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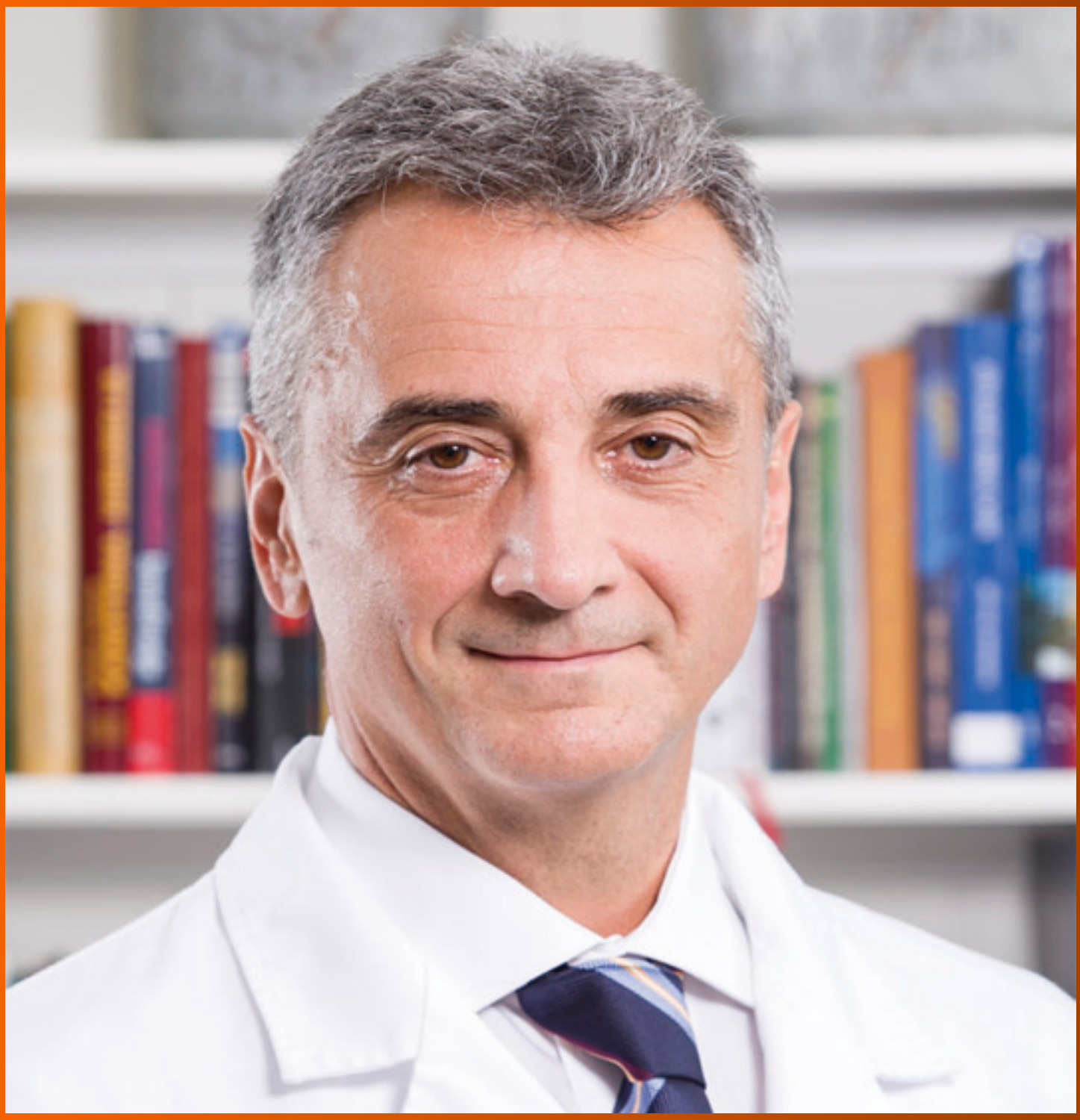

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prediction of overall survival following colorectal cancer surgery in elderly patients

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Author contributions: Chew MH conceived the research and study design; Seow-En I, Dorajoo SR, Soh SHL, Law YC and Park SY contributed to data acquisition and analysis; Seow-En I, Tan WJ, Dorajoo SR and Park SY were involved in interpretation of data and writing of the manuscript; Tan WJ, Choi GS, Tan WS, Tang CL and Chew MH contributed to editing and revision of the article; all authors read and approved the final manuscript.

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Abstract

BACKGROUND

With advanced age and chronic illness, the life expectancy of a patient with colorectal cancer (CRC) becomes less dependent on the malignant disease and more on their pre-morbid condition. Justifying major surgery for these elderly patients can be challenging. An accurate tool demonstrating post-operative survival probability would be useful for surgeons and their patients.

AIM

To integrate clinically significant prognostic factors relevant to elective colorectal surgery in the elderly into a validated pre-operative scoring system.

METHODS

In this retrospective cohort study, patients aged 70 and above who underwent surgery for CRC at Singapore General Hospital between 1 January 2005 and 31 December 2012 were identified from a prospectively maintained database. Patients with evidence of metastatic disease, and those who underwent emergency surgery or had surgery for benign colorectal conditions were

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excluded from the analysis. The primary outcome was overall 3-year overall survival (OS) following surgery. A multivariate model predicting survival was derived and validated against an equivalent external surgical cohort from Kyungpook National University Chilgok Hospital, South Korea. Statistical analyses were performed using Stata/MP Version 15.1.

RESULTS

A total of 1267 patients were identified for analysis. The median post-operative length of stay was 8 [interquartile range (IQR) 6-12] d and median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Following multivariate analysis, the factors significant for predicting overall mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen ≥ 20 μg/L, T stage 3 or 4, moderate tumor cell differentiation or worse, mucinous histology, rectal tumors, and pre-existing chronic obstructive lung disease. Advanced age alone was not found to be significant. The Korean cohort consisted of 910 patients. The Singapore cohort exhibited a poorer OS, likely due to a higher proportion of advanced cancers. Despite the clinicopathologic differences, there was successful validation of the model following recalibration. An interactive online calculator was designed to facilitate post-operative survival prediction, available at http://bit.ly/sgh_crc. The main limitation of the study was selection bias, as patients who had undergone surgery would have tended to be physiologically fitter.

CONCLUSION

This novel scoring system generates an individualized survival probability following colorectal resection and can assist in the decision-making process. Validation with an external population strengthens the generalizability of this model.

Key words: Colorectal cancer surgery; Elderly; Overall survival; Pre-operative prognostic score

Core tip: Ageing results in a decreased functional reserve along with various comorbid diseases. Many elderly patients express age-related concerns when advised for operative intervention. This is the first predictive survival model specific for older patients planned for elective colorectal surgery and provides a visual guide to facilitate the counselling process.

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INTRODUCTION

The world is facing a dramatic increase in the number and proportion of its elderly. Driven by remarkable improvements in life expectancy, the number of people aged 60 years and over is projected to grow from 901 million in 2015 to 1.4 billion in 2030, and more than double that in 2015 to 2.1 billion by 2050[1]. Whilst being a product of economic success and advancement in healthcare, an ageing population will suffer more death and disability from illnesses such as heart disease, diabetes, and cancer[2]. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death globally, accounting for 1.4 million new cases and almost 700 000 deaths in 2012[3]. The incidence and mortality rates for CRC increases with age, with 90% of new cases and over 90% of deaths occurring at 50 years and beyond[4]. This raises genuine concern that CRC will result in a greater burden on healthcare with the shift towards an older demographic.

The normal physiological process of ageing reduces functional capacity and

reserve, leading to a decreased ability to mount an adequate response to stress and resulting in a worse outcome should post-operative complications arise. Another problem is the increasing number and severity of comorbidities with age which may impact patient tolerance of anesthesia. With advanced age and chronic illness, the decision to undergo major surgery in the elderly patient can be challenging. Not infrequently, patients and their family members decline operative intervention due to age-related concerns. Even to the surgeon, the benefit of resection in certain individuals may not be so clear-cut. Moreover, the elderly are under-represented and under-prioritized in randomized trials[5], resulting in difficulty in generalizing existing data. Many clinicians now recognize that surgery in the elderly is different in terms of risks and meaningful outcomes[6].

We aimed to analyze our outcomes following major elective colorectal surgery in the elderly to determine factors significantly influencing mortality. A pre-operative scoring system predicting post-operative outcomes more objectively could then be derived, facilitating the decision-making process for both surgeons and patients.

MATERIALS AND METHODS

Data for all patients aged 70 and above who underwent elective surgery for non-metastatic CRC at Singapore General Hospital (SGH) Department of Colorectal Surgery from 1 January 2005 to 31 December 2012 were obtained from hospital electronic records. Patients with evidence of distant disease, those who underwent emergency surgery or had surgery for benign colorectal conditions were excluded from the analysis. Instances of surgery for CRC recurrence occurring in the same patient over the study period were also excluded. Information for an equivalent group of elderly patients electively operated on at Kyungpook National University Chilgok Hospital (KNUCH), Daegu, South Korea, was retrieved over the same duration.

Statistical analysis

Missing data were filled using multiple imputation, performed via sequential imputation using chained equations with predictive mean matching. The variable with the highest proportion of missing values in the model derivation dataset was 11.5%. All variables, apart from the variable being imputed, were included in the imputation model to avoid bias. A total of 100 imputations were performed. To simplify the eventual prognostic scoring, the "minimum *P* value approach" was adopted to detect appropriate cut points for continuous variables[7,8]. Cut point selection was guided by upper and lower limits of normal laboratory values and an attempt was made to keep cut points to the nearest whole number, tens or fives to facilitate clinical ease of use. As Cox models do not provide a straightforward estimation of the baseline survival function required for predicting absolute survival probabilities, a flexible parametric model [Royston-Parmar (RP)] was constructed instead with all-cause mortality as the outcome[9]. All outcomes were truncated at three years from the time of surgery and patients who had not died were censored at three years. All independent variables were included in the multivariate regression and backward elimination was used to remove variables with *P* values greater than or equal to 0.05 until all the remaining variables had *P* values of < 0.05. A survival score was calculated for all patients using the final RP model's beta coefficients. Patients were stratified by survival score and categorized into three arbitrary prognostic groups, defined using the 20th and 80th percentiles of the survival score. The observed survival profiles of the three prognostic groups were assessed using the Kaplan-Meier estimator and compared using the log-rank test. Calibration was evaluated by visually inspecting the agreement between observed and predicted 3-year survival by superimposing predicted survival profiles over the Kaplan-Meier curves.

