35.6)	<0.001
Former smokers	13 (10)	31 (24.2)	43 (31.9)	
Non-smokers	59 (45.4)	56 (43.8)	44 (32.6)	
Type of first surgery (%)				
Ileocaecal resection	108 (83.1)	120 (93.8)	125 (92.6)	0.01
Segmental ileal resection	20 (15.4)	7 (5.5)	10 (7.4)	
Both	2 (1.5)	1 (0.8)	0	
Indication of first surgery (%) <sup>a</sup>				
Failure of medical treatment	6 (4.6)	16 (12.5)	24 (17.8)	<0.001
Stenosis/obstruction	40 (30.8)	56 (43.8)	53 (39.3)	
Fistula/abscess	84 (64.6)	56 (43.8)	58 (43.0)	
Year of first surgery, median (IQR)	2009 (2006–2012)	2008 (2005–2011)	2009 (2004–2012)	0.12
Time between diagnosis and first surgery (months), median (IQR)	1.6 (0.1–3.2)	12 (9–17)	40 (33–50)	
Maximum treatment before first surgery (%) <sup>b</sup>				
No treatment	90 (69.2)	21 (16.4)	11 (8.1)	<0.001
Aminosalicylates	4 (3.1)	10 (7.8)	6 (4.4)	
Systemic steroids	23 (17.7)	38 (29.7)	31 (23.0)	
Immunosuppressants	7 (5.4)	40 (31.3)	48 (35.6)	
Biologics	6 (4.6)	19 (14.8)	39 (28.9)	

<sup>a</sup>Surgical indications are mutually exclusive.

<sup>b</sup>Defined as step-up treatments from no treatment to biologics, treatment categories are exclusive. Continuous variables: Non-parametric: Kruskal-Wallis test. Categorical variables: Chi squared test.

other ileal resection compared to 18 (14.1%) patients in the intermediate resection group and 28 (20.7%) in the late resection group. At 5 years, the cumulative risk of second resection was 12.7% (95% CI 7.9–20.3), 7.4% (95% CI 3.8–14.2) and 10.3% (95% CI 6.0–17.5) in the early, intermediate and late resection groups respectively (Figure 2). At 10 years, 25.0% (95% CI 17.4–35.2), 16.8% (95% CI 10.5–26.2) and 22.7% (95% CI 15.1–33.3) in the same order. Overall, the cumulative risk of second ileal resection was not statistically different in the three groups ( $p=0.22$ ). Separately, the cumulative risk of second ileal resection in the

early resection group was not statistically different neither from the intermediate group ( $p=0.17$ ) nor the late group ( $p=0.83$ ).

In subgroup analyses, the same results were observed in patients who underwent an ileocaecal resection as a first surgery (Figure S1). The patients who underwent an early surgery for a complicated disease, that is, abscesses or stenoses did not have an increased risk of second surgery compared to the patients who had an intermediate and late resection (Figure S2). The median year of first surgery in our cohort was 2009. The patients who had early surgery before 2009 did

not have an increased risk of second surgery compared to late resected patients, nor did those who had early surgery after 2009 (Figure S3). The risk of second surgery according to smoking status did not differ between the three groups (Figure S4).

### 3.3 | Secondary outcomes

#### 3.3.1 | Medical treatments after first surgery

The cumulative risk of advanced therapy introduction after first surgery was statistically lower in the early resection group compared to the late resection group (HR: 0.56 [95% CI 0.40–0.78];  $p < 0.001$ ; Figure S5). Likewise, intermediate resection group had a lower risk of advanced therapy introduction than the late resection group (HR: 0.71 [0.51–0.99];  $p = 0.04$ ; Figure S5). The cumulative risk of starting thiopurines or methotrexate after first surgery was not statistically different between the three groups: early versus late ( $p = 0.76$ ) and early versus intermediate ( $p = 0.48$ ; Figure S6).

#### 3.3.2 | Postoperative treatments (medical treatments or second resection)

In the early resection group, 44 (33.8%) patients had never been exposed to immunosuppressive treatments or advanced therapies or second ileal resection after first surgery, while it was the case for 37 (28.9%) patients in the intermediate resection group and 29 (21.5%) in late resection group (Figure 3). The median survival time without postoperative treatment was significantly higher in the early resection group with 3.67 years (95% CI 1.92–7.08) compared to the late resection group with 0.92 years (95% CI 0.58–2.33;  $p = 0.002$ ). Patients with early resection had a lower risk to receive postoperative treatments compared to late resected patients (HR: 0.65 [95% CI 0.49–0.86];  $p = 0.002$ ). This difference was not statistically significant for

the intermediate resection group compared to the other two groups. Analyses with medical treatments only (thiopurines, methotrexate and advanced therapies) showed similar results (Figure S7).

