Original article

Short-term outcomes after complete mesocolic excision compared with 'conventional' colonic cancer surgery

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Background: **Complete mesocolic excision (CME) seems to be associated with improved oncological outcomes compared with 'conventional' surgery, but there is a potential for higher morbidity.**

Methods: **Data for patients after elective resection at the four centres in the Capital Region of Denmark (June 2008 to December 2013) were retrieved from the Danish Colorectal Cancer Group database and medical charts. Approval from a Danish ethics committee was not required (retrospective study).**

Results: **Some 529 patients who underwent CME surgery at one centre were compared with 1701 patients undergoing 'conventional' resection at the other three hospitals. Laparoscopic CME was performed in 258 (48·8 per cent) and laparoscopic 'conventional' resection in 1172 (68·9 per cent). More extended right colectomy procedures were done in the CME group (17·4 *versus* 3·6 per cent). The 90-day mortality rate in the CME group was 6·2 per cent *versus* 4·9 per cent in the 'conventional' group ($P = 0·219$), with a propensity score-adjusted logistic regression odds ratio (OR) of 1·22 (95 per cent c.i. 0·79 to 1·87). Laparoscopic surgery was associated with a lower risk of mortality at 90 days (OR 0·63, 0·42 to 0·95). Intraoperative injury to other organs was more common in CME operations (9·1 per cent *versus* 3·6 per cent for 'conventional' resection; $P < 0·001$), including more splenic (3·2 *versus* 1·2 per cent; $P = 0·004$) and superior mesenteric vein (1·7 *versus* 0·2 per cent; $P < 0·001$) injuries. Rates of sepsis with vasopressor requirement (6·6 *versus* 3·2 per cent; $P = 0·001$) and postoperative respiratory failure (8·1 *versus* 3·4 per cent; $P < 0·001$) were higher in the CME group.**

Conclusion: **CME is associated with more intraoperative organ injuries and severe non-surgical complications than 'conventional' resection for colonic cancer.**

*Members of the COMES Group are collaborators of this study

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Introduction

The authors have shown previously that complete mesocolic excision (CME) is associated with improved 4-year oncological outcome compared with 'conventional' resections for colonic adenenocarcinoma[1]. The improvement was significant for each of stages I–III, by 6–14 per cent. CME was implemented at one of the four colorectal centres in the Capital Region of Denmark in 2008[2]. The other centres have been reluctant to implement extended surgery owing to safety concerns[3], although externally validated pathological parameters (lymph node yield, distance from tumour to vascular high tie, and intact mesocolic fascia) were higher in the centre performing CME[4].

CME in this study is defined[5,6] as dissection in the mesocolic plane with central vessel ligation. The dissection is performed close to organs and vessels that are not usually fully exposed in 'conventional' colonic cancer surgery, and

there is a risk of injury to, for example, the stomach or superior mesenteric vein (SMV)[7,8]. This has caused concern about possible higher mortality and morbidity related to CME compared with 'conventional' colonic cancer resection[3,9]. The need for randomized clinical trials has been emphasized[3,9], but many challenges are involved[1,9]. Large population studies may be helpful in suggesting potential associations between CME and higher perioperative mortality and morbidity[1,9]. The aim of this study was to investigate associations between CME and short-term outcomes compared with 'conventional' colonic cancer resection.

Methods

Data for all patients undergoing elective surgery for International Union Against Cancer (UICC) stage I–III colonic adenocarcinoma in the Capital Region of Denmark from 1 June 2008 to 31 December 2013 were retrieved from the national database of the Danish Colorectal Cancer Group (DCCG) as described previously[1]. The population of this region is approximately 1·75 million, more than 30 per cent of the population of Denmark, and it is served by only four public university colorectal cancer centres.

The CME group consisted of patients undergoing CME at Hillerød Hospital; the control group comprised patients having a 'conventional' colonic resection for adenocarcinoma at the other three centres. Medical records of all the patients were reviewed by a colorectal surgeon from Hillerød Hospital to validate and supplement DCCG data with data on follow-up, including in-hospital complications during the first 60 days after surgery. Demographic data were collected from the DCCG database, which is updated continuously from the National Central Office of Civil Registration. Data from pathological examinations were retrieved from the DCCG database, and missing data were retrieved from pathology reports by two colorectal pathologists. Patients were excluded if they had metachronous colorectal cancer, rectal cancer (15 cm or less from the anal verge) in the absence of synchronous colonic adenocarcinoma, appendix tumour or an R2 resection.

