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A systematic review of pre, peri and postoperative factors and their implications for the lengths of resected bowel segments in patients with Crohn's disease

Kristoffer Hendel [a, *], Sebastian Kjærgaard [a], Alaa El-Hussuna [b]

[a] University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen N, Denmark
[b] Aalborg University Hospital, Klinik Kirurgi og Kræftbehandling, Hobrovej 18-22, 9100 Aalborg, Denmark

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ABSTRACT

Aim: Several pre, peri and postoperative factors may have implications for the lengths of resected small bowel segments in Crohn's disease patients. It might also affect patient outcome. We reviewed the current literature on factors and their implications for the lengths of resected small bowel segments and possible correlations with postoperative outcome.
Method: Searches were independently engineered by the authors and a research-librarian in MEDLINE and OVID databases using PubMed and EMBASE engines in compliance with PRISMA recommendations. All original articles, reviews and guidelines published in the period of 1985–2016 with last search date 13th of February 2016 on bowel resection in Crohn's disease patients were assessed for inclusion.
Results: We identified 52 studies for synthesis. *Preoperative*: Perforation as indication for surgery and increased visceral obesity may be factors resulting in longer lengths of resected small bowel segments. Administration of total parenteral nutrition might reduce resection lengths. *Perioperative*: No difference in resection lengths in elective versus acute surgery, laparoscopic versus open approaches or in case of intra-operative blood transfusions. Stapled anastomoses might conserve more bowel than sutured ones. *Postoperative*: The lengths of the resected small bowel segments most likely have no impact on recurrence rates.
Conclusion: No pre, peri or postoperative factors were found to have definitive implications for the lengths of resected small bowel segments. Correlation between the lengths of resection and recurrence is weak.

1. Introduction

Crohn's disease (CD) is becoming more prevalent [1] with continually higher incidence rates argued to be 3.1 to 14.6 cases per 100,000 person-years [2,3]. While both medical and surgical treatment of CD is improving, the disease still presents itself with increased morbidity and an increasing burden of disease [4]. Surgical intervention has been shown to still be required in up to two-thirds of CD patients [5]. Furthermore, early surgery can be a factor in better patient outcome [4]. While it appears that strictureplasty procedures for CD have become an accepted treatment option, small bowel (SB) resection is still widely used and considered the only option in penetrative disease phenotypes and long affected segments [6–8]. Pre, peri and postoperative factors may have implications for the lengths of resected small bowel segments in Crohn's disease patients. There are a limited number of studies on the subject with conflicting reports [9].

Repeated bowel resections can lead to intestinal failure [10], yet it appears there is a lack of quality registries and statistical data on factors that might lead to resection of longer SB segments. Although two thirds or more of CD patients undergo repeated bowel resection during a life-time [9,11], measurements and documentation of the resected bowel segments remain scarce; this makes planning for additional resections more difficult.

A recent shift in favour of laparoscopic surgical approaches - and even a single port approach - has naturally demanded research comparing the laparoscopic versus open approaches in CD-related surgery [12–14]. A recent review on this includes only a single article reporting on a possible correlation between the two approaches and lengths of the resected segments [15].

While it has been argued that lengths of resection margins do

* Corresponding author. H.P. Ørums Gade 42, 2100 Copenhagen Ø, Denmark.
E-mail addresses: hendel@me.com (K. Hendel), sebastian@kjaergaard.cc (S. Kjærgaard), alaa@itu.dk (A. El-Hussuna).

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not affect surgical recurrence [16–18], a newer study suggests that the use of correct resection margins is crucial to avoid recurrence [19]. This further strengthens the need for data on the lengths of resected SB segments in CD patients, especially when margins can be as low as 2 cm [20].

Objectives: To review the current literature for pre, peri and postoperative factors and their implications for the lengths of resected SB segments and possible correlations with postoperative outcome.

2. Materials and methods

Search strategy: (KH) executed a broad-spectrum search strategy (see below) in the MEDLINE and EMBASE records with no limits using the Ovid EMBASE and PubMed search engines. An external research-assistant librarian repeated the search to ensure validity, integrity and robustness of the search strategy. All articles were screened for title and abstract by two authors (KH and SK), and select articles were included for review based on full-text assessments by two authors (KH and SK). All authors participated in the final selection of included studies (KH, SK and AE). Fig. 1 shows our PRISMA flowchart.

