Original article

Disease Recurrence after Right Hemicolectomy in Scotland: Is there Rationale to Adopt Complete Mesocolic Excision (CME)?

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Abstract

Aims

Complete mesocolic excision (CME) has been proposed as a way to improve the oncological outcomes in patients with colon cancer. To investigate whether there is a rationale for adopting the technique in Scotland, our aim was to define the current incidence of disease recurrence following right hemicolectomy and to compare this with published CME outcomes.

Methods

Data was collected on consecutive patients undergoing right or extended right hemicolectomy for colonic adenocarcinoma (2012 - 2017) at three hospitals in Scotland (Inverness, Aberdeen and Glasgow). Emergency or palliative surgery was excluded. Patients were followed up with CT scans and colonoscopy for a minimum of 3 years.

Results

689 patients (M 340, F 349) were included. 30-day mortality was 1.6%. Final pathological stage was Stage I (14%), Stage II (49.8%) and Stage III (36.1%). During follow-up, 10.5% developed loco-regional recurrence and 12.2% developed distant metastases. The 1, 3 and 5-year disease-free survival (DFS) was 94%, 84% and 82% respectively. Primary determinants of recurrence were T stage ($p<0.001$), N stage ($p<0.001$), apical node involvement ($p<0.001$) and EMVI ($p<0.001$). When compared to the literature, 30-day mortality was lower than many published series and DFS rates were similar to the largest CME study to date (4 year DFS 85.8% versus 83%).

Conclusion

The outcomes of patients undergoing right hemicolectomy in Scotland compare favourably with many published CME studies. The technique demands further evaluation before it can be recommended for adoption into routine surgical practice.

Introduction

Colorectal cancer is the second most common cause of cancer death in the United Kingdom and surgical resection remains the cornerstone of treatment (1, 2). The principles of total mesorectal excision (TME) surgery, pioneered by Heald and Ryall in the 1980's (3), improved the oncological outcomes of patients with rectal cancer and have since been universally adopted. In an effort to apply similar anatomical principles to patients with colon cancer, Hohenberger and colleagues proposed the concept of complete mesocolic excision (CME) in 2009 (4). The authors compared patients undergoing CME surgery to historic controls and reported a significant reduction in recurrence rate and a corresponding improvement in cancer-specific survival. While the definition of CME has evolved over the intervening years there is now broad agreement that the technique comprises a combination of central vascular ligation (CVL) and extended lymphadenectomy (EL) (5).

The difficulty with this approach is that while the anatomical principles appear sound, the operation is technically demanding, particularly when performed via a laparoscopic approach (5). One particular concern is that CME involves the dissection and ligation of the central venous pedicles that drain into the Trunk of Henle and vascular injury in this region can result in bleeding that is difficult to control. Although centres with a specialist interest appear able to perform the technique safely it remains questionable whether similar results can be achieved in standard surgical units. While the technical challenge of CME surgery has likely been a factor against its widespread adoption, it is the quality of evidence around its oncological benefit that has been the biggest barrier. Most studies to date have employed

either historic or no controls (4, 6) or have relied on surrogate markers of surgical quality, such as the total number of lymph nodes retrieved, as indicators of improved prognosis (7). While attempts have been made to synthesize the available evidence in several recent systematic reviews, the conclusions have been conflicting (8, 9).

The present study was designed to investigate whether CME should be adopted into routine surgical practice in Scotland. Our aims were to define the current incidence and pattern of disease recurrence following elective right hemicolectomy and to compare these results with published CME outcomes.

