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Review Article

Review Article

Non-conventional Versus Conventional Strictureplasties for Crohn's Disease. A Systematic Review and Meta-analysis of Treatment Outcomes

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Abstract

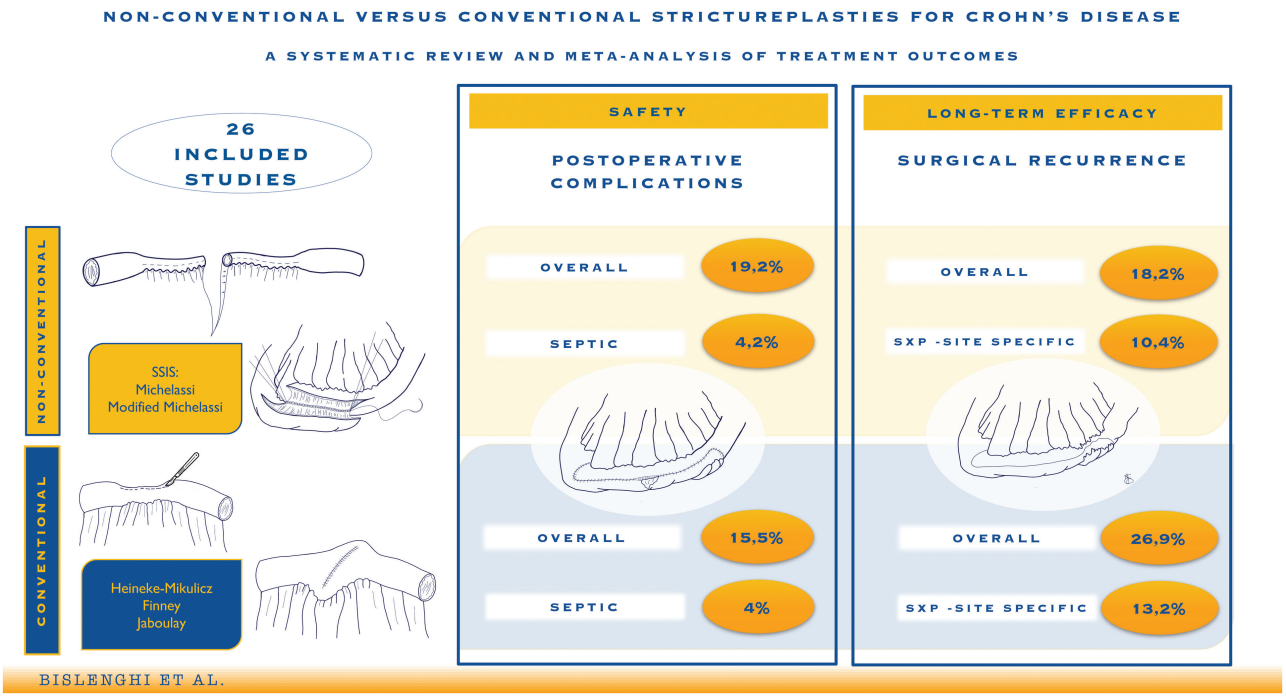
Background: Strictureplasties [SXP] represent an alternative to bowel resection in Crohn's disease [CD]. Over the years, there has been growing interest in the role of non-conventional SXP for the treatment of extensive CD. A systematic review was performed on complications and recurrence following conventional and non-conventional SXP.

Methods: The available literature was screened according to the PRISMA statement, until June 2020. Results were categorised into three groups: studies reporting on conventional SXPs; studies with a mixed cohort of conventional and non-conventional SXPs [% non-conventional SXPs ≤15%]; and studies reporting on non-conventional SXPs. Considered endpoints were postoperative complications and overall and SXP site-specific surgical recurrence. Random-effect meta-analysis and meta-regression were used to obtain and compare combined estimates between groups.

Results: A total of 26 studies for a total of 1839 patients with CD were included. The pooled postoperative complication rates were was 15.5% (95% confidence interval [CI] 11.2%-20.3%), 7.4% [95% CI 0.2%-22.9%], and 19.2% [95% CI 5-39.6%] for the three groups, respectively. The rates of septic complications were 4% [95% CI 2.2%-6.2%], 1.9% [95% CI 0.4%-4.3%], and 4.2% [95% CI 0.9%-9.8%], respectively. Cumulative overall surgical recurrence rates were 27.5% [95% CI 18.5%-37.6%], 13.2% [95% CI 8.6%-18.7%], and 18.1% [95% CI 6.8%-33.3%]; and SXP site-specific surgical recurrence rates were 13.2% [95% CI 6.9%-21.2%], 8.3% [95% CI 1.6-19.3%], and 8.8% [95% CI 2.2%-19%], respectively. Formal comparison between the groups revealed no differences.

Conclusions: Non-conventional SXP did not differ from conventional SXP with respect to safety and long-term recurrence. Consistent heterogeneity was observed and partially limits the conclusions of this study.

Graphical Abstract



Key Words: Crohn's disease; meta-analysis; surgery; strictureplasties; side-to-side isoperistaltic strictureplasties; morbidity, recurrence

1. Introduction

The occurrence of strictures leading to intestinal obstruction and surgical operations remains an important clinical challenge in Crohn's disease [CD]. At the time of diagnosis, strictures are present in about 5% of patients, whereas up to 30% of the patients develop stricturing complications within 10 years.[1,2] Available biologics play a minor role in this clinical situation. Recurrent symptoms and prestenotic bowel dilation indicate surgery. Endoscopic balloon dilatation is only indicated for short and accessible strictures. Surgical treatment consisted traditionally in the resection of the affected bowel segment. However, the rate of clinical and surgical recurrence after 10 years can reach 50% and 20%, respectively.[3,4] Repeated surgery is not infrequent and can eventually lead to short bowel and intestinal failure.[5] Strictureplasties [SXPs] have progressively gained a role in the treatment of Crohn's strictures and have been proven to be a valid alternative to bowel resections.[6,7] Over the years several techniques have been proposed. The length of the stricture and the characteristics of the affected bowel determine the technique to be used. Disparities can be better appreciated when SPXs are classified into conventional (short and intermediate procedures [e.g., Heineke–Mikulicz, Finney]) and non-conventional (long entero-enterostomies [e.g., Michelassi]).

A few meta-analyses on SXPs have been published. Yamamoto *et al.* reviewed safety and efficacy of SXPs.[8] Campbell *et al.* compared the short- and long-term outcomes of conventional and non-conventional SXPs.[9] However, both meta-analyses rely on studies performed before the introduction and widespread use of biologics in the pre- and postoperative period. Additionally, these studies included a minor proportion of non-conventional SXP and had a limited follow-up period.

Considering that extensive bowel disease probably defines a subtype of CD with a more aggressive biological behaviour, the interest of the surgical community has been progressively focusing on the role of bowel-sparing techniques in long-segment disease.[10] Several studies have only recently appeared in the literature, trying to clarify how long non-conventional SXPs [long isoperistaltic entero-enterostomies] affect the course of this specific subtype of CD, but have not been gathered in meta-analyses.[11–13][]

Hence, we performed a systematic review and pooled analysis of all published studies reporting on SXPs for small bowel [jejuno-ileal] CD, with the primary aim to describe safety and surgical recurrence of strictureplasties. The postoperative complications and recurrence rate after long non-conventional SXPs were separately analysed and compared with those of conventional SXPs.

2. Methods

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines[14] [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online].

