




ORIGINAL ARTICLE

Plane of mesocolic dissection as predictor of recurrence after complete mesocolic excision for sigmoid colon cancer: A cohort study

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Abstract

Aim: To investigate whether intramesocolic plane dissection assessed on fresh specimens by the pathologist is a risk factor for recurrence after complete mesocolic excision for sigmoid cancer when compared with mesocolic plane dissection.

Method: Single-centre study based on prospectively registered data on patients undergoing resection for UICC stage I–III sigmoid colon adenocarcinoma during the period 2010–2017. The patients were stratified into either an intramesocolic plane group or a mesocolic plane group. Primary outcome was risk of recurrence after 4.2 years using inverse probability treatment weighting and competing risk analyses.

Results: Of a total of 332 patients, two were excluded as the specimen was assessed as muscularis propria plane, 237 (72%) specimens were deemed as mesocolic and 93 (28%) as intramesocolic. The 4.2-year cumulative incidence of recurrence after inverse probability treatment weighting was 14.9% (10.4–19.3) in the mesocolic group compared with 9.4% (3.7–15.0) in the intramesocolic group, thus the absolute risk difference between the mesocolic plane and intramesocolic plane was 5.5% (–12.5–1.6; $p = 0.13$) in favour of the intramesocolic group.

Conclusion: Intramesocolic plane dissection was not a risk factor for recurrence after complete mesocolic excision for sigmoid cancer when compared with mesocolic plane dissection. No difference in risk of local recurrence, death before recurrence, and in overall survival after 4.2 years was observed between the two groups. With less than 1% of the specimens deemed as muscularis propria plane dissection, the classification appears unusable for the risk prediction of sigmoid colon cancer.

KEYWORDS

colon cancer, mesocolic dissection plane, recurrence, sigmoid colon

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INTRODUCTION

Hohenberger et al. introduced complete mesocolic excision (CME) [1] as an application of total mesorectal resection. The concept of CME consists of three components: dissection in the mesocolic plane, central vascular ligation and adequate resection of bowel with a minimum of 10 cm proximally and distally from the cancer with the exception of a distal resection margin of 5 cm for sigmoid tumours close to the rectosigmoid junction [1]. Studies have shown an association between CME and better long-term outcomes [2-6], but it remains controversial whether all three principles are associated with the better outcomes.

West et al. [7] have proposed a grading system similar to the one used for rectal cancer, to assess colon specimens [8]. Based on photos of specimens from unstandardized resections, they classified the plane of dissection into three categories: mesocolic ("good" plane of surgery), intramesocolic ("moderate" plane of surgery) and muscularis propria ("poor" plane of surgery) [8]. They showed an association between mesocolic and intramesocolic plane when compared with muscularis propria plane and higher 5-year overall survival in curative resections for stage III cancer. The classification might be biased by the level of vascular division and was not validated as a predictor for recurrence. Siani et al. [9] have validated the mesocolic plane classification in a population undergoing CME for right-sided colon cancer and found a higher 5-year overall survival in stage II and stage IIIA/B after mesocolic plane of resection compared with nonmesocolic plane of resection but did not report the risk of recurrence as an outcome. In a Danish study [10] of oncological outcomes for transverse colon cancer, nonmesocolic surgical plane was a significant risk factor of recurrence.

In a later study [11], West et al. demonstrated significant variation in the assessment of colon cancer specimens and concluded that care should be taken when comparing different hospitals and suggested that this grading system might not be useable in clinical studies [11]. Despite this, it has been widely assumed that the integrity of the specimen (that is, if the plane of resection is rated as mesocolic or not) is associated with a better oncological outcome, even though the classification system has never been fully validated in the clinical context of CME, that is, division of the supplying arteries at their central origin and sufficient bowel resection margin.

As studies suggest that right-sided colon cancer differs from left-sided colon cancer in clinicopathological features and prognosis [12-14], it may be of importance to assess the risk of recurrence and validate the classification system separately for each side. There are obvious differences in the anatomy of the mesocolon related to both different segments and individual variations, and extrapolation of outcomes from different segments should be performed with care. The sigmoid mesocolon consist of a mobile and a fixed apposed part [15]. The former is located inside the peritoneal cavity, and any lateral adherence is not to be considered as mesocolic plane. The apposed part determines the extent of the dissection of the sigmoid

What does this paper add to the literature?

To our knowledge, this is the first study to examine the association between the risk of recurrence and the pathologist's assessment of the plane of surgery and to validate the classification system's relevance as a predictor of recurrence in patients undergoing complete mesocolic excision for sigmoid cancer.

mesocolon. To achieve the most homogenous population as possible, we decided to conduct this study solely on sigmoid cancers a priori [3,16]. We knew that the proportion of specimens assessed as muscularis propria plane in our cohort was very low, thus our data would not be able to estimate the outcome for these patients.

This study aimed to investigate whether intramesocolic plane dissection assessed by the pathologist was a risk factor for recurrence after CME for sigmoid cancer when compared with mesocolic plane dissection.