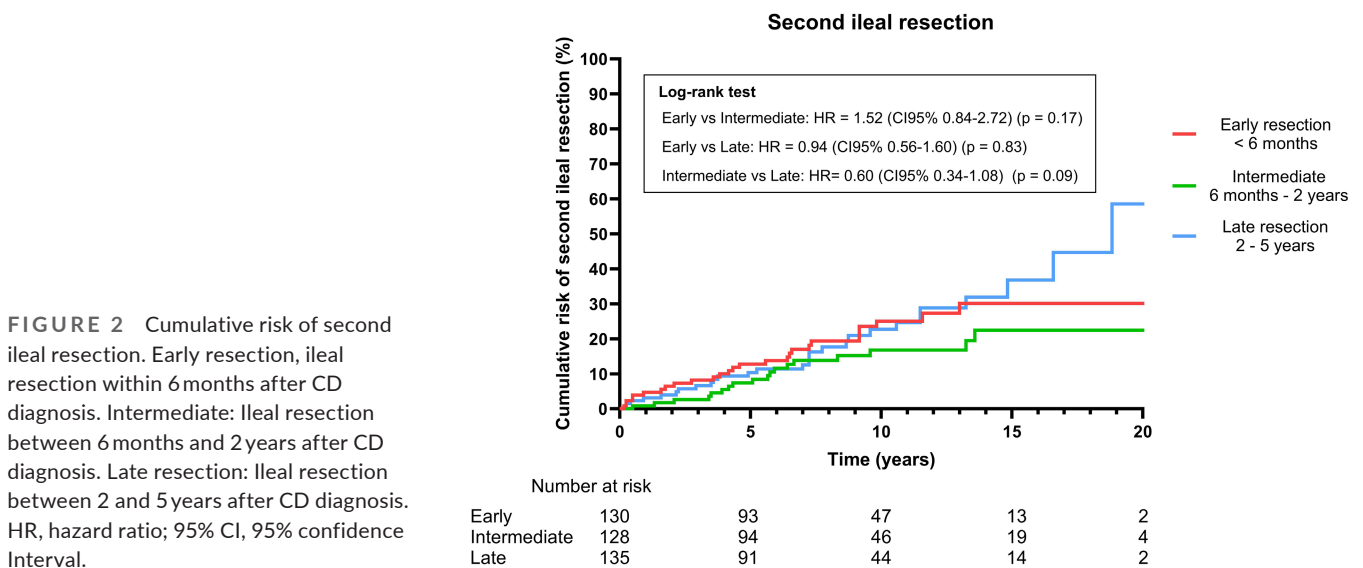
#### 3.3.3 | Sensitivity analysis excluding prophylactic treatment within 6 months

To distinguish prophylactic treatments from those prescribed for recurrence, treatments started within 6 months of first surgery were excluded from the analysis in Figure S8. There was no difference in prophylactic treatments in the first 6 months after first surgery (Early 28.5%, Intermediate 31.3% and Late 37.8%,  $p = 0.25$ ; Table S1). In the sensitivity analysis excluding prophylactic treatment in the first 6 months, there was no statistically significant difference in survival without medical treatment between the early and late resection groups ( $p = 0.11$ ) or compared with intermediate resections ( $p = 0.12$ ). However, sensitivity analysis showed the same trend as the analysis including prophylactic treatment. Similar results were obtained excluding prophylactic treatments within 3 months (Figure S9). Medical treatment strategies after first surgery are shown in Table S1.