2.1. Search strategy and inclusion criteria

An electronic search for relevant publications was performed using the following resources: PubMed, Embase, Scopus, and the Cochrane Collaboration database. Each of the relevant publication's reference section and Google Scholar were also screened for other relevant publications. The search was performed by combining the following search terms using the Boolean AND/OR operators: 'Strictureplasty', 'Stricturoplasty', 'Stricture', 'Surgery', 'Crohn',

'Crohn disease', 'Crohn's disease' 'Inflammatory bowel disease', 'Fibrostenosing', 'Fibrostenotic', 'Stricturing', 'Stenosing', 'Stenotic', 'Stenosis'. The date of the most recent search was June, 2020. This review has been registered in the PROSPERO database [registration number CRD42021252750]. Two independent authors [F.S., G.B.] searched for potentially eligible articles retrieved by the initial search, and disagreements were resolved by consensus with a third reviewer [A.D.]. References for the included studies and for previously published systematic reviews were manually assessed in order to detect any missing study. Studies were considered eligible if all of the following criteria were met: 1] data were reported on the outcomes [postoperative morbidity and/or recurrence]; 2] the study included at least five patients; and 3] the study was reported in English, French, or Italian. Exclusion criteria included the following: 1] studies reporting on SXPs in duodenal, colonic, or rectal CD; 2] reviews and meta-analyses; 3] editorials, commentaries, and letters; and 4] overlapping studies. In the case of duplicate publications, only the most recent or most informative study for a single centre was included in the analyses. Articles that fulfilled the inclusion criteria were retrieved for full-text evaluation and divided into three groups: 1] studies reporting exclusively on conventional SXPs; 2] studies with a mixed cohort of conventional and non-conventional SXPs [percentage of non-conventional SXPs ≤15%]; 3] studies reporting exclusively on non-conventional SXPs. The term conventional SXPs refers to Heineke–Mikulicz-like procedures [Heineke–Mikulicz, Judd, Moskel-Walske-Neumayer, double Heineke–Mikulicz, ileocolic Heineke–Mikulicz] and intermediate procedures [Finney, Jaboulay, combined Heineke-Mikulicz and Finney]. Non-conventional SXPs include side-to-side isoperistaltic entero-enterostomies according to the original technique described by Michelassi or to the modifications proposed over the years by several other groups.[15]

2.2. Data extraction

Extracted variables included: general study characteristics [author, year of publication, study design, number of patients, length of follow-up], clinical characteristics [sex, age, CD duration, use of perioperative medications, previous CD-related bowel surgery, type of previous surgery], treatment characteristics [type and number of SXPs, concomitant resections, length of spared bowel], short- and long-term outcomes [surgical complications, cumulative

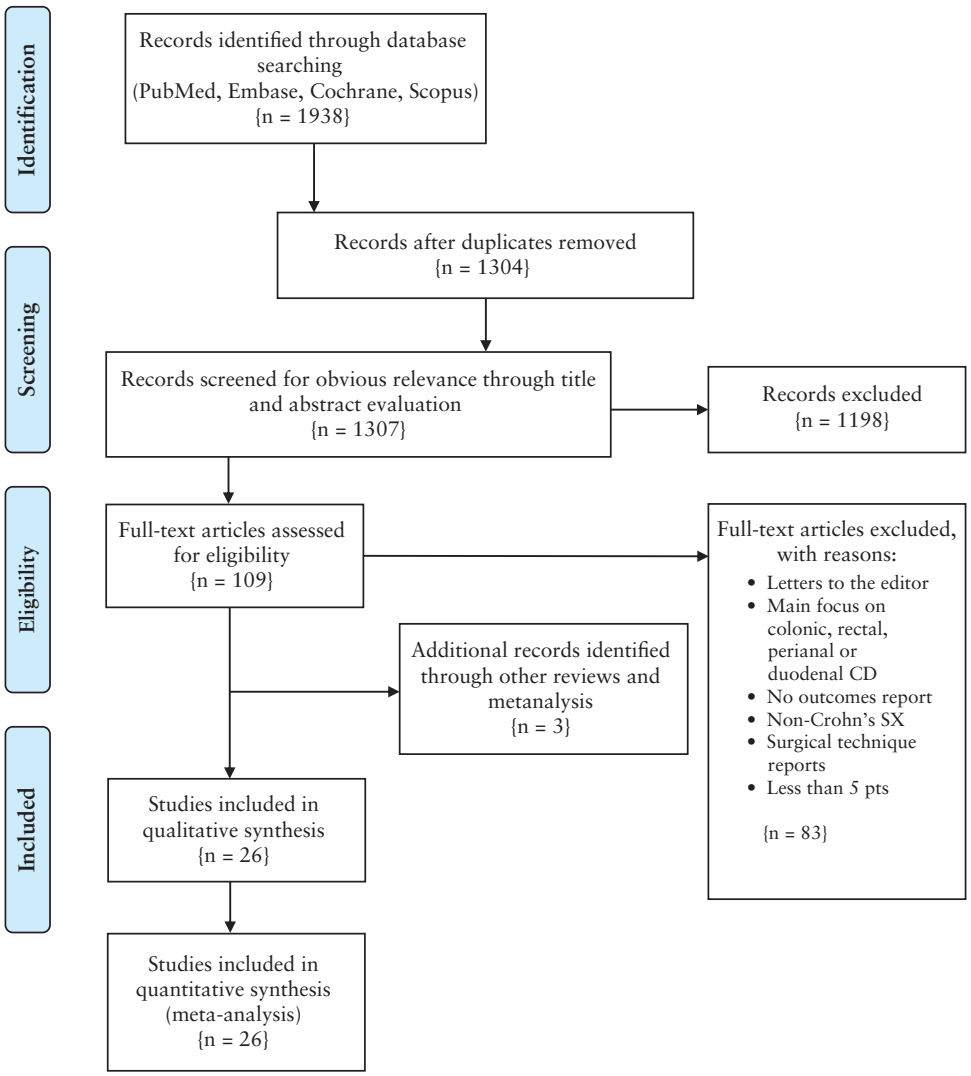


Figure 1. PRISMA flow diagram showing the selection of the studies included in the meta-analysis.

Table 1. Included studies and patients, disease, and surgery features.

										Type of strictureplasty				Site of strictureplasty			
Author, year	Institution	No. pts	Male [%]	Median* or mean age at SXP	CD duration before SXP [median* or mean in months]	Previous bowel surgery [no. pts]	Total no. of SXP	Mean no. of SXP [range]	Concomitant resection [no. pts]	H-M	Finney	SSIS	Others	Small bowel	Ileocolic	Prev. anast	Other sites
Conventional strictureplasties																	
Pritchard 1990	Burlington [USA], Lahey Clinic	13	8	37* [22-54]	168 [21-384]	7	52	4 [1-9]	4	50	2	0	0	52	0	0	0
Quandalle 1994	Lille, Clinique Chirurgicale Ouest	22	12	28* [15-48]	96 [24-240]	9	107	5 [1-10]	15	83	24	0	0	103	0	2	2
Spencer 1994	Rochester, Mayo Clinic	35	18	37 [19-52]	162 [NA-NA]	27	71	2 [1-8]	24	71	0	0	0	71	0	0	0
Yamamoto 1999	Birmingham, Queen Elisabeth Hospital	111	43	34* [15-70]	NA	87	285	3 [1-11]	46	236	49	0	0	258	0	27	0
Tonelli 2000	Florence, University of Florence	44	23	36* [16-61]	34	26	174	3 [1-9]	34	156	16	0	2	166	0	7	1
Broering 2001	Hamburg, University of Hamburg	24	10	26	26.8	16	68	3	0	NA	NA	NA	NA	65	0	3	0
Dietz 2001	Cleveland, Cleveland CF	314	180	37* [14-72]	156* [6-600]	204	1124	2 [1-19]	205	989	129	0	6	1096	0	28	0
Laurent 2002	Liege, CHU	18	10	42	144 [12-324]	11	68	4	15	NA	NA	NA	NA	68	0	0	0
Futami 2005	Fukuoka, Fukuoka UH	103	78	31 [16-72]	114 [7-324]	44	293	2.8 [1-16]	54	235	22	1	35	270	6	11	6
Fearnhead 2006	Oxford, John Radcliffe UH	100	57	34 [16.3-653]	NA	69	479	3 [1-21]	28	434	45	0	0	477	0	0	2
Roy 2006	London, St Georges Hospital	26	NA	36.5 [11-60]	27.5 [4-105]	14	96	3.1 [1-14]	7	74	22	0	0	93		3	
Greenstein 2009	New York, Mount Sinai Hospital	88	56	37 [18-72]	NA	49	339	3*	50	313	22	1	3	315	0	10	14
Dasari 2009	Belfast, Royal Victoria Hospital	27	14	33.5 [15-55]	151.2* [6-468]	20	100	2* [1-7]	NA	92	8	0	0	100	0	0	0
Uchino 2010	Hyogo, Hyogo College of Medicine Hospital	91	75	31 [16-54]	120*	30	199	2.2	87	167	14	1	17	198	0	0	1
Bellolio 2012	Toronto, Mount Sinai Hospital	94	52	33 [17-55]	NA	58	278	3 [1-11]	NA	258	17	3	0	264	0	5	9
Hayakawa 2012	Miyazaki, Miyazaki University Hospital	10	7	32.5* [23-44]	102* [46-204]	10	18	1.8	8	13	5	0	0	18	0	0	0