METHODS

Design

This study was conducted according to the predefined protocol and reported according to STROBE [17]. Patient data were extracted from the local database of prospectively registered data on colon cancer patients undergoing CME at Copenhagen University Hospital - Nordsjællands Hospital Hillerød (NOH). Previous publications have thoroughly described the data management and audit procedures [3,18]. The patients underwent elective curative intended CME for sigmoid adenocarcinoma at NOH during the period 2010-2017. The inclusion criteria were sigmoid cancer UICC stages I-III defined as primary adenocarcinomas located in the sigmoid colon assessed by the surgeon and more than 15 cm from the anal verge as measured preoperatively by rigid sigmoidoscopy. In the Danish guidelines the proximal limit is defined as the point where the direction of the colon changed from vertical to horizontal. This definition is limited by individual variations. The patients are included in the study based on the data reported by the surgeon with subsequent audit. Exclusion criteria were synchronous colorectal cancer, no residual tumour in the specimen after neoadjuvant chemotherapy, metachronous colorectal cancer or non-CME (ligation of the inferior mesenteric artery [IMA] after the branching of the left colic artery). All resections were assessed as macroradical intraoperatively.

The patients were stratified into a mesocolic group, intramesocolic group, and muscularis propria group with the expected few patients in the latter group being excluded.

Surgical intervention

Surgery was based on the principles of CME with the IMA divided at its origin from the aorta to perform central lymph node excision along the IMA between the aorta and the branching of the left colic artery. Sigmoid resection included the complete sigmoid colon, resection of the upper part of the rectum to ensure sufficient perfusion of the colorectal anastomosis and based on the current knowledge of the pattern of lymph node metastasizing [19] a minimum distal resection margin of 5 cm. To achieve sufficient distance at the proximal bowel resection margin and a tension free anastomosis, resections might include parts of the descending colon with left hemicolectomy being performed at the surgeon's discretion, and in some patients left hemicolectomy or total colectomy was indicated due to other pathology for example, large adenomas or severe diverticulosis. In most resections, the inferior mesenteric vein was divided at the inferior edge of the pancreas, despite this has no oncological impact.

Histopathological assessment

The assessment of the dissection plane according to West et al. [8] was performed prospectively on the fresh specimens by a group of pathologists specialized in colorectal pathology [9]. Only the mesocolic fascia of the apposed part of the mesocolon related to the tumour and supplying arteries was assessed. Based on the individual variation of vascular anatomy and the site of the sigmoid tumour, parts of the descending mesocolon and the mesorectum were included in the assessment (Figure 1). The pathologists had in 2008–2009 joined a regional training programme headed by Dr Nick West and Professor Philip Quirke [20]. Before 2013, the histopathological assessments were performed at NOH and afterwards at Copenhagen University Hospital – Herlev as the departments merged.

Measurements and follow-up

Resections were classified as left hemicolectomies only if the splenic flexure was included in the specimen and as laparoscopic only if not converted at any time. Both neoadjuvant and adjuvant chemotherapy were registered as dichotomized variables. Indication for chemotherapy was according to the Danish guidelines. Tumours were dichotomised as either classical adenocarcinoma or other subtypes of adenocarcinoma.

The follow-up was standardized with annual plasma carcinoembryonic antigen and contrast enhanced computerized tomography (CT) of thorax and abdomen for 5 years. If the local multidisciplinary team assessed radiology findings as a recurrence, histopathological verification was not needed. Local and distant recurrence was defined before data collection as described for the regional database [3,21,22]. Local recurrence was defined as metastases in (1) local mesocolic or infrarenal paraaortic lymph nodes; (2) metachronous colon tumours diagnosed in the anastomosis with the same