(KH) performed data extraction and (AE) re-checked it. Differences were resolved by discussion.

OVID EMBASE and OVID MEDLINE search by authors:

1. crohn* OR inflammatory bowel disease OR IBD.all fields.
2. resection OR resected OR small bowel length OR short bowel OR segment.keyword.
3. 1 AND 2

Yield: 336 on February 13th, 2016.

PubMed MEDLINE search by authors:

((crohn* OR inflammatory bowel disease OR IBD) AND length of resection).all fields.

Yield: 383 on February 13th, 2016.

In total 719 results of which 63 were duplicates resulting in a yield of 656 unique results for the internal searches.

PubMed MEDLINE search by external librarian:

((((((“Perioperative Period”[Mesh]) OR “Risk Factors”[Mesh]) OR “complications” [Subheading]) OR complication*[tw]) OR risk factor*[tw])) AND ((((((((resection*[tw] OR resected*[tw])) OR “Digestive System Surgical Procedures”[Mesh]) OR (“General Surgery”[Mesh] OR “surgery” [Subheading])) OR (surgery[tw] OR surgical[tw]))) AND (((“Intestine, Small”[Mesh]) OR (small bowel*[tw] OR short bowel*[tw])) OR (small intestine*[tw] OR short intestine*[tw]))) AND (((crohn*[tw] or Inflammatory Bowel Disease*[tw] or IBD[tw])) OR “Crohn Disease”[Mesh]))

Yield: 2010 results on February 13th 2016.

2.1. Inclusion criteria

All original articles, reviews and guidelines published in the period of 1985–2016 with last search date 13th February 2016 about bowel resection in CD patients were included. Inclusion criteria for full-text evaluation:

1. Studies/articles reporting the effect of pre, peri, and postoperative factors on the lengths of resected SB segments.
2. Studies/articles reporting the effect of resected segment length on short- and long-term postoperative outcome.

We retrieved these articles for full-length text reading and their reference lists screened for other relevant articles.

2.2. Exclusion criteria

We excluded articles that did not meet the above stated criteria as well as case reports, editorials, letters to editor, conference abstracts and articles where full text was not available.

2.3. Assessment of risk of bias

The quality of bias control in the included observational studies was assessed using the Newcastle-Ottawa scale (NOS). All the included studies present a high risk of bias.

3. Results

We included 52 articles in this review, please see Fig. 1 for a PRISMA flow-diagram. The following subsections and paragraphs present our findings in segments divided by types of comparisons made. Any article may appear in two or more segments if applicable. It was not possible to conduct meta-analysis of the included studies because of heterogeneity in outcome measurements, methodology and reporting of outcome measurements. An overview of the following results is available as Table 1.

3.1. Preoperative factors

3.1.1. Studies comparing the lengths of resected SB segments and different preoperative factors [11,21–28]

One study found that structuring versus fistulising indications for surgery does not affect the lengths of the resections [21]. Another study found the difference based on perforating versus stenotic indications to be of significance, the former patient group having more lengths resected $p < 0.001$ [22]. Both studies lack adjustment for other factors that might influence resection lengths. Another factor that shows an effect on the lengths of resected SB segments is *visceral obesity* (BMI and CT-scan evaluation); longer SB segments were resected in patients with visceral obesity VFA $\geq$ 130 cm squared, $p = 0.04$ tested in univariate analysis. The results were not adjusted for other factors [23]. This appears, however, not to be related to preoperative lipid profile after adjusting for confounding factors in multivariate analysis [24]. Furthermore, the post-surgical lipid profile also seems to be unaffected [28].

Preoperative medical treatment and the lengths of resected SB segments: One study showed no link between the use of a preoperative immunosuppressant and the lengths of the resected segments $p = 0.33$ in univariate analysis [22]. However, with the added cost of longer lengths of stay, total parenteral nutrition (TPN) administration appears to reduce the lengths of resected SB segments in patients undergoing ileo-colic resection $p < 0.001$, and near-significantly in patients undergoing segmental SB resection $p < 0.09$ when tested in multivariate analyses [25].