Table 1. Continued

Author, year	Institution	No. pts	Male [%]	Median* or mean age at SXP	CD duration before SXP [median* or mean in months]	Previous bowel surgery [no. pts]	Total no. of SXP	Mean no. of SXP [range]	Concomitant resection [no. pts]	Type of strictureplasty				Site of strictureplasty			
										H-M	Finney	SSIS	Others	Small bowel	Ileocolic	Prev. anast	Other sites
Landerholm 2020	Oxford, UH	59	39	38.8* [31–48]	12.7* [5.9–19.8]	NA	225	NA	48	218	6	1	0	225	0	0	0
		1179				**681**	**3976**		**625**	**3389**	**381**	**7**	**28**	**3839**	**6**	**96**	**35**
Conventional + non-conventional strictureplasties																	
Hurst 1998	Chicago, University of Chicago	57	35	39 [18-72]	NA	45	109	2 [1-7]	40	90	6	13	0	99	0	9	1
Di Abriola 2003	Rome Bambin Gesù CH + Montreal Saint Justine H	5	2	16 [14-20]	NA	0	5	1	NA	1	1	3	0	5	0	0	0
Sampietro 2004	Milan, University of Milan, Sacco UH	102	65	37	NA	54	201	2	19	80	0	80	41	128	0	73	0
Romeo 2012	Rome Bambin Gesù CH + Genoa Gaslini CH	19	14	15.3 [4-24]	38.6	0	20	1.05	0	9	0	11	0	4	16	0	0
Rottoli 2020	Bologna, Sant'Orsola H	266	171	39.5 [18-76]	98.4 [1.2-444]	85	718	2.7 [1-11]	196	599	50	53	16	718	0	0	0
		449	287			**184**	**1053**		**255**	**779**	**57**	**160**	**57**	**954**	**16**	**82**	**1**
Non-conventional strictureplasties																	
Sasaki 2004	Miyagi, Tohoku UH	8	5	NA	NA	8	8	1	NA	0	0	8	0	0	0	8	0
Fazi 2016	Florence, Careggi UH	91	48	39 [20-71]	97.9	52	94	1.03	41	0	0	94	0	43	46	0	5
Michelassi 2019	Chicago UCH + New York PWCMC	60	29	36* [12-96]	162 [12-576]	43	61	1.02	33	NA	NA	61	NA	61	0	0	0
Bislenghi 2020	Leuven, Leuven UH	52	24	32.7 [16-73]	75.6 [0-408]	14	52	1	10	NA	NA	52	0	47	0	5	0
		211	106			**117**	**215**		**84**	**0**	**0**	**215**	**0**	**151**	**46**	**13**	**5**
		1839	1075			**982**	**5244**		**964**	**4168**	**438**	**382**	**85**	**4944**	**68**	**191**	**41**

Pts, patients; SXP, strictureplasty; H-M, Heineke-Mikulicz; SSIS, side-to-side isoperistaltic strictureplasty; prev., previous; anast., anastomosis; UH, university hospital; NA, not available; H, hospital; Cleveland CF, Cleveland Clinic Foundation; CHU, Chu de Liege; CH, Children Hospital; PWCMC, Presbyterian Weill Cornell Medical Center.

rates of symptomatic and surgical recurrence, site of surgical recurrence, and incidence of cancer]. Quality of studies was evaluated with the Nottingham–Ottawa Scale for non-randomised studies[16] [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online].

2.3. Statistical analysis

Considered endpoints were rate of postoperative overall and septic complication, and overall and SXP site-specific surgical recurrence of SXPs for CD. Statistical analysis was performed to evaluate whether or not the outcomes of non-conventional SXPs were comparable to those of conventional SXPs. Meta-analyses were used to obtain for all studies, as well as for each group of studies separately, a summary estimate of the percentage of patients with overall postoperative complications, septic complications, and overall and SXP site-specific surgical recurrence. Septic complications were defined as the development of deep abdominal abscess or anastomotic leak after SXP procedures. Surgical recurrence was considered as the need for any surgical intervention [SXP or resection] related to CD reactivation. Strictureplasty site-specific recurrence was considered as any surgical intervention on a previous SXP site. Considered study estimates were the arcsine transformed [square-root] proportions. The arcsine is a variance-stabilising transformation which can also handle the presence of studies with zero events.[17] Differences between studies reflect true variability ['heterogeneity'] and sampling variability. Heterogeneity was quantified by the I^2 statistic,[18] which is the percentage of total variation in study estimates that is due to heterogeneity and tested by Cochran's chi square test. The random-effects approach of DerSimonian and Laird was used to obtain a combined estimate in each group.[19] A random-effects meta-regression on groups combined was used to compare the percentage complication between the three groups considered [see also 2.1.].[20] In the meta-regression for reoperation and surgical recurrence, a correction was added for differences in follow-up time by including the log-transformed follow-up time in the model. All analyses have been performed using SAS software, version 9.4, of the SAS System for Windows.

3. Results

3.1. Systematic review

3.1.1. General results

The 109 primarily eligible full-texts fit for inclusion were reviewed; 25 of these studies were produced by the same 13 departments. As a result, 26 studies were selected for the analyses [][11–13,21–43] [Figure 1]. Details of included studies, patients, and surgery are reported in Table 1.

A total of 1839 patients were included, with a prevalence of male sex [58%]. Median age throughout the included studies was between 15 and 40 years. The median duration of CD before surgery was between 27 and 168 months; 53% of patients [982/1839] had undergone previous bowel surgery. Seventeen studies reported data

