Complete Mesocolic Excision

An Assessment of Feasibility and Outcome

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ARTICLES INCLUDED IN THE THESIS

1. Bertelsen CA, Kirkegaard-Klitbo A, Nielsen M, Leotta SMG, Daisuke F, Gögenur I. Pattern of colon cancer lymph node metastases in patients undergoing central mesocolic lymph node excision: a systematic review. Dis Colon Rectum 2016;59:1209-21.
2. Bertelsen CA, Bols B, Ingeholm P, Jansen JE, Neuenschwander AU, Vilandt J. Can the quality of colon surgery be improved by standardisation of surgical technique with complete mesocolic excision? Colorectal Dis 2011;13:1123-9.
3. Bertelsen CA, Bols B, Ingeholm P, Jansen JE, Jepsen LV, Kristensen B, Neuenschwander AU, Gögenur I. Lymph node metastases in the gastrocolic ligament in patients with colon cancer. Dis Colon Rectum 2014;57:839-45.
4. Bertelsen CA, Neuenschwander AU, Jansen JE, Kirkegaard-Klitbo A, Tenma, JR, Wilhelmsen M, Rasmussen LA, Jepsen LV, Kristensen B, Gögenur I. Short-term outcomes after complete meso-colic excision compared with ‘conventional’ colonic cancer surgery. Br J Surg 2016;103:581-9.
5. Bertelsen CA, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma, JR, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Iversen ER, Kristensen B, Gögenur I. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a population-based study. Lancet Oncol 2015;16:161-8.

INTRODUCTION

Colon cancer is the third most common cancer in Denmark with 2,926 new cases diagnosed a year in the period 2009-13 [6]. According to the annual report 2013 of the Danish Colorectal Cancer Group (DCCG) 2,728 (93.2%) of these were primary adenocarcinomas, of which 2,249 (82.4%) were reported to undergo either surgical or endoscopic resection [7]. Radical surgical resection remains the main pillar in the treatment of most colon cancers with, if indicated, adjuvant chemotherapy.

Because of the high incidence, treatment of colon cancer is a considerable cost to the Danish public health system. In addition to the costs of the primary treatment, recurrences after radical surgery are considerably expensive as the treatment options are chemotherapy or, in some cases, surgery for local recurrences or metastases in liver, lungs, and lymph nodes (LN). Beside the psychological distress, recurrences and their treatment present a substantial risk of mortality and morbidity, and these factors are just as important as the economic issue. The goal of the resection of colon cancer must be to achieve the best long-term outcome (overall and disease-free survival), at the lowest acceptable costs in terms of short-term and long-term morbidity.

The long-term outcome after surgery for rectum cancer has improved after implementation of total mesorectal excision (TME), which was described by Bill Heald more than 30 years ago [8]. TME is performed as standard today worldwide. Between 1994 and 2006, the cumulative three-year crude survival improved in Denmark from 62% to 77% [9], and the five-year overall survival from 50% to 63% [10]. Survival for colon cancer has improved in Denmark since 2000, but not to the same extent. The improvement seems to be associated more with adjuvant chemotherapy for stage III cancers, implementation of laparoscopic surgery, and sparing patients with short expected life-span from surgery, than from improvements related to the extent of the resection [11].

It has been proposed to apply the principles of TME to colon cancer surgery by meticulous dissection in the mesocolic plane combined with central ligation of the tumour-supplying arteries - the latter often referred to as central vessel ligation (CVL). Werner Hohenberger et al from Erlangen, Germany have defined this as complete mesocolic excision (CME) and shown a significantly better cancer-specific survival after implementation of CME when compared with a historical control group [12]. This finding has been supported by the finding of improved outcome for stage I-II colon cancers in a Norwegian study of 84 patients undergoing CME [13], and by Japanese data showing higher overall survival after D3 resection (CVL) for pT3 and pT4 colon tumours [14]. The evidence has not been sufficient for most colorectal surgeons to implement CME or similar principles as standard, and there is a need for larger studies of patients without distant metastases (stage I-III) and without the use of historical controls, to clarify the potential of CME to improve the outcome of colon cancer surgery.

ABBREVIATIONS

ASA score - physical status classification system score of American Society of Anesthesiologists
BMI - body-mass index (kg/m2)
CI - confidence interval
CME - complete mesocolic excision
CVL - central vessel ligation

DCCG - Danish Colorectal Cancer Group
ERAS - enhanced recovery after surgery
GCL - gastrocolic ligament
GCLN - gastrocolic ligament lymph nodes
HR - hazard ratio
ICA - ileocolic artery
ICV - ileocolic vein
IMA - inferior mesenteric artery
IMV - inferior mesenteric vein
JSCCR - Japanese Society for Cancer of the Colon and Rectum
LCA - left colic artery
LN(s) - lymph node(s).
Suffices to any abbreviation of lymph nodes: + for one or more metastases, - for none
MCA - middle colic artery
MCV - middle colic vein
OR - odds ratio
RCA - right colic artery
RCT - randomised controlled trial
SMA - superior mesenteric artery
SMV - superior mesenteric vein
TME - total mesorectal excision
TNM - Tumour Node Metastasis system
c-prefix refers to clinical stage, p-prefix to pathologic examination
UICC - Union for International Cancer Control

BACKGROUND

Results from Erlangen were not published until 2009 [12]. Bokey et al [15] had earlier reported improved overall and cancer-specific five year survivals for stage I-III colon cancer compared with patients undergoing resection before implementation of their CME-like technique. They used an almost similar approach to that used in Erlangen with dissection in the mesocolic plane and CVL. They did not report any short-term outcome measures. An Austrian study from 2000 [16] reported cancer-specific survival rates comparable with the rates reported from Erlangen, but they described their technique only as central LN excision without further details regarding anatomical landmarks. A US population study [17] from 2006 supported more extensive LN excision, as survival rates for all stage I-III colon cancers were higher when more than 15 LNs were examined. The evidence was based on the number of LNs examined without specifying the extent related to anatomical structures. Though it had been recommended in the US guidelines [18] since 2001, one might question if "standard of utilizing the base of the mesentery as an anatomic landmark" [17] and sufficient pathological assessment had been performed in all included patients, as the number of LNs examined was considerably lower than the number reported from Erlangen [12]. Central LN dissection has been performed in Japan for many years, but reports [19, 20] of long-term outcome were scattered and, as later studies showed, patients included in Asian studies of short-term outcomes seem not to be comparable with European and American patients, as BMIs were lower and the patients had less co-morbidity [21-23]. The studies of Hohenberger [12] and Bokey [15] used historical control groups, and the improved outcome after CME might have been biased by other factors e.g. implementation of adjuvant chemotherapy.

As the evidence supporting CME in 2008 was limited so was evidence of better outcome after either CVL or dissection in the mesocolic plane. Utilisation of the mesocolic plane was described more than 80 years ago [24], but the only study investigating the association between dissection plane and survival was published in 2008 by West et al [25]. They reported a significantly better overall survival of patients undergoing resection in Leeds, UK for stage III colon cancer if the specimens were assessed as "mesocolic resection plane" compared with "muscularis propria resection" plane. The assessment was performed from photographs by expert pathologists. CVL was not the standard procedure in Leeds during the study period.

The evidence supporting CVL as a part of the CME concept was based mainly on studies showing improved outcome related to the LN yield [17, 26]. These studies were performed without standardised or validated pathological examination.

Studies investigating the risk of central mesocolic LN metastases (LN+), which could support CVL were without a uniform definition of method, anatomy, or inclusion criteria of patients [27-31]. Toyota et al [27] reported in 1995 that gastroepiploic and infrapyloric LNs were potential sites of LN+. These LNs are usually considered as extra-mesocolic, and this finding had not been reported by others, nor had any systematic reviews or meta-analyses describing the pattern of mesocolic LN+ been published by June 2008.

When we decided to implement CME in Hillerød, the evidence was limited and mainly based on single-centre cohort studies with historical controls. As no uniform tool of validation of performing "CME" was, or has since been, established, we trusted systematic feed-back from the pathologists to evaluate if CME was feasible.

A study was conducted to evaluate the quality of colon cancer specimens from the departments in the Capital and the Zealand Regions. It showed that the quality of the specimens from Hillerød was comparable to specimens from Erlangen, and that this was not the case for the other three centres in the Capital Region [32]. As patients were referred to the four colorectal centres according to their postcode, this quasi-randomisation offered a way to compare short-term and long-term outcome measures after CME with conventional colon cancer resections without using a historical control group.

The very essence of improvement in surgery by extended resection is based on a thorough understanding of surgical anatomy and its variations. In order to understand the basic principles of CME surgery and to perform it, it is important to understand the embryological development of the gastrointestinal tract. In addition there is disagreement on anatomical definitions in anatomy books and articles, as there also are differences between the definitions of LN location and vessels in the Eastern and the Western literature.

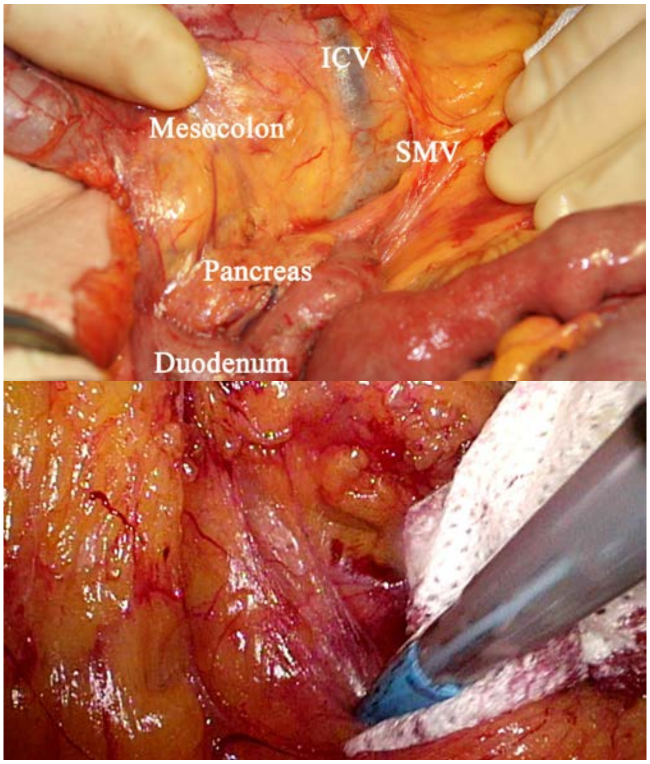
ANATOMY AND EMBRYOLOGY

Colon

The proximal limit of the colon is at the ileocaecal valve. In the Anglophone world and Scandinavia, the distal limit is defined as 15 cm from the anal verge measured by a rigid sigmoidoscope [33-36]. This is based on preoperative findings in order to be able to select patients for neoadjuvant therapy. Contrasting this clinical definition are the general anatomical (level of third sacral vertebra) [36, 37] and surgical (at the sacral promontory) [36] definitions. The anatomical or surgical distance from the anal verge to the sigmoid rectal junction is associated with the patient's height, and differences must be expected between European and Asian studies.