External validation

The final RP model derived on the cohort from SGH to predict 3-year post-operative survival was applied on the group of patients from KNUCH. Discrimination and calibration were evaluated as previously described. Where evidence of model miscalibration was observed, recalibration was performed by fitting an RP model to the validation data using the linear predictor of the existing model on the log relative hazard scale. All statistical analyses were performed using Stata/MP Version 15.1 (College Station, TX, United States) and R Version 3.3.4 (www.r-project.org).

Model productization

An online calculator was developed from our model to predict three-year survival profiles. The interactive calculator, generated *via* https://www.shinyapps.io/,

facilitates individualized point-of-care survival probability and aids the visualisation of the predicted survival probability profile over time, given the unique combination of risk factors present[10]. The study protocol has been approved by the SingHealth Institutional Review Board (CIRB Ref No. 2015/2374).

RESULTS

A total of 1643 elective colorectal resections were performed for 1623 patients aged 70 and above over the study duration. One hundred and eighty-seven patients who underwent surgery for non-malignant conditions and 169 patients known to have distant metastasis at the time of surgery were excluded from the analysis. Twenty instances of repeat surgery for cancer recurrence performed for the same patient during the study period were also excluded. Analysis of 1267 resections for colorectal malignancy was performed. Clinical characteristics are shown in Table 1.

Outcome measures used were the 30-d post-operative complication rate, classified according to the Clavien-Dindo tool, and overall survival (OS). Complication details are summarized in Table 2. While just under one-quarter of patients experienced early complications, high grade complications of Clavien-Dindo III or higher only occurred in 82 patients (6.5%). These included 30 deaths within the initial 30 post-operative days; 21 were secondary to cardiorespiratory complications, eight were attributable to anastomotic leaks and the remaining one was due to a cerebrovascular accident.

The median post-operative length of stay was 8 (IQR 6-12) dand median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Of 670 deaths occurring within the follow-up up period, 339 were attributable to CRC (51%), while 331 (49%) died of other causes. Disease recurrence occurred in 276 (22%), with a median time from surgery to recurrence of 13 (IQR 7-23) mo. Most cancer recurrences presented at distant locations only (65%), while locoregional recurrence without distant metastasis occurred in 30 patients (11%). Disease relapse in both local and distant organs accounted for a quarter of all recurrences (24%).

Univariate analysis of all suitable pre-operative variables is shown in Table 3. The final multivariate model for predicting OS is provided in Table 4 with the resultant survival curves generated from this model in Figure 1. The model stratifies OS reasonably well in terms of discrimination (separation of the three risk category curves) and calibration (agreement between observed and predicted survival curves for each risk category).

Baseline characteristics of patients from the Singapore and the Korean cohorts are compared head-to-head in Table 5. The SGH and KNUCH cohorts differ considerably in terms of survival, with the 80th percentile surviving 18 mo *vs* 85 mo respectively (Figure 2). Applying the model developed from the SGH cohort to stratify patients in the KNUCH dataset expectedly revealed model miscalibration. However, relative separation between the observed survival curves of patients in the three risk categories showed acceptable model discrimination (Figure 3). Model recalibration improved the agreement between the observed and predicted survival curves (Figure 4).

Interactive online calculators

Following successful external validation, the model was productized as an interactive online calculator, available at http://bit.ly/sgh_crc.

DISCUSSION

One of the biggest challenges in healthcare is coping with an ageing population. In Singapore, the proportion of over 65-year-old has doubled from 6.0% in 1990 to 11.8% in 2015. With an annual increase of 0.5%-0.7% per year, this figure is expected to reach 20%-25% of the population by 2030. Life expectancy at birth in 2015 was 82.9 years (males 80.5 years, females 85.1 years), with the old age-dependency ratio climbing steadily to reach 16.2 per 100 residents (aged 15 to 64 years old)[11]. This census highlights not only the increasing proportion of the elderly but the potential strain on the rest of the working population. A similar trend can be observed in many developed nations worldwide.

In 2000, the Colorectal Cancer Collaborative Group published a systemic review of 28 studies consisting of more than 34000 patients, looking at outcomes post-colorectal surgery[12]. Patients were stratified by age group; less than 65 years, 65-74 years, 75-84 years, and above 84 years. The median post-operative mortality rates across these age groups were 3.0%, 6.4%, 8.6%, and 19.4% respectively. Median anastomotic leak rates

Table 1 Patient, surgery, and disease characteristics

Variable	SGH cohort (*n* = 1267)
Age, median (range), yr	77 (70-102)
Gender	
Male	658 (51.9)
Female	609 (48.1)
Race	
Chinese	1148 (90.6)
Malay	50 (4.0)
Indian	30 (2.4)
Others	39 (3.1)
ECOG status	
0 (asymptomatic)	751 (59.3)
1	401 (31.6)
2	85 (6.7)
3	23 (1.8)
4 (bedbound)	7 (0.2)
ASA score	
1	178 (14.0)
2	857 (67.6)
3	225 (17.8)
4	7 (0.6)
Tumor site	
Colon	790 (62.3)
Rectum	477 (37.6)
Surgical approach	
Open	888 (70.1)
Laparoscopic	379 (29.9)
Surgery	
High Anterior resection	505 (40.0)
Low Anterior resection	163 (12.9)
Ultra-Low Anterior resection	150 (11.8)
Right Hemicolectomy	286 (22.6)
Abdominoperineal resection	58 (4.6)
Others	105 (8.3)
TMN stage[a]	
1	240 (18.9)
2	416 (32.8)
3	442 (34.9)
Tumor diameter, median (IQR), cm	4.5 (3–6)
Number of lymph nodes harvested, median (IQR)	15 (11–20)
Neoadjuvant therapy	22 (1.8)
Adjuvant therapy	219 (17.6)

[a]American Joint Committee on Cancer Staging, 7th edition. All values are reported as *n* (%) unless otherwise stated. ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; IQR: Interquartile range; SGH: Singapore General Hospital.

were 4.0%, 5.0%, 4.0% and 3.0% respectively. The data does suggest that good surgical outcomes can be achieved in the elderly, but individualized evaluation of treatment goals and communication of realistic anticipated outcomes are essential[13].

Several risk stratification systems have been developed. Established scoring methods such as the American Society of Anesthesiologists score and Charlson Comorbidity Index are commonly used but have well described flaws; the former is too subjective with little specificity, and the latter was not designed to predict peri-operative risks in surgical patients. Colorectal surgery-specific scoring, such as the

Table 2 30-d post-operative complications *n* (%)

	SGH cohort (*n* = 1267)
Overall 30-d complications	297 (23.4)
Clavien-Dindo classification	
I	75 (5.9)
II	140 (11.0)
III	21 (1.7)
IV	31 (2.4)
V (death)	30 (2.4)
Type of complication	
Cardiac/CVA	97 (7.7)
Respiratory	28 (2.2)
Urinary	24 (1.9)
Wound/stoma	55 (4.3)
Anastomotic leak	16 (1.3)
Others	77 (6.1)

SGH: Singapore General Hospital; CVA: Cerebrovascular accident.

ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (Cr-POSSUM) and the Association of Coloproctology of Great Britain and Ireland scoring systems are validated as accurate predictors of 30-d post-operative mortality[14], but contain intraoperative or tumor staging parameters, which limit their use as a pre-operative optimization or counselling tool. This motivated us to develop a prognostic assessment tool to quantify the risk of mortality and predict survival after surgery in the elderly.

In the Singapore cohort, the rates of anastomotic leak, 30-d morbidity and 30-d mortality were 1.3%, 23.4% and 2.4% respectively. These outcomes are comparable to existing data on the elderly published during the past 10 years, with reported anastomotic leak rates ranging from 0.8%-5.9%, 30-d complications rates 17%-38% and 30-d mortality rates 0%-16%[15-22].

Only the OS prediction model was selected for validation with the external cohort, for several reasons. High grade morbidity of Clavien-Dindo grade III or IV accounted for less than one-fifth of the overall complications arising within 30 d. This limited the clinical applicability of a model predicting early clinically-relevant morbidity due to the small number of events. Moreover, the main causes of post-operative morbidity in elderly patients are known to be cardiovascular or pulmonary in nature[12,22], each of which already have existing specific risk assessment tools[23,24]. Compared to OS, predicting disease-free survival may also not be as practical to the geriatric patient with several life expectancy-limiting illnesses. Cancer-specific survival in the elderly has previously already been shown to be similar to that of the younger age group[12]. In the multivariate model, factors significant for predicting 3-year all-cause mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen ≥ 20 μg/L, T stage 3 or 4, tumor cell differentiation of moderate or worse, mucinous histology, rectal tumors, and the presence of existing chronic obstructive lung disease (COPD). As the model was intended to serve as a pre-operative patient counselling tool, intra-operative findings and information only available following final histopathological examination of the resected specimen were not included in the analysis.

Determination of the local stage of colorectal cancer can be difficult before surgery. A recent meta-analysis of 13 studies showed that computed tomography had good overall sensitivity of 90% at differentiating T1-T2 from T3-T4 colonic tumors[25], although a lower specificity estimate of 69% likely stemmed from radiologists interpreting benign pericolic desmoplastic reaction as tumor invasion to reduce the risk of understaging. Nodal stage prediction pre-operatively is even less precise and this was therefore not included in the univariate analysis.

Of all comorbidities analyzed (Table 3), only COPD remained significant for poorer OS on multivariate analysis. While COPD is known to confer a higher risk of early morbidity and mortality following abdominal surgery[26], longer term survival may be adversely influenced by associated pulmonary hypertension as well as the extra-pulmonary inflammatory effects of the disease[27]. Active smoking per se did not prove significant on univariate analysis.

Interestingly, age did not significantly influence OS on multivariate analysis, unlike

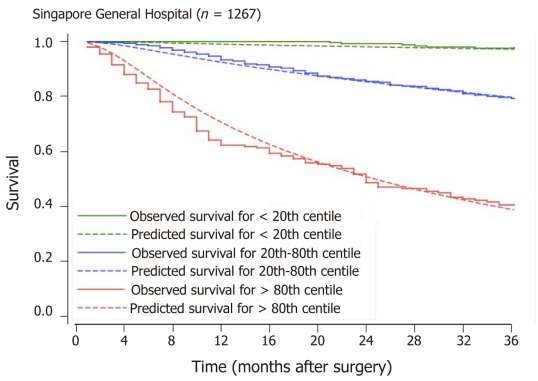

Figure 1 Observed survival probabilities of patients in the three risk score categories compared against model-based predicted probabilities for each group. *P* value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).

in previous studies[12,22]. This demonstrates that advanced age alone without the presence of other predictors will not necessarily lead to a poorer outcome and should not be a contraindication to major resection.

