Digestive and Liver Disease 52 (2020) 1323–1330

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Long-term outcome of Crohn's disease patients with upper gastrointestinal stricture: A GETAID study

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ARTICLE INFO

Article history:
Received 8 May 2020
Accepted 21 August 2020
Available online 20 September 2020

ABSTRACT

Background: There are few data concerning patients with Crohn's disease (CD) complicated by a stricture of the upper gastrointestinal tract (UGT).
Aims: We evaluated the outcome and management of CD patients complicated by a stricture of the UGT.

Abbreviations: 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; EBD, endoscopic balloon dilation; GEA, gastroenteroanastomosis; IQR, interquartile range; HBI, Harvey-Bradshaw Index; OR, odds ratio; TNF, tumor necrosis factor; UGT, upper gastrointestinal tract.

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https://doi.org/10.1016/j.dld.2020.08.034

Keywords:
Crohn's disease
Upper gastrointestinal tract
Stricture
Surgery
Endoscopic treatment

Methods: We performed a retrospective multicenter study including all CD patients with a non-passable symptomatic UGT stricture on endoscopy. Primary outcome measure was surgery-free survival from diagnosis of stricture. Efficacy of medical, endoscopic, and surgical treatments, and identification of predictors of surgery were also evaluated.
Results: 60 CD patients with an UGT stricture were included. 60% of the strictures were located in the duodenum. With a median follow-up of 5.5 (IQR: 3.0–12.0) years since stricture diagnosis, surgical-free survival was 75% and 64% at 1 and 5 years, respectively. At the end of the follow up, 27 (45%) patients underwent surgery. 77 endoscopic procedures were performed in 30 patients with an immediate success of 81% and a clinical benefit in 84% of the procedures. In multivariate analysis, anti-TNF treatment initiation was associated with a reduced risk of surgery.
Conclusion: CD UGT strictures are mainly located in the duodenum. Medical and endoscopic treatments allow to avoid surgery in half of the patients

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disorder that can affect any part of the gastro-intestinal tract [1]. The evolution of CD is often characterized by a sustained digestive inflammation that leads to the occurrence of strictures, abscess, and fistulae [2]. Stricture is a frequent complication in CD, it affects around 20% of the patients after 20 years of evolution of the disease [3]. The most common locations of stricture are the ileum and the ileocolonic areas [4]. Management of ileocolonic stricture is based upon endoscopic procedures (balloon dilation, stent) [5–7] surgery (stricturoplasty, intestinal resection) [8], and medical treatment, including anti-TNF (tumor necrosis factor) [9].

The upper gastrointestinal tract (UGT) involvement in CD has long been underestimated. A recent multicenter cohort study from Switzerland including 1361 CD patients reported 13% of patients with lesions of the UGT [10]. Overall, strictures of the UGT may occur in up to 70% of CD patients [11]. Few studies evaluated the management of the UGT strictures and they all included a small number of patients [12–15]. Sing et al. retrospectively studied the long-term outcomes of endoscopic balloon dilation (EBD) in 35 patients with UGT stricture reporting 87% of clinical success with a short median time to re-dilation of 2.2 months [12]. A recent meta-analysis performed by Bettenworth et al. including 94 patients reported a rate of technical success for EBD in 100% of cases, with 87% short-term clinical efficacy [13]. Data on the medical management of UGT strictures are scarce in the biologics era.

The aim of the present study was to evaluate the outcome and management of patients with CD complicated by a stricture of the UGT in a multicenter cohort from the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID).

2. Materials and methods

2.1. Study design and population

We performed a retrospective cohort study in 25 French and Belgian centers of the GETAID. The inclusion criteria were (1) patients older than 16 years, (2) with a diagnosis of CD according to the ECCO guidelines [16], (3) with a known UGT CD accessible to upper endoscopy, (4) and a symptomatic stricture of the UGT non-passable by an upper endoscope. Exclusion criteria were other causes of UGT stricture (neoplastic, peptic, infectious or secondary to radiation therapy). The protocol was approved by ethics committee (Comission nationale de l'informatique et des libertés MR003 and MR004).