As opposed to the other segments where different definitions are used, the caecum is well defined as the part of the colon below the upper edge of the ileocaecal valve. In European and American literature the ICD10 classification [38] is used, whereas

Figure 1:



Dissection in mesocolic plane/Toldt's fascia. A: Open right hemicolectomy. The mesocolon with an intact mesocolic fascia mobilised from the retro-peritoneal fascia, the duodenum, and the pancreas. The hairy fibres of Toldt's fascia are seen between the mesocolon and the pancreatic head. The ileocolic vein (ICV) and the superior mesenteric vein (SMV) are visual-ised. B: Laparoscopic right hemicolectomy. The hairy fibres of Toldt's fascia are seen in the centre of the photography between the mesocolon (above) and the retroperitoneal fascia (below).

the Japanese classification [39], used in many Asian studies, does not consider the hepatic and splenic flexure as separate tumour sites.

Mesocolon

The gastrointestinal tract develops from parts of the endodermal yolk sac, which is covered by the splanchnic mesodermal layer. The foregut, midgut, and hindgut are initially connected to the posterior abdominal wall only by the dorsal mesentery. The splanchnic mesodermal layer, covering what later develops into the colon and mesocolon, becomes the mesocolic fascia. During the embryogenesis the midgut rotates around the axis of the superior mesenteric artery, and the ascending and descending colon adhere to the posterior abdominal wall. The layer of hairy fibres between the mesocolic fascia and the retroperitoneal interface is called Toldt's fascia [24]. The posterior leaves of the greater omentum, which develops from the dorsal mesentery of the stomach, fuse during the second and third trimesters with the mesentery of the transverse colon to form the transverse meso-colon [40].

Dissection within Toldt's fascia (Figure 1) has the advantage of less bleeding, which eases the procedure and also ensures visibility in laparoscopic surgery. Oncological relevance of the mesocolon has been shown by West et al [25] as the disease-free survival after colon cancer resections seems to be associated with the achieved dissection plane. They have classified the resection

Table 1:

Dissection plane	
Mesocolic	There should be an intact and smooth meso-colic surface with only minor irregularities. Any peritoneal or fascial defects must be no deeper than 5 mm. There should be smooth retroperitoneal and mesocolic resection margins on the cross-sectional slices
Intramesocolic	There may be moderate bulk to the mesoco-lon but significant irregularity of the perito-neal or fascial surface in at least one area that is deeper than 5 mm. The muscularis propria should not be visible. There may be moderate irregularity of the retroperitoneal and mesocolic resection margins on the cross-sectional slices
Muscularis propria	There may be little bulk to the mesocolon and there will be extensive defects that extend down to the muscularis propria. The retroperitoneal and mesocolic resection margins may be formed partially by the muscularis propria on the cross-sectional slices

Definition of mesocolic dissection plane based on assessment of the spec-imen by pathologist according to West et al [41].

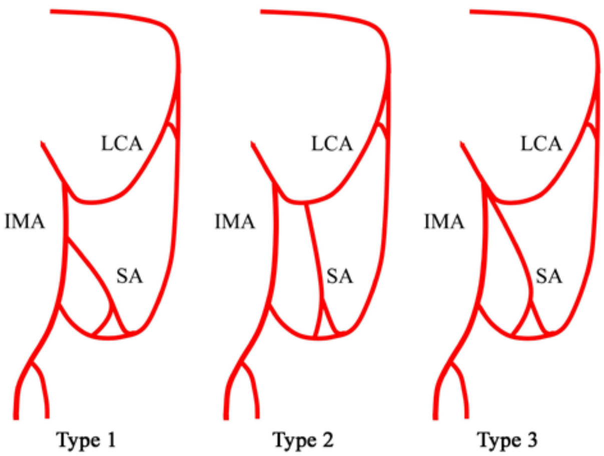
plane based on assessment of the specimen by a pathologist as shown in Table 1.

Arteries

The lymphatic drainage of the colon follows the arteries. Because the colon derives from the midgut and hindgut, its three main arteries are the ileocolic artery (ICA) and the middle colic artery (MCA), which both arises from the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA) from the aorta. The branches of these three main arteries create the marginal arcades which ultimately supply the colon.

The IMA supplies the colon from two-thirds of the way through the transverse colon to the mid rectum and it branches out of the aorta. The anatomy of the left sided colonic arteries is fairly simple, though variations occur (Figure 2). The left colic artery (LCA), which is absent in only 5% of individuals [42], sup-plies the splenic flexure and the descending colon and arises from the IMA as the first branch. The distance from the aorta to the root of the LCA is reported to be 25-40 mm in Caucasians [43, 44], with the mean distance (± SD) of 39 ± 11mm in Japanese [45] people, and with shorter distances reported in men with high BMI [42]. The IMA continues in the package of the sigmoid mesocolon with several sigmoid arteries branching out before becoming the superior rectal artery. The origin of the first sigmoid artery is variable, as it arises from the IMA as a separate artery (Type 1) in 41-58% of individuals, from the LCA (Type 2) in 27-45%, and at the angle between the LCA and IMA (Type 3) in 9-15% [31, 42, 45, 46]. The number of sigmoid arteries varies usually between one and five [31], with two (21-40%), three (32-50%), and four (7-25%) as the most common numbers [31, 46].

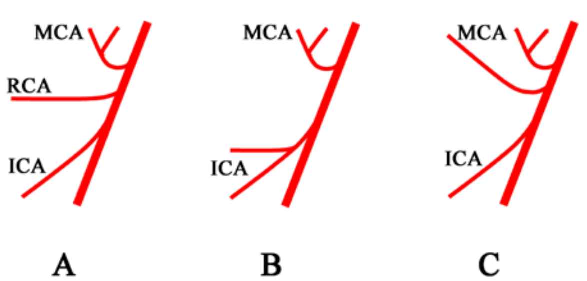
Figure 2:



Variations of the branching patterns of the left colic arterial supply after Yada et al [31] The first sigmoid artery arises from the inferior mesenteric artery (IMA) (Type 1), from the left colic artery (LCA) (Type 2), or from the angle between the LCA and IMA (Type 3).

The right side of the colon derives from the midgut and is supplied by the SMA. The ICA is consistent [31, 47-51], and supplies the caecum, ascending colon and, through anastomoses with the SMA, the terminal ileum (Figure 3). It can pass dorsally or ventrally to the superior mesenteric vein (SMV) (Table 2). There might be ethnic differences as passing ventrally seems more frequent in Asian studies [47, 48, 51, 52] compared to the Norwegian ones [50, 53-55].

Figure 3:



Some of the possible variations of arterial anatomy of the right and transverse colon. A: The ileocolic (ICA), the right colic (RCA) and the middle colic (MCA) arteries originating independently from the superior mesenteric artery (SMA). B: The RCA originating from the ICA and a common trunk of the MCA supply the hepatic flexure and the right two-thirds of the transverse colon. C: The two main branches of the MCA originating separately from the SMA, with the right branch of the MCA supply the distal part of the ascending colon and the hepatic flexure.

The anatomy of the MCA and the right colic artery (RCA) is not consistent. The MCA is almost consistent [49, 50, 56], and in general it crosses ventrally to the SMV [48, 54]. It has more than one separate branches arising directly from the SMA in 4-36% of cases [48-50, 56]. In a few cases a left branch might arise from the dorsal pancreatic artery (branch of the coeliac trunk) or the IMA [31, 49]. The RCA is not defined uniformly in the literature, which is emphasized by Park et al [57] who defined the RCA in three ways: as an artery originating independently from the SMA between the ICA and MCA; as either the right branch of the MCA, or a separate MCA branch arising from the SMA; or as a branch of the ICA. Others state that the RCA should be defined only as an artery supplying the middle part of the ascending colon, arising from the SMA, and running inferior to the avascular mesocolic window covering the duodenum [49]; that definition is used in Denmark by the DCCG [58]. Using the latter definition the RCA is present as a separate artery in only 11-13% of cases [49, 50, 56]. It is often impossible in the literature to distinguish between the different classifications used.

Table 2:

Study	Type	Country	Dorsally	Ventrally
Shatari [47]	Cadaver	Japan	18 (67%)	9 (33%)
Tajima [48]	Cadaver	Japan	88 (41%)	127 (59%)
Nesgaard [50]	Surgery	Norway	81 (58%)	58 (42%)
Lee [51]	Surgery	Korea	58 (50%)	58 (50%)
Hirai [52]	3D radiology	Japan	48 (48%)	52 (52%)
Ignjatovic [53]	Cadaver	Norway & Serbia	19 (63%)	11 (37%)
Spasojevic [54]	Cadaver	Norway, Serbia & Switzerland	19 (73%)	7 (27%)
Spasojevic [55]	3D radiology	Norway	38 (79%)	10 (21%)

Number of patients and frequencies of ileocolic artery passing dorsally and ventrally to the superior mesenteric vein reported in the literature.

Veins

The venous invasion of tumour cells is a potential route for metastasising. Venous invasion in the resection margin can be seen, but the association between the extended surgical resection related to the veins and oncological outcome remains unknown. The venous anatomy has some relevance to surgical strategy and in avoiding intraoperative bleeding.

The part of the colon deriving from the hindgut is drained by the inferior mesenteric vein (IMV), which usually terminates in the splenic vein, but variations occur as termination in the SMV or in the confluence of the SMV and the splenic vein has been observed [59, 60]. The mobilisation of the splenic flexure in the mesocolic plane in laparoscopic surgery is eased by incising the mesocolon between the IMV and the aorta [61]. Division of the IMV at the inferior edge of the pancreas is optional.

The venous draining of the midgut derived colon is more complex. The ileocolic vein (ICV) usually follows the artery and terminates in the SMV. The right colic and middle colic veins have more variations than the corresponding arteries, and the nomenclature is not uniform. The right branch of the middle colic is named by some the “right colic vein” or “the superior right colic vein”. The term “gastrocolic trunk of Henle“ is often mentioned in the literature as formed by the confluence of the right colic vein/superior right colic vein and the right gastroepiploic vein, and sometimes even the anterior pancreaticoduodenal vein (referred to as “pancreatic branch” by some) [51, 62-64] The SMV is the landmark in both open and laparoscopic CME surgery and, as it is exposed, the veins from the mesocolon terminating in the SMV can be divided centrally.

Lymph nodes

Lymph nodes with a potential risk of metastases can be divided into mesocolic and extramesocolic. The mesocolic LNs are contained within the mesocolic fascia and follow the supplying arteries [65]. They are divided into three groups as shown in Table 3, and the locations can be classified according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [39] (Figures 4 and 5). The number of mesocolic LNs found is dependent on the examiner, and may vary as many LNs, both in specimens with or without colon pathology, might be only a few mm in size [28, 66]. For example the median number of LNs in the D3 compartments for the right colon is reported to be 7-10 [54]. The mean number (± SD) of LNs in D3 around the IMA is reported to be 4.4 ± 3.2 [67].

