Postoperative Endoscopic Recurrence on the Neoterminal Ileum But Not on the Anastomosis Is Mainly Driving Long-Term Outcomes in Crohn's Disease

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INTRODUCTION: **Early ileocolonoscopy within the first year after surgery is the gold standard to evaluate recurrence after ileocolonic resection for Crohn's disease (CD). The aim of the study was to evaluate the association between the presence and severity of anastomotic and ileal lesions at early postoperative ileocolonoscopy and long-term outcomes.**

METHODS: **The REMIND group conducted a prospective multicenter study. Patients operated for ileal or ileocolonic CD were included. An ileocolonoscopy was performed 6 months after surgery. An endoscopic score describing separately the anastomotic and ileal lesions was built. Clinical relapse was defined by the CD-related symptoms, confirmed by imaging, endoscopy or therapeutic intensification; CD-related complications; or subsequent surgery.**

RESULTS: **Among 225 included patients, long-term follow-up was available in 193 (median follow-up: 3.82 years [interquartile range: 2.56–5.41]). Median clinical recurrence-free survival was 47.6 months. Clinical recurrence-free survival was significantly shorter in patients with ileal lesions at early postoperative endoscopy whatever their severity was (I(1) or I(2,3,4)) as compared to patients without ileal lesions (I(0)) (I(0) vs I(2,3,4): $P = 0.0003$; I(0) vs I(1): $P = 0.0008$ and I(1) vs I(2,3,4): $P = 0.43$). Patients with exclusively ileal lesions (A(0)I(1,2,3,4)) had poorer clinical long-term outcomes than patients with exclusively anastomotic lesions (A(1,2,3)I(0)) ($P = 0.009$).**

DISCUSSION: **A score describing separately the anastomotic and ileal lesions might be more appropriate to define postoperative endoscopic recurrence. Our data suggest that patients with ileal lesions, including mild ones (I(1)), could beneficiate from treatment step-up to improve long-term outcomes.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B512, http://links.lww.com/AJG/B513, http://links.lww.com/AJG/B514, http://links.lww.com/AJG/B515, http://links.lww.com/AJG/B516, http://links.lww.com/AJG/B517, http://links.lww.com/AJG/B518, http://links.lww.com/AJG/B519, and http://links.lww.com/AJG/B520

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INTRODUCTION

Despite improvements in the management of Crohn's disease (CD), surgery remains a major issue in the management of patients with CD (1–3). Furthermore, intestinal resection is not curative as the disease recurs in many patients. Clinical or surgical relapse is frequently preceded by an endoscopic recurrence mainly observed at the anastomosis or in the neoterminal ileum (4). We and others previously reported several risk factors associated with early

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postoperative endoscopic recurrences, including active smoking, previous intestinal surgery, male sex, and transmural inflammation of the ileal margin of resection (5–8). Whether the type of anastomosis could influence the recurrence rate remains controversial (5,7,9). We also recently demonstrated that patients with an increased proportion of mucosal T cell clonal expansions at the time of surgery have an increased risk of postoperative endoscopic recurrence and that recurrence is associated with changes in the microbiota composition and alpha diversity (10,11).

In the hallmark study performed by Rutgeerts et al. (12), severity of endoscopic recurrence, evaluated during an ileocolonoscopy 6 months after surgery (M6) by the Rutgeerts score (RS), predicts the patient's long-term outcome. The original RS included 5 grades of severity (i0–i4) depending on the presence of lesions found at the anastomosis or in the neoterminal ileum. The Post-Operative Crohn's Endoscopic Recurrence study confirmed the benefit of a treat-to-target strategy based on early endoscopy to improve patient outcomes and reduce the risk of clinical relapse (13).

If severe lesions (i3 or i4) are clearly correlated with poor long-term symptom-free survival, the association of isolated anastomotic lesions and mild ileal lesions (less than 5 aphthous ulcers) with clinical outcomes is more conflicting. A modified RS has been proposed to split patients with i2 recurrence in 2 groups according to the finding of ileal lesions (i2b) or to a strict anastomotic recurrence (i2a) (14). Discrepant results concerning the clinical outcome of these subgroups of patients have been reported (15,16). A recent publication showed that the existence of ileal lesions was associated with higher levels of fecal calprotectin and lactoferrin, suggesting a higher global inflammatory level in patients with i2b recurrence (17).

Large prospective multicenter data concerning the long-term outcome after ileocolonic resection in CD are lacking. Our aim in the present study was to evaluate the association between severity of lesions found at the ileocolonoscopy performed 6 months after surgery and clinical, endoscopic, imaging, and surgical long-term outcomes. We also defined a new score for postoperative endoscopic recurrence, describing separately anastomotic and ileal lesions, leading to a better and clearer characterization of patients at high risk of recurrence and anastomotic complications based on the results of their postoperative endoscopy.

METHODS

Postoperative cohort and patient selection

The present work was undertaken on a prospective multicenter study performed by the REMIND (groupe de REcherche sur les Maladies INflammatoires Digestives) group. Patients were included between September 2010 and December 2016. Inclusion criteria were as follows: age greater than 18 years, ileal or ileocolonic CD, and indication of CD-related intestinal surgery (ileocolonic resection). A postoperative treatment was recommended according to a preestablished algorithm based on the following risk factors: current smoking, previous bowel resection, penetrating phenotype, and active perianal disease. In this algorithm, no treatment or 5-aminosalycilic acid is proposed to patients with no risk factor; whereas thiopurines, or anti-tumor necrosis factor (TNF) agents in the case of previous thiopurine failure, is recommended in patients with 1 risk factor; and anti-TNF therapy (alone or in combination with azathioprine) in patients with 2 or more risk factors.

