5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study

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Summary

Background The benefits of extensive lymph node dissection as performed in complete mesocolic excision are still debated, although recent studies have shown an association with improved long-term outcomes. However, none of these studies had an intention-to-treat design or aimed to show a causal effect; therefore in this study, we aimed to estimate the causal oncological treatment effects of complete mesocolic excision on right-sided colon cancer.

Methods We did a population-based cohort study involving prospective data collected from four hospitals in Denmark. We compared the oncological outcome data of patients at one centre performing central lymph node dissection and vascular division after almost complete exposure of the proximal part of the superior mesenteric vein (ie, the complete mesocolic excision group) with three other centres performing conventional resections with unstandardised and limited lymph node dissection (ie, non-complete mesocolic excision; control group). We included data for all patients in the Capital Region of Denmark undergoing elective curative-intent right-sided colon resections for stages I–III colon cancer, as categorised by the Union for International Cancer Control (UICC; 5th edition), from June 1, 2008, to Dec 31, 2013. Patients were followed-up for 5·2 years after surgery. The primary outcome was the cumulative incidence of recurrence after 5·2 years of surgery. Inverse probability of treatment weighting and competing risk analyses were used to estimate the possible causal effects of complete mesocolic excision. This study is registered with ClinicalTrials.gov, number NCT03754075.

Findings 1069 patients (813 in the control group and 256 in the complete mesocolic excision group) underwent curative-intent elective surgery for right-sided colon cancer during the study period. None of the patients were lost to follow-up regarding survival or recurrence status, and consequently no patient was censored in the analyses. The 5·2-year cumulative incidence of recurrence was 9·7% (95% CI 6·3–13·1) in the complete mesocolic excision group compared with 17·9% (15·3–20·5) in the control group, and the absolute risk reduction of complete mesocolic excision after 5·2 years was 8·2% (95% CI 4·0–12·4; p=0·00015). In the control group, 145 (18%) of 813 patients were diagnosed with a recurrence and 281 (35%) died during follow-up, whereas in the complete mesocolic excision group 25 (10%) of 256 patients were diagnosed with a recurrence and 75 (29%) died during follow-up.

Interpretation This study shows a causal treatment effect of central mesocolic lymph node excision on risk of recurrence after resection for right-sided colon adenocarcinoma. Complete mesocolic excision has the potential to reduce the risk of recurrence and improve long-term outcome after resection for all UICC stages I–III of right-sided colon adenocarcinomas.

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Introduction

Findings from a recent population-based study[1] showed that oncological outcome was worse for right-sided colon cancers than left-sided colon cancers, and that overall survival after curative surgery for right-sided colon cancer was better in patients whose surgery led to a lymph node yield of 22 or more. The study supported the findings of better outcome after more extensive lymph node dissection for colon cancer in several other studies.[2–6] The surgical strategies used in these studies were very similar, with complete mesocolic excision being the most well defined strategy.[2] Complete mesocolic excision is based on the pattern of lymph node metastases[7] and comprises meticulous dissection in the mesocolic plane,[8] sufficient bowel resection of a minimum of 10 cm proximally and distally of the tumour (including the next tumour-supplying arteries on both sides), and central vascular ligation to ensure lymph node dissection around the superior mesenteric vessels. Complete mesocolic excision is more challenging than conventional resections because of the complex vascular anatomy of the right colon, and many surgeons have refrained from performing right-sided complete mesocolic excision, although it seems to be a safe procedure.[9–12]

Research in context

Evidence before this study

To identify previous studies regarding long-term outcome after complete mesocolic excision, we searched PubMed for articles published before Nov 25, 2018, using the search term "complete mesocolic excisions" without language restrictions. We manually searched the 249 references retrieved and found no randomised controlled trials. Most of the published literature regarding complete mesocolic excision focused on right-sided colon tumours because the surgical procedure for these tumours is more complex than for sigmoid tumours. The majority of studies are small single-centre studies, mostly without control groups, with a few larger single-centre studies with historical controls. During the PubMed search, we found only one population-based study comparing complete mesocolic excision with non-complete mesocolic excision resections during the same time period, but the study included both right-sided and left-sided colon cancer. These studies indicate that complete mesocolic excision is associated with improved oncological outcome, but no studies have been done with a randomised controlled or other type of design to estimate the causal treatment effect of complete mesocolic excision on the risk of recurrence or overall survival when compared with non-complete mesocolic excision resections.

Added value of this study

Randomised, controlled trials addressing the use of complete mesocolic excision for colorectal cancer seem impossible to do because of several design problems. The surgeons cannot be masked, and both designs with randomisation of patients to centres doing either complete mesocolic excision or non-complete mesocolic excision resections, or a design with surgeons doing both resections and the patient being randomly allocated on the operating table, will lead to bias. Firstly, there is no definition of non-complete mesocolic excision usable for an randomised, controlled trial, in contrast to complete mesocolic excision, which is well defined by specific anatomical structures. Second, surgeons who were pro complete mesocolic excision might tend to do more extensive resections in the non-complete mesocolic excision group, whereas surgeons opposed to complete mesocolic excision might tend to do less extensive resections in the complete mesocolic excision group. Most randomised controlled trials are also restricted by inclusion criteria, which would reduce the generalisability of the results. The design of the present study provides the strongest possible evidence to estimate the causal treatment effect of complete mesocolic excision on right-sided colon cancer using inverse probability treatment weighting to reduce the effect of potential confounders and secure high generalisability with a complete regional population-based cohort. We found a reduction in the cumulative incidence of recurrence after complete mesocolic excision for UICC (Union for International Cancer Control) stages I–III right-sided adenocarcinoma, and conclude that it can be safely achieved by standardising surgery according to the principle of complete mesocolic excision. The effect was evident for all stages I–III and for each of these stages.