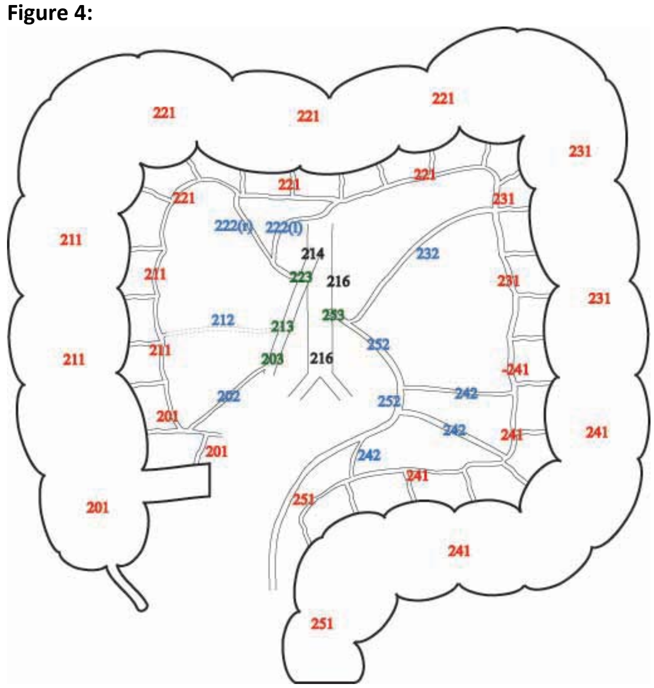
Lymphatic routes connecting the transverse colon and mesocolon to both the greater omentum and the pancreas have been identified [68]. This is the result of the embryonic fusion between these structures, and the infrapyloric and gastroepiploic LNs (gastrocolic ligament LN - GCLN) are potential locations for what usually is considered to be extramesocolic LN+. D4 LNs are extramesocolic and tumour tissue in these has been considered as distant metastases.

Table 3:

The extent of lymph node dissection (JSCCR - see Figure 4)	
D1	Complete dissection of epicolic lymph nodes attached to the colon and paracolic lymph nodes along the marginal artery in the relevant colon segments and no or incomplete dissection along the tumour-supplying arteries
D2	Complete dissection of D1 and intermediate lymph nodes along the tumour-supplying arteries (ileocolic, right colic, middle colic, left colic, sigmoid, or inferior mesenteric arteries from the origin of the last sigmoid artery to the origin of the left colic artery)
D3	Complete dissection of D1 to D2 and central lymph nodes, for left-sided tumours along the inferior mesenteric artery between the aorta and the left colic artery and for right-sided including midtransverse tumours, lymph nodes along the superior mesenteric vein and lateral to the superior mesenteric artery
D4	Complete D1 to D3 and along aorta and inferior vena cava or superior mesenteric artery/superior mesenteric vein central to the origin of the middle colic artery

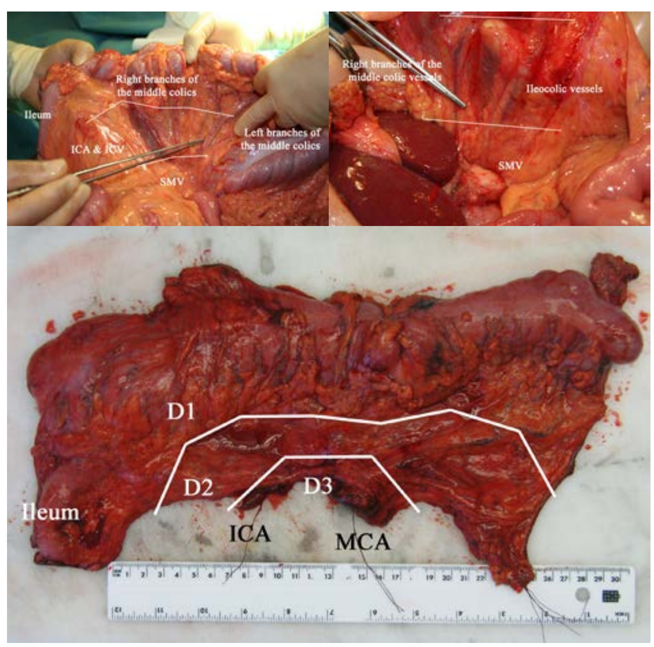
Definitions of mesocolic lymph node location related to extent of lymph node dissection. From Bertelsen et al [1] (Diseases of the Colon and Rectum. 2016;59:1209-21, Wolters Kluwer©. All Rights Reserved).

Figure 4:



Mesocolic lymph node stations according to the Japanese Society for Cancer of the Colon and Rectum. D1-D4 defined by colours: D1 = red, D2 = blue, D3 = green, and D4 = black. Right colic artery (dotted). From Bertelsen et al [1] (Diseases of the Colon and Rectum. 2016;59:1209-21, Wolters Kluwer©. All Rights Reserved).

Figure 5:



Intraoperative photographs of the mobilised right colon. Anterior view of the mesocolon (upper left) and posterior view of the mesocolon showing the D2 area between the lines and the D3 area between the line and the superior mesenteric vein’s (SMV) medial edge. Specimen from other patient (anterior view - extended right hemicolectomy). The ileocolic artery (ICA), the middle colic artery and the left gastroepiploic artery tie are marked with one, two and four sutures respectively.

Nerves
The SMA is surrounded by the superior mesenteric nerve plexus, which is a continuation of the coeliac nerve plexus and ganglions [69, 70]. Resection of these nerve plexuses in pancreatic surgery contains a potential risk of postoperative diarrhoea [71], but the knowledge of functional outcome after CME and colon surgery in general is limited. Other causes, such as bile acid diarrhoea after the ileal resection in right sided colon surgery, can also contribute to postoperative diarrhoea [72].

The IMA is surrounded by the inferior mesenteric nerve plexus which is divided when performing central ligation of the IMA. The plexus innervates the descending and sigmoid colon, and continues into the pelvis to innervate the rectum. It has been shown that these fibres connect to the autonomic pelvic plexus in some patients [70, 73]. During the D3 dissection at the root of the IMA and downwards to the pelvis, care must be taken to avoid injury to the nerve plexus surrounding the aorta and to the superior hypogastric nerve plexus [70].

Potential routes of metastasising
Tumour invasion of the serosa or other organs and LN+ are included in the UICC TNM classification. Other potential routes of metastasising are venous and perineural invasion, both of which are prognostic factors associated with early recurrence of colon cancer [74]. Little is known about the impact of CME on reducing the effects of these risk factors.

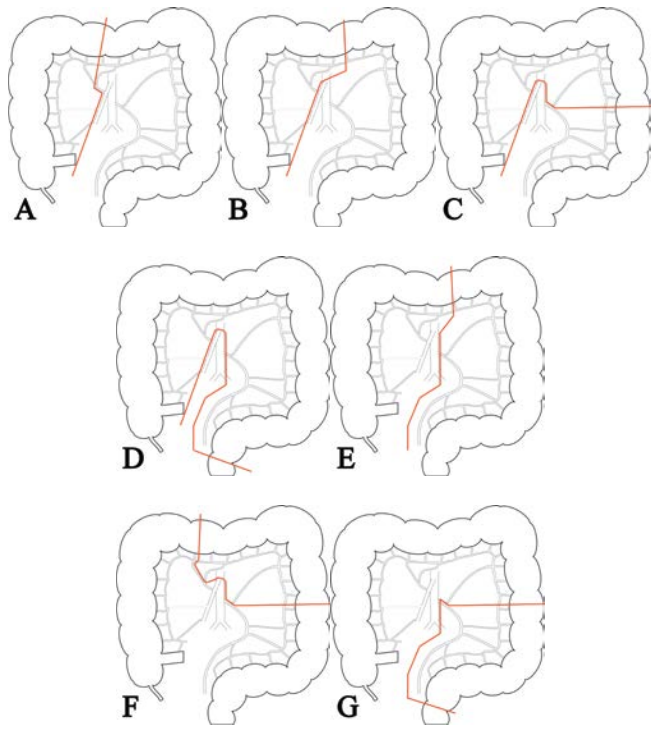
Complete mesocolic excision (CME)
CME was defined by Werner Hohenberger [12], even though the main principles of dissection in the mesocolic plane and CVL had been previously described [15]. D3 resections (CVL) have been recommended in cT3-4 tumours for decades according to the Japanese guidelines [75]. The Japanese D3 resection seems to be less longitudinally extensive but equivalent in terms of mesocolic plane dissection, LN yield and length of vascular high tie [76]. Some might consider the use of “complete” as a misnomer, because only the mesocolon related to the tumour site is excised, but terms like extended LN excision might also cover D4 and other extramesocolic LNs resections, or additional resection of colon segments and mesocolon not related to the tumour. In this thesis the definition of CME follows that of Hohenberger with bowel resections defined as in Figure 6.

Open CME surgery is usually performed with the lateral-to-medial approach [12], in contrast to the medial-to-lateral approach used in laparoscopic CME [77-79]. Dissection through Toldt’s fascia between the mesocolic fascia and the retroperitoneal is similar and usually performed by sharp dissection with e.g. electrosurgery. In open resections, complete mobilisation to the root of the mesocolon is performed before the supplying arteries are divided at their origin. This is in contrast to laparoscopic where the vessels are divided before the mesocolon is fully mobilised.

The SMV is the surgical landmark in both open and laparoscopic right sided resections (Figure 7). It is exposed to ensure the anatomy of the ICA and to ease CVL and D3 dissection. The ICA’s dorsal or ventral passing of the SMV is easily visualised. The ICA and ICV are divided first, followed by division of the right colics if these are present. For tumours in the caecum and the parts of the ascending colon located proximally to branches from the ICA, the right branches of the MCA and MCV are divided centrally. For tumours located more distally in the ascending colon, in the hepatic flexure or the transverse colon proximally to the left branch of the MCA, D3 resection is performed at the origin of the ICA and MCA, and these arteries divided centrally.

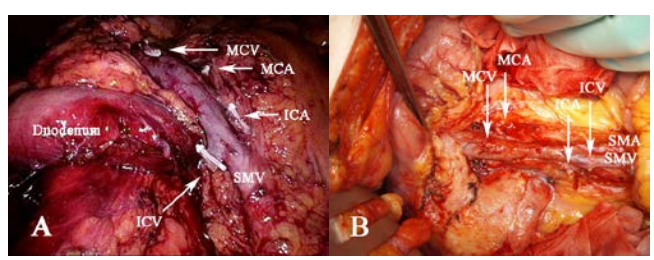
For both the latter group of tumour sites and for tumours in the rest of the transverse colon, the splenic flexure, and proximal part of the descending colon, LNs in the gastrocolic ligament are included in the specimen, as the gastroepiploic vessels and their branches to the stomach are divided for a length of approximately 10 cm on each side of the tumour (measured in vivo).