Patients and Methods

The study was carried out as a collaboration between three hospitals in Scotland; Raigmore Hospital in Inverness, a district general hospital serving a predominantly rural population of 220,000; Aberdeen Royal Infirmary in Aberdeen, a large teaching hospital serving a population of 500,000 and Glasgow Royal Infirmary, a tertiary referral centre serving an urban population of 350,000. None of the hospitals performed CME surgery during the study period. In each hospital, consecutive patients undergoing resection of right colon adenocarcinoma between 1st January 2012 and 31st December 2017 were identified using pathological codes. The electronic records for each patient were then accessed and clinical, pathological and outcome data were recorded retrospectively using a standardised proforma. Patients were included if they had undergone an elective right or extended right hemicolectomy with curative intent for Stage I - III colon cancer. Exclusion criteria included emergency resection, metastatic disease at diagnosis or discovered intra-operatively, surgery performed with palliative intent, benign pathology, appendiceal tumours, multi-visceral resection or left-sided synchronous colon cancer. Inclusion and exclusion criteria were chosen to allow direct comparison of outcomes with published CME literature. Patients were followed up according to contemporary guidelines (10) with annual computed tomography (CT) scans for 3 years and colonoscopy at 1 and 5 years post-surgery. Disease recurrence was defined as loco-regional (peritoneal disease, nodal disease or anastomotic recurrence) or metastatic (disease outwith the abdominal cavity). Radiological findings of loco-regional recurrence or distant metastases were considered recurrence even if a histological diagnosis was not obtained. Date of last follow up was defined as the date of last CT scan, colonoscopy or surgical clinic

review. Date of death was obtained from electronic health records and post-operative mortality defined as death from any cause within 30 days of operation. The study was registered with and approved by the local Quality Improvement committee, who classified it as a clinical audit, negating the need for further ethical approval.

Statistical analysis:

Continuous data are presented as median values while categorical variables are grouped according to clinically relevant or published thresholds. Disease-free survival (DFS) was calculated as the time from operation to the development of any disease recurrence (loco-regional or metastatic). Overall survival (OS) was calculated as the time from operation to death from any cause. Survival data were analysed after excluding post-operative deaths. Survival differences between groups were examined using Kaplan-Meier curves and log-rank tests. The relationships between categorical variables and survival were examined with Cox regression models with calculation of hazard ratios (HR) and 95% confidence intervals (CI). P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (Version 24.0, IBM SPSS Inc., Chicago, IL, USA).

Results

In total, 1045 patients who underwent right hemicolectomy or extended right hemicolectomy during the study period were identified. Of those, 356 were excluded for the reasons shown in Figure 1. The 689 patients included in the study therefore represented elective right-sided colonic resections undertaken with curative intent (Figure 1).

The clinico-pathological characteristics and short-term outcomes of the cohort are summarised in Table 1. There were 340 males (49.3%) and 349 females (50.7%) with a median age of 72 years. The majority of surgery (56.9%) was open with 41% completed laparoscopically and 5% converted. Eleven patients died within 30 days of surgery giving a post-operative mortality of 1.6%. Almost all patients (97.3%) had ≥ 12 lymph nodes retrieved and the median number of nodes harvested was 21. In total, 250 patients (36.2%) had evidence of lymph node metastases although the apical node was only involved in a minority (4.4%). Histological markers of poor prognosis included poor or mucinous differentiation in 31.8% and extra-mural venous invasion (EMVI) in 42.5%. Eleven patients had a pathologically involved (<1mm) margin giving an R1 rate of 2.4%. In total, 234 patients (34.7%) received adjuvant chemotherapy although data regarding the rationale of individual treatment decisions were not available.

The long-term outcomes of the cohort are shown in Table 2. The median length of follow up for the survivors was 69.5 months (range 27 - 105). During follow-up, loco-regional recurrence was identified in 71 patients (10.5%) with the site of disease predominantly peritoneal (n=44) or nodal (n=24). In many cases, the disease was not confined to one anatomical site and often

involved a combination of retroperitoneal lymphadenopathy and/or multi-focal peritoneal disease. Isolated luminal recurrence at the anastomosis was a rare event and occurred in just 2.4%. In terms of systemic disease recurrence, 83 patients developed distant metastases with the most common sites being the liver (n=54) and lungs (n=30). At the date of censor, 480 (70.8%) patients were alive, 198 (29.2%) were dead and 110 (16.2%) had evidence of disease recurrence (either loco-regional or metastatic). The 1, 3 and 5 year disease-free survival of the cohort was 94%, 84% and 82% respectively. The 1, 3 and 5 year overall survival was 94%, 81% and 74% (Table 2).