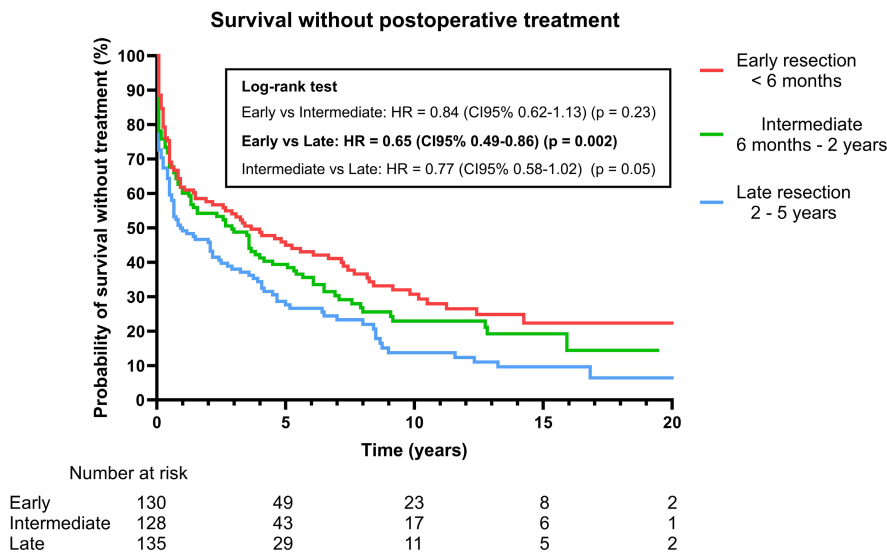
#### 3.3.4 | Predictive factors of second ileal resection

In univariate analysis, age, sex, smoking status, resection groups, disease location and perianal disease were not predictive factors of second ileal resection (Table 2). Having a segmental ileal resection was associated with a higher risk of having a second resection (HR: 2.30 [95% CI 1.25–3.94];  $p = 0.004$ ). Anti-TNFs exposure before first surgery was associated with a higher risk of second ileal resection (HR: 2.82 [1.66–4.64];  $p < 0.001$ ).

Multivariate Cox regression analysis showed that only segmental ileal resection (HR: 1.98 [1.07–3.44];  $p = 0.02$ ) and anti-TNFs



**FIGURE 2** Cumulative risk of second ileal resection. Early resection: ileal resection within 6 months after CD diagnosis. Intermediate: Ileal resection between 6 months and 2 years after CD diagnosis. Late resection: Ileal resection between 2 and 5 years after CD diagnosis. HR, hazard ratio; 95% CI, 95% confidence Interval.



**FIGURE 3** Survival without postoperative treatment. Postoperative treatments are defined as starting thiopurines/methotrexate or advanced therapies or having a second ileal resection. Early resection: Ileal resection within 6 months after CD diagnosis. Intermediate: Ileal resection between 6 months and 2 years after CD diagnosis. Late resection: Ileal resection between 2 and 5 years after CD diagnosis. CI 95%: 95% confidence interval; HR, hazard ratio.

Clinical variables at first surgery	Univariate hazard ratio (95% CI)	p-value	Multivariate hazard ratio (95% CI)	p-value
Age (year)	1.00 (0.98–1.00)	0.93		
Sex (female)	0.84 (0.53–1.33)	0.46		
Smoking <sup>a</sup>	1.32 (0.82–2.17)	0.27		
Group (reference: Late resection)				
Early resection (<6 months)	0.94 (0.55–1.60)	0.81	1.34 (0.75–2.43)	0.33
Intermediate (6 months–2 years)	0.61 (0.33–1.09)	0.1	0.77 (0.41–1.40)	0.39
Late resection (2–5 years)				
Type of surgery (reference: Ileocaecal resection)				
Segmental ileal resection	2.30 (1.25–3.94)	0.004	1.98 (1.07–3.44)	0.02
Indication (reference: Medical treatment failure)				
Stenosis or Abscess	0.55 (0.32–1.03)	0.048	0.59 (0.33–1.13)	0.09
Disease location (reference: L1)				
L3	1.16 (0.69–1.87)	0.57		
Upper digestive tract disease				
Perianal disease before first surgery	0.73 (0.32–1.44)	0.41		
First surgery between 2009 and 2015 (reference: 2001–2008)	0.93 (0.56–1.52)	0.77		
Anti-TNFs before first surgery	2.82 (1.66–4.64)	<0.001	2.82 (1.53–4.74)	<0.001
Prophylactic treatments <6 months after first surgery <sup>b</sup>	1.10 (0.67–1.90)	0.63		

**TABLE 2** Predictive factors of second ileal resection.

Note: Only clinical variables with  $p < 0.2$  in the univariate analysis were included in the multivariate analysis.

<sup>a</sup>Former smoker and active smoker were considered as ‘smoking’ in the model.

<sup>b</sup>Prophylactic treatments were defined as immunosuppressants, and advanced therapies prescribed within the first months after the first surgery.

exposure before first surgery (HR: 2.82 [1.53–4.74];  $p < 0.001$ ) were significantly associated with a higher risk of a second ileal resection. Early resection and intermediate resection groups were not predictive factors of second ileal resection both in univariate and multivariate analyses.