Implications of the available evidence

Complete mesocolic excision should be considered as the gold standard of right-sided colon cancer surgery because complete mesocolic excision is a well defined procedure based on specific anatomical structures and has a significant treatment effect on risk of recurrence. Although it is technically more difficult to perform, it is safe in both open and laparoscopic settings. To safely implement complete mesocolic excision and to shorten the learning curve, national and international training programmes with mentoring and proctoring by surgeons experienced in performing complete mesocolic excision should be initiated.

In Japan, central lymph node dissection similar to complete mesocolic excision is recommended for clinical stage T3–4 or pN1–2 tumours,[13] but no useable pre-operative or intraoperative methods exist to determine whether lymph node metastases are present. The pathological N category depends on several factors including the tumour stage, morphology, mismatch repair status, demography, extent of the resection, and the pathological examination.[14] Our preliminary results[4] suggested that even patients with stage I colon cancer, as categorised by the Union for International Cancer Control (UICC; 5th edition), have a better outcome after complete mesocolic excision than those who underwent the standard colon resection in Denmark.

Since the pathological tumour stage is unknown by the surgeon during surgery, the question in all cases is whether to perform complete mesocolic excision or not. To our knowledge, this clinical problem has never been addressed before and this study therefore aimed to estimate the causal oncological treatment effects of complete mesocolic excision on right-sided colon cancer.

Methods

Study design and participants

We did a population-based cohort study involving prospective data collected from four hospitals in Denmark. Complete mesocolic excision was implemented as the standard surgical approach for colon cancer at Nordsjællands Hospital (Hillerød, Denmark) on June 1, 2008, whereas the colorectal cancer centres in Bispebjerg (Copenhagen, Denmark), Herlev (Herlev, Denmark), and Hvidovre (Hvidovre, Denmark) Hospitals did not recommend it.[14] These four public university clinics provided all colorectal cancer surgery to the Capital Region of Denmark's 1·8 million inhabitants.

We obtained patient data registered prospectively in the colon cancer database in Hillerød (ie, the complete mesocolic excision group), and prospective data from the national database of the Danish Colorectal Cancer Group

covering patients undergoing conventional resection (non-complete mesocolic excision; ie, the control group) in the other three centres. The differences in surgical principles between the two groups have been assessed indirectly and showed substantial differences in quality between the specimens.[15] The medical records of all the patients in the control group were reviewed by colorectal surgeons from Hillerød. Data audit for all patients undergoing complete mesocolic excision and for patients in the control group having postoperative complications or recurrence was done by the coauthors working at the non-complete mesocolic excision centres.[4] Follow-up data were registered prospectively in the medical records of the participating departments during patient follow-up.

We included data for all patients who underwent elective macroradical resection for UICC stages I–III right-sided colon tumours in the capital region of Denmark between June 1, 2008, and Dec 31, 2013. Right-sided tumours were defined as any primary adenocarcinoma located in the caecum, the ascending colon, the hepatic flexure, and the right or mid-third of the transverse colon. We included patients receiving neoadjuvant chemotherapy, but excluded those with synchronous colon tumours.

This study was approved by the Danish Patient Safety Authority and the Danish Data Protection Agency. Approval from the ethics committee was not needed under Danish legislation. Patient consent was not required. The study protocol is available in the appendix (pp 17–28).

See Online for appendix

Procedures

Surgery in Hillerød was based on the principles of complete mesocolic excision. The superior mesenteric vein was exposed to perform central vessel ligation and lymph node dissection. Extended right hemicolectomies for tumours located from the ascending colon close to the hepatic flexure and distally were performed openly as standard during the study period. These resections included the prepyloric and gastroepiploic lymph nodes in the specimen.[2,16] The patients in the control group underwent what was considered the standard method of colon cancer resection in Denmark during the study period. No level of mesocolic vascular division was specified in the national guidelines, which only recommended early and central vessel ligation. With the lateral to medial approach recommended, the guidelines were ambiguous regarding the issue of level of division. The recommendations concerning the extent of the bowel resection were based on a figure published by the Danish Colorectal Cancer Group.[17] Laparoscopic resection was performed when preferred by the surgeon. The pathological assessment was done according to the clinical guidelines of the local departments by different colorectal pathologists. Some differences might have been present between the local guidelines (eg, in the use of ex-vivo methylene blue arterial injections). Only lymph nodes draining the tumour were included in the lymph node yields.

Resections were classified as laparoscopic only if they were not converted to open surgery at any time. Both neoadjuvant and adjuvant chemotherapy were registered as dichotomised variables. Indication for adjuvant chemotherapy was similar in both groups and according to the national guidelines.[18] Mesocolic plane was not included as a variable because it cannot be used in clinical studies.[19]

Preoperative staging was done in all centres by contrast-enhanced CT of the thorax and abdomen. Methods of follow-up for colon cancer were not standardised during the study period. In the complete mesocolic excision group, the standard follow-up comprised an annual CT of the thorax and abdomen, and an annual sample of plasma carcinoembryonic antigen for 5 years, whereas standard modalities used, frequencies, and duration of follow-up differed between the three centres including patients in the control group. A pragmatic definition of the last follow-up was used as the latest CT or PET-CT of the thorax and abdomen, the latest chest radiograph and contrast-enhanced ultrasound of the liver, or the latest laparotomy in case of suspicion of recurrence. Histological verification of radiological findings of metastases during follow-up was not needed if the local multidisciplinary team conference considered the finding to be a recurrence. Metachronous colon tumours were considered as recurrences only if located in the anastomosis and if sharing morphology with the primary tumour. Because some 5-year follow-up examinations were done between 5·0 and 5·2 years after surgery, the follow-up period in the study was a minimum of 5·2 years and the final data were collected on March 31, 2019.