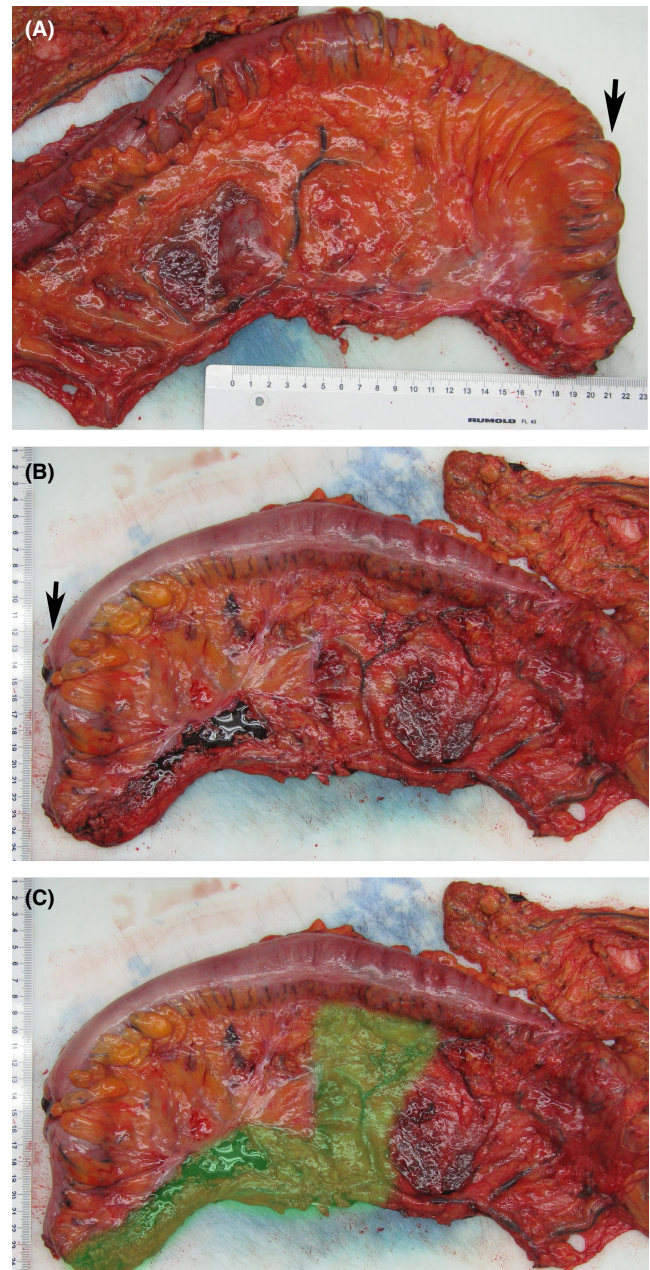


FIGURE 1 Photographs of specimen after left hemicolectomy for sigmoid cancer and adenoma in the proximal descending colon (not shown). (A) Anterior aspect of the mesocolon. The tumour in the distal part of the sigmoid colon is marked with an arrow. The vascular structures are shown, and the avascular window in the mesocolon cranial to the sigmoid vessels demarcates the area to be assessed. The inferior mesenteric artery (IMA) is marked with a white clip. (B) Posterior/medial aspect of the mesocolon. The tumour in the distal part of the sigmoid colon is marked with an arrow. The apposed mesocolon is shown. (C) Posterior/medial aspect of the mesocolon. The area to be assessed for mesocolic plane dissection assessment is marked with green, in this case assessed as mesocolic plane dissection

morphology as the primary tumour; (3) peritoneal carcinomatosis; (4) abdominal wall or cicatrix metastases; (5) recurrence in the retroperitoneum; (6) recurrence in the tumour bed or (7) pelvic bone

with relation to the resected colon segments. Distant recurrence was defined as all other recurrences diagnosed including the solid intraabdominal organs.

To include 4-year follow-up CT for all eligible patients, follow-up performed between 4 and 4.2 years after surgery is included. The last follow-up date was 7 May 2021.

Trial outcomes

The primary outcome was the absolute difference in cumulative incidence of recurrence after 4.2 years. Secondary outcomes were local recurrence, risk of death before recurrence and overall survival after 4.2 years.

Statistical analysis

Categorical variables are presented as numbers and proportions (%) and analysed by Fisher's exact test. Continuous values are expressed as median and interquartile range (IQR) and analysed by Kruskal-Wallis test. We considered death a competing risk to recurrence and the time-to-event analyses were done as competing risk analyses, obtaining the cumulative incidences for recurrence after 4.2 years. Cumulative incidence curves and survival curves are presented using unadjusted data.

By using inverse probability of treatment weighting (IPTW), we calculated unbiased estimates of marginal or population-averaged treatment effects. IPTW can be used in nonrandomized and observational studies to give unbiased estimates of average treatment effects in time-to-event analyses [23] and uses the propensity score to weight each patient's data based on the inverse probability of receiving the treatment that the patients actually received. IPTW can be used if there are no differences in the observed baseline covariates between the two groups [23,24], and to account for any differences in the patients' baseline data, we used the *ipw* R package to calculate stabilized weights. We chose these covariates based on clinical relevance: age, sex, BMI, American Society of Anaesthesiologists score, neoadjuvant chemotherapy, tumour morphology, extramural venous invasion, tumour stage, lymph node status and serosal invasion. By using the *cobalt* R package [24], we assessed the UICC stage, perineural invasion and all covariates, two-way interactions, and squared terms of continuous covariates for balance using absolute mean differences between the intramesocolic plane group and the control group after IPTW. Absolute mean differences in mean (using standardized mean difference) and proportions (using raw mean difference) below 0.1 and variance ratios between 0.5 and 2 [24] were accepted. The distribution of covariates was inspected graphically. Adjuvant chemotherapy was not included in the covariates to be balanced after IPTW because adjuvant chemotherapy could be a result of the plane of dissection. However, we performed a post-hoc analysis of covariate balance including adjuvant chemotherapy.

All available data was used. Primary and secondary outcomes are presented as absolute risk reductions. Model assumptions were checked. We considered a *p*-value below or equal to 0.05 significant. All analyses were performed using R statistical software, version 3.6.2 or later (R Foundation for Statistical Computing).

Ethical considerations

The database has been approved by the Danish Patient Safety Authority. Approval from the patients or the local ethics committee was not needed according to Danish legislation.

RESULTS

A total of 353 patients underwent complete mesocolic excision for UICC stages I–III sigmoid colon adenocarcinoma at NOH during the period 2010–2017. Twenty-three patients did not meet the inclusion criteria (Figure 2). The histopathological assessment deemed 237 (72%) of the specimens as mesocolic (control group) and 93 (28%) as intramesocolic (study group). The baseline characteristics and tumour characteristics of the two groups are shown in Tables 1 and 2.

