Journal of Crohn's and Colitis, 2018, 1139–1150
doi:10.1093/ecco-jcc/jjx187
Advance Access publication January 4, 2018
Original Article

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Inclusion of the Mesentery in Ileocolic Resection for Crohn's Disease is Associated With Reduced Surgical Recurrence

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Abstract

Background and Aims: Inclusion of the mesentery during resection for colorectal cancer is associated with improved outcomes but has yet to be evaluated in Crohn's disease. This study aimed to determine the rate of surgical recurrence after inclusion of mesentery during ileocolic resection for Crohn's disease.

Methods: Surgical recurrence rates were compared between two cohorts. Cohort A [n = 30] underwent conventional ileocolic resection where the mesentery was divided flush with the intestine. Cohort B [n = 34] underwent resection which included excision of the mesentery. The relationship between mesenteric disease severity and surgical recurrence was determined in a separate cohort [n = 94]. A mesenteric disease activity index was developed to quantify disease severity. This was correlated with the Crohn's disease activity index and the fibrocyte percentage in circulating white cells.

Results: Cumulative reoperation rates were 40% and 2.9% in cohorts A and B [P = 0.003], respectively. Surgical technique was an independent determinant of outcome [P = 0.007]. Length of resected intestine was shorter in cohort B, whilst lymph node yield was higher [12.25 ± 13 *versus* 2.4 ± 2.9, P = 0.002]. Advanced mesenteric disease predicted increased surgical recurrence [Hazard Ratio 4.7, 95% Confidence Interval: 1.71–13.01, P = 0.003]. The mesenteric disease activity index

correlated with the mucosal disease activity index [r = 0.76, p < 0.0001] and the Crohn's disease activity index [r = 0.70, p < 0.0001]. The mesenteric disease activity index was significantly worse in smokers and correlated with increases in circulating fibrocytes.
Conclusions: Inclusion of mesentery in ileocolic resection for Crohn's disease is associated with reduced recurrence requiring reoperation.

Key Words: Crohn's disease; mesentery; ileocolic resection; recurrence; fibrocyte

1. Introduction

Mesenteric-based surgical techniques are the basis of good quality surgery in the management of colorectal cancer.[1,2] Although it is suggested that they may lead to improved outcomes following surgery in Crohn's disease, they have yet to be evaluated in this context.[1,3] The surgical approach to Crohn's disease has developed relatively little since its first description. Earlier approaches emphasised ileocolic bypass.[4] This was followed by radical and thereafter by conservative intestinal resection.[4,5] Technical conservatism extended to the mesentery and, rather than mobilise and excise it as one might do for colorectal cancer, the mesentery is normally divided flush with the intestine and thus retained.

Conservative approaches to the mesentery have dominated the surgical management of Crohn's disease,[2,4,5] despite repeated recommendations that the mesentery be resected.[6–8] This inconsistency is explained as follows. Until recently, descriptions of core mesenteric anatomy were inaccurate.[1–3] This has particular implications for complex intestinal surgery where perforation, fistulation, and disease spread [common features of advanced Crohn's disease] lead to adherence of normally separate organs.[9,10] Unless one has a clear understanding of mesenteric anatomy, safe unravelling of the components of an inflammatory mass is challenging. The second explanation lies in the fact that the mesentery in Crohn's disease is characteristically thickened and bleeds heavily if divided across.[4,11,12] Unless one has a failsafe mechanism for haemostatic division of the Crohn's mesentery, rates of blood loss and associated complications increase.

Recent advances in our understanding of mesenteric anatomy mean that techniques are available by which the mesentery in Crohn's disease may be safely separated from adjacent structures, and haemostatically divided.[1–3] Clarification of the anatomy of the mesentery means one can better separate the components of an inflammatory mass, with minimal trauma to each. Following this, the intestine and mesentery can be fully detached from the retroperitoneum in a manner that facilities safe vascular division and disconnection.[1–3]

At present, 80% of patients with Crohn's disease will require at least one operation[13] and 40% will require multiple surgeries.[13,14] Most recurrences occur within 36 months of surgery.[15–18] Over the long term, surgical recurrence rates appear to decrease.[17,19,20] The introduction of biologic and immunomodulatory agents has had relatively limited impact on rates of surgery.[21,22] As a result, there is a need to refresh our surgical approach to Crohn's disease. With this in mind, the objective of this study was to determine rates of surgical recurrence in patients undergoing surgery for ileocolic Crohn's disease, in which the mesentery was included as part of the resection. These were compared with surgical recurrence rates in a cohort of patients who underwent conservative ileocolic resection. Mesenteric mesenchymal abnormalities were characterised in patients in whom the mesentery was included in the resection.

2. Materials and Methods

Ethical approval with informed consent was obtained from the HSE Mid-Western Regional Hospital Research Ethics Committee.

2.1. Cohorts examined

The incidence of recurrent Crohn's disease requiring surgical intervention [i.e. surgical recurrence] was compared between two cohorts in a population-based study. Cohort A [a historical cohort] comprised 30 consecutive patients undergoing ileocolic resection for a Crohn's-related indication during the interval from January 2004 to April 2010 [mean follow-up time: 69.9 ± 48.47 months] in University Hospital Limerick [UHL, then called the Mid-Western Regional Hospital]. In Cohort A, the mesentery was divided flush with the region of intestine to be resected [Figure 1A]. This was achieved by dividing the mesentery between arterial clamps, or by use of a haemostatic vessel-sealing device. The proximal and distal resection margins were positioned at levels where the ileum and colon [respectively] were macroscopically normal, regardless of the appearance of the mesentery. Before August 2010 all resections were conducted in this manner.

In Cohort B [n = 34], the mesentery was fully mobilised and partially excised [Figure 1B]. A description of the surgical technique is provided in Supplementary Methods, available at *ECCO-JCC* online. The mesentery was fully detached and the ileal division made just proximal to the mesenteric transition zone [Figure 1C–F; Supplementary Figure 1, available at *ECCO-JCC* online]. From this level, the mesentery was divided as close to the mesenteric root region as was deemed safe. The mesenteric division was then continued away from the root region to the colon, which was divided at a level where both colon and contiguous mesentery were normal in appearance. The technique of haemostatic mesenteric division using Kocher clamps is described in Supplementary Methods [Supplementary Figure 2, available at *ECCO-JCC* online]. After August 2010, 34 consecutive resections for Crohn's disease were prospectively conducted using this approach [mean follow-up time: 51.7 ± 20.98 months] in University Hospital Limerick. In both cohorts, reoperations for management of a postoperative complication were not considered as a 'reoperation for a Crohn's-related indication' and thus were not included in comparisons of surgical recurrence rates.