All patients had, 6 months after surgery, an ileocolonoscopy to assess the endoscopic recurrence and its severity according to the RS. All patients provided informed written consent. The study was approved by Agence Française de Sécurité Sanitaire et des Produits de Santé (AFSSAPS) (IDRCB: 2009-A00205-52) and the French Ethic Committee – Hôpital Saint-Louis (CPP 2009/17) and declared to ClinicalTrials.gov (NCT03458195).

Data collection

Clinical parameters were collected prospectively at the time of surgery and at postoperative endoscopy.

An endoscopy was performed 6 months after surgery. Endoscopic data were collected prospectively. All elementary lesions were reported and detailed in all segments, including the anastomotic region and the neoterminal ileum. The physician who performed the colonoscopy provided the modified RS for each patient (7).

Then, according to the description of elementary lesions in all the segments prospectively reported in a computer database, 2 physicians (M.A. and N.H.) graded together each postoperative endoscopy describing separately the anastomotic and ileal lesions blinded from postoperative treatment and outcomes. Two other physicians (C.A., M.-L.T.M.) regraded each endoscopy to evaluate the score consistency. For anastomotic lesions (<1 cm in length after the anastomosis), 4 grades were defined: A(0): no lesion, A(1): ulcerations covering less than 50% of the anastomosis circumference, A(2): ulcerations covering more than 50% of the anastomosis circumference, and A(3): anastomotic stenosis. For ileal lesions, 5 grades were defined according to the RS (11): I(0): no lesion, I(1): less than 5 aphthous ulcers, I(2): more than 5 aphthous lesions with normal intervening mucosa or skip areas of larger lesions, I(3): diffuse aphthous ileitis with diffusely inflamed mucosa, and I(4): diffuse inflammation with larger ulcers. Patients with endoscopically impassable anastomotic stenosis were not evaluated for ileal lesions and excluded from the corresponding survival analyses. Hence, each patient had a separated anastomotic and ileal evaluation with an overall score reported as following: A(x)I(x).

Long-term data of patients with a follow-up of at least 18 months were collected retrospectively. They included clinical data, treatment data, endoscopic data (colonoscopy performed during the follow-up), imaging data (magnetic resonance [MR] enterography and/or CT scan performed during the follow-up), and surgical data (subsequent surgery performed).

Evaluated outcomes

Clinical recurrence was defined by (i) CD-related clinical manifestations confirmed either by ileocolonoscopy, imaging (active lesions of the small bowel or colon confirmed by the center referring radiologist) or therapeutic intensification (treatment optimization or drug switch), (ii) CD-related complications (intra-abdominal abscess or occlusive manifestation), or (iii) CD-related subsequent surgery.

Clinical recurrence defined only by CD-related clinical manifestations, confirmed either by ileocolonoscopy or imaging (active lesions of the small bowel or colon confirmed by the center referring radiologist) was also evaluated.

Objective disease progression was evaluated for the patients who had at least 1 objective examination during a period of 5 years after surgery and defined by (i) endoscopic changes from ileal lesions graded I(0) or I(1) to ileal lesions I(3) or I(4) in subsequent colonoscopies, (ii) severe imaging lesions of the small bowel or colon, or (iii) CD-related complications.

Anastomotic occlusive complications were defined by obstructive clinical symptoms, confirmed by MR enterography or endoscopy, treated or not by either endoscopic dilation or subsequent anastomotic surgery.

Surgical recurrence was defined by a subsequent CD-related surgery at the anastomotic site (subsequent ileocolonic resection or stricturoplasty).

Statistical analyses

Descriptive statistics were calculated for all quantitative variables as medians with their respective interquartile ranges (IQRs).

For qualitative variables, comparison between groups was performed using the Fisher exact test. For quantitative variables, comparison between groups was performed using the Mann–Whitney test.

For both clinical and surgical recurrences, Kaplan–Meier survival curves and crude log rank tests were calculated. A multivariate Cox model combining demographical data (gender and age) and variables significantly associated with clinical recurrence in univariate analyses was built.

Interobserver agreement of the score was estimated using a weighted kappa coefficient.

All statistical analyses were 2 tailed, and a P value of less than 0.05 was considered as statistically significant. R software (3.2.2 version) and PrismGraphPad were used.

RESULTS

Patient characteristics

Two hundred twenty-five patients were included. Long-term clinical data and outcomes were available for 193 patients (86%) (Figure 1).

The median age at surgery was 30.7 years (IQR: 25.0–42.1) and median disease duration was 5.9 years (IQR: 1.9–11.8). Eighty-six patients (45%) were men, 53 (28%) active smokers and 34 (18%) had a previous ileocecal resection in their medical history (Table 1). Postoperative treatment was given to 97 patients (50%), including an anti-TNF treatment in 54 patients (28%) (Table 2).

