Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study

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Summary

Background Application of the principles of total mesorectal excision to colon cancer by undertaking complete mesocolic excision (CME) has been proposed to improve oncological outcomes. We aimed to investigate whether implementation of CME improved disease-free survival compared with conventional colon resection.

Methods Data for all patients who underwent elective resection for Union for International Cancer Control (UICC) stage I–III colon adenocarcinomas in the Capital Region of Denmark between June 1, 2008, and Dec 31, 2011, were retrieved for this population-based study. The CME group consisted of patients who underwent CME surgery in a centre validated to perform such surgery; the control group consisted of patients undergoing conventional colon resection in three other hospitals. Data were collected from the Danish Colorectal Cancer Group (DCCG) database and medical charts. Patients were excluded if they had stage IV disease, metachronous colorectal cancer, rectal cancer (≤15 cm from anal verge) in the absence of synchronous colon adenocarcinoma, tumour of the appendix, or R2 resections. Survival data were collected on Nov 13, 2014, from the DCCG database, which is continuously updated by the National Central Office of Civil Registration.

Findings The CME group consisted of 364 patients and the non-CME group consisted of 1031 patients. For all patients, 4-year disease-free survival was 85·8% (95% CI 81·4–90·1) after CME and 75·9% (72·2–79·7) after non-CME surgery (log-rank p=0·0010). 4-year disease-free survival for patients with UICC stage I disease in the CME group was 100% compared with 89·8% (83·1–96·6) in the non-CME group (log-rank p=0·046). For patients with UICC stage II disease, 4-year disease-free survival was 91·9% (95% CI 87·2–96·6) in the CME group compared with 77·9% (71·6–84·1) in the non-CME group (log-rank p=0·0033), and for patients with UICC stage III disease, it was 73·5% (63·6–83·5) in the CME group compared with 67·5% (61·8–73·2) in the non-CME group (log-rank p=0·13). Multivariable Cox regression showed that CME surgery was a significant, independent predictive factor for higher disease-free survival for all patients (hazard ratio 0·59, 95% CI 0·42–0·83), and also for patients with UICC stage II (0·44, 0·23–0·86) and stage III disease (0·64, 0·42–1·00). After propensity score matching, disease-free survival was significantly higher after CME, irrespective of UICC stage, with 4-year disease-free survival of 85·8% (95% CI 81·4–90·1) after CME and 73·4% (66·2–80·6) after non-CME (log-rank p=0·0014).

Interpretation Our data indicate that CME surgery is associated with better disease-free survival than is conventional colon cancer resection for patients with stage I–III colon adenocarcinoma. Implementation of CME surgery might improve outcomes for patients with colon cancer.

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Introduction

Improvements in the treatment of patients with rectal cancer in the past three decades have resulted in higher survival than patients undergoing treatment for colon cancer.[1] A major factor has been the implementation of total mesorectal excision.[2] A similar change of surgical technique has not been implemented in colon cancer surgery, although it has been suggested that the principles of total mesorectal excision could also be applied in colon cancer surgery through complete mesocolic excision (CME).[3,4] In CME, dissection is done in the embryologically defined mesocolic planes to create an intact envelope of the mesocolic fascia, and all lymph nodes along the tumour supplying vessels are contained in the specimen.[4] The specimens are characterised by a greater distance from the tumour to the ligation of the tumour supplying vessels. The technique remains controversial,[5,6] and the evidence of increased disease-free survival after CME is mainly based on two single centre studies by Hohenberger and colleagues[4] and Bokey and colleagues.[7] The improvements suggested in these studies could be confounded because historical control groups were used. Because it seems impossible to conduct randomised controlled trials of this technique,[6] population studies comparing CME with conventional

colon cancer resections might be the only way to clarify any differences between conventional resections and CME.

In June, 2008, CME was implemented for colon cancer at Hillerød Hospital, Denmark, because we were convinced that it would improve oncological outcomes.[8] After a short implementation period, with a few non-CMEs performed, CME has been undertaken as the standard procedure for all elective cases in Hillerød. The three other centres in the Capital Region of Denmark have been reluctant to implement CME during the study period.[5] These four centres cover the entire population of 1·75 million inhabitants of the Capital Region of Denmark.

During 2009, multidisciplinary team courses were held in Denmark to improve the outcome for colorectal cancer. As part of these courses, the quality of the colon cancer resection specimens of the participating departments was evaluated by external expert pathologists.[9] They showed substantial differences between specimens from Hillerød and those from the other three centres. The CME specimens from Hillerød had a significantly greater lymph node yield, greater distance between the tumour and vascular high tie, and more intact mesocolic fascia.

The aim of this study was to investigate whether implementation of CME surgery was associated with improved disease-free survival compared with conventional colon cancer surgery.