The above cohorts comprised patients with ileocolic Crohn's disease. Cohort C [n = 94, Supplementary Table 1, available at *ECCO-JCC* online] was an additional cohort included to determine the relationship between histological fat wrapping [a feature of severe mesenteric disease] and surgical recurrence in all intestinal forms of Crohn's disease. All Crohn's disease patients who underwent consecutive resections, irrespective of disease location, from January 2000 to August 2012 in UHL, were included in Cohort C. Fat wrapping was considered present if greater than 50% of the bowel circumference was covered by mesenteric adipose tissue.[23–25]

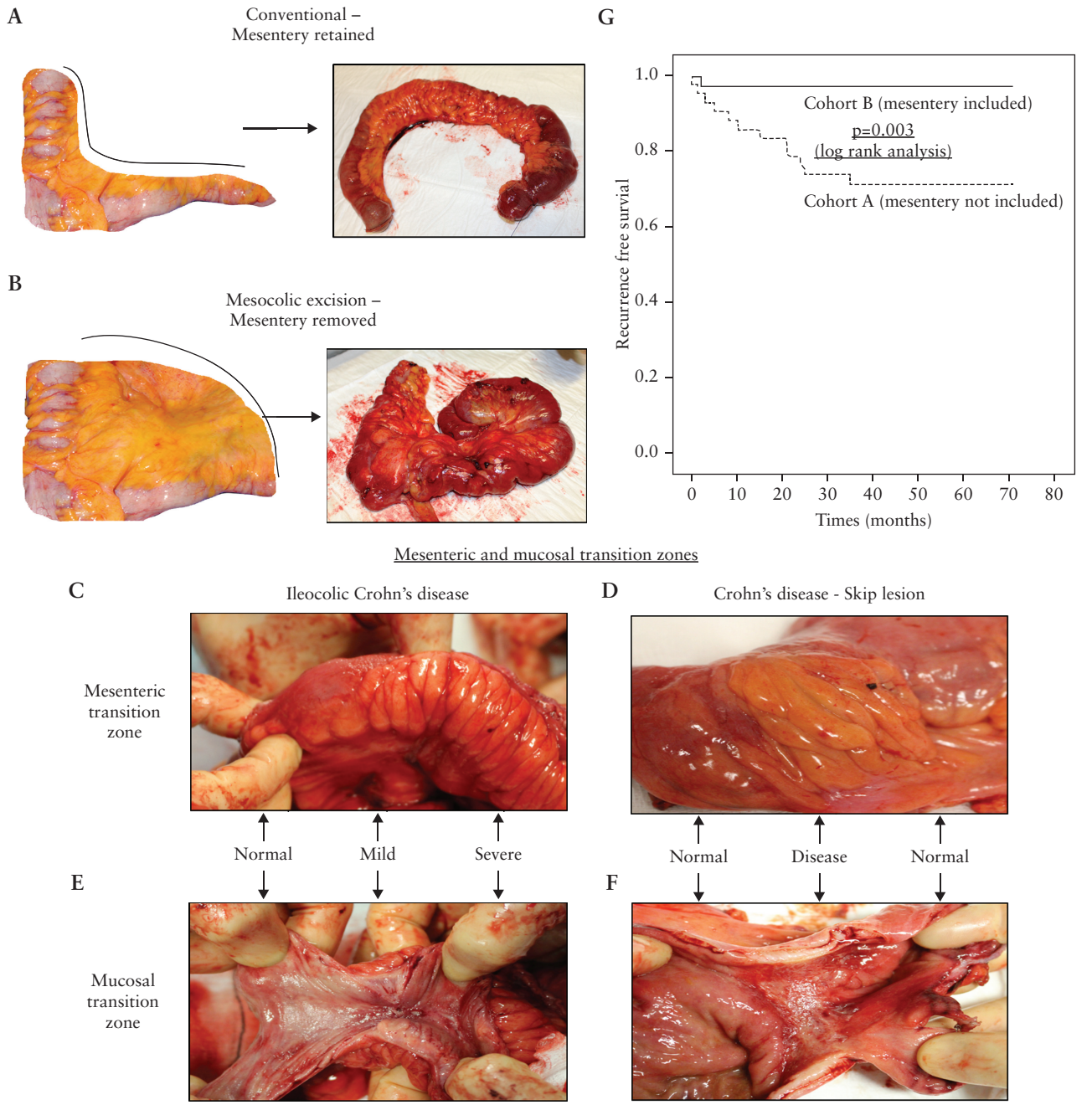


Figure 1. [A] [Left] Right colon and terminal ileum and line demonstrating mesenteric division flush with the intestinal margin, i.e. mesentery retained. [Right] Postoperative specimen following conventional resection and division of mesentery flush with the intestine. Both images are representative of conventional resection for Crohn's disease. [B] [Left] Right colon, terminal ileum, and mesentery, with a line demonstrating a mesenteric division wide of the intestinal margin, i.e. mesentery excised. [Right] Postoperative specimen following mesocolic excision. The entire right mesocolon is evident. A substantial volume of small intestinal mesentery is apparent. Both images are representative of concept of mesenteric resection for Crohn's disease. [C] Mesenteric transition zone in a postoperative specimen following resection for ileocolic Crohn's disease. [D] Mesenteric transition zone at a skip lesion. [E] Mucosal transition zone adjacent mesenteric transition zone in specimen in [C]. [F] Mucosal transition zone adjacent mesenteric transition zone in specimen in [D]. [G] Kaplan-Meier estimates demonstrating the cumulative incidence of reoperation for a Crohn's-related indication in patients in Cohort A [i.e. mesentery excluded] and Cohort B [i.e. mesentery included]. Estimates were compared using log-rank analysis.

In all cases, diagnosis of Crohn's disease was based on a combination of radiological, endoscopic and pathological findings. Retrieved data are listed in Supplementary Methods [available at *ECCO-JCC* online: see section on demographics]. All specimens [i.e. endoscopic and surgical] were examined by a team of pathologists who reviewed and discussed each specimen together. All patients were managed pre- and postoperatively by the same team of gastroenterologists. A greater number of patients in Cohort B were treated with preoperative biologics before [but not after] index surgery [Table 2]. Postoperatively, 20% and 21% of patients were considered at high risk of postoperative surgical recurrence and were placed on prophylactic medication, in cohorts A and B respectively [Table 2]. Patients developing recurrent disease were managed using a step-up approach.

Management was guided using a multidisciplinary team [MDT] approach and was based on MDT consensus. Indications for surgery included: [i] development of a complication arising due to Crohn's disease [i.e. obstruction, perforation, fistulation]; and [ii] failure of symptoms to improve on medical therapy.

2.2. Mesenteric, mucosal and Crohn's disease activity indices

Resection specimens from Cohort B were examined for mesenteric and mucosal disease, and a separate index was generated to quantify each of these. The 'mesenteric disease activity index' was developed using fat wrapping and mesenteric thickening as severity parameters [Figure 2A–C, Table 1A]. Fat wrapping was graded according to the proportion of intestinal circumference affected [Figure 2A, B, Table 1A]. Mesenteric thickening was graded based on appearance of vascular and avascular mesenteric regions [Figure 2C, Table 1A]. In mild mesenteric disease, these could be differentiated [Figure 2C].[26,27] In moderate mesenteric disease, thickening was confined to vascular pedicles [Figure 2C]. In severe disease, thickening also involved avascular regions. As a result, pedicular and interpedicular regions could not be differentiated [Figure 2C].

