Crohn's disease and postoperative recurrence.
The role of anastomotic configurations and the kono-s anastomosis.

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Rosario Fornaro*, Giuseppe Caristo***, Emanuela Stratta*, Alba Oliva*, Davide Giovinazzo**, Matteo Mascherini*, Marco Frascio*

**Department of Surgery, San Martino Policlinic Hospital, Genoa, University of Genoa, Genova, Italy*
***Department of Surgery, Hôpital Louis Mourier, Paris, France*
****San Paolo Hospital, Savona, Italy*

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BACKGROUND: *The observation that in more than 90% of Crohn's disease patients the postoperative recurrences are located in the pre-anastomotic tract leads us to suppose that the anastomosis would play a role in the appearance of recurrences.*
AIM AND METHODS: *To focus the role of different anastomotic configurations in the incidence of recurrences, the Authors have conducted a review of the literature of the last two decades and have revised critically their experience.*
RESULTS: *The rate of recurrences seem to be lower in patients in whom the anastomotic configuration is such as to present a wide lumen; it seems that they are lower after stapled side-to-side anastomosis. The Kono-S anastomosis, recently introduced technique, seems to offer better results.*
CONCLUSIONS: *The role of the various types of anastomosis remains uncertain. Further large-scale controlled trials with long term follow-up are needed.*

KEY WORDS: Anastomosis, Crohn's disease, Postoperative Recurrences

Introduction

More than two thirds of patients affected by Crohn's disease (CD) will undergo one or more surgeries, with a re-operative risk estimated at around 1-2% per year. Intestinal resection and stricturoplasty are both valid surgical options, but, besides being not curative, they are burdened by a high incidence of postoperative recurrences, that in many cases require a re-intervention. Since more than 90% of recurrences occurs in the pre-anastomotic tract, a growing interest has been directed, not only to the resection, but also to the anastomotic configuration.

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Correspondence to: Rosario Fornaro,Department of Surgery, University of Genoa, San Martino Hospital, Largo Rosanna Benzi n 10, 16132 Genoa, Italy (e-mail: rfornaro@unige.it)

Aims and Methods

The aim of the study was to evaluate the role of the anastomotic configuration in order to prevent recurrences, or at least to reduce their impact. The Authors conducted a review of the literature of the last 20 years and a critical analysis of their experience. For bibliographic research were used Medline, Embase, Ovid Journals, Science Direct, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. The studies were selected using the following keywords: "Crohn's disease and surgical treatment", "Crohn's disease and postoperative recurrences". Manuscripts in English/French/German/Italian were included. Items mentioned in the references of the selected articles were also included as considered relevant. Were analyzed the different anastomotic configurations (end-to-end anastomosis, side-to-side anastomosis, end-to side anastomosis, handsewn end-to-end anastomosis, stapled side-to-side anastomosis); moreover, more recent-

