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The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit

On behalf of the 2015 European Society of Coloproctology collaborating group*

**collaborating members shown at the end of the manuscript text*

Corresponding author:
Mr Thomas Pinkney, Senior Lecturer in Colorectal Surgery, Academic Department of Surgery, Room 29, 4th Floor, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TH, UK, thomas.pinkney@uhb.nhs.uk

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Abstract

Background: Anastomosis technique following right sided colonic resection is widely variable and may affect patient outcomes. This study aimed to assess the association between leak and anastomosis technique (stapled versus handsewn) .

Methods: This was a prospective, multicentre, international audit including patients undergoing elective or emergency right hemicolectomy or ileo-caecal resection operations over a two-month period in early 2015. The primary outcome measure was the presence of anastomotic leak within 30 days of surgery, using a pre-specified definition. Mixed effects logistic regression models were used to assess the association between leak and anastomosis method, adjusting for patient, disease and operative cofactors, with centre included as a random effect variable.

Results: This study included 3208 patients, of whom 78.4% (n=2515) underwent surgery for malignancy and 11.7% (n=375) for Crohn's disease. An anastomosis was performed in 94.8% (n=3041) of patients, which was handsewn in 38.9% (n=1183) and stapled in 61.1% (n=1858) cases. Patients undergoing handsewn anastomosis were more likely to be emergency admissions (20.5% handsewn versus 12.9% stapled) and to undergo open surgery (54.7% versus 36.6%). The overall anastomotic leak rate was 8.1% (245/3041), which was similar following handsewn (7.4%) and stapled (8.5%) techniques (p=0.3). After adjustment for cofactors, the odds of a leak were higher for stapled anastomosis (adjusted odds ratio 1.43, 95% confidence interval 1.04-1.95, p=0.03).

Discussion: Despite being used in lower risk patients, stapled anastomosis was associated with an increased anastomotic leak rate in this observational study. Further research is needed to define patient groups in whom a stapled anastomosis is safe.

Introduction

Morbidity following colorectal resection is common. Up to 65.3% of patients suffer a complication in the first 30 days after surgery, which is major in 17.1% (Clavien-Dindo grade III-V) [1]. These complications impact upon both morbidity and mortality rates, as well as increasing healthcare costs[2-4]. Anastomotic leak is considered as one of the most devastating of these adverse events, and is associated with a reduction in both survival and quality of life, and an increased risk of disease recurrence in those patients with cancer[2].

Many factors are known to be associated with anastomotic leak including patient comorbidity, underlying pathology and anastomotic technique. There is a wide variation in the use of handsewn versus stapled anastomosis, illustrating the lack of high quality evidence supporting either method[5]. More evidence is required to guide surgical practice. Right hemicolectomy (including ileo-caecal resection) is the most common colonic resection, is performed in both elective and emergency settings, and for neoplastic and non-neoplastic conditions. It therefore represents an appropriate patient cohort in which to assess.the relationship between method of anastomosis method and outcome.

Multicentre snapshot audits have the ability to gather large patient numbers in short periods of time from many hospitals. They provide contemporaneous and population based data that is representative of current practice, and which is unconstrained by the confines often required in clinical trials. This first report from an international prospective cross-sectional cohort study of right hemicolectomy and ileocaecal resections investigates the relationship between anastomosis method and subsequent anastomotic leak.

Methods

This prospective, observational, multicentre study was performed according to a pre-specified protocol (http://www.escp.eu.com/research/cohort-studies/2015-audit). The protocol and data entry system were tested and modified following an external pilot conducted in eight centres across five countries prior to the start of the main project. Follow-up and data collected was restricted to routinely collected data fields.

Centres

Any unit performing gastrointestinal surgery was eligible to register and enter patients into the study. No unit size or case volume stipulations were made and centres from any country were able to take part. The study was launched at the European Society of Coloproctology (ESCP) Scientific & Annual Meeting in Barcelona, September 2014 and invitations to participate were subsequently distributed directly to all registered members of the ESCP. Further dissemination was obtained via the national ESCP country representatives, including through national surgical or colorectal societies. In addition, the study was endorsed and disseminated by the surgical arm of the European Crohn's and Colitis Organisation.

Approvals

Participating centres were responsible for completion of local approvals prior to the start of the data collection period. Regional or national ethics approval or indemnity was obtained where possible. Centres were asked to ensure that appropriate pathways and local investigators were in place to be able to include all consecutive eligible patients during the study period and provide >95% completeness of data entry.

Patients

Adult patients undergoing right hemicolectomy or ileo-caecal resection for any pathological indication, via any operative approach in both the elective and emergency settings were included. Patients were excluded if their right sided colonic resection was as part of a larger procedure (e.g. subtotal colectomy or panproctocolectomy), as defined by a distal colonic transection point beyond the splenic flexure. In patients with Crohn's disease, those undergoing additional proximal strictureoplasty or resection/anastomosis of more proximal small bowel disease during the same operation were also excluded.

Outcome measures

The primary outcome for this study was overall anastomotic leak, pre-defined as either i) gross anastomotic leakage proven radiologically or clinically and classified according to intervention necessary (figure 1), or ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging. Secondary outcome measures included mortality, overall morbidity and length of hospital stay. An exploratory sensitivity analysis was also undertaken of those with only a 'proven' anastomotic leak (i.e. excluding those with an intraperitoneal fluid collection alone) for comparison purposes.

Data collection

Sites were asked to include all consecutive eligible patients over an eight week period, which could start at any time between the 15th and 30th January 2015. This flexible starting date was designed to maximise centre participation. The final date for any new patient inclusions at any site was March 27th 2015.

There were three main phases of data collection for each patient:

a) Pre-operative	patient (e.g. age, gender, co-morbidities) and disease demographics (e.g. indication, previous treatment)
b) Operative	technical details about the operation performed (e.g. handsewn or stapled anastomosis; laparoscopic or open approach; elective or emergency)
c) Follow-up	individual outcomes data (anastomotic leak, length of hospital stay, mortality); completed at 30 days post-operation.

Each of these phases had a separate clinical reporting form (CRF) that contained 10-12 main questions and was designed to fit in with data collected as part of normal clinical practice and be completed in 'real-time' with minimal extra work from the clinical team. Despite no changes being made to existing patients' pathways during this observational study, local investigators were asked to be proactive in identifying postoperative events. Methods included review of patient notes (paper and electronic) during admission and before discharge, reviewing hospital systems to check for re-attendances or re-admissions, and reviewing postoperative radiology reports. Some centres routinely reviewed patients 30 days after surgery or used a telephone review, both of which were used to identify adverse events. Data was recorded contemporaneously and stored on a dedicated, secure, web-based platform without using patient identifiable information. Data was collected by a team of 4-5 people at each site, one of whom had to be a consultant surgeon who was responsible for the data quality at that centre.

Statistical analysis

This report has been prepared in accordance to guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies[6].

The primary aim of this study was to assess the association between the primary outcome measure (overall anastomotic leak) and the main explanatory variable of interest, anastomosis method (handsewn versus stapled anastomosis). Univariate and multivariate mixed effects logistic regression models (with centre included as a random effect) were fitted for overall anastomotic leak and the pre-specified explanatory variables: anastomosis method (handsewn or stapled), age, gender (male or female), body mass index (normal, underweight, overweight or obese), smoking status (never, ex-smoker, current or not known), history of ischaemic heart disease or cerebrovascular disease (no or yes), history of diabetes (none, diet/tablet controlled or insulin controlled), indication for operation (malignancy, Crohn's disease or other), American Society of Anaesthesiologists (ASA) grade (low or high risk), surgery type (elective or emergency), operation type (laparoscopic or open) and extent of surgery (complete, extended or limited; figure 2). These factors were chosen based on clinical significance and were all pre-specified in the statistical analysis plan. All the explanatory variables were included in the multivariate model irrespective of statistical significance in the univariate model, as this allowed potential confounding factors relating to the patient, disease and operation to be taken into consideration in the multivariate model.

Effect estimates are presented as odds ratios (OR) with 95% confidence intervals (95% CI) and two-sided p-values. An OR>1 indicated increased likelihood of anastomotic leak with the relevant explanatory variable compared to the reference category for that variable. Statistical significance was defined at the level of $P<0.05$. Data analysis was undertaken using Stata version 14.