### 3.3.5 | Cumulative risk of morphological recurrence

At 5 years, the proportion of patients with morphological recurrence was 54.4% in the early resection group, 60.0% in the intermediate group and 68.2% in the late resection group (Figure 4). The median time before morphological recurrence was statistically higher in the early resection group with 4.00 years (95% CI 3.08–6.58) compared to the late resection group with 2.08 years (95% CI 1.50–3.50;  $p = 0.02$ ). Patients with early resection had a lower risk of morphological recurrence compared to the late resection group (HR: 0.71 [95% CI 0.53–0.95];  $p = 0.02$ ). This difference was not statistically significant for the intermediate resection group compared to the other two groups.

### 3.3.6 | Morphological assessment at 1 year after first surgery

In the total cohort of 393 patients, 198 (50.4%) had an endoscopy and/or imaging in the first year after initial surgery (Table S2). The number of patients with endoscopy at 1 year was not statistically different in the three groups (55.5% vs. 40.8% vs. 44.8%;  $p = 0.07$ ). There were no differences in surveillance when endoscopy and imaging were combined (53.1% vs. 45.3% vs. 52.6%;  $p = 0.38$ ). Among patients who underwent endoscopy within 1 year after initial surgery, there was significantly less endoscopic recurrence, defined as a Rutgeerts score  $< 2$ , in the early resection group compared to the other groups (Early 70.0% vs. Intermediate 44.9% vs. Late 35.7%;  $p < 0.001$ ). Overall, including patients who underwent endoscopy or imaging within 1 year after initial surgery, morphological recurrence was statistically lower in the early resection group at 37.7% compared to 53.4% in the intermediate group and 64.8% in the late resection group ( $p = 0.008$ ). In a stratified analysis using the modified Rutgeerts score for patients operated on after 2010, early resected patients had a lower endoscopic recurrence rate compared to late resected patients (early 28.1% vs. late 60.7%;  $p = 0.03$ ; Table S2).

### 3.3.7 | Outcomes at 10 years

There was no difference at 10 years in terms of cumulative risk of third surgery, appearance of perianal disease after first surgery, perianal surgery and endoscopic dilation of the ileocolonic anastomosis (Table S3). The need for second-line advanced therapies (ustekinumab/vedolizumab/tofacitinib) was significantly higher in the late resection group compared to early resection group ( $p = 0.02$ ).

## 4 | DISCUSSION

Our study shows that patients who underwent an early ileal resection within 6 months of diagnosis did not have a higher risk of second ileal resection compared with patients who underwent later ileal resection. They also required less advanced therapies and had fewer morphological recurrences.

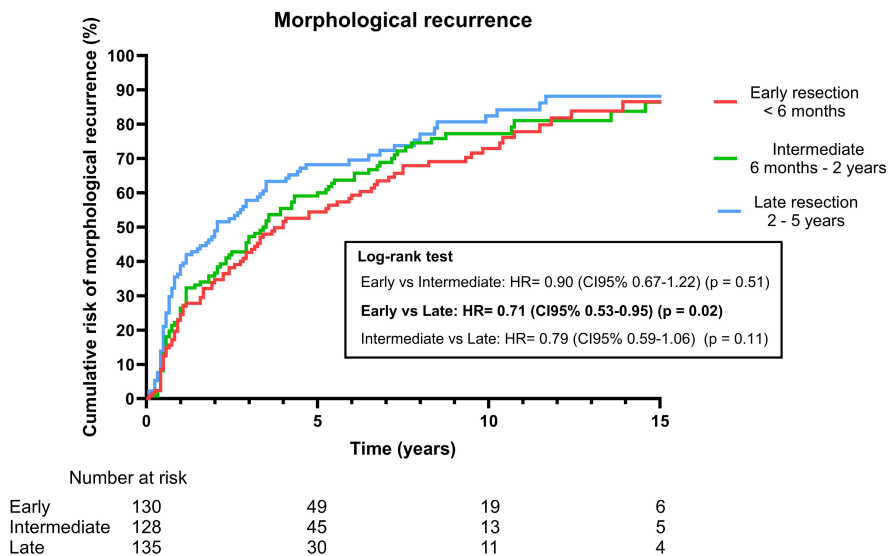
In contrast to other studies,<sup>11,12</sup> our patients had well-defined phenotypes at first surgery thanks to the SUVIMIC database, which is used in daily clinical practice by the medical staff of Saint-Antoine and the Beaujon Hospital.<sup>14</sup> In fact, previous studies on the natural history of early resected patients have not collected data on the location and behaviour of the disease. In our two centres, the indications for initial surgery were mostly stenoses or abscesses, especially in the early resection group and most of them had never been exposed to IBD treatments compared to the intermediate or late resection groups, showing that early surgery is performed only as a last resort. Again, this is a major advantage of our study over national registries,<sup>12</sup> because we had access to detailed clinical information at the time of the first surgery.