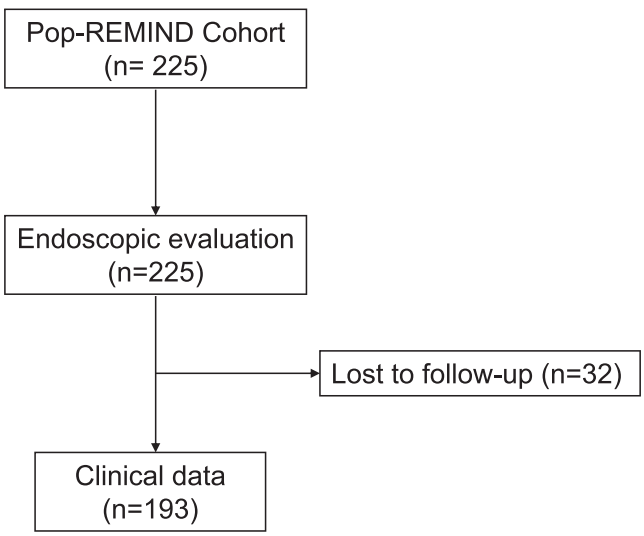

Figure 1. Flowchart of the study.

Description and scoring of postoperative recurrence

Postoperative endoscopy was performed in all patients with a median time between resection and colonoscopy of 6.8 months.

At the anastomosis, 103 patients (53%) had no lesion A(0) and 24 (12%) more than semicircumferential ulcerations (A(2) or A(3)) including 11 (6%) anastomotic stenosis A(3). In the neoterminal ileum, 99 patients (51%) had no lesions (I(0)), 26 (13%) less than 5 aphthous ulcers (I(1)), and 62 (32%) more severe lesions (I(2), I(3), or I(4)). For 6 patients (3%), the ileum was not technically assessable. The length of the ileum explored was not significantly different between the 5 groups (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B512). Patients with anastomotic lesions (A(1,2,3)) did not have significantly more ileal lesions than patients without (A(0)). (54% vs 42%, $P = 0.14$, χ^2 test) (Table 3). There was no discrepancy between the physicians who graded the endoscopies concerning anastomotic lesions, and interobserver agreement was good for the ileal score (weighted kappa coefficient: 0.82).

By contrast, according to the modified RS evaluating concomitantly the anastomotic and ileal lesions, 64 patients (33%) had no lesion (i0), 32 (17%) were graded i1, and 38 (20%) had severe endoscopic recurrence (i3 or i4). Among the 32 patients evaluated as i1, 10 (31%) had no ileal lesions, less than 5 aphthous ulcers confined to the anastomosis, and 21 (66%) presented ileal lesions. Among the 33 patients classified as i2b, 6 (18%) had no more than mild ileal lesions (less than 5 aphthous ulcers) associated with anastomotic ulcers.

Among the 153 patients (79%) for whom the type of surgical anastomosis was known, no significant association between these data and the anastomotic lesions was found (see Table 1, Supplementary Digital Content 6, http://links.lww.com/AJG/B517). Patients with handsewn side-to-side anastomosis presented a trend toward less anastomotic lesions but more ileal lesions without reaching significance (see Figure 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B513).

Postoperative treatment adaptation according to the RS

After M6 ileocolonoscopy, CD's treatment was adapted for 59 patients (31%). Therapeutic adaptation was decided for most patients with a RS of i2b, i3, or i4 (76%, 75%, and 68%, respectively). By contrast, 98%, 94%, and 85% of patients with a RS at M6 endoscopy of i0, i1, or i2a, respectively, had no treatment modification after this examination (Table 2).

Long-term clinical and surgical recurrences

The median follow-up after surgery was 3.82 years (IQR: 2.56–5.41). Ninety patients (47%) experienced clinical relapse during the follow-up. Among them, 74 patients (82%) had an endoscopy, an imaging examination, or both showing CD lesions (see Table 2, Supplementary Digital Content 7, http://links.lww.com/AJG/B518). From the time of surgery, the median clinical recurrence-free survival was 47.6 months (Figure 2a). The cumulative clinical recurrence rate was 4%, 36%, and 60% at 1, 3, and 5 years, respectively. In both univariate and multivariate analyses, clinical parameters significantly associated with long-term clinical recurrence were the following: active smoking at surgery ($P = 0.01$), previous intestinal surgery ($P = 0.05$), extraintestinal manifestations at surgery (i.e., cutaneous, articular and ophthalmologic lesions) ($P = 0.01$), and transmural lesions at the ileal resection margin ($P = 0.03$) (defined in 8) (see Table 3,

Table 1. Patients' characteristics at the time of surgery

	Patients n = 193 (%)
Men	86 (45%)
Median age, yr, (IQR)	30.7 (25.0–42.1)
Age at Crohn's disease diagnosis (Montreal classification)	
≤16 yr (A1)	18 (9%)
17–40 yr (A2)	156 (81%)
>40 yr (A3)	19 (10%)
Median disease duration, yr (IQR)	5.9 (1.9–11.8)
Median time between resection and colonoscopy, mo (IQR)	6.8 (6.1–8.0)
Smoking	
Active smoker	53 (28%)
Smoking cessation at surgery	12 (6%)
Nonsmoker	128 (66%)
Previous intestinal resection	34 (18%)
<10 yr	13 (7%)
Number of previous resection(s)	
0	159 (82%)
1	25 (13%)
2	7 (4%)
3	2 (1%)
Surgical indication	
Stricturing complication	107 (56%)
Penetrating complication	73 (38%)
Failure of drug therapy	13 (7%)
Disease location (Montreal classification)	
Ileal (L1)	121 (63%)
Ileocolonic (L3)	72 (37%)
Anoperineal lesion	44 (23%)
Extradigestive symptoms	
Joint manifestations	35 (18%)
Skin manifestations	10 (5%)
Eye manifestations	4 (2%)
Previous exposure to anti-TNF therapy	124 (64%)
Anti-TNF therapy within 3 mo before surgery	100 (52%)
Previous exposure to thiopurines	134 (69%)
Thiopurines within 3 mo before surgery	59 (31%)

IQR, interquartile range; TNF, tumor necrosis factor.