Figure 6:



Standardised definitions of CME colon resections used in this thesis and articles I-V. A: Right hemicolectomy. B: Extended right hemicolectomy. C: Right sided subtotal colectomy (if CME then it includes D3 resection around the root of the inferior mesenteric artery). D: Colectomy. E: Left hemicolectomy. F: Segmental resection of the splenic flexure (if CME then it includes D3 resection around the roots of the middle colic and the inferior mesenteric arteries). G: Sigmoid resection.

Figure 7:



Extended right hemicolectomies, laparoscopic (A) and open (B), for tumours in the anal part of the ascending colon. D3 lymph node resection has been performed at the base of the ileocolic (ICA and ICV) and the middle colic (MCA and MCV) arteries and veins. The superior mesenteric veins (SMV) and arteries (SMA) are exposed and the D3 lymph nodes have been excised together with the complete mesocolon. The head of the pancreas is exposed without any sign of remaining parts of the mesocolon.

In open right sided resections, the duodenum and to some extent the pancreatic head is mobilised to ensure mobility of the mesenteric root. This is not done for oncological reasons, but to ease dissection and control bleeding if this should occur, as it enables the superior mesenteric vessels to be lifted anteriorly without tension.

For tumours within the parts of the colon distally to the left branch of the MCA and the splenic flexure, D3 resection is performed around the MCA and IMA, because these are the potential sites of D3 LN+. To spare the remaining parts of the left colon, central division of the LCA can be performed with D3 LN resection around the IMA saving it when e.g. subtotal colectomy is performed.

The superior gastroepiploic vein often drains into the right branch of the MCV and in many patients it involves a pancreatic branch. To avoid bleeding from this vein, it is usually divided in open right sided resections before the exposure of the SMV, in contrast to after division of the ileocolic vessels in laparoscopic resections.

In left sided resections the IMA is divided at its origin, or if it is saved in some tumours located at the splenic flexure or transverse colon, the IMA is cleared from surrounding LNs and the LCA is divided at its origin. In sigmoid resections or left hemicolectomies, the bowel is divided in the upper part of the rectum to ensure sufficient perfusion of the anastomosis from the inferior and middle rectal arteries. For sigmoid tumours the bowel is divided proximally in the descending colon and at least 10 cm from the tumour. For tumours in the mid and distal part of the descending colon the procedure is similar, but the colon is divided in the transverse colon. For descending colon tumours close to the splenic flexure the strategy depends on whether it is located proximally or distally to the LCA.

AIM

The aim of this thesis was to describe the feasibility and potential oncological advantages of complete mesocolic excision for colon cancer by:

1. describing the pattern of lymphatic metastasising in the mesocolon and related structures
2. assessing changes in quality of specimens and short-term outcome related to implementation of CME in a colorectal cancer centre
3. comparing short-term outcome after CME with conventional colon cancer surgery
4. comparing oncological outcome after CME with conventional colon cancer surgery

METHODS

Data collection for article I

The PRISMA guidelines for reporting systematic reviews were used for article I. PRISMA focuses on reviews evaluating randomised trials, where PICO (population, intervention, comparison, and outcome) is defined. The PRISMA guidelines can also be used for systematic review of other types of research. To ensure the optimal validity of the systematic review of the pattern of lymphatic metastasising in the mesocolon and related structures, the PRISMA checklist [80] was used. The checklist could be used only to a certain extent, because only the risk of LN metastases and no specific intervention was investigated. Screening and selection of abstracts and full-text review of the relevant studies were done with the online software at www.covidence.org.

Data collection for articles II-V

The data for articles II-V were collected in two databases. The first included all patients undergoing colon cancer surgery in Hillerød from January 1 2008. The second database covered patients undergoing elective colon cancer resection between June 1 2008 and December 31 2013 at one of the other three colorectal centres in the Capital Region of Denmark.

Hillerød database

From 2006-2009 all colorectal cancer resections in Hillerød were recorded prospectively in a database at the Department of Surgery. This preliminary database contained only few variables related to the procedure, because preoperative and postoperative variables together with most data on surgery were registered in the nationwide DCCG database. Data on pathology variables were prospectively registered in a local database at the Department of Pathology from 2003, with variables subsequently added e.g. mesocolic plane and microsatellite instability status as these became implemented in the pathological assessment.

Patients included in article II were identified by cross-checking the local surgical database with the database of the Department of Pathology and the DCCG database to ensure completeness of patient inclusion. The data were retrospectively recorded from the electronic medical records by four colorectal surgeons. Before 2014 the DCCG database was limited regarding data on co-morbidity, surgery, and postoperative complications, and it still does not contain any information on long-term follow-up including recurrences. As a consequence of these limitations of the nationwide database, a more extensive local database was created. This was programmed with the use of EpiData Software [81]. From 2010 registration in the more extensive database was implemented with prospective registration of preoperative and perioperative data on paper sheets, and retrospective registration of variables related to the postoperative course (e.g. complications and their severity, length of stay, admission to intensive care unit, readmission after discharge, cause of death), and data on oncological variables (recurrence and adjuvant chemotherapy). Data for the latter group of variables were obtained from the electronic medical records covering the entire Capital Region. Data for patients undergoing resection in 2008-9 were retrospectively supplemented in the new extended database.

The retrospective data collection for 2008-9 and the postoperative data from 2010 were done by the author, whereas the preoperative and perioperative data from 2010 were recorded by the colorectal surgeon at the preoperative assessment and just after surgery respectively.

Non-CME database

The DCCG database has a patient completeness of 96% of colorectal cancer resections performed in Denmark since May 2001 [82], so it offers the possibility of extracting a potential control group based on the complete population in a specific geographical area. This reduces the selection bias, as almost all colon cancer patients in Denmark are treated at public hospitals and referred to them according to their postcode. It makes it possible to conduct a population based cohort study.

It has previously been shown that none of the three other centres in the Capital Region has implemented CME or similar resections [32] as standard and patients undergoing elective conventional (non-CME) resections for colon adenocarcinomas at these three centres were used as control groups in articles IV and V.

The DCCG data were limited before 2014, and definitions of the variables were either vague or even missing (e.g. definitions of type of resection and complications including their severity). To reduce the information bias in terms of misclassification of data, the data in the non-CME database were recorded from the medical journals by six colorectal surgeons, using the same definitions as in the Hillerød database.

Data audit

An external audit was performed to ensure the validity of the data used in articles IV and V. To avoid any negative outcome in the non-CME group becoming questionable, this was performed for both the Hillerød database and the data for the patients in the non-CME groups. As the data in both groups were recorded by surgeons from Hillerød they might have been biased during their review of the medical records. The external audit was performed by surgeons with no prior or present connection to the Department of Surgery in Hillerød each representing the centres contributing the patients in the non-CME group. This assured that data are as valid as possible when partly recorded retrospectively.

Similar to the data recorded during review of the medical records, data in the DCCG database might be biased as they are recorded by local surgeons. Data for the non-CME group were drawn from the DCCG database and retrieved from medical records. Variables occurring in both databases were checked for discrepancies and corrected by the author of this thesis based on information from the medical records before the data underwent external audit. The external audit was performed by reviewing the medical records of the patients. To reduce the number of patients to be audited in the non-CME group, only patients with either complications during the first 60 postoperative days or recurrence were audited by a co-author representing the centre where the surgery was carried out. This presents a risk of underreporting the true rate of complications and recurrences in the non-CME group, but the risk was considered small. A total of 671 (39.4%) of the patients in the non-CME group in article IV have been audited for article IV and V.

The data for all 529 patients in the CME group were audited by the three co-authors representing each of the three centres contributing patients in the non-CME group.

At the outset it was established that any conflicts occurring during audit were to be resolved by consensus between the auditing co-author, the author and the academic advisor of this thesis, who served as an “arbitrator”, however agreement was easily achieved in all cases.

Short-term outcome

Short-term mortality

In article II the short-term mortality is measured as 30-day mortality. In article IV 30-day and 90-day mortalities were the primary outcome measures, as patients with colon cancers are elderly with a considerably high proportion of co-morbidity. It has been shown that the risk of dying from postoperative complications is increased even after day 30 [83-85].

Postoperative complications

Data on postoperative complications were recorded retrospectively. Severity of complication was classified according to the Clavien-Dindo classification [86] and used for article IV. Complications requiring surgical, endoscopic or radiological intervention under general anaesthesia (grade IIIb) and life-threatening complications or those requiring intensive or intermediate care management (single or multi organ dysfunction (grade IVa or IVb)) were considered as severe. The retrospective design of the studies contains a risk of information bias (differentiated misclassification), as there might be differences between the four centres in managing organ dysfunction outside intensive or intermediate care units.

Complications treated outside the hospitals by general practitioners or home care nurses, and complications observed in hospitals outside the Capital Region, are not recorded if not mentioned in the medical records covering the hospitals of the Capital Region. Complications managed outside the hospitals were either minor or fatal (death outside hospitals). The latter would always be registered in the database as survival data were drawn from the National Civil Registry through the DCCG database; however as a consequence of the study designs there is a potential risk of underreporting minor complications treated by general practitioners or home care nurses.

Oncological outcome

The long-term outcome after cancer treatment can be measured in different ways each of which has its strengths and limitations. These are well-defined in the National Cancer Institute’s “Dictionary of Cancer Terms” [87]. The definitions presented below are used in the articles related to this thesis.

Overall survival

Overall survival is defined as the length of time from e.g. randomisation, diagnosis, exposure, or treatment (T_0) until death from all causes. The overall survival does not exclude competing events (deaths from other causes), which can be related to demographic variables such as age and sex when comparing two groups in a cohort study. The disease might have recurred during follow-up but not have been fatal. As a measure for the effect of a treatment for diseases like cancer, its value can be limited if recurrences only slowly progress or the treatment of the recurrences is so effective that death is delayed beyond the end of the study period, and a difference between two treatments might be underestimated.

Cancer-specific survival

Cancer-specific survival presents the net survival related to the specific cancer (or disease when not related to cancer). The event is deaths caused only from the specific cancer, whereas deaths from other causes are censored. Deaths related to the treatment of the cancer can and should be considered as an event, as they would not occur if the patient did not have the cancer. In article IV cancer-specific deaths was defined as all deaths occurring within 90 days of surgery, those occurring after day 90 from complications occurring after surgery, those related to treatment with adjuvant chemotherapy, and those from complications after surgery as a consequence of the colon resection e.g. stoma closure, or from recurrences. These events would not have occurred if the patients did not have colon cancer. As for overall survival its value can be limited if mortality or treatment from recurrence occur after the study period.