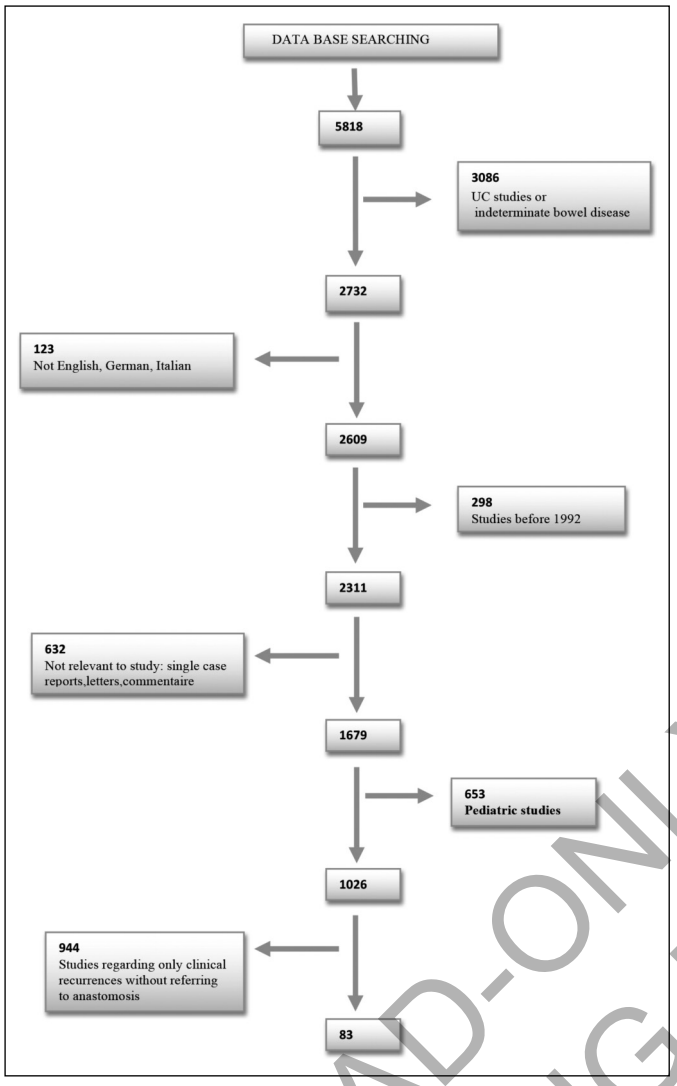

Fig. 1: Diagram for search strategy.

ly introduced techniques (the nipple valve anastomosis and the Kono-S anastomosis) were also analyzed (Fig. 1).

Results and Discussion

Postoperative recurrences usually appear in the neoileum, at the level of anastomosis, in the mesenteric side of the intestine, site were recurrence originate. The high incidence of recurrences mandates a strict follow up (clinical, laboratory and instrumental monitoring), because, identifying patients with an increased risk, would enable physicians to plan a surveillance program and to implement a rational therapeutic prophylaxis. In numerous studies it has been suggested that prophylactic medication decreases the rate of clinical and endoscopic recurrences following intestinal resection. Also randomized controlled trials have demonstrated that a prophylactic postoperative strategy is effective in reducing recurrences in high-risk patients [1-19]. New prospective studies are needed to establish, on the one hand, which patients must be considered at risk of postoperative recurrences and therefore be subjected to prophylaxis, and, on the other hand, to establish the timing and type of therapy most indicated and the efficacy of newer biologic agents. In patients suffering from CD and undergoing surgery the factors that can influence outcomes and could influence a lower or a greater rate of recurrences are numerous. The suspicion of the presence of dysplasia or cancer requires a radical intervention that does not take this aspect into consideration [20,21]. Risk factors foer recurrences, in addition to cigarette smoking, are represented by a disease extension of more than 100 cm and the absence of post-operative pharmacological treatment; moreover, localitation of disease in the colon, penetrative behavior of disease, perianal manifestations, small

Table I - *Crohn's disease. potential risk factors for post-operative recurrences.* (*)

Factors related to the patients	Factors related to the disease	Factors related to the surgery	Factors related to the postoperative treatment
- Age (onset of the disease at a young age)	- Duration	- Anastomotic configuration (**)	- 5-Asa
- Sex (male gender)	- Localitation (colon/ileum)	- Involvement of the margins of section	- Immunosup presants
- Familiarity	- Perianal manifestations	- Presence of granuloma in the specimen	- Steroids
- Smoking (cigarettes)	- Extension (> 100 cm)	- Mioenteric plexitis at resection margin	- Antibiotics
	- Type (penetrative behavior of disease)	- Mesenteric and visceral fat inclusion	- Probiotics
	- Length of resected segment,	- Resection or stricturoplasty,	- AntiTNF
	- Small bowel resection	- Traditional or laparoscopic surgery	- New biologics
	- Prior intestinal surgery	- Postoperative complications	- New drugs
	- Postoperative corticosteroid need	- Blood transfusions	

*To date, factors affecting the incidence of postoperative recurrences have not been fully determined. Further studies are needed to better define any additional risk factors, in particular there is a need for studies that take into account the histological features.
**We agree with those who think that a stapled side-to-side anastomosis (ie functional end-to-end anastomosis), would be the technique to be preferred, especially after ileocolic resection. However still today the real effectiveness of the anastomotic configuration in reducing the rate of recurrences remains unclear. Controlled randomized prospective trials with long-term follow-up are needed.