	Non-CME (n=1031)	CME (n=364)	p value
Age (years)	73·0 (66·0–79·9)	71·5 (64·3–77·8)	0·021*
Men	472 (46%)	188 (52%)	0·054†
BMI (kg/m²)	24·8 (22·5–27·8)	25·0 (22·3–28·4)	0·43*
ASA score			0·0024†
ASA score I	226 (22%)	98 (27%)	..
ASA score II	660 (64%)	196 (54%)	..
ASA score III–IV	145 (14%)	70 (19%)	..
Tumour site of primary tumour			0·59†
Caecum	227 (22%)	79 (22%)	..
Ascending colon	138 (13%)	50 (14%)	..
Hepatic flexure	64 (6%)	16 (4%)	..
Transverse colon	100 (10%)	46 (13%)	..
Splenic flexure	35 (3%)	10 (3%)	..
Descending colon	40 (4%)	17 (5%)	..
Sigmoid colon	427 (41%)	146 (40%)	..
Synchronous tumours	35 (3%)	13 (4%)	..
Tumour site (side)‡			0·50†
Left sided tumour(s)	531 (52%)	175 (48%)	..
Right sided tumour(s)	479 (47%)	182 (50%)	..
Both sides	18 (2%)	7 (2%)	..
Primary colon resection			<0·0001†
Right hemicolectomy	415 (40%)	104 (29%)	..
Extended right hemicolectomy	35 (3%)	65 (18%)	..
Transverse colectomy	17 (2%)	0	..
Right sided subtotal colectomy	18 (2%)	19 (5%)	..
Left hemicolectomy	110 (11%)	35 (10%)	..
Sigmoid resection	403 (39%)	132 (36%)	..
Other segmental resection	1 (<1%)	0	..
Colectomy	29 (3%)	7 (2%)	..
Proctocolectomy	3 (<1%)	2 (<1%)	..
Supplementary colon resection	11 (1%)	4 (1%)	0·96†
Laparoscopic	667 (65%)	179 (49%)	<0·0001†
Conversion to open surgery	129/796 (16%)	52/231 (22%)	0·059†
Resection of other organ	146 (14%)	39 (11%)	0·096†
Fixation of tumour	177 (17%)	46 (12%)	0·043†
30-day mortality	38 (4%)	17 (5%)	0·41†

Data are median (IQR) or n (%). CME=complete mesocolic excision. ASA=American Society of Anesthesiologists. Tumour site of primary tumour=colon tumour with highest T and subsequent N stage in case of synchronous adenocarcinomas. Tumour site (side)=missing data for location of transverse colon cancers in three patients in the non-CME group. Supplementary colon resection=resection of two separate segments—eg, invasion of sigmoid tumour in the caecum → sigmoid resection and supplementary—eg, ileocaecal resection. Laparoscopic=completed laparoscopically. Conversion to open surgery=conversion of intended laparoscopic resection. Resection of other organ did not include other segment of the colon or rectum. Fixation of tumour was assessed by surgeon not by pathologist *t test. †Pearson's χ^2 test. ‡n=1028 in the non-CME group.

Table 1: **Baseline and tumour characteristics, surgical procedures done, and 30-day mortality**

Methods

Study design and participants

Data for all patients who underwent elective resection for Union for International Cancer Control (UICC) stage I–III colon adenocarcinomas in the Capital Region of Denmark between June 1, 2008, and Dec 31, 2011, were retrieved from the national database of the Danish Colorectal Cancer Group (DCCG). The CME group consisted of patients who underwent CME in Hillerød; the control group consisted of patients who underwent elective conventional colon resection for adenocarcinomas at one of the three other colorectal cancer centres. None of these three cancer centres performed CME in the study period. All four hospitals are public university hospitals associated with Copenhagen University with patient referral based on postal address.

Medical records of all the patients were reviewed by a colorectal surgeon from Hillerød, and DCCG data were supplemented with data for follow-up. Data from pathological examination of the specimens were retrieved from the DCCG database and missing data were retrieved from pathology reports by colorectal pathologists. Patients were excluded if they had stage IV disease, metachronous colorectal cancer, rectal cancer (≤15 cm from anal verge) in the absence of synchronous colon adenocarcinoma, tumour of the appendix, or R2 resections. Survival data were collected on Nov 13, 2014, from the DCCG database, which is continuously updated by the National Central Office of Civil Registration.

