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Title

The role of Kono-S anastomosis and mesenteric resection in reducing recurrence after surgery for Crohn's disease. A systematic review.

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The role of Kono-S anastomosis and mesenteric resection in reducing recurrence after surgery for Crohn's disease. A systematic review.

Alshantti A, Hind D, Hancock L, Brown SR,

Abstract

Objectives

Recurrence after surgery for Crohn's disease is common. Anastomotic configuration may influence recurrence and the mesentery may be key. Recently the Kono-S anastomosis and radical mesenteric excision have been proposed as methods of reducing recurrence. We analysed the literature pertaining to these novel techniques

Methods

We searched MEDLINE, EMBASE and the Cochrane Library for, and selected, studies evaluating Kono-S anastomosis and/or radical mesenteric excision in Crohn's disease.

We assessed methodological quality and risk of bias using the Cochrane risk of bias tool for randomized controlled trials and the Joanna Briggs Institute tool for non randomized trials. Narrative synthesis was used to summarise the findings.

Results

Nine studies (896 patients) were identified. Apart from one RCT with a low risk of bias the overall level of evidence was poor (Grade IV). The Kono-S anastomosis was associated with a lower incidence of endoscopic and surgical recurrence (0-3.4% vs 15-24.4% respectively).

Complications, particularly anastomotic leak rate were also lower (1.8% vs 9.3% respectively). Evidence from a single poor quality study suggested that mesenteric excision may reduce surgical recurrence rates when compared mesentery preservation.

Discussion

Existing literature suggests the Kono-S anastomosis is safe and may reduce endoscopic and surgical recurrence, but level of evidence is mainly poor. One element of the Kono-S technique, preservation of the mesentery, may be detrimental to recurrence. Further, higher quality, studies are required to investigate these techniques. Such studies should consider the impact of the degree of mesenteric resection in addition to the anastomosis on disease recurrence.

Word count 244

Alternative structure

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Existing literature suggests the Kono-S anastomosis is safe and may reduce endoscopic and surgical recurrence, but level of evidence is mainly poor. One element of the Kono-S technique, preservation of the mesentery, may be detrimental to recurrence. Further higher quality studies are required to investigate these techniques. Such studies should consider the impact of the degree of mesenteric resection in addition to anastomosis on disease recurrence.

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Introduction

Crohn's disease is a well recognised chronic inflammatory condition of the gastrointestinal tract. Notwithstanding the relatively high incidence, particularly in the West, the underlying aetiology remains elusive. Optimal treatment involves a multidisciplinary approach including gastroenterologists, surgeons, radiologists and nursing staff (1,2). Despite advances in all aspects of treatment, Crohn's disease remains incurable and relapse and recurrence are common (2,3).

After surgical resection it is recognised that the majority of recurrences occur at and proximal to the anastomosis, implying that the surgery itself may have a role, with faecal stasis a possible underlying aetiology. With this in mind numerous studies have explored the effect of anastomotic configuration on recurrence. Whilst there have been several studies and meta-analyses, results remain conflicting (4-6). Current consensus supports a wide lumen configuration, most easily accomplished with a stapled side-to-side anastomosis (2,3).

Recently a novel anastomotic configuration has been described (7). The Kono-S anastomosis is a combination of stapled and hand sewn techniques with 3 underlying principles;- mesentery preservation, a supporting column to prevent anastomotic distortion, and an anti-mesenteric anastomosis based on endoscopic observations that recurrence occurs initially on the mesenteric border (8) and that anti-mesenteric strictureplasty does not tend to lead to site specific recurrence (9). Several studies suggest this technique results in a dramatic reduction in surgical recurrence. However, a thorough systematic review of the literature is absent.

One particular aspect of the Kono-S anastomosis is preservation of the mesentery. A rationale based on the premise that this preserves vascular and nervous supply to the remaining resection margin (7). However, others feel the mesentery is the underlying driver

to the disease process (10) and a more radical resection of the mesentery is appropriate. Given the potential importance of the mesentery and the fact that mesenteric preservation is an integral part of the Kono-S technique, studies comparing the degree of mesenteric preservation for Crohn's disease where a Kono-S anastomosis may be considered are also relevant to a systematic review.

Our primary aim was to systematically review the literature on the safety and efficacy of the Kono-S anastomosis in reducing both endoscopic and surgical recurrence. A secondary aim was to systematically review the literature with regard to the degree of mesenteric preservation and its effect on recurrence.

Methods

This systematic review followed Cochrane guidelines (11) and the PRISMA statement (12). It was registered prospectively on the PROSPERO database (CRD4201913259).

Studies were included if they involved participants of any age who had undergone surgical resection for Crohn's disease. Interventions included a Kono-S anastomosis to restore bowel continuity after Crohn's resection as well as studies examining the degree of mesenteric preservation where a Kono-S anastomosis would have been appropriate. Where there were comparators, these included a standard anastomosis as defined by the study authors. For studies investigating radical mesenteric excision the comparator was mesenteric preservation.

Primary outcomes included surgical recurrence and endoscopic recurrence, defined by the Rutgeerts score. Secondary safety outcomes included anastomotic leakage, bowel obstruction, and surgical site infections.

Search strategy

A definitive search strategy of three main bibliographic databases was created in four stages: a scoping search was conducted in MEDLINE via PubMed to find related keywords, substitutes, and word variants related to the review theme. Keywords were further complemented and translated into free-text search terms. Then, a 'comprehensive pearl growing' (13) method using 16 known and topic-relevant studies (3, 7, 14-27) as 'pearls', was utilized. These studies were explored by title in MEDLINE and EMBASE to establish

the free-text search terms and indexed subject headings. Further, search strategies form these systematic reviews were checked for related search terms.

This identified the following MeSH themes; 'Crohn Disease', 'Crohn's disease', 'Anastomosis', 'Surgical', 'Digestive System Surgical Procedures', Kono-S anastomosis, 'Kono', 'Functional end-to-end', 'mesenter* adj3 resect*', 'mesenter* adj3 remov', 'mesenter* adj3 surg* Themes were consecutively entered in the MeSH function MEDLINE via OvidSP (1946 to March 2020), EMBASE via OvidSP (1974 to March 2020) the Web of Science (April 2000 to March 2020) and the Cochrane Central Register of Controlled Trials (CENTRAL) (to March 2020).