A 'mucosal disease activity index' was developed using oedema, ulceration [aphthous, linear, or confluent], stricture, and fistula as severity parameters [Figure 2D, Table 1B]. Points were attributed to each finding and the final score was the sum of all points. Mesenteric and mucosal disease activity scores were generated by examination of surgical specimens immediately following resection. Mesenteric, mucosal, and preoperative Crohn's Disease Activity Index [CDAI] were recorded by separate investigators and correlated [see below].

2.3. Light and scanning electron microscopic characterisation of the mesentery in Crohn's disease

In all patients in Cohort B, sections were prepared for light microscopic examination and stained using haematoxylin and eosin as previously described.[28] The thicknesses of [i] surface mesothelial/connective tissue complex, and [ii] connective tissue septations, were determined in regions of mild, moderate, and severe mesenteric disease. Adipocyte cell numbers were determined in each region (manually counted cells in 10 high-powered fields [HPF] and then averaged). The mesentery, adjacent intestine, and intervening zone of intersection were examined using scanning electron microscopy [SEM] in cadavers to establish a normal reference [n = 5] and in randomly chosen patients from Cohort B [n = 5] [Supplementary Methods, available at *ECCO-JCC* online]. SEM analysis was performed using a Hitachi S2600N Variable Pressure Scanning Electron Microscope [Hitachi, Tokyo, Japan].

2.4. Quantification of fibrocyte levels in peripheral circulation

As fibrocytes are circulating progenitors that can differentiate into either fibroblasts or adipocytes,[29] they may contribute to mesenteric mesenchymal abnormalities in Crohn's disease [see below]. To investigate this possibility, the fibrocyte percentage in peripheral blood mononuclear cells [called the fibrocyte percentage] was measured in Cohort B. Peripheral venous samples were obtained from patients in Cohort B [n = 15] and healthy controls [n = 16]. Cells were stained for Collagen-I and CD45 [Supplementary Methods, available at *ECCO-JCC* online].[30–32] All analysis was done on a BD FACSVerse [BD Biosciences] using BD FACSuite v1.0.5 [BD Biosciences]. Fibrocyte levels were displayed as a percentage of the total white blood cell population.

2.5. Immunohistochemical characterisation of mesenteric $CD45^+\alpha SMA^+$ fibrocytes

Tissue myofibrocytes can be immunohistochemically identified by dual staining for CD45 and alpha smooth muscle actin [αSMA].[33–35] The distribution of $CD45^+\alpha SMA^+$ cells was immunohistochemically examined in normal and in diseased mesentery in patients in Cohort B [n = 5] [Supplementary Methods, available at *ECCO-JCC* online]. All reviews were conducted by a pathologist and the principal investigator.

2.6. Statistical analyses

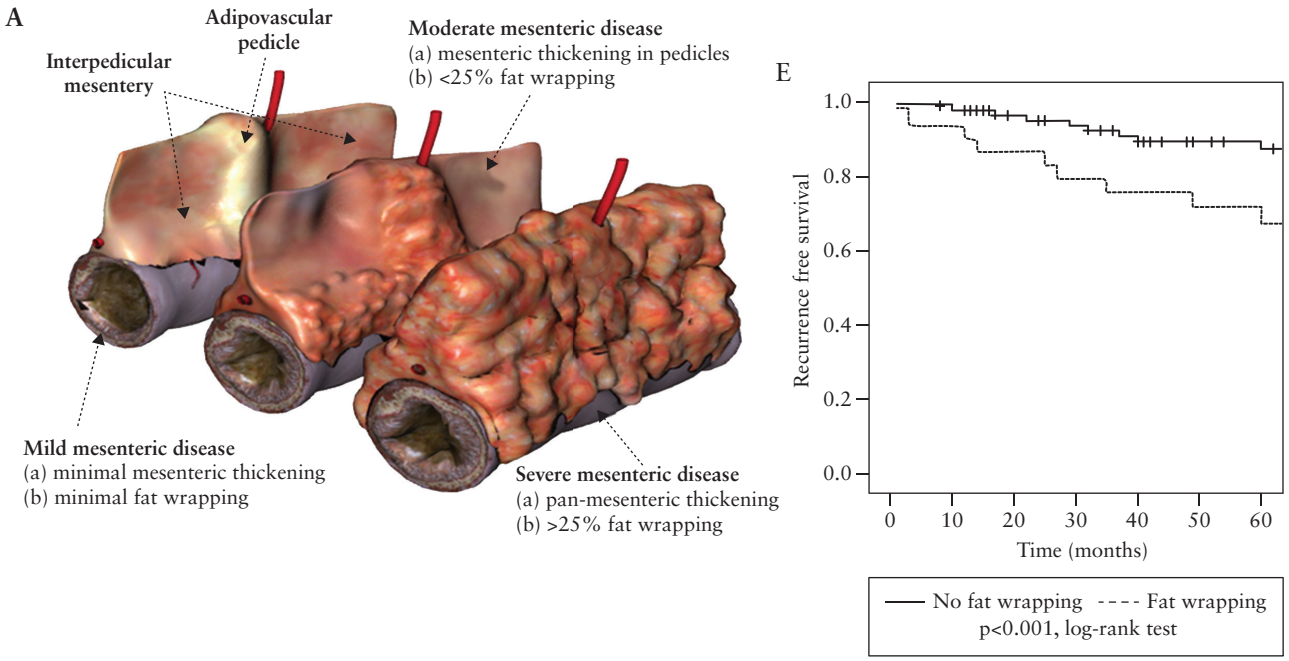
Data are presented as mean ± standard deviation [SD]. Pearson's correlation coefficient was used to determine correlations between mesenteric, mucosal, and systemic parameters using SPSSv22 [SPSS Inc., Chicago, USA]. A two-tailed t-test was used to compare parametric variables, and a Mann-Whitney U test was utilized for non-parametric comparisons. Chi-square tests and Z-tests for proportions were used to compare nominal data. To determine the relationship between fat wrapping and surgical recurrence, data were analysed using SPSSv22 and were presented as mean ± standard deviation and odds ratio [OR] with 95% confidence interval [CI]; 'n' represented the number of patients included in the analysis. Kaplan-Meier estimates and logistic regression analysis were performed to determine recurrence-free survival in both cohorts and the association between fat wrapping and surgical disease recurrence. Fisher's exact test was used to determine correlation between categorical variables, and continuous variables were assessed using analysis of variance. A 5% level of significance was used for all statistical tests.

3. Results

3.1. Clinical findings

3.1.1. Inclusion of the mesentery as part of intestinal resection is associated with reduced surgical recurrence

Cumulative reoperation rates were compared between patients who underwent a standard ileocolic resection [i.e. mesentery excluded] for Crohn's disease [cohort A] and those undergoing a resection in which mesentery was also resected [Cohort B]. One patient in Cohort B [2.9% of total cohort] required reoperation for a Crohn's-related indication. Nine patients in Cohort A [30%] required reoperation for a Crohn's-related indication. Three patients [10%] in Cohort A required reoperation for a Crohn's-related indication on more than one occasion. Overall, 12 reoperations for a Crohn's disease-related indication were required in Cohort A. The cumulative rate of reoperation in Cohort A was 40% [Figure 1G]. The majority [92%] of all reoperations occurred within 24 months [12.0 ± 10.15 months] of the preceding operation. The mean length of resected intestine, in surgical specimens, trended towards being greater in Cohort A [33.3 ± 15.77 cm versus 28.6 ± 10.99 cm, p = 0.198, t-test]. Lymph node yield was greater in specimens in Cohort B [12.25 ± 13 versus 2.4 ± 2.9, p = 0.002, t-test]. Distribution of known risk factors for surgical recurrence [i.e. active smoking, disease duration, age of diagnosis, family history, and disease location] were similar between groups [Table 2]. A greater number of patients had a history of smoking in Cohort A [Table 2]. On a multivariable analysis of factors known to predict surgical recurrence in Crohn's disease, retention of the mesentery [i.e. mesentery not included in the resection] was an independent predictor of recurrence requiring surgical intervention [p = 0.007] [Table 3].