2.2. Data collection

Patients were included from January 1978 to January 2018. Date of inclusion was the time of diagnosis of the upper GI stricture. Demographic, clinical, and endoscopic data were retrospectively reviewed from the medical records on a standardized form. The following data were recorded for each included patient at baseline: age, gender, smoking status, disease duration, disease location, previous intestinal surgery, location of the stricture (esophagus, stomach, duodenum, proximal jejunum), type of stricture (native or anastomotic), and ongoing medical treatment received at the time of diagnosis of the stricture. During follow up, medical, all endoscopic and surgical treatments of the stricture have been collected until time of first stricture surgery, last news or death. All lines of medical treatment received by one patient were evaluated.

2.3. Primary and secondary outcome measures

The primary outcome was surgery-free survival at 1 and 5 years. The secondary outcomes were (1) clinical efficacy of medical, endoscopic and surgical treatments, defined by an improvement of obstructive symptoms according to physician global assessment, (2) immediate endoscopic efficacy of endoscopic treatment defined by a stricture passable by a standard endoscope after the procedure, and (3) rate of complications of medical, endoscopic and surgical procedures. Duration of effectiveness was also evaluated and was defined as maintenance of the treatment without any change in medical treatment, nor endoscopic procedure or surgery intervention. We also looked at factors associated with surgery.

2.4. Statistical analysis

Descriptive data were presented in frequency (number), median (interquartile range (IQR)) or average. The Kaplan-Meier method was used to assess cumulative surgery-free survival at 1 and 5 years after diagnosis of the non-passable stricture. Univariate and multivariate logistic regression were performed to identify factors associated with surgery expressed as odds ratio (OR) with 95% confidence interval (95%CI). Variables with a $p \leq 0.2$ were included for multivariate analysis, and a p value of 0.05 was considered to be significant.

3. Results

3.1. Patients' characteristics

Sixty consecutive CD patients with one symptomatic non-passable stricture of the UGT identified at upper endoscopy were

Table 1
Demographic and clinical characteristics.

Number of patients	60
Female, n (%)	20 (33%)
Age at diagnosis of CD according to Montreal classification	
A1 (< 17 years)	16 (27%)
A2 (17- 40 years)	40 (67%)
A3 (> 40 years)	4 (6%)
Age at diagnosis of stricture, median (y)	31.0 (IQR: 23.0–40.0)
Median disease duration before diagnosis of stricture (y)	5.5 (IQR: 0.0–12.0)
Smoker status	
Non smoker	34 (57%)
Former smoker	17 (28%)
Active smoker	9 (15%)
History of intestinal surgery (other than UGT) related for CD	20 (33%)
Other location of CD according to Montreal classification	
None	12 (20%)
L1 (ileal)	23 (39%)
L2 (colonic)	5 (8%)
L3 (ileocolonic)	20 (33%)
p (perianal)	13 (22%)
Treatment at diagnosis of the stricture	
None	33 (55%)
Corticosteroids	11(18%)
5-ASA	7 (12%)
Immunosuppressants	6 (10%)
Anti-TNF	9 (15%)
Combotherapy	3 (5%)
Ustekinumab	2 (3%)

Abbreviations: CD: Crohn's disease; 5-ASA: 5-Aminosalicylic acid, UGT: Upper Gastrointestinal Tract, TNF: Tumor Necrosis Factor.

included. Demographic and clinical characteristics are summarized in Table 1. Twenty (33%) patients were women, median age at diagnosis of the stricture was 31.0 years old (IQR: 23.0–40.0) with a median disease duration of 5.5 years (IQR: 0.0–12.0). Nine (15%) patients were active smoker, 34 (57%) patients were non-smoker, and 17 (28%) patients were former smoker. Twenty (33%) patients had a history of intestinal surgery (concerning another digestive segment than upper tract) related to CD. UGT CD location was associated with an ileal location in 23 patients (39%), a colonic location for 5 patients (8%), both ileal and colonic locations for 20 (33%) patients. Twelve (20%) patients had an isolated UGT CD.

Location of the UGT stricture was: the esophagus in 4 (7%) cases, the stomach in 6 (10%) cases, the duodenum in 36 (60%) cases, and the proximal jejunum in 7 (12%) cases; in 6 (10%) cases the stricture concerned the stomach and the duodenum, and the duodenum and the jejunum in one (1%) case (Fig. 1). Fifty-seven (95%) strictures were native and three (5%) were anastomotic.