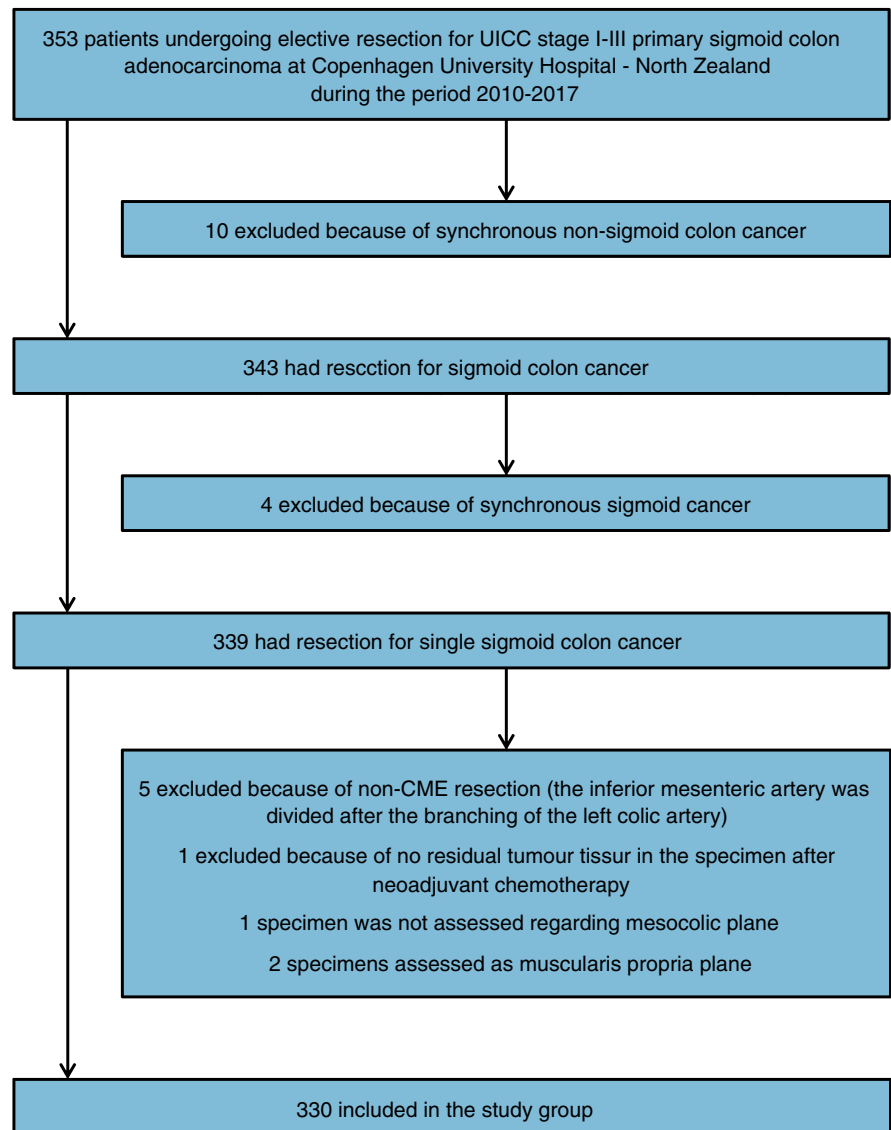
The absolute mean differences of the baseline covariates to be balanced are shown in Figure S1 before and after IPTW. All the covariates, their two-way interactions, and squared terms of continuous covariates had absolute means and variance ratios within the predefined thresholds after IPTW. The post hoc analysis showed that adjuvant chemotherapy was also well balanced within the predefined thresholds.

In the mesocolic plane group, 36 (15.4%) of 237 patients were diagnosed with a recurrence and 31 (13.2%) died during follow-up. In the intramesocolic plane group, nine (9.7%) of 93 patients were diagnosed with a recurrence and 15 (16.7%) died during the 4.2-year follow-up. Distribution of type and location of recurrences are shown in Table 3. After IPTW, the risk of recurrence in the mesocolic group was 14.9% (10.4–19.3) compared with 9.4% (3.7–15.0) in the intramesocolic group, thus the absolute risk difference between the mesocolic plane group and intramesocolic plane group on the 4.2-year cumulative incidence of recurrence was 5.5% (–12.5–1.6; *p* = 0.13) in favour of the intramesocolic group.

The risk of recurrence, local recurrence, death before recurrence and the overall mortality rates after 4.2 years with and without IPTW are shown in Table 4. The absolute risk difference between the mesocolic and intramesocolic groups regarding death before recurrence was 6.3% (–1.1–13.8; *p* = 0.10) before IPTW and 4.0% (–2.1–10.0; *p* = 0.20) after IPTW. Cumulative incidence and survival curves of the unadjusted data are presented in Figures 3 and 4. Post-hoc Cox regression showed an HR of recurrence in the intramesocolic group of 0.63 (95% CI: 0.30–1.31; *p* = 0.21 Wald test) and after an HR of 0.67 (0.32–1.40; *p* = 0.29).

None of the patients were lost to follow-up regarding survival or recurrence status, but 39 patients were awaiting 4 years follow-up.