Disease-free survival

Disease-free survival is also called relapse-free or recurrence-free survival. T_0 is defined similarly, but the event is defined as recurrence of the disease (e.g. cancer). Time to event was defined in article V as the length of time between resection and diagnosis of recurrence. Disease-free survival measures how well a new treatment works, and was the primary outcome in article V.

Ethical considerations
CME was implemented at Hillerød as the standard treatment for colon cancer from June 1 2008. As the studies were conducted as follow-up of a treated population and not within a prospective trial, according to Danish legislation these did not need to be accepted by the local ethics committee. The data collection was approved by the Danish Data Protection Agency. The use of data from the DCCG database was approved by the scientific committee of the DCGG, and the three other colorectal centres in the Capital Region approved their patients' inclusion as the control groups for articles IV-V.

STATISTICS
The statistical methods used in articles I-III are mostly descriptive or univariable. Articles IV-V include control groups in a retrospective study design in contrast to randomised controlled trials (RCT) which imply a risk of bias in terms of confounding from variables other than the exposure variable (CME). By using multivariable regression analyses one can attempt to control and adjust for possible known confounding variables when investigating the effect of exposure variables on the outcome. Logistic regression models are usually used if the outcome event is not time-dependent or if time is not measured. Cox proportional hazard regression models are used if the risk of the event changes over time.

When building regression models the usual approach is to minimise the number of variables to present the most parsimonious model (Occam's razor) that is numerically stable and ensures external validity i.e. generalisability of the results [88]. Reducing the models can be done with forward selection or backward reduction of the number of variables, or by stepwise selection of variables in groups. A fourth possibility, purposeful selection, has been described by Hosmer and Lemeshow for both logistic [89] and Cox proportional hazard regression [90] analyses.

Purposeful selection
Purposeful selection was used to reduce the regression models in articles IV and V. These models were fitted using a predictor inclusion criterion of p values less than 0.50 (based on Wald statistics) identified in univariable regression analyses of available variables. This criterion was larger than 0.25 described by others [88]. The models in article IV were reduced by elimination of variables one by one with a retention criterion of p values less than 0.15 and accepting a maximum change in parameter estimates of 15% to indicate confounding. In article V the retention criterion was p values less than 0.10. To prevent elimination of any potential confounders, the usual limit of significance of p values less than 0.05 was not used and exact p values were reported. The reduced models were tested with all predictors eliminated one by one; and if the tested variable had p values less than the retention criterion used for elimination it was included in the final model. As CME was the exposure variable it was retained in all models during the model fitting, even when the p value was larger than the retention criterion. For article V it was decided in the design phase that UICC stage was to be retained in all models during the elimination processing, even if p values were larger than 0.10.

Possible interaction terms of clinical relevance were checked in both articles. In article IV the logistic regression model fits were analysed with the C-statistic, test for goodness-of-fit and residual analysis. Graphical assessment and Schoenfeld residuals [91] were used to check the adequacy and fit of the Cox regression models in article V. Variables showing non-proportionality were stratified.

Propensity score
Cohort studies like the ones forming the basis of this thesis may contain bias due to the non-randomised controlled retrospective design, and with the use of regression models one can describe only associations and suggest causality, as opposed to RCTs, which can estimate causal effects. Methods based on propensity scores can be used to reduce or eliminate the confounding from selection bias in observational studies as discussed in articles IV and V. With the use of propensity scores one can design the analyses of a non-randomised study to investigate or indicate causality as propensity score methods mimic RCTs. The two propensity score methods used in this thesis are covariate adjustment using the propensity score (article IV) and propensity score matching (article V).

A propensity score is a conditional probability of being assigned to a particular treatment (e.g. CME or non-CME) given a set of predictor variables. It is estimated for each patient and based on baseline observed variables and usually derives from logistic regression models. The distribution of observed baseline variables is similar between the two treatment groups, as they would be in an RCT. In RCTs the true propensity score (p=0.50) is known, as it is defined by the study design, which is considered to be without any selection bias. In observational studies one can estimate the true propensity score, and the effects of the measured confounders can be eliminated as in RCTs. One separates the design and analysis in an observational study when using propensity score methods, and this allows one to estimate marginal treatment effects and to generalise the result to a population [92].

There is no gold standard with respect to which variables should be included in the propensity score model [93]. We included variables that potentially could be associated with the treatment assignment to eliminate the bias from the quasi-randomisation of assigning the patients to the two groups according to their postcode. In the study of short-term outcome after CME (article IV) the selected variables were:

- demographic: age and sex
- year of resection (2008 and 2009 pooled)
- co-morbidity: body mass index (BMI), and American Society of Anesthesiologists (ASA) score
- macroscopic tumour pathology: pT4 or pT1-3 tumour, peroperatively assessed fixation of tumour, primary tumour location (caecum, ascending colon, hepatic flexure to mid transverse colon (hepatic flexure, right and mid third of transverse colon), left transverse and splenic flexure, descending colon, or sigmoid)
- surgical procedure: laparoscopic or open resection, anastomosis

In the study of oncological outcome (article V) UICC stage was added to the variables, which were:

- demographic and co-morbidity variables mentioned above
- tumour variables: tumour side (left or right sided), synchronous tumours, and UICC stage

These listed variables were known, present or determined preoperatively. Propensity score models should include only variables, that are present at the time of treatment, and not post-treatment variables, that might have been influenced or modified by the treatment [92].

Covariate adjustment using the propensity scores was chosen for article IV. As the outcomes (30-day and 90 day mortality) were dichotomous the propensity score was used to adjust the variable CME in logistic regression models. The balance of the variables included in the estimation of the propensity scores was checked graphically and by evaluating the distribution of continuous variables within the quintiles of the propensity scores [94] before the two logistic models were fitted. As selection bias is one of the most challenging problems in observational studies, the possibility of hidden bias due to unmeasured confounders was estimated according to Rosenbaum's sensitivity analysis approach. Using his methodology a sensitivity analysis gives an answer as to how much hidden bias can be present before the qualitative interpretation, e.g. the conclusion of the study, changes. Sensitivity is presented as Γ.

Propensity score matching was used in article V. It requires large samples and adjusts for selection bias and minimizes group differences across many variables between the two groups. It is more suitable for large samples than hard matching [93]. A 1:1 match without replacement, with the nearest neighbouring matching, and without a specified calliper was used. The disease-free survival was analysed with Kaplan-Meier curves and log-rank test of the matched groups.

ARTICLE I

Pattern of colon cancer lymph node metastases in patients undergoing central mesocolic lymph node excision: a systematic review [1].

Aim

Systematic review of studies describing central mesocolic LN+, skip metastases, aberrant and gastrocolic ligament (GCL) lymph node metastases from colon cancer.

Methods

Embase and PubMed searches were performed using the terms:

- "colon" or "colorectal" with "sentinel node", "lymph node mapping" or "skip node"
- "lymph node resection colon", and
- "complete" or "total" and "mesocolic excision"

The inclusion criteria were studies of the risk of metastases in central mesocolic LNs, GCLN+, or prevalence of skip metastases from colon adenocarcinomas. Studies with a population of less than ten were excluded. No languages were excluded as external translation of relevant articles was possible. The guidelines for reporting systematic review developed by the PRISMA group were followed as much as appropriate, as the review did not include intervention or outcome measures.

Results

A total of 2,052 articles were screened, and 277 of these were full-text reviewed. Forty-seven studies described the different issues to be investigated and were included. Meta-analyses were not considered appropriate, because the intra- and inter-study populations were very heterogeneous as there were large variations in anatomical definitions, inclusion criteria, surgical procedures and pathological assessment. The reported risk of central mesocolic LN+ in right sided colon adeno-carcinomas varied between 1 and 22%, and was reported in up to 12% of the patients with sigmoid tumours. There was an association with advanced pT-stage. Epi-/paracolic LN+ located between 5-10 cm from tumour were reported in up to 23% of the patients, except for very distal sigmoid tumours where mesocolic LN+ seem rarely to occur more than 5 cm distally to the tumour. The risk of skip metastases seems dependent on the methodology used for detection, as the use of immunohistology or molecular methods detects micrometastases which are not detected with conventional staining techniques. The proportion of skip metastases to the central mesocolic LNs without metastases in the epi-/paracolic or intermediate LNs is reported in up to 7% of the cases.

Conclusion

The quality of the current literature is not sufficient to give a theoretical explanation of a better oncological outcome after extended LN dissection. A standardization of anatomical definitions, surgery and pathological assessment is warranted for future mapping studies.

Strengths and limitations

Strengths

A substantial part of the relevant literature was in Chinese, Japanese or Italian, so the inclusion of all relevant studies with no linguistic limitations was important to make this review comprehensive.

Limitations

Many of the studies had a retrospective design and both internal and external validity is questionable. All except one were single-centre studies with a limited number of patients included or long study periods. There is large risk of selection bias as e.g. the Japanese guidelines suggest D3 resection only in clinical stage T3-4 tumours, while some surgeons performed D3 resection based on intraoperative risk assessment of LN+ by size and firmness. Neither this intraoperative risk assessment nor preoperative CT staging have been proven accurate to determine pN-stage. There is a considerable variation in the distribution of UICC-stages between the studies, and stage IV has also been included by some. There are also differences between inclusion criteria for tumour sites, morphology, and pathological parameters. Both definitions of mesocolic LN location and the nomenclature of the branches of the SMA were not uniform between Asian and European studies.

Definitions and pathological assessment techniques have changed over time, so the studies were limited by the time span (1946-2013); the techniques for preparation of LNs were biased by the use of different methods, which might influence the LN yield and metastases detected.

Meta-analyses were not performed because of these issues, and the risk of bias was not assessed with standard tools such as the Cochrane Risk of Bias Tool.

ARTICLE II

Can the quality of colon surgery be improved by standardisation of surgical technique with complete mesocolic excision?[2]

Aim

The aim of the study was to analyse the influence of implementation of a standardised surgical technique with complete mesocolic excision for colon cancer. Primary outcome was the quality of the specimens in terms of LN yield, high tie of supplying vessels, plane of mesocolic resection and rate of R0 resections. Secondary outcomes were 30-day mortality, postoperative complications and intraoperative bleeding.

Methods

Retrospective designed study of 93 patients with colon carcinoma or large adenomas undergoing curative-intended CME between June 1 2008 and February 28 2009. These were compared with a control group of 105 similar patients undergoing radical surgery between September 1 2007 and May 31 2008 before complete mesocolic excision (CME) was introduced as standard at Hillerød Hospital. Pathological variables were registered prospectively except for post hoc grading from photographs of mesocolic plane and high tie if these were not included in the primary reports. These variables were implemented before CME.