The relationships between individual clinico-pathological variables and the development of disease recurrence are summarised in Table 3. There were significant relationships between T stage ($p<0.001$), N Stage ($p<0.001$), apical node involvement ($p<0.001$), EMVI ($p<0.001$) and R1 resection ($p<0.001$) and the development of loco-regional recurrence. Similar relationships were observed between T4 tumour ($p<0.001$), N Stage ($p<0.001$), apical node involvement ($p<0.001$), EMVI ($p<0.001$) and R1 resection ($p<0.001$) and the development of distant metastases. There was no relationship between the number of lymph nodes removed and the development of disease recurrence (Table 3).

The pathological features of the 71 patients who developed loco-regional recurrence were then examined (Table 4). 68 patients (95.8%) had at least one high-risk pathological feature, defined as pT4 tumour, nodal disease, apical node involvement, poor or mucinous differentiation, EMVI or R1 resection. Of these, 43 patients (63.0%) received adjuvant chemotherapy. Three of the patients who developed loco-regional recurrence had no conventional adverse pathological features in their resected specimens (Table 4).

Finally, results from the present study were compared with data from published CME series (Table 5). Studies were selected only if they provided comparable short-term (post-operative mortality) or long-term outcomes (DFS or OS). The published 30 day mortality rates varied from 2.8% to 8.6% (11). The largest published series (12) reported a mortality rate of 5% in the CME group and 4% in the non-CME group. The 30 day mortality in the present series was 1.6%. In terms of long-term outcomes, the published rates of DFS ranged from a 3 year DFS rate of 82.1% in a series of patients undergoing CME surgery for node negative disease to 97.2% in the CME arm of a study (13) of patients with Stage I-III disease. The largest series reported a 4 year DFS rate of 85.8% in patients undergoing CME surgery compared to 75.9% in the non-CME group. The comparable rate for 4 year DFS in the present study was 83% (Table 5).

Discussion

The present study has reported the oncological outcomes for patients undergoing elective resection of right-sided colon cancer in Scotland. Our results are derived from three hospitals disparate in size, location and population served and are likely to be representative of the country as a whole. Accurately defining the current incidence and pattern of disease recurrence is an important first step in considering whether CME surgery has a role in future surgical practice and has enabled us to compare our results with published data.

In terms of short-term outcomes, it is clear that very few patients in Scotland die in the post-operative period. Our 30-day mortality rate of 1.6%, similar to the 2% rate reported for elective colorectal resections by the National Bowel Cancer Audit (NBOCA) in England in 2018 (14), compares favourably with the rates reported in most CME series. For example, the largest study to date by Bertleson and colleagues in Denmark describes a post-operative mortality rate of 5% for CME and 4% for standard surgery (12). Other studies report mortality rates that are difficult to understand such as the 8.6% post-operative death rate reported by Storli et al in Norwegian patients undergoing standard surgery for early stage disease (11). These results raise questions over the quality of surgery to which CME is being compared and mean the survival data in such studies must be interpreted with caution.

With regard to long-term outcomes, we report that loco-regional recurrence rates following right hemicolectomy are approximately 10% and distant metastases occurs in around 12%. One of the difficulties of comparing these rates to published data is that there is no current definition of what constitutes local recurrence after colon cancer resection. Studies variably

report figures relating to anastomotic recurrence (11), nodal disease confined to the right colic bed (4), peritoneal disease (6) or a combination of the above. When surveillance CT images were examined in our series it was evident that disease recurrence in the abdominal cavity rarely fits precisely into these categories, often involving a combination of nodal and/or peritoneal disease and rarely confined to a particular anatomical site. We therefore considered the most informative term to be 'loco-regional' recurrence which encompasses any intra-abdominal disease identified on CT or endoscopic surveillance. The length and intensity of follow-up within each published series must also be examined closely because longer and more intense surveillance programmes are more likely to find disease recurrence~~. For example, after examining the long-term outcomes of patients with colon cancer in France, Bouvier et al reported that an additional 2.9% of patients developed local recurrence and 4.3% developed distant metastases between 5 – 10 years after their initial surgery~~ (15). Although colon cancer follow-up in Scotland is dependent on patient preference and fitness, the majority of patients in our cohort were followed according to ACPGBI guidelines (10) with annual CT scans for at least three years and colonoscopy at 1 then 5 years post-surgery. With a median follow up of more than 5 years, we believe our results are likely to accurately reflect the true rates of disease recurrence after right hemicolectomy.