Sensitivity analyses were undertaken which included (1) fitting a multivariate model including anastomosis method and only those explanatory variables where p≤0.1 in the univariate analysis; (2) fitting a multivariate model including only those explanatory variables where p≤0.1 in the univariate analysis; and (3) fitting a multivariate model as per the primary analysis, but only including those patients with a 'proven' anastomotic leak in the outcome variable.

Results

Data completeness

Overall 97.4% of records had all data fields completed. Patient demographic details, basic operation details and 30-day outcome data were mandatory fields for records to be locked and as such had a 100% completion rate. The small levels of missing data predominantly related to patient smoking status and pre-operative medical therapy (in the case of Crohn's disease patients) subsections.

Patients and centres

This study included 3208 patients from 284 centres in 39 countries (figure 3). There were five participating centres outside of Europe. The mean age of patients was 66 years (range: 16-99), 50.8% were male, the majority were never-smokers (62%), did not have history of ischaemic heart disease or cerebrovascular disease (80.5%) and were not diabetic (84.4%) (table 1). Most patients underwent surgery for malignancy (78.4%; n=2515) or Crohn's disease (11.7%; n=375). Overall, 81.3% (n=2609) of patients underwent elective surgery, and 54.6% (n=1751) of operations were started laparoscopically; 9.6% undergoing subsequent conversion to open. Further demographic details are shown in table 1.

Anastomosis technique

An anastomosis was performed in 94.8% (n=3041) of patients, which was handsewn in 38.9% (n=1183) and stapled in 61.1% (n=1858) cases (table 1). There was no difference in stapled anastomosis rates in those undergoing surgery for malignancy (59.8%) and for Crohn's disease (58.7%). Patients undergoing handsewn anastomosis were more likely to be emergency admissions (20.5% versus 12.9% stapled) and to undergo open surgery (54.7% versus 36.6%).

Incidence of Anastomotic Leak

The primary outcome measure of anastomotic leak and/or intraperitoneal fluid collection was present in 8.1% (245/3041) (table 2).

Univariate Analysis of Anastomotic Leak

The mixed effects logistic regression analysis included 3013 patients and 242 leaks (there were 28 patients (0.9%) with missing data on extent of surgery who were excluded from this analysis). There was no evidence of an association between leak and anastomosis method (stapled vs. handsewn: OR 1.16, 95% CI 0.86-1.57, p=0.3) (table 3). Female gender was significantly associated with a reduced risk of leak (OR 0.70, 95% CI 0.53-0.92, p=0.011), whilst being a current smoker (vs. never-smoker: OR 1.68, 95% CI 1.15-2.43, p=0.007), other indication for surgery (vs. malignant: OR=2.39, 95% CI 1.62-3.54, p<0.001), emergency surgery (vs. elective: OR 2.33, 95% CI 1.70-3.19, p<0.001), and open incision (vs. laparoscopic: OR=2.32, 95% CI 1.74-3.08, p<0.001) were all associated with an increased risk of leak (table 3). Weaker associations were found with age (OR 0.99, 95% CI

0.98-1.00, p=0.06) and higher ASA grade (vs. low grade: OR=1.30, 95% CI 0.98-1.72, p=0.07).

Multivariate Analysis of Anastomotic Leak

When a multivariate mixed effects logistic regression model was fitted including all the pre-specified variables, a significant association was found between leak and stapled anastomosis (vs. handsewn: OR 1.43, 95% CI 1.04-1.95, p=0.03). Other variables found to be significant under multivariate analysis were age (OR 0.99, 95% CI 0.98-1.00, p=0.04), other indication for surgery (vs. malignant: OR=1.73, 95% CI 1.05-2.85, p=0.03) and open incision (vs. laparoscopic OR=2.09, 95% CI 1.53-2.87, p<0.001). Similar results were seen when the multivariate models were restricted to only those variables where p≤0.1 in the univariate analysis, with anastomosis method included and excluded as a co-factor. Another sensitivity analysis including only those patients with a 'proven' anastomotic leak (150/3041; 4.9%) also gave similar results (Supplementary tables).

Secondary Outcomes

The overall 30-day death rate was 3.2% (103/3208) (table 4); for those undergoing elective operations this reduced to 1.5% (38/2609). The median length of hospital stay was 7 days (range: 1-30+ days), and the 30-day re-operation and re-admission rates were 6.6% and 5.7% respectively. In those patients undergoing anastomosis who had an anastomotic leak and/or intraperitoneal fluid collection, the 30-day death rate increased to 9.8%, and the length of hospital stay was more than doubled to a median of 18 days (table 4). When assessing only those patients with a 'proven' anastomotic leak, similar outcomes were seen; 30-day death rate, 11.3% and length of hospital stay, median 21 days (table 4).

Discussion

This multicentre international snapshot audit has identified a possible association between stapled anastomosis and anastomotic leak. This became apparent following multivariate analysis that adjusted for other patient and disease characteristics, and operative information (with centre included as a random effect). This finding was perhaps surprising given that stapling was used more frequently in the lower risk groups, such as in elective and laparoscopic operations.

Multivariate analysis also found an association between operative approach and leak, with a greater risk of leak with open operations. This increased risk associated with open surgery was readily identifiable in both the emergency and elective settings and might be interpreted as suggesting that in modern surgical practice, the need for an operation to be undertaken using an open approach may be a surrogate marker of operative difficulty.

The association between anastomotic leakage and stapling only became apparent following multivariate analysis. There was a strong association between high risk patients and handsewn anastomosis which may have influenced our results. It is impossible to assign causation to this association, but it is interesting to speculate on the possible explanations: the effects of operative approach (open versus laparoscopic), operation urgency (elective versus emergency) and anastomosis method (stapled versus handsewn) are all likely to have contributed to this effect. This situation, where findings are non-significant in univariate but significant in multivariate analysis is well recognised in observational studies. Lo and colleagues identified various scenarios in which this situation may occur; one of which was indeed the presence of hidden interactions[7].

Strengths of this study

The prospective nature of data collection, using a standardised protocol and predesigned reporting system, ensured the quality and homogeneity of data returns. The wide variety of

surgeons, sites and countries entering patients into this study increases the generalisability of the findings. Of the 39 countries involved, 34 were based in one continent (Europe), with other countries being spread across the world: Argentina, Brazil, China, Japan and USA. Bringing such a group together and coordinating over 1000 local researchers from 284 different centres to simultaneously collect uniform data and form a research network in this manner has been one of the most important successes of this first ESCP project. The number of sites involved, and patients entered, far exceeded our expectations when designing this project. Now the model has been shown to work, it is currently being used to undertake another prospective international audit[8] and the research network will also be perfectly poised to deliver future prospective interventional studies based on the areas of uncertainty identified in these audits.

Limitations

Selection bias will always be an issue in this type of observational research. We have attempted to minimise the effects of this by undertaking adjusted analyses using mixed effects logistic regression models, but we accept that this can never fully counteract the nuances involved in clinical decision-making. Nonetheless, one might have predicted that any major selection bias effect on the primary outcome would favour stapling being actually at a diminished risk, given the prevalence of its use within the lower risk groups.

Reporting bias is also difficult to control for in this kind of study, where sites might have omitted uploading data for certain eligible patients within the study time period, either accidentally or deliberately, and the impact this could have on the results. We feel that this is unlikely given our study design, where the first two phases of data collection were prospectively and contemporaneously uploaded onto the online system in the pre-operative and immediate post-operative setting. This effectively 'locked' these patients into the audit and there was no case at any site where the follow-up data form was not completed for a

patient whose data had been already entered into the first sections. Further, our results showing a high overall anastomotic leak rate, an overall 30-day death rate of 3.2%, and an elective 30-day death rate of 1.5% would suggest that patients with poor early post-operative outcomes have not been omitted.

It is possible that some patients included in the study may have undergone additional procedures such as simultaneous liver resection or extended resection due to pathological involvement of other local organs, as these were not pre-specified exclusion criteria. The numbers of such patients are likely to be very small and as such are unlikely to have conferred any major impact upon the main findings.