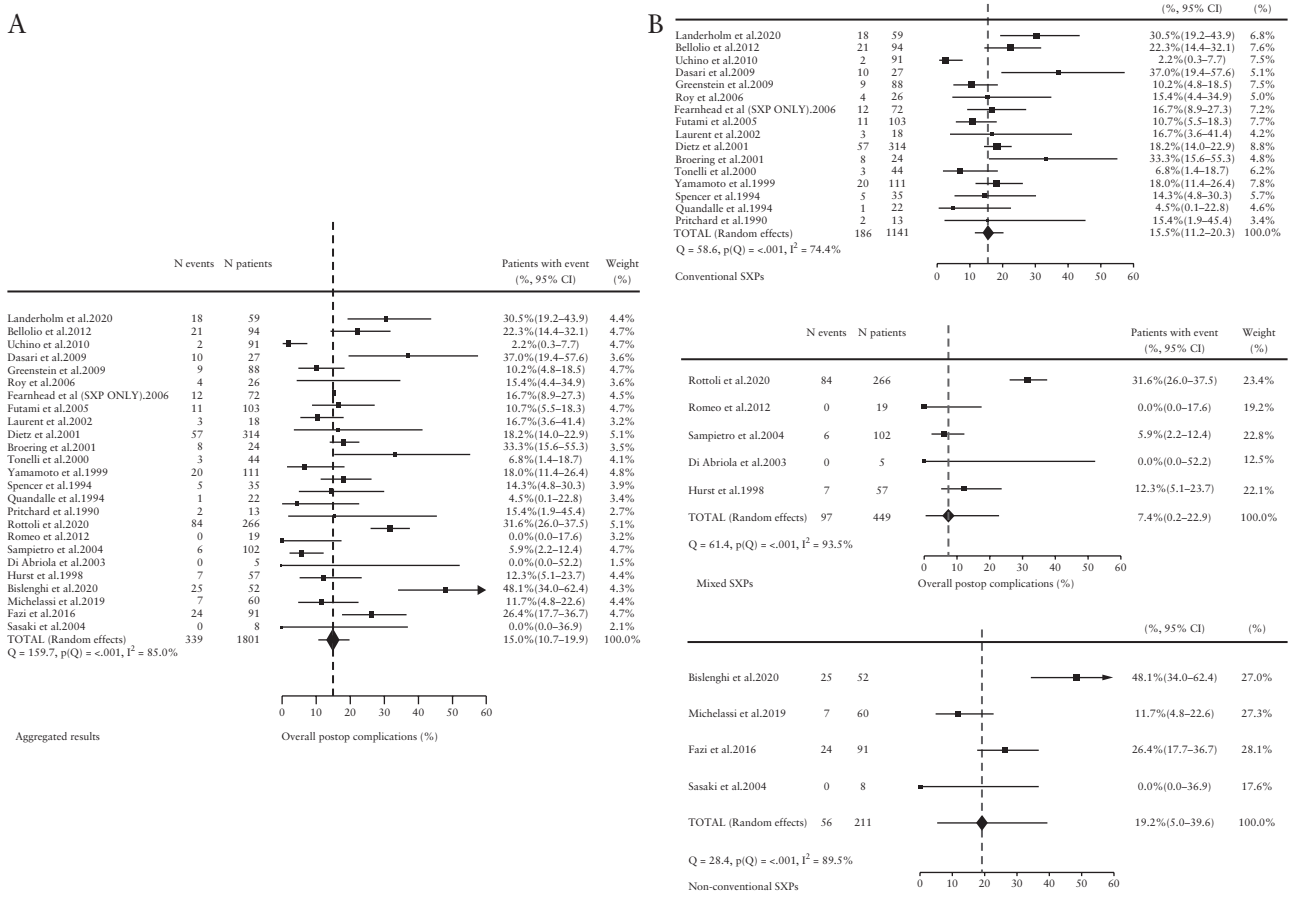


Figure 2. Forest plots for overall postoperative complications; a] aggregated results, b] results for conventional, mixed, and non-conventional strictureplasties, separately.

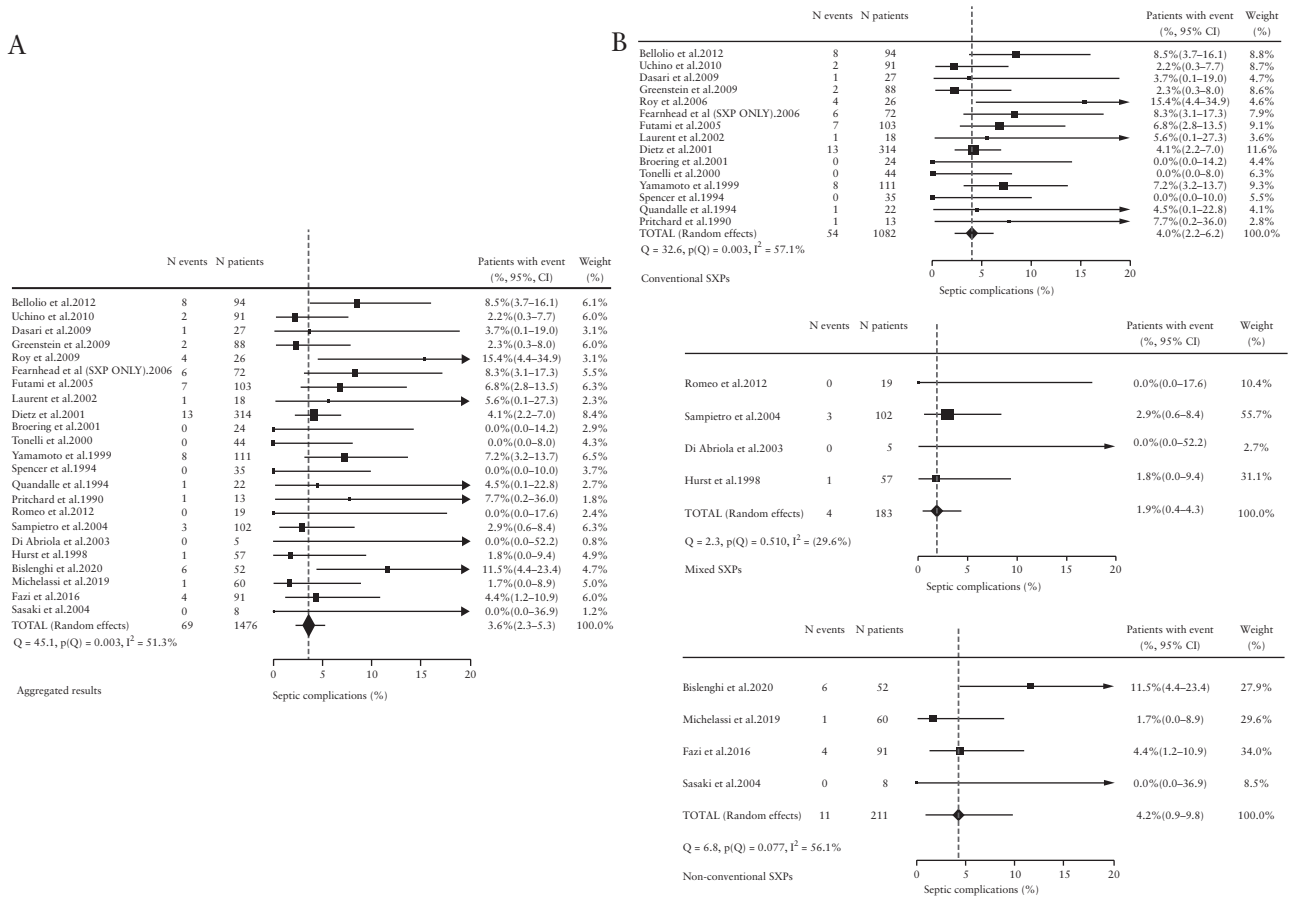


Figure 3. Forest plots for postoperative septic complications; a] aggregated results, b] results for conventional, mixed, and non-conventional strictureplasties, separately.

regarding the type of previous bowel surgery: 73% of the patients had undergone resections exclusively, 23% had resections and SXPs, and 4% had no previous bowel surgery.

A total of 5244 SXPs were performed. The mean number of SXPs per patient ranged from one to five; 56% of the patients [964/1705] underwent concomitant bowel resection. The most commonly performed SXP was the Heineke\-Mikulicz [83.4%, 4168/4995 procedures], followed by the Finney [8.7%, 438/4995 procedures], and the side-to-side isoperistaltic SXP [7.5%; 329/4390 procedures]. The most common sites where SXPs were performed were jejunum and ileum [94.3%; 4944/5244 sites]. Strictureplasties were adopted on previous anastomotic sites in 3.6% [191/5244] of the cases and used for primary ileocaecal strictures in 1.3% [68/5244 sites] of the strictures. Five studies reported data on the median length of spared bowel, ranging between 188 cm and 302 cm. Preoperative use of corticosteroids and immunomodulators was reported for 49.7% and 50.9% of the patients, respectively. Preoperative use of anti-tumour necrosis factor [TNF] agents and other biologics was observed in 20.6% and 20% of the patients and was available for 12 and 10 studies, respectively.

Seven patients [0.4%] developed adenocarcinomas arising from a previous SXP site. Fearnhead *et al*.[34] reported on a patient who had SXPs and who died of small bowel cancer, without specifying if this was directly related to the SXPs [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

3.1.2. Conventional SXPs

The conventional SXPs group included 17 studies with a total of 1179 patients and a prevalence of male sex [59.2%].[][21–23,25–29,33–40,42] Median age at SXP was between 26 and 38.8 years. The median duration of CD before surgery was between 12.7 and 168 months. Almost 61% of patients [681/1120] had undergone previous bowel surgery.

A total of 3976 SXPs were performed in the conventional SXPs group. The mean number of SXPs per patient ranged from 1.8 to 5; 56% of the patients [625/1058] underwent concomitant bowel resection. The most commonly performed SXP was Heineke-Mikulicz [85.2%, 3389/3976 procedures], followed by Finney [9.6%, 381/3976 procedures]. The most common site where SXPs were performed was the small bowel [96.6%; 3839/3976 sites]. Strictureplasties were adopted on previous anastomotic sites in 2.4% [96/3976] of the cases and were used for primary ileocaecal strictures in 0.2% [6/3976 sites] of the strictures.