FIGURE 2 Flowchart of patient selection. CME, complete mesocolic excision; UICC, Union for International Cancer Control



DISCUSSION AND CONCLUSIONS

In this study, we found no significant difference in cumulative incidence of recurrence 4.2 years after CME for stages I–III sigmoid colon cancer between mesocolic plane and intramesocolic plane assessed by the pathologist. As for the secondary outcomes, our study showed no difference in risk of local recurrence, no difference in risk of death before recurrence after 4.2 years, and no difference in overall survival after 4.2 years.

Clinical context

To our knowledge, this is the first study to investigate the association between the risk of recurrence of sigmoid colon cancer and the pathologist's assessment of the plane of surgery. Other studies [8,9] have found a higher 5-year overall survival after mesocolic plane of resection compared with nonmesocolic plane in either CME for

right-sided cancer only or retrospectively using photographs after unstandardised resections for both right and left-sided cancer. In our study, the grading was performed on fresh specimens with the purpose of reporting the plane of dissection in the pathology reports. All seven pathologists worked within the same department, which aimed to standardize the histopathological assessment and reporting. Furthermore, our primary outcome was recurrence, which in this oncological context is the most relevant outcome to investigate.

Primarily, West et al. described the intramesocolic plane specimen as “moderate bulk to mesocolon with irregularity but the incisions do not reach down to the muscularis propria” [8]. That definition was vague, and they later modified it to “defects in the mesocolic surface deeper than 5 mm, not reaching the muscularis propria” [11]. It is difficult to imagine that even minor lesions deeper than 5 mm in the mesocolon would have significant impact on the overall survival in a large population, but defects deemed as intramesocolic are often small. Thus an impact on the risk of recurrence seems small if the tumour deposits including lymph nodes

Characteristics	Mesocolic	Intramesocolic	p-value
Patients (n)	237	93	
Median age (IQR) – year	69.1 [61.1–75.1]	71.4 [67.2–75.5]	0.035 ^a
Male sex – no. (%)	128 (54.0)	63 (67.7)	0.026 ^b
Median BMI (IQR) – kg/m ²	25.0 [22.6–27.8]	26.3 [24.4–29.8]	0.001 ^a
ASA physical status (%)			0.12
I	85 (36)	23 (25)	
II	113 (48)	49 (53)	
III–IV	39 (16)	21 (23)	
Invasion	24 (10)	9 (10)	1.00 ^b
Neoadjuvant chemotherapy (%)	6 (3)	2 (2)	1.00 ^b
Procedure (%)			0.088 ^b
Sigmoid resection	216 (91)	88 (95)	
Left hemicolectomy	20 (8)	3 (3)	
Colectomy	1 (0)	2 (2)	
Laparoscopic resection (completed) (%)	205 (86)	73 (78)	0.092 ^b
Conversion to open resection (%)	24 (10)	15 (16)	0.13 ^b
Major complication	16 (7)	11 (12)	0.18 ^b
30-day mortality	3 (1)	2 (2)	0.62 ^b
90-day mortality	4 (2)	3 (3)	0.41 ^b
Adjuvant chemotherapy (%)	96 (41)	31 (33)	0.26 ^b

Note: Demographics based on plane of surgery. Major postoperative complications = Clavien-Dindo grade > 3a.

Abbreviations: ASA, American Society of Anaesthesiologists; CMA, complete mesocolic excision.

^aKruskal-Wallis test.

^bFisher's exact test.

in the mesocolon are not located exactly at the point of the mesocolic lesion and in the resection margin [25]. In that study, most cases with 1 mm or less from tumour tissue to resection margin (R1) were related to the mesocolic resection margin. Furthermore, if reporting overall survival as primary outcome, the competing causes of death would dilute the impact of the mesocolic plane of surgery.

In contrast to West et al. [8], we included only patients undergoing CME, often referred to as high tie of the inferior mesenteric artery. Our population was more homogeneous, and we eliminated the level of vascular division as a confounding factor. It enabled us to contradict the assumption that the treatment effect of CME on risk of recurrence after sigmoid cancer is associated to the mesocolic dissection plane assessed by the pathologist.

Since the surgeon will always seek to dissect in the anatomical/mesocolic plane to avoid unnecessary bleeding and make the best dissection/specimen possible, our findings are of little therapeutic consequence. Despite this, our findings emphasize the need for other standardized, validated and more objective methods to assess the quality of sigmoid cancer surgery. Benz et al. [26] proposed a new classification system for right-sided colon cancer that includes both an assessment of the preservation of the mesocolon and an assessment of the extent of mesocolic excision with focus on the level

of vascular division. That classification has not been validated, and they are yet to report on the prognostic oncological results. Similar classifications have to our knowledge so far not been proposed for sigmoid or left-sided colon cancers.

In our previous study [3], there was a low incidence of recurrence between 4 and 5 years of follow-up, thus we chose a follow-up time of 4.2 years and did not wait until complete 5-year follow-up. Post-hoc, we chose to pool classic adenocarcinomas against other subtypes of adenocarcinoma morphology, as the number of tumours with other morphologies was very small; thus, it did not seem plausible to distribute them in subtypes. Also, the classification of morphology is associated with a risk of misclassification in the less differentiated subtypes as many of these often have large mucinous components.