At diagnosis of the stricture, 33 (55%) patients had no medical treatment for CD, 7 (12%) received 5-ASA (5-aminosalicylic acid), 11 (18%) corticosteroids, 6 (10%) immunosuppressants, 9 (15%) an anti-TNF treatment, three (5%) a combotherapy associating an anti-TNF treatment and an immunosuppressant, and two (3%) ustekinumab.

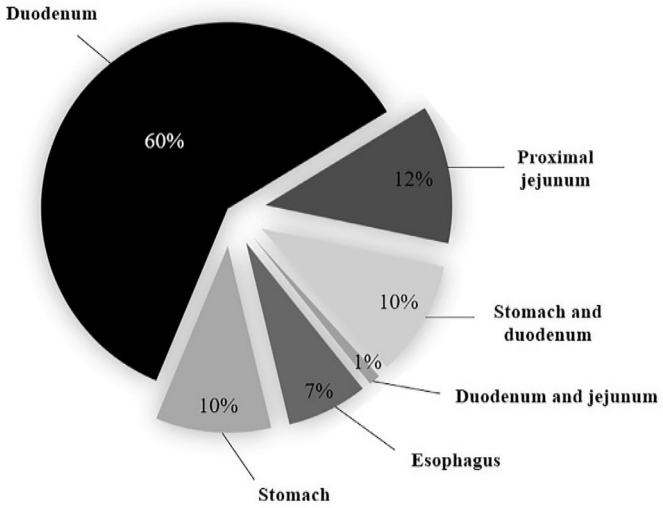

Fig. 1. Location of upper gastrointestinal tract strictures.

3.2. Need for surgery

With a median follow-up duration of 5.5 years (IQR 3.0–12.0), one patient died and 27 (45%) patients underwent surgery: 14 (51%) gastro-entero-anastomosis (GEA), 8 (30%) duodeno-jejunal resections (including isolated duodenal or jejunal resection), two (7%) cephalic duodeno-pancreatectomy, one (4%) duodeno-jejunal anastomosis, one (4%) gastro-entero-anastomosis associated with a small bowel resection, and one (4%) stricturoplasty associated with a small bowel resection (Table 2).

Rates of surgery-free survival were 75% at 1 year and 64% at 5 years (Fig. 2). Clinical efficacy of the surgery was observed in 96% of the cases (Table 2). The remaining patient was a 53-year-old woman with a stricture of the proximal jejunum without other CD location. She underwent duodenal and jejunal resection with duodeno-jejunal anastomosis without improvement of obstructive symptoms and required endoscopic dilation of the anastomosis and concomitant introduction of medical treatment (immunosuppressant). After surgery, symptoms recurrence occurred in 44% of the patients with a median time of 7.0 months (IQR: 1.5 – 72.0).

In two patients, adenocarcinoma was found in the resected intestinal fragment. The first patient was a 41-year-old man who had an anastomotic stricture of the jejunum and underwent jejunal resection 4 years after diagnosis of the stricture and 27 years after the diagnosis of CD; he received only corticosteroid for the treatment of his stricture. The other patient was a 41-year-old woman who had a duodenal stricture, who underwent duodenectomy without pancreatectomy 6 years after diagnosis of

Table 2
Surgical interventions for the stricture, clinical efficacy, and complications.

	No. of patients	Clinical efficacy	Complications
Surgical interventions	27	96%	8/27 (30%)
Gastroenteronastomosis, n (%)	14 (51%)		1 mesenteric hematoma
		100%	1 pulmonary embolism
			1 ulcer
Duodenojejunal resection, n (%)	8 (30%)	87%	2 anastomotic strictures
			1 hemorrhage
			1 death
Cephalic duodenopancreatectomy, n (%)	2 (7%)	100%	1 fistulae of a pancreatico-jejunal anastomosis
Duodenojejunal anastomosis, n (%)	1 (4%)	100%	0
Gastroenteroanastomosis with small bowel resection, n (%)	1 (4%)	100%	0
Stricturoplasty with small bowel resection, n (%)	1 (4%)	100%	0