bowel resection and prior intestinal surgery, postoperative corticosteroid need, onset of the disease at a young age, male gender should also be considered predictive factors [10,22-48]. In a recent trial we analyzed the role of potential risk factors for postoperative recurrences related to surgery: length of resected segment, involvement of the margins of section, presence of granuloma in the specimen, mioenteric plexitis at resection margin, mesenteric and visceral fat inclusion, type of anastomosis, resection or stricturoplasty, traditional or laparoscopic surgery, postoperative complications, blood transfusions[33] (Table I). To date, factors affecting the incidence of postoperative recurrences have not been fully determined. Further studies are needed to better define any additional risk factors, in particular there is a need for studies that take into account the histological features [49,50]. Many observatons support the hypothesis that anastomosis could play a role in the pathogenesis of recurrences. In numerous trials the various anastomotic techniques were compared: handsewn or stapled anastomosis, end-to-end anastomosis, side-to-side anastomosis, end-to-side anastomosis, handsewn end-to-end anastomosis, stapled side-to-side anastomosis (ie stapled functional end-to-end anastomosis) (Figs. 2-5) [1,45,51-69] (Table II). He et al. (2014), in a recent metaanalysis comparing stapled side-to-side anastomosis with handsewn end-to-end anastomosis after ileocolic resection, achieve good results, showing an overall reduction of postoperative complications (OR 0.54, 95% CI 0.32-0.93, P = 0.03), of anastomotic dehiscences (OR 0.45 , 95% CI 0.20-1.00, P = 0.05), of recurrences (OR 0.20, 95% CI 0.07-0.55, P = 0.002) and of reoperations for recurrence (OR 0.18, 95% CI 0.07-0.45, P = 0.0002) in the stapled side-to-side anastomosis group. The Authors report that this anastomosis is superior in therms of overall postoperative complications, anastomotic leak, recurrence and reoperation for recurrence; hospital stay, mortality and complications other than anastomotic leak were comparable; the Authors conclude that stapled side-to-side anastomosis appear to be the preferred procedure after ileocolic resection (64). Anuj et al (2017), in a retrospective study, including 233 patients with entero-enteric or entero-colic anastomoses, evaluated the role of various anastomoses in surgical recurrence. The type of anastomosis performed was side-to-side in 199 patients (85%), side-to-end in 11 (5%), and end-to-end and in 23 patients (10%). No differences in terms of reoperation-free survival were noted among the 3 groups. The Authors conclude that the roles of the anastomotic configuration, the material used, and the operating surgeon were not significantly correlated with reoperations or complications rate, irrespective of the higher risk of anastomosis site stricture for end-to-end anastomoses [67]. Aaltonen et al (2018), in a recent analysis of risk factors for recurrence after ileocaecal resection, found that hand-sewn anastomosis with an opening of the bowel's antimesenteric border seems to be a safe choice for ileocaecal resection [45]. Recently Feng et al (2018), in a systematic review and network meta-analysis (1113 patients in 11 trials) compared different type of anastomosis. Stapled side-to-side anastomosis was shown to be superior to hand-sewn end-to-end anastomosis for postoperative complications, for clinical recurrence and for surgical recurrence. There were no significant difference for postoperative hospital stay, complications other than anastomotic leak, wound infection and mortality. The

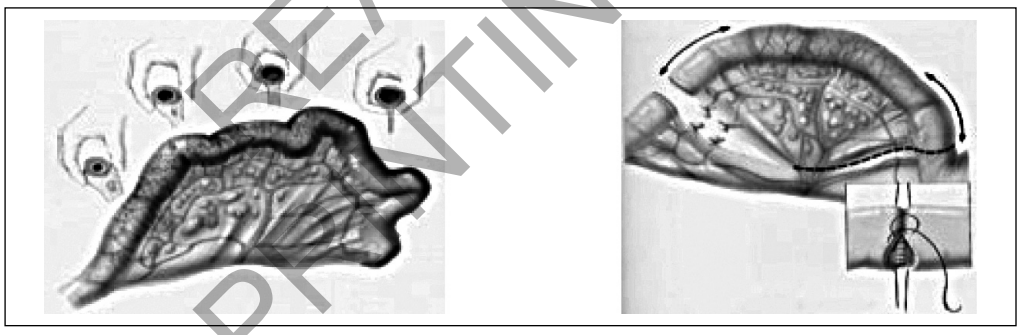

Fig. 2: The length of the intestinal resection does not affect the rates of endoscopic and surgical postoperative recurrences. The presence of the disease at the resection margins does not increase their frequency. A radical resections must be avoided, and a 2 centimeter margin of macroscopically normal intestine appears to be adequate.