To ensure the validity of the data, all patient data in the CME group were audited by the three coauthors (MW, AK-K, and JRT) presenting each of the three centres contributing non-CME patients. Data in the non-CME group were first audited by the primary author for discrepancies between data from the review of medical records by a Hillerød surgeon and those in the DCCG database. Subsequently, all patients in the non-CME group with events in favour of better outcome after CME

(eg, recurrence or complications) were audited by the three mentioned coauthors. An audit of all the non-CME patients was thus not done. Any disagreement between the registered data and the audit was resolved in consensus between the auditing coauthor, primary author, and last author.

Because this was a retrospective study, approval from the local ethics committee was not needed according to Danish legislation. All participating departments approved the study protocol. Data collection was approved by the Danish Data Protection Agency and the study was done on behalf of the DCCG.

Procedures

Procedures performed in Hillerød have been defined previously.[10] The same definitions were applied to the control group, except for left hemicolectomies, which were often segmental resections of the colon (eg, only the splenic flexure) in the centres performing conventional colon resection. The resection was classified as laparoscopic if it was not converted at any time. Tumour sites in the left third of the transverse colon or distally were defined as left sided, the remainder as right sided.

Staging was done according to UICC TNM system (5th edition).[8] The mesocolic plane was assessed as defined by West and colleagues.[11] Adjuvant chemotherapy was registered as a dichotomised variable.

Date of last follow-up was defined as the latest CT or PET/CT of thorax and abdomen, the last chest radiograph and contrast-enhanced ultrasound of the liver, or the last laparotomy in case of suspicion of recurrence. Duration and methods of follow-up for colorectal cancers in Denmark are not standardised. Radiological findings of metastases during follow-up were considered as recurrence even if histological verification was not obtained. Subsequent metachronous colon cancers were recurrences only if located in the anastomosis and with the same morphology as the primary tumour.

Statistical analysis

Continuous data are presented as medians with IQR. Categorical variables were analysed by Pearson's χ^2 tests and continuous variables by Student *t* tests. Disease-free survival was evaluated with Kaplan-Meier curves and log-rank tests for categorical data, and with univariable Cox proportional hazards regression models for all variables. Multivariable proportional hazards Cox regression models were used with purposeful selection.[12] Possible predictive variables were selected if p values in the univariable regression models were less than 0·50 based on Wald statistics, and multivariable models were fitted with the variables identified in the univariable analyses. After the stepwise elimination of all variables with p values of more than 0·10, the reduced Cox regression models were tested one by one with all variables eliminated, and if the tested variable had a p value of less than 0·10 it was included in the final model. The variables CME and UICC stage were retained in all models during stepwise elimination, even with p values greater than 0·10. The adequacy and fit of the models were checked graphically and with Schoenfeld residuals. In case of variables showing non-proportionality, the models were stratified by these variables. Clinically relevant interactions were tested. Results are presented as hazard ratios (HRs) with 95% CIs. Propensity scores were created with logistic regression modelling the probability of a patient

	Non-CME (n=1031)	CME (n=364)	p value
UICC stage (TNM5)			0·57*
Stage I	167 (16%)	55 (15%)	..
Stage II	499 (48%)	169 (46%)	..
Stage III	365 (35%)	140 (38%)	..
T stage (highest T stage if synchronous) tumours			0·44*
pT1	82 (8%)	25 (7%)	..
pT2	122 (12%)	41 (11%)	..
pT3	621 (60%)	211 (58%)	..
pT4	206 (20%)	87 (24%)	..
Lymph nodes resected			<0·0001†
Mean (SD)	20·9 (10)	36·5 (15·9)	..
Median (IQR)	19 (14–26)	34 (25–45)	..
Specimens with 12 or more lymph nodes	913 (89%)	362 (99%)	<0·0001†
Lymph node metastases			0·0006†
Mean (SD)	1·3 (2·9)	2·2 (4·7)	..
Median (IQR)	0 (0–1)	0 (0–2)	..
Lymph node ratio, mean (SD)	0·07 (0·14)	0·07 (0·14)	0·94†
N stage			0·0003*
pN0	667 (65%)	224 (62%)	..
pN1	249 (24%)	70 (19%)	..
pN2	116 (11%)	70 (19%)	..
Serosal invasion	188 (18%)	84 (23%)	0·045*
Perineural invasion	95 (9%)	31 (9%)	0·68*
Extramural venous invasion	200 (19%)	101 (28%)	0·0009*
Tumour morphology of primary tumour			<0·0001*
Adenocarcinoma	782 (76%)	224 (62%)	..
Poorly differentiated adenocarcinoma	72 (7%)	57 (16%)	..
Mucinous adenocarcinoma	155 (15%)	55 (15%)	..
Signet ring cell carcinoma	7 (<1%)	18 (5%)	..
Undifferentiated carcinoma	2 (<1%)	10 (3%)	..
Medullary carcinoma	13 (1%)	10 (3%)	..
R1 resection	47 (5%)	10 (3%)	0·13*
Tumour perforation	45 (4%)	5 (1%)	0·0083*
Resection plane‡			<0·0001*
Mesocolic	432 (60%)	296 (82%)	..
Intramesocolic	261 (36%)	58 (16%)	..
Muscularis	28 (4%)	8 (2%)	..