In addition the following were carried out

- search in ClinicalTrials.gov
- grey literature search using Google Scholar for the first 200 related citations screened (28). The term 'Kono S ' and 'mesenteric' in combination with one of the following terms was successively searched: 'anastomosis', 'Crohn's' 'resection', 'surgery', 'removal', 'sparing', 'intestine'
- hand search of the Journal of Crohn's and Colitis and meeting abstracts from the European Crohn's and Colitis Organization.
- all reference lists of relevant studies from of eligible articles.
- investigators of included records were contacted to ask about relevant completed, ongoing or planned studies and to provide any provisional results.

Study selection

Two reviewers (AA, SB) independently reviewed all identified abstracts. There was no restriction on the design of the studies included, setting, country of origin, type, status, language or date of publication. All relevant papers were obtained in full, evaluated and included only with the agreement of both reviewers. Disparities were resolved by consensus with arbitration by a third reviewer (DH). For multiple citations of the same study, the citation with the most complete data was included.

Data included

1) Study characteristics (study ID, type, country of origin, study period, inclusion/exclusion criteria).
2) Patient demographics (Numbers, age, risk factors, gender)
3) Description of interventions and comparators

4) Results for all pre-specified outcomes.

Risk of bias

Risk of bias was assessed and described in the narrative synthesis. For randomised controlled trials (RCT) the Cochrane (RoB2) assessment tool was used. For case series and cohort studies the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series was used**.** As there was only one RCT, we used the Centre for Evidence-Based Medicine Tool (CEBM), rather than GRADE, to understand risk of bias across studies.

Synthesis of results

Statistical synthesis of results was not possible as insufficient data were available. Instead a descriptive synthesis is presented. Predefined outcomes are presented in a summary of findings table and explained in the text.

Study results were described in order according to their evidence level, risk of bias, or methodological quality. Each outcome was explained in a separate paragraph for each comparison.

Results

Study selection

The process of study selection and literature search are shown in Figure 1. A total of 830 studies (excluding any duplicates) were identified for screening with 808 discarded on title and abstract alone. Twenty two citations underwent a full-text assessment with a further 11 records excluded. Of the 11 remaining included studies there were two incomplete RCTs (30, 32). All studies are summarised in table 1 but Michelassi (30) and Li (32) have been excluded from subsequent text and tables. A total of 896 patients were included.

Of the included studies, one was classified as an RCT (29), three were comparative studies with an historical control (7,14,23) and five were case series (15, 16, 19, 20, 31). Three studies originated from Japan (7,14,19) one each from Italy (29), USA (31) and Germany (15) and 3 were multinational (16,20,23). Follow-up ranged from 12-126 months (median 48 months). Participant characteristics are given in table 2. For the analysis involving the Kono-S anastomosis the studies involving a comparator included either end-to-end (14), side-to-side anastomoses (29) or both (7). For the analysis involving mesenteric excision, the comparator was preservation of the mesentery (division of the mesentery flush with the intestine).

Risk of bias

Table 3 and 4 shows the methodological quality and risk of bias of included studies. For the one RCT overall risk of bias was low, although there lack of clarity over blinding of outcome assessment. The overall methodological quality of the five case series studies was generally good as they were judged to have a low risk of bias in most domains. Two exceptions were Krane (31) and Fischera (20) because of insufficient information in published form. All except Kono (16) were deemed high risk for statistical analysis due to lack of detail. Additionally, follow up duration was deemed inadequate in order to detect surgical recurrence in three studies (15, 20, 31). The comparative studies with historical control were deemed low risk in most domains. However, again two of the three studies (7,14) were deemed high risk due to inadequate follow up to detect surgical recurrence.

For risk of bias across non-randomized studies, the highest level of evidence was level IV (case-series and poor quality cohort and case-control studies) for both the Kono-S and the degree of mesenteric excision analysis.

Synthesis of results

Table 5 summarises the primary outcomes of surgical and endoscopic recurrence.

Surgical recurrence after Kono-S anastomosis

In general, surgical recurrence was lower in the Kono-S anastomosis group compared with the standard anastomosis. Recurrence ranged from 0-3.4% after a median follow up of 35 months compared with 15-24.4% after a median of 60 months for the comparator anastomosis.

Endoscopic recurrence after Kono-S anastomosis

Endoscopic recurrence was defined using the Rutgeert's score. Patients with a score of i,1, or less have low-grade mucosal inflammation and are deemed at low risk of symptom recurrence (32). Endoscopic recurrence was significantly lower in the Kono-S group compared to the standard anastomosis group. Results from the RCT (29) showed a mean Rutgeerts score of i,1.05+/-1.06 at 18 months for the Kono-S group compared with i,2.30 +/-1.32 in the conventional group. A Rutgeerts score of above i,2, indicating a higher risk of symptomatic recurrence, was seen in 9/36 patients (25%) after a Kono S anastomosis

compared with 29/43 (67.4%) in the conventional anastomosis group. Long term data from one comparative historical control study (7) also showed a lower score for the Kono-S group but the mean score was above i,2 in this group. Conversely 2 case series suggest a median score of less than i,1 at 1 year (20) and 3 years post Kono-S (31).

Surgical recurrence after mesenteric excision

In one study (23), radical mesenteric excision resulted in surgical recurrence in 2.9% after 51 months follow up compared with 30% recurrence at 70 months follow up of an historical control group where the mesentery was preserved. There was no endoscopic assessment in this study.

Secondary outcomes

Table 6 shows the results of the secondary outcomes

Anastomotic leak

Three studies on the Kono-S anastomosis have sufficient data to allow a comparison of anastomotic leak. The RCT showed no leak in either group although one patient from the conventional group developed a fistula (suspicious for a contained leak) (29). In the Shimada study (14), anastomotic leak was significantly lower in Kono S group (5.1% vs 17.3%). There was evidence in favour of the Kono-S anastomosis from the Kono 2011 study (7), (0% leak Kono-S vs 4.1% comparator). Overall the leak rate for the Kono-S anastomosis was 1.8% (11/606) and 9.3% (20/214) for the control group.

Infection

Three Kono-S studies compared superficial site infection rates after Kono-S anastomosis with a control group (7,14,29). In the RCT the incidence was the same in both groups. In one comparative study superficial site infection was nearly doubled in the Kono-S group. Organ specific infection rates were also higher in the Kono-S group in this study (14). In the other comparative study (7) and the RCT (29) superficial site infection rates were the same in both groups. Deep site infection rates were similar in all studies. Overall the incidence of superficial surgical site infection was 7.1% (36/507) for Kono-S and 8.4% (18/214) for the comparator anastomosis. Incidence of deep infection was 5.7% (25/441) for Kono-S and

8.9% (19/214) for the comparator anastomosis. For organ specific infection the incidence was 8.5% (13/153) for Kono-S and 12.1% (17/141) for the comparator anastomosis.