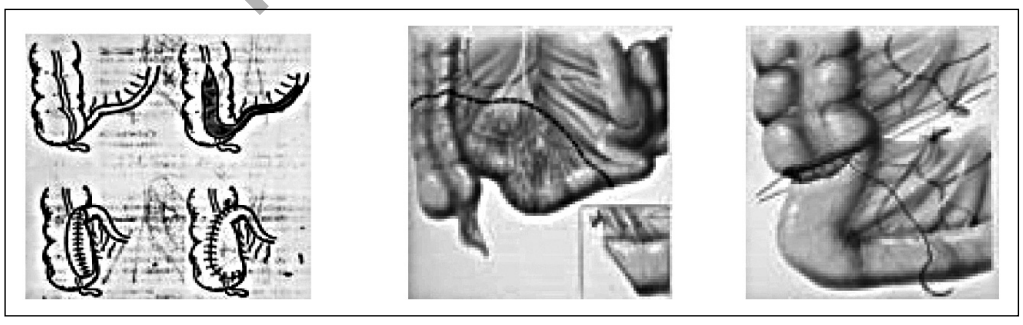

Fig. 3: Side-to-side enterocolic anastomosis is a valid alternative to ileo-cecal resection.

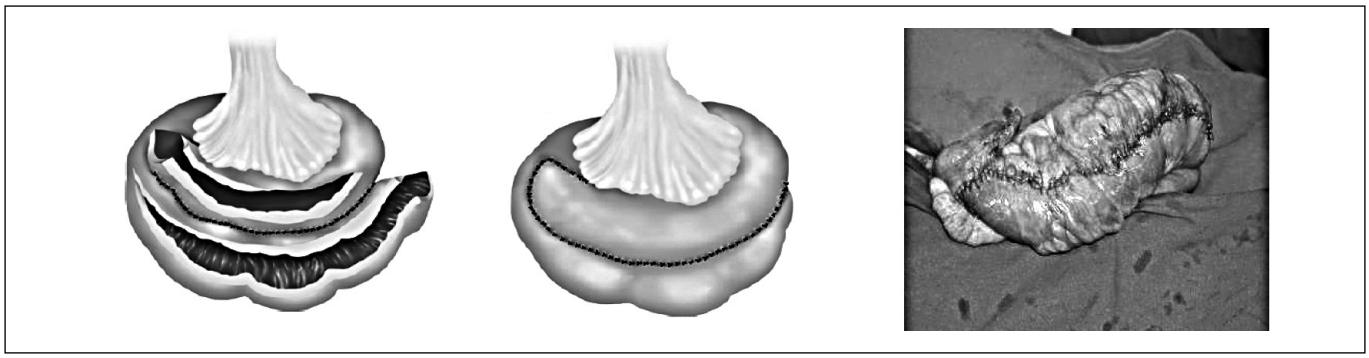

Fig. 4: In patients with strictures longer than 20 cm or with multiple close strictures the side-to-side entero-enteric anastomosis (Michelassi) is an alternative to resection.

Fig. 5: Side-to-side anastomosis. The anastomotic configuration seem to affect the surgical outcome and probably the rate of postoperative recurrences. The recurrences rate would be lower after a wide lumen anastomosis, which results in less fecal stasis and less bacterial overgrowth, factors that would be implicated in pathogenesis of the recurrences. Stapled side-to-side anastomosis (ie functional end-to-end anastomosis), would be the technique to be preferred. Laparoscopy should be preferred when possible.

Authors conclude that stapled side-to-side anastomosis appeared to be the optimal anastomotic strategy after intestinal resection for patients with CD [68].