While initial SB lengths and postoperative residual SB lengths appear not to influence the likelihood of recurrence [26,27], one study found a correlation between preoperative extent of diseased segments and extent at recurrence $r = 0.7$, $p < 0.001$ [11]. This result has however not been adjusted for other factors.

3.2. Perioperative factors

3.2.1. Studies comparing the lengths of resected SB segments in patients undergoing elective vs acute surgery [10,22,29]

A single-centre retrospective study found no difference in the lengths of resected SB segments based on whether the surgery was elective or acute $p = 0.14$ [29]. Another retrospective study analysed patients with intestinal failure and found in agreement with this,

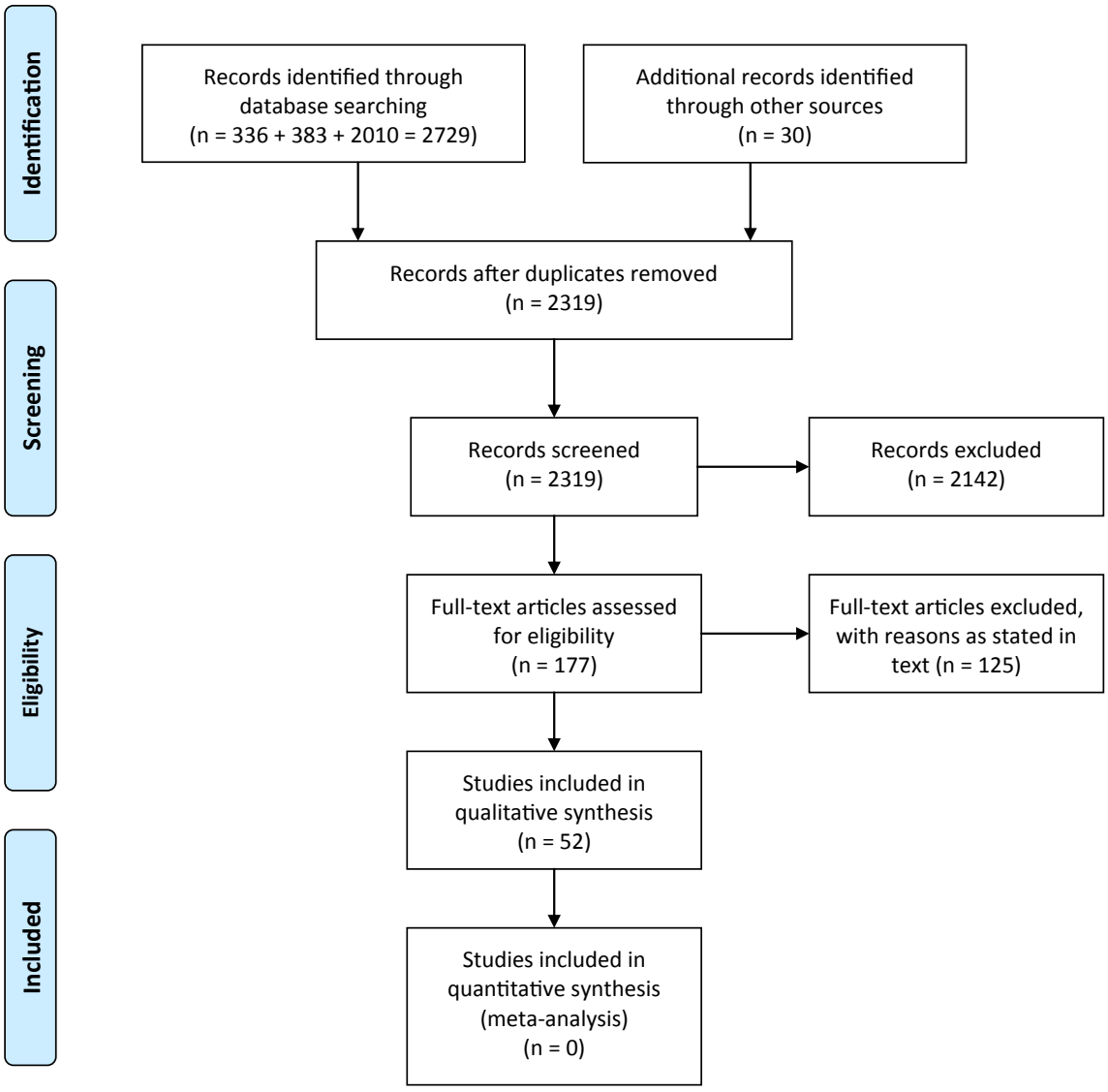

Fig. 1. (a) first picture; (b) second picture.