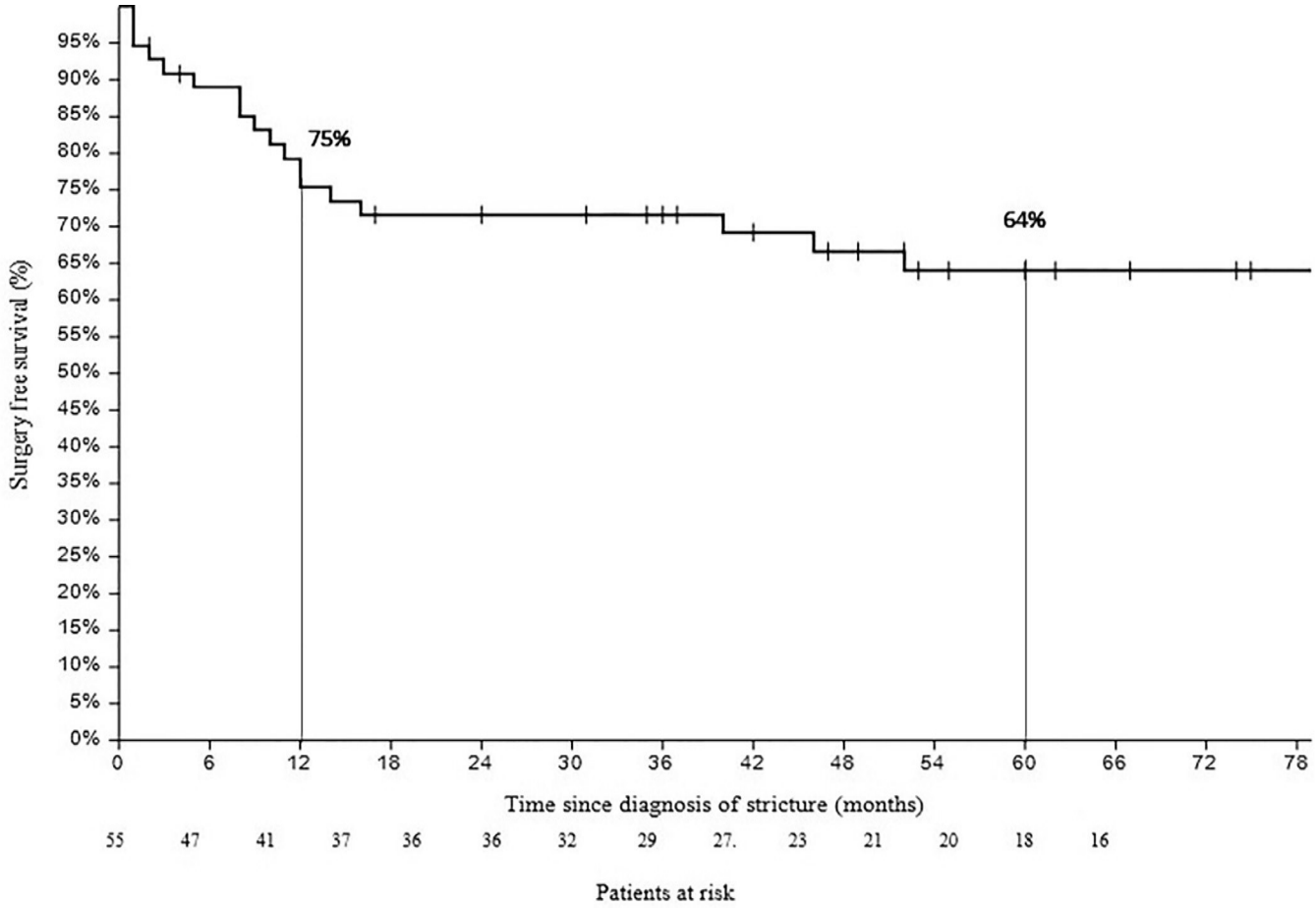

Fig. 2. Kaplan Meier survival curve of surgery free survival after the diagnosis of the stricture.
The surgery free survival free survival at 1 and 5 years were 75% and 64% respectively. The median follow-up after the diagnosis of stricture was 5.5 years (IQR 3.0–12.0).

the stricture and 21 years after the diagnosis of CD; she received 5 years of immunosuppressant (azathioprine) followed by three months of anti-TNF treatment for the stricture.