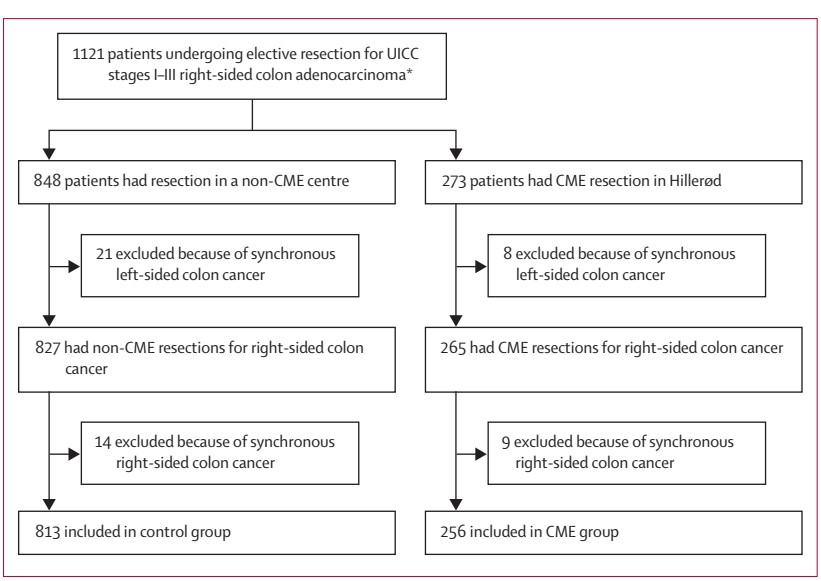

Figure 1: **Flowchart of patient selection**
CME=complete mesocolic excision. UICC=Union for International Cancer Control. *In the Capital Region of Denmark from June 1, 2008, to Dec 31, 2013.

	Control group (n=813)	Complete mesocolic excision group (n=256)	p value
Age, years	74·0 (67·7–80·9)	73·5 (67·2–79·6)	0·18
Men	332 (41%)	116 (45%)	0·22
BMI, kg/m²*	24·6 (22·2–27·8)	24·6 (22·3–27·3)	0·72
BMI >30 kg/m²	114/806 (14%)	34/254 (13%)	0·85
ASA physical status	..	..	0·27
I	167 (21%)	57 (22%)	..
II	495 (61%)	142 (55%)	..
III–IV	151 (19%)	57 (22%)	..
Neoadjuvant chemotherapy	12 (1%)	7 (3%)	0·18
Procedure	..	..	<0·0001
Right hemicolectomy	710 (87%)	154 (60%)	..
Extended right hemicolectomy	59 (7%)	87 (34%)	..
Transverse colectomy	13 (2%)	0	..
Right-sided subtotal colectomy	12 (1%)	12 (5%)	..
Other segmental colon resection	3 (<1%)	0	..
Colectomy	13 (2%)	2 (1%)	..
Proctocolectomy	3 (<1%)	1 (<1%)	..
Surgery by specialist†	782 (96%)	256 (100%)	0·0003
Laparoscopic resection (completed)	520 (64%)	84 (33%)	<0·0001
Conversion to open resection	85/605 (14%)	23/107 (21%)	0·057
Excision of other organ	117 (14%)	22 (9%)	0·019
Adjuvant chemotherapy	242 (30%)	78 (30%)	0·88
60-day major postoperative complications‡	138 (17%)	45 (18%)	0·85
30-day mortality	39 (5%)	13 (5%)	0·87
90-day mortality	49 (6%)	19 (7%)	0·46

Data are median (IQR), n (%), or n/N (%). p values for age and BMI were calculated with Kruskal-Wallis test; other p values calculate with Fisher's exact test. ASA=American Society of Anesthesiologists. BMI=body-mass index. *Data of two (1%) of 256 patients in the complete mesocolic excision group and for seven (1%) of 813 in the control group were unavailable for BMI. †Resection was done or supervised by a specialist, not necessary being a consultant. ‡Classified as a Clavien–Dindo score of ≥3b.

Table 1: **Baseline characteristics of the full dataset (patients undergoing resection from 2008 to 2013)**

	Control group (n=813)	Complete mesocolic excision group (n=256)	p value
Tumour location	..	..	0·049
Caecum	373 (46%)	112 (44%)	..
Ascending colon	220 (27%)	73 (29%)	..
Hepatic flexure	112 (14%)	23 (9%)	..
Transverse colon	108 (13%)	48 (19%)	..
UICC stage	..	..	0·89
I	111 (14%)	32 (13%)	..
II	422 (52%)	133 (52%)	..
III	280 (34%)	91 (36%)	..
pT category	..	..	0·99
1	37 (5%)	11 (4%)	..
2	91 (11%)	27 (11%)	..
3	515 (63%)	166 (65%)	..
4	170 (21%)	52 (20%)	..
Serosal invasion	157 (19%)	50 (20%)	1·00
Lymph node yield	21 (16–30)	38 (28–48)	<0·0001
pN category	..	..	0·18
0	533 (66%)	165 (64%)	..
1	175 (22%)	47 (18%)	..
2	105 (13%)	44 (17%)	..
Lymph node ratio*	0·00 (0·00–0·06)	0·00 (0·00–0·04)	0·91
Perineural invasion	68 (8%)	18 (7%)	0·60
Extramural venous invasion	141 (17%)	58 (23%)	0·065
Tumour morphology	..	..	0·0025
Adenocarcinoma	539 (66%)	170 (66%)	..
Medullary carcinoma	24 (3%)	22 (9%)	..
Mucinous adenocarcinoma	155 (19%)	33 (13%)	..
Poorly differentiated adenocarcinoma	80 (10%)	25 (10%)	..
Signet ring cell carcinoma	11 (1%)	4 (2%)	..
Undifferentiated carcinoma	4 (<1%)	2 (1%)	..
Microsatellite instability†	313/787 (40%)	107/251 (43%)	0·46
R1 resection‡	45 (6%)	9 (4%)	0·26

Data are median (IQR), n (%), or n/N (%). p values for lymph node yield and lymph node ratio were calculated with Kruskal-Wallis test; other p values calculate with Fisher's exact test. UICC=Union for International Cancer Control. *Number of lymph node metastases divided by number of lymph nodes detected in the specimen. †Data of five (2%) of 256 patients in the complete mesocolic excision group and 26 (3%) of 813 in the control group were unavailable for microsatellite instability. ‡Macroradical resection, but ≤1 mm from tumour tissue to resection margin (lateral resection margin at tumour site).