Data are mean (SD), median (IQR), or n (%). CME=complete mesocolic excision. UICC=Union for International Cancer Control. R1 resection=macroradical resection, but 1 mm or less from tumour tissue to resection margin (lateral resection margin at tumour site). Resection plane for colon cancer as defined by West and colleagues[11] was not evaluated as standard in the non-CME group during the entire study period. *Pearson's χ^2 test. †t test. ‡n=721 in the non-CME group, n=362 in the CME group.

Table 2: **Pathological data**

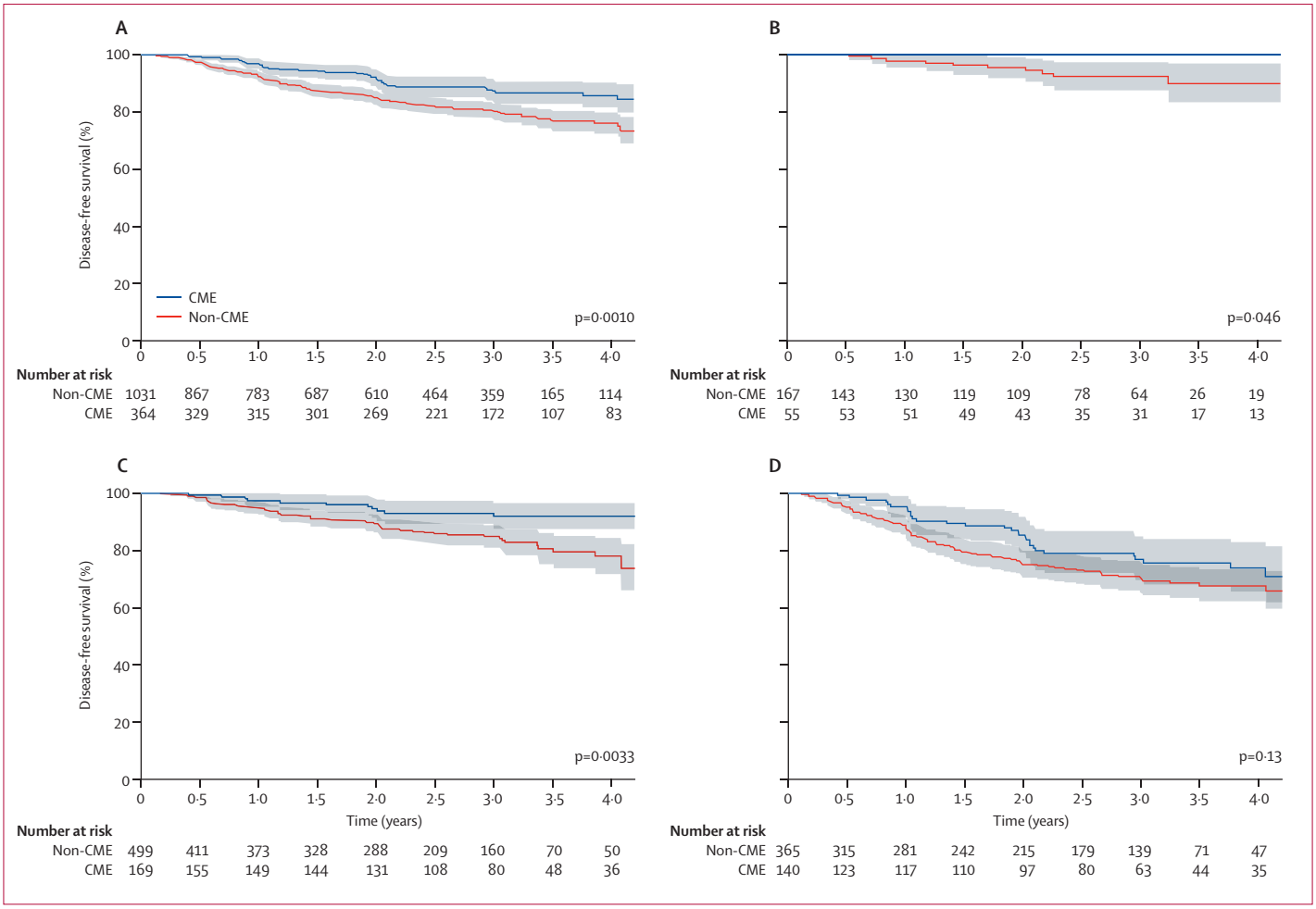

Figure 1: **Kaplan-Meier disease-free survival curves**
(A) All patients. (B) UICC stage I. (C) UICC stage II. (D) UICC stage III. p values from log-rank tests. Grey shaded areas are 95% CIs. UICC=Union for International Cancer Control.