3.3. Post-operative complications

Eight post-operative complications were reported: two anastomotic strictures after resection of a duodenal and a proximal jejunal strictures, one fistulae of a pancreatico-jejunal anastomosis after a duodeno-pancretactomy which required a subsequent surgery, one hemorrhage after a duodeno-jejunal resection, one mesenteric hematoma after a GEA, one pulmonary embolism after a GEA, one anastomotic ulcer of a GEA, and one death due to pneumonia with septic shock. This was a 41-year-old man patient who underwent stenting of a duodenal stricture. The procedure was complicated with a perforation; two weeks after the patient was operated with a duodenectomy without pancreatectomy; he died two weeks after the surgery because of a pneumonia complicated with a septic shock.

3.4. Factors associated with surgery

Factors associated with surgery in univariate and multivariate analysis are presented in Table 3. In multivariate analysis, factors associated with a decreased risk of surgery were: introduction of an anti-TNF treatment whether alone (OR 0.2 CI95% 0.04 – 0.9; $p = 0.03$), or in association with an immunosuppressant (OR 0.2 CI95% 0.05– 0.9; $p = 0.03$).

Table 3
Univariate and multivariate logistic regression analysis of factors predicting surgery.

Factor predicting surgery	Univariate odds ratio (95%CI)	p value	Multivariate odds ratio (95%CI)	p value
Sex (male)	0.5 (0.2–1.6)	0.3		
Smoker	2.9 (0.6–12.7)	0.2	6.3 (0.8–47.4)	0,08
Type of stricture (anastomotic)	2.6 (0.2–29.9)	0.4		
Age at diagnosis of Crohn's disease	3.1 (1.1–8.9)	0.03	2.2 (0.6– 8.2)	0.2
Age at diagnosis of the stricture	1.7(0.6–4.9)	0.3		
Disease duration at diagnosis of stricture	1.7 (0.6–4.9)	0.3		
Anti-TNF at diagnosis of stricture	0.2 (0.04–1.0)	0.05	0.2 (0.04–1.3)	0.1
Anti-TNF alone introduced for the stricture	**0.4 (0.1–1.2)**	**0.09**	**0.2 (0.04–0.9)**	**0.03**
Immunosuppressants introduced for the stricture	0.6 (0.2–1.8)	0.3		
Anti-TNF + immunosuppressant introduced for the stricture	**0.2 (0.05 – 0.7)**	**0.009**	**0.2 (0.05–0.9)**	**0.03**
Endoscopic treatment before surgery	0.3 (0.1–0.8)	0.02	0.4(0.1–1.6)	0.2

Bold value indicates statistically significant odds ratios in the multivariate analysis.

Table 4
Endoscopic procedures, clinical efficacy, and complications.

	No. of procedures	Clinical efficacy	Complications
Endoscopic procedures	77	84%	4
Balloon dilation, n (%)	57 (74%)	81%	2 duodenal perforations
Stent, n (%)	11 (14%)	90%	1 duodenal perforation 1 duodenal hemorrhage
Dilation with candle, n (%)	3 (4%)	100%	0
Corticosteroid injection alone, n (%)	2 (3%)	50%	0
Gastroenteroanastomosis, n (%)	2 (3%)	100%	0
Dilation with local injection of corcosteroid, n (%)	2 (3%)	100%	0