Results

The rate of mesocolic resection plane was already high before implementation and did not improve (p=0.15). The overall mean LN yield increased from 24.5 (95% CI 22.8-26.2) to 26.7 (95% CI 24.6-28.8) (p=0.0095) and mean high tie from 7.1 cm (95% CI, 6.5-7.6 cm) to 9.6 cm (95% CI, 8.9-10.3 cm) (p<0.0001). There were no significant increases in these end-points in open right hemicolectomy (p=0.41 and p=0.51). For laparoscopic resections for tumours in the caecum, appendix, and proximal ascending colon mean high tie increased from 7.7 cm to 9.4 cm (p=0.0018) and mean LN yield from 23.6 to 26.8 (p=0.010). Resections for distal ascending, transverse, hepatic and splenic tumours were performed as open only in the study group. Mean high tie for these increased from 6.0 cm to 8.8 cm (p=0.0013) and mean LN yield from 26.0 to 30.0 (p=0.045). Mean high tie in laparoscopic resection of sigmoid tumours increased from 7.1 cm to 9.2 cm (p<0.001), while the LN yield did not change (p=0.41). The risks of 30-day or in-hospital mortality (p=0.79), major postoperative complications (p=0.73), and intraoperative bleeding (p=0.89) were unchanged.

Conclusion

Standardization of colon cancer surgery with CME seems to improve the quality of surgery measured as LN yield and distance to vascular high tie for some tumour locations and procedures. The proportion of mesocolic plan was already high before the implementation of CME and was not improved. The risks of 30-day or in-hospital mortality, complications and intraoperative bleeding did not increase.

Strengths and limitations

Strengths

The study has a simple design to evaluate the safety of implementing CME in a colorectal centre to ensure that CME not was associated with a large increase in short-term mortality and complications, and to show that CME is a feasible approach in colon cancer surgery without an increased risk for the patients in further studies. It also gives the opportunity to indicate improvements in the outcome of the specimens.

Limitations

Article II is limited by the retrospective design, as also are articles III-V. All patients were registered in three separate databases, the surgical, pathological and National Patient Registry, with data in the latter coming directly from electronic health records, so the risk of selection bias by omitting patients is limited, but there was another important selection bias as the primary outcomes were not registered prospectively. If the outcome parameters were not included in the pathology reports, the measures were retrospectively assessed by photographs. Photographs of the fresh and fixed specimens were not taken as standard before 2008, and the dataset for the control group was incomplete, with length of vascular high tie and mesocolic plane not assessed in 23.8% and 28.6% of the patients. The use of photographs to assess these parameters has been used by others [32, 41, 76] but might contain a risk of information bias. The way the specimens are presented on the photographs presents a risk of misclassifying the mesocolic plane and questions the accuracy of measuring the vascular tie retrospectively. There is always a risk of intra- and interobserver variability, especially related to assessing the mesocolic plane, but all specimens were assessed by three dedicated colorectal pathologists, who often assessed the specimens together, so the interobserver variability in this study might have been reduced by these “grand rounds”.

Data on postoperative short-term outcome also contain a risk of information bias. Survival data are completely valid, as the electronic health records are updated daily with data from the National Civil Registry, but there is a risk of underreporting and misclassification of retrospectively collected data regarding postoperative morbidity, as only complications observed in hospital and regarded as potentially life-threatening or requiring reoperation were recorded. Prospective collection of data, clear definitions of the complications and the use of a scoring system like Clavien-Dindo score would have been preferred.

The population size is a limitation, as the finding of significantly longer distance between tumour and vascular tie in some subgroups was based on 7 or 8 patients. The short study period did not offer an opportunity of investigating the length of the learning phase of CME. There was no significant difference in the 30-day or in-hospital mortality before and after implementing CME, but the 7.6% before and 6.5% after is higher than the national average in that period. A potential decrease from the reduction of the number of surgeons might have biased the short-term mortality of the study group, but probably not to an extent that might cause a type II error.

Before and during the study period the pathology team at Hillerød Hospital underwent continuous improvement as part of an internal education programme in cooperation with expert colorectal pathologists in the UK. This might bias the results in favour of the study group. The reduction of the number of colorectal surgeons from June 1 2008 might similarly have contained bias, even though CME was not implemented at once, and not all the procedures in the study group were performed by the then future group of CME surgeons.

As the surgeons were aware of CME principles before the implementation, this might have influenced them to perform CME-like surgery even before, which might explain lack of improved outcome for open right hemicolectomies, where a medial to lateral approach with high ligation was used by many surgeon before June 1 2008. All these limitations reduce the external validity and question the generalisability of the study.

ARTICLE III

Lymph node metastases in the gastrocolic ligament in patients with colon cancer [3].

Aim

To estimate the prevalence of metastases in the gastrocolic ligament lymph nodes (GCLN) in tumours with main blood supply from the middle colic artery. These are located along the gastroepiploic artery (gastroepiploic LNs) and anteriorly to pancreatic head (infrapyloric LNs).

Methods

Retrospectively registered data supplemented prospective data from local databases of colon cancer surgery and pathology. All resections for colon adenocarcinoma with relevant tumour location between June 1 2008 and December 31 2012 were included.

Results

Of 712 patients undergoing colon cancer resections during the study period, gastrocolic ligament resection was indicated in 168 (23.6%). It was not performed in 38 cases because of dissemination (n=6), age or severe comorbidity (n=8), previous colon resection (n=1), malrotation (n=1), adenomas where adenocarcinoma was not preoperatively suspected (n=2), or in cases where no reason was stated by the surgeon (n=20). A further 32 patients were excluded because the gastrocolic ligament was not marked by the surgeon sufficiently to be recognised by the pathologist (n=19), the pathology report did not include a specific description of GCLN (n=12), or the gastrocolic ligament was inseparable from the tumour (n=1). Median mesocolic LN and GCLN yields in the 98 specimens were 39 (range 15-99) and 4 (range 0-16) respectively, and GCLNs were found in 86 (88%) of the specimens. GCLN metastases were demonstrated in four specimens including one among the 12 (12%) stage IV patients. GCLN+ was demonstrated only in the subgroup of 32 (33%) patients with mesocolic LN+ resulting in a proportion of 13% of these, and 4% of all 98 patients.

Conclusion

Metastases in the gastroepiploic or infrapyloric LNs occur from colon adenocarcinomas, which are mainly supplied by the MCA.

Strengths and limitations

Strengths

The patients are referred to public hospitals according to their postcode, and as Hillerød served a population of 390,000 throughout most of the study period, and the results are similar to other studies [27, 79, 95, 96], they seem to have large external validity. The study period is relatively short compared to the five decades in Toyota et al [27], and the size is larger than later published studies [79, 95, 96]. The pathological assessment in Hillerød during the study period was in accordance with the highest international recommendations, and the use of methylene blue was implemented during the study period to optimise the number of LNs detected.

Limitations

Limitations of this study include the retrospective design with the lack of GCLN status in the pathology report in some patients. There is a risk of selection bias as GCL was not resected in all patients and, if resected, GCLNs were not examined in all specimens.

The GCL was not resected in all patients because some surgeons were concerned about the risk of necrosis of the stomach. This occurred in only one patient, but can occur even without GCLN resection [4]. The reason for omitting GCL resection was not stated for all patients.

We did not implement a standard method of marking the gastroepiploic artery resection margins until it was evident that the pathologists were not always able to locate it in the specimen.

It is not possible to estimate the clinical relevance related to GCLN+ regarding the risk of recurrence and survival based on this study. A future study would require inclusion of multiple centres, as the number of patients with tumours located in the relevant sites is limited, and the outcome had to be adjusted for potential risk factors e.g. tumour stage and morphology, perineural venous invasion and stage, and chemotherapy.

The impact on short-term and long-term bowel function from GCL resection remains unknown, but bowel function might be impaired with increased time to postoperative bowel function from gastroparesis. GCL resection might lead to increased length of stay (LOS) beyond any effects of enhanced recovery after surgery (ERAS).

ARTICLE IV

Short-term outcomes after complete mesocolic excision compared with ‘conventional’ colonic cancer surgery [4].

Aim

The study aim was to investigate the association between CME and short-term outcome when compared with conventional colon cancer surgery. The primary outcomes were 30-day and 90-day mortality, and secondary postoperative morbidity.

Methods

Patients undergoing curative-intended elective surgery for stage I-III colon adenocarcinoma in the Capital Region of Denmark from 1 June 2008 to 31 December 2013 were included. Data for the CME group, which consisted of patients undergoing CME at Hillerød Hospital, were retrieved from the local database. The control group consisted of patients having conventional colon resection at the other three colorectal centres. The medical records of the non-CME patients were reviewed by a colorectal surgeon from Hillerød Hospital to validate and supplement data from the DCCG database with data on in-hospital complications during the first 60 days after surgery. Data on status “dead” or “alive were retrieved from the National Civil Registry through the DCCG database. Data from pathological examinations were retrieved from the Hillerød and the DCCG databases, and missing data for the latter were retrieved by two colorectal pathologists from pathology reports. Exclusion criteria were: metachronous colorectal cancer, rectal cancer (15 cm or less from the anal verge) in the absence of synchronous colon adenocarcinoma, appendix tumour or an R2 resection. An audit to ensure internal validity of the data was performed as described above.

Results

From article

The CME group consisted of 529 patients and the non-CME group of 1,701. Severe co-morbidity (ASA score III) was more common in the CME group with 21.4% (113 patients) compared with 17.1% (291) in the control group (Fisher’s exact test p=0.028). Transverse colectomies were not performed in the CME group, as patients with transverse colon tumours underwent extended right-sided hemicolectomies according to the principles of CME. Median LN yield was higher in the CME group 36 (IQR: 26-47) compared with 20 (IQR: 15-28) in the non-CME group (t-test p<0.001), and so was microradical resection (98.1% compared with 95.7%; Fisher’s exact test p=0.008). Laparoscopic resection was performed more often in the non-CME group (68.9%) compared with 48.8% in the CME group (Fisher’s exact test p<0.001). Intraoperative recognized injury to other organs was reported more often in the CME group (9.1% compared with 3.6%; Fisher’s exact test p<0.001) mainly because of injury to other segments of the colon, spleen and SMV.

There was no significant difference in one-year cancer-specific survival (log-rank test p=0.846), with observed mortality rate of 6.8% (95% CI 4.9-9.3) after CME compared with 7.1% (6.0-8.5).