To investigate whether CME might have the potential to improve these oncological outcomes, the next logical step was to compare our figures with published CME results. It was apparent however that heterogeneity in the CME literature would make meaningful comparisons challenging. In 2013, Killeen and co-workers attempted to give a comprehensive overview of the existing evidence for CME and EL~~, but after assessing more than 100 relevant articles, the authors concluded that study heterogeneity precluded a meta-analysis and instead focused~~

~~on producing a systematic review~~. In total, 21 studies met their inclusion criteria and using weighted mean values, they calculated the 5 year DFS rate for CME/EL patients as 77.4% compared to 66.7% for controls (8). Our results compare favourably to these with a 5 year DFS of 82%. ~~More recently~~In 2017~~,~~ a Chinese group led by Wang et al (9) published an updated systematic review and meta-analysis ~~in 2017. After appraising more than 600 citations, the group included 12 studies, comprising~~ with data on 8586 patients from 12 studies~~,~~ in their final analysis. They reported CME was associated with greater intra-operative blood loss and more post-operative complications but resulted in a specimen with a larger mesenteric area and greater number of harvested lymph nodes. In terms of oncological outcomes, CME had a positive effect on survival but the authors admitted that the scarcity of long-term outcome data led them to construct a surrogate endpoint consisting of overall survival (OS), cancer-specific survival (CSS) or disease-free survival (DFS) and labelled simply as 'survival'.

Based on these systematic reviews alone, the evidence for adopting CME in Scotland appears to be relatively weak. However, one particular study is worthy of further attention and is widely regarded as providing the best evidence to date for the technique. In 2014, Bertleson et al published a study from Denmark that compared 364 patients with colon cancer who underwent CME surgery in Hillerod with 1031 controls who had standard surgery in three adjacent university hospitals (12). Despite the inherent sources of bias that exist in such comparisons, the methodology was sound and the standard of surgery in the non-CME group appears broadly similar to that currently carried out in Scotland. Although Bertleson was unable to demonstrate a difference in overall survival between the two groups, the 4-year DFS was significantly better in patients undergoing CME surgery compared to those undergoing standard resection (85.8% versus 75.9%). Interestingly, the survival benefit was

most evident in patients with node-negative disease and leads us to consider the underlying reasons as to why this type of surgery might be of benefit.

There seems little doubt that CME surgery results in a pathological specimen that is measurably different from that produced by conventional resection. CME is consistently associated with a greater distance from the tumour to the high tie (16), a larger mesenteric surface area (7) and a higher lymph node count (17), but the reasons why these factors may lead to improved survival are not immediately obvious. One possibility is that clearance of involved central nodes might result in 'up-staging' of disease and mean the patient receives adjuvant chemotherapy that would not otherwise have been offered. However, this argument is based on the historical concept of nodal spread in colon cancer occurring in a linear or 'stepwise' fashion down the lymphatic chain and on into the systemic circulation (18). In practice, tumours are unlikely to be up-staged because it is unusual to have positive central nodes with negative peripheral nodes. Although so-called 'skip' metastases can occur they are estimated to account for less than 2% of nodal metastases (19) and their removal appears unlikely to fully explain a survival benefit for CME. It is also worth noting that recent studies of tumour biology now support the 'parallel spread' model proposed by Fisher (20) which considers distant metastases to occur early in the natural history of the disease. In this model, lymph node metastases are simply a marker of aggressive tumour behaviour and efforts to remove them will not impact on survival which is primarily determined by systemic metastases. Our own results suggest that the vast majority of patients who develop disease recurrence have existing high-risk pathological features that cannot obviously be moderated or influenced by removing more lymph nodes. The realisation that extended lymphadenectomy alone seems unlikely to explain the benefit of CME has led some

researchers to investigate the role of the mesentery in cancer recurrence. A new hypothesis suggests that some of the benefits of an extensive mesenteric excision may relate to the resection of isolated mesenteric tumour deposits; if this holds true then adequate surgery for colon cancer should involve not only removal of the draining lymph nodes but the root of the mesentery itself (21).