3.5. Endoscopic treatment

At the end of follow up, 77 endoscopic procedures were performed in 30 patients: 57 EBD 11 stents, three dilations with bougies, two injections of corticosteroids alone, two endoscopic gastro-entero-anastomosis, two dilations associated with local injection of corticosteroids. The immediate success defined by a stricture passable by the endoscope after the procedure was reached in 81% of cases (Table 4). The clinical efficacy was reached in 84% of cases, with a median time of 8.0 months (IQR: 1.0–22.0) until the next endoscopic procedure, surgery or last news. Twenty-four patients underwent 57 EBD with an immediate success of 79% and a clinical efficacy of 81% with a median time of 10.0 months (IQR: 1.0–24.0) until the next endoscopic procedure, surgery or last news. Thirteen patients had one endoscopic procedure, and 17 patients had at least two endoscopic procedures with a mean number of three procedures (IQR: 2.0–3.0) and a median time of 7.0 months (IQR: 1.5–20.0) between two procedures. Four complications were recorded: three duodenal perforations (one after a stenting procedure and two after EBD), and one duodenal hemorrhage after a stenting procedure. Among the three patients with duodenal perforation, one was treated medically, and two underwent surgery. Among all patients with an endoscopic treatment of the stricture, 9 (30%) underwent surgery during follow-up, with a median time between last endoscopy and surgery of 1.0 months (IQR 0.0–5.0).

3.6. Medical treatment

During the follow-up, 51 patients received 70 medical treatments. Immunosuppressants were used in 21 cases (azathioprine in 18 cases and methotrexate in 3 cases) with an improvement in obstructive symptoms, in 50% of the cases during 35 months (IQR: 16.5–53.5). Anti-TNF treatment alone were used in 20 cases with a clinical efficacy in 70% during 6.5 months (IQR: 3.0 – 16.8). Anti-TNF treatment in association with an immunosuppressant were used in 22 cases with a clinical efficacy in 61% during 23 months (IQR: 4.0 – 47.0). Ustekinumab alone was used alone in two cases with a clinical efficacy in 50% of the cases during 4 months. Ustekinumab in association with an immunosuppressant was used in three cases with a clinical efficacy in 67% during 10.5 months (IQR: 10.3 – 10.8) (supplementary Table 1). After failure of an anti-TNF treatment, vedolizumab was used alone in one patient and in association with an immunosuppressant in another patient without clinical efficacy reported. In 7 cases, medical treatment must have been stopped because of adverse events: two cases of allergy with anti-TNF treatment, two cases of intolerance with immunosuppressants, one case of skin infections with anti-TNF treatment, one case of abscess formation after anti-TNF treatment in association with methotrexate and one case of hepatitis following anti-TNF treatment in association with azathioprine.

At the end of the follow-up, 25 patients (42%) received a medical treatment alone without endoscopic procedures. Among them 13 (52%) underwent surgery in a median time of 9.0 months (IQR: 2.0–12.0). Medical treatment was associated with an endoscopic procedure in 26 (43%) patients. Among them 8 (31%) underwent surgery in a median time of 63.0 months (IQR: 12.5–84.3). At the end of follow-up endoscopic and/or medical treatment allowed to avoid surgery in 33 (55%) patients.

4. Discussion

We here report the largest multicenter study of CD patients with a non-passable stricture of the UGT. Strictures concerned the duodenum in 2/3 of cases and occurred with a median disease duration of more than 5 years. At the end of follow-up, medical treatment and/or endoscopic procedures allowed to avoid a surgery in more than half of the patients. Factors associated with a decreased risk of surgery were medical treatment of the stricture consisting in anti-TNF therapy alone or in association with an immunosuppressant.

Few studies have evaluated the management of UGT stricture, with a very heterogenous definition of stricture, based on computerized tomography scanner, magnetic resonance imaging, barium or endoscopy. In 1999, Yamamoto et al. reported 41 patients with gastroduodenal stricture related to CD, but only 10% of them had a frank stricture, non-passable by upper endoscopy [11]. In our study, we have decided to include only patient with an endoscopic evaluation and a non-passable stricture during endoscopy, to get

a more objective and reproducible definition of UGT stricture. At the end, we included 60 patients with a non-passable stricture of the UGT, that represents the largest study evaluating the efficacy of medical treatment of UGT stricture. We reported good clinical results with an improvement of obstructive symptoms in half of the cases with immunosuppressant and up to 70% of the cases with anti TNF treatment alone. Near half of the patients received only medical treatment without any endoscopic procedure and half of them underwent surgery in a median time of 9.0 months. These results underline that half of patients with non-passable UGT stricture might receive medical treatment only with satisfactory results. In multivariate analysis, introducing an anti-TNF treatment alone or in association with an immunosuppressant for the UGT stricture were both associated with a significant lower risk of surgery, highlighting the necessity of introducing powerful treatment at time of UGT stricture diagnosis. This is consistent with the few data available on medical management of CD strictures in other locations; recently Bouhnik et al. showed that adalimumab was an efficient treatment of symptomatic small bowel strictures in 2/3 of the patients 6 months after introducing adalimumab [9]. Moreover, in our study, medical treatment must have been stopped because of adverse events in only 10% of the cases. These data should encourage to propose anti-TNF treatment alone or in association with an immunosuppressant in CD patients with UGT stricture.