To ensure validity of the data, an audit was performed for all patients in the CME group by three co-authors representing each of the three centres contributing patients to the 'conventional' resection group. The same three co-authors audited the data for patients in the control group with recurrence or complications. In case of disagreement between the registered data and the audit, agreement was reached through consensus with other authors.

Under Danish legislation, because this was a retrospective study, approval from the local ethics committee was not required. All participating departments approved the study protocol. Data collection was approved by the Danish Data Protection Agency, and the study was conducted on behalf of the DCCG.

Procedures

CME in the present context has been defined previously[7]. The same definitions were applied to the control group, except for left hemicolectomies, which in the control group centres were often segmental resections (involving only the splenic flexure). The resection was classified as laparoscopic if it was not converted at any time. Tumours located in the left third of the transverse colon or distally were defined as left-sided, whereas locations proximal to this were defined as right-sided. Staging was performed according to the UICC TNM system (5th edition), which is used as standard in Denmark[2].

The Clavien–Demartines–Dindo classification[10] was used to describe the severity of complications, which were stratified with grades I–IIIa being classified as minor complications and IIIb–IVb as severe. Complications registered in the medical records from hospitals in the Capital Region during the first 60 postoperative days were recorded for all patients. Short-term mortality was presented as both 30- and 90-day mortality. Cancer-specific deaths were defined as 90-day mortality, deaths caused by postoperative complications, late complications after treatment for colonic cancer (for example complications from stoma closure or chemotherapy), or recurrence. Follow-up was performed to 17 January 2015.

Statistical analysis

Continuous data are presented as median (i.q.r.) values. Continuous predictors were analysed by Student's t test and categorical predictors by Fisher's exact test or Pearson's χ^2 test.

Multivariable logistic regression models were performed for risk of 30- and 90-day mortality. Purposeful selection was used for the multivariable analyses[11,12]. The multivariable models were fitted using a predictor inclusion criterion of $P < 0{\cdot}500$ (Wald statistics) identified in the univariable regression analyses. With a stepwise elimination of predictors with a retention criterion of $P < 0{\cdot}150$ and a maximum change in parameter estimates of 15 per cent to indicate confounding, the reduced models were tested with all predictors eliminated one by one; if the tested variable had $P < 0{\cdot}150$ it was included in the final model. The exposure

Table 1 Patient demography and tumour characteristics of complete mesocolic excision and 'conventional' colonic resection groups

	CME ($n = 529$)	'Conventional' resection ($n = 1701$)	*P*#
Age (years)*	71·7 (65·0–78·3)	72·9 (66·0–80·1)	0·015**
Sex ratio (M : F)	270 : 259	807 : 894	0·149
Body mass index (kg/m^2)*	25·1 (22·5–28·4)	24·8 (22·2–27·8)	0·571**
ASA grade			0·004
I	136 (25·7)	371 (21·8)	0·065
II	280 (52·9)	1039 (61·1)	0·001
III–IV	113 (21·4)	291 (17·1)	0·028
Tumour site (primary tumour)†			0·267††
Caecum	114 (21·6)	388 (22·8)	0·592
Ascending colon	73 (13·8)	227 (13·3)	0·771
Hepatic flexure	25 (4·7)	116 (6·8)	0·101
Transverse colon	66 (12·5)	159 (9·3)	0·039
Splenic flexure	15 (2·8)	57 (3·4)	0·673
Descending colon	26 (4·9)	75 (4·4)	0·632
Sigmoid colon	210 (39·7)	679 (39·9)	0·959
Synchronous tumours	17 (3·2)	52 (3·1)	0·886
Pathological tumour category‡			0·850
pT1	39 (7·4)	137 of 1700 (8·1)	0·645
pT2	63 (11·9)	216 of 1700 (12·7)	0·653
pT3	316 (59·7)	1014 of 1700 (59·6)	1·000
pT4	111 (21·0)	333 of 1700 (19·6)	0·493
UICC stage‡			0·631
I	86 (16·3)	297 of 1700 (17·5)	0·553
II	249 (47·1)	816 of 1700 (48·0)	0·727
III	194 (36·7)	587 of 1700 (34·5)	0·375
No. of lymph nodes resected*	36 (26–47)	20 (15–28)	< 0·001**
R1 resection§	10 (1·9)	73 (4·3)	0·008
Fixed tumour¶	55 (10·4)	268 (15·8)	0·002
Abdominal wall	21 (4·0)	130 (7·6)	0·003
Bladder	9 (1·7)	49 (2·9)	0·160
Small bowel	14 (2·6)	42 (2·5)	0·874
Retroperitoneum including ureter	15 (2·8)	40 (2·4)	0·523
Other organs	11 (2·1)	71 (4·2)	0·024