With the aim to reduce the incidence of the recurrences, new anastomotic techniques have been introduced: the nipple valve anastomosis [70] and the Kono-S anastomosis [61].

In the nipple valve anastomosis, the teminal ileus is invaginated as a telescope in the colon; reduction of faecal reflux in the small intestine should result in a lower rate of recurrences in the neoterminal ileum after ileocecal or ileocolic resection. A series of 59 patients undergoing this intervention showed a rate of clinical recurrences of 24% and of surgical recurrences of 16% at 5 years; this seems to be better when compared to the published series for standard anastomosis [70].The technique of performing the nipple valve anastomosis is well described by Bakkevold et al. (2009).

The Kono-S anastomosis is a new anastomotic configuration introduced by Kono in 2011 [61] The Kono-S anastomosis, has been used for CD patients in Japan and in USA since 2003 and 2010, respectively. This technique was designed to reduce the risk for anastomotic surgical recurrence. The technique of performing the intervention is well described by Fichera, Zoccali and Kono (2012) [71] (Fig. 6). The operation includes three phases: mesentery and bowel division, creation of the supporting column and performing of the anastomosis. The segment of bowel to be resected is identified and mobilized.The section of the mesentery must be close to the bowel wall to preserve vascularitation and innervation. The bowel is divided transversely with a linear stapler–cutter device, perpendicular to the intestinal lumen and to the mesentery. The two stapled lines, reinforced with a Lambert suture, are approximated with a interrupted sutures (4/0 silk). Thus a sort of column is created, that works as a support to maintain the diameter and the size of the anastomosis. Two longitudinal enterotomies are made at the antimesenteric side of the two intestinal tracts, which are then transversally sutured in a single or double layer. The enterotomy start no more than 1 cm away from the staple line, and is of length equal to 7 cm in the small bowel and 8 cm in the colon, in cases of ileocolic anastomosis. This leads to the creation of a lumen of 7-8 cm. This technique, as result, is a stapled and hand-swen antimesenteric side-to-side anastomosis (ie antimesebteric functional end-to-end anastomosis) [61,71,72]. The theoretical basis of this technique is that the support column withstands the anastomotic distortions, caused by disease when the anastomotic tract

Table II - *Anastomotic configuration and recurrence rates.*

Authors	Anastomosis	Recurrence rates
Cameron (1992)	end-to-side anastomosis vs end-to-end anastomosis	no significant difference.
Yamamoto (1999)	stapled side-to-side anastomosis vs others anastomotic configurations	lower after stapled side-to-side anastomosis.
Ikeuchi (2000)	stapled and handsewn anastomosis vs manual double-layer anastomosis	lower after stapled side-to-side anastomosis.
Muñoz-Juárez (2001)	wide lumen stapled anastomosis vs conventional end-to-end anastomosis	lower after stapled side-to-side anastomosis.
Similis (2007)	handsewn end-to-end anastomosis vs other anastomotic configurations	no difference in recurrence rates; higher rates of anastomotic leakage with handsewn end-to-end anastomosis.
McLeod (2009)	stapled side-to-side anastomosis vs handsewn end-to-end anastomosis	no difference in clinical recurrences and endoscopic recurrences.
Riss (2010)	wide-lumen mechanical anastomosis after ileocolic resection	lower short-term complication rate with stapled anastomosis.
Kono (2011)	Kono-S anastomosis	lower endoscopic and surgical recurrence rates.
Van Loo (2012)	end-to-side and side-to-side anastomosis vs end-to-end anastomosis	no difference in clinical recurrences.
Guo (2013)	side-to-side anastomosis and other anastomotic configurations	lower incidence of postoperative complications and of recurrences with side-to-side anastomosis.
He (2014)	stapled side-to-side anastomosis vs handsewn end-to-end anastomosis	lower postoperative complications, recurrences and reoperations for recurrence after stapled side-to-side anastomosis.
Kono (2016)	Kono-S anastomosis	lower risk for surgical recurrence.
Anuj (2017)	entero-enteric or entero-colic anastomoses, side-to-side, side-to-end, end-to-end	no differences in terms of reoperation-free survival.
Aaltonen (2018)	hand-sewn anastomosis with opening of the bowel's antimesenteric border	safe alternative choice for ileocaecal resection.
Feng (2018)	stapled side-to-side anastomosis vs handsewn end-to-end anastomosis	lower rate of postoperative complications, of clinical recurrence, and of surgical recurrence after stapled side-to-side anastomosis; no difference for postoperative hospital stay, complications other than anastomotic leak, wound infection and mortality.
Seyfried (2018)	Kono-S anastomosis	no early anastomotic recurrence; few early and late postoperative complication.
Shimada (2018)	Kono-S anastomosis vs end-to-end anastomosis	low risk of anastomotic surgical recurrence after > 1 year.
Conclusion	The association between anastomotic configurations and surgical outcomes are controversial. Further trials with a larger number of patients and a longer period of follow-up are needed. Also, in the biological era, the role of infliximab and other new biological drugs should be considered.	
Our opinion	A stapled side-to-side anastomosis would be the technique to be preferred. A wide lumen anastomosis reduce the faecal stasis and the bacterial overgrouth and would be more effective in achieving the goal.	