Supplementary Digital Content 8, http://links.lww.com/AJG/B519). Twenty-four patients (12%) received no treatment during the whole follow-up (Figure 2b). One patient (0.5%) presented an intra-abdominal abscess and 18 (9%) occlusive manifestations. Among these patients, 6 needed a subsequent surgery (5 ileocolonic resections and 1 stricturoplasty), 5 an endoscopic dilation, and 7 had occlusive symptoms with a stenosis at MR enterography or endoscopy. One patient had abdominoperineal resection during follow-up because of the severe anoperineal active lesions.

Long-term clinical outcomes according to the modified RS

Clinical recurrence-free survival was significantly longer in patients with no lesion at M6 colonoscopy (RS i0) as compared to patients with RS i1, i2b, i3, or i4 (median clinical recurrence-free survival: not reached vs 48.3, 34.6, 38.5, and 34.9 months, respectively; $P = 0.05$, $P = 0.002$, $P = 0.01$, and $P = 0.0003$, respectively) (see Figure 3, Supplementary Digital Content 3, http://links.lww.com/AJG/B514). By contrast, recurrence-free survival was not significantly different between RS i0 and i2a patients ($P = 0.63$).

Long-term clinical outcomes describing separately anastomotic and ileal lesions

Clinical recurrence-free survival was significantly shorter in patients with ileal lesions whatever their severity was (I(1) or I(2,3,4)) at postoperative endoscopy as compared to patients without ileal lesions (I(0)) (median recurrence-free survivals: 68.5, 33.0, and 39.1 months, respectively for I(0), I(1), and I(2,3,4); I(0) vs I(2,3,4): $P = 0.0003$; I(0) vs I(1): $P = 0.0008$ and I(1) vs I(2,3,4): $P = 0.43$) (Figure 3a). By contrast, anastomotic occlusive complications were not significantly different between the 3 groups (I(0) vs I(2,3,4): $P = 0.34$; I(0) vs I(1): $P = 0.51$; and I(1) vs I(2,3,4): $P = 0.75$) (Figure 3b).

Clinical recurrence-free survival was not significantly different between patients with no anastomotic lesion (A(0)), few anastomotic lesions (A(1)), and more than semicircumferential ulcerations (A(2,3)) (median survivals 53.3, 48.3, and 35.1 months, respectively; A(0) vs A(2,3): $P = 0.09$; A(0) vs A(1): $P = 0.69$; and A(1) vs A(2,3): $P = 0.19$) (Figure 3c). Patients with at least semicircumferential anastomotic ulcerations (A(2,3)) had more anastomotic occlusive complications than patients without (A(0) or A(1)) (A(0) vs A(2,3): $P = 0.01$; A(0) vs A(1): $P = 0.83$; A(1) vs A(2,3): $P = 0.05$) (Figure 3d). When excluding from the analysis patients with early postoperative treatment and those who underwent more than 1 ileocolonic resection, the results were similar (Figure 4, see Figure 4, Supplementary Digital Content 4, http://links.lww.com/AJG/B515 and see Table 4, Supplementary Digital Content 9, http://links.lww.com/AJG/B520). When defining clinical recurrence by CD-related clinical symptoms confirmed either by ileocolonoscopy or imaging, the results were also similar (see Figure 5, Supplementary Digital Content 5, http://links.lww.com/AJG/B516 and see Table 4, Supplementary Digital Content 9, http://links.lww.com/AJG/B520).

Patients with exclusively ileal lesions (A(0)I(1,2,3,4)) had poorer clinical long-term outcomes than patients with exclusively anastomotic lesions (A(1,2,3)I(0)) (median recurrence-free survivals of 41.8 vs 68.5 months, respectively, $P = 0.009$) (Figure 3e).

Patients with mild ileal lesions at early postoperative endoscopy have more objective disease progression than patients without ileal lesions

Among the 99 patients graded I(0) and the 26 graded I(1) at first postoperative endoscopy, respectively, 76 (77%) and 21 (81%) had at least 1 subsequent objective disease evaluation (endoscopy or MR enterography) within 5 years after surgery. For

Table 2. Postoperative treatment adaptation according to the modified Rutgeerts Score