Limitations

While our study has many strengths, there is a potential risk of selection bias since it is observational and not randomized. The nonrandomized design increases the risk of confounding, although in this context it seems difficult to perform a randomized controlled trial study since the plane of surgery the surgeon dissects in cannot

TABLE 1 Baseline characteristics of 330 patients undergoing CME for sigmoid colon cancer from 2010 to 2017

TABLE 2 Baseline characteristics of 330 patients undergoing CME for sigmoid colon cancer from 2010 to 2017

Characteristics	Mesocolic	Intramesocolic	p-value
Patients (n)	237	93	
Postoperative UICC stage (%)			0.65 ^a
I	70 (29.5)	32 (34)	
II	84 (35)	29 (31)	
III	83 (35)	32 (34)	
pT-category (%)			0.28 ^a
1	37 (15)	23 (25)	
2	48 (20)	18 (19)	
3	115 (49)	41 (44)	
4	37 (16)	11 (12)	
Serosal invasion (%)	36 (15)	10 (11)	0.38 ^a
Median lymph node yield (IQR)	36 [27–45]	34 [24–45]	0.22 ^b
pN-category (%)			0.97 ^a
0	153 (65)	61 (66)	
1	57 (24)	21 (23)	
2	27 (11)	11 (12)	
Median lymph node ratio (IQR)	0.00 [0.00–0.04]	0.00 [0.00–0.04]	0.97 ^b
Perineural invasion (%) ^c	23 (10)	8 (9)	0.84 ^a
Extramural venous invasion (%)	76 (32)	24 (26)	0.29 ^a
Nonclassical adenocarcinoma (%)	27 (11)	11 (12)	1.00 ^a
Microsatellite instability (%)	8 (3)	3 (3)	1.00 ^a
R1 resection (%)	9 (4)	4 (4)	0.76 ^a
R1 resection at tumour site (%)	4 (2)	1 (1)	1.00

Note: Tumour characteristics based on plane of surgery. Lymph node ratio: number of lymph node metastases detected in the specimen: lymph nodes detected in the specimen. R1 resection: macroradical resection with 1 mm or less from tumour tissue to lateral resection margin at tumour site, at the mesocolic resection margin or at the central division of the IMA. R1 resection at tumour site: macroradical resection with 1 mm or less from tumour tissue to lateral resection margin at tumour site.

Abbreviations: CME, complete mesocolic excision.

^aFisher's exact test.

^bKruskal-Wallis test.

^cFour patients with missing values.

be randomized due to ethical considerations. Our patients were mostly well balanced in baseline characteristics, although there was a significant overrepresentation of patients with higher median age, a higher share of males and a higher BMI in the intramesocolic group. Also, the proportion of patients with ASA 1 was significantly higher in the mesocolic group. This may explain the insignificantly higher proportion of death before recurrence in the intramesocolic group, since this group generally may have been disadvantaged by the higher median age, higher BMI, lower ASA and being male with a potential higher degree of intra-abdominal fat. This association between more favourable characteristics and the mesocolic plane of surgery may be attributed to easier surgery and better access in leaner patients and generally better outcome for patients with better physical status. To account for the nonrandomized design, we used IPTW to reduce the potential confounding from any baseline

difference between the groups. After IPTW the baseline differences were no longer significant. Adjuvant chemotherapy was not a confounder of the primary outcome recurrence.

Another limitation is that this is a single-centre study with a relatively limited number of patients which may increase the risk of type II error. As mentioned, we only had a limited number of specimens assessed as muscularis propria plane of surgery and thus we cannot draw any conclusions about this group. Although, this may seem like a flaw, it can be argued that this plane of surgery is of less interest due to the generally small share of specimen graded as muscularis propria [3]. Presumably, most surgeons are now aware of the importance of radical excision around the tumour.

In conclusion, we found that intramesocolic plane dissection was not a risk factor for recurrence after complete mesocolic excision for sigmoid cancer when compared with the mesocolic plane dissection.

Types and sites of recurrence	Mesocolic plane	Intramesocolic	p-value ^a
Patients (n)	237	93	
No recurrence (%)	201 (84.8)	84 (90.3)	0.22
Local recurrence (%)	8 (3.4)	4 (4.3)	0.75
Distant recurrence (%)	31 (13.1)	8 (8.6)	0.34
Local recurrence			
Local lymph node draining resected tumour (%)	2 of 9 (22)	1 of 4 (25)	1.00
Recurrence at the anastomosis (%)	2 of 9 (22)	0	0.27
Peritoneal carcinomatosis (%)	5 of 9 (56)	2 of 4 (50)	1.00
Abdominal wall metastasis (%)	1 of 9 (23)	0	1.00
Recurrence in retroperitoneum including lymph nodes (%)	5 of 9 (56)	2 of 4 (50)	1.00
Distant recurrence			
Liver metastasis (%)	20 of 31 (65)	4 of 8 (50)	0.69
Lung metastasis (%)	13 of 31 (42)	6 of 8 (75)	0.13
Mediastinal lymph node metastasis (%)	1 of 31 (3)	0	1.00
Other extra-abdominal lymph node metastasis (%)	1 of 31 (3)	0	1.00
Nonpelvic bone metastasis (%)	1 of 31 (3)	0	1.00
Adrenal gland metastasis (%)	1 of 31 (3)	0	1.00

Note: Both local and distant recurrence were diagnosed in two patients in the mesocolic plane group and three in the intramesocolic plane group.