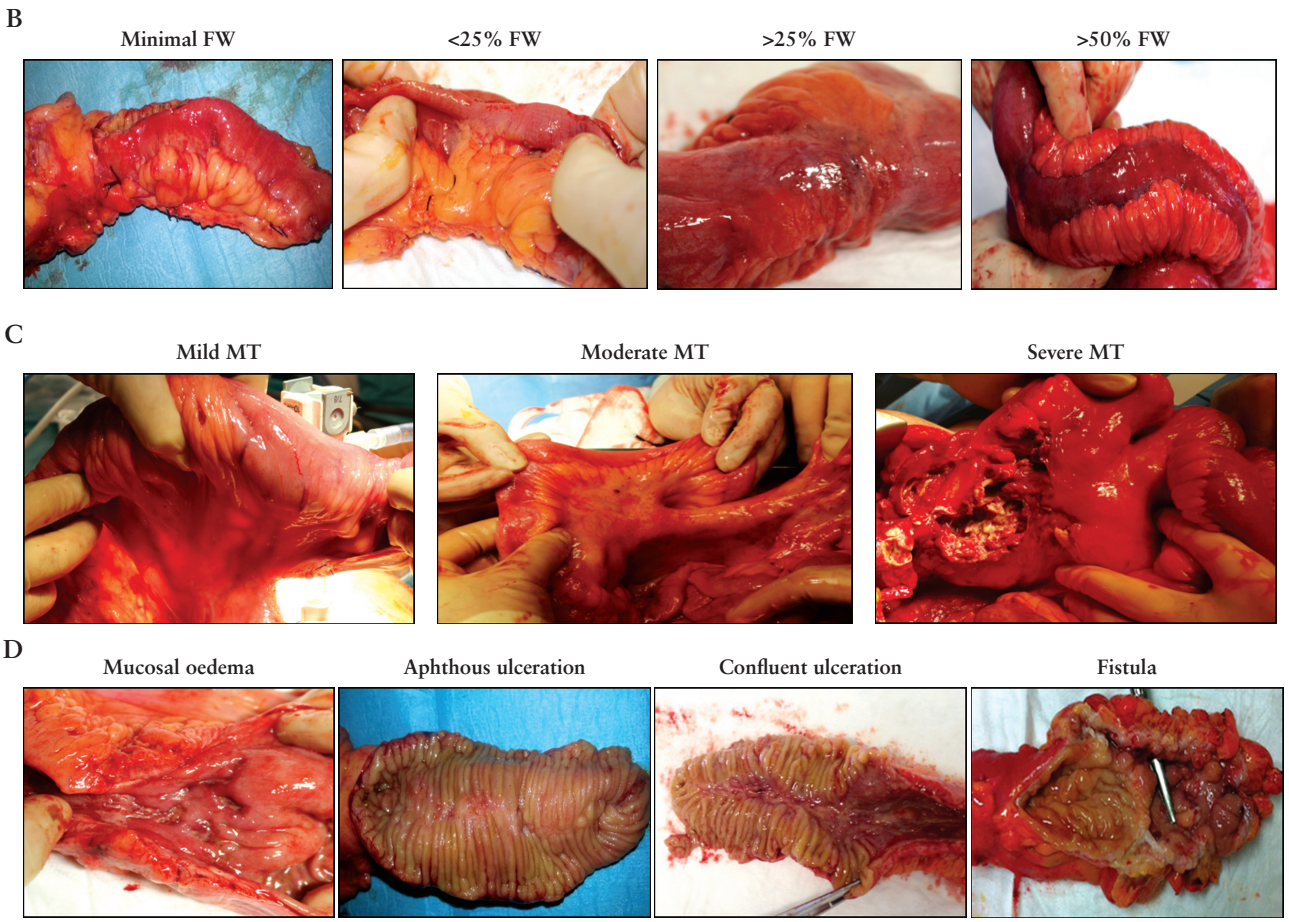


Figure 2. Key: FW refers to fat wrapping, MT refers to mesenteric thickening. [A] Digitally sculpted mesentery and intestinal tract demonstrating fat wrapping and mesenteric thickening. In mild mesenteric disease, thickening was confined to adipovascular regions. Fat wrapping commenced at the intestinal margin of the mesentery and was limited. In moderate mesenteric disease, adipovascular thickening was more pronounced but pedicles could still be differentiated. Fat wrapping increased but covered less than 25% of the bowel circumference. In severe mesenteric disease, thickening was pan-mesenteric. Adipovascular pedicles could not be differentiated. Fat wrapping extended beyond 25% of the circumference. [B–D] Macroscopic features of mesenteric (fat wrapping [B], mesenteric thickening [C]) and mucosal disease [D], as seen in postoperative surgical specimens. [E] Kaplan-Meier estimates demonstrating the percentage of patients reoperation-free following surgery for Crohn's disease. Patients were subdivided into cohorts with and without fat wrapping of greater than 50% of the intestinal circumference at the index operation.

Table 1A. Mesenteric disease activity index in Crohn's disease [see Figure 2].

Mesenteric disease score	Severity	Stage	Score
FW minimal, MT minimal	Mild	One	1
FW <25%, MT adipovascular pedicle only	Moderate I	Two A	2
FW <25%, pan-mesenteric MT	Moderate II	Two B	4
FW >25%, pan-mesenteric MT	Severe	Three	6

FW, fat wrapping; MT, mesenteric thickening.

Table 1B. Intestinal disease activity index. For each feature present, points were attributed. The final score was the sum of all points accumulated.

Intestine	Scores
Oedema	1
Aphthous ulcer	2
Confluent ulcer	3
Stricture	4
Fistula	5

Smoking at time of surgery and phenotype [as per the Vienna classification] were also predictors of surgical recurrence [p = 0.010, p = 0.048, respectively] [Table 3].

3.1.2. Mesenteric and mucosal disease were topographically linked

As the mesentery was included in all resections in Cohort B, the topographic relationship between mesenteric and mucosal abnormalities was characterised. In all specimens examined, mucosal and mesenteric disease were topographically coupled [Supplementary Figure 1, available at *ECCO-JCC* online]. A short transition [the mesenteric transition zone] occurred between regions of normal and diseased mesentery [Figure 1C, D]. A corresponding mucosal transition zone occurred in adjacent mucosa [Figure 1E, F]. The severity of mucosal and mesenteric abnormalities increased in tandem. Mucosal oedema, polyposis, and aphthous ulceration occurred adjacent to mild or moderate mesenteric disease. Their distribution was limited to the mesenteric pole of the intestinal circumference. Confluent mucosal ulceration, stricture, and fistulas occurred adjacent regions of severe mesenteric disease.