Bowel obstruction

Intestinal obstruction (ileus) following Kono-S surgery was reported in six studies. Similar rates were seen in both the Kono-S and comparator groups. The overall incidence for the Kono-S group was 4.6% (23/501) and 7.0% (12/171) in the comparator group.

Discussion

The results of this systematic review suggest that that Kono-S anastomosis is associated with a very low incidence of surgical recurrence compared with mainly historical controls utilising 'standard' anastomotic techniques. The technique also reduces endoscopic recurrence, seen most convincingly in one RCT. It appears safe with the limited evidence suggesting that the anastomotic leak rate may be lower than seen with 'standard' anastomoses. Other complications are also low. Data on mesenteric preservation is limited to one historical control comparative study (23) suggesting more radical mesenteric excision results in lower recurrence with no comment on safety.

Some principles of the Kono-S anastomosis make anatomical and pathological sense and may explain this low surgical recurrence. It is recognised that recurrence occurs initially on the mesenteric border of an anastomosis, presumably related to the lack of collateral blood supply compared with the anti-mesenteric border. Mesenteric inflammation is more likely to compromise the end arterial blood supply of this bowel region whereas more extensive inflammation is required to compromise the 'dual' supply of the anti-mesenteric bowel (8). An anti-mesenteric anastomosis is therefore likely to delay any mesenteric border recurrence becoming symptomatic and requiring surgical intervention. This is particularly the case if the resection margin of the bowel is also away from the anastomosis as in the Kono-S. There are similarities between the Kono-S and a strictureplasty where again evidence suggests site specific surgical recurrence is low (9).

If the anti-mesenteric anastomosis is key to delaying surgical recurrence, it follows that endoscopic recurrence on the mesenteric border should be similar for the Kono-S and conventional anastomosis. However, studies including the highest quality evidence would

suggest this is not the case. Endoscopic recurrence is also substantially reduced (29). Why this should be remains unexplained. It is possible that this result is spurious despite being seen in an RCT. There is an element of subjectivity to the Rutgeert's endoscopic assessment tool and it is not possible to blind the endoscopist. However, if endoscopic recurrence is truly reduced it does have implications for on-going and future comparative trials as the primary outcome does not necessarily have to be surgical recurrence; prolonged follow up (>5 years), whilst preferable, may not be absolutely necessary.

There is less anatomical evidence for the supporting column aspect of the Kono-S anastomosis. It does make pathological sense as distortion of the anastomosis due to inflammation and fibrosis is frequently seen when carrying out redo surgery. The third principle of the Kono-S anastomosis is preservation of the mesentery, theoretically preserving the neuro-vascular supply of the resection margins. However, this contradicts another school of thought that it is the mesentery that drives recurrence. Coffey and Li have argued this extensively (10, 34). We were only able to identify one published study supporting the concept of radical mesenteric resection (23) and there are significant drawbacks to this study with inherent bias and little data about potential harm (10). Radical mesenteric resection is more challenging in the era of laparoscopic surgery, and could lead to more extensive bowel resection in order to avoid vascular compromise of resected edges. Despite this limited evidence for radical mesenteric resection other data indirectly supports the mesenteric disease concept. de Groof et al. suggested that the presence of mesorectum after proctectomy for Crohn's disease results in a higher incidence of perineal complications essentially due to the presence of the pro-inflammatory mesenteric tissue (35).

There are potential explanations for why both a Kono-S anastomosis with mesenteric preservation and radical mesenteric resection techniques might reduce surgical recurrence. Both aim to isolate the anastomosis as much as possible from the diseased mesentery. If true it may be that a combination of more radical mesenteric resection and a Kono-S type anastomotic configuration is the optimal technique. An alternative, less plausible, explanation (in our view) is the existence of different phenotypes of disease: a mesentery dependent phenotype that requires radical excision and a mesentery independent phenotype where radical mesenteric excision is unnecessary (36).

The strengths of this review are in the comprehensive and unrestricted systematic search strategy that included, with confidence, all relevant literature which was rigorously assessed. One other recent review only included 5 of the 9 published studies (excluding the one RCT), gave minimal comment on endoscopic recurrence and failed to assess risk of bias (37). However, both reviews have significant weaknesses in the low volume and mainly poor quality of the literature and many of the studies involve one particular author who advocates a specific technique. Some studies may include the same groups of participants. Nevertheless, our data does include one higher quality trial where, although follow up was too short for conclusions to be drawn about surgical recurrence, does mirror other studies that suggest endoscopic recurrence is reduced substantially with a Kono-S anastomosis. We have identified 2 quality trials that are ongoing and these may allow more robust conclusions to be drawn (30, 32).

Further trials are needed because the results so far compellingly suggest that surgery could be more effective. If recurrence rates are indeed reduced by the magnitude suggested, the technique will have profound implications in terms of the need for adjuvant medical therapy after surgery. Future trials should preferably include long term follow up for surgical recurrence and should probably be in the form of a 2 by 2 design to include the extent of mesenteric resection as well as anastomosis type. In the meantime, a well governed registry of cases may give useful data as to efficacy and safety of both the Kono-S anastomosis and mesenteric resection.

Conclusion

Whilst the level of evidence is mainly poor, there is a suggestion of a significant reduction in endoscopic and surgical recurrence with the Kono-S and the procedure appears safe. Whereas the Kono-S anastomosis includes mesenteric sparing one other study suggests that more radical excision of the mesentery may also reduce recurrence. On-going trials, of better quality, may confirm these data but further trials including the degree of mesenteric resection should be considered.