The Singapore and Korean cohorts were similar in terms of patient age, cancer location and tumor differentiation. Disparity in survival between the populations was likely a result of a larger distribution of advanced cancers in the Singapore group; 18.2% *vs* 11.5% had T4 tumors, and 19.1% *vs* 10.9% had N2 disease. Median pre-operative CEA levels were also significantly higher in the SGH cohort (4.3 μg/L *vs* 2.4 μg/L). This may reflect a trend of elderly patients presenting later in the disease process in the Singapore population compared to Korean. The advent of national healthcare electronic records implemented in Singapore may also mean that mortality events are more readily captured even if they had discontinued follow-up at our institution.

Despite the differences in OS between the Singapore and Korea cohorts, observably distinct separation between survival curves was displayed when the Singapore model was applied to the external population (Figure 3). This suggests discriminatory capacity of the predictors for revealing relative survival differences amongst elderly patients who had undergone surgery for CRC. In absolute terms, however, the predicted survival probabilities generated did not match the observed survival profile of the external validation cohort and appeared miscalibrated. Regressing the original scores on observed survival in the external cohort allowed for the identification of an appropriate correction factor (beta coefficient). This was used to recalibrate the original scores following which successful validation was evident in the improved agreement between the observed and predicted survival curves (Figure 4).

Our study was subject to the limitations and bias inherent in observational retrospective research. The most important limitation was selection bias. Elderly patients who had already undergone elective surgery would have tended to be physiologically fitter based on traditional methods of patient evaluation. While it would have been ideal to compare our cohort with cancer patients who had not had surgery over the study duration, this information was unavailable. Measures of patient frailty or function, *e.g.*, hand grip strength or ambulatory distance, while increasingly recognized as predictors of surgical morbidity and mortality in the elderly[28], was neither consistently recorded during the study duration nor has any part of current practice at our institution. The dissimilarity in survival between the cohorts may reflect the shortcomings of comparison between the populations of two distinct geographical locations, but eventual validation of the model notwithstanding these variations can be considered a strength. To ensure predictive accuracy of the model, further validation including re-identification of a correction factor with possible recalibration should be undertaken before use in separate populations.

In conclusion, while clinical decision-making for elderly patients with CRC can be challenging, advanced age per se is not a risk factor for poorer survival outcomes and patients should not be denied surgery based on age alone. However, there is a need for more objective pre-operative risk stratification in this vulnerable group of patients. Our novel scoring system predicting mortality following major resection uses parameters which are available before the surgery and can assist in the counselling and decision-making process between surgeons, their patients and families. Validation with an external Asian population strengthens the generalizability of this scoring method, although further validation may be necessary prior to adoption in

Table 3 Unadjusted hazard ratios of individual predictors in association with 3-year survival duration obtained via univariate Royston-Parmar regression

Predictors	*n*	HR (95%CI)	*P* value
Gender	1267	1.03 (0.81-1.31)	0.807
Age	1267	1.00 (0.98-1.03)	0.826
Race			
Chinese	1148	1.00 (ref)	
Malay	50	1.14 (0.60-2.14)	0.682
Indian	30	1.43 (0.78-2.68)	0.272
Others	39	0.67 (0.25-1.82)	0.433
Smoking status			
Non-smoker	1055	1.00 (ref)	
Smoker	212	1.07 (0.78-1.47)	0.692
Primary lesion site			
Colon	790	1.00 (ref)	
Rectum	477	1.40 (1.09-1.80)	0.008
Tumor stage			
Tis/T1	97	1.00 (ref)	
T2	188	1.52 (0.31-7.41)	0.605
T3	752	10.8 (2.7-43.1)	0.001
T4a	97	42.9 (10.5-173.5)	< 0.001
T4b	133	37.9 (9.38-153.2)	< 0.001
Tumor grade			
Well differentiated	117	1.00 (ref)	
Moderately differentiated	1009	3.85 (1.82-8.15)	< 0.001
Poorly differentiated or mucinous	141	8.59 (3.90-18.94)	< 0.001
Past medical history			
Diabetes Mellitus	331	1.07 (0.81-1.41)	0.655
Hypertension	416	1.17 (0.91-1.51)	0.217
End stage renal failure	26	1.73 (0.54-5.53)	0.354
Previous myocardial infarction	47	0.95 (0.50-1.81)	0.881
Previous PCI, cardiac surgery or angina	140	1.36 (0.88-2.09)	0.161
Congestive heart failure	41	1.18 (0.52-2.69)	0.698
Peripheral vascular disease	30	1.14 (0.52-2.53)	0.744
Impaired sensorium, *e.g.*, dementia	14	2.77 (0.40-19.2)	0.304
Chronic obstructive pulmonary disease	61	0.44 (0.29-0.68)	< 0.001
Previous stroke or TIA	90	1.08 (0.66-1.76)	0.758
Previous stroke with neurological deficits	38	1.19 (0.53-2.69)	0.675
Dependent functional status	60	0.81 (0.43-1.54)	0.529
ECOG			
0	751	1.00 (ref)	
1	404	0.98 (0.76-1.28)	0.903
2 or more	116	1.13 (0.72-1.79)	0.595
ASA			
1	178	1.00 (ref)	
2	857	0.75 (0.53-1.06)	0.099
3 or more	232	0.78 (0.51-1.19)	0.250
Laboratory parameters			
Serum albumin (g/L)	1119	0.94 (0.92-0.96)	< 0.001
Carcinoembryonic antigen (μg/L)	1196	1.01 (1.00-1.01)	< 0.001
White blood cell count ($\times 10^9$/L)	1267	1.11 (1.06-1.15)	< 0.001
Platelet count ($\times 10^3$/L)	1267	1.00 (1.00-1.00)	< 0.001
Serum sodium (mmol/L)	1247	0.95 (0.91-0.98)	0.002
Serum creatinine (μmol/L)	1265	1.00 (0.99-1.00)	0.244
Serum potassium (mmol/L)	1263	0.75 (0.56-0.99)	0.049

Serum urea (mmol/L)	1264	0.98 (0.93-1.04)	0.517
Hemoglobin (g/dL)	1243	0.85 (0.79-0.91)	0.002
Lesion size (cm)	1267	2.03 (1.53-2.70)	< 0.001
Dichotomized predictors[a]			
Age ≥ 80 yr	1267	0.92 (0.70-1.21)	0.540
Serum albumin < 35 g/L	1266	2.16 (1.69-2.76)	< 0.001
Carcinoembryonic antigen ≥ 20 μg/L	1247	4.33 (3.39-5.54)	< 0.001
White blood cell count ≥ 8.5×10^9/L	1265	1.78 (1.40-2.28)	0.001
Platelet count ≥ 450×10^3/L	1263	2.36 (1.67-3.35)	< 0.001
Serum sodium < 135 mmol/L	1264	1.62 (1.20-2.20)	0.002
Serum creatinine ≥ 135 μmol/L	1243	0.56 (0.31-1.02)	0.057
Serum potassium < 3.5 mmol/L	1267	1.37 (1.01-1.85)	0.043
Serum urea ≥ 7 mmol/L	1267	1.00 (0.71-1.40)	0.999
Hemoglobin < 11 g/dL	1243	1.48 (1.16-1.89)	0.002
Lesion size ≥ 4 cm	1267	2.03 (1.53-2.70)	< 0.001

[a]Corrected *P* values for dichotomized variables due to multiple testing. ECOG: Eastern Cooperative Oncology Group; Ref: Reference; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack.

differing patient cohorts.

Table 4 Multivariable model predicting all-cause mortality, truncated at 3 years from time of surgery

Variable	Hazard ratio	2.5thpercentile	97.5thpercentile	*P* value
Serum albumin < 35 g/dL	1.41	1.08	1.83	0.011
CEA ≥ 20 μg/L	2.51	1.92	3.28	< 0.001
T stage				
T1/Tis	1.00 (ref)	-	-	-
T2	1.11	0.23	5.41	0.894
T3	6.18	1.55	24.6	0.010
T4	17.9	4.45	72.1	< 0.001
Tumor grade				
Well differentiated	1.00 (ref)	-	-	-
Moderately differentiated	2.24	1.04	4.82	0.040
Poorly differentiated or mucinous	3.54	1.54	8.15	0.003
Rectal lesion	1.47	1.11	1.96	0.007
Chronic obstructive lung disease	1.87	1.11	3.17	0.019

These factors were identified following progressive elimination of non-significant candidate predictors until all predictors retained in the final model had *P* values below 0.05. CEA: Carcinoembryonic antigen; ref: Reference.

Table 5 Comparison between Singapore General Hospital; and Kyungpook National University Chilgok Hospital cohorts

Variable	SGH(*n* = 1267)		KNUCH(*n* = 910)	
	n		*n*	
Age, median (range), yr	1267	77 (70-102)	910	75 (70-96)
Gender				
Male	658	(51.9)	496	(54.5)
Female	609	(48.1)	414	(45.5)
Lesion sites				
Colon	790	(62.3)	540	(59.3)
Rectum	477	(37.6)	370	(40.7)
Tumor grade				
Well differentiated	117	(9.0)	29	(3.2)
Moderately differentiated	1009	(79.6)	809	(88.9)
Poorly differentiated	70	(5.5)	29	(3.2)
Mucinous/signet ring cell	71	(5.6)	43	(4.7)
Laboratory parameters, mean (SD)				
Creatinine, μmol/L	1267	88.9 (54.9)	910	83.8 (38.6)
Urea, mmol/L	1267	5.5 (2.7)	910	2.7 (1.1)
Hemoglobin, g/dL	1267	11.8 (1.8)	910	12.0 (2.1)
WBC count, × 10^9/L	1267	7.9 (2.6)	908	8.0 (18.2)
Platelet count, × 10^9/L	1267	300.6 (104.6)	910	287.1 (95.3)
Serum albumin, g/L	1119	33.7 (5.5)	910	39.9 (4.6)
CEA, median (IQR), μg/L	1196	4.3 (2.6–14.2)	887	2.4 (1.5–4.8)
Comorbidities				
Diabetes	331	(26.1)	167	(18.4)
Hypertension	416	(32.8)	415	(45.6)
Ischemic heart disease	47	(3.7)	14	(1.5)
Congestive heart failure	41	(3.2)	20	(2.2)
PVD	30	(2.4)	0	(0.0)
COPD	61	(4.8)	66	(7.3)
Previous stroke	90	(7.1)	50	(5.5)
End stage renal disease	26	(2.1)	6	(0.7)
ASA				