The counter argument is that CME does not in itself provide any measurable oncological benefit over modern 'standard' surgery. Studies comparing CME to historic controls may simply be demonstrating the multitude of improvements that have taken place in the field over the years in terms of surgical techniques, adherence to embryological planes, high quality pathological reporting and of provision of effective chemotherapy. Although it is tempting to assume that removing more lymph nodes will reduce the chance of colon cancer recurrence, the reality is that this approach has not proven beneficial in any of the gastrointestinal tumour types (22). One cannot help observe the transition towards more precise or image-based techniques such as sentinel node biopsy in a number of tumour types - melanoma, vulval and breast - in which radical lymph node dissection was once the norm (23, 24). Why should colon cancer be different?

In summary, CME surgery demands further evaluation before it can be recommended for adoption into routine surgical practice in Scotland. Ideally, the technique should be assessed by adequately powered Randomised Controlled Trials (RCTs) or if this proves impossible research collaborations should endeavor to produce large prospective datasets with standardized endpoints. Pertinent research questions include the safety of performing the technique using an MIS approach and whether CME surgery should be considered only for

selected cases based on, for example, specific patient-related factors or radiological nodal criteria. These principles of rigorous assessment apply to all novel surgical techniques but are especially pertinent to CME because of the inherent risk of significant complications. For CME surgery to be adopted there must be unequivocal evidence of its oncological benefit and confidence that it will not compromise the low rates of surgical mortality that currently exist in Scotland.

References

1. Most common causes of cancer deaths UK Cancer Research UK: Cancer Research UK; 2018 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero.
2. Mitry E, Bouvier AM, Esteve J, Faivre J. Improvement in colorectal cancer survival: a population-based study. Eur J Cancer. 2005;41(15):2297-303.
3. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479-82.
4. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 2009;11(4):354-64; discussion 64-5.
5. Strey CW, Wullstein C, Adamina M, Agha A, Aselmann H, Becker T, et al. Laparoscopic right hemicolectomy with CME: standardization using the “critical view” concept. Surgical Endoscopy. 2018;32(12):5021-30.
6. Galizia G, Lieto E, De Vita F, Ferraraccio F, Zamboli A, Mabilia A, et al. Is complete mesocolic excision with central vascular ligation safe and effective in the surgical treatment of right-sided colon cancers? A prospective study. Int J Colorectal Dis. 2014;29(1):89-97.
7. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol. 2012;30(15):1763-9.
8. Killeen S, Mannion M, Devaney A, Winter DC. Complete mesocolic resection and extended lymphadenectomy for colon cancer: a systematic review. Colorectal Dis. 2014;16(8):577-94.
9. Wang C, Gao Z, Shen K, Shen Z, Jiang K, Liang B, et al. Safety, quality and effect of complete mesocolic excision vs non-complete mesocolic excision in patients with colon cancer: a systemic review and meta-analysis. Colorectal Disease. 2017;19(11):962-72.
10. Leong K, Hartley J, Karandikar S. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) - Follow Up, Lifestyle and Survivorship. Colorectal Dis. 2017;19 Suppl 1:67-70.
11. Storli KE, Søndenaa K, Furnes B, Nesvik I, Gudlaugsson E, Bukholm I, et al. Short term results of complete (D3) vs. standard (D2) mesenteric excision in colon cancer shows improved outcome of complete mesenteric excision in patients with TNM stages I-II. Tech Coloproctol. 2014;18(6):557-64.
12. Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, et al. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. The Lancet Oncology. 2015;16(2):161-8.
13. Gao Z, Wang C, Cui Y, Shen Z, Jiang K, Shen D, et al. Efficacy and Safety of Complete Mesocolic Excision in Patients With Colon Cancer: Three-year Results From a Prospective, Nonrandomized, Double-blind, Controlled Trial. Ann Surg. 2020;271(3):519-26.
14. National Bowel Cancer Audit Annual Report. NBOCA: Healthcare Quality Improvement Partnership Ltd; 2018.