undergoing CME based on age, sex, body-mass index (BMI), American Society of Anesthesiologists score, tumour side, synchronous tumours, and UICC stage. Through determination of possible interactions between covariates, a significant interaction between age and BMI was noted, and an interaction term grade×stage was also included in the logistic regression code to create the propensity scores. A 1:1 match without replacement was done. Overall survival was analysed with Kaplan-Meier curves and log-rank test.

p values of less than 0·05 was deemed to be significant, but all variables with p values of less than 0·10 are shown in the final Cox regression models. All analyses were done using R (version 3.1.0) and the survival package.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

364 patients underwent CME surgery and 1031 underwent conventional colon surgery during the inclusion period. An audit was done for the 394 (38·2%) patients in the non-CME group who had complications or recurrence. CME procedures were undertaken or supervised by a specialist in all 364 CME cases and in 989 (95·9%) of the non-CME cases. The remainder were done by senior residents trained in colorectal surgery. None of the specialists in Hillerød undertook surgery in any of the non-CME centres.

Table 1 shows the baseline and tumour characteristics, surgical procedures performed, and 30-day survival, and table 2 shows the data from the pathology reports. The mesocolic plane was not assessed by the pathologist as standard in the non-CME group during the study period (table 2). Because classification of tumour morphology differed between the centres in the study period, for the purposes of this analysis, signet ring cell and mucinous carcinomas were pooled and the remainder were classified as adenocarcinomas in the subsequent analyses.

In the CME group, 103 (73·6% of 140 patients with UICC stage III cancer received adjuvant chemotherapy compared with 254 (69·6%) of 365 in the non-CME group (difference: 4·0%, 95% CI −5·2 to 13·2; p=0·44). Adjuvant chemotherapy was given to 42 (24·9%) of the 169 patients with UICC stage II disease in the CME group compared with 75 (15·0%) of the 499 patients with UICC stage II disease in the non-CME group (difference: 9·8%, 95% CI 2·2–17·4; p=0·0053).

Follow-up was significantly longer in the CME group with a median of 2·98 years (IQR 1·99–3·93) compared with 2·14 years (1·02–3·11) in the non-CME group (p<0·0001). Recurrences occurred in 41 (11·3%) of the 364 patients in the CME group and in 167 (16·2%) of the 1031 patients in the non-CME group (difference: 5·0%, 95% CI 0·8–9·1, p=0·028). No recurrences were reported in patients with UICC stage I disease who underwent CME compared with ten (6·0%) of 167 patients with UICC stage I disease in the non-CME group. 11 (6·5%) of 169 patients with UICC stage II disease in the CME group had a recurrence, as did 62 (12·4%) of 499 patients with the same stage disease in the non-CME group. 30 (21·4%) of 140 patients with UICC stage III disease in the CME group, compared with 95 (26·0%) of 365 patients with UICC stage III disease in the non-CME group.

4-year disease-free survival was 85·8% (95% CI 81·4–90·1) after CME and 75·9% (72·2–79·7) after non-CME (log-rank p=0·0010; figure 1A). 4-year disease-free survival for patients with UICC stage I disease was 100% in the CME group compared with 89·8% (83·1–96·6) in the non-CME group (log-rank p=0·046; figure 1B). For patients with UICC stage II disease, 4-year disease-free survival was 91·9% (95% CI 87·2–96·6) in the CME group compared with 77·9% (71·6–84·1) in the non-CME group (log-rank p=0·0033; figure 1C). For patients with UICC stage III disease, 4-year disease-free survival was 73·5% (95% CI 63·6–83·5) in the CME group compared with 67·5% (95% CI 61·8–73·2) in the non-CME group (log-rank p=0·13; figure 1D).

Multivariable Cox regression showed CME to be a significant independent predictive factor for higher disease-free survival for all patients (table 3), and for patients with UICC stage II (table 4) and UICC stage III disease (table 4). Adjuvant chemotherapy was not a significant predictive factor of outcome in patients with UICC stage II disease and was eliminated early in the stepwise process of elimination of variables during the statistical model development. After propensity score matching, disease-free survival was significantly improved after CME compared with non-CME surgery, irrespective of UICC stage (4-year disease-free survival of 85·8% [95% CI 81·4–90·1] after CME and of 73·4% [66·2–80·6] after non-CME; log-rank p=0·0014) (figure 2). 5-year overall survival was 74·9% (95% CI 69·9–80·0) in the CME group compared with 69·8% (95% CI 66·7–73·0) in the non-CME group (log-rank p=0·12; figure 3).