A potentially contentious decision was our inclusion of intra-abdominal and pelvic collections in with the 'proven' anastomotic leak group in our primary outcome definition. There is a lack of validated scoring system for anastomotic leak[9-11] and intraperitoneal fluid collections are considered by many surgeons as representative of an anastomotic leak until proven otherwise. One recent study confirmed that isolated free intraperitoneal fluid was not a benign finding after anterior resection and another showed that many patients with ultimately proven anastomotic leakage did not have classical peri-anastomotic signs or extravasation of contrast on imaging[12,13]. It is our opinion that inclusion of patients with an intraperitoneal collection within the primary outcome group of anastomotic leak was justified given the similarities in adverse outcome rates between this group and others with a confirmed leak. Similarly, the sensitivity analysis that included only the confirmed leak patients produced very similar results to those found in the main analysis We consider therefore that the majority of patients with isolated intraperitoneal collections had sustained an occult anastomotic leak.

Comparison with the literature

The anastomotic leak rate in this study compares closely with two other large-scale national audits utilising prospective data collection. The Spanish ANACO group recently identified an overall leak rate of 8.4% in 1102 patients undergoing elective right hemicolectomy for cancer[5] and a Dutch analysis of 15,667 patients undergoing anastomosis after colorectal cancer resection found anastomotic leak rates in the right hemicolectomy (n=7788) and ileocaecal resection (n=240) subgroups of 6.4% and 7.5% respectively[14].

Our identification of stapling as a possible risk factor for anastomotic leak is contrary to a Cochrane review on the same topic[15]. This pooled data from 1125 patients undergoing an ileo-colic anastomosis within seven randomised trials and found fewer leaks after stapled anastomosis (2.5%;11/441) compared to handsewn (6.1%; 42/684), which was statistically significant: OR 0.48 [0.24, 0.95] p=0.03. The authors rightly commented on the small patient numbers and the very low event rate. Whilst an apparently significant difference was found in leak rates, this did not correspond to a parallel impact upon re-operation rate, length of stay or mortality. Nevertheless this review concluded that “stapled anastomoses are associated with fewer anastomotic leaks than handsewn, and should be considered the standard against which all other techniques should be compared”. It is likely that surgeons may have changed their practice based on the conclusions from this highly respected data source. Our conflicting message on stapled anastomoses could perhaps be written off as statistical anomaly, were it not for the very same finding being identified in the recent Spanish ANACO multicentre study[5]. This prospective observational study from 52 centres found major anastomotic leak (requiring intervention) rates of 3.4% in handsewn and 7.8% in stapled anastomoses (OR 2.1 [1.1 - 4.2]; p = 0.007). Together with the current study, and accepting the potential shortfalls of observational research, this suggests that a more detailed investigation of stapled versus handsewn anastomosis is certainly warranted.

Further research and analyses ongoing

We recognise that another limitation of this study relates to the fact that there are many different stapling techniques used in anastomosis and grouping them together may be inappropriate. These include bowel orientation (side-side, side-end, end-side), the type of stapler used (linear, circular), the stapler used for apical transection (linear cutting, linear non-cutting) as well as other associated technical factors such as the use of staple line oversewing and staple height selection. Similar but less numerous variabilities also exist within the handsewn group. These technical details were all collected prospectively during the project but will be analysed and reported in a subsequent paper. It is possible that certain technical aspects , might account for a disproportionate number of leaks or make up the apparent difference in leak rates compared to the handsewn patients. Other subsequent reports from the study will explore the geographic variability in patients and techniques, and the impact of unit characteristics on outcome, and a detailed analysis of the perioperative management of Crohn's Disease patients against outcome is planned.

Despite being used in seemingly lower risk patients, stapled anastomosis was associated with increased anastomotic leak in this observational study. These findings indicate the need for further high quality, prospective and targeted research. It is likely that an updated large scale randomised trial of anastomotic technique in patients undergoing right sided bowel resection is needed.

Table 1: Patient, disease and operative characteristics by anastomosis type

Variable	Handsewn (N=1183)	Stapled (N=1858)	No Anastomosis (N=167)	Total (N=3208)
Patients Characteristics				
Age				
Mean [SD]	66.4 [16]	66.1 [15.8]	63.4 [18.6]	66 [16.1]
Median [IQR]	70 [59-78]	69 [59-77]	68 [54-77]	69 [59-77]
Min - Max	16 - 97	16 - 99	20 - 94	16 - 99
Gender				
Male	605 (51.1%)	935 (50.3%)	89 (53.3%)	1629 (50.8%)
Female	578 (48.9%)	923 (49.7%)	78 (46.7%)	1579 (49.2%)
Body Mass Index				
Normal	439 (37.1%)	671 (36.1%)	71 (42.5%)	1181 (36.8%)
Underweight	39 (3.3%)	60 (3.2%)	8 (4.8%)	107 (3.3%)
Overweight	384 (32.5%)	631 (34%)	39 (23.4%)	1054 (32.9%)
Obese	321 (27.1%)	496 (26.7%)	49 (29.3%)	866 (27.0%)
Smoking Status				
Never	754 (63.7%)	1141 (61.4%)	94 (56.3%)	1989 (62.0%)
Ex-smoker	204 (17.2%)	354 (19.1%)	28 (16.8%)	586 (18.3%)
Current	160 (13.5%)	224 (12.1%)	24 (14.4%)	408 (12.7%)
Not known	65 (5.5%)	139 (7.5%)	21 (12.6%)	225 (7.0%)
History of Ischaemic heart disease or cerebrovascular disease*				
No	918 (77.6%)	1532 (82.5%)	134 (80.2%)	2584 (80.5%)
Yes	265 (22.4%)	326 (17.5%)	33 (19.8%)	624 (19.5%)
History of Diabetes				
None	1000 (84.5%)	1564 (84.2%)	142 (85%)	2706 (84.4%)
Diet/Tablet controlled	141 (11.9%)	239 (12.9%)	18 (10.8%)	398 (12.4%)
Insulin controlled	42 (3.6%)	55 (3%)	7 (4.2%)	104 (3.2%)
Disease Characteristics				
Indication				
Malignant	939 (79.4%)	1503 (80.9%)	73 (43.7%)	2515 (78.4%)
Crohn's disease	123 (10.4%)	220 (11.8%)	32 (19.2%)	375 (11.7%)
Other**	121 (10.2%)	135 (7.3%)	62 (37.1%)	318 (9.9%)
ASA Grade				
Low risk	697 (58.9%)	1250 (67.3%)	60 (35.9%)	2007 (62.6%)
High risk	486 (41.1%)	608 (32.7%)	107 (64.1%)	1201 (37.4%)
Operative Information				
Surgery type				
Elective	941 (79.5%)	1618 (87.1%)	50 (29.9%)	2609 (81.3%)
Emergency	242 (20.5%)	240 (12.9%)	117 (70.1%)	599 (18.7%)
Operation type				
Laparoscopic	536 (45.3%)	1178 (63.4%)	37 (22.2%)	1751 (54.6%)
Open	647 (54.7%)	680 (36.6%)	130 (77.8%)	1457 (45.4%)
Extent of surgery				
Complete (C4)	345 (29.2%)	543 (29.2%)	38 (22.8%)	926 (28.9%)
Extended (C5-7)	596 (50.4%)	912 (49.1%)	61 (36.5%)	1569 (48.9%)
Limited (C1-3)	232 (19.6%)	385 (20.7%)	66 (39.5%)	683 (21.3%)
Missing	10 (0.8%)	18 (1%)	2 (1.2%)	30 (0.9%)

% shown by column. SD=Standard deviation; IQR=Interquartile range.