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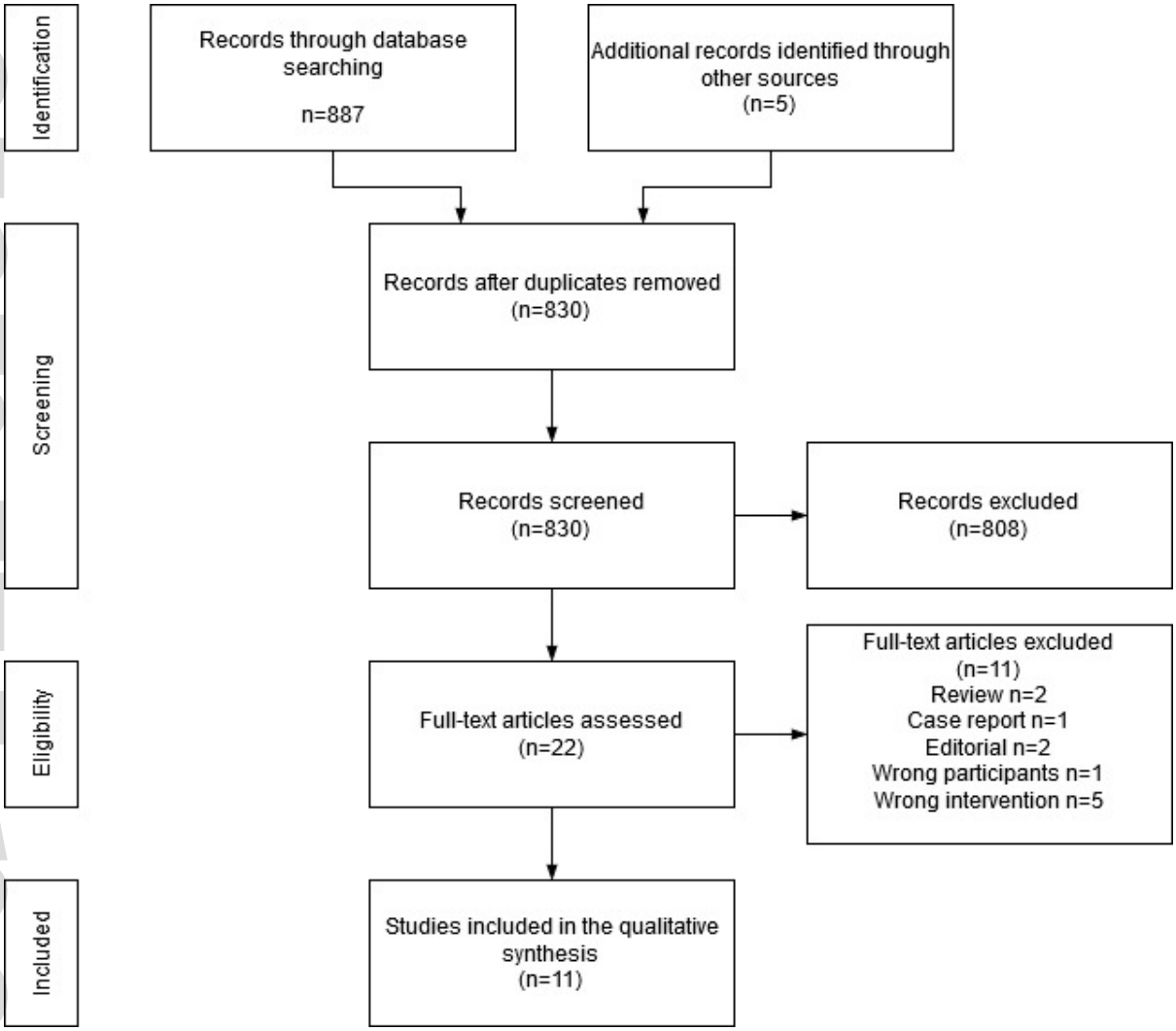


Figure 1. PRISMA Flow Diagram

First author, date, country	Study design	Intervention	Comparator	Study period (months)
Shimada 2018, Japan (14)	Comparative study with historical control	Kono-S anastomosis	End-to-end anastomosis	126
Kono 2011, Japan (7)	Comparative study with historical control	Kono-S anastomosis	end-to-end or side-to-side anastomosis	72
Seyfried 2019, Germany (15)	Case series	Kono-S anastomosis	-	19
Katsuno 2015, Japan (19)	Case series	Kono-S anastomosis	-	48
Krane 2015, USA (31)	Cases series	Kono-S anastomosis	-	34
Kono T 2015, Japan/USA (16)	Case series	Kono-S anastomosis	-	96
Fichera 2012, Japan/Italy (20)	Case series	Kono-S anastomosis	-	14
Luglio 2018, Italy (29)	Randomised clinical trial	Kono-S anastomosis	stapled side-to-side anastomosis	24
Michelassi USA (30)	Randomised clinical trial	Kono-S anastomosis	side-to-side anastomosis	Ongoing (expected Dec 2020)
Coffey 2018, Ireland/USA (23)	Comparative study with historical control	Extensive mesenteric resection	Mesenteric preservation	75
Li China (32)	Randomised clinical trial	Extensive mesenteric resection	Mesenteric preservation	Ongoing (expected Jan 2025)

Table 1. Study characteristics

Study ID	Total population Age	Number in each group		Age (yrs) median		Sex ratio (m:f)		Active smoking status	
1st comparison (Kono S)		Kono-S	Comparator	Kono-S	Comparator	-	Comparator	Kono-S	Comparator
Shimada (14)	215 37yrs (median)	117	98	39	34 (median)	84:33	74:24	-	-
Kono 2011(7)	142	69	73	31 (19-62)	28 (14–62)	57:12	58:15	25/69 (36%)	22/73 (30%)
Seyfried (15)	53 37yrs (median)	-	-	-	-	-	-	-	-
Katsuno (19)	30	30	-	34 (23-48)	-	22:8	-	9/30 (38%)	
Krane (31)	96	-	-	-	-	-	-	-	-
Kono 2015 (16)	171	Japan 144 USA 45	-	Japan 31 USA 32	-	Japan 110:34 USA21:22	-	Japan 35/135 (26 %) USA 12/36 (33 %)	-
Fichera (20)	46 33.5yrs (mean)	-	-	-	-	-	-	-	-
Luglio (29)	79 39yrs(mean)	36	43	34 (mean)	43 (mean)	18:18	22:21	11 (38%)	10 (27%)
2nd comparison (mesenteric resection)		Mesenteric resection	Mesenteric preservation	Mesenteric preservation	Mesenteric preservation	Mesenteric resection	Mesenteric preservation	Mesenteric resection	Mesenteric preservation

Coffey (23)	64	34	30	35.9 (mean)	37.7 (mean)	-	-	14/34 (47%)	18/30 (53%)

Table 2: Participant characteristics

Table 3 Risk of Bias assessment for randomized controlled trials (key + =low risk of bias, - = high risk of bias, ?= unclear)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Luglio (29)	+	+	?/-	-	+	+	+

Table 4 Overview of judgement of risk of bias and methodological quality of included studies