Rutgeerts score at M6 endoscopy	n = 193	Immediate postoperative treatment		Therapeutic adaptation after M6 endoscopy	
Whole cohort	193	No treatment	96 (50%)	No adaptation	134 (70%)
		IS	38 (20%)	Drug initiation	47 (24%)
		Anti-TNF	43 (21%)	Drug switch	6 (3%)
		IS + anti-TNF	11 (6%)	Drug optimization	6 (3%)
		Vedolizumab	2 (1%)		
		Ustekinumab	3 (2%)		
i0	64	No treatment	22 (34%)	No adaptation	63 (98%)
		IS	12 (18%)	Drug initiation	1 (2%)
		Anti-TNF	23 (36%)	Drug switch	0
		IS + anti-TNF	5 (8%)	Drug optimization	0
		Vedolizumab	1 (2%)		
		Ustekinumab	1 (2%)		
i1	32	No treatment	21 (66%)	No adaptation	30 (94%)
		IS	6 (19%)	Drug initiation	2 (6%)
		Anti-TNF	4 (12%)	Drug switch	0
		IS + anti-TNF	1 (3%)	Drug optimization	0
		Vedolizumab	0		
		Ustekinumab	0		
i2a	26	No treatment	11 (42%)	No adaptation	22 (85%)
		IS	8 (31%)	Drug initiation	3 (12%)
		Anti-TNF	5 (19%)	Drug switch	1 (3%)
		IS + anti-TNF	2 (8%)	Drug optimization	0
		Vedolizumab	0		
		Ustekinumab	0		
i2b	33	No treatment	20 (61%)	No adaptation	8 (24%)
		IS	5 (15%)	Drug initiation	17 (52%)
		Anti-TNF	5 (15%)	Drug switch	3 (9%)
		IS + anti-TNF	1 (3%)	Drug optimization	5 (15%)
		Vedolizumab	1 (3%)		
		Ustekinumab	1 (3%)		
i3	16	No treatment	8 (50%)	No adaptation	4 (25%)
		IS	3 (19%)	Drug initiation	9 (56%)
		Anti-TNF	3 (19%)	Drug switch	2 (13%)
		IS + anti-TNF	1 (6%)	Drug optimization	1 (6%)
		Vedolizumab	0		
		Ustekinumab	1 (6%)		
i4	22	No treatment	14 (64%)	No adaptation	7 (32%)
		IS	4 (18%)	Drug initiation	15 (68%)
		Anti-TNF	3 (14%)	Drug switch	0
		IS + anti-TNF	1 (4%)	Drug optimization	0
		Vedolizumab	0		
		Ustekinumab	0		

IS, immunosuppressant; TNF, tumor necrosis factor.

Table 3. Correlation between anastomotic and ileal lesions at early postoperative endoscopy

	A				
I	0	1	2	3	Total
0	60 (32%)	29 (15%)	6 (3%)	4 (2%)	99 (52%)
1	15 (8%)	9 (4.5%)	2 (1%)	0	26 (13.5%)
2	16 (8%)	17 (9%)	1 (0.5%)	0	34 (17.5%)
3	7 (3.5%)	7 (3.5%)	2 (1%)	1 (0.5%)	17 (8.5%)
4	5 (2.5%)	4 (2%)	2 (1%)	0	11 (5.5%)
NA	0	0	0	6 (3%)	6 (3%)
Total	103 (54%)	66 (34%)	13 (6.5%)	11 (5.5%)	193 (100%)

respectively, 52 (53%) and 14 (54%) of them, an ileocolonoscopy was available during this period.

Objective disease progression was significantly more frequent in patients with ileal lesions graded I(1) as compared to patients with no ileal lesions I(0) (26/76 (34%) vs 13/21 (62%) for I(0) and I(1) groups, respectively; $P = 0.03$, Fisher's exact test). Endoscopic progression was also significantly different between the 2 groups (14/52 (27%) vs 10/14 (71%) for I(0) and I(1) groups, respectively; $P = 0.004$, Fisher exact test).

DISCUSSION

In this large multicentric cohort, we evaluated the long-term clinical outcome of patients with CD after ileocolonic surgery. Median clinical recurrence-free survival was of 47.6 months and 47% of patients experienced recurrence during the follow-up. These data are in the higher part of the recurrence rates reported in the recent literature on the subject (18–20) using clinical recurrence as the main outcome. It underlines the improvements needed in the postoperative management after ileocolonic resection in CD.

All the patients included underwent a postoperative ileocolonoscopy, and we analyzed the association between the severity of early postoperative endoscopic lesions, describing separately anastomotic and ileal lesions, and long-term clinical outcomes. We found that ileal lesions, whatever their severity, 6 months after surgery were significantly associated with a reduced recurrence-free survival. This finding was particularly interesting for patients with less than 5 ileal ulcers (classified I(1)) who presented significantly more clinical relapses than patients without any ileal lesions at the first postoperative ileocolonoscopy (classified I(0)). Patients with severe anastomotic lesions (more than semi-circumferential ulcerations) had a significant increase of occlusive anastomotic complications but only a trend toward a poorer clinical long-term outcome.

At the end of the follow-up, only 12% of patients did not receive any CD-specific medical treatment. These data underline the difficulty to achieve remission after surgery without medical specific therapy and the crucial place of these treatments in the current CD postoperative management. The low surgical recurrence rate found in this cohort reflects that, although insufficient to achieve clinical remission in a large number of patients, medical therapeutic intervention may reduce the severe complications leading to subsequent surgery.

Ileocolonoscopy performed 6 months after surgery is the gold standard to evaluate early postoperative recurrence. We showed that tailored treatment according to early postoperative colonoscopy reduces clinical recurrence in a retrospective study (21). The Post-Operative Crohn's Endoscopic Recurrence study confirmed that an early endoscopy with treatment step-up for recurrence was better than conventional management in preventing postoperative CD recurrence (13). The endoscopic cutoff to optimize medical therapy was a RS of i2.