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Colonic tumour with highest pT and subsequent pN category in patients with synchronous adenocarcinomas. ‡One specimen in the 'conventional' resection group showed no residual tumour after neoadjuvant chemotherapy. §Positive microscopic lateral margin (1 mm or less). ¶Assessed by the surgeon, not the pathologist. CME, complete mesocolic excision; ASA, American Society of Anesthesiologists; UICC, International Union Against Cancer (TNM system, 5th edition). #Fisher's exact test, except **t test and ††Pearson's χ^2 test.

variable CME was retained in all models during stepwise elimination, even when $P > 0{\cdot}150$. Injury to other organs was not included in the multivariable analysis, as, based on clinical considerations, these events were related to the more extended resection performed during CME. Possible interaction terms of clinical relevance were checked, and analysis of model fit was done with the C-statistic, test for goodness-of-fit and residual analysis[12].

These analyses were supplemented with logistic regression analysis of CME adjusted for propensity score. Balance was checked graphically and by looking at the distribution of continuous variables within the quintiles of the propensity scores[13]. Predictors included in propensity score analysis were age, sex, body mass index, American Society of Anesthesiologists (ASA) fitness grade, pT4 tumour category, fixation of tumour, laparoscopic resection, anastomosis, year of resection (2008 and 2009 pooled) and primary tumour location grouped as: caecum, ascending colon, hepatic flexure to mid transverse colon (hepatic flexure, right and mid third of transverse colon), left transverse and splenic flexure, descending colon, and sigmoid. Results are presented as odds ratios with 95 per cent c.i. $P < 0{\cdot}050$ was considered statistically significant. The possibility of hidden bias was estimated according to Rosenbaum's sensitivity analysis[13]. All analyses were done using R statistical software, version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 529 patients in the CME group and 1701 in the 'conventional' resection group. Patient demography

Table 2 Procedures performed in the complete mesocolic excision and 'conventional' colonic resection groups

	CME ($n = 529$)	'Conventional' resection ($n = 1701$)	P¶
Primary procedure			< 0·001#
Right hemicolectomy	155 (29·3)	723 (42·5)	–
Extended right hemicolectomy	92 (17·4)	62 (3·6)	–
Transverse colectomy	0 (0)	21 (1·2)	–
Right-sided subtotal colectomy	25 (4·7)	27 (1·6)	–
Left hemicolectomy*	52 (9·8)	181 (10·6)	–
Sigmoid resection	191 (36·1)	637 (37·4)	–
Other segmental resection	0 (0)	2 (0·1)	–
Colectomy	11 (2·1)	45 (2·6)	–
Proctocolectomy	3 (0·6)	3 (0·2)	–
Supplementary colonic resections†	4 (0·8)	15 (0·9)	1·000
Laparoscopic resection‡	258 (48·8)	1172 (68·9)	< 0·001
Conversion to open surgery	64 of 322 (19·9)	224 of 1396 (16·0)	0·099
Reasons for conversion			0·134
Oncological	31 of 64 (48)	88 of 224 (39·3)	0·198
Adhesions	8 of 64 (13)	60 of 224 (26·8)	0·019
Technically not possible	15 of 64 (23)	41 of 224 (18·3)	0·373
Bleeding	5 of 64 (8)	13 of 224 (5·8)	0·562
Other surgical complication	5 of 64 (8)	22 of 224 (9·8)	0·809
Resection of other organ§	46 (8·7)	143 (8·4)	0·858
Bladder	11 (2·1)	38 (2·2)	1·000
Small bowel	11 (2·1)	49 (2·9)	0·360
Other organ/structure	31 (5·9)	74 (4·4)	0·159