Half of the patients had an endoscopic procedure; EBD was the most frequent procedure representing 74% of the interventions. Even if EBD is mostly described for stricture of the ileum and the colon, recent data concerning this procedure for UGT stricture have been published. Bettenworth et al. have published a meta-analysis including 141 EBD in 94 patients with UGT stricture [13]. Short term clinical efficacy was reached in 87% which is similar to our results (84%). We reported a higher complication rate of endoscopic interventions (5% per procedure vs 3%) probably because we included other endoscopic procedures than EBD, with two over the four complications occurring after stenting. In multivariate analysis, endoscopic treatment was not significantly associated with a lower risk of surgery, that could be explained by the low number of patients (30) who had an endoscopic procedure. In our cohort, 27 (55%) patients underwent surgery at the end of the follow up. In the literature, the surgery rate of patient with an UGT stricture was less important (30%) but these studies only included patient with prior endoscopic treatment and the follow-up was shorter [12,13,17]. Surgery was effective with an improvement of obstructive symptoms in 96% of the cases. The most frequent surgical procedure was GEA in half of the patient operated. Complications occurred in 30% of the procedures with one patient who died after a pneumoniae with septic choc, which is comparable to complication rate found in the study of Shapiro et al. (27%) [14]. Of note, in two patients who underwent surgery, adenocarcinoma was found in the resected piece 4 and 6 years after the diagnosis of the stricture. These results suggest that surgery should be highly considered especially for patients with a long-standing stricture in order to prevent the risk of neoplasia, even though results of biopsies performed during upper endoscopy were negative. Fumery et al. reported that IBD patients who underwent surgery for colonic strictures without prior dysplasia under biopsies results, 3.5% were found to have dysplasia or cancer [18].

Our study had some limitations, mainly due to its retrospective nature. Also, we included consecutive data from 25 centers, during a long study period (1978 to 2018) with heterogeneity in the management of these patients presenting a frank UGT stricture. However, this is the largest study ($n=60$) that evaluated the long-term outcome and management of stricture of the UGT in CD patients. Furthermore, we used a stringent definition of stricture as inclusion criterion, which was characterized by a stricture non passable by an endoscope, limiting the risk of heterogeneity related to physicians' judgement. Finally, median duration of follow-up was 5.5 years (IQR 3.0–12.0). As we collected data from 1978 to 2018, radiological examinations of stricture were rarely available. Endoscopy is considered as the gold standard examination to diagnose UGT stricture and provided a reproducible inclusion criterion in our multicenter study. Even though radiological length of stricture could explain failure of endoscopic treatment, immediate success of endoscopic procedure (defined by a stricture passable by the endoscope after the procedure) was reached in 81% of cases in our study, showing that length of stricture was short in the majority of the situations [19]. As the design of our study was retrospective, we were not able to collect Harvey-Brashaw Index (HBI) or C-reactive protein (CRP) for all patients. HBI or CRP might be not suitable to evaluate symptoms linked to UGT stricture. Of note, 80% of our patients had another disease location than UGT that could interfere with the evaluation of treatment efficacy. We used physician global assessment because it was probably more suitable to evaluate symptoms related to UGT stricture. We also assessed endoscopic immediate success defined by a stricture passable by the endoscope after the procedure, which is an objective criterion and was available in 90% of endoscopic procedures.

In conclusion, two-third of the non-passable strictures of the UGT complicating CD were located in the duodenum. A surgical treatment is often necessary but medical and endoscopic treatments allowed to avoid surgery in half of the patients with severe UGT strictures. Failure to a medical strategy should lead to consider surgery, as far as dysplasia and cancer may occur in longstanding UGT strictures. Predictors of surgery may help identifying patients needing early surgical management.