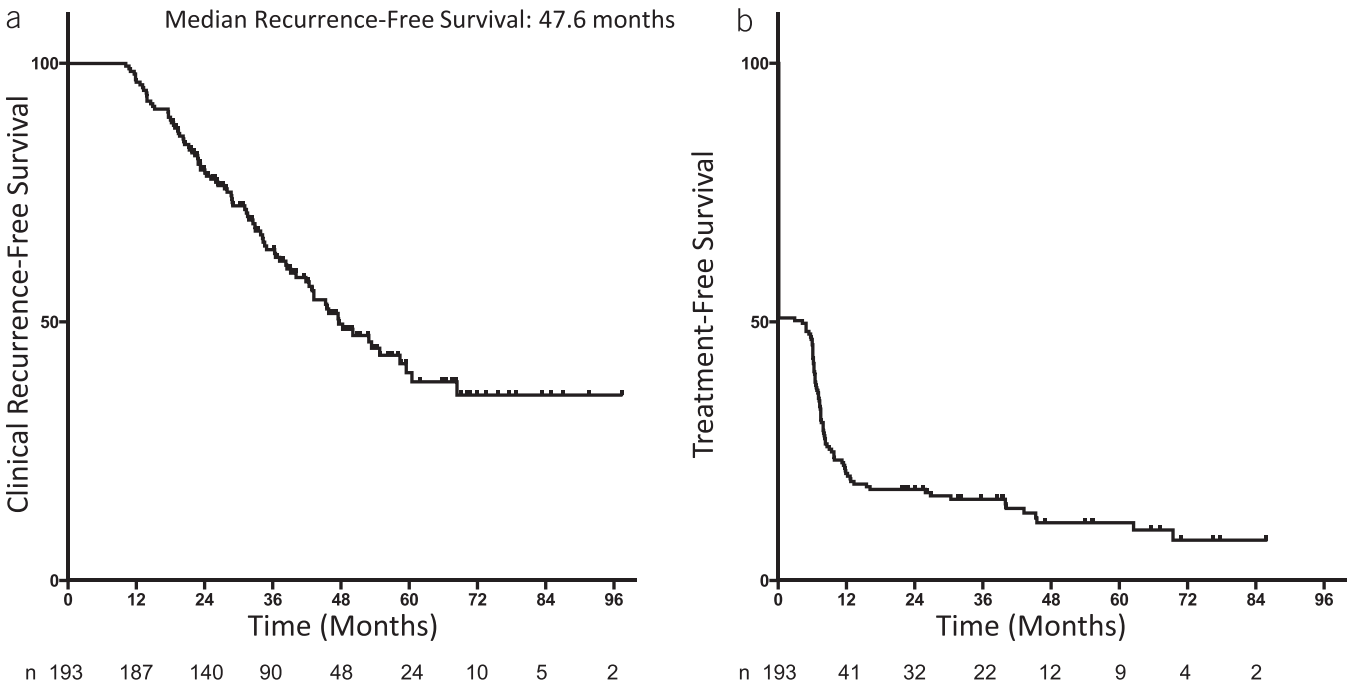

Figure 2. Clinical recurrence-free survival. (**a**) Overall clinical recurrence-free survival. (**b**) Treatment-free survival.