Table 2: **Tumour characteristics of the full dataset (patients undergoing resection from 2008 to 2013)**

Outcomes

The primary outcome was the absolute difference in the cumulative incidence of recurrence 5·2 years after surgery. Secondary outcomes were absolute risk difference in 5-year overall survival, 30-day and 90-day mortality, and 60-day postoperative major complications (defined as a Clavien–Dindo score ≥3b[20]).

Statistical analysis

Continuous data are presented as median and IQRs, and categorical data as frequencies and proportions. We used

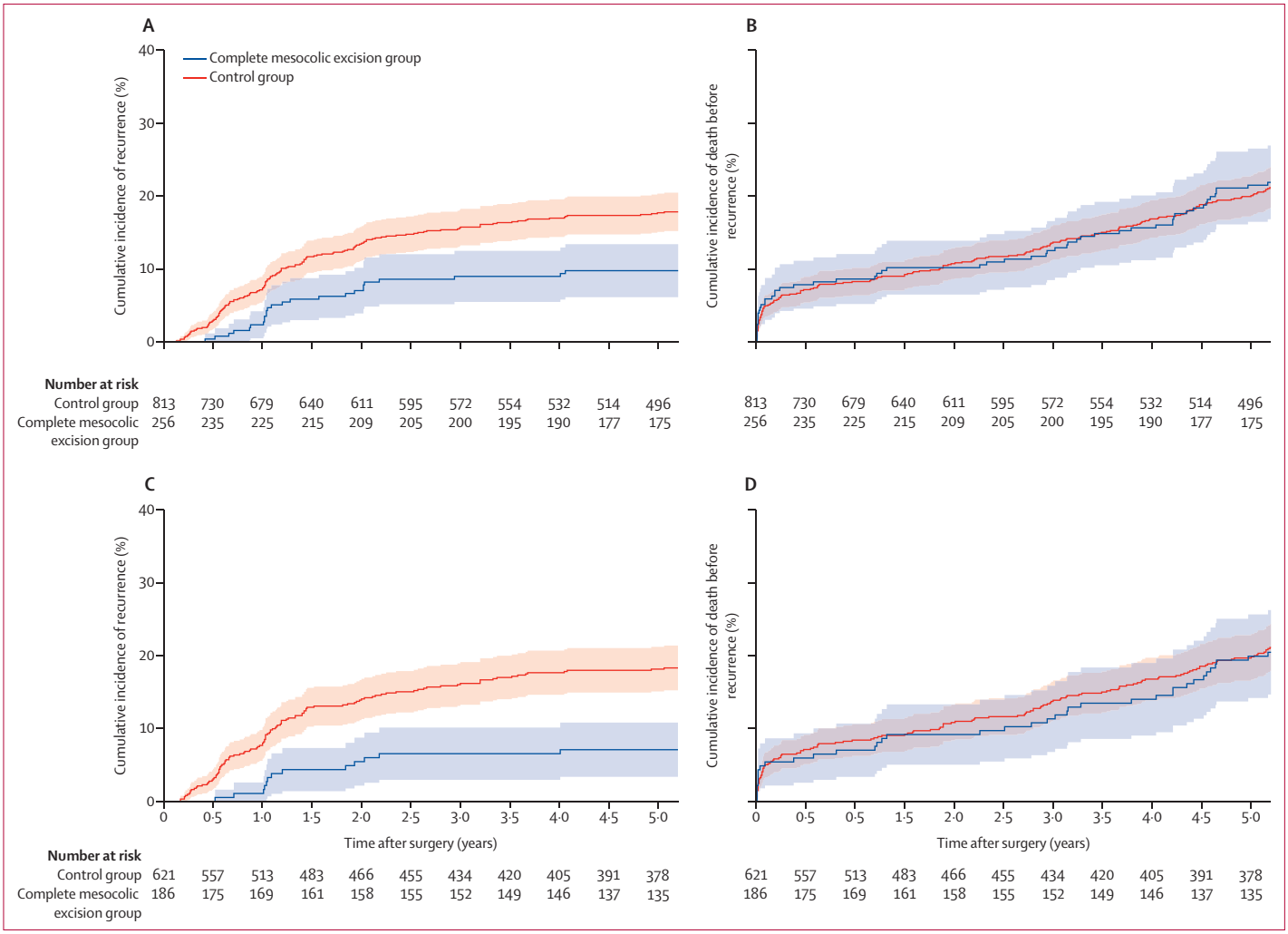

Figure 2: **5·2-year cumulative incidences of recurrence and death for patients with UICC stages I–III colon cancer**
Shaded areas are 95% CIs. (A) Cumulative incidence of recurrence in patients undergoing resection between June 1, 2008, and Dec 31, 2013. (B) Cumulative incidence of death before recurrence in patients undergoing resection between June 1, 2008, and Dec 31, 2013. (C) Cumulative incidence of recurrence in patients undergoing resection between 2010 and 2013. (D) Cumulative incidence of death before recurrence in patients undergoing resection between 2010 and 2013. UICC=Union for International Cancer Control.

the Kruskal-Wallis test and Fisher's exact test as appropriate. We did the analyses using the intention-to-treat principle.

We considered death as a competing risk to recurrence; and time-to-event analyses were done as competing risk analyses, obtaining the cumulative incidences for recurrence after 5·2 years. Cumulative incidence curves and survival curves are presented using unadjusted data.