Values are parentheses are percentages. *Included segmental resections of the splenic flexure in the 'conventional' resection group. †Resection of two separate segments; for example, invasion of sigmoid tumour into the caecum resulting in sigmoid resection and supplementary (ileocaecal) resection. ‡Laparoscopic resection was initially planned in 322 patients in the complete mesocolic excision (CME) group and 1396 in the 'conventional' resection group. §Did not include other segment of the colon or rectum, or abdominal wall. ¶Fisher's exact test, except #Pearson's χ^2 test.

and tumour characteristics are shown in *Table 1*. Only four patients had an ASA grade of IV; these patients were pooled with those with an ASA grade of III. The proportion of patients with severe co-morbidity was significantly different: 21·4 per cent (113 patients) in the CME group and 17·1 per cent (291) in the control group ($P = 0·028$). Nine patients (1·7 per cent) in the CME group and 20 (1·2 per cent) in the control group ($P = 0·379$) received neoadjuvant chemotherapy.

All of the CME procedures were performed or supervised by a specialist, and this was also the case for 1658 patients (97·5 per cent) in the control group ($P < 0·001$), with the remainder performed by senior residents trained in colorectal surgery. Extended right-sided hemicolectomies were performed more frequently and there were no transverse colectomies in the CME group (*Table 2*) as a consequence of the differences between the principles of CME and 'conventional' resections. An anastomosis was performed in 495 patients (93·6 per cent) in the CME group and in 1586 (93·2 per cent) in the control group ($P = 0·842$). Stomas, including diverting stomas, were fashioned in 37 (7·0 per cent) and 141 (8·3 per cent) patients respectively ($P = 0·360$).

Recognized intraoperative injury to other organs and postoperative complications are shown in *Table 3*. Injuries were more common in the CME group (intestinal, splenic and vascular). Postoperative complications are shown in *Table 4*. The only differences in the risk of complications during the first 60 days after surgery were for severe non-surgical complications, because of higher proportions of pulmonary failure and sepsis (defined as a need for vasopressors for more than 24 h after surgery in the intensive care unit).

The 1-year cancer-specific survival curves are shown in *Fig. 1*. Although higher in the CME group, 30- and 90-day overall mortality rates were not statistically significantly different between the two groups. Based on the univariable logistic regression models of 30- and 90-day mortality (*Table 5*), multivariable models were generated (*Table 6*), with odds ratios for CME of 1·07 (95 per cent c.i. 0·62 to 1·80; $P = 0·795$) and 1·25 (0·77 to 1·94; $P = 0·334$) respectively. There was no imbalance, with a sufficient overlap in the propensity-adjusted models.

Discussion

Despite the higher risk of injury to the SMV, spleen and non-tumour-bearing segments of the colon, and the risk of postoperative respiratory failure and sepsis, this study did not show a statistically significant increased risk of 30- or

Table 3 Injury to other organs recognized during surgery, in-hospital postoperative complications during the first postoperative 60 days, and cause of death during the first 90 days after surgery following complete mesocolic excision and 'conventional' colonic resection