* Stroke or TIA

** Other includes: appendix-related resections, ischaemia, volvulus, trauma and miscellaneous.

Table 2: Patient, disease and operative characteristics by overall anastomotic leak in patients for whom an anastomosis was performed

(Note - Overall anastomotic leak rate includes those with clinically or radiologically proven leak or intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging)

Variable	Overall anastomotic leak		Total (N=3041*)
	No (N=2796)	Yes (N=245)	
Patient Characteristics			
Age			
Mean [SD]	66.4 [15.9]	64.1 [16]	66.2 [15.9]
Medium [IQR]	69 [59-78]	67 [57-75]	69 [59-77]
Min - Max	16 - 99	18 - 96	16 - 99
Gender			
Male	1396 (90.6%)	144 (9.4%)	1540 (50.6%)
Female	1400 (93.3%)	101 (6.7%)	1501 (49.4%)
Body Mass Index			
Normal	1023 (92.2%)	87 (7.8%)	1110 (36.5%)
Underweight	88 (88.9%)	11 (11.1%)	99 (3.2%)
Overweight	942 (92.8%)	73 (7.2%)	1015 (33.4%)
Obese	743 (90.9%)	74 (9.1%)	817 (26.9%)
Smoking Status			
Never	1759 (92.8%)	136 (7.2%)	1895 (62.3%)
Ex-smoker	513 (91.9%)	45 (8.1%)	558 (18.4%)
Current	340 (88.5%)	44 (11.5%)	384 (12.6%)
Not known	184 (90.2%)	20 (9.8%)	204 (6.7%)
History of Ischaemic heart disease or cerebrovascular disease**			
No	2255 (92.0%)	195 (8.0%)	2450 (80.6%)
Yes	541 (91.5%)	50 (8.5%)	591 (19.4%)
History of Diabetes			
None	2363 (92.2%)	201 (7.8%)	2564 (84.3%)
Diet/Tablet controlled	344 (90.5%)	36 (9.5%)	380 (12.5%)
Insulin controlled	89 (91.8%)	8 (8.2%)	97 (3.2%)
Disease Characteristics			
Indication			
Malignant	2267 (92.8%)	175 (7.2%)	2442 (80.3%)
Crohn's Disease	312 (91.0%)	31 (9.0%)	343 (11.3%)
Other	217 (84.8%)	39 (15.2%)	256 (8.4%)
ASA grade			
Low risk	1802 (92.6%)	145 (7.4%)	1947 (64.0%)
High risk	994 (90.9%)	100 (9.1%)	1094 (36.0%)
Operative Information			
Anastomosis method			
Handsewn	1096 (92.6%)	87 (7.4%)	1183 (38.9%)
Stapled	1700 (91.5%)	158 (8.5%)	1858 (61.1%)
Surgery type			
Elective	2383 (93.1%)	176 (6.9%)	2559 (84.1%)
Emergency	413 (85.7%)	69 (14.3%)	482 (15.9%)
Operation type			
Laparoscopic	1621 (94.6%)	93 (5.4%)	1714 (56.4%)
Open	1175 (88.5%)	152 (11.5%)	1327 (43.6%)
Extent of surgery			
Complete (C4)	819 (92.2%)	69 (7.8%)	888 (29.2%)
Extended (C5-C7)	1383 (91.7%)	125 (8.3%)	1508 (49.6%)
Limited (C1-C3)	569 (92.2%)	48 (7.8%)	617 (20.3%)
Missing	25 (89.3%)	3 (10.7%)	28 (0.9%)

% shown by row. SD=Standard deviation; IQR=Interquartile range.

*Note excludes patients who are classed as anastomosis category "none"; ** stroke or TIA.

Table 3: Univariate and multivariate mixed effects logistic regression analysis

Outcome (Anastomotic leak + Abscess)	Univariate analysis*				Multivariate analysis			
	Odds Ratio	*95% CI*	*P-value*	*Overall p-value*	*Odds Ratio*	*95% CI*	*P-value*	*Overall p-value*
Anastomosis method								
Handsewn	-	-	-		-	-	-	
Stapled	1.16	(0.86, 1.57)	0.342	0.342	1.43	(1.04, 1.95)	0.026	0.026
Patient Characteristics								
Age	0.99	(0.98, 1.00)	0.064	0.064	0.99	(0.98, 1.00)	0.037	0.037
Gender								
Male	-	-	-		-	-	-	
Female	0.70	(0.53, 0.92)	0.011	0.011	0.76	(0.57, 1.02)	0.066	0.066
Body Mass Index								
Normal	-	-	-		-	-	-	
Underweight	1.46	(0.73, 2.91)	0.289		1.25	(0.61, 2.56)	0.543	
Overweight	0.93	(0.66, 1.30)	0.665		0.98	(0.69, 1.38)	0.888	
Obese	1.23	(0.87, 1.72)	0.241	0.315	1.14	(0.80, 1.64)	0.463	0.768
Smoking Status								
Never	-	-	-		-	-	-	
Ex-smoker	1.13	(0.79, 1.63)	0.504		0.99	(0.67, 1.46)	0.968	
Current smoker	1.68	(1.15, 2.43)	0.007		1.38	(0.93, 2.04)	0.106	
Not known	1.47	(0.86, 2.49)	0.158	0.040	1.41	(0.81, 2.44)	0.222	0.269
History of Ischaemic heart disease or cerebrovascular disease								
No	-	-	-		-	-	-	
Yes	1.05	(0.75, 1.47)	0.766	0.766	1.00	(0.69, 1.47)	0.983	0.983
History of Diabetes								
None	-	-	-		-	-	-	
Diet/Tablet controlled	1.21	(0.82, 1.78)	0.338		1.34	(0.89, 2.02)	0.165	
Insulin controlled	1.10	(0.51, 2.35)	0.811	0.624	1.16	(0.53, 2.55)	0.717	0.375
Disease Characteristics								
Indication								
Malignant	-	-	-		-	-	-	
Crohns disease	1.27	(0.83, 1.93)	0.270		1.29	(0.71, 2.34)	0.398	
Other	2.39	(1.62, 3.54)	<0.001	<0.001	1.73	(1.05, 2.85)	0.031	0.095
ASA Grade								
Low risk	-	-	-		-	-	-	
High risk	1.30	(0.98, 1.72)	0.068	0.068	1.24	(0.89, 1.72)	0.197	0.197
Operative Information								
Surgery type								
Elective	-	-	-		-	-	-	
Emergency	2.33	(1.70, 3.19)	<0.001	<0.001	1.40	(0.94, 2.09)	0.101	0.101
Operation type								
Laparoscopy	-	-	-		-	-	-	
Open	2.32	(1.74, 3.08)	<0.001	<0.001	2.09	(1.53, 2.87)	<0.001	<0.001

Extent of surgery								
Complete (C4)	-	-	-		-	-	-	
Extended (C5-C7)	1.07	(0.77, 1.48)	0.688		1.10	(0.79, 1.53)	0.568	
Limited (C1-C3)	0.98	(0.66, 1.47)	0.925	0.869	0.70	(0.44, 1.11)	0.132	0.139

* Univariate analysis included centre as a random effect to taken into account variation across centres.

Table 4: The impact of overall anastomotic leak (and the group with only a 'proven' leak) on clinical outcomes

Group	n	30-day death rate (n; %)	Length of stay (days; median (IQR))
Full cohort	3208	103 (3.2%)	7 (5-11)
No anastomosis made	167	30 (18.0%)	11 (7-20)
In those undergoing anastomosis:	3041	73 (2.4%)	7 (5-10)
No leak or collection evident	2796	49 (1.8%)	7 (5-10)
Anastomotic leak and/or collection*	245	24 (9.8%)	18 (10-27)
Proven anastomotic leak only	150	17 (11.3%)	21 (13-30)

*the primary outcome of this study. IQR=Interquartile range.

Collaborators

Writing group and ESCP Cohort Studies + Audits Sub-Committee: T Pinkney (chair and overall guarantor), N Battersby, A Bhangu, S Chaudhri, A El-Hussuna, M Frasson, D Nepogodiev, B Singh, S Vennix, O Zmora.

ESCP Research Committee: D Altomare, W Bemelman, P Christensen, A D'Hoore, S Laurberg, D Morton (chair), T Pinkney, M Rubbini, C Vaizey.

Logistical support and data collation: L Magill, R Perry, N Sheward (Birmingham Surgical Trials Consortium, University of Birmingham)

Statistical analysis: N Ives, S Mehta (Birmingham Clinical Trials Unit, University of Birmingham)

Local Investigators:

Argentina: M. Cillo, D. Estefania, J. Patron Uriburu, H. Ruiz, M. Salomon (Hospital Britanico de Buenos Aires).

Belarus: A. Makhmudov, L. Selnyahina, A. Varabei, Y. Vizhynis (Surgical Department of the Belarusian Medical Academy of Postgraduate Education).