Unbiased estimation of marginal or population-averaged treatment effects in observational and non-randomised studies can be obtained through different propensity score methods.[21] Inverse Probability of Treatment Weighting (IPTW) uses the propensity score to weight each patient's data based on the inverse probability of receiving the treatment that the patients actually received.[22] IPTW gives unbiased estimates of average treatment effects in time-to-event analyses if no differences in observed baseline covariates exist between the treatment groups.[21,23] To account for baseline difference between patients in the two groups, we used the ipw R package to calculate stabilised weights truncated at the 0·99 interval.[24] The following baseline covariates were selected a priori based on clinical relevance: age, sex, American Society of Anesthesiologists score, neoadjuvant chemotherapy, tumour location, tumour morphology, perineural invasion, extramural venous invasion, tumour stage, and serosal invasion. We assessed all covariates used and the UICC stage, two-way interactions, and squared terms of continuous covariates for balance using absolute mean differences between the complete mesocolic excision group and the control group after IPTW using the cobalt R package.[23] Absolute mean differences in mean (using standardised mean difference) and proportions (using raw mean difference) less than 0·1 and variance ratios between

0·5 and 2 were accepted.[22] Graphical inspection of the distribution of covariates was done. We also did cumulative incidence analyses after IPTW using the riskRegression R package[25] to estimate any potential absolute risk reduction of complete mesocolic excision on recurrence after 5·2 years and 5-year mortality. We analysed the binary outcomes using an IPTW logistic regression, and we used a robust sandwich estimator to ensure correct variance estimation.[23]

To eliminate any bias from a potential learning phase related to implementation of laparoscopic resections in both groups and to implementing complete mesocolic excision in Hillerød, we decided to do post-hoc analyses of the cumulative incidence of recurrence and overall survival for the subpopulation undergoing surgery during 2010–13.

The assumption of proportional hazards for the Cox regression models was met and tested using cumulative residuals. We used all available data and did all the analyses using R (version 3.6.0). This study is registered with ClinicalTrials.gov, number NCT03754075.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, and writing of the report, or the decision to submit for publication. 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

1069 eligible patients (813 in the control group and 256 in the complete mesocolic excision group) underwent curative-intent elective surgery for right-sided colon cancer (UICC stages I–III) during the study period (figure 1). Baseline characteristics and the tumour characteristics of the complete mesocolic excision and control groups of the full dataset (2008–13) are presented in tables 1 and 2, and for the 2010–13 dataset in the appendix (pp 1, 2). The mean time to last follow-up examination was 3·80 years (95% CI 3·56–4·04) in the CME group compared with 2·91 (2·76–3·05; p<0·0001) in the control group. None of the patients were lost to follow-up regarding survival or recurrence status, and consequently no patient was censored in the analyses. In the control group, 145 (18%) of 813 patients were diagnosed with a recurrence and 281 (35%) died during follow-up. In the complete mesocolic excision group, 25 (10%) of 256 patients were diagnosed with a recurrence and 75 (29%) died during follow-up. Histological confirmation of a recurrence was done in 96 (66%) of 145 patients with a recurrence in the control group and 14 (56%) of 25 in the complete mesocolic excision group (p=0·64).

The appendix (pp 3–10) shows the absolute mean differences of the baseline covariates, used for the propensity score, before and after IPTW for the full dataset (2008–13) and the 2010–13 dataset, including stratification for each UICC stages I–III. None of the covariates, their two-way interactions, or squared terms of continuous covariates had absolute means or variance ratios above the predefined thresholds after IPTW for the full and the 2010–13 datasets (appendix pp 3–10 for absolute means; other data not shown). For the stratified datasets based on UICC stages, it was not possible to get all two-way interactions below the predefined thresholds after IPTW (data not shown). On graphical inspection, the distributions of covariates were practically identical (appendix pp 3–10).

	Control group	Complete mesocolic excision group	Absolute risk reduction of complete mesocolic excision group	p value
Cumulative incidences of recurrence without IPTW				
2008–13				
All stages	17·8% (15·2–20·5)	9·8% (6·1–13·4)	8·1% (3·6–12·6)	0·00042
UICC I	7·2% (2·4–12·0)	0	7·2% (2·4–12·0)	0·0033
UICC II	11·1% (8·1–14·1)	3·8% (0·5–7·0)	7·4% (3·0–11·8)	0·0010
UICC III	32·1% (26·7–37·6)	22·0% (13·5–30·5)	10·2% (0·0–20·3)	0·049
2010–13				
All stages	18·4% (15·0–21·1)	7·0% (3·3–10·7)	11·0% (6·3–15·8)	<0·0001
UICC I	7·6% (2·2–13·0)	0	7·6% (2·2–13·0)	0·0060
UICC II	10·8% (7·4–14·1)	2·0% (1·4–4·8)	8·7% (4·4–13·1)	<0·0001
UICC III	34·3% (27·8–40·8)	17·5% (8·1–26·8)	16·9% (5·4–28·3)	0·0038
Cumulative incidences of recurrence with IPTW				
2008–13				
All stages	17·9% (15·3–20·5)	9·7% (6·3–13·1)	8·2% (4·0–12·4)	0·00015
UICC I	7·4% (2·4–12·4)	0	7·4% (2·4–12·4)	0·0035
UICC II	11·1% (8·2–14·1)	3·5% (0·6–6·5)	7·6% (3·4–11·8)	0·00034
UICC III	32·5% (26·9–38·0)	20·5% (12·7–28·3)	11·9% (2·5–21·4)	0·013
2010–13				
All stages	18·0% (14·9–20·9)	7·5% (3·8–11·2)	10·4% (5·8–15·1)	<0·0001
UICC I	7·9% (2·3–13·6)	0	7·9% (2·3–13·6)	0·0060
UICC II	10·6% (7·3–13·9)	1·5% (0·0–3·5)	9·1% (5·3–12·8)	<0·0001
UICC III	34·8% (27·0–42·8)	17·3% (8·3–26·3)	17·5% (5·8–29·2)	0·0035

Data are % (95% CI), unless otherwise specified. IPTW=inverse probability of treatment weighting. UICC=Union for International Cancer Control.