15. Landreau P, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Lepage C, et al. Incidence and survival in late liver metastases of colorectal cancer. Journal of Gastroenterology and Hepatology. 2015;30(1):82-5.
16. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272-8.
17. Ouyang M, Luo Z, Wu J, Zhang W, Tang S, Lu Y, et al. Comparison of outcomes of complete mesocolic excision with conventional radical resection performed by laparoscopic approach for right colon cancer. Cancer Manag Res. 2019;11:8647-56.
18. Halsted WS. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. Annals of surgery. 1907;46(1):1-19.
19. Herrera-Ornelas L, Justiniano J, Castillo N, Petrelli NJ, Stulc JP, Mittelman A. Metastases in small lymph nodes from colon cancer. Arch Surg. 1987;122(11):1253-6.
20. Fisher B. Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res. 1980;40(11):3863-74.
21. Bunni J, Coffey JC, Kalady MF. Resectional surgery for malignant disease of abdominal digestive organs is not surgery of the organ itself, but also that of the mesenteric organ. Tech Coloproctol. 2020;24(7):757-60.
22. Willaert W, Ceelen W. Extent of surgery in cancer of the colon: is more better? World J Gastroenterol. 2015;21(1):132-8.
23. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized Multicenter Trial of Sentinel Node Biopsy Versus Standard Axillary Treatment in Operable Breast Cancer: The ALMANAC Trial. JNCI: Journal of the National Cancer Institute. 2006;98(9):599-609.
24. Navarrete-Dechent C, Veness MJ, Droppelmann N, Uribe P. High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: A literature review. Journal of the American Academy of Dermatology. 2015;73(1):127-37.