becomes site of recurrence with restenosis. In addition, the anti-mesenteric anastomosis technique excludes the mesenteric side of the lumen, were the recurrences originate. In the past was considered important only the size of the anastomotic lumen, not the original site of the recurrence. Kono et al. (2011), in their first study, compared Kono-S anastomosis (69 patients) with standard anastomoses (73 patients), and reported a significant decrease in endoscopic recurrence rates at 5-year follow-up in Kono-S anastomosis group, with a reduced risk for surgical recurrence (0 vs 15%, p = 0.0013). The Authors conclude that the Kono-S anastomosis is a safe anastomotic technique and that long-term studies are needed to confirm its efficacy in preventing surgical recurrence [61]. The same promising results have been reported recently in others study [66,69,73-74]. Kono et al (2016), in a large international multicentric study (five hospitals, 4 in Japan and 1in the USA), including 187

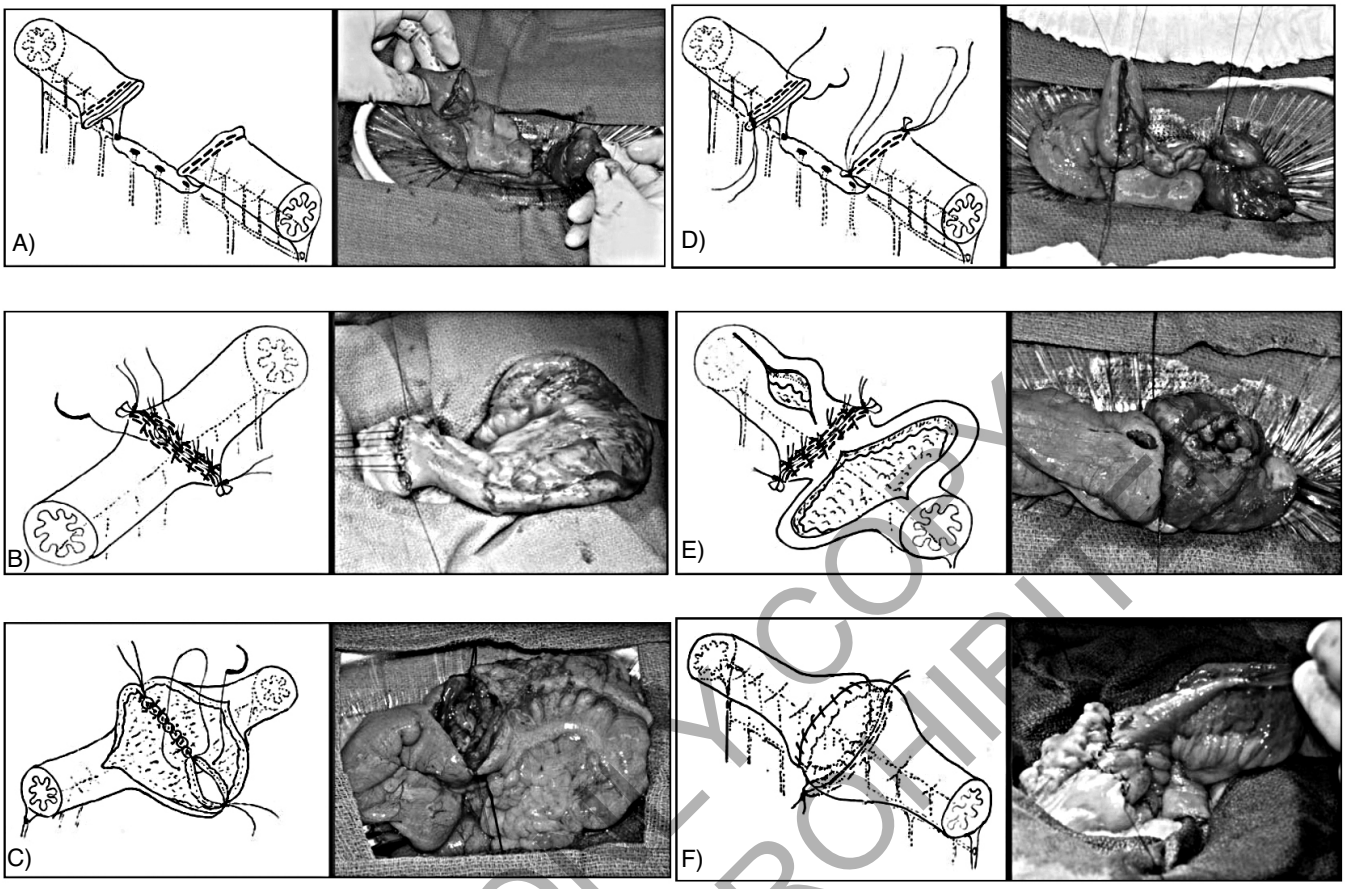

Fig. 6 - Kono-S Anastomosis (antimesenteric functional end-to-end handsewn). **A**) The intestinal segments are divided with the staple lines perpendicular to the axis of the mesentery. The mesentery is divided very close to the intestinal wall to preserve innervation and vascularization. **B**) The corners of the staple lines are imbricated and reinforced with silk sutures and then tied to each either to construct the supporting column. **C**) The supporting column is constructed by suturing the two staple lines together. **D**) A longitudinal enterotomy and colotomy are performed. They start no more than 1 cm away from the supporting column, extending proximally and distally to allow a transverse lumen of 7 cm on the small intestine and close to 8 cm on the large intestine. **E**) The longitudinal enterotomy and colotomy are closed transversely with an outer layers of 4/0 silk Lembert interrupted sutures, and an inner layer of running 3/0 absorbable suture starting on the posterior wall. **F**) The complete anastomosis is shown. (from Alessandro Fichera & Marco Zoccali & Toru Kono. J Gastrointest Surg 2012, 16:1412–16).