	Hazard ratios (95% CI)	p value
Complete mesocolic excision	0·59 (0·42–0·83)	0·0025
ASA score		
I	1·00	..
II	1·43 (1·01–2·02)	0·042
III–IV	1·77 (1·10–2·84)	0·018
UICC stage (TNM5)		
I	1·00	..
II	2·26 (1·16–4·39)	0·016
III	5·24 (2·74–10·0)	<0·0001
Mucinous or signet ring cell carcinoma	1·50 (1·05–2·15)	0·026
R1 resection	3·74 (2·47–5·67)	<0·0001

ASA=American Society of Anesthesiologists. UICC=Union for International Cancer Control. R1 resection=macroradical resection, but tumour tissue 1 mm or less from the resection margin (lateral resection margin at tumour site).

Table 3: **Reduced multivariable Cox regression model analysis of disease-free survival in all patients**

	Hazard ratios (95% CI)	p value
UICC stage II (n=667)		
Complete mesocolic excision	0·44 (0·23–0·86)	0·018
Perineural invasion	2·50 (1·22–5·08)	0·011
R1 resection	1·99 (0·94–4·23)	0·072
Laparoscopic	0·65 (0·40–1·07)	0·089
UICC stage III (n=504)		
Complete mesocolic excision	0·64 (0·42–1·00)	0·048
Mucinous or signet ring cell carcinoma	1·59 (1·02–2·49)	0·042
Serosal involvement	2·21 (1·51–3·23)	<0·0001
Perineural invasion	2·20 (1·49–3·25)	<0·0001
Lymph node ratio	10·9 (4·81–24·5)	<0·0001
Fixation of tumour	1·75 (1·13–2·69)	0·0112
Adjuvant chemotherapy	0·62 (0·41–0·93)	0·020
Laparoscopic	1·40 (0·94–2·08)	0·095

R1 resection=macroradical resection, but tumour tissue 1 mm or less from the resection margin (lateral resection margin at tumour site). Laparoscopic=completed laparoscopically without conversion to open surgery. Lymph node ratio=number of lymph node metastases:number of resected lymph nodes. Fixation of tumour was assessed by surgeon not by pathologist. In reduced multivariable Cox regression model analysis of disease-free survival in patients with UICC stage III disease, tumour side did not meet the proportional hazard assumption and the variable was stratified in the final model.

Table 4: **Reduced multivariable Cox regression model analyses of disease-free survival in UICC stage II and III patients**

Discussion

Our data indicate that CME is associated with significantly improved disease-free survival compared with conventional colon resections (panel), in particular for patients with UICC stage I or II disease. Our findings also show that CME is a significant, independent predictive factor for improved disease-free survival for all patients, and for those with UICC stage II and III disease. Although further studies are needed to clarify the

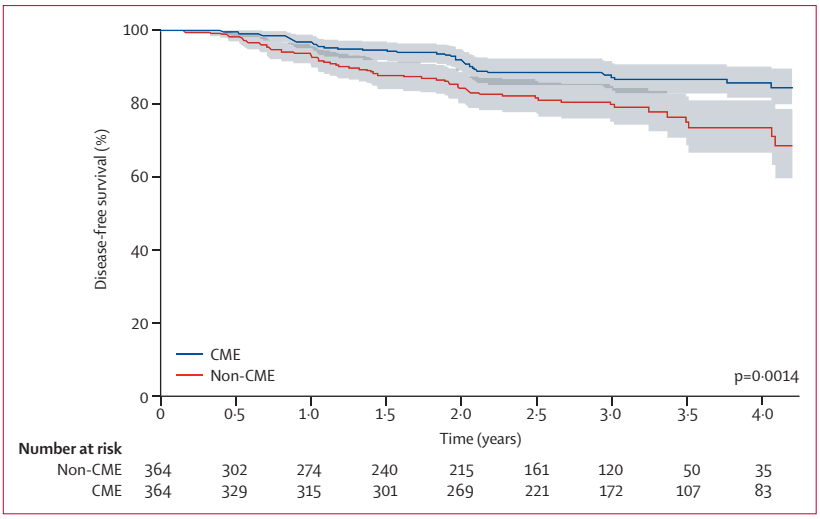

Figure 2: **Kaplan-Meier disease-free survival curves in matched pairs after propensity scoring**
p value from log-rank test. Grey shaded areas are 95% CIs.