that residual lengths of SB were the same regardless of elective vs acute indication for surgery $p < 0.001$ [10]. These findings were cemented in a multi-centre retrospective study that showed no difference $p = 0.07$ [22]. All three studies failed to provide multivariate analyses.

3.2.2. Studies investigating the lengths of resected SB segments, surgical approach, anastomosis type and blood transfusion [12–14,30–39]

Several retrospective studies have assessed the influence of open versus laparoscopic approach on the lengths of resected bowel segments and found no difference [13,14,30]. However, a Hungarian study [40] suggests that laparoscopic access resulted in shorter lengths of resected SB segments $p = 0.03$. None of these studies made correlation analyses. Two prospective studies failed to provide thorough statistical data [12,31], but came to the same conclusions as a randomised study finding no difference in multivariate analyses [32]. A systematic review also found no difference [39]. The type of laparoscopic approach whether it being a single-port or multi-port approach, had no effect on the lengths of the resected segments [33].

The only available research about anastomosis type is a retrospective study showing that shorter lengths of SB segments were resected using a stapled anastomosis vs a sutured one $p = 0.04$ [38].

Perioperative blood transfusion appears to have no effect on SB resection lengths in a retrospective study using multivariate analyses [34]. This is in agreement with a later meta-analysis [35].

3.3. Postoperative outcome

3.3.1. Studies investigating the length of resected SB segments and correlation with recurrence [9,11,17,18,26,27,34,35,39,41–64,65]

Although symptomatic recurrence correlated to preoperative affected segment length $p = 0.001$ in one retrospective study [11], the finding could not be reproduced in two prospective studies [26,27]. None of the studies above are adjusted for possible confounders in multivariate analyses.

Surgical recurrence: Two retrospective studies on surgical recurrence [41,42] found that more extensive resections correlate with lower rates of recurrence. While the former does not provide any statistical data, the latter reported statistically significant results at $p < 0.05$ based on 45 patients that had resection of >25 cm

Table 1
Studies presenting pre, peri and postoperative factors and their implications on the lengths of resected small bowel segments in patients with Crohn's disease.