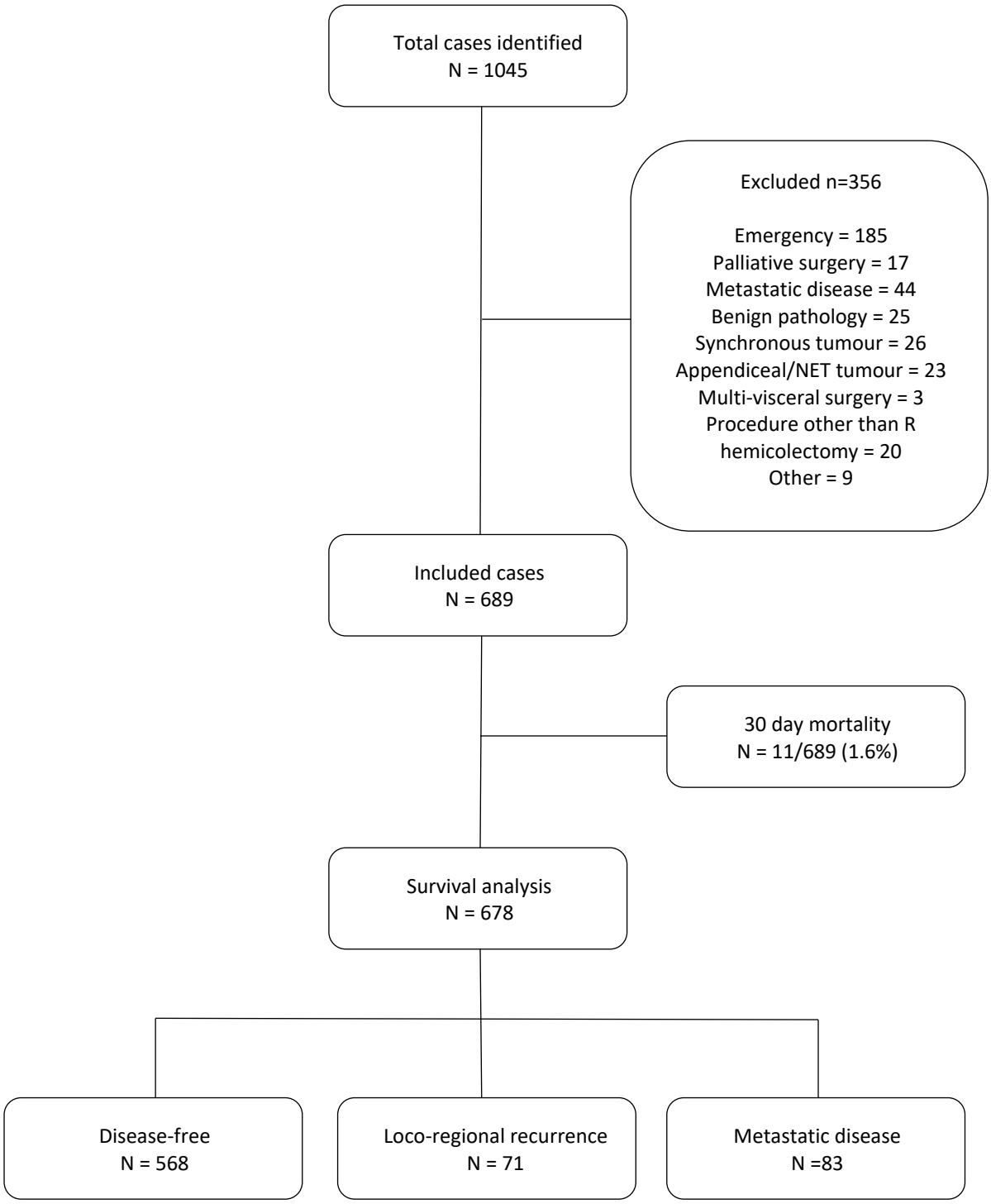

Figure 1. Flow chart of inclusion criteria

Table 1. Clinicopathological characteristics and short-term outcomes of the cohort.

Variable		**N** 689 (%)
Age	Median (range)	72 (25-93)
Sex	Female	349 (50.7)
	Male	340 (49.3)
BMI (kg/m^2)	Median (range)	27 (14-45)
Operation	Right hemicolectomy	604 (87.9)
	Extended right hemicolectomy	83 (12.1)
Approach	Open	358 (56.9)
	Laparoscopic	258 (41.0)
	Converted	13 (5.0)
Length of stay (days)	Median (IQR)	7 (6)
30 day mortality	No	677 (98.4)
	Yes	11 (1.6)
T stage	pT1 or pT0	32 (4.7)
	pT2	82 (11.9)
	pT3	406 (58.9)
	pT4	168 (24.4)
N stage	pN0	439 (63.7)
	pN1	167 (24.2)
	pN2	83 (12)
TNM stage	Stage I	97 (14.1)
	Stage II	343 (49.8)
	Stage III	249 (36.1)
Lymph node harvest	Median (range)	21 (7-61)
≥ 12 lymph nodes resected	No	18 (2.6)
	Yes	671 (97.3)
Apical lymph node	Involved	30 (4.4)
	Not involved	635 (92.2)
Differentiation	Well/Moderate	457 (68.2)
	Poor/Mucinous	213 (31.8)

EMVI	Absent	396 (57.5)
	Present	293 (42.5)
Resection margin	R0	448 (97.6)
	R1	11 (2.4)
Length of ileum (mm)	Median (IQR)	87 (136.5)
Length of colon (mm)	Median (IQR)	150 (140)
Adjuvant chemotherapy	No	441 (65.3)
	Yes	234 (34.7)

For a small number of cases full pathology and operative data was missing. Where this was the case percentages given are for cases with data rather than total number of cases

Table 2. Long-term outcomes and details of disease recurrence.

Variable		**N 678 (%)**
Length of follow-up (months)	Median (range)	69.5 (27-105)
Loco-regional recurrence	No	607 (89.5)
	Yes	71 (10.5)
Loco-regional recurrence site	Anastomosis	16 (2.4)
	Nodal	24 (3.5)
	Peritoneal	44 (6.5)
	Multiple sites	11 (1.6)
Distant metastases	No	595 (87.8)
	Yes	83 (12.2)
Distant metastases site	Hepatic	54 (8.0)
	Pulmonary	30 (4.4)
	Brain	5 (0.7)
	Other site	10 (1.5)
	Multi-organ	18 (2.7)
Status at follow-up	Alive	480 (70.8)
	Dead	198 (29.2)
Status at follow-up	Disease-free	568 (83.8)
	Disease recurrence*	110 (16.2)
Disease-free survival	1 year	94%
	2 year	87%
	3 year	84%
	4 year	83%
	5 year	82%
Overall survival	1 year	94%
	2 year	86%
	3 year	81%
	4 year	78%
	5 year	74%

*loco-regional or metastatic disease

Table 3. Relationships between pathological characteristics and the development of loco-regional recurrence and distant metastases.