As there is no clear definition of early intervention in CD, we arbitrarily chose the 6 months interval between diagnosis of CD and first bowel resection, whereas other studies have used surgery at the very time of diagnosis to qualify the procedure as early.<sup>11</sup> Recent data from a Danish nationwide cohort study also used the 30-day threshold.<sup>12</sup> The 6 months threshold was designed to avoid excluding patients who received first-line medical treatment, such as corticosteroids for stenoses or antibiotic therapy for abscesses. Although the definition of early is not the consistent from one study to another, our results are in line with those of other retrospective studies, particularly with regard to the lower use of postoperative treatments in patients who underwent early resection.<sup>11,12</sup>

The most striking finding emerging from our study was the survival rate without postoperative treatment. Early resected patients had a 50% chance of remaining treatment-free for almost up to 4 years after the first surgery. Recent data from Agrawal et al. showed similar results with half of the patients not requiring immunosuppressants, biologics or re-resection.<sup>9</sup> It is important to note that we find the same proportion of patients without treatment at 5 years, which supports the robustness of our results. We performed sensitivity analyses by censoring treatments initiated within 6 months after surgery to distinguish prophylactic treatments from reactive treatments during recurrences. Survival without postoperative treatment was not statistically different between the three groups. Nevertheless, we still observed a trend towards higher survival without postoperative treatment in the early resection group, suggesting that these patients may have an attenuated disease course.

While Sarikaya et al. showed a lower risk of re-resection in their early resected patients compared to those who underwent surgery after 5 years after CD diagnosis, the risk of second ileal resection was not statistically different between these two groups in our study.<sup>12</sup> This may be explained by a relative lack of power





**FIGURE 4** Cumulative risk of morphological recurrence. Morphological recurrence: Endoscopic or imaging recurrence. Early resection: Ileal resection within 6 months after CD diagnosis. Intermediate: Ileal resection between 6 months and 2 years after CD diagnosis. Late resection: Ileal resection between 2 and 5 years after CD diagnosis. HR, hazard ratio; 95% CI, 95% confidence interval.

with a more limited number of patients studied compared to the nationwide cohort study. Of note, because we had access to detailed medical information, we focused on the clinically relevant anastomotic resections, whereas their definition of re-resection included all types of bowel surgery.

Likewise, Aratari et al. compared resection at diagnosis and late resection defined as more than 1 month after diagnosis.<sup>11</sup> While they used a similar method of study, the definition of early surgery was different. They found no difference in terms of second surgery and the need for immunosuppressants. To note, in this work thiopurines and methotrexate were not separated from biologics. Also, one of the main differences between the two studies might have been the substantial number of patients included before anti-TNF approval as suggested by their limited number of patients treated with biologics after surgery.

Furthermore, the early resection group showed a lower risk of morphological recurrences. As far as we know, only one retrospective study showed similar results.<sup>11</sup> However, in their study, morphological recurrence was defined as the need for systemic steroids for symptomatic disease in the presence of endoscopic and/or radiologic recurrence. In our work, data on morphological recurrence were collected independently from medical treatment prescriptions, which adds robustness to our results.

Only half of our patients had a morphological assessment in the first year after surgery and this result can be explained by several factors. Firstly, Rutgeerts score or imaging were not systematically assessed in the first year. The proportion of patients with morphological assessment in the first 18 months after surgery was up to 58.1% in the whole cohort, suggesting that the lack of morphological assessment was not only caused by a late assessment but may have been explained by lost to follow-up. However, this result was consistent with a previous Dutch study that evaluated endoscopic and radiological recurrence after primary ileocaecal resection.<sup>20</sup> Only 63.1% of the patients in this study had an endoscopy and/or imaging in the real-world setting. Although in our study only half of the patients had a morphological evaluation in the year following the initial surgery, it is still possible to compare the three groups with

a significant number of patients. The endoscopic results at 1 year confirm a lower recurrence rate in the first year in patients with early resection.