Author(s)	Year	Type	No. of patients or (articles included in review)	Follow-up in months	Parameters	Results of univariate analyses	Results of multi-variate analyses
Comparing the lengths of resected SB segments or outcome in grouping elective vs acute surgery							
Brihier et al. [29]	2005	Retrospective	162	N/A	Difference	$p = 0.14$	N/A
Elriz et al. [22]	2011	Retrospective Multi-centre	38	N/A	Difference	$p = 0.07$	N/A
Agwunobi et al. [10]	2001	Retrospective	41	6–324	No difference	$p < 0.001$	None
Comparing the lengths of resected SB segments and recurrence to different preoperative factors							
Cayci et al. [21]	2015	Retrospective	74	N/A	Stricture vs fistula	$p = 0.91$	N/A
Elriz et al. [22]	2011	Retrospective	38	N/A	Medical treatment/Perforation vs stenosis	Ns/$p < 0.001$	None
Ding et al. [23]	2016	Retrospective	164	N/A	Visceral Fat Area correlated to increased SB resection lengths	$p = 0.003$	None
Romanato et al. [24]	2008	Prospective	24	N/A	Lipid profile correlation to lengths of resected SB segments		ns
D'Haens et al. [11]	1995	Retrospective	23	32–242	Extent of disease correlation with symptomatic recurrence	$p = 0.001$	None
Glehen et al. [26]	2003	Prospective	93	24–216	Residual SB length correlation with recurrence	ns	N/A
Nordgren et al. [27]	1997	Prospective	155	192 (mean)	Initial SB length correlation with recurrence	ns	N/A
Lashner et al. [25]	1989	Prospective	17	N/A	TPN therapy correlation with resection lengths		$p < 0.09$
Comparing the lengths of resected segments and recurrence to perioperative factors by type of surgery, anastomosis and use of blood transfusion							
Bemelman et al. [13]	2000	Retrospective	78	N/A	Open vs laparoscopy	ns	N/A
Diamond et al. [14]	2001	Retrospective	12	N/A	Open vs laparoscopy	ns	N/A
Eshuis et al. [30]	2009	Retrospective	78	N/A	Open vs laparoscopy-assisted	ns	N/A
Benoist et al. [12]	2003	Prospective	56	N/A	Open vs laparoscopy	ns	N/A
Sica et al. [31]	2008	Prospective	28	N/A	Open vs laparoscopy	ns	N/A
Horvath et al. [40]	2014	Prospective	133	N/A	Open > laparoscopy	$p = 0.03$	None
Dunker et al. [32]	2003	RCT	34	N/A	Open vs laparoscopy		ns
Yamamoto et al. [39]	2013	Review	(17)	N/A	Open vs laparoscopy	No difference	
Yamamoto et al. [38]	1999	Retrospective	123	N/A	Stapled < sutured anastomosis	$p = 0.04$	None
Gardenbroek et al. [33]	2013	Prospective	63	N/A	Single-port vs multi-port	ns	N/A
Silvis et al. [34]	1994	Retrospective	148	56 (median)	Correlation to blood-transfusion		ns
Hollaar et al. [35]	1995	Meta-analysis	(7) 622	N/A	Correlation to blood-transfusion		ns
Stebbing et al. [36]	1995	Retrospective	52	1–182	Lengths of resection correlation to Strictureplasty vs strictureplasty and resection		ns
Yamamoto et al. [37]	2007	Review	(8)		Recurrence correlation to strictureplasty vs resection	False	
Comparing the lengths of resected SB segments to recurrence and other defined outcomes							
Atwell et al. [42]	1965	Retrospective	117	0–240	Lengths of resected SB segments in correlation to recurrence	No statistics	
Ellis et al. [41]	1984	Retrospective	45	280 (mean)	>25 cm resection length protective vs recurrence	$p = 0.002$	None
Martin et al. [43]	1994	Retrospective	286	55 (mean)	Recurrence correlation to conservative > extended resection	$p = 0.046$	None
Said et al. [46]	2011	Retrospective	52	1–126	Correlation between shorter resection lengths and recurrence	$p = 0.03$	ns
Welsch et al. [45]	2007	Prospective	100	60 (mean)	Correlation between > 20 cm resection lengths and recurrence		RR 0.42 (CI 0.21–0.84)
Aguas et al. [47]	2012	Prospective	29	12	>100 cm resection lengths correlation to endoscopic recurrence	$p = 0.03$	N/A
Trnka et al. [17]	1982	Retrospective	113	96–456	Lengths of resected SB segments in correlation to recurrence	ns	N/A
Kameyama et al. [48]	1982	Retrospective	8	36	Lengths of resected SB segments in correlation to recurrence	ns	N/A
Silvis et al. [34]	1994	Retrospective	148	56 (median)	Lengths of resected SB segments in correlation to recurrence	ns	N/A
Eshuis et al. [30]	2009	Retrospective	71	50–124	Lengths of resected SB segments in correlation to recurrence		ns
Michelassi et al. [52]	1988	Retrospective	582	120	Lengths of resected SB segments in correlation to recurrence		ns
Heimann et al. [44]	1993	Prospective	164	36	Lengths of resected SB segments in correlation to recurrence		ns
Speranza et al. [50]	1995	Retrospective	172	1–21	Lengths of resected SB segments in correlation to recurrence	ns	N/A
Mirow et al. [51]	2008	Prospective	412	180	Lengths of resected SB segments in correlation to recurrence	ns	N/A
Buisson et al. [54]	2012	Review	(3)	N/A	Lengths of resected SB segments in correlation to recurrence	True	
Hollaar et al. [35]	1995	Meta-analysis	(7) 622	72,8 (mean)			ns