JBI critical appraisal checklist for case series	Kono 2015 [12]	Seyfried [15]	Fichera [10]	Katsuno [19]	Krane [20]	JBI critical appraisal checklist for Cohort Studies	Shimada [13]	Kono 2011 [21]	Coffey [22]
Were there clear criteria for inclusion in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the two groups similar and recruited from the same population?	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the exposures measured similarly to assign people to both exposed and unexposed groups? Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were confounding factors identified?	Yes	Unclear	Unclear
Did the case series have consecutive inclusion of participants?	Yes	No	Yes	Yes	Unclear	Were strategies to deal with confounding factors stated?	Unclear	No	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	Unclear	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	No	Yes	No	Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	No	Yes	Yes	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	No	Unclear	Yes	No	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	No	No	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	No	Yes	No	Were strategies to address incomplete follow up utilized?	No	No	Yes
Was statistical analysis appropriate?	Yes	No	No	No	No	Was appropriate statistical analysis used?	No	Yes	Yes

Table 5 Study results for surgical and endoscopic recurrence

Study ID	**Surgical Recurrence**				**Endoscopic recurrence (Mean Rutgeerts score)**			
	Kono S	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**	**Kono S**	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**
Shimada (14) vs. end-to-end	4/117 (3.4%)	47.3 (mean)	24/98 (24.4%)	99	-	-	-	-
Kono 2011 (7) vs. end-to-end or side-to-side	0/69	60	11/73 (15%)	60	2.6i	60	3.4i	60
Luglio (29) vs. side-to-side	0/36	24	2/43	24	1.05i	18	2.3i	18
Seyfried (15)	0/53	12	-	-	-		-	-
Katsuno (19)	0/30	35	-	-	-	-	-	-
Krane (31)	0/96	36	-		0.7i	36	-	-
Kono 2015(16)	Japan 2/144 (1.8 %) USA 0/29 (0%)	Japan 120 USA 32	-	-	Japan 3i USA 1i	Japan 60 USA 6	-	-
Fichera (20)	0/46 (0%)	14	-	-	0.7i	14	-	-
2nd comparison	**Excision of mesentery**		**Preservation of mesentery**		**Excision of mesentery**		**Preservation of mesentery**	
Coffey (23)	1/34 (2.9%)	51	9/30 (30%)	69.9 (mean)	-	-	-	-

Table 6 Study results for the review's secondary outcomes intervention versus comparators (where applicable).

Study ID	Anastomotic leak Kono S	Anastomotic leak control	Superficial SSI Kono S	Superficial SSI control	Deep SSI Kono S	Deep SSI control	Organ SSI Kono S	Organ SSI control	Bowel obstruction Kono S	Bowel obstruction control
Shimada (14)	6/117 (5.1%)	17/98 (17.3%)	15/117 (12.8%)	6/98 (6.1%)	17/117 (14.5%)	17/98 (17.4%)	13/117 (11.1%)	17/98 (17.4%)	13/117 (11.1%)	11/98 (12.2%)
Seyfried (15)	1/ 53 (1.8%)	-	-	-	-	-	-	-	-	-
Luglio (29)	0/36	0/43 (one fistula)	4/36 (11.1%)	6/43 (13.9%)	1/36 (2.7%)	1/43 (2.3%)	0/36	0/43	1/36 (2.7%)	1/43 (2.3%)
Coffey (23)	-	-	-	-	-	-	-	-	-	-
Krane (31)	1/ 96 (1%)	-	5/96 (5%)	-	-	-	-	-	5/96 (5%)	-
Katsuno (19)	-	-	-	-	2/30 (6.6%)	-	-	-	1/30 (3.3%)	-
Kono 2015 (16)	Japan 1/144 (0.7 %) USA 1/45 (2.3 %)	-	Japan 8/144 (5.6 %) USA 2/45 (4.7 %)	-	Japan 4/144 (2.8 %) USA 1/45 (2.3 %)	-	-	-	Japan 3/144 (2.1 %) USA 1/45 (2.3 %)	-
Fichera (20)	1/46 (2.1%)	-	-	-	-	-	-	-	-	-

Kono 2011 (7)	0/69 (0%)	3/73 (1.2%)	2/69 (2.3%)	2/73 (2.7%)	0/69 (0%)	1/73 (1.36%)	-	-	1/69 (1.1%)	1/73 (1.36%)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11 table 4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11 table 4-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