3.1.3. Mixed [conventional + non-conventional] SXPs

The conventional + non-conventional SXPs group included five studies with a total of 449 patients and a prevalence of male sex [63.9%].[24,30,31,41,43] Median age at SXP was between 15.3 and 39.5 years. The median duration of CD before surgery was between 38.6 and 98.4 months. Almost 41% of patients [184/449] had undergone previous bowel surgery.

A total of 1053 SXPs were performed in this group. The mean number of SXPs per patient ranged from 1 to 2.7; 57% of the patients [255/444] underwent concomitant bowel resection. The most commonly performed SXP was Heineke-Mikulicz [74.0%, 779/1053 procedures], followed by side-to-side isoperistaltic SXPs [15.2%, 160/1053 procedures] and Finney [5.4%, 57/1053 procedures]. The

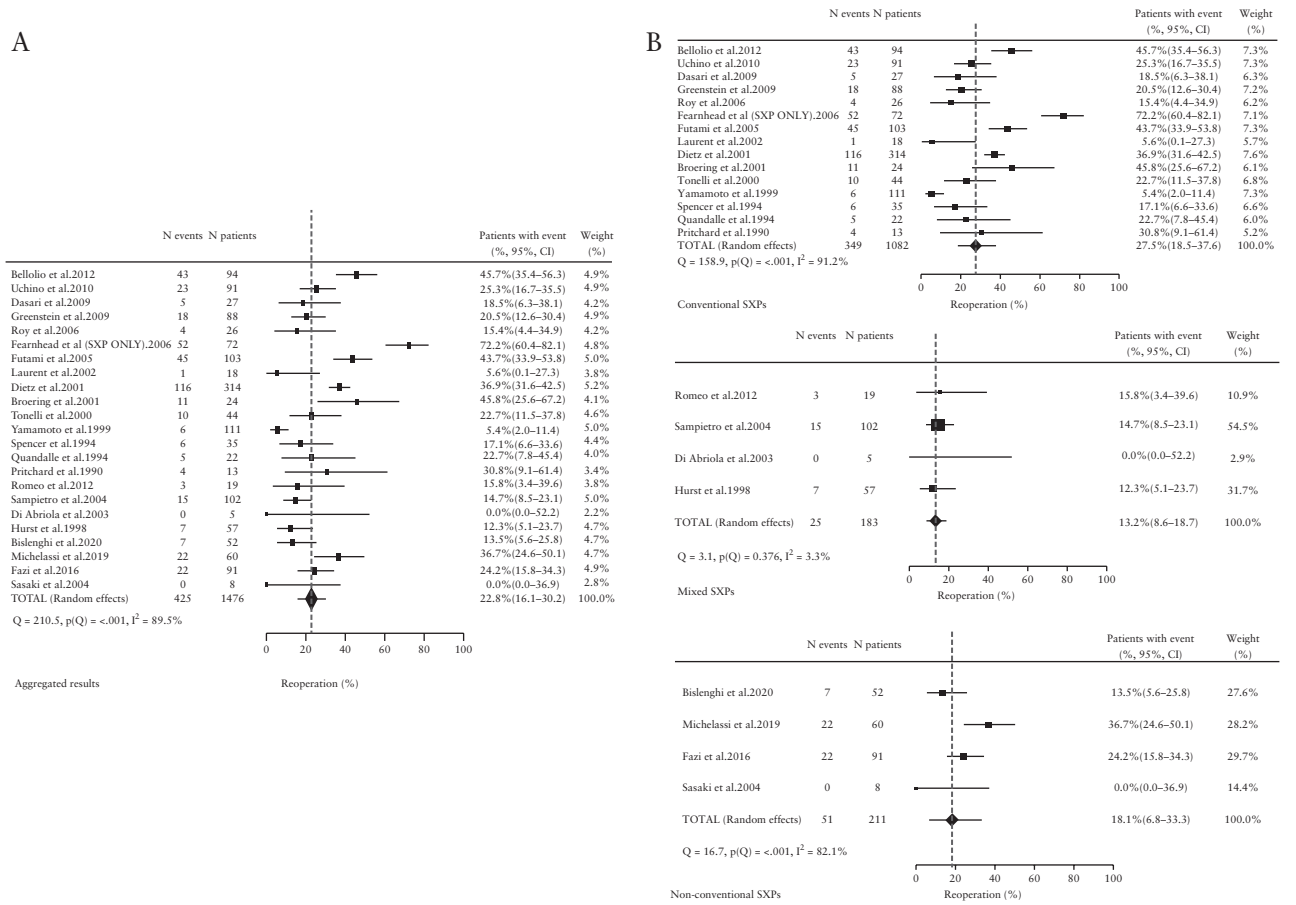


Figure 4. Forest plots for overall surgical recurrence; a] aggregated results, b] results for conventional, mixed, and non-conventional strictureplasties, separately.

most common site where SXPs were performed was the small bowel [90.6%; 954/1053 sites]. Strictureplasties were adopted on previous anastomotic sites in 7.8% [82/1053] of the cases and used for primary ileocaecal strictures in 1.5% [16/1053 sites] of the strictures.

3.1.4. Non-conventional SXPs

The non-conventional SXPs group included four studies with a total of 211 patients and a minimal prevalence of male sex [50.2%]. [][11–13,32] Median age at SXP was between 32.7 and 39 years. The median duration of CD before surgery was reported between 75.6 and 162 months. More than 55% of patients [117/211] had undergone previous bowel surgery.

A total of 215 SXPs were performed. The mean number of SXPs per patient ranged from 1 to 1.03. Almost 40% of the patients [84/211] underwent concomitant bowel resection. Strictureplasties were adopted on previous anastomotic sites in 6.1% [13/215] of the cases and used for primary ileocaecal strictures in 21.4% [46/215 sites] of the strictures.

Details for each of the considered groups [conventional, mixed, and non-conventional SXPs] are specified in Table 1.

3.2. Meta-analysis

3.2.1. Postoperative complications

Data on early postoperative complications are summarised in [Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online]. These were available for 25 studies. Hayakawa *et al.*[40] reported on recurrence and did not report on postoperative complications. Reporting of postoperative complications was heterogeneous: Rottoli *et al.*[43] reported data on overall postoperative complications rate without mentioning the specific cause; Bellolio *et al.*[39] and Landerholm *et al.*[42] reported complications in relation to the number of procedures. For Fearnhead *et al.*,[34] only data related to SXP procedures were included in the pooled analysis.

Overall, 339 out of 1801 patients developed complications. Septic complications occurred in 69 out of 1476 patients and leakage in 44 patients. Other postoperative complications included surgical site infection [34/1525], bleeding [41/1525], prolonged ileus [35/1466], and bowel obstruction [16/1466]. The range of median postoperative stay was 8-17 days [data available for 19 studies].

From the pooled analyses, the cumulative overall complication rates for conventional, mixed, and non-conventional SXP group were 15.5% (95% confidence interval [CI] 11.2%-20.3%), 7.4% [95% CI 0.2%-22.9%], and 19.2% [95% CI 5-39.6%]. The aggregated cumulative overall complication rate over the three groups was 15% [95% CI 10.7%-19.9%]. Significant heterogeneity was present between the studies for each group considered [p <0.001] [Figure 2].

The cumulative rates of septic complications were 4% [95% CI 2.2%-6.2%], 1.9% [95% CI 0.4%-4.3%], and 4.2% [95% CI 0.9%-9.8%], respectively. The aggregated cumulative septic complication rate over the three groups was 3.6% [95% CI 2.3%-5.3%]. Significant heterogeneity between studies was only observed for the conventional SXP group [I^2 = 57.1; p = 0.003] [Figure 3].