The 30-day mortality rates were 4.2% (n=22) in the CME group compared with 3.7% (n=63) in the non-CME group (difference: 0.5%, 95% CI -1.5-2.5, p=0.605). The 90-day mortality rates were 6.2% (n=33) and 4.9% (n=83) respectively (difference: 1.4%, 95% CI -1.1-3.8, p=0.219). The 30-day and 90-day mortality rates were not statistically significantly different in univariable, multivariable, and propensity score adjusted logistic regression models as shown in Table 4. ASA score was the most significant predictor of 30-day and 90-day mortality rates in the multivariable analyses. The ORs for 30-day mortality rates were 3.41 (95% CI 1.20-14.34, p=0.044) for ASA grade II and 9.71 (95% CI 3.36-41.17, p <0.001) for grade III-IV. The similar ORs for 90-day mortality were 2.41 (95% CI 1.09-6.40, p=0.047) and 7.06 (95% CI 3.14-18.95, p<0.001). Laparoscopic resection was associated with less 30-day and 90-day mortality with ORs of 0.63 (95% CI 0.39-1.00, p= 0.052) and 0.63 (95% CI 0.42-0.95, p=0.028) respectively. There were no differences in the 60-day overall postoperative or surgical complication rates. Only severe non-surgical complications (Clavien-Dindo score IIIb-IVb) were more common after CME (8.1% compared with 5.1%; Fisher's exact test p=0.010). This was caused by higher rates of pulmonary failure (defined as a need for respiratory support from ventilator or non-invasive ventilation postoperatively) and sepsis (defined as a need for vasopressors more than 24 hours postoperatively).

Table 4:

	OR	30-day mortality (95% CI)	p value
Univariable logistic regression			
Non-CME	1.00		
CME	1.12	(0.67-1.82)	0.633
Reduced model multivariable logistic regression			
Non-CME	1.00		
CME	1.07	(0.62-1.80)	0.795
Propensity score adjusted			
Non-CME	1.00		
CME	1.22	(0.79-1.87)	0.363
	OR	**90-day mortality (95% CI)**	**p value**
Univariable logistic regression			
Non-CME	1.00		
CME	1.30	(0.85-1.95)	0.220
Reduced model multivariable logistic regression			
Non-CME	1.00		
CME	1.25	(0.77-1.94)	0.334
Propensity score adjusted			
Non-CME	1.00		
CME	1.22	(0.79-1.87)	0.363

Complete mesocolic excision (CME) as a risk factor for 30-day and 90-day mortality after 2,230 resections of UICC stage I-III colon adenocarcinomas analysed with univariable, multivariable and propensity score adjusted logistic regression analyses. Propensity score adjusted models without imbalance and with a sufficient overlap. In sensitivity analyses $\Gamma = 1.52$ for 30-day mortality, and $\Gamma = 1.21$ for 90-day mortality. OR: odds ratio. CI: confidence intervals [4].

Pulmonary failure occurred in 8.1% (95% CI 6.0-10.9%) in the CME group compared with 3.4% (95% CI 2.6-4.4%) in the non CME group (difference: 4.7%, 95% CI 2.1-7.3, p<0.0001). Sepsis occurred in 6.6% (95% CI 4.7-9.2%) in the CME group compared with 3.2% (95% CI 2.5-4.2%) in the non CME group (difference: 3.4%, 95% CI 0.9-5.8, p=0.001).

Supplementary and post-hoc results

The year of surgery was included as a variable in the propensity adjusted analyses, as the results in article II and from the DCCG database indicated higher 30-day mortality in Hillerød than in the other centres. In general the mortality after colon cancer surgery in Denmark has decreased during the study period [11]. The absolute risks of 30-day and 90-day mortality for each year (2008-9 pooled) were analysed and compared to indicate time dependent changes. The 30-day and 90 day mortality rate were not significantly higher in the CME group compared with the non-CME group for any year period (Figure 8). The 90-day mortality seems to decrease from 2008-9 to 2012 in the CME group as the mortality decreased by more than 50%, and it remained low in 2013.

The risk of complications was the secondary outcome. Multivariable analyses were not performed despite the finding of significantly higher risk of respiratory failure and need for vasopressors during the postoperative period. The data have undergone post-hoc analyses after publication of the article in order to investigate possible causes of these complications and to indicate explanations. The causes are shown in *Table 5*. Anastomotic leakage is the main cause of both respiratory failure and sepsis in both groups. Reoperation for anastomotic leakage was needed in 41 (97.6%) of 42 patients in the CME group compared with 99 (87.6%) of 113 patients in the non-CME group (difference: 10.0%, 95% CI -0.7 to 19.3; p=0.071), and the severity of the leakage could be associated with the higher risk of respiratory failure and with the need for vasopressors in the CME group. Open resection was a potential risk factor for both respiratory failure (p<0.001) and sepsis (p<0.001). Increasing ASA score was also a risk factor (p<0.001) for both complications.

Conclusion

There was no association between CME and 30-day and 90 day mortality when compared with non-CME. Pulmonary failure defined as need for respiratory support from ventilator (including non-invasive) or continuous positive airway pressure in intensive care unit, and sepsis (measured as need for vasopressors) occurred significantly more often after CME.

Strengths and limitations

Strengths

The material is population-based, and patients were referred to the hospitals according to their postcode, which can be considered as quasi-randomisation. Together with the 100% valid data on status (dead or alive), the external validity regarding mortality in this study was high. Data from the DCCG database were supplemented by more parameters and complemented by the review of the medical records to improve internal validity. The audit further ensured the internal validity.

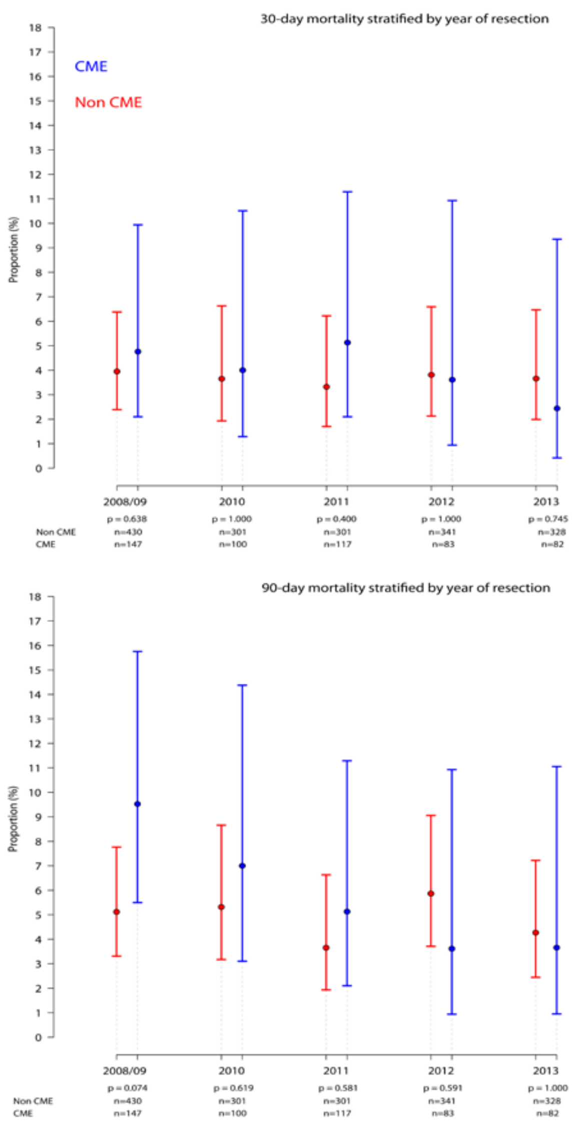
Limitations

The retrospective design contains several limitations regarding both external and internal validity. There was a risk of misclassification of some parameters, as reporting complications in a retrospective study contains a great risk of information bias. Postoperative complications were not defined in the DCCG database during the study period, and there are several issues related to the article which need to be underlined.

The definition of sepsis used was not based on a scoring system documented in the clinical records as standard, so cases with Clavien-Dindo score IV-V only were registered. Vasopressors can be used on other indications e.g. hypotension caused by sedation during and after surgery, and there is a risk of overestimating the risk of “sepsis” in both groups; differences in local procedures might bias this parameter.

The definition of respiratory failure was first used in the Hillerød database, because none of the treatment modalities was possible without transferring the patients to the intensive or intermediate care units. The non-invasive treatments were possible outside special care units in the departments of pulmonary medicine in one non-CME hospital. The retrospective design contains a risk of underreporting respiratory failure.

Figure 8:



30-day and 90-day mortality per year with 95% confidence intervals (2008 and 2009 combined) after CME and non-CME colon cancer surgery.

Table 5:

	Non-CME (n=1,701)	CME (n=529)
Respiratory failure caused by (all)	58 (3.4%)	43 (8.1%)
Anastomotic leakage	26 (45%)	20 (47%)
Perforation of GI tract	5 (9%)	2 (5%)
Fascial dehiscence	0 (0%)	1 (2%)
Pneumonia	10 (17%)	10 (23%)
Preoperative co-morbidity	2 (3%)	2 (5%)
Other surgical complication	9 (16%)	3 (7%)
Other non-surgical complication	6 (10%)	5 (12%)
Sepsis caused by (all)	55 (3.2%)	35 (6.6%)
Anastomotic leakage	30 (55%)	17 (49%)
Intraoperative hypotension	0 (0%)	2 (6%)
Perforation of GI tract	6 (11%)	2 (6%)
Fascial dehiscence	1 (2%)	1 (3%)
Pneumonia	2 (4%)	8 (23%)
Preoperative co-morbidity	0 (0%)	1 (3%)
Other surgical complication	10 (18%)	2 (6%)
Other non-surgical complication	6 (11%)	2 (6%)
Respiratory failure and sepsis caused by	39 (2.3%)	30 (5.7%)
Anastomotic leakage	21 (54%)	14 (47%)
Perforation of GI tract	4 (10%)	2 (7%)
Fascial dehiscence	0 (0%)	1 (3%)
Pneumonia	2 (5%)	8 (27%)
Preoperative co-morbidity	0 (0%)	1 (3%)
Other surgical complication	7 (18%)	2 (7%)
Other non-surgical complication	5 (13%)	2 (7%)

Cause of respiratory failure defined as a need for respiratory support from ventilator or non-invasive ventilation postoperatively, sepsis defined as need for vasopressors for more than 24 hours, and both complications in the first 60 days postoperatively after CME and non-CME for stage I-III colon cancer.

The surgeon is a potential risk factor of bias. The DCCG database includes data only on the level of specialisation, rather than the identity of the surgeon. The procedure is also a risk factor with more anastomotic leakages after sigmoid resection and especially left hemicolectomy. There might also be a difference between surgeons of indication for stoma, which could bias the results. These biases should be limited by the population size and number of surgeons (four centres).

The significantly higher preoperative co-morbidity in the CME group might bias the outcome of e.g. respiratory failure and sepsis. Logistic regression analyses of postoperative complications with propensity score adjustment were not appropriate because of the issues regarding internal validity of the secondary outcome parameters mentioned above.

ARTICLE V

Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a population-based study [5].

Aim

To investigate whether CME is associated with improved disease-free survival compared with conventional colon cancer resection.

Methods

Data for all patients who underwent curative-intended elective resection for UICC stage I-III primary colon adenocarcinomas in the Capital Region of Denmark between June 1 2008, and Dec 31 2011, were retrieved from either the local database in Hillerød or from the Danish Colorectal Cancer Group (DCCG) database supplemented with data from medical records. The CME group consisted of patients undergoing CME at Hillerød Hospital; the control group was patients undergoing conventional colon resection in three other centres. Data were audited to ensure validity.