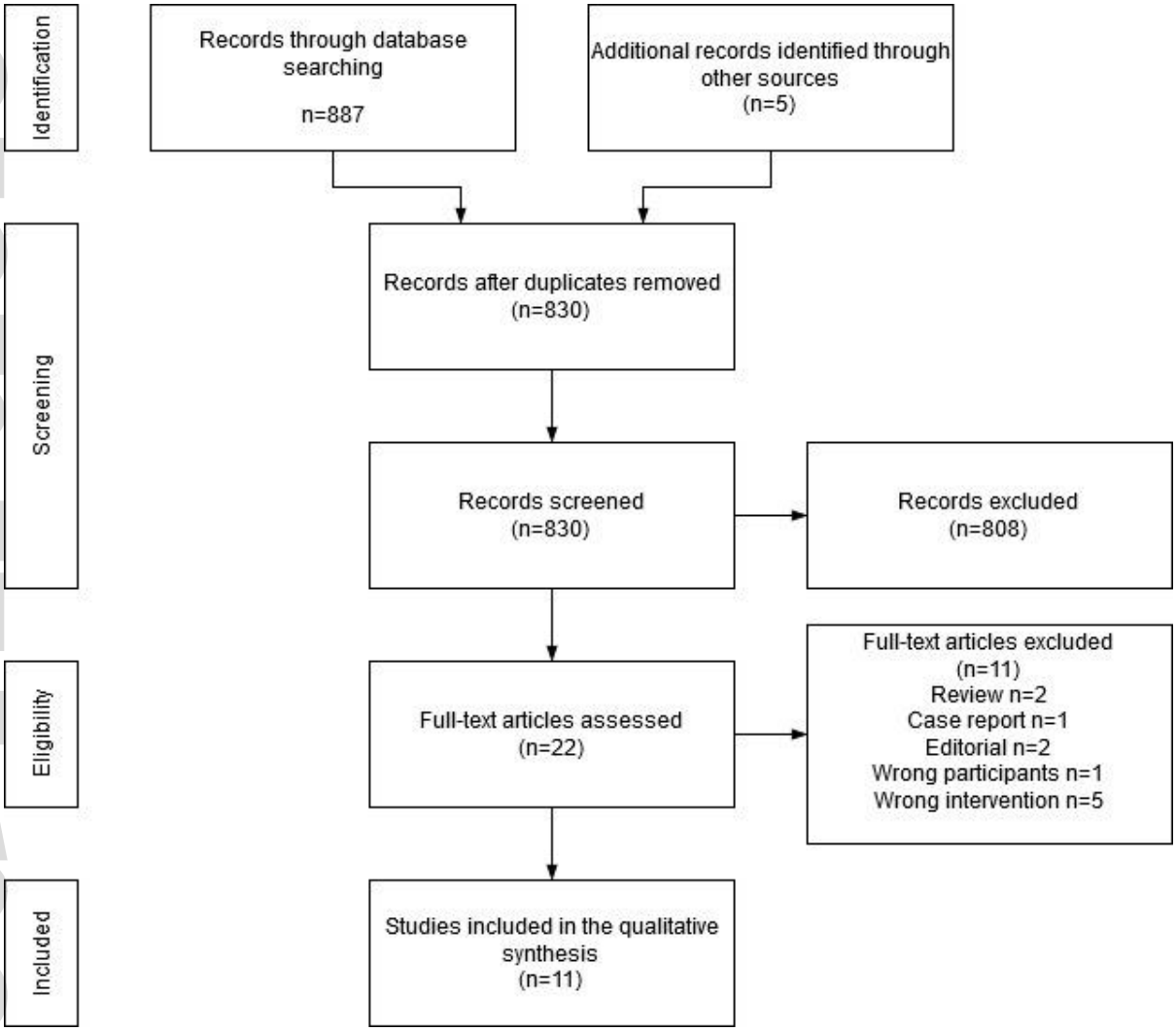


Figure 1. PRISMA Flow Diagram

First author, date, country	Study design	Intervention	Comparator	Study period (months)
Shimada 2018, Japan (14)	Comparative study with historical control	Kono-S anastomosis	End-to-end anastomosis	126
Kono 2011, Japan (7)	Comparative study with historical control	Kono-S anastomosis	end-to-end or side-to-side anastomosis	72
Seyfried 2019, Germany (15)	Case series	Kono-S anastomosis	-	19
Katsuno 2015, Japan (19)	Case series	Kono-S anastomosis	-	48
Krane 2015, USA (31)	Cases series	Kono-S anastomosis	-	34
Kono T 2015, Japan/USA (16)	Case series	Kono-S anastomosis	-	96
Fichera 2012, Japan/Italy (20)	Case series	Kono-S anastomosis	-	14
Luglio 2018, Italy (29)	Randomised clinical trial	Kono-S anastomosis	stapled side-to-side anastomosis	24
Michelassi USA (30)	Randomised clinical trial	Kono-S anastomosis	side-to-side anastomosis	Ongoing (expected Dec 2020)
Coffey 2018, Ireland/USA (23)	Comparative study with historical control	Extensive mesenteric resection	Mesenteric preservation	75
Li China (32)	Randomised clinical trial	Extensive mesenteric resection	Mesenteric preservation	Ongoing (expected Jan 2025)

Table 1. Study characteristics

Study ID	Total population Age	Number in each group		Age (yrs) median		Sex ratio (m:f)		Active smoking status	
1st comparison (Kono S)		Kono-S	Comparator	Kono-S	Comparator	-	Comparator	Kono-S	Comparator
Shimada (14)	215 37yrs (median)	117	98	39	34 (median)	84:33	74:24	-	-
Kono 2011(7)	142	69	73	31 (19-62)	28 (14–62)	57:12	58:15	25/69 (36%)	22/73 (30%)
Seyfried (15)	53 37yrs (median)	-	-	-	-	-	-	-	-
Katsuno (19)	30	30	-	34 (23-48)	-	22:8	-	9/30 (38%)	
Krane (31)	96	-	-	-	-	-	-	-	-
Kono 2015 (16)	171	Japan 144 USA 45	-	Japan 31 USA 32	-	Japan 110:34 USA21:22	-	Japan 35/135 (26 %) USA 12/36 (33 %)	-
Fichera (20)	46 33.5yrs (mean)	-	-	-	-	-	-	-	-
Luglio (29)	79 39yrs(mean)	36	43	34 (mean)	43 (mean)	18:18	22:21	11 (38%)	10 (27%)
2nd comparison (mesenteric resection)		Mesenteric resection	Mesenteric preservation	Mesenteric preservation	Mesenteric preservation	Mesenteric resection	Mesenteric preservation	Mesenteric resection	Mesenteric preservation

Coffey (23)	64	34	30	35.9 (mean)	37.7 (mean)	-	-	14/34 (47%)	18/30 (53%)

Table 2: Participant characteristics

Table 3 Risk of Bias assessment for randomized controlled trials (key + =low risk of bias, - = high risk of bias, ?= unclear)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Luglio (29)	+	+	?/-	-	+	+	+

Table 4 Overview of judgement of risk of bias and methodological quality of included studies

JBI critical appraisal checklist for case series	Kono 2015	Seyfried	Fichera	Katsuno	Krane	JBI critical appraisal checklist for Cohort Studies	Shimada	Kono	Coffey
Were there clear criteria for inclusion in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the two groups similar and recruited from the same population?	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the exposures measured similarly to assign people to both exposed and unexposed groups? Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were confounding factors identified?	Yes	Unclear	Unclear
Did the case series have consecutive inclusion of participants?	Yes	No	Yes	Yes	Unclear	Were strategies to deal with confounding factors stated?	Unclear	No	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	Unclear	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	No	Yes	No	Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	No	Yes	Yes	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	No	Unclear	Yes	No	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	No	No	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	No	Yes	No	Were strategies to address incomplete follow up utilized?	No	No	Yes
Was statistical analysis appropriate?	Yes	No	No	No	No	Was appropriate statistical analysis used?	No	Yes	Yes