Table 3: **5·2-year cumulative incidences of recurrence without and with IPTW**

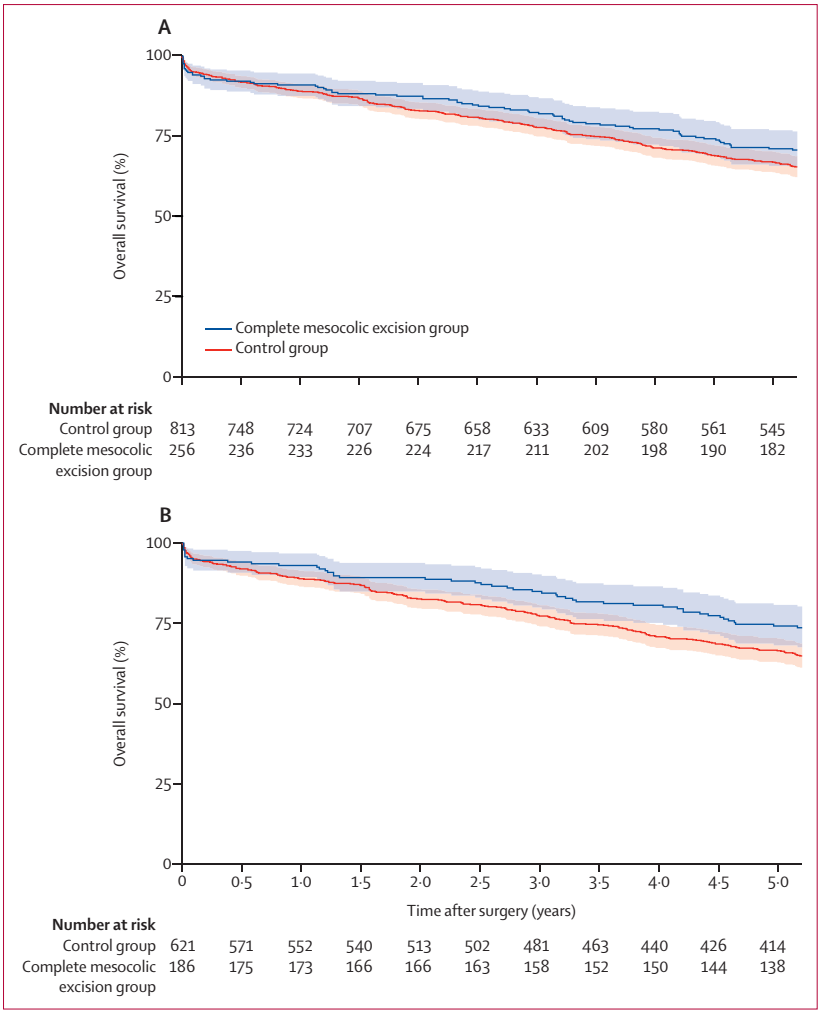

Figure 3: **Overall survival of patients with UICC stages I–III colon cancer undergoing elective surgery**
Shaded areas are 95% CIs. (A) Overall survival of patients undergoing resection between June 1, 2008, and Dec 31, 2013. (B) Overall survival of patients undergoing resection between 2010 and 2013. UICC=Union for International Cancer Control.

The cumulative incidence curves of recurrence and of death before recurrence are shown in figure 2 and the appendix (pp 11–16). The 5·2-year cumulative incidence of recurrence after IPTW was 9·7% (95% CI 6·3–13·1) in the complete mesocolic excision group compared with 17·9% (15·3–20·5) in the control group (table 3). The absolute risk reduction of complete mesocolic excision on the 5·2-year cumulative incidence of recurrence was 8·2% (95% CI 4·0–12·4; p=0·00015) for patients undergoing resection during the complete study period from June 1, 2008, to Dec 31, 2013, and 10·4% (5·8–15·1; p<0·0001) for those having surgery between 2010 and 2013 inclusive. The number needed to treat was 13 (95% CI 9–25) for those who had complete mesocolic excision from June 1, 2008, to Dec 31, 2013, and 10 (7–18) for those who had complete mesocolic excision between 2010 and 2013. Table 3 shows the effect of complete mesocolic excision compared with non-complete mesocolic excision on preventing recurrence was significant for all UICC stages when data were stratified. The absolute effect increased with increasing UICC stage (table 3). No recurrences were observed in the complete mesocolic excision group in patients with UICC stage I tumours. Adjusting for adjuvant chemotherapy did not change the outcome (data not shown).

Figure 3 shows the overall survival curves of the full dataset (2008–13) and the 2010–13 dataset. After IPTW, the absolute difference in the 5-year mortality in the full dataset (June 1, 2008, to Dec 31, 2013) was 4·7% (95% CI –1·4 to 10·8; p=0·13). Table 4 summarises the 5-year mortalities stratified by UICC stage and for the 2010–13 datasets. The short-term outcomes did not differ between the control and complete mesocolic excision groups during the entire study period, with odds ratios (ORs) calculated after IPTW of 0·94 (95% CI 0·48–1·83; p=0·85) for 30-day mortality after complete mesocolic excision, 1·18 (0·67–2·09; p=0·57) for 90-day mortality, and 0·94 (0·64–1·38; p=0·75) for the risk of major postoperative complications within 60 days of complete mesocolic excision. These results are in accordance with the findings shown in table 1. The same was true for the 2010–13 period regarding 30-day mortality after complete mesocolic excision (OR 0·83, 95% CI 0·38–1·82; p=0·64), 90-day mortality (0·74, 0·35–1·56; p=0·43), and the risk of postoperative major complications within 60 days of complete mesocolic excision (0·86, 0·54–1·35; p=0·50).