Belgium: D. Claeys, B. Defoort, F. Muysoms, P. Pletinckx, V. Vergucht (AZ Maria Middelares Gent); I. Debergh, T. Feryn, H. Reusens (AZ Sint-Jan); M. Nachtergaele (AZ St Jozef Malle); D. Francart, C. Jehaes, S. Markiewicz, B. Monami, J. Weerts (Clinique St Joseph, Liege); W. Bouckaert, B. Houben, J. Knol, G. Sergeant, G. Vangertruyden (Jessa Hospital Hasselt); L. Haeck, C. Lange, C. Sommeling, K. Vindevoghel (OLV van Lourdes Ziekenhuis); S. Castro, H. De Bruyn, M. Huyghe (St Augustinus General Hospital); E. De Wolf, D. Reynders (St Vincentius General Hospital); A. D'Hoore, A. de Buck van Overstraeten, A. Wolthuis (University Hospitals Leuven).

Bosnia and Herzegovina: S. Delibegovic (University Clinical Center Tuzla).

Brazil: A. Christiani, M. Marchiori Jr, C. Rocha de Moraes, V. Tercioti Jr (Centro Médico Campinas).

Bulgaria: E. Arabadjieva, D. Bulanov, D. Dardanov, V. Stoyanov, A. Yonkov (First Surgical Department, University Hospital Alexandrovska); K. Angelov, S. Maslyankov, M. Sokolov, G. Todorov, S. Toshev, (Second Surgery Clinic, Sofia Medical University). Y. Georgiev, A. Karashmalakov, G. Zafirov (Virgin Mary Hospital, Burgas).

China: X. Wang, (West China Hospital).

Croatia: D. Condic, D. Kraljik, H. Mrkovic, V. Pavkovic, K. Raguž (GCH Dr Josip Bencevic Slavonski Brod).

Czech Republic: V. Bencurik, E. Holášková, M. Skrovina (Hospital & Oncological Centre Nový Jičín); M. Farkašová, T. Grolich, Z. Kala (Masaryk University Hospital); F. Antos, V. Pruchova (Nemocnice Na Bulovce); O. Sotona, M. Chobola, T. Dusek, A. Ferko, J. Örhalmi (University Hospital Hradec Kralove); J. Hoch, P. Kocian, L. Martinek (University Hospital Motol).

Denmark: I. Bernstein, K. Gotschalck Sunesen, J. Leunbach, O. Thorlacius-Ussing, A. Uth Oveson (Aalborg University Hospital); P. Christensen, S. Dahl Chirstensen, V. Gamez, M. Oeting, U. Schou Loeve, A. Ugianskis (Randers Regional Hospital/Aarhus University Hospital); M. Jessen, P. Krarup, K. Linde (Bispebjerg Hospital); Q. Mirza, J. Overgaard Stovring (Esbjerg Hospital); L. Erritzøe, H. Loft Jakobsen, J. Lykke, E. Palmgren Colov (Herlev Hospital); A. Husted Madsen, T. Linde Friis (Herning Regional Hospital); J. Amstrup Funder, R. Dich (Hospitalsenheden Horsens); S. Kjær, S. Rasmussen, N. Schlesinger (Hvidovre Hospital); M. Dilling Kjaer, N. Qvist (OUH, Svendborg); A. Khalid (Regionshospitalet Viborg); G. Ali, A. El-Hussuna, S. Hadi, L. Rosell Walker (Slagelse Hospital).

Finland: A. Kivelä, T. Lehtonen, A. Lepistö, T. Scheinin, P. Siironen (Helsinki University Central Hospital); J. Kössi, P. Kuusanmäki, T. Tomminen, A. Turunen (Kanta-Häme Central Hospital); T. Rautio, M. Vierimaa (Oulu University Hospital); H. Huhtinen, J. Karvonen, M. Lavonius, A. Rantala, P. Varpe (Turku University Hospital).

France: E. Cotte, Y. Francois, O. Glehen, V. Kepenekian, G. Passot (Centre Hospitalier Lyon-Sud); L. Maggiori, G. Manceau, Y. Panis (CHU Beaujon); M. Gout (CHU Le Bocage); E. Rullier, B. van Geluwe (Hôpital Saint-André); N. Chafai, J. H. Lefevre, Y. Parc, E. Tiret (Hôpital Saint-Antoine); C. Couette, E. Duchalais (University Hospital of Nantes).

Germany: A. Agha, M. Hornberger, A. Hungbauer, I. Iesalnieks, I. Weindl (Klinikum Bogenhausen); F. Crescenti (Klinikum Verden); M. Keller, N. Kolodziejski, R. Scherer, D. Sterzing (Krankenhaus Waldfriede); B. Bock, G. Boehm, M. El-Magd, C. Krones, M. Niewiera (Marienhospital Aachen); J. Buhr, S. Cordesmeyer, M. Hoffmann, K. Krückemeier, T. Vogel (Raphaelsklinik Münster); M. Schön, J. Baral, T. Lukoschek, S. Münch, F. Pullig (Städtisches Klinikum Karlsruhe); K. Horisberger, P. Kienle, J. Magdeburg, S. Post (Universitätsmedizin).

Greece: K. Batzalexis, S. Germanos (General University Hospital of Larissa); C. Agalianos, C. Dervenis, N. Gouvas, P. Kanavidis, A. Kottikias (Konstantopouleio Hospital of Athens); I. E. Katsoulis, D. Korkolis, G. Plataniotis, G. Sakorafas (St. Savvas Cancer Hospital, Athens); I. Akrida, M. Argentou, C. Kollatos, C. Lampropoulos, S. Tsochatzis (University Hospital of Patras).

Hungary: I. Besznyák, A. Bursics, T. Egyed, G. Papp, I. Svastics (Uzsoki Hospital).

Iceland: J. Atladottir, P. Möller, H. Sigurdsson, T. Stefánsson, E. Valsdottir (The National University Hospital in Iceland).

Ireland: E. Andrews, N. Foley, D. Hechtl, M. Majeed, M. McCourt (Cork University Hospital); A. Hanly, J. Hyland, S. Martin, P. R. O'Connell, D. Winter (St Vincent's University Hospital); T. Connelly, W. Joyce, P. Wrafter (The Galway Clinic).

Israel: R. Berkovitz (Hadassah Medical Center); S. Avital, I. Haj Yahia, N. Hermann, B. Shpitz, I. White (Meir Medical Center); Y. Lishtzinsky, A. Tsherniak, N. Wasserberg (Rabin Medical Center, Beilinson Campus); N. Horesh, U. Keler, R. Pery, R. Shapiro, O. Zmora (Sheba Medical Centre); H. Tulchinsky (Tel Aviv Sourasky Medical Center); B. Badran, K. Dayan, A. Iskhakov, J. Lecaros, N. Nabih (Wolfson Medical Center).

Italy: I. Angrima, R. Bardini,E. Pizzolato,M. Tonello (Azienda Ospedaliera - Università degli Studi di Padova); F. Arces, R. Balestri, C. Ceccarelli, V. Prosperi, E. Rossi (Azienda Ospedaliero Universitaria Pisana); I. Giannini, L. Vincenti (Azienda Ospedaliero Universitaria Policlinico Bari); D. F. Altomare, F. Di Candido, M. Di Iena, A. Guglielmi, O. Caputi-Iambrenghi (Department of Emergency and Organ Transplantation, University of Bari); P. Marsanic, A. Mellano, A. Muratore (Candiolo Cancer Institute - FPO - IRCCS); M. Annecchiarico, L. Bencini, S. Amore Bonapasta, A. Coratti, F. Guerra (Careggi Hospital); C. R. Asteria, L. Boccia, L. Gerard, A. Pascariello (ASST- Mantova); G. Manca, F. Marino (Di Summa - Perrino Hospital); A. Casaril, M. Inama, G. Moretto (Hospital “Dott. Pederzoli” Peschiera del Garda - Verona); C. Bacchelli, M. Carvello, N. Mariani, M. Montorsi, A. Spinelli (Humanitas Research Hospital); E. Romairone, S. Scabini (IRCCS San Martino IST); A. Belli, F. Bianco, S. De Franciscis, G. Maria Romano (Istituto Nazionale dei Tumori, Napoli, Unitá di Oncologia Addominale); P. Delrio, U. Pace, D. Rega, C. Sassaroli, D. Scala, (Istituto Nazionale Tumori Napoli); R. De Luca, E. Ruggieri (National Cancer Research Center Instituto “G.Paolo II” IRCCS-BARI); C. Elbetti, A. Garzi, L. Romoli, M. Scatizzi, A. Vannucchi (Ospedale S. Stefano); G. Curletti, V. Durante, R. Galleano, F. Mariani, L. Reggiani (Ospedale Santa Corona); R. Bellomo, A. Infantino (Ospedale Santa Maria dei Battuti); L. Franceschilli, P. Sileri (Policlinico di Tor Vergata); I. Clementi, D. Coletta, F. La Torre, A. Mingoli, F. Velluti (Policlinico Umberto I "La Sapienza" University of Rome); A. Di Giacomo, A. Fiorot, M. Massani, L. Padoan, C. Ruffolo (Regional Hospital Cà Foncello, Treviso); S.