1	178	(14.0)	152	(16.7)
2	857	(67.6)	724	(79.6)
3	225	(17.8)	34	(3.7)
4	7	(0.6)	0	(0.0)
T stage[a]				
Tis	2	(0.2)	8	(0.9)
T1	95	(7.5)	72	(7.9)
T2	188	(14.8)	134	(14.7)
T3	752	(59.4)	587	(64.5)
T4a	97	(7.7)	76	(8.4)
T4b	133	(10.5)	29	(3.2)
ypCR	0	(0.0)	4	(0.4)
N stage[a]				
N0	688	(54.3)	577	(63.4)
N1a	148	(11.7)	124	(13.6)
N1b	185	(14.6)	109	(12.0)
N1c	4	(0.3)	1	(0.1)
N2a	99	(7.8)	58	(6.4)
N2b	143	(11.3)	41	(4.5)
Short term outcomes				
Anastomotic leak	16	(1.3)	44	(4.8)
30-d morbidity	297	(23.4)	212	(23.3)
30-d mortality	30	(2.4)	1	(0.001)

[a]American Joint Committee on Cancer Staging, 7th edition. All values are reported as *n* (%) unless otherwise stated. KNUCH: Kyungpook National University Chilgok Hospital; SGH: Singapore General Hospital; WBC: White blood cell; CEA: Carcinoembryonic antigen; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists; ypCR: Pathological complete response following neoadjuvant therapy.

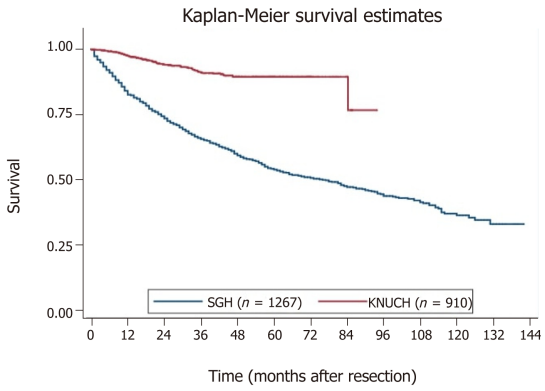

Figure 2 Kaplan-Meier overall survival curves of the 2 cohorts. SGH: Singapore General Hospital; KNUCH: Kyungpook National University Chilgok Hospital.

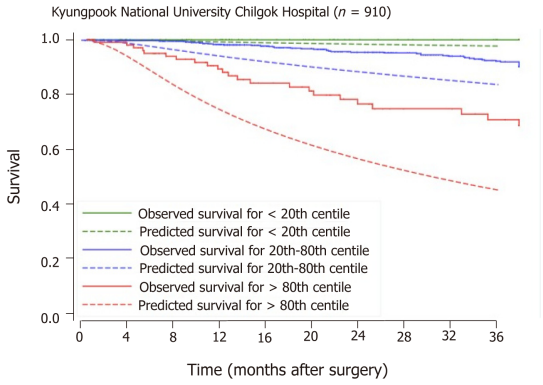

Figure 3 Observed survival probabilities of patients in the three risk score categories of the validation cohort compared against model-based predicted probabilities for each risk categories. *P* value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).

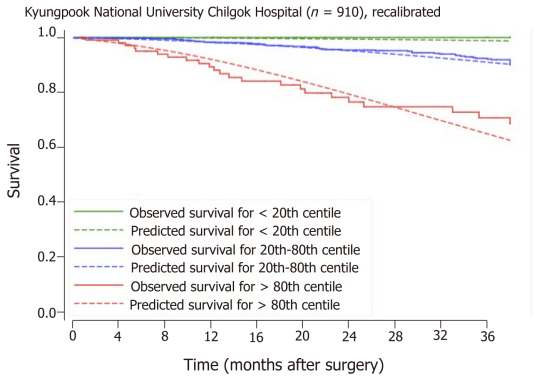

Figure 4 Recalibrated model applied to the Korean cohort. *P* value < 0.001 for separation of Kaplan-Meier survival curves (solid lines).

ARTICLE HIGHLIGHTS

Research background

Driven by remarkable improvements in life expectancy, the world is facing a dramatic increase in the number and proportion of its elderly. The incidence and mortality rates for colorectal cancer (CRC) increases with age, resulting in a greater burden on healthcare. Moreover, the life expectancy of an elderly patient with CRC may depend less on the malignant disease and more on their pre-morbid condition. Data shows that good surgical outcomes can be achieved in the elderly, but individualized evaluation of treatment goals and communication of realistic anticipated outcomes are essential.

Research motivation

With advanced age and chronic illness, the decision to undergo major surgery in the elderly patient can be challenging. Not infrequently, patients and their family members decline operative intervention due to age-related concerns. Even to the surgeon, the benefit of resection in certain individuals may not be so clear-cut. Moreover, the elderly are under-represented and under-prioritized in randomized trials, resulting in difficulty in generalizing existing data. Established risk stratification methods are commonly used but have well described flaws. This motivated us to develop a specific prognostic assessment tool to quantify the risk of mortality and predict survival after surgery in the elderly.

Research objectives

We aimed to analyze our outcomes following major elective colorectal surgery in the elderly to determine factors significantly influencing mortality. A pre-operative scoring system predicting post-operative outcomes more objectively could then be derived, facilitating the decision-making process for both surgeons and patients.

Research methods

Data for all patients aged 70 and above who underwent elective surgery for non-metastatic CRC at Singapore General Hospital Department of Colorectal Surgery from 1 January 2005 to 31 December 2012 were obtained from hospital electronic records. Patients with evidence of distant disease, those who underwent emergency surgery or had surgery for benign colorectal conditions were excluded from the analysis. Instances of surgery for CRC recurrence occurring

in the same patient over the study period were also excluded. Information for an equivalent group of elderly patients electively operated on at Kyungpook National University Chilgok Hospital, Daegu, South Korea, was retrieved over the same duration.

Research results

A total of 1267 patients were identified for analysis. The median post-operative length of stay was 8 [interquartile range (IQR) 6-12] d and median follow-up duration was 47 (IQR 19-75) mo. Median OS was 78 (IQR 65-85) mo. Following multivariate analysis, the factors significant for predicting overall mortality were serum albumin < 35 g/dL, serum carcinoembryonic antigen ≥ 20 μg/L, T stage 3 or 4, moderate tumor cell differentiation or worse, mucinous histology, rectal tumors, and pre-existing chronic obstructive lung disease. Advanced age alone was not found to be significant. The Korean cohort consisted of 910 patients. The Singapore cohort exhibited a poorer OS, likely due to a higher proportion of advanced cancers. Despite the clinicopathologic differences, there was successful validation of the model following recalibration. An interactive online calculator was designed to facilitate post-operative survival prediction, available at http://bit.ly/sgh_crc.

Research conclusions

Advanced age per se is not a risk factor for poorer survival outcomes and patients should not be denied surgery based on age alone. However, there is a need for more objective pre-operative risk stratification in this vulnerable group of patients. Our novel scoring system predicting mortality following major resection uses parameters which are available before the surgery and can assist in the counselling and decision-making process between surgeons, their patients and families. Validation with an external Asian population strengthens the generalizability of this scoring method.

Research perspectives

While it was not possible compare our cohort with cancer patients who had not had surgery over the study duration, this information should be considered for future studies. The dissimilarity in survival between the cohorts may reflect the shortcomings of comparison between the populations of two distinct geographical locations, but eventual validation of the model notwithstanding these variations can be considered a strength. To ensure predictive accuracy of the model, further validation including re-identification of a correction factor with possible recalibration should be undertaken before use in separate populations.

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ORIGINAL ARTICLE

Prospective Study

Patients with Crohn's disease have longer post-operative in-hospital stay than patients with colon cancer but no difference in complications' rate

2015 European Society of Coloproctology (ESCP) collaborating group

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Author contributions: Conception of the study, analyses of data and writing the article: S. Dich Grandt and A. El-Hussuna (guarantor and corresponding author); Statistical analysis: Rikke Nørmark Mortensen (department of epidemiology- Aalborg University Hospital-Aalborg- Denmark); Writing group: M. Frasson, B Singh, G. Gallo, F. Pata and I. Negoi (draft reading and corrections); ESCP Cohort Studies Committee: T. Pinkney (chair), O Zmora, A Bhangu, N Battersby, S Chaudhri, D Nepogodiev, S Vennix, J Glasbey, A Minaya, L Basso, M Pukuotukai, M E Kelly, L Sánchez- Guillén, G Pellino, N. Buchs. ESCP Research Committee: D Morton (chair), T Pinkney, W Bemelman, P Christensen, A D'Hoore, S Laurberg, M Rubbini, C Vaizey; Logistical support and data collation: L Magill, R Perry, N Sheward (Birmingham Surgical Trials Consortium, University of Birmingham).

Institutional review board statement: The study was reviewed and approved by the European Society of Coloproctology Institutional Review Board.

Informed consent statement: This is not applicable as this paper reports a prospective audit conducted bt European Society of Colo-Proctology in 2015.

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Abstract

BACKGROUND

Right hemicolectomy or ileocecal resection are used to treat benign conditions like Crohn's disease (CD) and malignant ones like colon cancer (CC).

AIM

To investigate differences in pre- and peri-operative factors and their impact on post-operative outcome in patients with CC and CD.

METHODS

This is a sub-group analysis of the European Society of Coloproctology's prospective, multi-centre snapshot audit. Adult patients with CC and CD undergoing right hemicolectomy or ileocecal resection were included. Primary outcome measure was 30-d post-operative complications. Secondary outcome measures were post-operative length of stay (LOS) at and readmission.