(*continued on next page*)

Table 1 (*continued*)

Author(s)	Year	Type	No. of patients or (articles included in review)	Follow-up in months	Parameters	Results of univariate analyses	Results of multi-variate analyses
					Resection length and perioperative blood transfusion correlation to recurrence		
Strong et al. [55]	1998	Review	(6)	N/A	Lengths of resected SB segments in correlation to recurrence	Inconclusive	
Vuitton et al. [56]	2013	Review	(4)	N/A	Lengths of resected SB segments in correlation to recurrence	True	
Yamamoto et al. [9]	2005	Review	(7)	N/A	Lengths of resected SB segments in correlation to recurrence	False	
Yamamoto et al. [39]	2013	Review	(17)	N/A	Lengths of resected SB segments in correlation to recurrence	False	
Carlstedt et al. [62]	1987	Prospective	203	12–312	Lengths of resected SB segments in correlation ileostomy complications	ns	N/A
Kangas et al. [61]	1990	Retrospective	52	144 (median)	Longer lengths of resected SB segments in correlation presence of gallstones	$p < 0.001$	None
Lapidus et al. [28]	1991	Retrospective	10	N/A	Lengths of resected SB segments on lipid profile	ns	N/A
Comparing the length of resection margins to recurrence							
Gump et al. [57]	1972	Retrospective	64		Recurrence in correlation to conservative vs radical margins of resection		ns
Trnka et al. [17]	1982	Retrospective	113	96–456	Recurrence in correlation to conservative vs radical margins of resection	ns	N/A
Raab et al. [18]	1996	Retrospective	353	0–216	Recurrence in correlation to conservative vs radical margins of resection		ns
Yamamoto et al. [39]	2013	Review	(17)	N/A	Recurrence in correlation to conservative vs radical margins of resection	False	
Wettergren et al. [53]	1991	Retrospective	48	36–324	Recurrence in correlation to conservative vs radical margins of resection	ns	N/A
Bergman et al. [59]	1977	Retrospective	186	126 (mean)	Recurrence in correlation to conservative vs radical margins of resection	No statistics	
Kåresen et al. [58]	1981	Retrospective	59	12–288	Symptomatic recurrence in correlation to conservative vs radical margins of resection		No values
Nygaard et al. [60]	1977	Retrospective	76	24–132	Recurrence in correlation to conservative > radical margins of resection	$p < 0.01$	None
Martin et al. [43]	1994	Retrospective	286	55 (mean)	Recurrence in correlation to conservative > radical margins of resection	$p = 0.003$	None
Fazio et al. [65]	1996	Prospective	131	55 (median)	Recurrence in correlation to resection margins 2 cm vs 12 cm	ns	N/A
Recurrence and additional surgeries:							
Ellis et al. [41]	1984	Retrospective	18	7–384	Correlation between loss of length and additional hospitalisations	ns	N/A
Mappes et al. [63]	1994	Retrospective	65	N/A	Correlation between additional surgeries and loss of length	$r = 0,8$	None
Elriz et al. [22]	2011	Retrospective	38	N/A	Correlation between first and last resection in loss of length	$p < 0.001$	None
Pelletier et al. [64]	2011	Retrospective	24	N/A	Correlation between additional surgeries and loss of length	$p = 0.005$	None

correlating with lower rate of recurrence. Different literature reviews attained conflicting results [9,39,55,56], but most of these studies found no correlation between the lengths of the resected SB segments and recurrence.

Endoscopic recurrence: A prospective study of 29 patients [47] investigated endoscopic recurrence and found a correlation with extensive resection at > 100 cm ($p = 0.03$), increasing the risk of recurrence. Even less aggressive resections (>20 cm) may carry risk of recurrence RR of 0.42 (CI 0,21-0,84) as shown in another study [45].

These findings are supported by retrospective studies [17,34,35,43,44,46,48–53] that found no correlation in addition to a meta-analysis [54] reviewing three articles including one of the above cited articles [48].