Regarding predictive factors of second surgery, segmental ileal resection as well as anti-TNF exposure before first surgery were independently associated with a higher risk of second surgery. A pathophysiological explanation may be that the removal of the ileocaecal valve limits the risk of recurrence by reducing the exposure to the microbiota. Indeed, the removal of the ileocaecal may accelerate the faecal stream by suppressing the ileal brake. This could also be explained with a higher resected length during segmental ileal resection compared to ileocaecal resection. Aaltonen et al. showed that small bowel resections have higher risk of re-resection, approximately three times more than ileocaecal resection.<sup>21,22</sup> Previous studies and our own suggest that CD confined to the small bowel may be more severe than ileocaecal disease. Given that patients with segmental ileal resection are predictive of second surgery, it would be more reasonable to propose close monitoring of these patients and to propose treatment with advanced therapies from the outset to prevent the risk of a second surgery. As for anti-TNF exposure before first surgery as a predictive factor of second surgery, we can hypothesise that patients with anti-TNF failure before surgery would be more refractory to medical treatments after surgery and so be more severe. This result highlights the importance of anti-TNF failure as an independent factor of postoperative recurrence, suggesting that this criterion could be used in clinical practice to predict relapse.

The strengths of our study are the large number of patients with a well-detailed cohort in a multicentric setting. Data are robust as they were prospectively collected daily using a routine medical chart record software. The risk of a second surgery, the need for postoperative medical treatment and the morphological results were collected independently and show in three complementary ways that early ileal resection is not associated with severe long-term outcomes. After adjusting the risk of second surgery for multiple confounders such as type of surgery, disease

phenotype, calendar year of first surgery, smoking and anti-TNF exposure prior to first surgery, no analysis showed a poor prognosis with early surgery.

Some limitations need to be discussed. Seventy-seven patients were lost to follow-up after the first operation, which can be explained by the fact that our two tertiary centres are referral centres for IBD in a large region of France, where patients are transferred for complications and then followed back again in their original centre. Another limitation lies in the definition of morphological recurrence, which we consider to be a morphological examination at any time point. Due to the real-life data, not all patients underwent endoscopic or radiological assessment within 1 year of ileal resection. However, stratified analysis at 12 months showed lower rates of endoscopic recurrence in the early group. In addition, our cohort does not include postoperative complications such as the need for antibiotics or readmission to hospital, which remain a major concern for patients. Surprisingly, smoking was not a risk factor for second surgery. Smoking status was assessed at the time of first surgery with a significant number of patients who subsequently quit smoking. The time of smoking cessation was not reported in our study, and this information is crucial to quantify the effect of smoking on recurrence. However, there is a trend towards an increased risk of second surgery in smokers in the univariate analysis. In addition, as our cohort began in the early 2000's, the availability of treatments and postoperative therapeutic strategies may have changed. Given their efficacy, the increasingly low cost of advanced treatments and the advent of biosimilars, their prescription is now widespread. Finally, prophylactic treatments within 6 months after first surgery did not decrease the risk of second surgery. This result may be explained by the small number of patients systematically treated after surgery, especially the small number of patients who received immediate postoperative anti-TNF. Again, this result can be explained by the time period of our study when physicians used less immediate advanced therapies to prevent recurrence.

In summary, we demonstrate that early ileal resection in CD is not associated with worse long-term outcomes compared with late resection. On the contrary, early resected patients may require less postoperative treatment and have fewer morphological recurrences after surgery. Further studies are needed to determine whether an early surgery strategy can maintain a prolonged remission and, most importantly, to identify the subgroups of patients who may benefit.

#### AUTHOR CONTRIBUTIONS

**N. Grellier:** Conceptualization; writing – original draft; methodology; investigation; visualization; formal analysis; software; data curation. **J. Kirchesner:** Conceptualization; writing – review and editing; methodology; supervision; data curation; formal analysis. **M. Uzzan:** Writing – review and editing. **P. McLellan:** Writing – review and editing. **C. Stefanescu:** Writing – review and editing. **J. H. Lefevre:** Writing – review and editing. **X. Treton:** Writing – review and editing. **Y. Panis:** Writing – review and editing. **H. Sokol:** Writing – review

and editing. **L. Beaugerie:** Writing – review and editing. **P. Seksik:** Conceptualization; supervision; validation; writing – review and editing; funding acquisition; project administration; resources.

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study, including raw data, analytic methods and study materials are available from the corresponding author, (PS), upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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## APPENDIX A

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