Caruso, F. Franceschini, R. Laessig, I. Monaci, M. Rontini (S.M.Annunziata Azienda Sanitaria Firenze 10); P. De Nardi, U. Elmore, M. Lemma, R. Rosati, A. Tamburini (San Raffaele Scientific Institute and Vita Salute University); M. De Luca, A. Sartori, (San Valentino Hospital); A. Benevento, C. Bottini, C. C. Ferrari, F. Pata, G. Tessera (Sant'Antonio Abate Hospital, Gallarate); G. Pellino, F. Selvaggi (Second University of Naples); A. Lanzani, F. Romano, G. Sgroi, F. Steccanella, L. Turati (Treviglio Hospital).

Japan: T. Yamamoto (Yokkaichi Hazu Medical Centre).

Latvia: G. Ancans, S. Gerkis, M. Leja, A. Pcolkins, A. Sivins (Riga East University Hospital, Latvia Oncology Center);

Lithuania: T. Latkauskas, P. Lizdenis, Ž. Saladžinskas, S. Švagždys, A. Tamelis (Lithuanian University of Health Sciences, Faculty of Medicine, Department of Surgery); A. Razbadauskas, M. Sokolovas (Klaipeda Seamen's Hospital); A. Dulskas, N. Samalavicius (National Cancer Institute); V. Jotautas, S. Mikalauskas, E. Poskus, T. Poskus, K. Strupas (Vilnius University Hospital Santariskiu Klinikos).

Malta: C. Camenzuli, C. Cini, A. Predrag, J. Psaila, N. Spiteri (Mater Dei Hospital).

Netherlands: W. Bemelman, C. Buskens, E. J. de Groof, J. Gooszen, P. Tanis (Academic Medical Center Amsterdam); E. Belgers (Atrium Medical Center Heerlen); P. Davids, E. Furnee, E. Postma, A. Pronk, N. Smakman (Diakonessenhuis); S. Clermonts, D. Zimmerman (Elisabeth-Tweesteden); J. Omloo, E. van der Zaag P. van Duijvendijk, E. Wassenaar (Gelre Hospital Apeldoorn); M. Bruijninckx, E. de Graff, P. Doornebosch, G. Tetteroo, M. Vermaas (IJsselland Ziekenhuis); G. Iordens, S. Knops, B. Toorenvliet (Ikazia Ziekenhuis); H. L. van Westereenen (Isala Hospital Zwolle); E. Boerma, P. Coene, E. van der Harst,A. Van Der Pool (Maasstad Ziekenhuis); M. Raber (Medisch Spectrum Twente Hospital); J. Melenhorst (MUMC+/AZM); S. de Castro, M. Gerhards (Onze Lieve Vrouwe Gasthuis); M. Arron, A. Bremers, H. de Wilt, F. Ferenschild, S. Yauw (Radboud University Medical Center); H. Cense, A. Demirkiran, M. Hunfeld, I. Mulder (Rode Kruis Hospital); J. Nonner (Sint Franciscus Gasthuis); H. Swank, B. van Wagensveld (Sint Lucas Andreas Ziekenhuis); M. Bolmers, J. Briel, A. van Geloven, C. van Rossem (Tergooi Hospital Hilversum); V. Klemann, J. Konsten, B. Leenders, T. Schok (VieCuri Medical Center voor Noord-Limburg); W. Bleeker (Wilhelmina Hospital Assen).

Northern Ireland: A. Gidwani, R. Lawther, P. Loughlin, B. Skelly, R. Spence (Altnagelvin Hospital).

Norway: M. Brun, M. Helgeland, D. Ignjatovic, T. Øresland, P. Yousefi (Akershus University Hospital); I. Flåten Backe, O. Helmer Sjo, A. Nesbakken, M. Tandberg-Eriksen (Oslo University Hospital); A. Cais, J. Hallvard Træland, R. Herikstad, H. Kørner, N. Lauvland (Stavanger University Hospital).

Poland: D. Jajtner, W. Kabiesz, M. Rak (Beskidian Oncological Center); L. Gmerek, K. Horbacka, N. Horst, P. Krokowicz (General and Colorectal Surgery Department University of Medical Sciences); A. Kwiatkowski, K. Pasnik (Military Institute of Medicine); P. Karcz, M. Romaniszyn, T. Rusek, P. Walega (Third Department of General Surgery, Jagiellonian University Medical College); R. Czarencki, Z. Obuszko, M. Sitarska, W. Wojciech, M. Zawadzki (Wroclaw Regional Hospital).

Portugal: S. Amado, P. Clara, A. Couceiro, R. Malaquias, N. Rama (Centro Hospitalar de Leiria); A. Almeida, E. Barbosa, E. Cernadas, A. Duarte, P. Silva (Centro Hospitalar s. João); S. Costa, C. Martinez Insua, J. Pereira, C. Pereira, M. Sacchetti (Centro Hospitalar Tâmega e Sousa); B. Carvalho Pinto, P. Jorge Vieira Sousa, R. Marques, A. Oliveira (Centro Hospitalar Trás os Montes e Alto Douro); R. Cardoso, S. Carlos, J. Corte-Real, P. Moniz Pereira, R. Souto (Garcia de Orta); C. Carneiro, R. Marinho, V. Nunes, R. Rocha, M. Sousa (Hospital Prof.Dr. Fernando Fonseca); J. Leite, F. Melo, J. Pimentel, L. Ventura, C. Vila Nova (Universidade Coimbra).Romania: C. Copăescu (Ponderas Hospital); V. Bintintan, C. Ciuce, G. Dindelegan, R. Scurtu, R. Seicean (Univeristy Emergency Hospital Cluj Napoca).

Russia: N. Domansky, A. Karachun, A. Moiseenko, Y. Pelipas, A. Petrov, I. Pravosudov (N.N.Petrov Research Institute of Oncology); R. Aiupov, Y. Akmalov, A. Parfenov, N. Suleymanov, N. Tarasov (Oncological Centre); H. Jumabaev, Z. Mamedli, A. Rasulov (Russian Cancer Research Center); I. Aliev, I. Chernikovskiy, V. Kochnev, K. Komyak, I. Pravosudov, A. Smirnov (St. Petersburg Clinical Research Center); S. Achkasov, K. Bolikhov, Y. Shelygin, O. Sushkov, A. Zapolskiy (State Scientific Center of Coloproctology).

Serbia: M. Gvozdenovic, D. Jovanovic, Z. Lausevic (Center of Emergency Surgery, Clinical Center of Serbia); D. Cvetković, M. Maravić, B. Milovanovic, N. Stojakovic, I. Tripković (City Hospital Valjevo); D. Mihajlovic, M. Nestorovic, V. Pecic, D. Petrovic, G. Stanojevic (Clinical Centre Nis); G. Barisic, I. Dimitrijevic, Z. Krivokapic, V. Markovic, M. Popovic (First Surgical Clinic, Cilinical Centre of Serbia, Belgrade); A. Aleksic, D. Dabic, I. Kostic, A. Milojkovic, V. Perunicic (General Hospital Cacak); D. Lukic, T. Petrovic, D. Radovanovic, Z. Radovanovic (Oncology Institute of Vojvodina); V. M. Cuk, V. V. Cuk, M. Kenic, B. Kovacevic, I. Krdzic (University Clinical Center Zvezdara).