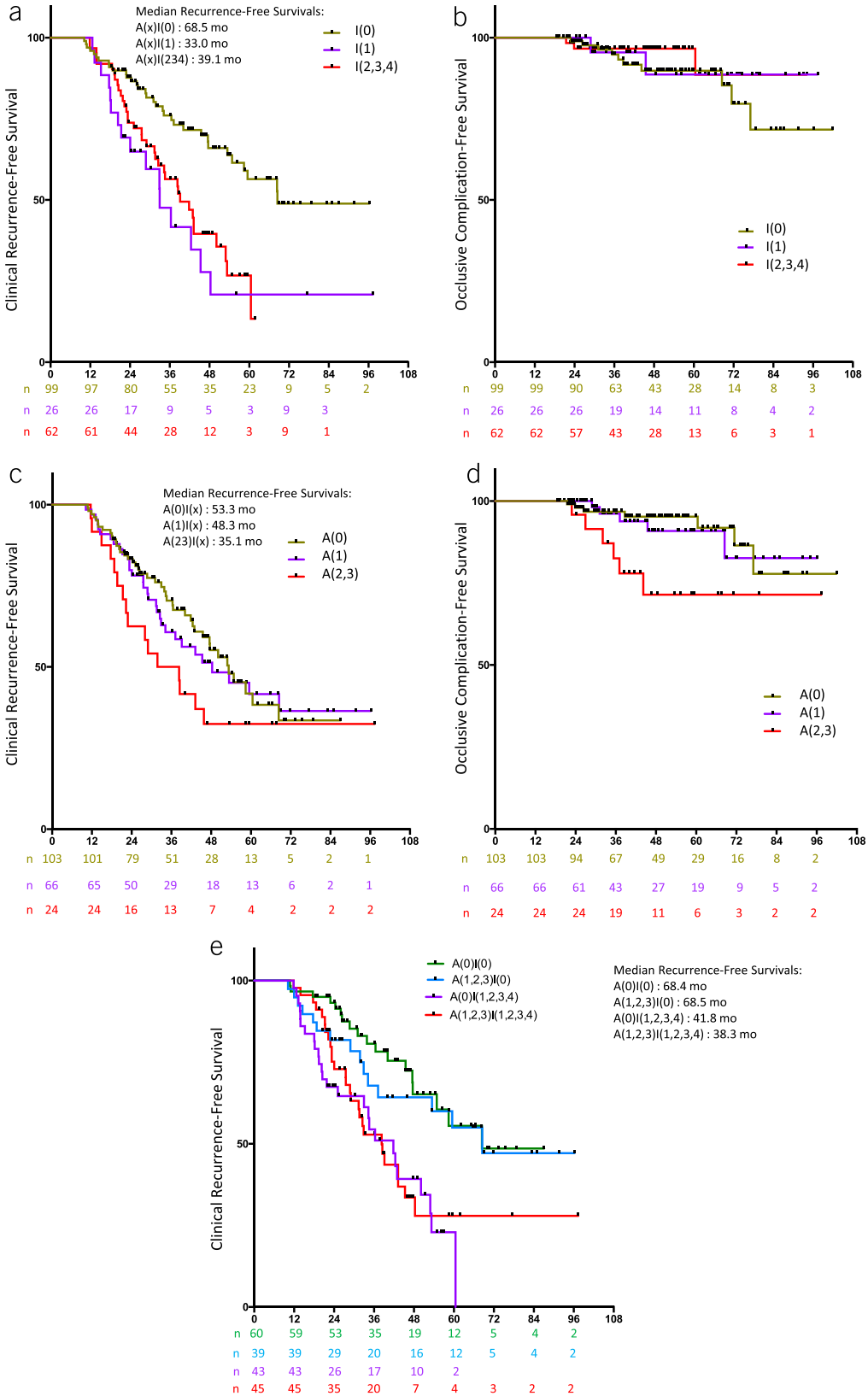

Figure 3. Recurrence-free survival according to the score, describing separately the ileal and anastomotic lesions. (**a**) Clinical recurrence-free survival depending on ileal evaluation (I). (**b**) Occlusive complication-free survival depending on ileal evaluation (I). (**c**) Clinical recurrence-free survival depending on anastomotic evaluation (A). (**d**) Occlusive complication-free survival depending on anastomotic evaluation (A). (**e**) Clinical recurrence-free survival depending on both anastomotic and ileal lesions. Survival curves were built using the Kaplan–Meier method, and crude log rank tests were calculated. Significance was reached if $P < 0.05$.