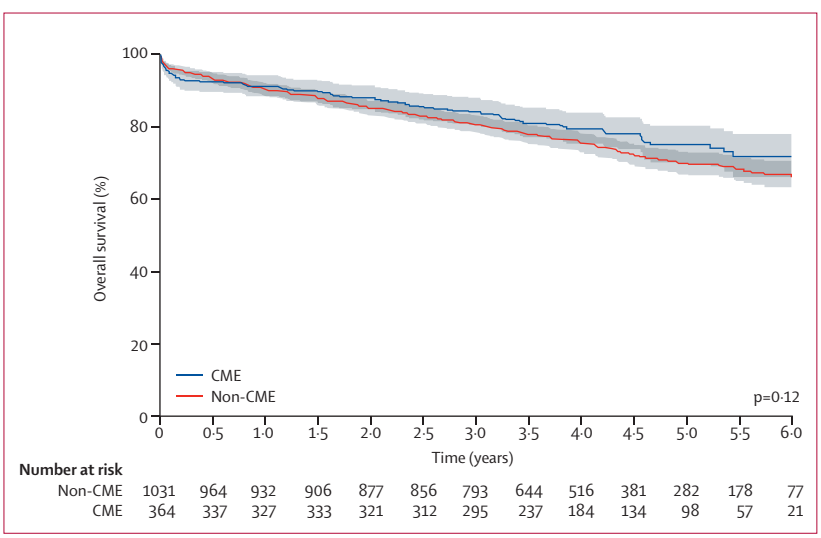

Figure 3: **Kaplan-Meier overall survival curves**
p value from log-rank test. Grey shaded areas are 95% CIs.

potential risks of CME, we suggest that an increased focus should be put on implementation of CME surgery, possibly leading to improved survival in patients resected for stage I–III colon cancer.

The non-CME group in our study represents about a quarter of the resections of UICC stage I–III colon cancers done in Denmark during the study period, and seems representative of standard conventional colon cancer surgery done in most Danish departments[1] and equivalent to what is deemed conventional colon cancer surgery worldwide.[9,11] Although this validation[9] was done in 2009, the principles of surgery were unchanged in the non-CME group during the study period with no increase in proportion of specimens graded as mesocolic resection plane, and number of lymph nodes resected as reported to the DCCG database.[1]

Our results for disease-free survival with CME are equivalent to those reported from Hohenberger and colleagues from their centre in Erlangen, Germany.[4] The only other multicentre study of CME,[21] which compared only 84 CME resections with 105 conventional resections in a similar design to ours, reported a similarly improved outcome for UICC stage I–II cancers, but not for patients with UICC stage III disease. One might suspect that the absence of an effect of CME surgery in patients with stage III disease might be due to upstaging from stage II to stage III in the CME group as a result of extended lymph-node resection and subsequent identification of lymph-node metastases only in the more apical lymph nodes in the mesocolon. Such metastases, present only in apical lymph nodes but not in lymph nodes close to the tumour (known as skip nodes), are reported in as many as 18% of cases.[22] However, the proportion of patients with stage I–II disease was similar in the two groups in the our study and similar to the proportions across Denmark,[1] and suggests that there was no upstaging of disease due to CME surgery. Another hypothesis could be that the pathological examination techniques used during the study period were not sensitive enough to detect all micrometastases. In the CME group, resected micro-metastases located in the apical lymph nodes could have gone undetected, and the tumours would have been classified as stage I–II if other metastases were not found. In the non-CME group, similar micrometastases would not be resected because of the more limited lymph-node resection in conventional surgery, and recurrence might occur later, because micrometastases are associated with worse prognosis.[23] Further studies are needed to identify other possible reasons for these findings. Injection of methylene blue to the tumour-supplying arteries is associated with upstaging in early colorectal cancers after improved lymph node yield.[24] Methylene blue injection was implemented in Hillerød in May, 2010, but was not used in the non-CME group, so a small effect of upstaging after methylene blue injection might be a confounder.

We found that CME was a significant predictive factor for disease-free survival in patients with stage III disease, although the effect was not as large as in patients with stage I–II disease. This difference could be due to the effect of adjuvant chemotherapy, which most patients with stage III disease received. Lymph-node metastases that were not removed in the non-CME group would have been affected by adjuvant chemotherapy, thus reducing the number of recurrences in the non-CME group.

Randomised controlled trials comparing CME with non-CME surgery would be difficult to undertake[6] because the preferences of CME surgeons would be entrenched and a usable definition of how they should undertake conventional resections would be difficult. A prospective study could be possible if other centres implemented CME. Potential selection bias can be reduced with the use of propensity score matching, but our study design has several other limitations. The

patients in the CME group underwent surgery during an implementation phase, during which the skills of the surgeons improved. This process could have confounded the data in favour of the non-CME group. Because of the difference in duration and methods of follow-up, the recurrence rates in the non-CME group might have been underestimated. Asymptomatic late recurrences in the non-CME group also might not have been diagnosed because of the shorter follow-up. CT was the standard follow-up examination in the CME group. The use of chest radiograph and contrast-enhanced ultrasound as follow-up for some patients in the non-CME group might have underestimated the rate of locoregional recurrences in this group.[25] The use of chest radiography does not detect lung and mediastinal metastases with the same sensitivity as CT of the thorax,[26] and this might also bias results in favour of conventional surgery.