Variable	Group	Loco-regional recurrence			Distant metastases		
		HR	95% CI	p	HR	95% CI	p
T stage	T1/2	1.00			1.00		
	T3	3.63	0.86-15.34	0.08	1.18	0.54-2.56	0.682
	T4	19.63	4.76-80.95	<0.001	4.81	2.26-10.23	<0.001
N Stage	N0	1.00			1.00		
	N1	5.76	3.11-10.76	<0.001	5.18	2.96-9.09	<0.001
	N2	13.16	6.96-24.87	<0.001	12.03	6.76-21.39	<0.001
Apical node	Clear	1.00					
	Involved	9.24	5.20-16.40	<0.001	6.96	3.90-12.41	<0.001
Number of nodes	≥21	1.00					
	<21	0.796	0.50-1.28	0.344	0.883	0.57-1.36	0.574
Differentiation	Well/Moderate	1.00					
	Poor/Mucinous	1.07	0.65-1.78	0.793	0.98	0.61-1.57	0.935
EMVI	No	1.00					
	Yes	4.33	2.56-7.33	<0.001	3.28	2.07-5.19	<0.001
Resection margin	R0	1.00					
	R1	5.76	2.63-12.6	<0.001	4.14	1.80-9.51	<0.001

Table 4. Pathological features of the 71 patients who developed loco-regional recurrence.

Variable		**N** 71(%)
T stage	pT1	1(1.4)
	pT2	1 (1.4)
	pT3	24 (33.8)
	pT4	45 (63.4)
N stage	pN0	15 (21.1)
	pN1	30 (42.3)
	pN2	26 (36.6)
Apical lymph node	Clear	55 (77.5)
	Involved	15 (21.1)
Differentiation	Well/Moderate	47 (66.2)
	Poor/Mucinous	22 (31.0)
EMVI	Absent	19 (26.8)
	Present	52 (73.2)
Resection margin	R0	64 (90.1)
	R1	7 (9.9)
Any high-risk feature*	Yes	68 (95.8)
	No	3 (4.2)

* High-risk features include pT4 tumours, node positive disease, poor differentiation, mucinous tumours, EMVI or R1 resection.
For a small number of cases full pathology data was missing. Where this was the case percentages given are for cases with data rather than total number of cases

Table 5. Comparison of published series of CME versus Non-CME with equivalent data from the present study.

Study	No. patients	Stage	Outcome	Group	Result	Equivalent Scotland data
Hohenberger (2008)	411	Stage I-III	5 year CSS	CME	89.1%	82%
	404			Non-CME	82.1%	
Galizia (2014)	45	Stage I-IV	5 year CSS	CME	90%	82%
	58			Non-CME	74%	
Storli (2014)	89		30 day mortality	CME	2.8%	1.6%
	105			Non-CME	8.6%	
		Stage I-II	3 year DFS	CME	82.1%	94%
				Non-CME	74.3%	
			3 year OS	CME	88.1%	88%
				Non-CME	79.0%	
Bertleson (2015)	364		30 day mortality	CME	5%	1.6%
	1031			Non-CME	4%	
		Stage I-III	4 year DFS	CME	85.8%	83%
				Non-CME	75.9%	
			5 year OS	CME	74.9%	74%
				Non-CME	69.8%	
Ouyang (2019)	107		3 year DFS	CME	91.6%	84%
	60	Stage I-III		Non-CME	80%	
			3 year OS	CME	93.5%	81%
				Non-CME	85%	
Gao (2020)	220		3 year DFS	CME	97.2%	84%
	110	Stage I-III		Non-CME	98.3%	
			3 year OS	CME	92.2%	81%
				Non-CME	90.0%	