Ethics approval

The protocol was approved by ethics committee (Commission nationale de l'informatique et des libertés MR003 and MR004).

Author contributions

- T.L. and B.P.: study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, or material support, study supervision, and approval of the final version
- L.P.B: study supervision
- All authors: acquisition of data, critical revision of the manuscript for important intellectual content,and approval of the final version

Declaration of Competing Interest

T. Lambin: Travel accommodation: Adacyte therapeutics. A. Amiot: Consulting fees from Abbvie, Hospira, Janssen, Tillotts, Pfizer, Takeda, Gilead and Biocodex. Lecture fees and travel accommodation from Abbvie, Janssen, Biocodex, Hospira, Ferring, Pfizer, Ferring, Tillotts, Takeda and MSD. Advisory board fees from Gilead, Takeda and Abbvie. C. Stefanescu: Consulting: Takeda. Lecture fees: Abbvie, Fresenius Kabi, Pfizer, Janssen. Travel acomodation: MSD, Takeda, Abbvie, Pfizer, Janssen. P. Seksik: Consulting fees : Takeda, Abbvie, Merck-MSD, Biocodex, Janssen, Amgen, Astellas, Pfizer Grants : Biocodex. Sponsored travel : Merck-MSD and Takeda, Amgen. D. Laharie: Counseling, boards, transports or personal fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots. A. Bourreille: Personal fees from AbbVie, Janssen, Ferring, Tillots, Celltrion, Takeda, Pfizer, MSD, Roche, Fresenius Kabi OSE Immunotherapeutics, Medtonic. Grants: Abbvie, MSD, Takeda, MaunaKea Technology, Medtronic. G.Cadiot: Consulting fees: Ipsen,

Novartis, AAA, Pfizer, Keocyt. Lecture fees: Takeda. N. Dib: Abbvie, Janssen, Pfizer, Takeda. M. Fumery: Consulting fees : AbbVie, Takeda, Janssen, Pfizer, Celgene, Gilead. Lecture Fees : Boehringer and Biogen Abbvie, MSD, Takeda, Janssen, Ferring, Tillots. C. Gilletta de St Joseph: Lecture fees: Abbvie, Takeda, Janssen, Pfizer. Consulting fees: Abbvie, Takeda, Janssen, Celltrion. J. Filippi: Abbvie, Amgen, Biogen, Celltrion, Ferring, HAC Pharma, Hospira, Janssen, MSD, Pfizer, Takeda, Vifor. S. Viennot: Abbvie, Amgen, Celltrion, Ferring, Janssen, MSD, Pfizer, Takeda. L. Plastaras: Personnal fees or boards from AbbVie, Janssen, Tillots, Takeda, Pfizer, MSD. M. Serrero: Abbvie, Amgen, Biogen, Celltrion, Gilead, Janssen, Ferring, MSD, Pfizer, Takeda, Tillots. S. Nahon: Lecturer or advisory board fees from AbbVie, MSD, Vifor Pharma, Pfizer, Janssen and Ferring. G. Pineton de Chambrun: Lecture fees from Pfizer, MSD, AbbVie, Takeda and Ferring. Consulting fees from Takeda, Tillots Pharma and Janssen. JF. Rahier: Lecture fees from AbbVie, MSD, Takeda, Pfizer, Ferring, and Falk, consulting fees from AbbVie, Takeda, Hospira, Mundipharma, MSD, Pfizer, GlaxoSK, Janssen and Amgen, and research support from Takeda and AbbVie. X. Roblin: Consultant fees from MSD,Pfizer, Abbvie, Amgen, Biogen, Takeda, janssen, crlltrion, Ferring. M. Boualit: Travel accommodation : abbvie, Janssen, Pfizer, Takeda. G. Bouguen: Lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer and consultant fees from Takeda, Janssen. L. Peyrin-Biroulet: Personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine ; Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance. Grants: Abbvie, MSD, Takeda. B. Pariente: Consulting fees: AbbVie, MSD, Takeda, Janssen, Lilly, Pfizer, and Biogaran. Lecture fees: Abbvie, MSD, Takeda, Janssen, and Ferring, and other authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.08.034.

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