Discussion

The findings of this study suggest a causal treatment effect of complete mesocolic excision can reduce the risk of recurrence after resection for right-sided UICC stages I–III colon adenocarcinoma. The effect on risk of recurrence is supported by our findings for each stage, and the absolute effect increases with increasing UICC stage.

The surgical procedure in the complete mesocolic excision group was standardised, whereas the non-complete mesocolic excision procedures were considered as the conventional cancer surgery done in Denmark. During the study period, there was no recommended level of mesocolic vascular division based on anatomical structures. By recommending both early and central vessel ligation and with the lateral to medial approach used, the Danish guidelines were ambiguous regarding the level of vascular division. The extent of the bowel resection recommended was based on a figure showing bowel resections and vascular ligation similar to complete mesocolic excision,[17] but this was not the case.[15] The proportion of extended right hemicolectomies in the control group was 7%. Because 27% of tumours were located in the hepatic flexure or transverse colon, the validation of specimens suggests that the Danish guidelines were not used in daily practice.[15] The procedures done in the control group were probably

similar to those done in most European and North American hospitals.

Only lymph nodes draining the tumour were included in the lymph node yields. However, even with the risk of bias from a potentially more meticulous pathological assessment of the complete mesocolic excision specimen, including the use of ex-vivo methylene blue arterial injections, the difference in lymph node yield between the two groups (38 in the complete mesocolic excision group *vs* 21 in the control group) supports the assumption of considerable differences in the extent of the central lymph node dissection.

The follow-up in the control group, with shorter duration and use of chest radiograph and contrast-enhanced liver ultrasonography in some patients, is a limitation; however, this limitation only has a risk of underestimating the recurrence risk in the control group. Similarly, the higher proportion of no histological confirmation of recurrences after complete mesocolic excision than after non-complete meoscolic excision is in favour of the control group.

All known confounders present at the time of intervention were included in the IPTW. The two groups were well balanced in terms of baseline characteristics even before the IPTW. The cumulative incidence of recurrence did not differ substantially between the unbalanced and balanced datasets, suggesting that the risk of selection bias is negligible and cannot account for the large differences in outcome between the groups.

The differences in classification of medullary and mucinous carcinomas might be caused by interobserver differences between the pathological departments. With the intention-to-treat design, the differences seem negligible and preoperative treatment decisions were not based on morphology. The fact that 4% of the resections in the control group were done by non-specialists (ie, final-year senior residents) might bias the differences in risk of recurrence, but all centres are university clinics with the senior residents affiliated to the colorectal teams.

The study was well powered in terms of the size of the population for the primary outcome, whereas the post-hoc stratified analyses of overall survival seem under-powered to be able to show any significant difference for stage I to III tumours in the full dataset and stage I and III in the 2010–13 dataset. In the overall patient population, the absolute reduction of 8·2% in the cumulative incidence of recurrence after 5·2 years from complete mesocolic excision from June 1, 2008, to Dec 31, 2013, and the reduction of 10·4% in 2010–13, show that standardised colon resection with central mesocolic lymph node dissection as described by Hohenberger and colleagues[2] does seem to be more efficacious than the conventional colon cancer surgery.

As expected, the lymph node yield and number of lymph node metastases were higher after complete mesocolic excision. This finding could potentially have upstaged some patients undergoing this type of surgery, but there were no differences in the proportions of patiens with stage III tumours between the groups. Adjusting for adjuvant chemotherapy did not change the outcome, and if some patients in the complete mesocolic excision group received adjuvant chemotherapy because of upstaging, it did not seem to bias the results.

The finding of a treatment effect of complete mesocolic excision on UICC stages I–II suggests that patients in both groups might have been understaged by the pathologist. An important fact to remember is that the histopathological examination is a sample based on the

	Control group	Complete mesocolic excision group	Absolute risk reduction of complete mesocolic excision group	p value
5-year mortality without IPTW				
2008–13				
All stages	33·1% (29·9–36·3)	28·9% (23·4–34·5)	4·2% (–2·2 to 10·6)	0·20
UICC I	26·1% (18·0–34·3)	21·9% (7·6–36·2)	4·3% (–12·2 to 20·7)	0·61
UICC II	32·2% (27·8–36·7)	25·6% (18·2–33·0)	6·7% (–2·0 to 15·3)	0·13
UICC III	37·1% (31·5–42·8)	36·3% (26·4–46·1)	0·9% (–10·5 to 12·3)	0·88
2010–13				
All stages	33·5% (29·8–37·2)	25·8% (19·5–32·1)	7·7% (0·4 to 15·0)	0·039
UICC I	25·0% (16·6–34·0)	25·0% (7·7–42·3)	0 (–19·5 to 19·5)	1·00
UICC II	31·1% (26·0–36·1)	22·2% (14·0–30·4)	8·9% (–0·8 to 18·5)	0·071
UICC III	41·2% (34·4–47·9)	31·7% (20·3–43·2)	9·4% (–3·9 to 22·8)	0·17
5-year mortality with IPTW				
2008–13				
All stages	33·1% (29·9–36·3)	28·4% (23·0–33·8)	4·7% (–1·4 to 10·8)	0·13
UICC I	28·2% (19·8–36·5)	21·7% (7·9–35·5)	6·4% (–9·6 to 22·5)	0·43
UICC II	32·0% (27·7–36·4)	24·4% (17·7–31·1)	7·7% (–0·2 to 15·5)	0·056
UICC III	37·3% (31·6–43·0)	34·0% (25·1–43·0)	3·3% (–7·2 to 13·7)	0·54
2010–13				
All stages	33·7% (30·0–37·3)	25·5% (19·4–31·5)	8·0% (1·1 to 14·9)	0·024
UICC I	27·5% (18·2–36·7)	21·1% (7·1–35·0)	6·4% (–10·1 to 22·9)	0·45
UICC II	30·9% (26·0–35·8)	20·9% (13·7–28·0)	10·0% (1·6 to 18·4)	0·020
UICC III	41·1% (32·9–49·4)	29·0% (18·8–39·3)	12·1% (–0·6 to 24·8)	0·061

Data are % (95% CI), unless otherwise specified. IPTW=inverse probability of treatment weighting. UICC=Union for International Cancer Control.