RESULTS

Three hundred and seventy-five patients with CD and 2,515 patients with CC were included. Patients with CD were younger (median = 37 years for CD and 71 years for CC ($P < 0.01$), had lower American Society of Anesthesiology score (ASA) grade ($P < 0.01$) and less comorbidity ($P < 0.01$), but were more likely to be current smokers ($P < 0.01$). Patients with CD were more frequently operated on by colorectal surgeons ($P < 0.01$) and frequently underwent ileocecal resection ($P < 0.01$) with higher rate of de-functioning/primary stoma construction ($P < 0.01$). Thirty-day post-operative mortality occurred exclusively in the CC group (66/2515, 2.3%). In multivariate analyses, the risk of post-operative complications was similar in the two groups (OR 0.80, 95%CI: 0.54-1.17; $P = 0.25$). Patients with CD had a significantly longer LOS (Geometric mean 0.87, 95%CI: 0.79-0.95; $P < 0.01$). There was no difference in re-admission rates. The audit did not collect data on post-operative enhanced recovery protocols that are implemented in the different participating centers.

Conflict-of-interest statement: None.

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CONCLUSION
Patients with CD were younger, with lower ASA grade, less comorbidity, operated on by experienced surgeons and underwent less radical resection but had a longer LOS than patients with CC although complications' rate was not different between the two groups.

Key words: Crohn's disease; Colon cancer; Complications; Length of stay; Bowel resection; Right hemicolectomy

Core tip: This paper shows that patients with Crohn's disease (CD) have longer post-operative stay at the hospital although they were younger than those with colon cancer (CC), had a lower American Society of Anesthesiology score grade and had less comorbidity. They were also operated on by experienced surgeons and had undergone less radical resection than those with CC. This may stimulate further researches to investigate the factors influencing post-operative length of stay at hospital in patients with CD.

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INTRODUCTION

Surgery is definitive treatment for patients with colon cancer (CC) and an option for patients with Crohn's disease (CD) in case of complications or non-response to medical treatment.

CC and CD have some common features like geographical distribution where both diseases have high incidence in western countries. Incidences are rising in countries adopting western lifestyles[1,2], and among immigrants from low-incidence countries that move to western countries, suggesting that lifestyle is a risk factor[3,4]. Inexpedient diet and smoking are well known risk factors for both CC and CD[5-8]. Moreover, there is an evidence of genetic components in the pathogenesis of both diseases[2,9].

The two diseases differ in incidence. CD incidence is higher among women and the average age at diagnosis is approximately 30 years[10]. In contrast, the incidence of CC is slightly higher among men[11,12], with 90% of patients over 50 years when diagnosed[13]. Although bowel resection is performed for both diseases, the techniques implemented may differ. The extent of resection in CC is based on vascular supply and lymphatic drainage of the tumour. Therefore, central ligation of tumour draining blood vessels, lymph nodes harvest and free resection margin are important[11]. In contrast, central ligation of blood vessels and lymph nodes harvest are less important for patients with CD. The disease-free resection margin might influence recurrence rate[14,15].

Literature search showed no large prospective study investigating the effect of pre- and peri-operative risk factors in CD and CC on post-operative outcome. Retrospective and small series prospective studies showed divergent results[16-21]. There is a need for a large prospective study investigating post-operative outcome in patients with CC and CD to identify areas warranting further research like allocation of resources, pre-operative optimization and surgical techniques in the two patient groups respectively.

The aim of this study is to investigate differences in pre- and peri-operative factors and their impact on post-operative outcome in patients with CC and CD undergoing Right hemicolectomy or ileocecal resection. The two groups have previously been investigated separately within the ESCP snapshot audit, but this analysis presents the two in the same paper to demonstrate how the same surgical procedure have different post-operative outcome depending on the underlying disease.

MATERIALS AND METHODS

Patients

The ESCP snapshot audit included adult patients undergoing right hemicolectomy or ileocecal resection, regardless of the operative approach, in both elective and emergency settings. The inclusion period extended over a 2-mo period from January 15th to March 15th, 2015. Thirty-day post-operative outcome was reported. Details of centre inclusion, data entry and collection, follow up, approvals and patient recruitment as well as inclusion and exclusion criteria were based on a prespecified protocol[22] and have been explained in the main study of this audit[23]. No details about enhanced recovery after surgery program were registered in the snapshot audit however, ERAS is now standard in most of the world. Criteria for admission to critical care unit was decided by routine guidelines in the participating centers. Details on pre-operative characteristics, surgery for CD and post-operative outcome in patients with CD is explained in the recently published paper on this cohort[24] while details about the CC cohort are reported in another paper (in press). ESCP study on CD reported pre-operative characteristics and indication for surgical interventions in CD. It investigated and adjusted for risk factors which are specific to CD[24] for example steroid, biological treatment and pre-operative sepsis while the other cohort studied factors specific for CC like chemotherapy, details of resection and anastomosis.

Outcome measures

Primary outcome measure was 30-d overall post-operative complication. Secondary outcome measures were post-operative length of stay (LOS) in hospital measured in days after operation and re-admission rates. Clinically suspected anastomosis leak, intraabdominal pelvic collection, surgical site infection (SSI) and reoperation were investigated as specific complications.

Statistical analysis

For univariate analyses, Mann-Whitney *U* test was used to test continuous variables while categorical variables were tested using Pearson's Chi-Square or Fisher's exact test when relevant. Continuous variables were reported by median and interquartile range (IQR) while categorical variables were reported as frequencies. Variables that showed a significant association with the outcome in the univariate analyses ($P < 0.05$) and variables deemed clinically important were included as covariates in the multivariate analysis model. We used logistic regression models for binary outcome variables (*e.g.*, complication yes/no) and linear regression models for the continuous variables. Results of the logistic regression analyses are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). The LOS variable was log-transformed, and results of the linear regression models are presented as the geometric mean with corresponding 95%CI. *P*-value < 0.05 was considered statistically significant. Statistician (RN) chose geometric mean due to the type of data from the audit. A multivariate model was constructed for each of the outcome variables that the study investigated. Analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.2010) and the R statistical software version 3.2.2.

RESULTS

The ESCP snapshot audit included 3208 patients from 284 centres in 39 countries. The included patients underwent ileo-ceal resection or right hemi-coloectomy due to CC, CD or other reasons. Overall data completeness record in this audit was 97.4%. This is a sub group analysis of the original data from the audit. This subgroup includes 375 patients with CD and 2,515 patients with CC.

Pre- and peri-operative characterization

Patients with CD were significantly different from those with CC in most of the pre-operative characteristics as shown in Table 1. Patients with CD were predominantly female, more likely to be smokers and had more previous surgeries. In contrast patients with CC were older, had higher body mass index (BMI), more comorbidities, higher serum creatinine and lower haemoglobin. Patients with CD were more likely to be operated on by colorectal surgeons 83.5% (313/375) compared to patients with CC 71.5% (1798/2515, $P < 0.01$). Two thirds of patients with CD had ileocecal resection while almost all patients with CC had right hemicolectomy. Details of anastomosis explained in the main study[23]. Patients with CD were at higher risk of de-functioning/primary stoma construction compared to patients with CC ($P < 0.01$). The rate of unplanned intraoperative adverse events (UIAE) was higher in CD (14.9%)

compared to CC (9.15%).

Univariate analysis of post-operative outcomes

In unadjusted analysis, both groups had a median LOS in hospital of 7.0 d (IQR 5.0) as shown in Figure 1. There was no significant difference in risk of post-operative complications (33.6% in CD *vs* 38% in CC, $P = 0.099$). A closer look at anastomotic leak, SSI and reoperation did not show a significant difference between the two groups. Nevertheless, CC patients were more likely to be admitted to a critical care unit (773/2515, 30.7%) compared to patients with CD (70/375, 18.7%, $P < 0.01$). Sixty-six patients with CC died within the follow up period (2.3%) while no mortality was reported in patients with CD [details about causes of death are explained in the study of CC cohort (in press)]. Post-operative CRP levels (within first 3 d) were significantly higher in patients with CD [median (IQR) 133 (162)] compared to patients with CC [108 (134), $P < 0.01$].

Multivariate analyses

After adjustment for confounding factors the risk of post-operative complications and the risk of admission to critical care unit were not significantly different between the two cohorts (OR 0.80, 95%CI: 0.54-1.17 and OR 1.43, 95%CI: 0.94-2.18, respectively), as shown in Table 2. However, patients with CC had a significantly shorter stay in hospital compared to patients with CD (Geometric mean 0.87, 95%CI: 0.79-0.95). Factors associated with longer LOS are shown in Table 3.

Post-operative complications do not explain the longer LOS in patients with CD as Figure 2 illustrates. Emergency surgery increased the risk of complications (OR 1.55, 95%CI: 1.18-2.05, $P = 0.002$) and admission to critical care unit (OR 1.47, 95%CI: 1.12-1.93, $P = 0.006$) in the combined cohort data of CD and CD. There was, however, no significant difference between patients with CD and patients with CC who underwent emergency surgery.

DISCUSSION

This study showed that patients with CD had the same risk of post-operative complications but longer post-operative LOS at hospital compared to patients with CC. To the authors knowledge, this has not previously been investigated in a prospective study. A large retrospective database study, examining the cost of elective surgery for diverticulitis compared to other diseases, found that patients with inflammatory bowel diseases (IBD) were more likely to develop post-operative complications, compared to patients with CC[16]. An older retrospective study found higher morbidity and mortality rates for patients with CC compared to patients with IBD[17]. A recent retrospective observational study including 109 patients found no significant differences between patients with CC and CD regarding risk of post-operative complications, anastomotic leakage, SSI and death[18]. In other smaller series studies, SSI rates were higher in patients with CD compared to patients with CC[19,20]. However, no difference in readmission rates was shown[21].

Tables 2 and 3 show pre- and peri-operative risk factors and their effect on post-operative outcome. Patients with CC might have higher risk of post-operative complications and longer LOS due to their older age, higher pre-operative creatinine, higher American Society of Anesthesiology score (ASA) grade, comorbidities, higher BMI and having undergone more radical resections compared to patients with CD. Risk factors for longer LOS in patients with CD like smoking, de-functioning stoma, previous surgeries and emergency setting were adjusted in a multivariate model, indicating that there might be other explanations for the longer LOS in this group of patients, which are not accounted for in this paper. A BMI below 18.5 is another factor which significantly increases the LOS, but this is also adjusted for in the LOS model, which shows that a low BMI cannot explain the increased LOS in patients with CD either. This was not investigated in this study, thus further studies are needed to rule out that elements of malnutrition play a part in the LOS and post-operative status of patients with CD.

Timing of operation may be a modifiable risk factor for un-favourable post-operative outcome in patients with CD[24] but emergency surgery cannot explain the longer LOS because both groups of patients had the same rate of emergency operations. UIAEs increase the risk of post-operative complications as well as LOS. It is expected to have higher risks for UIAEs in patients with CD due to the inflammatory nature of the disease and previous surgeries in the area, but this was not the case after adjusting for other factors in the multivariate analyses.