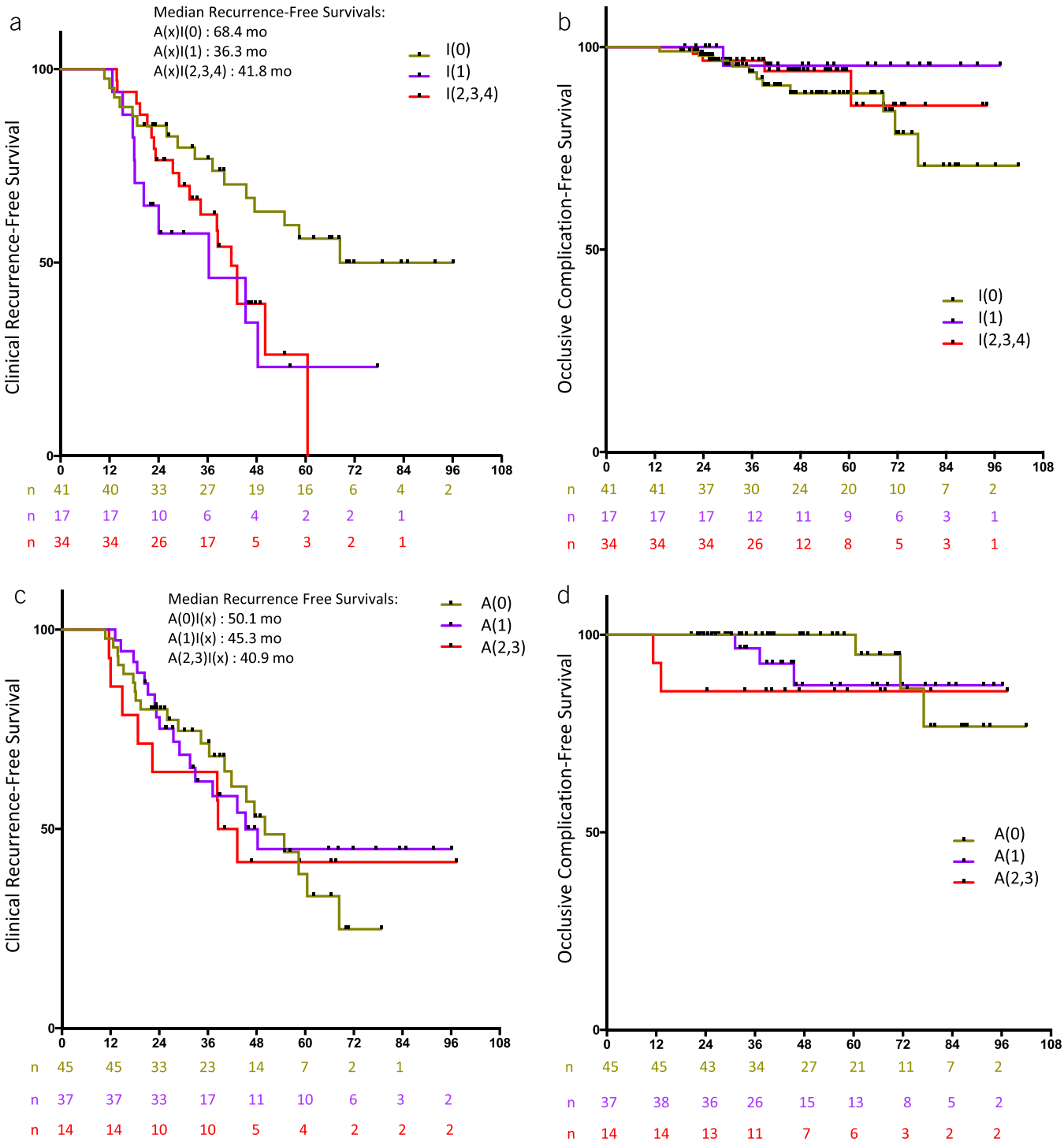

Figure 4. Recurrence-free survival according to the score, describing separately the ileal and anastomotic lesions excluding patients with early post-operative treatment. (**a**) Clinical recurrence-free survival depending on ileal evaluation (I). (**b**) Occlusive complication-free survival depending on ileal evaluation (I). (**c**) Clinical recurrence-free survival depending on anastomotic evaluation (A). (**d**) Occlusive complication-free survival depending on anastomotic evaluation (A) survival curves were built using the Kaplan–Meier method, and crude log rank tests were calculated. Significance was reached if $P < 0.05$.

Severe endoscopic lesions at 6-month endoscopy (RS of i3 or i4) are clearly correlated with poorer clinical outcomes. Concerning mild to moderate lesions (i.e. i1 or i2 lesions), data are controversial. A modified RS has been proposed splitting grade i2 in 2 groups corresponding to lesions confined to the ileocolonic anastomosis (i2a) and moderate lesions on the neoterminal ileum (i2b). A recent retrospective single-center study showed that patients with a RS of i2a within 1 year after surgery did not have a higher rate of progression to more severe disease as compared to those without any lesion found at M6

endoscopy (22). By contrast, lesions in the neoterminal ileum (i2b) were significantly associated with poorer outcomes. We here confirm these data in a prospective multicentric cohort considering clinical recurrence.

We found that some endoscopic evaluations were difficult to classify according to the modified RS. It was particularly true for i1, i2a, and i2b patients. Thirty percent of the patients classified as i1 only presented anastomotic lesions (less than 5 aphthous ulcers) and, by contrast, 18% of patients classified as i2b presented only mild ileal lesions (less than 5 aphthous ulcers, associated with anastomotic ulcers).

We propose a new endoscopic score, describing separately the anastomotic and ileal lesions. With this new approach, we found that ileal lesions at endoscopy, whatever their severity, were associated with a significantly poorer clinical evolution and higher disease progression, independently from the anastomotic evaluation. This observation was also true for mild lesions of the neoterminal ileum (I(1)). Early publications evaluating CD postoperative relapse pooled patients with RS i0 or i1 endoscopic recurrence who presented better outcomes compared with more severe lesions. However, pathophysiologically, ileal lesions, although mild, are linked to a higher level of local inflammation and could be associated with more active disease. Overall, in this large cohort, we show that ileal lesions, whatever their severity, are the most relevant lesions to consider for treatment escalation or optimization.

By contrast, mild anastomotic lesions were not associated with a poorer clinical outcome as compared to patients with no anastomotic lesions (A(0)). However, severe anastomotic lesions (more than semicircumferential ulcers here graded A(2) or A(3)) were associated with significantly more occlusive complications and a trend toward a higher clinical recurrence rate in the long-term, independently from the presence of ileal lesions. Anastomotic ulcers are reported in the literature in patients without CD who underwent ileocolonic resections (23–25). Anastomotic recurrence could be partly because of other lesion mechanisms, including local ischemia secondary to the anastomosis confection.

The correlation between digestive symptoms after CD-related surgery and objective lesions identified by endoscopy or imaging remains poor (26). We found the same trend concerning the association between ileal lesions at early postoperative endoscopy and recurrence when considering either a clinical outcome or a more objective endpoint (based on either endoscopy, imaging strategies, or CD-related complications).

The major limitation of our study is the absence of endoscopic central reading, which could have led to misclassifications of the endoscopic lesions. However, we determined our score based on an electronic database filled prospectively and detailing all the elementary lesions visualized in the anastomosis and the neoterminal ileum. With this approach, the score reproducibility was good; there was no discrepancy between the physicians who graded the endoscopies concerning anastomotic lesions, and interobserver agreement was good for the ileal score (weighted kappa coefficient: 0.82).

In conclusion, in this multicentric cohort, we found an important rate of clinical long-term recurrence underlining the crucial need to improve our postoperative management and treatment strategies. Ileal lesions, including mild to moderate ones, at early postoperative colonoscopy were significantly associated with higher clinical long-term recurrence and objective relapse rates. These results suggest that mild lesions (I(1)) should be taken into account for treatment escalation or optimization. The REMIND score proposed here, describing separately anastomotic and ileal lesions, might be more appropriate to predict the postoperative outcomes.

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CONFLICTS OF INTEREST

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Study Highlights

WHAT IS KNOWN

- ✓ Early ileocolonoscopy within the first year after surgery is the gold standard to evaluate early postoperative recurrence after ileocolonic resection for CD.
- ✓ Severity of endoscopic recurrence, as assessed by the RS, predicts long-term outcomes.

WHAT IS NEW HERE

- ✓ A score describing separately the anastomotic and ileal lesions might be more appropriate to define postoperative endoscopic recurrence after ileocolonic resection in CD.
- ✓ Clinical recurrence-free survival is significantly shorter in patients with ileal lesions at early postoperative endoscopy, whatever their severity is as compared to patients without ileal lesions.

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