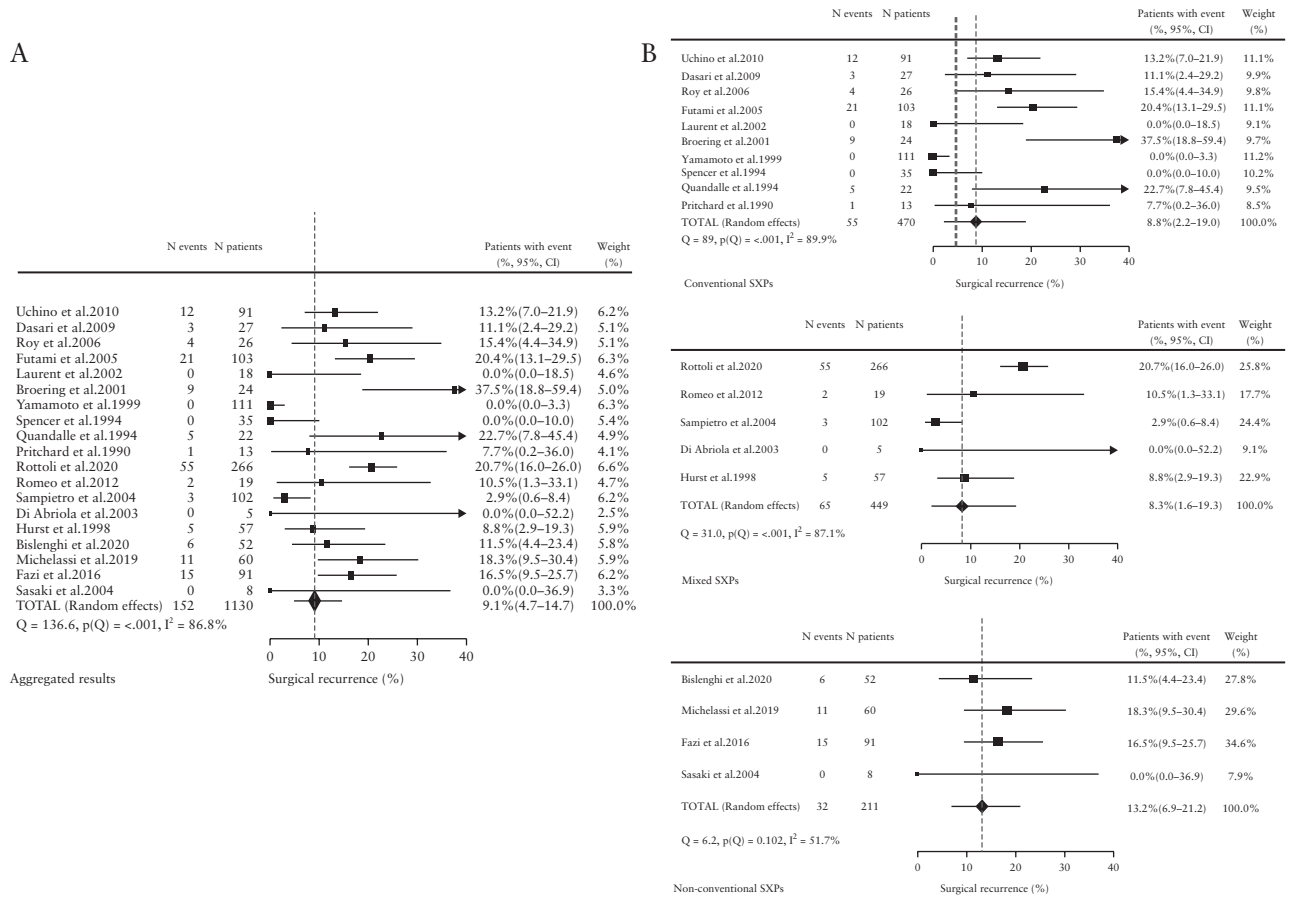


Figure 5. Forest plots for strictureplasty site-specific surgical recurrence; a] aggregated results, b] results for conventional, mixed, and non-conventional strictureplasties, separately.

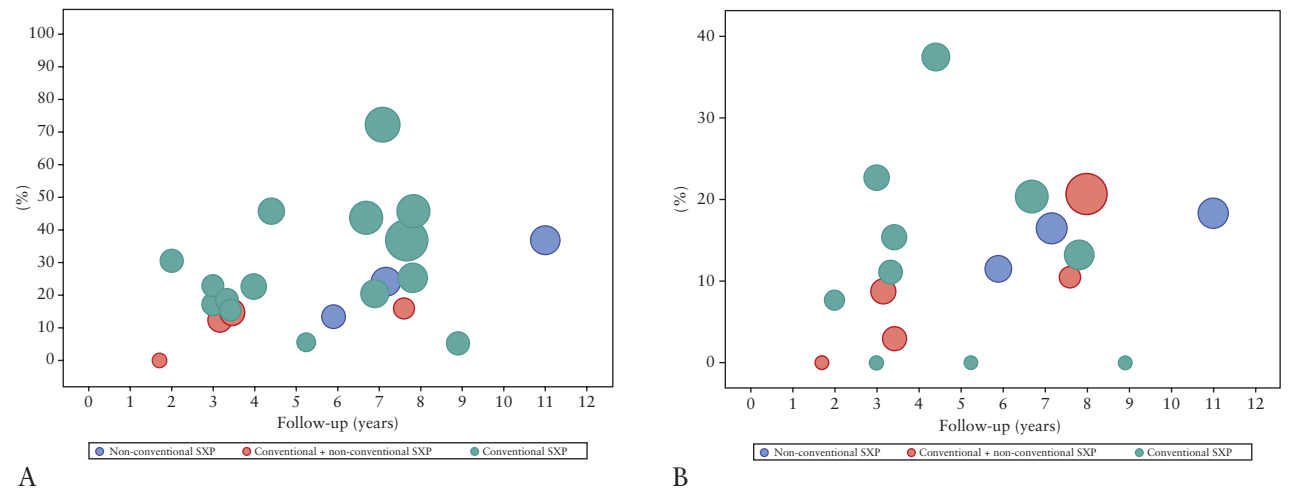


Figure 6. Plot of observed percentages versus follow-up for overall surgical recurrence [a] and site-specific surgical recurrence [b]. The area of the bubbles represents the length of the follow-up.

Meta-regression did not reveal significant differences for both overall [$p = 0.53$] and septic complications [$p = 0.58$].

3.2.2. Recurrence

Recurrence rates are summarised in Supplementary Table 4, available as Supplementary data at *ECCO-JCC* online. For the 24 studies reporting data on follow-up, the mean [range] of the reported mean/median length of follow-up was 65.3 [40.5-88.5], 57.4 [38-91.2], and 96.3 [70.8-132] months for conventional, mixed, and non-conventional SXP groups, respectively. Overall, symptomatic recurrence was reported in 13 studies and accounted for 293 out of 1060 patients. Data on overall surgical recurrence were available for 23

studies. Data on SXP site-specific surgical recurrence site were available for 19 studies.

From the pooled analyses, the cumulative overall surgical recurrence rates for conventional, mixed, and non-conventional SXP groups were 27.5% [95% CI 18.5%-37.6%], 13.2% [95% CI 8.6%-18.7%], and 18.1% [95% CI 6.8%-33.3%], respectively. After correction for differences in length of follow-up, the overall surgical recurrence rate equalled 26.9% [95% CI 17.4%-37.6%], 17.2% [95% CI 10.7%-24.9%], and 18.2% [95% CI 9.6%-28.7%] for the three considered groups, respectively. The aggregated cumulative overall surgical recurrence rate over the three groups was 22.8% [425/1476] [95% CI 16.1%-30.2%].

Significant heterogeneity was present between the studies for the conventional and the non-conventional SXP groups [I^2 = 92.2 and 82.1; p <0.001 and p = 0.008, respectively] [Figure 4].

The rates of SXP site-specific surgical recurrence were 13.2% [95% CI 6.9%-21.2%], 8.3% [95% CI 1.6-19.3%], and 8.8% [95% CI 2.2%-19%] in the groups, respectively. After correction for differences in length of follow-up, the overall SPX-site specific recurrence rate equalled 9.3% [95% CI 9.8%-21.7%], 9.3% [95% CI 4.1%-16.3%], and 10.4% [95% CI 4.6%-18%] for the three considered groups, respectively. The aggregated cumulative SXP site-specific recurrence rate was 9.1% [152/1130] [95% CI 4.7%-14.7%]. Significant heterogeneity was present between the studies for the conventional and the non-conventional SXP groups [I^2 = 89.9 and 87.1, respectively; p <0.001] [Figure 5].