Being a chronic disease not curable by surgery or medical treatment, patients with CD might have a higher inflammatory profile in response to surgery. This is

Table 1 Patients' demographics, pre- and peri-operative patient characterization *n* (%)

Variables	CC *n* = 2515	CD *n* = 375	*P* value
Age (yr)[1]	71 (15)	37 (23)	< 0.01
Haemoglobin (g/dL)[1]	11.9 (3)	12.8 (2)	< 0.01
Gender Male Female	1310 (52.1) 1205 (48.9)	161 (42.9) 214 (57.1)	0.01
History of diabetes	463 (18.4)	7 (1.9)	< 0.01
History of IHD	548 (21.8)	10 (2.7)	< 0.01
BMI ≤ 18.5 18.6-25 25.1-30 > 30 Missing	57 (2.5) 926 (39.9) 867 (37.4) 468 (20.2) 197 (7.8)	43 (12.4) 209 (60.4) 72 (20.8) 22 (6.4) 29 (7.7)	< 0.01
ASA grade I II III IV V	250 (9.9) 1261 (50.1) 903 (35.9) 98 (3.9) 3 (0.01)	88 (23.5) 239 (63.7) 45 (12.0) 3 (0.8) 0 (0)	< 0.01
Abnormal s. creatinine	294 (11.6)	13 (3.5)	< 0.01
Smoking status Non-smoker Current smoker Ex-smoker Missing	1587 (63.1) 268 (10.7) 486 (19.3) 174 (6.9)	219 (58.4.1) 81 (23.1) 52 (14.8) 23 (6.1)	< 0.01
Previous surgery in the area	607 (24.1)	122 (32.5)	< 0.01
Urgency of surgery Elective/expedited Emergency	2216 (88.1) 299 (11.9)	321 (85.6) 54 (14.4)	0.130
Surgeon in charge Colorectal surgeon General surgeon	1798 (71.5) 717 (28.5)	313 (83.5) 62 (16.5)	< 0.01
Operative approach Laparoscopy Converted to open Open	1221 (48.5) 219 (8.7) 1075 (42.7)	177 (47.2) 42 (11.2) 156 (41.6)	0.317
Type of resection Ileocecal resection Right hemicolectomy	125 (5.0) 2390 (95.0)	266 (70.9) 109 (29.1)	< 0.01
De-functioning stoma	78 (3.1)	46 (12.3)	< 0.01
Skin closure technique Suture closure Stapled Others	842 (33.5) 1450 (57.7) 223 (8.9)	196 (52.2) 145 (38.7) 34 (9.1)	< 0.01
Unplanned Intra-operative events[2]	230 (9.15)	56 (14.9)	< 0.01
Duration of operation (minutes)[1]	130 (65)	128 (59)	0.831

Patients with Crohn's disease were younger, with lower American Society of Anesthesiology score grade, less comorbidity, operated on by experienced surgeons and underwent less extensive surgery. Pre- and peri-operative patient characterization (*n*/%). Missing data were observed in the following variables: "Age", "BMI", "Smoking status", "Haemoglobin" and "Duration of operation".

[1]Median (IQR);

[2]Some patients may have more than one unplanned intra-operative event. IHD: Ischemic heart diseases; CRP: C-reactive protein; BMI: Body mass index; CD: Crohn's disease; CC: Colon cancer; UIAEs: Unplanned intraoperative adverse events; ASA: American Society of Anesthesiology score.

supported by higher peak CRP when compared to patients with CC. Early surgical intervention after non-response to medical treatment as well as pre-operative optimization might therefore be beneficial in this group[25], especially when standard optimization schemes are implemented[26]. Patients with CD have higher risk for post-operative psychiatric morbidity[27] which might be a factor influencing LOS in this group of patients.

A similar paper was by Piessen *et al*[28] about prevalence of and risk factors for morbidity after left colectomy showed that disease entity can affect post-operative outcome for the same type of surgical intervention. A population-based study compared elective sigmoidectomy for diverticular disease with same intervention for cancer[29] showing different types of complications in the two groups. Our study on right side colectomy showed that same intervention can have different outcome according to underlying disease. This is important to plan pre-operative optimization in different diseases.

The strengths of this study include a prospective standardized approach, large geographical diversity (34 European countries, Argentina, Brazil, China, Japan and United States), and a large patient sample. The audit did not collect detailed data about nutritional status, disease severity in CD, pre-operative staging and neo-adjuvant chemo-radiotherapy in CC. These might influence the outcome and present a limitation. Another limitation might be reporting bias although it is unlikely given the method of data entry, where patient data is locked/saved pre- and peri-operatively, before any complications are registered. Comparison of LOS in patients with CD and CC might be tricky, as there are no standardized recovery pathways for either patient group in this study however, this study provides a valuable snapshot of reality.

Despite these limitations, this sub-group analysis of data from the ESCP snapshot audit can generate hypotheses and stimulate further studies. This study shows that

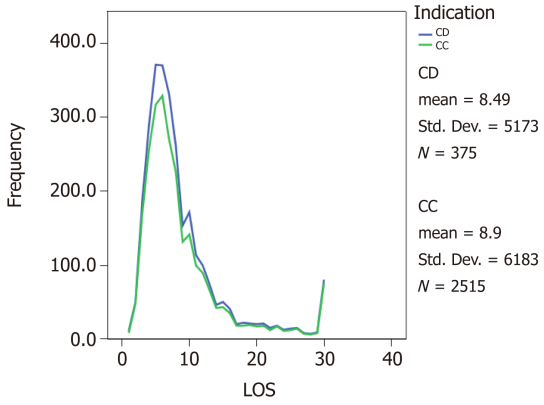

Figure 1 Post-operative length of stay at hospital in patients with Crohn's disease compared to those with colon cancer. CD: Crohn's disease; CC: Colon cancer; LOS: Length of stay.

patients with CD, despite their young age and relatively good health have a tendency for longer LOS in hospital, which cannot be fully explained by any of the investigated variables. This indicates that more can be done to improve the post-operative outcome in patients with CD. Further studies are needed to shed a light on the complexities of CD surgery and to examine whether certain approaches, such as standardized pre-operative optimization schemes or earlier surgical intervention, can improve the post-operative outcome for patients with CD. The power of this study is to be a brick in the design of a post-operative recovery program for patients with CD who seemed to be slow in recovering compared to patients with CC.

In conclusion, patients with CD were younger, with lower ASA grade, less comorbidity, operated on by experienced surgeons and underwent less radical resection, but had a longer post-operative stay in hospital compared to patients with CC. More studies are needed to investigate this association.

Table 2 Risk factors of post-operative complications in multivariate analyses

Variable	Units	OR	95%CI	*P* value
Indication	CC *vs* CD	0.80	0.54-1.17	0.25
Gender	Male *vs* female	1.53	1.28-1.83	< 0.01[a]
Age	Years	1.01	1.01-1.02	< 0.01[a]
BMI	≤ 18.5 *vs* 18.6-25	1.37	0.87-2.17	0.18
	25.1-30 *vs* 18.6-25 > 30 *vs* 18.6-25	0.88 1.11	0.72-1.07 0.87-1.42	0.21 0.39
ASA grade	IV-V *vs* I-III	1.63	1.04-2.56	0.03
IHD	IHD *vs* no IHD	1.17	0.94-1.46	0.16
Diabetes	History of diabetes *vs* no history of diabetes	1.05	0.84-1.32	0.66
Smoking	Ex-smoker *vs* never smoker	1.27	[1.02-1.58	0.04[a]
	Current smoker *vs* never smoker	1.31	1.01-1.70	0.04[a]
Haemoglobin		0.99	0.95-1.03	0.62
Operating surgeon	General surgeon *vs* colorectal surgeon	1.11	0.91-1.34	0.31
Urgency	Emergency *vs* eLective/expedited	1.55	1.18-2.05	< 0.01[a]
De-functioning/primary stoma	De-functioning stoma *vs* no de-functioning stoma	1.13	0.52-2.45	0.77
Duration of operation	≥ 120 min *vs* < 120 min	1.34	1.13-1.59	< 0.01[a]
Operative approach	Converted *vs* laparoscopy	0.97	0.72-1.32	0.85
	Open *vs* laparoscopy	1.52	1.24-1.85	< 0.01[a]
Unplanned intraoperative adverse events	Any UIAES *vs* no UIAEs	1.54	1.21-1.95	< 0.01[a]
CRP		1.01	1.00-1.01	< 0.01[a]
Previous surgery	Any previous surgery *vs* no previous surgery	1.26	1.04-1.52	0.02[a]
Resection type	Right hemicolectomy *vs* ileocecal resection	0.86	0.63-1.19	0.37
Skin closure	Stapled *vs* suture	1.44	1.19-1.75	< 0.01[a]

Logistic regression. The model was adjusted for: Gender, age, BMI, ASA grade, ischemic heart disease, diabetes, smoking, haemoglobin, operating surgeon, urgency, defunctioning/primary stoma, duration of operation, operative approach, anastomosis type, unplanned intraoperative adverse events, CRP, previous surgery, resection type and skin closure.
[a]Significant outcomes. IHD: Ischemic heart diseases; CRP: C-reactive protein; BMI: Body mass index; CD: Crohn's disease; CC: Colon cancer; UIAEs: Unplanned intraoperative adverse events; ASA: American Society of Anesthesiology score.