Slovakia: J. Korcek (Teaching Hospital Nitra).

Slovenia: M. Rems, J. Toplak (General Hospital Jesenice).

Spain: J. Escarrâ, M. Gil Barrionuevo, T. Golda, E. Kreisler Moreno, C. Zerpa Martin (Bellvitge University Hospital); C. Álvarez Laso, P. Cumplido, H. Padin (Cabueñes); J. Baixauli Fons, J. Hernández-Lizoain, P. Martinez-Ortega, M. Molina-Fernández, C. Sánchez-Justicia (Clínica Universidad de Navarra); J. Antonio Gracia Solanas , E. Córdoba Díaz de Laspra, E. Echazarreta-Gallego, M. Elia-Guedea, J. Ramirez (Clinico Universitario, Zaragoza); J. Arredondo Chaves, P. Diez González, T. Elosua, J. Sahagún, A. Turienzo Frade (Complejo Asistencial Universitario de León); J. Álvarez Conde, E. Castrillo, R. Diaz Maag, V. Maderuelo, L. Saldarriaga (Complejo asistencial Universitario de Palencia); I. Aldrey Cao, X. Fernández Varela, S. Núñez Fernández, A. Parajó Calvo, S. Villar Álvarez (Complejo Hospitalario de Ourense); I. Blesa Sierra, A. Duarte, R. Lozano, M. Márquez, O. Porcel (Complejo Hospitalario Torrecárdenas); P. Menendez (Gutierrez Ortega); M. Fernández Hevia, L. Flores Sigüenza, M. Jimenez Toscano, A. Lacy Fortuny, J. Ordoñez Trujillo (Hospital Clínic de Barcelona); A. Espi, S. Garcia-Botello, J. Martín-Arévalo, D. Moro-Valdezate, V. Pla-Martí (Hospital Clínico Universitario de Valencia); F. Blanco-Antona (Hospital Clínico Universitario de Valladolid); J. Abrisqueta, N. Ibañez Canovas, J. Lujan Mompean (Hospital Clínico Universitario Virgen de la Arrixaca); D. Escolá Ripoll, S. Martinez Gonzalez, J. Parodi (Hospital Comarcal de Vilafranca); A. Fernández López, M. Ramos Fernández (Hospital Costa del Sol); J. Castellvi Valls, L. Ortiz de Zarate, R. Ribas, D. Sabia, L. Viso (Hospital de Sant Joan Despí Moisès Broggi); S. Alonso Gonçalves,M. José Gil

Egea,M. Pascual Damieta, M. Pera, S. Salvans Ruiz (Hospital del Mar); J. Bernal, F. Landete (Hospital General de Requena); G. Ais, J. Etreros (Hospital General de Segovia); J. Aguiló Lucia, A. Boscá, S. Deusa, J. García del Caño, V. Viciano (Hospital Lluís Alcanyís); J. García-Armengol, J. Roig (Hospital NISA 9 de Octubre); J. Blas, J. Escartin, J. Fatás, J. Fernando, R. Ferrer (Hospital Royo Villanova); R. Arias Pacheco, L. García Flórez, M. Moreno Gijón, J. Otero Díez, L. Solar Garcia (Hospital San Agustin); F. Aguilar Teixido, C. Balaguer Ojo, J. Bargallo Berzosa, S. Lamas Moure (Hospital Terrassa); J. Enrique Sierra, A. Fermiñán, F. Herrerias, M. Rufas, J. Viñas (Hospital Universitari Arnau de Vilanova); A. Codina-Cazador, R. Farrés, N. Gómez, D. Julià, P. Planellas (Hospital Universitari de Girona Doctor Josep Trueta); J. López, A. Luna, C. Maristany, A. Muñoz Duyos, N. Puértolas (Hospital Universitari Mútua Terrassa); M. Alcantara Moral, X. Serra-Aracil (Hospital Universitari Parc Tauli de Sabadell); P. Concheiro Coello, D. Gómez (Hospital Universitario de A Coruña); C. Carton, A. Miguel, F. Reoyo Pascual, X. Valero Cerrato, R. Zambrano Muñoz (Hospital Universitario de Burgos); J. Cervera-Aldama, J. García González, J. Ramos-Prada, M. Santamaría-Olabarrieta, A. Urigüen-Echeverría (Hospital Universitario de Cruces); R. Coves Alcover, J. Espinosa Soria, E. Fernandez Rodriguez, J. Hernandis Villalba, V. Maturana Ibañez (Hospital Universitario De Elda); F. De la Torre Gonzalez, D. Huerga, E. Pérez Viejo, A. Rivera, E. Ruiz Ucar (Hospital Universitario de Fuenlabrada); J. Garcia-Septiem, V. Jiménez, J. Jiménez Miramón, J. Ramons Rodriquez, V. Rodriguez Alvarez (Hospital Universitario de Getafe); A. Garcea, L. Ponchietti (Hospital Universitario de Torrevieja); N. Borda, J. Enriquez-Navascues, Y. Saralegui (Hospital Universitario Donostia); G. Febles Molina, E. Nogues, Á. Rodríguez Méndez, C. Roque Castellano, Y. Sosa Quesada (Hospital Universitario Dr Negrín); M. Alvarez-Gallego, I. Pascual, I. Rubio-Perez, B. Diaz-San Andrés, F. Tone-Villanueva (Hospital Universitario La Paz); J. Alonso, C. Cagigas, J. Castillo, M. Gómez, J. Martín-Parra (Hospital Universitario Marqués de Valdecilla); M. Mengual Ballester, E. Pellicer Franco, V. Soria Aledo, G. Valero Navarro (Hospital Universitario Morales Meseguer); E. Caballero Rodríguez, P. Gonzalez De Chaves, G. Hernandez, A. Perez Alvarez, A. Soto Sanchez, (Hospital Universitario Ntra Sra de Candelaria); F. Cesar Becerra Garcia , J. Guillermo Alonso Roque , F. López Rodríguez Arias, S. R. Del Valle Ruiz, G. Sánchez De La Villa (Hospital Universitario Rafael Méndez); A. Compañ, A. García Marín, C. Nofuentes, F. Orts Micó, V. Pérez Auladell (Hospital Universitario San Juan de Alicante); M. Carrasco, C. Duque Perez, S. Gálvez-Pastor, I. Navarro Garcia, A. Sanchez Perez (Hospital Universitario Santa Lucía); D. Enjuto, F. Manuel Bujalance, N. Marcelin, M. Pérez, R. Serrano García (Hospital Universitario Severo Ochoa); A. Cabrera, F. de la Portilla, J. Diaz-Pavon, R. Jimenez-Rodriguez, J. Vazquez-Monchul (Hospital Universitario Virgen del Rocío); J. Daza González, R. Gómez Pérez, J. Rivera Castellano, J. Roldán de la Rua (Hospital Virgen de la Victoria); J. Errasti Alustiza, L. Fernandez, J. Romeo Ramirez, J. Sardon Ramos, B. Cermeño Toral (Hospital Universitario Araba); D. Alias, D. Garcia-Olmo, H. Guadalajara, M. Herreros, P. Pacheco (Quironsalud); F. del Castillo Díez F. Lima Pinto, J. Martínez Alegre, I. Ortega, A. Picardo Nieto Antonio (Infanta Sofia University Hospital); A. Caro, J. Escuder, F. Feliu, M. Millan (Joan XXIII University Hospital); R. Alos Company, A. Frangi Caregnato, R. Lozoya Trujillo, R. Rodríguez Carrillo, M. Ruiz Carmona (Sagunto); N. Alonso, D. Ambrona Zafra, B. Amilka Ayala Candia J. Bonnin Pascual, C. Pineño Flores (Son Espases); J. Alcazar Montero, M. Angoso Clavijo, J. Garcia, J. Sanchez Tocino (Universitario de Salamanca); C. Gómez-Alcazar, D. Costa-Navarro, J. Ferri-Romero, M. Rey-Riveiro, M. Romero-Simó (University General Hospital of Alicante); B. Arencibia, P. Esclapez, M. Frasson, E. García-Granero, P. Granero (University Hospital La Fe); F. J. Medina Fernández, A. B. Gallardo Herrera, C.