Meta-regression did not reveal significant differences for both overall [p = 0.35] and site-specific surgical recurrence [p = 0.22] after correction for the length of follow-up.

For overall and site-specific surgical recurrence, a bubble plot is added. plotting the percentage versus the follow-up [Figure 6].

4. Discussion

Fibrostenotic CD defines a specific subgroup of patients, often refractory to medical therapy, in need for endoscopic and surgical interventions.

Resection surgery has the drawback of significant postoperative endoscopic and clinical recurrence and repeated surgery.[44,45] To maximise bowel preservation and to reduce the risk of intestinal failure, SXPs have been established as valid alternatives to bowel resections. The indications have been progressively expanded and techniques were developed to bridge long segment of affected bowel.[4]

Consistent overlap and similarity between SXP techniques exist.[15] Disparities can be better appreciated when SXPs are classified into conventional [short-segment and intermediate-segment procedures] and non-conventional SXPs [long-segment procedures].

Beside the technical aspects, there is major heterogeneity in the clinical presentation of stricturing disease—short versus long, single versus multiple segments—and this certainly reflects a different biological behaviour. Recurrence after intestinal resection tends to mimic the location and the length of the primary disease.[46] This puts those patients undergoing extensive resections at risk of short bowel syndrome. Literature has shown that CD is among the leading causes of intestinal failure. Approximately one-third of patients on long-term parenteral nutrition are estimated to have CD with a history of repetitive surgery and post-surgical complications.[47]

The available literature suggests safety and feasibility of SXP for CD with low overall morbidity rate, ranging from 13% to 20%, and nil mortality rate.[8,9] Septic complications, such as anastomotic leak, abscess formation, and fistula, occur in the minority of the cases [4%]. Strictureplasties do not confer increased morbidity when compared with small bowel resections + anastomosis, as shown in a meta-analysis by Reese *et al.*[48] The results of the present meta-analysis [postoperative overall and septic complication rates 15% and 3.6%, respectively] corroborate these previous findings. Moreover, it is of interest to note that long non-conventional SXPs are not prone to more complications [especially risk of leakage] in comparison with shorter conventional SXPs, as already observed by Campbell *et al.*[9]

Surgical recurrence after SXPs reaches 38% and 51%, at 7.5- and 10-year follow-up, respectively.[25,28] Procedure-specific recurrence rates are available only for a few SXP techniques. Campbell *et al.* reported recurrent stricturing disease in 28.4% of patients with conventional SXPs and 22.9% of patients with non-conventional SXPs, over a mean follow-up of 5 years.[9] In the present study, overall surgical recurrence was 22.8%. Although not statistically significantly so, recurrence for non-conventional SXPs was lower than that reported for conventional SXPs, even after correction for the length of follow-up [18.2% vs 26.9%, respectively]. Site-specific surgical recurrence for non-conventional SPXs at 8-year follow-up was 10.4%, not significantly different from that observed after conventional SXPs [9.3%]. Although patients with long-segment disease belong probably to a high-risk profile population, site-specific recurrence for non-conventional SXPs was only slightly higher than those reported in the aforementioned meta-analyses which included studies with limited follow-up and a prevalence of conventional SXPs.[8,9,28,48] This might reflect the attitude to treating this specific subgroup of patients aggressively and in a timely manner, suggesting a possible benefit of the prophylactic use of biologics in the prevention of recurrences after long-segment SXPs.

Meta-analysis comparing SXPs with bowel resections found an increased likelihood of disease recurrence, with reduced recurrence-free survival in SXP patients.[48,49] However, a recent retrospective comparative study of SXPs vs resections performed for extensive [>30 cm] terminal ileitis partially contradicts these results, showing non-inferiority of SXPs in terms of postoperative morbidity and long-term surgical recurrence.[50] In view of these reassuring data, there is an urgent need to consider SXP over the ileocaecal valve as a primary intervention. All types of SXP [conventional and non-conventional] can be performed over the ileocaecal valve, depending upon the length of the affected terminal ileum.

The widespread involvement of the mesentery in CD has recently led to reconsidering the mesentery as an individual organ implicated in the development of the local and systemic inflammation typical of CD.[51,52] Resections of larger portions of the mesentery and anastomotic techniques excluding the mesentery from the anastomotic rhyme [Kono-S] seem to be associated with less recurrences.[53,54] However, the observation that mucosal healing occurs in affected areas of intestine treated with SXPs seems to contradict this mesenteric-related theory and suggests that the mesentery may be safely retained.[11,55] The recent finding that the 'creeping fat' is triggered by the translocation in the mesentery of a specific subset of mucosal-associated bacteria, indicates that the relief of the intestinal obstruction is probably the most important factor to be addressed during surgery. This leads to the alleviation of the fecal stasis and modification of the composition of the gut flora with ultimate effects on the microbial-mucosal interaction.[56]

Consistent heterogeneity was found throughout all the analyses. This reflects the retrospective, observational nature of the most studies included. Data on functional results after SXP [residual motility and absorptive function] are largely absent. The same can be said about data on postoperative use of biologics. It might be obviously argued that the encouraging long-term results of non-conventional

SXPs are a direct consequence of a more intensive use of biologics in the perioperative period in this specific subgroup of patients, although efficacy of biologics in preventing recurrence after surgery is still debated.[57] Finally, it is worth mentioning that SXPs, in particular non-conventional SXPs, remain a niche procedure and only a limited number of surgical groups publish on SXPs since their initial description. This is a result of the limited indications, with difficult patient selection, and the challenging surgical technique.

To conclude, the present meta-analysis confirms the central role of SXP in the surgical treatment of CD. In light of data on safety and long-term recurrence, non-conventional SXP should be considered as a primary surgical intervention to avoid extensive loss of bowel and short gut syndrome.