Table 3 Risk factors affecting the post-operative length of stay at hospital in multivariate analyses

Variable	Units	Estimates	95%CI	*P* value
Indication	CC *vs* CD	0.87	0.79; 0.95	< 0.01[a]
Gender	male *vs* female	1.06	1.01; 1.10	0.01[a]
Age		1.01	1.00; 1.01	< 0.01[a]
BMI	≤18.5 *vs* 18.6-25	1.23	1.10; 1.38	< 0.01[a]
	25.1-30 *vs* 18.6-25 >30 *vs* 18.6-25	0.98 1.04	0.92; 1.04 0.96; 1.12	0.54 0.35
ASA grade	IV-V *vs* I-III	1.04	0.94; 1.16	0.45
IHD	IHD *vs* no IHD	1.07	1.01; 1.13	0.01[a]
Diabetes	History of diabetes *vs* no history of diabetes	1.02	0.96; 1.08	0.50
Smoking	Ex-smoker *vs* never smoker	0.98	0.92; 1.04	0.43
	Current smoker *vs* never smoker	1.05	0.98; 1.11	0.15
Haemoglobin		0.99	0.98; 1.00	0.06
Operating surgeon	General surgeon *vs* colorectal surgeon	1.10	1.05; 1.15	< 0.01[a]
Urgency	Emergency *vs* elective/expedited	1.06	0.99; 1.14	0.08
De-functioning/primary stoma	De-functioning stoma *vs* no de-functioning stoma	1.46	1.21; 1.77	< 0.01[a]
Duration of operation	≥ 120 *vs* < 120	1.08	1.04; 1.13	< 0.01[a]
Operative approach	Converted *vs* laparoscopy	1.10	1.02; 1.18	0.01[a]
	Open *vs* laparoscopy	1.35	1.29; 1.42	< 0.01[a]
Unplanned intraoperative adverse events	Any UIAES *vs* no UIAEs	1.08	1.02; 1.15	0.01[a]
CRP		1.00	1.00; 1.00	< 0.01[a]
Previous surgery	Any previous surgery *vs* no previous surgery	1.03	0.98; 1.08	0.23
Resection type	Right hemicolectomy *vs* ileocecal resection	1.03	0.96; 1.11	0.42

Skin closure	Stapled *vs* suture	1.06	1.01; 1.11	0.02[a]

Linear regression: The outcome is log-transformed. The model is adjusted for: Gender, age, BMI, ASA grade, ischemic heart disease, diabetes, smoking, haemoglobin, operating surgeon, urgency, defunctioning/primary stoma, duration of operation, operative approach, anastomosis type, unplanned intraoperative adverse events, CRP, previous surgery, resection type and skin closure.
[a]Significant outcomes. IHD: Ischemic heart diseases; CRP: C-reactive protein; BMI: Body mass index; CD: Crohn's disease; CC: Colon cancer; UIAEs: Unplanned intraoperative adverse events; ASA: American Society of Anesthesiology score.

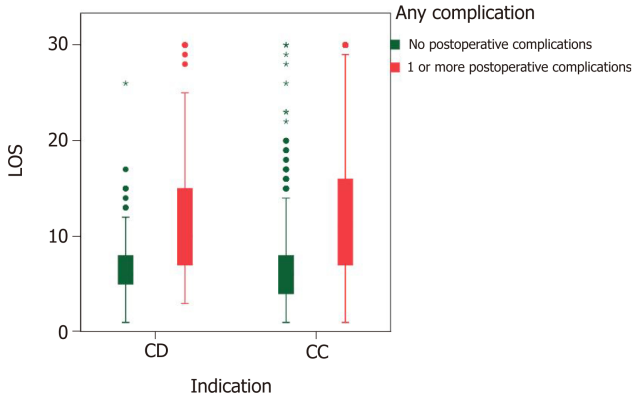

Figure 2 Post-operative length of stay at hospital in patients with Crohn's disease compared to those with colon cancer showing length of stay in patients with and without post-operative complications. CD: Crohn's disease; CC: Colon cancer; LOS: Length of stay.

ARTICLE HIGHLIGHTS

Research background
Right hemicolectomy or ileocecal resection are used to treat benign conditions like Crohn's disease (CD) and malignant ones like colon cancer (CC).

Research motivation
There is a need for a large prospective study investigating postoperative outcome in patients with CC and CD to identify areas warranting further research like allocation of resources, preoperative optimization and surgical techniques in the two patient groups respectively.

Research objectives
The objective of this study is to investigate differences in pre- and peri-operative factors and their impact on postoperative outcome in patients with CC and CD.

Research methods
This is a sub-group analysis of the European Society of Coloproctology's prospective, multi-centre snapshot audit. Adult patients with CC and CD undergoing right hemicolectomy or ileocecal resection were included. Primary outcome measure was 30-d postoperative complications. Secondary outcome measures were postoperative length of stay at and readmission.

Research results
375 patients with CD and 2,515 patients with CC were included. Patients with CD were younger, with a median of 37 years for CD and 71 years for CC ($P < 0.01$), had lower ASA grade ($P < 0.01$) and less comorbidity ($P < 0.01$), but were more likely to be current smokers ($P < 0.01$). Patients with CD were more frequently operated on by colorectal surgeons ($P < 0.01$) and frequently underwent ileocecal resection ($P < 0.01$) with higher rate of de-functioning/primary stoma construction ($P < 0.01$). Thirty-day postoperative mortality occurred exclusively in the CC group (66/2515, 2.3%). In multivariate analyses, the risk of postoperative complications was similar in the two groups (OR 0.80, 95%CI: 0.54-1.17; $P = 0.25$). Patients with CD had a significantly longer length of stay (Geometric mean 0.87, 95%CI: 0.79-0.95; $P < 0.01$). There was no difference in re-admission rates.

Research conclusions
Patients with CD were younger, with lower American Society of Anesthesiology score grade, less comorbidity, operated on by experienced surgeons and underwent less extensive surgery but had a longer length of stay than patients with CC although complications' rate was not different between the two groups.

Research perspectives
This study is hypothesis-generating study. It will stimulate further researches to explore the factors that affect the length of postoperative stay in the hospital.

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The list of the full authors and their contributions are listed in the supplementary file.

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CASE REPORT

Novel technique for anastomotic salvage using transanal minimally invasive surgery: A case report

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Abstract

BACKGROUND

Anastomotic leak (AL) after low anterior resection (LAR) can be a highly morbid complication. The incidence of AL ranges from 5% to 20% depending on patient characteristics and the distance of the anastomosis from the anal verge. Low anastomoses and leaks pose technical challenges for endoscopic treatment. The aim of this report was to describe the use of a commercially available laparoscopic energy device through a transanal minimally invasive surgery (TAMIS) port for the management of a symptomatic leak not requiring relaparotomy (grade B) after a LAR with diverting loop ileostomy.

CASE SUMMARY

A TAMIS GelPOINT Path port was inserted into the anus to access the distal rectum. Pneumorectum was achieved with AirSeal insufflation and a 30 degree laparoscope was introduced through a trocar. A LigaSure™ Retractable L-Hook device was then used to perform a septotomy of the chronic sinus tract identified posterior to the coloproctostomy. The procedure was then repeated twice in three weeks intervals with ultimate resolution of the chronic leak cavity. Several months after serial TAMIS septotomies, barium enema demonstrated a patent anastomosis with no evidence of persistent leak or stricture. The patient subsequently underwent ileostomy reversal and has had no significant post-operative issues.

CONCLUSION

TAMIS septotomy with the LigaSure™ Retractable L-Hook is a feasible and

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effective, minimally invasive salvage technique for the treatment of grade B ALs. Larger studies are needed to assess the generalizability and long-term results of this technique.

Key words: Transanal minimally invasive surgery; Ligasure hook; Anastomotic leak; Low anterior resection; Septotomy; Case report

Core tip: Anastomotic leaks (ALs) after low anterior resection for the treatment of rectal cancer are highly morbid complications and often pose a technical challenge for its treatment. We report a case of a transanal minimally invasive septotomy of a chronic sinus secondary to an AL, with the use of the Ligasure retractable L-Hook device. This safe and effective technique may help avoid re-operations which are associated with higher mortality and higher permanent stoma rates.

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INTRODUCTION

Colorectal cancer remains the third most common cause of cancer related deaths in the United States among men and women. The American Cancer Society estimates there to be over 43000 new patients diagnosed with rectal cancer yearly[1]. Mortality associated with this pathology is proportionally related to the staging of the disease prior to surgical treatment.

Over the past decades, significant advancements have been made in the management of rectal cancer in efforts to improve locoregional control. Among these, universal adoption of neoadjuvant therapy has been as important as the improvements in surgical techniques to control local spread of cancer and recurrence rates. After the introduction of restorative anterior resection by Dixon in 1948, boosted by the advent of surgical staplers and total mesorectal excision (TME) during proctectomy, there was an increase in the proportion of low anterior resection (LAR) over abdominoperineal resection (APR) for the treatment of rectal cancer[2-6]. However, the improved oncologic and functional outcomes resulted in higher leak rates associated with colorectal and coloanal anastomoses[7,8].

LAR for colorectal cancer has a reported morbidity of 20% with anastomotic leak (AL) being among the most dreaded complications. Multivariate analysis and logistic regression models evaluating risk factors for AL after LAR demonstrate that the lower the anterior resection, the more likely an AL will occur[9,10]. Reported rates of AL range between 5% to 20%[11-14]. This variation is in part attributed to the lack of a universally accepted nomenclature and classification of ALs. In 2010, the International Study Group of Rectal Cancer proposed a definition and severity grading system for AL after anterior resection of the rectum[15]. The proposed grading system constituted three groups based on the severity of the AL: Grade A represents an AL identified on imaging not requiring therapeutic interventions. Grade B is a leak requiring interventions such as administration of antibiotics, transanal lavage and/or radiologic assisted placement of a pelvic drain, but not re-laparotomy. And lastly, grade C is a leak requiring re-laparotomy.

Within the options for management of grade B ALs, endoscopic interventions are often used to diagnose and treat the underlying pathology. The ability to treat the AL with minimally invasive techniques is paramount as re-operation is associated with higher mortality rates and higher rates of a permanent stoma[14,16,17].

The purpose of this study was to describe the utility of a commercially available laparoscopic energy device, LigaSure™ Retractable L-Hook (Medtronic, Minneapolis, MN), through transanal minimally invasive surgery (TAMIS) as a novel technique for the management of a grade B AL after LAR.

CASE PRESENTATION

Chief complaints

A 69-year-old hispanic male initially presented with abdominal pain, weight loss, and hematochezia.

History of present illness

Patient was seen in gastroenterology clinic after 6-month having experienced lower abdominal pain, malaise, unintentional weight loss and loose bowel movement with occasional blood in the stool. Patient denied any similar symptoms prior to that time.

History of past illness

Past medical history was positive for benign essential hypertension.

Personal and family history

Personal and family history were negative for colorectal cancer, inflammatory bowel disease or other gastrointestinal diseases.

Physical examination upon admission

On physical examination, abdomen was soft, non-tender, with no palpable masses. Digital rectal examination revealed a palpable circumferential mass at approximately 7 cm from anal verge.