Diaz López, E. Navarro Rodriguez, E.Torres Tordera (University Hospital Reina Sofía de Córdoba); J. Arenal, M. Citores, J. Marcos, J. Sánchez, C. Tinoco (University Hospital Río Hortega); E. Espin, A. Garcia Granero, L. Jimenez Gomez, J. Sanchez Garcia, F. Vallribera (Valle de Hebron).

Sweden: J. Folkesson, F. Sköldberg (Akademiska Sjukhuset); K. Bergman, E. Borgström, J. Frey, A. Silfverberg, M. Söderholm (Blekingesjukhuset); J. Nygren, J. Segelman (Karolinska Institutet and Ersta Hospital); D. Gustafsson, A. Lagerqvist, A. Papp, M. Pelczar (Hudiksvalls Hospital); M. Abraham-Nordling, M. Ahlberg, A. Sjovall (Karolinska University Hospital); J. Tengstrom (Lidköping); K. Hagman (Ryhov County Hospital); A. Chabok, E. Ezra, M. Nikberg, K. Smedh, C. Tiselius (Västmanlands Hospital Västerås).

Switzerland: N. Al-Naimi, M. Dao Duc, J. Meyer, M. Mormont, F. Ris (Geneva University Hospitals); G. Prevost, P. Villiger (Kantonsspital Graubünden); H. Hoffmann, C. Kettelhack, P. Kirchhoff, D. Oertli, B. Weixler (University Hospital Basel).

Turkey: B. Aytac, S. Leventoglu, B. Mentes, O. Yuksel (Gazi University Medical School, Dep. of Surg); S. Demirbas (Gülhane Military Medical Academy, School of Medicine); B. Busra Ozkan, G. Selçuk Özbalci (Ondokuz Mayis University Medical Faculty); U. Sungurtekin (Pamukkale University School of Medicine); B. Gülcü, E. Ozturk, T. Yilmazlar (Uludag University School of Medicine Hospital).

UK: C. Challand, N. Fearnhead, R. Hubbard, S. Kumar (Addenbrooke's Hospital); J. Arthur, C. Barben, P. Skaife, S. Slawik, M. Williams (Aintree University Hospitals NHS Foundation Trust); M. Zammit (Basildon Hospital); J. Barker, J. French, I. Sarantitis, C. Slawinski (Blackpool Victoria); R. Clifford, N. Eardley, M. Johnson, C. McFaul, D. Vimalachandran (Countess of Chester); S. Allan, A. Bell, E. Oates, V. Shanmugam (Darlington Memorial Hospital); A. Brigic (Doncaster Royal Infirmary); M. Halls, P. Pucher, B. Stubbs (Dorset County Hospital); T. Agarwal, A. Chopada, S. Mallappa, M. Pathmarajah, C. Sugden (Ealing Hospital); C. Brown, E. Macdonald, A. Mckay, J. Richards, A. Robertson (Forth Valley Royal Hospital); M. Kaushal, P. Patel, S. Tezas, N. Touqan (Furness General Hospital); S. Ayaani, K. Marimuthu, B. Piramanayagam, M. Vourvachis (George Eliot Hospitals NHS Trust); N. Iqbal, S. Korsgen, C. Seretis, U. Shariff (Good Hope Hosptal); S. Arnold, N. Battersby, H. Chan, E. Clark, R. Fernandes, B. Moran (Hampshire Hospitals NHS Trust); A. Bajwa, D. McArthur (Heartlands Hospital); K. Cao, P. Cunha, H. Pardoe, A. Quddus, K. Theodoropoulou (Homerton Hospital); C. Bolln, G. Denys, M. Gillespie, N. Manimaran, J. Reidy (Inverclyde Royal Hospital); A. I. Malik, A. Malik, J. Pitt (Ipswich Hospital NHS Trust); K. Aryal, A. El-Hadi, R. Lal, A. Pal, V. Velchuru (James Paget University Hospital); S. Chaudhri, M. Oliveira Cunha, B. Singh, M. Thomas (Leicester General Hospital); S. Bains, K. Boyle, A. Miller, M. Norwood, J. Yeung (Leicester Royal Infirmary); L. Goian, S. Gurjar, W. Saghir, N. Sengupta, E. Stewart-Parker (Luton & Dunstable Hospital); S. Bailey, T. Khalil, D. Lawes, S. Nikolaou, G. Omar (Maidstone and Tunbridge Wells NHS Trust); R. Church, B. Muthiah (Manor Hospital); W. Garrett, P. Marsh, N. Obeid (Medway Maritime Hospital); S. Chandler, P. Coyne, M. Evans (Morriston Hospital); L. Hunt, J. Lim, Z. Oliphant, E. Papworth, H. Weaver, (Musgrove Park Hospital); K. Cuiñas Leon, G. Williams, (New Cross Hospital); J. Hernon, S. Kapur, R. Moosvi, I. Shaikh, L. Swafe (Norfolk and Norwich University Hospital); M. Aslam, J. Evans, U. Ihedioha, P. Kang, J. Merchant (Northampton General Hospital); R. Hompes, R. Middleton (Oxford University Hospitals); A. Broomfield, D. Crutten-Wood, J. Foster, G. Nash (Poole General Hospital); M. Akhtar, M. Boshnaq, S.

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USA: A. Iqbal, A. Khan, K. Perrin, A. Raza, S. Tan (University Hospital of Florida).

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Figure 1: Classification of anastomotic leak

Grade A - Anastomotic leakage requiring no active intervention (diagnosed radiologically)
Grade B - Anastomotic leakage requiring active radiological intervention but manageable without surgical re-intervention
Grade C - Anastomotic leakage requiring surgical re-intervention

NB - Highest score during follow up; e.g. Grade C if percutaneous drainage is followed by laparotomy

Figure 2: Extent of resection – distal resection (colonic) margins as allocated on post-operative CRF

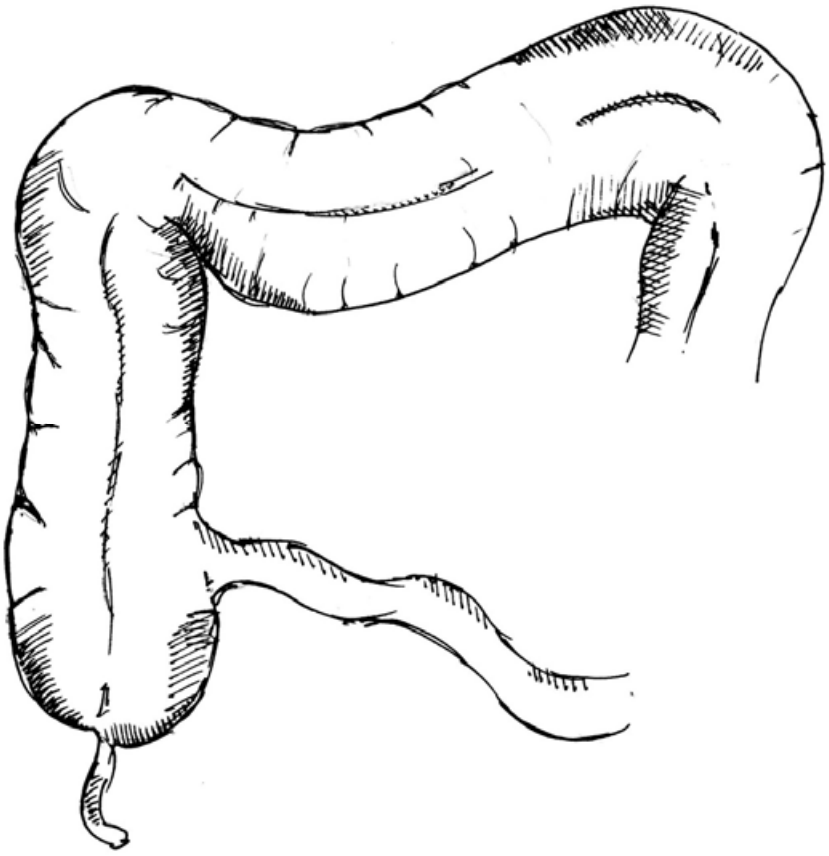

Figure 3: Total number of sites including patients in the audit by European country