	CME ($n = 529$)	'Conventional' resection ($n = 1701$)	P**
Injury to other organ*	48 (9·1)	61 (3·6)	< 0·001
Injury to superior mesenteric vein	9 (1·7)	4 (0·2)	< 0·001
Splenic injury	17 (3·2)	21 (1·2)	0·004
Injury to other (non-tumour) segments of colon	6 (1·1)	4 (0·2)	0·015
Postoperative complications (total)	162 (30·6)	484 (28·5)	0·351
Surgical complications†	110 (20·8)	329 (19·3)	0·491
Anastomotic leakage	42 of 495 (8·5)	113 of 1586 (7·1)	0·327
Relaparotomy after anastomotic leakage	41 of 42 (98)	99 of 113 (87·6)	0·071
Fascial dehiscence	15 (2·8)	34 (2·0)	0·239
Intra-abdominal abscess	14 (2·6)	44 (2·6)	1·000
Wound infection	42 (7·9)	142 (8·3)	0·856
Intra-abdominal bleeding‡	4 (0·8)	18 (1·1)	0·801
Postoperative obstruction‡	5 (0·9)	31 (1·8)	0·234
Other surgical complication	10 (1·9)	33 (1·9)	1·000
Non-surgical complications	100 (18·9)	276 (16·2)	0·163
Pneumonia	31 (5·9)	108 (6·3)	0·758
Respiratory failure§	43 (8·1)	58 (3·4)	< 0·001
Sepsis¶	35 (6·6)	55 (3·2)	0·001
Renal failure (dialysis indicated)	10 (1·9)	29 (1·7)	0·849
Other non-surgical complication#	52 (9·8)	174 (10·2)	0·869
Cause of mortality (90-day)	33 (6·2)	83 (4·9)	–
MODS (surgical complication)	5 (15)	19 (23)	–
Surgical complication without MODS	1 (3)	8 (10)	–
MODS (surgical non-complication)	3 (9)	4 (5)	–
Cardiovascular	4 (12)	6 (7)	–
Pulmonary	8 (24)	18 (22)	–
Other cause including unknown	12 (36)	28 (34)	–

Values in parentheses are percentages. *Injury recognized during surgery (only significant differences specified). †Complications after reoperation for surgical complication are included. ‡Includes only intra-abdominal bleeding and postoperative obstruction leading to relaparotomy alone, organ failure or death. §Respiratory failure indicates treated with ventilator including non-invasive or continuous positive airway pressure in intensive care unit (ICU). ¶Sepsis indicates need for vasopressors owing to systemic inflammatory response syndrome, administered in ICU. #Non-surgical complications with proportions of less than 1 per cent in both groups and unknown postoperative complications if fatal outcome. CME, complete mesocolic excision; MODS, multiple organ dysfunction syndrome. **Fisher's exact test.

90-day mortality after CME compared with 'conventional' surgery.

No randomized clinical trials comparing short-term outcomes after CME with 'conventional' colonic cancer resection have been reported, and this is the first population-based study. The only comprehensive meta-analysis[9] found no increase in 30-day in-hospital mortality after CME, but the evidence for short-term outcomes after CME is based mainly on single-centre studies, with few including more than 100 patients undergoing CME[5,14–18]. Based on the literature, there may be selection and publication bias. The 30-day mortality rate found in this study is similar to findings reported previously by others[5,14,19,20]. This study also reported 90-day mortality, as the elderly and patients with co-morbidities have an increased risk of dying between 30 and 90 days after surgery[21–23]. The finding of no statistical significance for higher mortality associated with CME indicates that CME might be performed safely in terms of postoperative mortality, although further studies are needed.

Injury to other organs observed during resection was significantly more common in the CME group. This difference was significant only for injuries to other (non-tumour) segments of the colon, spleen and SMV during CME resections, and is probably partly a consequence of the more central dissection. Injury to the SMV can occur during resection of right-sided tumours[2,8]. Although this may appear to be a nightmare scenario, the usual experience of CME surgeons is that it is easily managed with the use of a flexible collagen or fibrin haemostatic patch, as the SMV is fully exposed. The significant finding of higher postoperative morbidity associated with CME was attributed to the proportion of patients with sepsis and respiratory failure, which were both significantly higher in the CME group.