Table 4: **5-year mortality without and with IPTW**

macroscopic assessment by the pathologist and a few slices from each resected lymph node. In the complete mesocolic excision specimens, small tumour deposits in the mesocolon could have been left unnoticed and micrometastases in the resected lymph nodes not included in the slices examined.[26] Our findings could be explained by these limitations of the pathological assessments. Potential micrometastases and small tumour satellites left behind in the non-resected mesocolon in the control group could have caused the absolute differences in the risk of recurrences. There is no evidence supporting that the difference is attributable to better planes of surgery. West and colleagues[27] showed only an association between mesocolic plane or intramesocolic plane and 5-year overall survival after curative-intent resection for stage III colon cancer, when compared with muscularis propria plane. There was no difference between mesocolic plane and intramesocolic plane and for stages I–II tumours.[27] Recurrence was not an outcome and they did not include microradicality, which arguably is the most important risk factor for recurrence. Muscularis plane dissection is likely to be associated with an increased risk of R1 resection. A new grading system[28] based on photos of the specimens has been proposed in 2019, but has not yet been validated regarding long-term outcomes. However, retrospective grading according to this system was not possible because many specimens in the control group had been photographed.

We showed no differences in the 30-day and 90-day mortalities between the two groups, but the earlier reported decrease in 90-day mortality in Hillerød from 2008 to 2010 might be responsible for the smaller absolute difference in overall survival in the full dataset compared with the 2010–13 dataset. The short-term mortalities in the two groups are similar to the short-term mortality rates after elective colon resection in Denmark, which has been decreasing since 2013.[14] Since the proportions of conversion to open resection might be related to the implementation of laparoscopic resections in all four centres, we find these findings acceptable.

Some individuals[29] argue that a similar oncological outcome can be achieved without excision of the most central lymph nodes, but right-sided complete mesocolic excision does not seem to be associated with increased short-term mortality or morbidity.[2,9–11] The advantage of complete mesocolic excision is the surgical landmark of the superior mesenteric vein, which ensures complete and safe standardised mesocolic lymph node excision. In our opinion, complete mesocolic excision is easy to do in lean patients, and in patients who are obese we find it safer to expose the complex vascular anatomy before dividing these structures when covered in fatty tissue.

Similar to our post-hoc stratification by UICC stage, previous studies[2–5] investigating complete mesocolic excision included variables based on postoperative information in their outcome analyses. This method might predict the outcome based on the final pathology report, but does not guide the surgeon or patient to decide preoperatively the extent of the mesocolic resection. Preoperative CT scans can distinguish between pathological (p)T1–2 and pT3–4 category in the hands of experts, but neither CT nor other preoperative or intraoperative diagnostic methods can predict the pN category.[30] Although the risk reduction of recurrence is larger for UICC stage III tumours, the absolute risk reduction is also substantial for UICC stages I and II. This finding justifies our conclusion that complete mesocolic excision should be the standard approach regardless of any preoperative or intraoperative staging.

In the present study, all extended right hemicolectomies in Hillerød (the complete mesocolic excision group) were performed openly, making any comparison between open and laparoscopic complete mesocolic excision using the current dataset very sensitive to selection bias. Until 2015, we were not confident that laparoscopic extended right hemicolectomies were as oncologically safe as open resections. The published literature[31,32] indicates that even laparoscopic extended complete mesocolic excision hemicolectomies are at least as safe as the open procedures, with similar morbidity and oncological outcomes.

The higher absolute risk reductions of the cumulative incidence of recurrence in the 2010–13 dataset and our earlier report of a decreasing 90-day mortality[14] during the study period suggests that our learning curve for performing complete mesocolic excision was long-lasting. Complete mesocolic excision is more challenging and complex to perform than standard colon cancer surgery because of the central dissection around the superior mesenteric vein and the anatomical vascular variations. Although the arterial variations are few and rather simple to recognise, the venous variations are multiple and more complex, with venous drainage from the colon, small bowel, pancreas, and stomach. With national and international training programmes, including mentoring and proctoring by surgeons who are experienced in complete mesocolic excision and subspecialisation on a departmental level, the results we have obtained seem to be a feasible target for most colorectal centres.

We believe that this study has high external validity, since it is a population-based study without the restrictive inclusion criteria of randomised trials. Randomised, controlled trials with patient allocation at the surgeon level seem impossible to do with the risk that surgeons trained in complete mesocolic excision might unconsciously perform more extensive resections in the control group. The present study used a quasi-randomisation with patient allocation determined only according to the patient's home address, and with the use of IPTW analyses, our study design offers the most favourable method of investigating outcomes after complete mesocolic excision without either historical controls[2,3] or a retrospective case–control study design.[6]

On the basis of our findings, we advocate standardisation of surgery for right-sided colon cancer by performing complete mesocolic excision.

Contributors

CAB and JK were responsible for the study concept. All authors contributed to the study design. CAB, AUN, JEJ, JRT, MW, AK-K, ERI, BB, PI, LAR, LVJ, and PWB collected, audited, and assembled these data. CAB, BK, and JK analysed and interpreted the data. CAB wrote the initial draft. All the authors reviewed the manuscript and approved the final version.

Declaration of interests

CAB and AUN have been affiliated with Olympus Finland by performing live surgery at courses for educational purposes only. All other authors declare no competing interests.

Data sharing

After de-identification, individual participant data will be made available to investigators who provide a methodologically sound proposal for meta-analyses. Proposals should be directed to Claus A Bertelsen (cabertelsen@gmail.com).

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