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Conflict of Interest

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Author Contributions

GB and FS contributed to the concept of the manuscript, to the bibiliographical research, to the extraction of data, and to the writing of the manuscript. SF performed the statistical analysis. ADH contributed to the interpretation of the data, to the writing of the manuscript, and to its extensive revision. JS, MF, and SV contributed to the concept and design of the manuscript. They have actively contributed to its extensive review, refinement, and improvement.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut* 2013;**62**:1072–84.
2. Froehlich F, Juillerat P, Mottet C, *et al*. Obstructive fibrostenotic Crohn's disease. *Digestion* 2005;**71**:29–30.
3. Greenstein AJ, Sachar DB, Pasternack BS, Janowitz HD. Reoperation and recurrence in Crohn's colitis and ileocolitis. Crude and cumulative rates. *N Engl J Med* 1975;**293**:685–90.
4. Lennard-Jones JE, Stalder GA. Prognosis after resection of chronic regional ileitis. *Gut* 1967;**8**:332–6.
5. Watanabe K, Sasaki I, Fukushima K, *et al*. Long-term incidence and characteristics of intestinal failure in Crohn's disease: a multicenter study. *J Gastroenterol* 2014;**49**:231–8.
6. Laureti S, Fazio VW. Obstruction in Crohn's disease: strictureplasty versus resection. *Curr Treat Options Gastroenterol* 2000;**3**:191–202.
7. Adamina M, Bonovas S, Raine T, *et al*. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis* 2020;**14**:155–68.
8. Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2007;**50**:1968–86.
9. Campbell L, Ambe R, Weaver J, Marcus SM, Cagir B. Comparison of conventional and nonconventional strictureplasties in Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2012;**55**:714–26.
10. Michelassi F. Side-to-side isoperistaltic strictureplasty for multiple Crohn's strictures. *Dis Colon Rectum* 1996;**39**:345–9.
11. Bislenghi G, Ferrante M, Sabino J, *et al*. Short- and long-term outcomes following side-to-side strictureplasty and its modification over the ileocaecal valve for extensive Crohn's ileitis. *J Crohns Colitis* 2020;**14**:1378–84.
12. Michelassi F, Mege D, Rubin M, Hurst RD. Long-term results of the side-to-side isoperistaltic strictureplasty in Crohn disease: 25-year follow-up and outcomes. *Ann Surg* 2020;**272**:130-7.
13. Fazi M, Giudici F, Luceri C, Pronestì M, Tonelli F. Long-term results and recurrence-related risk factors for Crohn disease in patients undergoing side-to-side isoperistaltic strictureplasty. *JAMA Surg* 2016;**151**:452–60.
14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.
15. Ambe R, Campbell L, Cagir B. A comprehensive review of strictureplasty techniques in Crohn's disease: types, indications, comparisons, and safety. *J Gastrointest Surg* 2012;**16**:209–17.
16. Deeks JJ, Dinnes J, D'Amico R, *et al*.; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;**7**:iii–x, 1–173.
17. Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med* 2008;**27**:746–63.
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
20. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;**21**:589–624.
21. Pritchard TJ, Schoetz DJ Jr, Caushaj FP, *et al*. Strictureplasty of the small bowel in patients with Crohn's disease. An effective surgical option. *Arch Surg* 1990;**125**:715–7.
22. Quandalle P, Gambiez L, Colombel JF, Paris JC, Cortot A. Long-term follow-up of strictureplasty in Crohn's disease. *Acta Gastroenterol Belg* 1994;**57**:314–9.
23. Spencer MP, Nelson H, Wolff BG, Dozois RR. Strictureplasty for obstructive Crohn's disease: the Mayo experience. *Mayo Clin Proc* 1994;**69**:33–6.
24. Hurst RD, Michelassi F. Strictureplasty for Crohn's disease: techniques and long-term results. *World J Surg* 1998;**22**:359–63.
25. Yamamoto T, Bain IM, Allan RN, Keighley MR. An audit of strictureplasty for small-bowel Crohn's disease. *Dis Colon Rectum* 1999;**42**:797–803.
26. Tonelli F, Ficari F. Strictureplasty in Crohn's disease: surgical option. *Dis Colon Rectum* 2000;**43**:920–6.
27. Broering DC, Eisenberger CF, Koch A, Bloechle C, Knoefel WT, Izbicki JR. Quality of life after surgical therapy of small bowel stenosis in Crohn's disease. *Dig Surg* 2001;**18**:124–30.
28. Dietz DW, Laureti S, Strong SA, *et al*. Safety and longterm efficacy of strictureplasty in 314 patients with obstructing small bowel Crohn's disease. *J Am Coll Surg* 2001;**192**:330–7.
29. Laurent S, Detry O, Detroz B, *et al*. Strictureplasty in Crohn's disease: short- and long-term follow-up. *Acta Chir Belg* 2002;**102**:253–5.
30. Di Abriola GF, De Angelis P, Dall'oglio L, Di Lorenzo M. Strictureplasty: an alternative approach in long segment bowel stenosis Crohn's disease. *J Pediatr Surg* 2003;**38**:814–8.
31. Sampietro GM, Corsi F, Maconi G, *et al*. Prospective study of long-term results and prognostic factors after conservative surgery for small bowel Crohn's disease. *Clin Gastroenterol Hepatol* 2009;**7**:183–91.
32. Sasaki I, Shibata C, Funayama Y, *et al*. New reconstructive procedure after intestinal resection for Crohn's disease: modified side-to-side isoperistaltic

anastomosis with double Heineke-Mikulicz procedure. *Dis Colon Rectum* 2004;**47**:940–3.
33. Futami K, Arima S. Role of strictureplasty in surgical treatment of Crohn's disease. *J Gastroenterol* 2005;**40**[**Suppl 16**]:35–9.
34. Fearnhead NS, Chowdhury R, Box B, George BD, Jewell DP, Mortensen NJ. Long-term follow-up of strictureplasty for Crohn's disease. *Br J Surg* 2006;**93**:475–82.
35. Roy P, Kumar D. Intervention-free interval following strictureplasty for Crohn's Disease. *World J Surg* 2006;**30**:1020–6.
36. Greenstein AJ, Zhang LP, Miller AT, *et al*. Relationship of the number of Crohn's strictures and strictureplasties to postoperative recurrence. *J Am Coll Surg* 2009;**208**:1065–70.
37. Dasari BV, Maxwell R, Gardiner KR. Assessment of complications following strictureplasty for small bowel Crohn's Disease. *Ir J Med Sci* 2010;**179**:201–5.
38. Uchino M, Ikeuchi H, Matsuoka H, Matsumoto T, Takesue Y, Tomita N. Long-term efficacy of strictureplasty for Crohn's disease. *Surg Today* 2010;**40**:949–53.
39. Bellolio F, Cohen Z, MacRae HM, *et al*. Strictureplasty in selected Crohn's disease patients results in acceptable long-term outcome. *Dis Colon Rectum* 2012;**55**:864–9.
40. Hayakawa S, Hotokezaka M, Ikeda T, Uchiyama S, Chijiiwa K. Difference in recurrence patterns between anastomosis and strictureplasty after surgical treatment for Crohn disease. *Int Surg* 2012;**97**:120–8.
41. Romeo E, Jasonni V, Caldaro T, *et al*. Strictureplasty and intestinal resection: different options in complicated pediatric-onset Crohn disease. *J Pediatr Surg* 2012;**47**:944–8.
42. Landerholm K, Reali C, Mortensen NJ, Travis SPL, Guy RJ, George BD. Short- and long-term outcomes of strictureplasty for obstructive Crohn's disease. *Colorectal Dis* 2020;**22**:1159–68.
43. Rottoli M, Tanzanu M, Manzo CA, *et al*. Strictureplasty for Crohn's disease of the small bowel in the biologic era: long-term outcomes and risk factors for recurrence. *Tech Coloproctol* 2020;**24**:711–20.
44. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289–97.
45. Buisson A, Chevaux JB, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. *Aliment Pharmacol Ther* 2012;**35**:625–33.
46. D'Haens GR, Gasparaitis AE, Hanauer SB. Duration of recurrent ileitis after ileocolonic resection correlates with presurgical extent of Crohn's disease. *Gut* 1995;**36**:715–7.
47. Limketkai BN, Parian AM, Shah ND, Colombel JF. Short bowel syndrome and intestinal failure in Crohn's disease. *Inflamm Bowel Dis* 2016;**22**:1209–18.
48. Reese GE, Purkayastha S, Tilney HS, von Roon A, Yamamoto T, Tekkis PP. Strictureplasty vs resection in small bowel Crohn's disease: an evaluation of short-term outcomes and recurrence. *Colorectal Dis* 2007;**9**:686–94.
49. Butt WT, Ryan ÉJ, Boland MR, *et al*. Strictureplasty versus bowel resection for the surgical management of fibrostenotic Crohn's disease: a systematic review and meta-analysis. *Int J Colorectal Dis* 2020;**35**:705–17.
50. Bislenghi G, Fieuws S, Wolthuis A, *et al*. Positioning strictureplasty in the treatment of extensive Crohn's disease ileitis: a comparative study with ileocecal resection. *Int J Colorectal Dis* 2021;**36**:791–9.
51. Coffey JC, O'Leary DP. The mesentery: structure, function, and role in disease. *Lancet Gastroenterol Hepatol* 2016;**1**:238–47.
52. Coffey JC, O'Leary DP, Kiernan MG, Faul P. The mesentery in Crohn's disease: friend or foe? *Curr Opin Gastroenterol* 2016;**32**:267–73.
53. Coffey CJ, Kiernan MG, Sahebally SM, *et al*. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. *J Crohns Colitis* 2018;**12**:1139–50.
54. Luglio G, Rispo A, Imperatore N, *et al*. Surgical prevention of anastomotic recurrence by excluding mesentery in Crohn's disease: the SuPREMe-CD Study - a randomized clinical trial. *Ann Surg* 2020;**272**:210–7.
55. Michelassi F, Hurst RD, Melis M, *et al*. Side-to-side isoperistaltic strictureplasty in extensive Crohn's disease: a prospective longitudinal study. *Ann Surg* 2000;**232**:401–8.
56. Ha CWY, Martin A, Sepich-Poore GD, *et al*. Translocation of viable gut microbiota to mesenteric adipose drives formation of creeping fat in humans. *Cell* 2020;**183**:666–83.e17.
57. Regueiro M, Feagan BG, Zou B, *et al*.; PREVENT Study Group. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. *Gastroenterology* 2016;**150**:1568–78.