Laparoscopic surgery was associated with a lower risk of mortality than open surgery[24–26]. The difference in proportions of laparoscopic resection was associated with

Table 4 In-hospital postoperative complications during the first postoperative 60 days after complete mesocolic excision and 'conventional' colonic resections graded according to the Clavien–Demartines–Dindo classification[10]

	CME ($n = 529$)	'Conventional' resection ($n = 1701$)	P*
Postoperative complications	162 (30·6)	484 (28·5)	0·351
Grade I–IIIa	62 (11·7)	216 (12·7)	0·653
Grade IIIb–IVb	70 (13·2)	188 (11·1)	0·186
Grade V	30 (5·7)	80 (4·7)	0·360
Surgical complications	110 (20·8)	329 (19·3)	0·491
Grade I–IIIa	36 (6·8)	130 (7·6)	0·570
Grade IIIb–IVb	60 (11·3)	163 (9·6)	0·246
Grade V	14 (2·6)	36 (2·1)	0·501
Non-surgical complications	100 (18·9)	276 (16·2)	0·163
Grade I–IIIa	37 (7·0)	138 (8·1)	0·459
Grade IIIb–IVb	43 (8·1)	86 (5·1)	0·010
Grade V	20 (3·8)	52 (3·1)	0·400

Values in parentheses are percentages. When a patient had more than one complication, the highest Clavien–Demartines–Dindo grade is given. CME, complete mesocolic excision. *Fisher's exact test.

tumour location, as the CME resections of tumours in the proximity of the flexures and in the transverse colon were performed as open procedures. These resections can be performed laparoscopically, but during the study interval the central dissection of the middle colic vessels was considered too challenging. Further studies might show laparoscopic extended right CME hemicolectomies to be feasible.

Postoperative perforation or necrosis of the stomach after gastrocolic ligament excision performed during CME for tumours located in the flexures or transverse colon has been described[7]. Resection of the gastroepiploic artery might, in theory, reduce the blood supply to the stomach and be associated with a higher risk of perforation or necrosis. This was not performed in any patient in the 'conventional' resection group. One patient in each group had perforation or necrosis of the stomach, and these complications appear to occur sporadically after all types of colonic resection.

In CME sigmoid resections the length of resected bowel is longer[4,27,28] to ensure sufficient length and perfusion of the anastomosis, and the left flexure is often mobilized. Injury to the spleen can occur during this mobilization. However, the only randomized trial[29] investigating the extent of bowel resection as a risk factor for complications in left-sided colonic cancer did not find any differences.

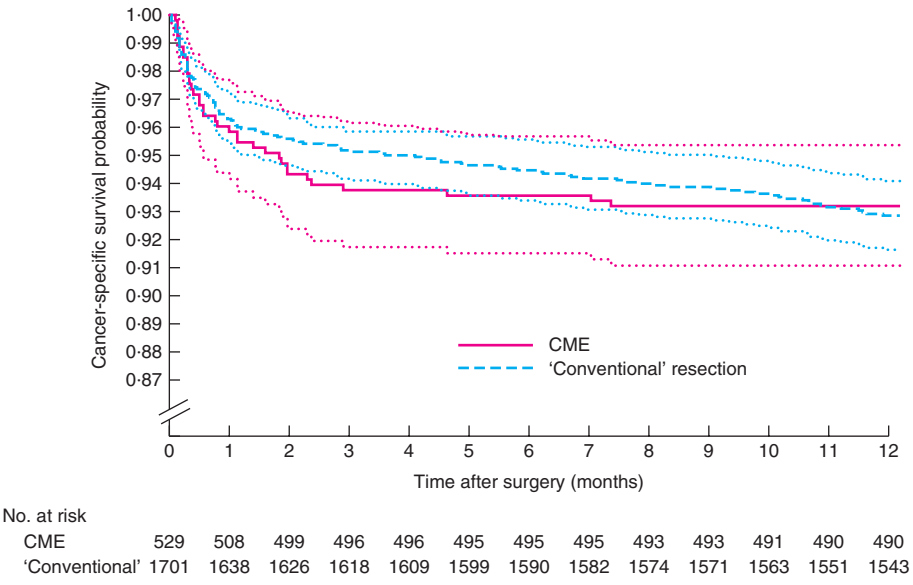

Fig. 1 One-year cancer-specific survival curves for 2230 patients stratified by complete mesocolic excision (CME) or 'conventional' resection for International Union Against Cancer (UICC) stage I–III colonic adenocarcinoma. Dotted lines indicate 95 per cent c.i. The 30-day mortality rate was 4·2 (95 per cent c.i. 2·7 to 6·3) per cent in the CME group compared with 3·7 (2·8 to 4·7) per cent in the 'conventional' group ($P = 0·605$; Fisher's exact test). The 90-day mortality rates were 6·2 (4·4 to 8·7) and 4·9 (3·9 to 6·0) per cent respectively ($P = 0·219$). The 1-year cancer-specific mortality rate was 6·8 (4·9 to 9·3) per cent in the CME group compared with 7·1 (6·0 to 8·5) per cent in the 'conventional' group ($P = 0·846$)