^aFisher's exact test.

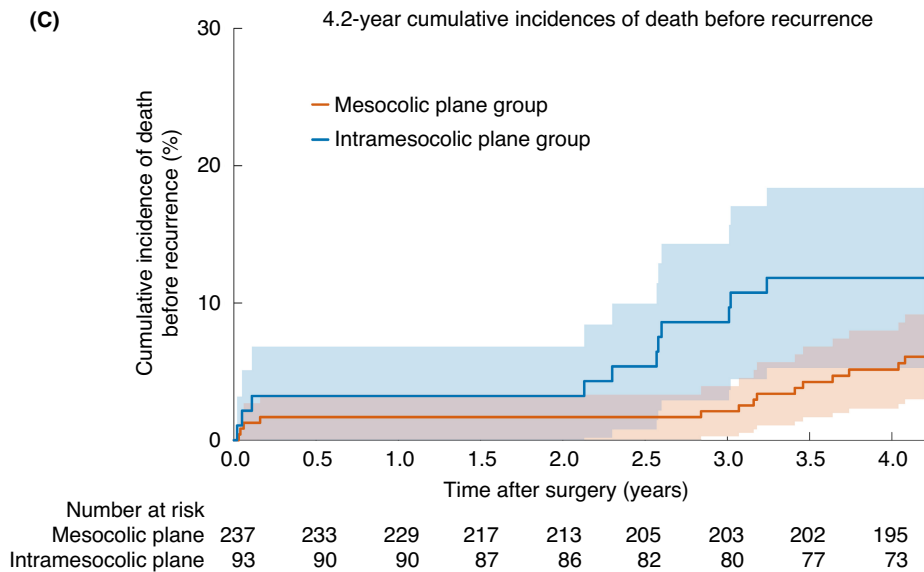
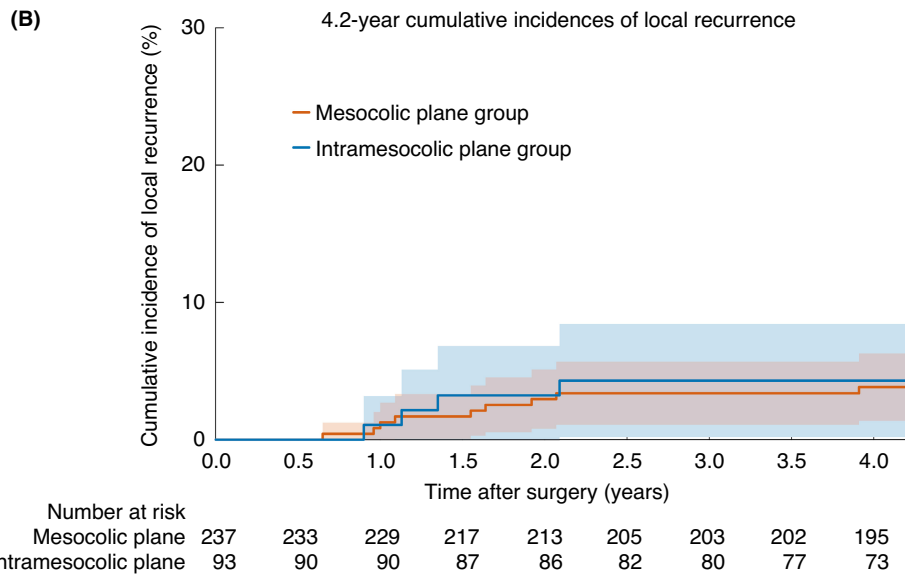
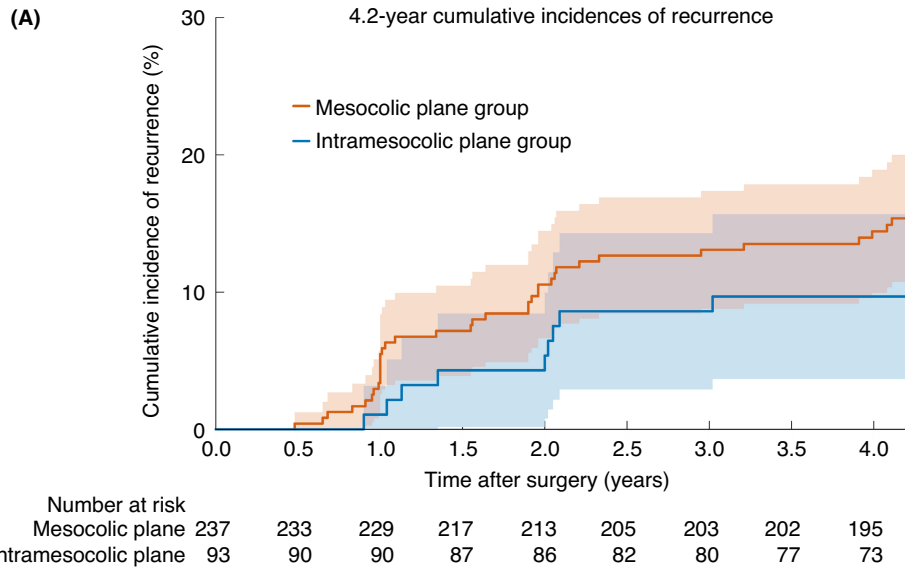
TABLE 3 Pattern of recurrence diagnosed within 4.2 years after surgery