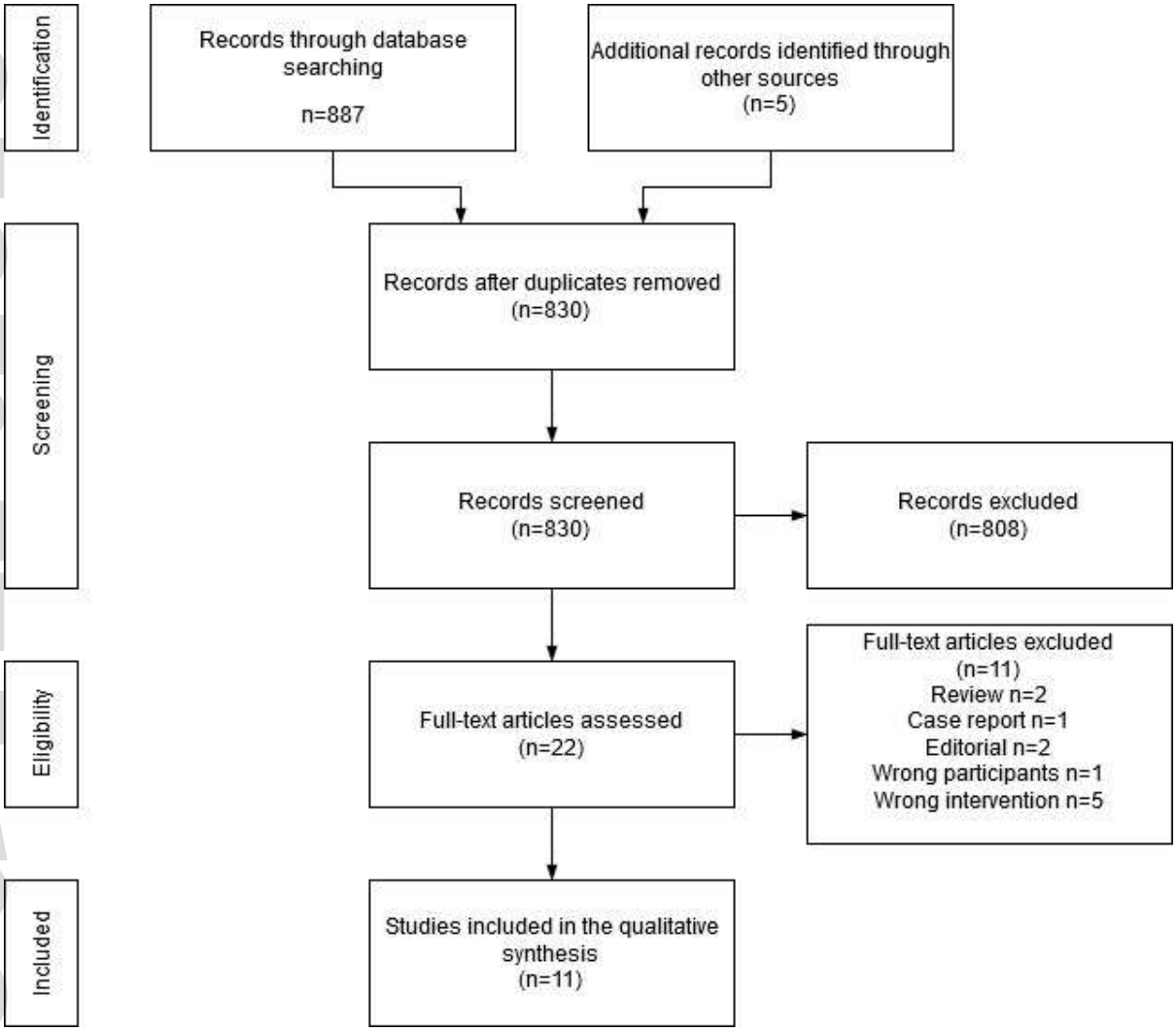
Table 5 Study results for surgical and endoscopic recurrence

Study ID	**Surgical Recurrence**				**Endoscopic recurrence (Mean Rutgeerts score)**			
	Kono S	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**	**Kono S**	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**
Shimada (14) vs. end-to-end	4/117 (3.4%)	47.3 (mean)	24/98 (24.4%)	99	-	-	-	-
Kono 2011 (7) vs. end-to-end or side-to-side	0/69	60	11/73 (15%)	60	2.6i	60	3.4i	60
Luglio (29) vs. side-to-side	0/36	24	2/43	24	1.05i	18	2.3i	18
Seyfried (15)	0/53	12	-	-	-		-	-
Katsuno (19)	0/30	35	-	-	-	-	-	-
Krane (31)	0/96	36	-		0.7i	36	-	-
Kono 2015(16)	Japan 2/144 (1.8 %) USA 0/29 (0%)	Japan 120 USA 32	-	-	Japan 3i USA 1i	Japan 60 USA 6	-	-
Fichera (20)	0/46 (0%)	14	-	-	0.7i	14	-	-
2nd comparison	**Excision of mesentery**		**Preservation of mesentery**		**Excision of mesentery**		**Preservation of mesentery**	
Coffey (23)	1/34 (2.9%)	51	9/30 (30%)	69.9 (mean)	-	-	-	-

Table 6 Study results for the review's secondary outcomes intervention versus comparators (where applicable).

Study ID	Anastomotic leak Kono S	Anastomotic leak control	Superficial SSI Kono S	Superficial SSI control	Deep SSI Kono S	Deep SSI control	Organ SSI Kono S	Organ SSI control	Bowel obstruction Kono S	Bowel obstruction control
Shimada (14)	6/117 (5.1%)	17/98 (17.3%)	15/117 (12.8%)	6/98 (6.1%)	17/117 (14.5%)	17/98 (17.4%)	13/117 (11.1%)	17/98 (17.4%)	13/117 (11.1%)	11/98 (12.2%)
Seyfried (15)	1/ 53 (1.8%)	-	-	-	-	-	-	-	-	-
Luglio (29)	0/36	0/43 (one fistula)	4/36 (11.1%)	6/43 (13.9%)	1/36 (2.7%)	1/43 (2.3%)	0/36	0/43	1/36 (2.7%)	1/43 (2.3%)
Coffey (23)	-	-	-	-	-	-	-	-	-	-
Krane (31)	1/ 96 (1%)	-	5/96 (5%)	-	-	-	-	-	5/96 (5%)	-
Katsuno (19)	-	-	-	-	2/30 (6.6%)	-	-	-	1/30 (3.3%)	-
Kono 2015 (16)	Japan 1/144 (0.7 %) USA 1/45 (2.3 %)	-	Japan 8/144 (5.6 %) USA 2/45 (4.7 %)	-	Japan 4/144 (2.8 %) USA 1/45 (2.3 %)	-	-	-	Japan 3/144 (2.1 %) USA 1/45 (2.3 %)	-
Fichera (20)	1/46 (2.1%)	-	-	-	-	-	-	-	-	-

Kono 2011 (7)	0/69 (0%)	3/73 (1.2%)	2/69 (2.3%)	2/73 (2.7%)	0/69 (0%)	1/73 (1.36%)	-	-	1/69 (1.1%)	1/73 (1.36%)



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Michelassi USA (30)	Randomised clinical trial	Kono-S anastomosis	side-to-side anastomosis	Ongoing (expected Dec 2020)
Coffey 2018, Ireland/USA (23)	Comparative study with historical control	Extensive mesenteric resection	Mesenteric preservation	75
Li China (32)	Randomised clinical trial	Extensive mesenteric resection	Mesenteric preservation	Ongoing (expected Jan 2025)