Correction added on 11 February 2016, after online publication: *Fig. 1* legend should be 'The 1-year cancer-specific **mortality** rate was 6·8 (4·9 to 9·3) per cent … '

Table 5 Univariable logistic regression analysis of 30- and 90-day mortality in 2230 resections of International Union Against Cancer (UICC) stage I–III colonic adenocarcinomas

	30-day mortality		90-day mortality	
	Odds ratio	*P*§	Odds ratio	*P*§
Procedure				
'Conventional' colonic resection	1·00 (reference)		1·00 (reference)	
CME	1·12 (0·67, 1·82)	0·633	1·30 (0·85, 1·95)	0·220
Sex				
M	1·00 (reference)		1·00 (reference)	
F	0·95 (0·62, 1·48)	0·834	1·00 (0·68, 1·45)	0·996
Age (per decade)	2·42 (1·87, 3·18)	< 0·001	2·33 (1·87, 2·94)	< 0·001
Body mass index (per kg/m^2)	0·95 (0·90, 1·00)	0·070	0·94 (0·89, 0·98)	0·007
ASA grade				
I	1·00 (reference)		1·00 (reference)	
II	5·39 (1·95, 22·33)	0·005	3·63 (1·68, 9·48)	0·003
III–IV	18·98 (6·83, 78·81)	< 0·001	13·16 (6·07, 34·47)	< 0·001
No. of colonic tumours				
1	1·00 (reference)		1·00 (reference)	
≥ 2	2·03 (0·10, 4·72)	0·138	2·13 (0·87, 4·45)	0·066
Tumour site(s)*				
Left-sided	1·00 (reference)		1·00 (reference)	
Right-sided	1·74 (1·11, 2·75)	0·015	1·65 (1·13, 2·44)	0·011
Both sides	1·32 (0·07, 6·51)	0·791	1·92 (0·30, 6·73)	0·383
Fixation of tumour†				
Mobile	1·00 (reference)		1·00 (reference)	
Fixed	1·70 (0·99, 2·79)	0·044	1·60 (1·00, 2·48)	0·041
Pathological T category				
pT1–pT3	1·00 (reference)		1·00 (reference)	
pT4	2·82 (1·79, 4·39)	< 0·001	2·31 (1·55, 3·43)	< 0·001
Type of resection				
Open or converted	1·00 (reference)		1·00 (reference)	
Laparoscopic	0·50 (0·32, 0·77)	0·002	0·51 (0·35, 0·74)	< 0·001
Extended organ resection‡				
Only colonic	1·00 (reference)		1·00 (reference)	
Other organ	1·69 (0·70, 2·75)	0·270	1·50 (0·81, 2·63)	0·156
Injury to other organ				
No	1·00 (reference)		1·00 (reference)	
Yes	3·47 (1·74, 6·38)	< 0·001	3·19 (1·72, 5·54)	< 0·001
Anastomosis				
No	1·00 (reference)		1·00 (reference)	
Yes	1·15 (0·51, 3·31)	0·764	0·96 (0·49, 2·19)	0·924

Values in parentheses are 95 per cent c.i. CME, complete mesocolic excision; ASA, American Society of Anesthesiologists. *Site of primary tumour defined as colonic tumour with highest pT and subsequent pN category in patients with synchronous adenocarcinomas. †Determined by the surgeon, not the pathologist. ‡Resection of other abdominal organ for oncological reasons or owing to peroperative injury. §Wald test.

With the better general oncological outcome from CME reported[1], and the possible increased risk of recurrence reported after 'conventional' resections of tumours at the hepatic flexure and in the sigmoid performed 15–20 years ago[30], further studies are needed to investigate whether a reduced risk of recurrence associated with tumour site is apparent after CME.