Potential advantage : The Kono-S technique allows preservation of blood supply and of innervation and prevents better the fecal stasis and bacterial overgrowth; furthermore, excludes the mesenteric side of the lumen, site were recurrences originate; moreover this anastomotic configuration creates a support column that withstands the anastomotic distortions caused by recurrences. Long-term data must clarify whether this technique is advantageous.

patients (144 patients in Japan, group J and 43 patients in USA, group US), reviews the outcomes a decade after the introduction of the Kono-S anastomosis. In group J occurred two surgical anastomotic recurrences at a median follow-up of 65 months and surgical recurrence-free survival rate was 98.6%. In group US no surgical anastomotic recurrences have been detected at a median follow-up of 32 months. The Authors conclude that the Kono-S anastomosis appears to be safe and effective in reducing the risk of surgical recurrence in CD patients [66]. Luglio et al (2016), in a RCT, report promising results, as presented at the ECCO congress in Amsterdam [73]. Seyfried et al (2018), in a study including 53 patients who underwent Kono-S anastomoses after intestinal resection, evaluate the early and late postoperative complications and recurrence rate. The median follow-up was 12 months (range 4-23 months). Of the patients, 3 developed early postoperative complications and in 25 patients, controlled by endoscopy and/or magnetic resonance imaging, no anastomotic recurrence was detected. The Kono-S anastomosis is a safe anastomotic method with low morbidity. A potential advantage of the morphological end-to-end configuration of the Kono-S anastomosis is the better endoscopic dilatation compared to a side-to-side anastomosis. Long-term data must clarify whether this technique is advantageous [69].
Recently Shimada N et al (2018) report the results of Kono-S and end-to-end anastomosis after bowel resec-