On resection margins: Indirectly connected to the matter on the lengths of resected SB segments is data on resection margins. Five studies [17,18,53,57,65] found no difference in recurrence based on different lengths of resection margins, cemented by reviews of the literature [39,55]. Conversely, four studies [43,58–60] found that conservative or non-radical margins are linked to higher rates of recurrence at $p < 0.01$ and $p = 0.003$.

On gallstones: Patients undergoing >50 cm of resection are more likely to have gallstones requiring surgery $p < 0.001$ in multivariate analysis [61]. This might be due more to the total loss of length than the incremental loss of length; it is however yet another reason in favour of a conservative approach.

On ileostomy: In a patient population in need of long-term ileostomy for either CD or UC, no association was demonstrated between the lengths of resected SB segments and ileostomy complications [62].

On repeated surgeries: It is still controversial whether the lengths of resected SB segments in repeated surgeries correlates with that of resected SB segments in primary surgery. There are few studies supporting such correlation [41,63] and few that do not [27,64].

4. Discussion

We present a systematic review of the literature on pre, peri and postoperative factors and their implications for the lengths of resected SB segments and outcome in CD patients. Due to high risk of bias and a highly heterogeneous pool of data for comparable parameters, meta-analysis was not an option for the present review.

As shown in our results, most factors do not appear to have any implications for the lengths of resected SB segments.

However, due in part to the already stated problems with the included studies, great caution must be taken accepting this conclusion. Generally, the studies researching the same parameters differed greatly in methodology, objectives and outcome reporting. Often, investigated factors only accounted for a minor part of a greater study and many articles lacked proper multivariate analyses. Most of the included studies did not differentiate between different phenotypes of CD. These are all limitations to this review while strengths include a very broad-spectrum search strategy and very generous inclusion criteria.

Considering the above, the present review most importantly exposes a lack of homogenous well-researched data on resection surgery in CD patients. Furthermore, different practices of resection lengths, lengths of clear margin and supportive care appear to be based on speculation.

To properly research methods to increase quality of life, outcome and evaluate pharmacological treatment for CD patients in need of surgery, we believe it is of great importance to report the lengths of resected SB segments in CD surgery in addition to factors like phenotype, loss of blood and length of remaining SB. This is often neglected due to the traditional view that surgery and SB resection is only a consequence of non-response to medical treatment. In this traditional view, the surgeon's role is to resect SB and return the patient to a medical gastroenterologist for further management. This concept has been challenged in the last few years. Multi-disciplinary team management is becoming the gold standard in leading IBD centres with a IBD-surgeon as part of the team managing the patient and suggesting which modalities may suit individual patients [66]. In this context, the lengths of resected SB segments are important for the following reasons:

1. The probability of surgery is 30% during the first year of the disease and ranges between 30% and 70% in the following 10 years after diagnosis [67,68]. One third of CD patients may need repeated SB resections. It is important to report the lengths of resected SB segments as well as the total length of remaining SB to allow planning of new surgical intervention.
2. Attempts to avoid surgery by switching patients from one medical treatment to another for long periods of time may lead to poor quality of life as well as longer lengths of SB resections. This can only be confirmed or ruled out if SB length is reported.
3. Claims that biologics decrease the lengths of resected SB segments have not been properly investigated due to lack of recording of such data.
4. Postoperative recurrence and its correlation with lengths of resected SB segments have been investigated in small series studies with high risk of bias. More well-designed studies cannot be conducted properly without an emphasis on reporting resected SB lengths.

The traditional fear of repeated surgeries leading to short bowel syndrome has led to extended periods of medical treatment attempts before the patient is assessed for both initial and repeated surgical resections. In an era of bowel sparing surgery, this route of treatment options is not based on well-researched evidence; regardless of various kinds of approaches, the best course of action cannot be properly assessed without studies comparing the lengths of resected SB segments using different modalities.

Nowadays, different national and international cancer register databases exist. These databases report many factors like ASA score, performance level, perioperative blood loss and site of ligation of blood vessels etc. With a challenging disease like CD, the need for such databases is essential to provide better treatment options. Lengths of resected SB segments is one of the parameters that should be reported in such databases and be investigated in future studies.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijso.2017.04.002.

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