The retrospective design is the main limitation of this study, but as a large population-based study it offers good possibility to investigate short-term outcomes after CME. In observational studies, selection bias is one of the most challenging problems. The Γ values from the sensitivity analyses are not large, suggesting that the results are sensitive to hidden bias (such as differences in socioeconomic status or deprivation). Unfortunately the DCCG database does not allow access to data on specific surgeons, and this variable could not be included in the analyses. A randomized trial, as proposed by some[3], would be preferable, but challenging to conduct. Inclusion of patients in an expertise-based trial with random allocation to centres performing CME or 'conventional' resections would be one option.

The study was also limited by the fact that one centre implemented robot-assisted laparoscopic resections, and another implemented single-incision laparoscopic surgery during the study interval. This might have influenced the

Table 6 Univariable, reduced multivariable model and propensity score-adjusted logistic regression of complete mesocolic excision as a risk factor for 30- and 90-day mortality in 2230 resections of International Union Against Cancer (UICC) stage I–III colonic adenocarcinomas

	30-day mortality		90-day mortality	
	Odds ratio	*P*†	Odds ratio	*P*†
Univariable logistic regression				
Procedure				
'Conventional' colonic resection	1·00 (reference)		1·00 (reference)	
CME	1·12 (0·67, 1·82)	0·633	1·30 (0·85, 1·95)	0·220
Reduced multivariable logistic regression model				
Procedure				
'Conventional' colonic resection	1·00 (reference)		1·00 (reference)	
CME	1·07 (0·62, 1·80)	0·795	1·25 (0·77, 1·94)	0·334
Age (per decade)	1·93 (1·45, 2·60)	< 0·001	1·87 (1·46, 2·41)	< 0·001
ASA grade				
I	1·00 (reference)		1·00 (reference)	
II	3·41 (1·20, 14·34)	0·044	2·41 (1·09, 6·40)	0·047
III–IV	9·71 (3·36, 41·17)	< 0·001	7·06 (3·14, 18·95)	< 0·001
Body mass index (kg/m^2)	0·98 (0·93, 1·03)	0·466	0·96 (0·92, 1·01)	0·097
Pathological T category				
pT1–T3	1·00 (reference)		1·00 (reference)	
pT4	2·54 (1·57, 4·07)	< 0·001	2·06 (1·34, 3·13)	< 0·001
Type of resection				
Open or converted	1·00 (reference)		1·00 (reference)	
Laparoscopic	0·63 (0·39, 1·00)	0·052	0·63 (0·42, 0·95)	0·028
Propensity score-adjusted				
Procedure				
'Conventional' colonic resection	1·00 (reference)		1·00 (reference)	
CME	1·05 (0·63, 1·74)	0·861	1·22 (0·79, 1·87)	0·363

Values in parentheses are 95 per cent c.i. Confounding variables in reduced multivariable model are shown. Variables included in propensity score-adjusted analyses are age, sex, body mass index, American Society of Anesthesiologists (ASA) grade, pT4 category, fixation of tumour, laparoscopic resection, anastomosis, year of resection (2008 and 2009 pooled) and primary tumour location grouped as: caecum, ascending colon, hepatic flexure to mid transverse colon (hepatic flexure, right and mid third of transverse colon), left transverse and splenic flexure, descending colon, and sigmoid. CME, complete mesocolic excision. The area under the receiver operating characteristic (ROC) curve was 0·796 for 30-day and 0·783 for 90-day mortality. In sensitivity analysis (Rosenbaum approach based on Wilcoxon signed rank test), Γ was 1·52 for 30-day and 1·21 for 90-day mortality. †Wald test.

outcome for 'conventional' procedures. Another limitation is that CME surgery was performed in only one centre, compared with three centres performing 'conventional' surgery. Thus, for outcomes concerning morbidity and mortality, there is a need for other reports on CME before safety can be declared.

Collaborators

Other members of the COMES Group contributed substantially to this study: B. Bols and P. Ingeholm (Department of Pathology, Herlev University Hospital) and E. R. Iversen (Department of Surgery, Hillerød University Hospital).

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