Table 1. Study characteristics

Table 2: Participant characteristics

Study ID	Total population Age	Number in each group		Age (yrs) median		Sex ratio (m:f)		Active smoking status	
1st comparison (Kono S)		Kono-S	Comparator	Kono-S	Comparator	-	Comparator	Kono-S	Comparator
Shimada (14)	215 37yrs (median)	117	98	39	34 (median)	84:33	74:24	-	-
Kono 2011(7)	142	69	73	31 (19-62)	28 (14–62)	57:12	58:15	25/69 (36%)	22/73 (30%)
Seyfried (15)	53 37yrs (median)	-	-	-	-	-	-	-	-
Katsuno (19)	30	30	-	34 (23-48)	-	22:8	-	9/30 (38%)	
Krane (31)	96	-	-	-	-	-	-	-	-
Kono 2015 (16)	171	Japan 144 USA 45	-	Japan 31 USA 32	-	Japan 110:34 USA21:22	-	Japan 35/135 (26 %) USA 12/36 (33 %)	-
Fichera (20)	46 33.5yrs (mean)	-	-	-	-	-	-	-	-
Luglio (29)	79 39yrs(mean)	36	43	34 (mean)	43 (mean)	18:18	22:21	11 (38%)	10 (27%)
2nd comparison (mesenteric resection)		Mesenteric resection	Mesenteric preservation	Mesenteric preservation	Mesenteric preservation	Mesenteric resection	Mesenteric preservation	Mesenteric resection	Mesenteric preservation
Coffey (23)	64	34	30	35.9 (mean)	37.7 (mean)	-	-	14/34 (47%)	18/30 (53%)

Table 3 Risk of Bias assessment for randomized controlled trials (key + =low risk of bias, - = high risk of bias, ?= unclear)

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Luglio (29)	+	+	?/-	-	+	+	+

Table 4 Overview of judgement of risk of bias and methodological quality of included studies

JBI critical appraisal checklist for case series	Kono 2015 (16)	Seyfried (15)	Fichera (20)	Katsuno (19)	Krane (21)	JBI critical appraisal checklist for Cohort Studies	Shimada (14)	Kono 2011(7)	Coffey (23)
Were there clear criteria for inclusion in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the two groups similar and recruited from the same population?	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were the exposures measured similarly to assign people to both exposed and unexposed groups? Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Unclear	Yes	Yes	Were confounding factors identified?	Yes	Unclear	Unclear
Did the case series have consecutive inclusion of participants?	Yes	No	Yes	Yes	Unclear	Were strategies to deal with confounding factors stated?	Unclear	No	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	Yes	Yes	Unclear	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	No	Yes	No	Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	No	Yes	Yes	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	No	Unclear	Yes	No	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	No	No	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	No	Yes	No	Were strategies to address incomplete follow up utilized?	No	No	Yes
Was statistical analysis appropriate?	Yes	No	No	No	No	Was appropriate statistical analysis used?	No	Yes	Yes

Table 5 Study results for surgical and endoscopic recurrence

Study ID	**Surgical Recurrence**				**Endoscopic recurrence (Mean Rutgeerts score)**			
	Kono S	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**	**Kono S**	**Follow up Months (median)**	**Comparator**	**Follow up Months (median)**
Shimada (14) vs. end-to-end	4/117 (3.4%)	47.3 (mean)	24/98 (24.4%)	99	-	-	-	-
Kono 2011 (7) vs. end-to-end or side-to-side	0/69	60	11/73 (15%)	60	2.6i	60	3.4i	60
Luglio (29) vs. side-to-side	0/36	24	2/43	24	1.05i	18	2.3i	18
Seyfried (15)	0/53	12	-	-	-		-	-
Katsuno (19)	0/30	35	-	-	-	-	-	-
Krane (31)	0/96	36	-		0.7i	36	-	-
Kono 2015(16)	Japan 2/144 (1.8 %) USA 0/29 (0%)	Japan 120 USA 32	-	-	Japan 3i USA 1i	Japan 60 USA 6	-	-
Fichera (20)	0/46 (0%)	14	-	-	0.7i	14	-	-
2nd comparison	**Excision of mesentery**		**Preservation of mesentery**		**Excision of mesentery**		**Preservation of mesentery**	
Coffey (23)	1/34 (2.9%)	51	9/30 (30%)	69.9 (mean)	-	-	-	-

Table 6 Study results for the review's secondary outcomes intervention versus comparators (where applicable).

Study ID	Anastomotic leak Kono S	Anastomotic leak control	Superficial SSI Kono S	Superficial SSI control	Deep SSI Kono S	Deep SSI control	Organ SSI Kono S	Organ SSI control	Bowel obstruction Kono S	Bowel obstruction control
Shimada (14)	6/117 (5.1%)	17/98 (17.3%)	15/117 (12.8%)	6/98 (6.1%)	17/117 (14.5%)	17/98 (17.4%)	13/117 (11.1%)	17/98 (17.4%)	13/117 (11.1%)	11/98 (12.2%)
Seyfried (15)	1/ 53 (1.8%)	-	-	-	-	-	-	-	-	-
Luglio (29)	0/36	0/43 (one fistula)	4/36 (11.1%)	6/43 (13.9%)	1/36 (2.7%)	1/43 (2.3%)	0/36	0/43	1/36 (2.7%)	1/43 (2.3%)
Coffey (23)	-	-	-	-	-	-	-	-	-	-
Krane (31)	1/ 96 (1%)	-	5/96 (5%)	-	-	-	-	-	5/96 (5%)	-
Katsuno (19)	-	-	-	-	2/30 (6.6%)	-	-	-	1/30 (3.3%)	-
Kono 2015 (16)	Japan 1/144 (0.7 %) USA 1/45 (2.3 %)	-	Japan 8/144 (5.6 %) USA 2/45 (4.7 %)	-	Japan 4/144 (2.8 %) USA 1/45 (2.3 %)	-	-	-	Japan 3/144 (2.1 %) USA 1/45 (2.3 %)	-
Fichera (20)	1/46 (2.1%)	-	-	-	-	-	-	-	-	-
Kono 2011 (7)	0/69 (0%)	3/73 (1.2%)	2/69 (2.3%)	2/73 (2.7%)	0/69 (0%)	1/73 (1.36%)	-	-	1/69 (1.1%)	1/73 (1.36%)