tion in 215 CD patients divided into two groups: Kono-S anastomosis (n= 117) and end-to-end anastomosis (n=98). The median follow-up was 54 months.
Anastomotic surgical recurrence occurs in 28 patients: 4 (3.4%) in the Kono-S group and 24 (24.4%) in the end-to-end group. The leaks were 6 (5.1%) in the Kono-S group and 17 (17.3%) in the end-to-end group; all were successfully treated conservatively. Patients with age <45 years, body mass index of ≥18 kg/m^2 at the first surgery, and with end-to-end anastomosis and leakage had a higher risk of anastomotic surgical recurrence. The risk of anastomotic surgical recurrence after 1 year in the Kono-S anastomosis was significantly reduced (odds ratio, 0.14). Anastomotic leakage influenced anastomotic surgical recurrence within 1 year (odds ratio, 4.84). The 5-year surgery-free survival rate with Kono-S anastomosis (95.0%) was significantly higher than that with end-to-end anastomosis (81.3%; P<0.001). The Authors conclude that anastomotic leakage increased surgical recurrence within 1 year, and that the Kono-S anastomosis has a low risk of anastomotic surgical recurrence after > 1 year [75].
To date there is not consensus about the superiority of a specific tipe of anastomosis and the association between anastomotic types and surgical outcomes are controversial. Further trials with a larger number of patients and a longer period of follow-up are needed. Also, in the biological era, the role of infliximab and other new biological drugs in reducing the rate of recurrences should be considered [2,7,14,76-78].

Conclusions

The anastomotic configuration seem to affect the surgical outcome and probably the rate of postoperative recurrences. The recurrences rate would be lower after a wide lumen anastomosis, which results in less fecal stasis and less bacterial overgrowth, factors that would be implicated in pathogenesis of the recurrences. We agree with those who think that a stapled side-to-side anastomosis (ie functional end-to-end anastomosis), would be the technique to be preferred, especially after ileocolic resection [64,68,79-82]. A wide lumen anastomosis offer potential benefits and would be more effective in achieving these goals. Recently a new tecnique was introducted, the Kono-S anastomosis, whose packaging leads to the formation of a wide side-to-side antimesenteric anastomosis (ie functional end-to-end anastomosis). The Kono-S technique allows preservation of blood supply and of innervation and prevents better the fecal stasis and bacterial overgrowth; furthermore, excludes the mesenteric side of the lumen, site were recurrences originate; moreover this anastomotic configuration creates a support column that withstands the anastomotic distortions caused by recurrences. Howewer still today the real effectiveness of the anastomotic configuration in reducing the rate of recurrences, remains unclear. Controlled randomized prospective trials with long-term follow-up are needed.

Riassunto

L'osservazione che in oltre il 90% dei pazienti affetti da malattia di Crohn le recidive postoperatorie si trovano nel tratto pre-anastomotico ci porta a supporre che il tipo di anastomosi svolga un ruolo nella comparsa delle recidive.
Per analizzare il ruolo delle diverse configurazioni anastomotiche nell'incidenza delle recidive, gli Autori hanno condotto una revisione della letteratura degli ultimi due decenni e hanno fatto una revisione critica della loro personale esperienza.
Da questa analisi sembra risultare che il tasso di recidive sia inferiore nei pazienti nei quali la configurazione anastomotica è tale da presentare un ampio lume e quando si tratta di anastomosi laterolaterali fatte con suturatrice meccanica. L'anastomosi Kono-S, illustrata nell'iconografia è una tecnica introdotta di recente, e sembra offrire risultati migliori.
In conclusione il ruolo dei vari tipi di anastomosi rimane incerto, e sono necessari ulteriori studi controllati su larga scala con follow-up a lungo termine ponendo attenzione in particolare ad tipo di anastomosi adottato.

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