The improved outcome after CME is likely to be related to resection in the mesocolic plane[11,27] and to high ligation of the tumour-supplying vessels.[4,27] Data for resection plane were available for only 70% of the patients in the non-CME group, because validation of assessment of the resection plane by pathologists was not done during the whole study period. Because of this, the resection plane was not included in the multivariable analyses. Validation of tumour morphology classification was also not done, so tumours were dichotomised as mucinous or signet-ring cell carcinomas or other morphologies. The more frequent use of adjuvant chemotherapy for patients with stage II disease in the CME group could be related to more patients having had extramural vascular invasion and serosal invasion in this group. Even though these factors were not significant independent factors in the multivariable analysis, they show that the effectiveness of a pathologist could be a potential bias to the findings.

The lower proportion of laparoscopic resection in the CME group relative to the non-CME group was related to a standard open approach for tumours located in the proximity of the flexures or in the transverse colon.[10] Whether the apparent advantage of CME surgery shown in this study will translate into populations where there is an increased rate of laparoscopy for tumours near the flexures and in the transverse colon is unclear. Further studies must be done to determine whether open or laparoscopic CME provide the best oncological outcome for different tumour sites. Because of the central ligation of the middle colic artery, extended right hemicolectomy is the standard procedure when CME is undertaken for tumours with this tumour site. This led to a higher proportion of extended right hemicolectomy in the CME group.

Overall survival was not significantly improved in the CME group compared with the non-CME group. This lack of effect may be due to the relatively short follow-up of our study, the improved surgical outcomes for resection of lung and liver recurrences, or advances in chemotherapy for patients with non-resectable recurrences.

Panel: Research in context

Systematic review

Complete mesocolic excision (CME) has been suggested to improve oncological outcomes on the basis of data from two large single-centre studies.[4,7] However, the improvements suggested in these studies could be confounded because historical control groups were used. Because randomised controlled trials to compare CME surgery with conventional colon cancer resection are likely impossible to do,[6] population studies comparing the two approaches might be the only way to clarify any differences between conventional resections and CME. We searched PubMed using the term "complete mesocolic excision" for articles published in English, German, Danish, Swedish, or Norwegian, with no restrictions on publication date (last publication identified was Sept 13, 2014), and identified only other single-centre studies[13,14] with historical controls, small single-centre studies without controls,[15–18] small reports of open compared with laparoscopic CME,[19,20] and a study comparing only 84 patients undergoing CME with 105 undergoing conventional colon cancer surgery.[21] No randomised controlled trials comparing CME with conventional colon cancer surgery were identified.

Interpretation

Our data indicate that CME is associated with significantly improved disease-free survival compared with conventional colon resections, in particular for patients with UICC stage I or II disease. CME is also a significant independent predictive factor for improved disease-free survival for all patients, and for those with UICC stage II and III disease. Although further studies are needed to clarify the potential risks of CME, we suggest that an increased focus should be put on implementation of CME surgery, possibly leading to improved outcomes in patients resected for stage I–III colon cancer.

Some authors[5] have concerns about an increased risk of complications after CME surgery. A higher mortality rate was reported in the CME group during the first 10·5 months postoperatively than in the non-CME group (figure 3). From a theoretical point of view, this could be related to the extended resection of the mesocolon. Central dissection could involve a risk of injury—eg, to the superior mesenteric vein and autonomous nerves. Although the literature is sparse, it shows acceptable and comparable risks of complication for both open[4] and laparoscopic CME,[28] but further, and preferably larger, population studies are needed to clarify the potential risks of CME with regard to short-term outcomes and any effect of a potential learning curve for surgeons.

Contributors

CAB, BB, PI, BK, and IG were responsible for the study concept. All authors contributed to the study design. CAB, AUN, JEJ, MW, AK-K, JRT, BB, PI, LAR, LVJ, and ERI collected and assembled these data. CAB, BK, and IG analysed and interpreted these data. CAB wrote the initial draft and all the authors approved the final draft of the report.

Declaration of interests
CAB is supported by grants from The Tvergaards Fund and Edgar and Hustru Gilberte Schnohrs Fund for this study and a forthcoming study of short-term outcomes. We declare no competing interests.

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