In all patients in Cohort B, the ileal resection [i.e. proximal] margin was placed immediately proximal to the mesenteric transition zone. When this approach was adopted, the proximal mucosal margin was histologically normal [i.e. not inflamed] in 84% of patients. In Cohort A, placement of the proximal resection was guided by surface intestinal rather than mesenteric parameters. In this cohort, mucosal inflammation occurred at the proximal margin in 79% of resection specimens.

3.1.3. Mesenteric, mucosal, and Crohn's disease activity indices correlated

Mesenteric, mucosal, and Crohn's disease activity indices were determined for patients in Cohort B. The mesenteric disease activity index correlated with the CDAI [r = 0.7, p <0.0001] and mucosal disease activity index [r = 0.76, p <0.0001]. The mucosal disease activity index and CDAI correlated [r = 0.68, p = 0.001]. Smoking was associated with an increase in the mesenteric disease activity index [4.5 ± 1.41 versus 3.0 ± 1.41, for smokers and non-smokers respectively, p = 0.041, Mann-Whitney U test]. Smoking was not associated with an increase in the mucosal or Crohn's disease activity index.

3.1.4. Advanced mesenteric disease predicted increased surgical recurrence

In Cohort C, fat wrapping was observed in 13 [41.9%] index resection specimens, and 18 [72%] recurrence specimens. Fat wrapping was associated with: stricture formation [p = 0.036] but not with transmural inflammation [p = 1.0]; fissuring ulceration [p = 0.255]; granuloma [p = 0.373]; increased body mass index [p = 0.314]; histological neuronal hyperplasia [p = 0.287]; or fistula formation [p = 0.193] [Supplementary Table 2, available at *ECCO-JCC* online]. On univariable analysis [Supplementary Table 3, available at *ECCO-JCC* online], both penetrating (hazard ratio [HR] 3.8, 95% CI: 1.3–10.6, p = 0.012) and non-penetrating phenotype [HR 0.38, 95% CI: 0.15–0.98, p = 0.045], as well as fat wrapping [HR 4.5, 95% CI: 1.77–11.5, p = 0.002], were associated with surgical recurrence. On multivariable analysis [Table 4], only fat wrapping increased the risk of surgical recurrence [HR 4.7, 95% CI: 1.71–13.01, p = 0.003]. Fat wrapping was associated with a shortened time to recurrence [Figure 2E, p <0.001].

3.2. Histological findings

3.2.1. Mesenteric mesenchymal abnormalities in Crohn's disease

Surface mesothelium, submesothelial connective tissue, and connective tissue septations were examined in regions of normal and diseased mesentery [Figure 3A]. The surface mesothelium/connective tissue complex was 24 ± 13 µm in width in normal mesentery [Figure 3B, left]. In Crohn's disease, the complex thickened in a graduated manner in mild [62 ± 16 µm, p <0.001, t-test], moderate [215 ± 70 µm, p <0.001, t-test], and severe mesenteric disease [408 ± 73 µm, p <0.001, t-test] [Figure 3B, right]. Connective tissue septa followed the same pattern, increasing stepwise from 16 ± 7 µm [normal], to 53 ± 17 µm [p <0.001, t-test], 101 ± 21 µm [p <0.001, t-test], and 245 ± 100 µm [p <0.001, t-test] in mild, moderate, and severe mesenteric disease, respectively [Figure 3B, C, and E]. Adipocytes numbered 23 ± 6 per HPF in normal mesentery [Figure 3C]. Adipocyte numbers increased in mild [28 ± 4/HPF, p = 0.02, t-test], moderate [37 ± 7/HPF, p <0.001, t-test], and severe [60 ± 7/HPF, p <0.001, t-test] mesenteric disease, respectively [Figure 3E].

The intestinal hilum [i.e. where mesentery and adjacent intestine intersect] was examined. In normal mesentery, a distinct intestinal serosa occurred between mesentery and longitudinal muscle layers [Figure 3D; Supplementary Figure 3A, available at *ECCO-JCC* online]. In Crohn's disease, a distinct serosa was not evident [Figure 3F, Supplementary Figure 3B]. At the intersection between the mesentery and intestine, mesenteric mesenchymal abnormalities continued into adjacent longitudinal muscle and deeper intestinal layers [Figure 3F, Supplementary Figure 3B].

3.2.2. Mesenteric mesenchymal changes correlated with the percentage of circulating fibrocytes

Mesenteric mesenchymal [i.e. fibrotic and adipose] abnormalities could be explained by changes in circulating and tissue-based fibrocytes. The circulating fibrocyte percentage was significantly increased in Crohn's disease compared with healthy controls [8.0 ± 5.64 *vs.* 2.6 ± 1.68%, p = 0.003] [Figure 4A, B]. The circulating fibrocyte percentage was similar in Crohn's disease and other inflammatory bowel conditions requiring surgery [8.0 ± 5.64 *vs.* 5.7 ± 4.28, p = 0.656] [Figure 4B]. The circulating fibrocyte percentage decreased 4 weeks after intestinal and mesenteric

Table 2. Demographics of Cohorts A and B. Ileocolic resection for Crohn's disease. Where stated, anti-tumour necrosis factor [TNF] medication consists of Humira® or infliximab. Data are presented as mean ± standard deviation [SD].