TABLE 4 Cumulative incidences of recurrence, death before recurrence and overall mortality with and without IPTW at 4.2 years after curative intended surgery for UICC stages I–III

Variables	Mesocolic plane	Intramesocolic plane	Absolute risk difference in favour of mesocolic plane	p-value
Cumulative incidences – without inverse probability of treatment weighting				
Recurrence	15.4 (10.8–20.0)	9.7 (3.7–15.7)	-5.7 (-13.2–1.9)	0.14
Local recurrence	3.8 (1.4–6.3)	4.3 (0.2–8.4)	0.5 (-4.3–5.3)	0.85
Death before recurrence	6.0 (2.9–9.0)	12.3 (5.5–19.1)	6.3 (-1.1–13.8)	0.10
Death	13.2 (8.9–17.6)	16.7 (8.9–24.4)	3.5 (-5.4–12.3)	0.44
Cumulative incidences – with inverse probability of treatment weighting				
Recurrence	14.9 (10.4–19.3)	9.4 (3.7–15.0)	-5.5 (-12.5–1.6)	0.13
Local recurrence	3.8 (1.4–6.1)	5.0 (0.5–9.5)	1.2 (-3.7–6.2)	0.63
Death before recurrence	5.9 (2.9–8.9)	9.9 (4.5–15.2)	4.0 (-2.1–10.0)	0.20
Death	13.0 (8.8–17.2)	13.9 (7.5–20.3)	0.9 (-6.6–8.4)	0.82

Abbreviations: IPTW, inverse probability of treatment weighting.

FIGURE 3 4.2-year cumulative incidences of recurrence, local recurrence and death before recurrence in patients undergoing complete mesocolic excision for UICC stages I–III sigmoid colon cancer during 2010–17 using unadjusted data and stratified by dissection plane assessed by the pathologists. Shaded areas are 95% CIs. (A) Cumulative incidence of recurrence in patients undergoing resection between 2010 and 2017. (B) Cumulative incidence of local recurrence in patients undergoing resection between 2010 and 2017. (C) Cumulative incidence of death before recurrence in patients undergoing resection between 2010 and 2017



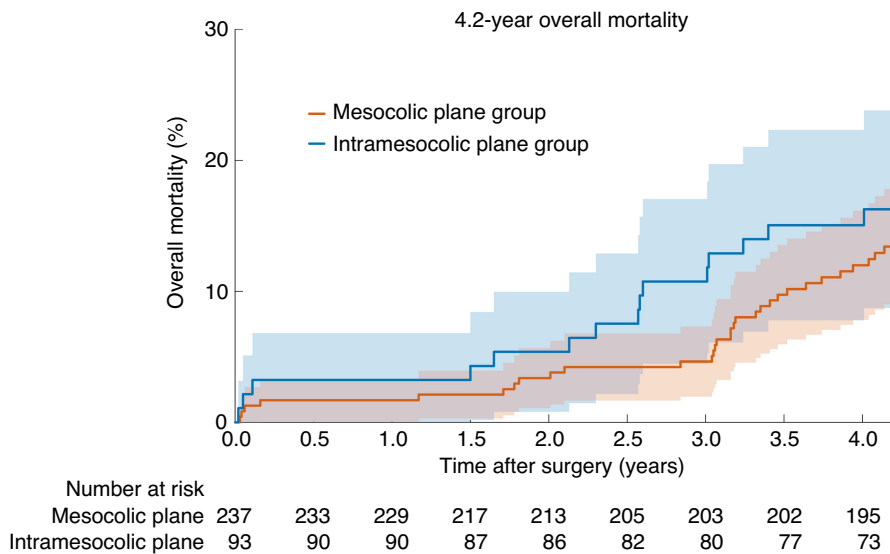


FIGURE 4 Overall mortality of patients with UICC stages I–III colon sigmoid cancer undergoing elective surgery between 2010 and 2017 stratified by dissection plane assessed by the pathologists. Shaded areas are 95% CIs

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CONFLICT OF INTEREST

No conflicts of interest.

AUTHOR CONTRIBUTIONS

SS: Study design, data interpretation, writing original draft, review and editing the drafts, approving the final draft. ASFO: Study design, data acquisition, quality control of data and algorithms, review and editing the draft, approving the final draft. AKG: Study design, data acquisition, quality control of data and algorithms, review and editing the draft, approving the final draft. PB: Data acquisition, quality control of data and algorithms, review and editing the draft, approving the final draft. BB: Study design, data acquisition, quality control of data and algorithms, review and editing the draft, approving the final draft. PI: Study design, data acquisition, quality control of data and algorithms, review and editing the draft, approving the final draft. JK: Study concepts, study design, data analysis and interpretation, statistical analysis, review and editing the draft, approving the final draft. CAB: Study concepts, study design, funding acquisition, data acquisition, quality control of data and algorithms, data analysis and interpretation, review and editing the drafts, approving the final draft.

ETHICAL APPROVAL

The database has been approved by the Danish Patient Safety Authority. Approval from the patients or the local ethics committee was not needed according to Danish legislation.

DATA AVAILABILITY STATEMENT

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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