Laboratory examinations

Routine blood tests including complete blood count, comprehensive metabolic panel and urinalysis were all within normal limits, except hypochromic microcytic anemia with a hemoglobin of 7.4 g/dL and carcinoembryonic antigen was elevated to 4.1 ng/dL (normal range 0.0-3.0 ng/dL)

Imaging examinations

Patient underwent a diagnostic colonoscopy which revealed a near-obstructing, circumferential, ulcerated rectal mass at 7 cm from anal verge (Figure 1). Magnetic resonance imaging of the pelvis was consistent with extramural invasion of the tumor into the muscularis propria with mesorectal nodal involvement.

FINAL DIAGNOSIS

Biopsy performed during colonoscopy revealed an invasive, moderately differentiated adenocarcinoma of the rectum (T3N1).

TREATMENT

The patient underwent neoadjuvant chemotherapy with 5-Fluorouracil in combination with radiation therapy. Ten weeks after completion of neoadjuvant therapy, he was taken to the operating room for a robotic assisted laparoscopic LAR with TME, stapled coloproctostomy and diverting loop ileostomy. Post-operative course was complicated by a grade B AL with presacral abscess (Figure 2) requiring intravenous antibiotic therapy and percutaneous drainage by interventional radiology. The drain was kept in place for 2 wk and was ultimately removed when output was minimal. The patient recovered uneventfully and plans were made for subsequent ileostomy takedown.

Pre-operative workup for ileostomy takedown including a barium contrast enema (Figure 3) revealed a posterior sinus tract which was confirmed on flexible sigmoidoscopy (Figure 4). In order to prevent future sinus tract drainage and abscess formation, the decision was made to surgically intervene prior to ileostomy reversal. Endoscopic management was not considered given that the staple line and sinus tract location (posterolateral) were 4 cm from the anal verge. Visualization was suboptimal without pneumorectum. Therefore, the decision was made to proceed with a TAMIS approach.

Patient was brought to the operating room, placed under general anesthesia and transitioned into high lithotomy position. A GelPOINT Path® TAMIS port (Applied Medical, Rancho Santa Margarita, CA, United States) was inserted into the anus and secured to the skin with 2-0 silk sutures. Three trocars were placed through the TAMIS port. Pneumorectum was achieved with AirSeal® (Conmed, Utica, NY) insufflation and a 30 degree laparoscope was introduced through the trocar. The chronic sinus tract was identified just posterior to the coloproctostomy at 4 cm from

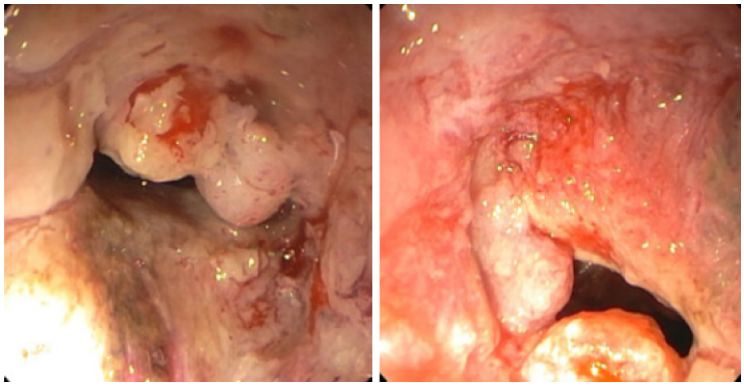

Figure 1 Rectal mass on colonoscopy.

the anal verge. The LigaSure™ Retractable L-Hook device was used to perform partial septotomies to create a wide opening of the mucosal bridge present between the sinus tract and the lumen (Figure 5). The cavity was then bluntly cleared of granulation and fibrotic tissue. The procedure was sequentially repeated twice, under general anesthesia, in three weeks intervals until the sinus tract was completely opened.

OUTCOME AND FOLLOW-UP

After three total septotomy treatments over the course of 9 wk, the sinus tract completely resolved. Post intervention barium contrast enema revealed resolution of the sinus tract and leak (Figure 6). The patient ultimately underwent ileostomy takedown without complications and was doing well at the 6 mo post-operative visit, having 2-3 bowel movements per day with no continence issues.

DISCUSSION

With the advent of emerging techniques for the treatment of rectal cancer in past decades, significant advances have been made in improving oncologic and functional outcomes[6]. LAR has been coined as the standard of care in selected cases which were previously treated with APR, often preventing the need for a permanent stoma. Unfortunately, this led to the emergence of new challenges inherent to the LAR technique including ALs which can be difficult complications to manage.

Minimally invasive septotomies have been endorsed for the treatment of chronic sinus tracts not only after colorectal interventions but also after foregut procedures including sleeve gastrectomies and roux-en-y gastric bypass for weight loss complicated with staple line leaks[18-21]. During this intervention the septum separating an abscess cavity and the true lumen is divided resulting in a larger communication of both lumens (true lumen and abscess lumen). By these means, internal drainage is favored through a path of low resistance with redirection of the leak flow from the abscess cavity towards the true lumen, resulting in contraction and scarring of the chronic leak/abscess cavity.

Minimally invasive management of AL after low and ultralow anterior resections has the benefit of minimizing the risk of temporary and permanent stomas[13]. Specifically, endoscopic therapies such as fibrin glue application, endoscopic stenting, endoluminal vacuum drainage and clipping have all been described as options to manage varying grades of ALs[22,23]. However, these techniques tend to be less effective for chronic leaks and are limited by several factors including the distance from the anal verge, size of the defect, or ability to traverse the anastomosis.

In cases where endoscopic means are incapable of managing the leak, TAMIS via rectal insufflation can be effective[24,25]. This provides an alternate route to access to the distal rectum with use of conventional laparoscopic instruments[26].

In this report, we describe a minimally invasive technique using a commercially available transanal port and energy device to induce insufflation within the rectum and complete sequential septotomies of a chronic draining sinus tract of the rectum after a LAR. When compared to other energy sources such as bovie and harmonic scalpel, the LigaSure L-Hook offers advantages such as less thermal spread, additional reach and better control due to the retractable technology, and ability to get

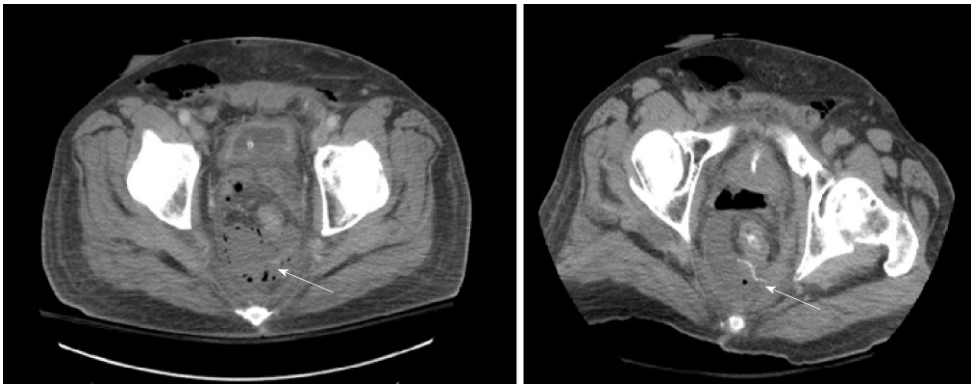

Figure 2 Presacral abscess with evidence of posterior leak of rectal contrast.

into tight spaces. Although the concept of endoscopic enlargement and eventual obliteration of a sinus tract after a colorectal leak has been reported in the literature, to our knowledge, this is the first report of the use of the LigaSure™ Retractable L-Hook device during this technique[24,27,28].

No consensus exists for the management of ALs and the determination must be individualized for each patient. Minimally invasive techniques are safe and effective at managing symptomatic, small, contained leaks. However, few studies have compared effectiveness among different modalities and even fewer studies have looked at long term results after these are performed.

CONCLUSION

The treatment of grade B ALs after LAR for rectal cancer can be challenging. TAMIS septotomy with the LigaSure™ Retractable L-Hook device is a feasible and effective technique for the treatment of select grade B ALs. Larger studies with longer follow up are needed to assess the generalizability and long-term results of this technique.

Figure 3 Posterior sinus tract evidence in barium contrast enema.

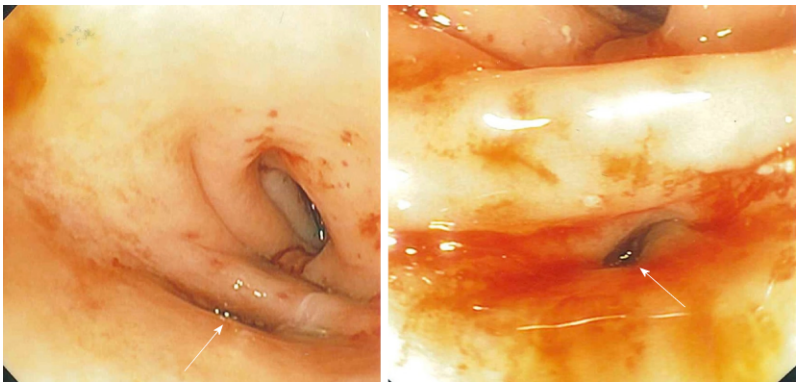

Figure 4 Posterior sinus tract at the healed staple line on flexible sigmoidoscopy.

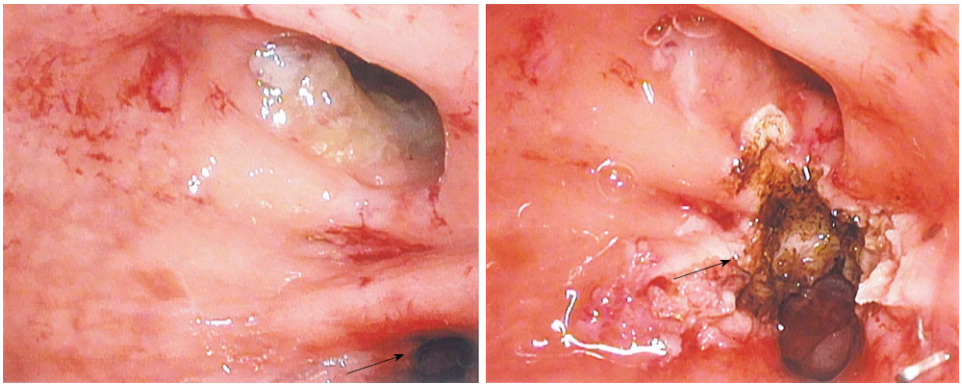

Figure 5 Rectal lumen and posterior sinus tract and sinus tract after septotomy. A: Rectal lumen and posterior sinus tract; B: Sinus tract after septotomy.

Figure 6 Absence of posterior sinus tract in post-operative barium contrast enema.

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