Variable	Cohort A [*n* = 30]	Cohort B [*n* = 34]	*p*-Value
Gender			*0.659 [overall chi²]*
Male	14 [47%]	14 [41%]	0.660 [Z-test]
Female	16 [53%]	20 [59%]	0.660 [Z-test]
Age at diagnosis [years]	30.3 ± 11.93	28.0 ± 10.93	0.445 [t-test]
Age at index surgery [years]	37.7 ± 13.67	35.9 ± 11.87	0.574 [t-test]
Disease duration [months]	75.0 ± 117.42	70.7 ± 78.83	0.838 [MW-U]
Length of intestine resected [cm]	33.3 ± 15.77	28.6 ± 10.99	*0.198 [t-test]*
Ileum	25.2 ± 15.71	22.1 ± 11.13	0.430 [t-test]
Colon	9.9 ± 12.08	7.4 ± 5.55	0.383 [t-test]
Smoking status at index surgery			*0.393 [overall chi²]*
Active	14 [47%]	18 [53%]	0.617 [Z-test]
History	6 [20%]	2 [6%]	0.089 [Z-test]
Non-smoker	9 [30%]	13 [38%]	0.490 [Z-test]
Data unavailable	1 [3%]	1 [3%]	0.928 [Z-test]
Family history			*0.437 [overall chi²]*
Yes	8 [27%]	12 [35%]	0.459 [Z-test]
No	19 [63%]	21 [62%]	0.897 [Z-test]
Data unavailable	3 [10%]	1 [3%]	0.246 [Z-test]
Medications at time of index surgery	*24 [80%]*	*27 [79%]*	*0.878 [overall Chi²]*
Anti-inflammatory	15 [50%]	9 [27%]	0.151 [Chi² test]
Steroid	13 [43%]	12 [35%]	0.752 [Chi² test]
Immunosuppressant	11 [37%]	10 [29%]	0.766 [Chi² test]
Biologic	5 [17%]	15 [44%]	**0.043 [chi2 test]**
None	5 [17%]	5 [15%]	0.878 [chi² test]
Data unavailable	1 [3%]	2 [6%]	0.878 [chi² test]
Prophylactic medication after index surgery	*6 [20%]*	*7 [21%]*	*0.166 [overall chi²]*
Imuran®	4 [13%]	3 [9%]	0.125 [chi² test]
6MP	0 [0%]	1 [3%]	0.117 [chi² test]
Anti-TNF	2 [7%]	4 [12%]	0.150 [chi² test]
None	19 [63%]	26 [76%]	0.166 [chi² test]
Data unavailable	5 [17%]	1 [3%]	0.166 [chi² test]
Vienna Classification			
Age at diagnosis			*0.875 [overall chi²]*
A1 <40 years old	23 [77%]	26 [76%]	0.984 [Z-test]
A2 ≥40 years old	6 [20%]	6 [18%]	0.810 [Z-test]
Data unavailable	1 [3%]	2 [6%]	0.631 [Z-test]
Location			*0.257 [overall chi²]*
L1 terminal ileum	23 [77%]	26 [76%]	0.984 [Z-test]
L2 colonic	2 [6%]	0 [0%]	0.126 [Z-test]
L3 ileocolic	5 [17%]	6 [18%]	0.920 [Z-test]
L4 upper GI	0 [0%]	2 [6%]	0.177 [Z-test]
Disease phenotype			***0.040 [overall chi²]***
B1 non-stricturing, non-penetrating	16 [53%]	8 [24%]	**0.014 [Z-test]**
B2 stricturing	6 [20%]	14 [41%]	0.069 [Z-test]
B3 penetrating	8 [27%]	12 [35%]	0.459 [Z-test]

Bold text indicates statistically significant results. Italicised text indicates results for overall statistical tests.
MW-U, MannWhitney U test; 6MP, 6-mercaptopurine; GI, gastrointestinal.

resection [5.7 ± 2.12% *vs*. 1.7 ± 1.20%, $p = 0.005$] [Figure 4C], when levels were similar to healthy controls [1.7 ± 1.20% *vs*. 2.6 ± 1.68%, $p = 0.1$]. The circulating fibrocyte percentage correlated with the CDAI [r = 0.87, $p = 0.009$] as well as with mesenteric [r = 0.81] and mucosal [r = 0.77] disease activity indices.

$CD45^+\alpha SMA^+$ fibrocytes were not identified in normal mesentery. In Crohn's mesentery, they were readily identifiable both in and nearby mesenteric vessels [arrows, Figure 4D; Supplementary Figure 4A, B, available at *ECCO-JCC* online] and in clusters at the intestinal surface [arrows, Figure 4E]. In adjacent intestine, $CD45^+\alpha SMA^+$ fibrocytes were identifiable in the connective tissue septa of the outer muscle layers [Figure 4E and insets].

4. Discussion

Recent advances have made it possible to examine the mesentery and its role in disease in a systematic manner.[1,2] This study evaluated the role of the mesentery in ileocolic Crohn's disease. First, rates of surgical recurrence [defined as recurrence requiring surgical intervention] were compared between patients who underwent a conventional ileocolic resection [i.e. the mesentery was retained] versus those in whom the mesentery was also resected. The surgical recurrence rate was significantly reduced in the latter group. In addition, intestinal length and margin positivity rates were both reduced while nodal yield was increased, following mesenteric resection. To quantify and

Table 3. Multivariable analysis of association between known factors of surgical recurrence and development of recurrence requiring surgical intervention.

Variable	Univariable analysis [*p*-value]	Multivariable analysis [*p*-value]
Gender	1.000	
Smoking at time of surgery	**0.015**	**0.010**
Age at diagnosis	0.934	
Disease phenotype	**0.029**	**0.048**
Disease location	0.469	
Age at surgery	0.788	
Non-mesenteric resection	**0.004**	**0.007**
Duration of disease	0.584	
Duration of follow-up	0.363	

Bold text indicates statistically significant results.

Table 4. Multivariable analysis of association between clinicohistopathological features and development of recurrence requiring surgical intervention.

Variable	HR	95% CI	*P*-value
Non-stricturing/non-penetrating phenotype	0.764	0.241–2.428	0.649
Penetrating phenotype	2.729	0.772–9.649	0.119
Fat wrapping	4.722	1.713–13.017	**0.003**

Bold text indicates statistically significant results.
HR, hazard ratio; CI, confidence interval.

compare mesenteric disease, an activity index was developed that correlated with mucosal and Crohn's disease activity indices, and worsened significantly with smoking. Advanced mesenteric disease [i.e. fat wrapping] independently predicted surgical recurrence and reduced time to recurrence.

The above findings lend support to inclusion of mesentery in resections for ileocolic Crohn's disease. Several authors previously proposed that mesenteric inclusion would lead to improved outcomes by increasing the volume of lymphatic tissue removed.[6–8] The present findings support this, as lymph node harvest was greater following mesenteric inclusion. Lack of take-up of mesenteric resection is explained by the fact that the mesentery bleeds extensively during division, and that radical resection is technically challenging due to Crohn's-related complications.[36] Trials aiming to further investigate the suggestion [i.e. that the mesentery be included in ileocolic resection] are increasingly required and are aided by recent clarification of mesenteric anatomy.[1–3,26–28,37,38] They are further prompted by the findings of the present study which found that conventional ileocolic resection [in which the mesentery was retained] was a predictor of surgical recurrence.

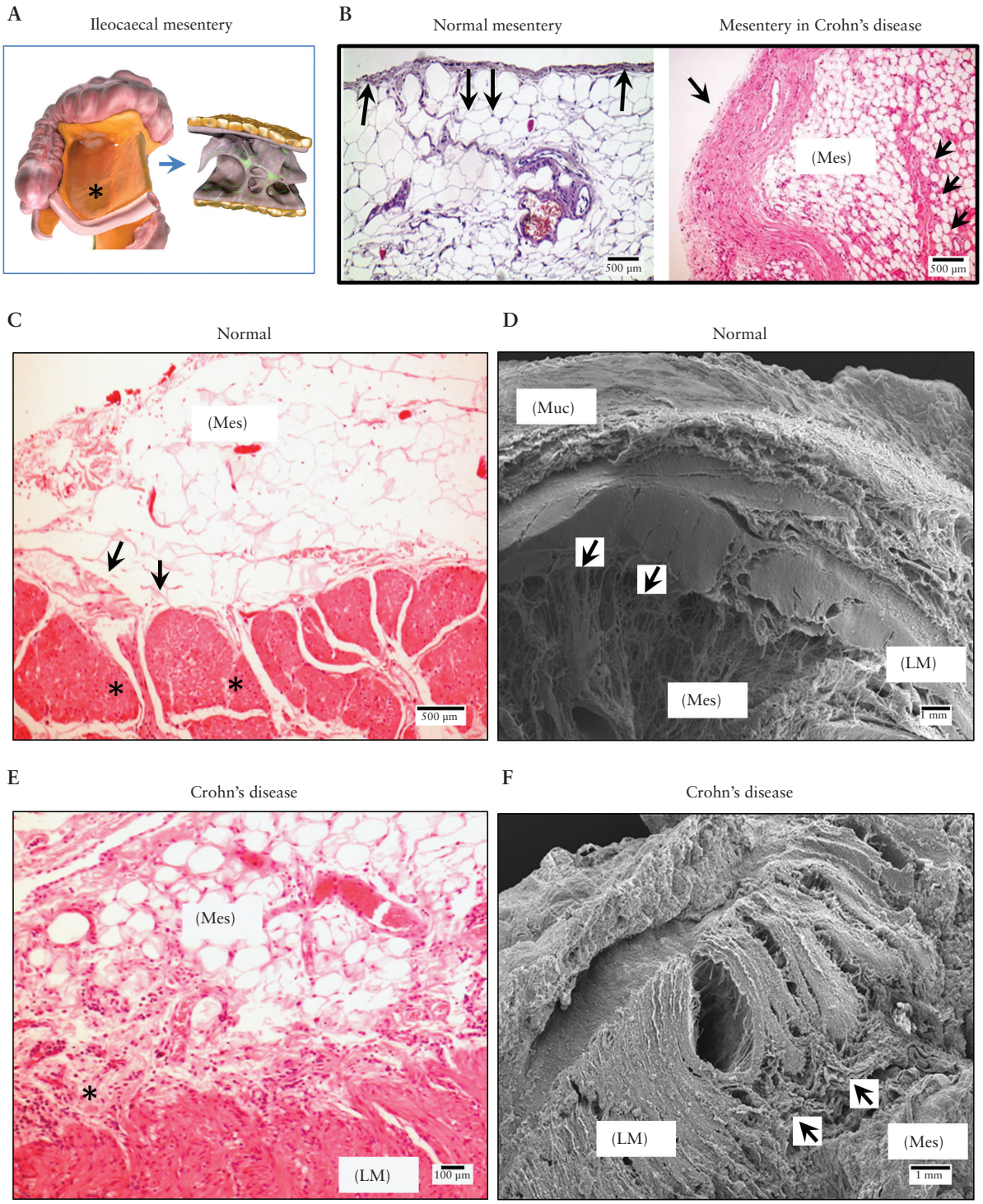
Positioning of the proximal intestinal division remains a topic of debate in Crohn's disease.[6,7,9,24,36,39–43] The present study is the first to describe a mesenteric and mucosal transition zone where both types of disease manifestation were topographically coupled. When the mesenteric transition zone was used to guide placement of the proximal intestinal division, the proximal margin was non-inflamed in the majority of patients. Mesenteric disease features can also be used to aid in the assessment of disease activity and identification of patients at increased risk of surgical recurrence. The severity of mesenteric disease correlated with mucosal disease and with the Crohn's disease activity index. Fat wrapping greater than 50% independently predicted increased rates of recurrence requiring reoperation.

One of the main questions arising from this study is whether the mesentery should be included as part of resection for patients undergoing surgery for ileocolic Crohn's disease. Some suggest that mesenteric abnormalities such as fat wrapping are immunologically protective.[44–50] If this relationship held, then radical mesenteric resection could lead to poorer [rather than improved] clinical outcomes. During stricturoplasty, the mesentery is retained. Notwithstanding this, mucosal healing is observed in regions that have undergone stricturoplasty.[51–53] These findings suggest that the mesentery may be retained. However, rates of surgical recurrence following stricturoplasty are variable, and often high, with a mean and median of 28% and 26%, respectively.[51–64] In many instances, repeat surgery is required at or near the site of previous stricturoplasty.[55,56,63,64] It is difficult to reconcile mucosal healing with high rates of repeat surgery, unless other non-mucosal [e.g. mesenteric] factors are determinants of recurrence requiring reoperation after stricturoplasty. Whether this is the case after stricturoplasty or not, is an important question that arises from the present study.

The cumulative rate of surgical recurrence in Cohort A, i.e. patients undergoing conventional resection for ileocolic Crohn's disease, was 40%. This rate is relatively high, as rates of surgical recurrence range from 4% to 60%.[14,16,18,20,39,65–78] Low rates of surgical recurrence have been quoted for conventional [i.e. mesentery-sparing] resection.[65–68,79] In general however, the mean and median rates of surgical recurrence following conventional surgery [i.e. 21% and 17.6%, respectively,] are such that patients are mostly cautioned that the possible requirement for reoperation is significant. That said, mesenteric resection adds to the radicality of intestinal surgery and, if it is possible to avoid this, then one should. Multi-institutional trials will be required to determine whether mesenteric-based or mesenteric-sparing approaches are best suited to different geographical cohorts of patients diagnosed with ileocolic Crohn's disease.

The question also arises as to how inclusion of the mesentery could lead to improved outcomes following resection in patients with ileocolic Crohn's disease. The present study demonstrated that in ileocolic Crohn's disease, mesenteric mesenchymal abnormalities extend into the outer layers of adjacent intestine. This may partially explain the transmural appearance of Crohn's disease. Mesenteric excision could reduce mesenteric mesenchymal inputs and in this manner lead to improved outcomes. As removal of the mesentery is associated with a greater lymphadenectomy [compared with that observed in conventional resection], it is feasible that removal reduces immunological inputs, thereby leading to improved postoperative outcomes. Mesenteric resection may also interrupt local recruitment of fibroblast precursors, i.e. fibrocytes.[80] These can differentiate into either adipocytes or fibroblasts.[29] The present study found that the fibrocyte percentage in circulating white cells was increased in Crohn's disease, normalised following surgical resection, and correlated with mesenteric disease severity. The immunohistochemical findings indicate that fibrocytes are recruited to the mesentery in which they migrate to the intestinal surface. Fibrocyte recruitment to the intestinal surface may be interrupted by inclusion of the mesentery in the resection.

The present study is limited in that it compares relatively small-sized prospective and historical cohorts. Although this approach has been used previously,[81] it is subject to bias that could be obviated in a randomised control trial. However, the magnitude of the difference in surgical recurrence rates between Cohorts A and B suggests that this cannot be fully explained as a type 2 error. In addition, a randomised controlled trial has recently been completed, examining outcomes after inclusion of the mesentery in resections for Crohn's



Key: LM - longitudinal muscle, **Mes** - mesentery, **Muc** - mucosa

Figure 3. [A] [Left] Digital sculpture demonstrating the junction between the small intestinal mesentery and the right mesocolon, and [right] mesenteric connective tissue lattice [grey]. [B] [Left] Photomicrograph (haematoxylin and eosin [H&E]) demonstrating normal mesentery, surface mesothelium [single arrow], and connective tissue [4X]. A connective tissue septation [double arrows] extended from the submesothelial connective tissue. [Right] H&E photomicrograph demonstrating mesentery in Crohn's disease [4X]. The surface mesothelium, submesothelial [single arrow], and interlobular connective tissue were thickened [multiple arrows]. [C] H&E photomicrograph demonstrating interface between normal mesentery and longitudinal muscle of adjacent intestine [4X]. The connective tissue serosa [arrows] separated mesentery from longitudinal muscle. The serosa was continuous with mesenteric connective tissue and extended into the outer longitudinal circular layer [asterix]. [D] Scanning electron microscopic [SEM] photomicrograph demonstrating mesentery, serosa [arrows], and adjacent intestine, in normality [30X]. [E] H&E photomicrograph demonstrating serosal thickening in a region of fat wrapping in Crohn's disease [asterix] [10X]. [F] SEM photomicrograph demonstrating mesentery, serosa [arrows], and adjacent intestine, in Crohn's disease [45X]. Mesenteric connective tissue thickening extended into the intestinal longitudinal muscle.

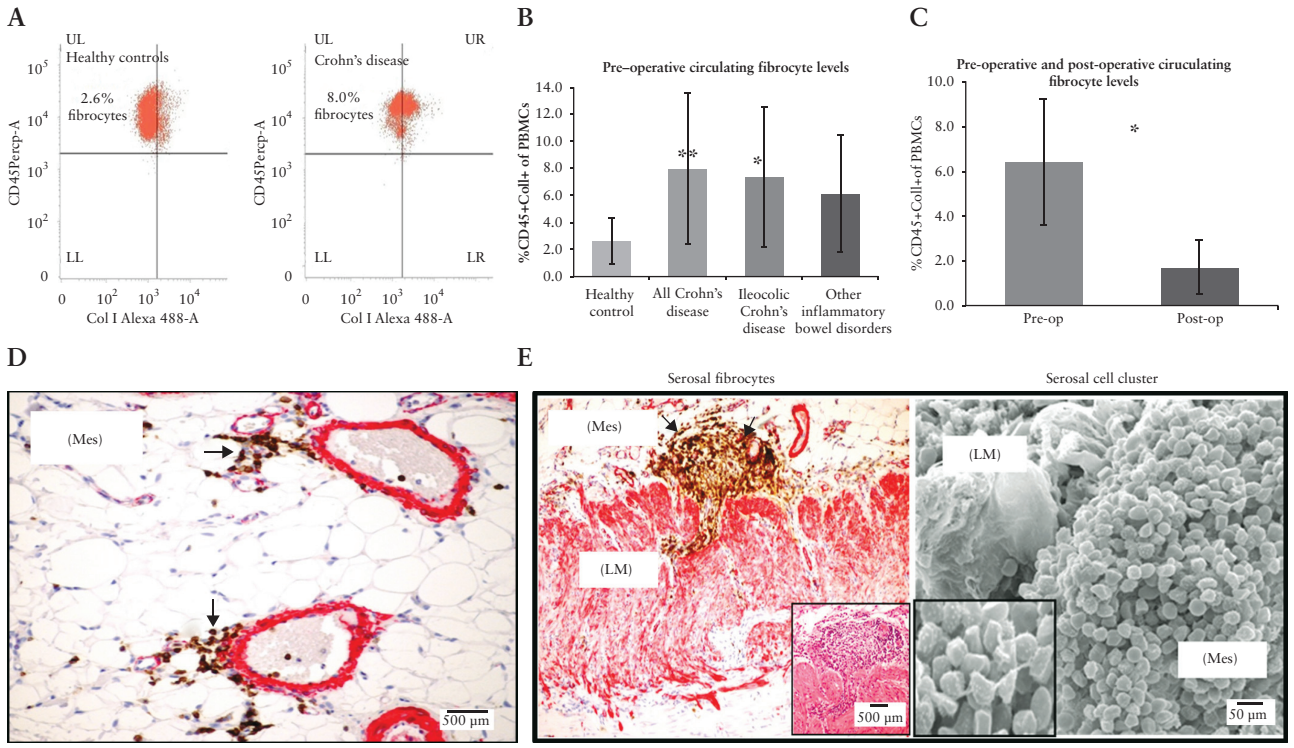


Figure 4. [A] Scatter plots demonstrating differences in the percentage of fibrocytes in circulating white cells, between a healthy control and a patient with ileocolic Crohn's disease. [B] Bar chart summarising percentage of fibrocytes in circulating white cells, in all resection types, in ileocolic resections alone [ileocolic Crohn's disease], and in patients with 'other' inflammatory conditions [including ulcerative colitis and diverticular disease]. [C] Bar chart demonstrating preoperative and long-term postoperative percentage of fibrocytes in circulating white cells in patients undergoing ileocolic resection for Crohn's disease. [D] Photomicrograph [dual staining for $CD45^{+}\alpha SMA^{+}$ with an eosin counterstain] demonstrating immune-positive cells within and nearby mesenteric vessels [4X]. [E] [Left] Photomicrograph [dual staining for $CD45^{+}\alpha SMA^{+}$ with an eosin counterstain] demonstrating immune-positive cells clustered at the serosal surface and within connective tissue of the longitudinal muscle layer [2X]. The inset is taken from a corresponding haematoxylin and eosin-stained serial section. [Right] Scanning electron photomicrograph demonstrating a cell cluster at the serosal surface, i.e. interposed between mesentery and adjacent intestinal surface, in Crohn's disease [700X]. The inset demonstrates a cell cluster at the serosal surface.

disease [Yi Li, personal communication].[82] Preliminary analyses of the trial data point to a reduction in postoperative recurrence of Crohn's disease, when the mesentery is included as part of intestinal resection. A further limitation of the present study relates to the fact that the mesenteric and mucosal disease activity indices have not been formally validated. However, both correlated with the CDAI, and the mesenteric disease score worsened with active smoking.

In summary, our study suggests that adoption of mesenteric-based strategies is associated with improved clinical outcomes after ileocolic resection in Crohn's disease. Mesenchymal inputs contribute to mesenteric abnormalities and their reduction may partly explain the benefits of mesenteric-based surgical strategies. Mesenteric mesenchymal inputs may provide novel cellular and molecular targets for future pharmaco-therapeutic interventions in Crohn's disease.

Funding

This work was supported by the University of Limerick's Graduate Entry Medical School Strategic Research Fund.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

The authors would like to thank Dara Walsh for his assistance with digitally sculpted images, Dr Sean Fair and his laboratory of the Department of Life Sciences, University of Limerick, for their use of the flow cytometer and their assistance in flow cytometry techniques, and Dr Mary Dillon for her help in data collection.

Author Contributions

JCC, study concept and design, laboratory analysis, specimen scoring, consultant colorectal surgeon, drafting of manuscript. MGK, SS, laboratory analysis, clinical data collation, drafting of manuscript. AJ, drafting of manuscript. JPB, study design. PK, laboratory analysis. BS, PR'OC, FS, DPOL, CF, CD, drafting of manuscript. DW, CP, consultant colorectal surgeon. MM, MS, consultant gastroenterologists. PF, VH, histological analysis. PT, HH, clinical data collation. SM [St Vincent's University Hospital], sample contribution, drafting of manuscript. LW, PD, laboratory analysis and scanning electron microscopy. All authors had access to the study data. All authors read, contributed to, and approved the final manuscript.

Supplementary Data

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

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