Follow-up was not standardised between centres, but recurrences had to be diagnosed by the CT or PET/CT of thorax and abdomen, chest radiograph and contrast-enhanced ultrasound of the liver or laparotomy. Histological verification was not necessary. Metachronous colon cancers were classified only as recurrences if located in the anastomosis and with the same morphology as the primary cancer.

The association between CME and four-year disease-free survival was evaluated with multivariable Cox proportional hazards regression models after purposeful selection of possible predictive variables identified by univariable Cox proportional hazards regression models as described above. As CME was the exposure variable it was retained during the stepwise elimination despite any p values. A 1:1 match without replacement was done. It was based on propensity scores created with logistic regression modelling the probability of a patient undergoing CME based on age, sex, BMI, ASA score, tumour side, synchronous tumours, and UICC stage, and included a significant interaction between age and BMI.

Results

The CME group consisted of 364 patients and the non-CME group consisted of 1,031 patients. There was no significant difference in the distribution of UICC stages between the two groups (Table 6). A total of 103 (73.6%) patients with stage III in the CME group receive adjuvant chemotherapy compared with 254 (69.6%) in the non-CME group (difference: 4.0%, 95% CI -5.2 to 13.2; p=0.44), but for stage II patients there was a significant difference as chemotherapy was given to 42 (24.9%) in the CME group and to 75 (15.0%) in the non-CME group (difference: 9.8%, 95% CI 2.2-17.4; p=0.0053).

Table 6:

UICC stage (TNM5)	Non-CME (n=1,031)	CME (n=364)
Stage I	167 (16%)	55 (15%)
Stage II	499 (48%)	169 (46%)
Stage III	365 (35%)	140 (38%)

Distribution of UICC stage between the non-CME and CME groups. Pearson's χ^2 test p=0.57. Data from Bertelsen et al. Lancet Oncol 2015; 16:161-8 [5].

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 (IQR 1.02-3.11) in the non-CME group (p<0.0001). Recurrence was diagnosed in 41 (11.3%) in the CME group compared with 167 (16.2%) in the non-CME group (difference: 5.0%, 95% CI 0.8-9.1, p=0.028). No recurrences were reported after CME in stage I patients compared with 10 (6.0%) in the non-CME group. For stage II the proportions were 11 (6.5%) and 62 (12.4%) respectively, and for stage III 30 (21.4%) and 95 (26.0%) respectively. The four-year disease-free survival for stage I-III was 85.8% (95% CI 81.4-90.1) after CME and 75.9% (95% CI 72.2-79.7) after non-CME surgery (log-rank p=0.0010). Propensity score matched populations showed similar higher four-year disease-free survival of 85.8% (95% CI 81.4-90.1) after CME compared with 73.4% (95% CI 66.2-80.6) after non-CME (log-rank p=0.0014).

Four-year disease-free survival for stage I in the CME group was 100% compared with 89.8% (95% CI 83.1-96.6) in the non-CME group (log-rank p=0.046), for stage II it was 91.9% (95% CI 87.2-96.6) in the CME group compared with 77.9% (95% CI 71.6-84.1) in the non-CME group (log-rank p=0.0033), and, for stage III disease, it was 73.5% (95% CI 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). In multivariable Cox regression models CME surgery was a significant, independent predictive factor for higher disease-free survival for all patients (hazard ratio (HR) 0.59, 95% CI 0.42-0.83, p=0.0025), in UICC stage II (HR 0.44, 95% CI 0.23-0.86, p=0.018) and stage III disease (HR 0.64, 95% CI 0.42-1.00, p=0.048).

Conclusion

CME surgery is associated with better disease-free survival compared with conventional colon cancer resection for patients with stage I-III colon adenocarcinoma. The improvement was most significant in stage I and II disease.

Strengths and limitations

Strengths

As a population-based study all relevant patients were included, which makes the external validity high. It is the only study comparing CME with conventional surgery without the use of historical control, except for a small Norwegian study of 84 CME patients [13]. As a randomised controlled trial (RCT) seems almost impossible to conduct, our study design is the most preferable.

Limitations

Article V is limited by the retrospective design in the same manner as article IV. Quasi- randomisation was performed, as the patients are submitted to the hospital according to postcode, but there were differences in duration of follow-up and methods used to diagnose recurrences. Some centres follow their patient for only three years compared with five years for Hillerød, and asymptomatic late recurrences in the non-CME group might not have been diagnosed. In Hillerød CT of the thorax and abdomen has been the standard follow-up examination for many years, while one of the non-CME centres used chest radiograph and contrast-enhanced ultrasound as follow-up during the study period. They performed CT only in cases of positive findings or symptoms of recurrence. As ultrasound of the liver does not diagnose local recurrences, which might be detected with CT; there might have been a risk of underestimating the rate of loco-regional recurrences in the non-CME group [97]. Similarly chest radiography does not detect lung and mediastinal metastases with the same sensitivity as does CT of the thorax. All these issues might have biased the results in favour of conventional surgery by underestimating the recurrence rates in the non-CME group. This decreases the risk of type I error.

One might suspect a risk of upstaging, but the distributions of UICC stages were similar. Differences in proportion of stage II patients receiving adjuvant chemotherapy might be a consequence of better and more standardised pathological assessment in the CME group, as extramural venous invasion was detected more often in that group, but adjuvant chemotherapy was a non-significant predictive variable eliminated early in the reduction of models when analysing stage II patients.

DISCUSSION

Basic findings

The studies included in this thesis show an association between CME and better oncological outcome after curative-intended elective resection for colon cancer, as the four-year disease-free survival was higher after CME for stage I-III and for each of these stages. It was shown that the perioperative mortalities measured after 30 and 90 days were not significantly higher after CME, though there seem to be an increased risk of postoperative non-fatal respiratory failure and need for vasopressors. It was also shown that LNs+ occur along the gastroepiploic LNs in case of tumours located in the transverse colon, in the ascending or descending colon close to or in the flexures. The risk was 4% of all tumours and 13% of the pN+ tumours.

Clinical considerations

Oncological outcome

No RCTs comparing CME and non-CME have ever been performed. Storli et al [13] have, as the only other study, compared CME with non-CME without the use of historical controls. They included only patients with stage I-II from three Norwegian centres, and showed better three-year disease-free survival after CME for LN- colon cancers (82.1% after CME compared with 74.3%; HR 1.95, 95% CI 1.06-3.59, p=0.032). The study was limited by its size (84 and 105 patients in the CME and non-CME groups respectively), retrospective design and exclusion of stage III. In another study [98] from the same group they reported no difference in three-year disease-free survival between open and laparoscopic resections.

Though the findings of the large single-centre studies of Hohenberger at al [12] and Bokey et al [15] supports better outcome after CME, both studies contain a risk of bias from unknown factors related to the use of a historical control group. Both studies report cancer-specific survivals as the oncological outcome, which, as mentioned above, has some limitations compared with disease-free survival. A later update from Bokey et al [99] showed similar cancer-specific survival as reported from Erlangen [12], and a risk of recurrence (local and distant) as reported in article V. These studies are supplemented with two European/American single-centre cohort studies [16, 100] without a control group, all supporting CME. A systematic review [101] considered to investigate outcome after CME included studies without standardised CME, because Tentes et al [102] compared CVL with CVL and en bloc resection of the lymphatic from periaortic and inferior vena cava regions in left sided tumours, and Ovrebo and Rokke [103] compared D1 with D2-3 excision.

D3 LN resection for cT3-4 or cT1-2 with apparent LN+ is recommended in the Japanese guidelines for colorectal cancer treatment, because the risk of central LN+ increases with T-stage [75]. This selection of patients presents a problem and is in contrast to the knowledge of preoperative [104, 105] and intraoperative [30, 106-108] N-staging be unreliable. The only population-based study comparing D3 with D2 resection is based on the Japanese national database, and investigated the five-year overall survival of 10,098 stage II-III colon cancer patients [14]. They reported better outcome after D3 than D2 resection for both stages. The outcome after D3 resection for stage I colon cancer was not reported. Several Asian cohort studies [22, 106, 107, 109-113] support D3 resection in some patients. The findings in article V indicate that all patients with stage I-III benefit from CME.

The findings of better outcome for stage I-II in article V is in accordance with the findings of Storli et al [13], although the benefit of CME would have been expected to be mainly for pN+ patients. They reported a three-year disease-free survival for stage I-II of 82.1% with the four-year disease-free survivals of 89.8% (83.1-96.6) for stage I and 77.9% (71.6-84.1) for stage II.

Storli at al. have not published any outcome after CME compared with non-CME for stage III patients, and article V remains the only European study investigating these patients with the current regimes of adjuvant chemotherapy. The difference of only 6% for stage III patients between the CME and non-CME group, found in article V, was smaller than anticipated, but CME was a predictor of better disease-free survival in the multivariable analyses. The use of adjuvant chemotherapy in 70-74% of the stage III patients might have reduced the effect of CME, and the HR for adjuvant chemotherapy was 0.62 (95% CI 0.41-0.93, p=0.020) in the multivariable analyses. A possible explanation for this finding might be that adjuvant chemotherapy, in some stage III patients in the non-CME group, eradicated residual tumour deposits in the central parts of the mesocolon, which were resected in similar patients in the CME group.

Short-term mortality and morbidity

No studies, except article IV, have compared perioperative mortality and morbidity without historical controls. Storli et al [13] reported only a 30-day/in-hospital mortality of 2.8% after CME compared with 8.8 % after non-CME (p=0.072). They did not report postoperative complications. In their study of 251 patients undergoing CME [98] they reported a 30-day/in-hospital mortality of 3.6% with no significant difference between open and laparoscopic resection. They did not specify postoperative complications, but the risk was significantly higher after open CME than laparoscopic.

Several cohort studies [21, 23, 98-100, 102, 107, 114-116] without control groups have reported short-term outcomes after CME or extended LN excisions. The results vary, and in none of these are either the complications or their severity specified in a standardised manner, e.g. Clavien-Dindo score. Some are limited by no information on the preoperative co-morbidity, e.g. ASA score [23, 99, 100, 102, 107, 114-116], or by having a low proportion of patients with an ASA score 3-4 [21, 22, 98]. The latter limitation is especially related to Asian studies, and comparing results of short-term outcomes between Asian and European studies must be done with care. Many studies only report the outcome of right-sided [22, 114-116] or left-sided resections [102].

Patients included in a Finnish study [117] showed a similar high proportion with an ASA III-IV as the patients included in article IV, but they reported lower 30-day mortality and fewer severe complications (Clavien-Dindo score IIIb-IVb). Their material was selected by including only laparoscopic resections, and by reporting only complications within 30 days.

A recent meta-analysis emphasised this issue of low methodological quality in studies concerning short-term outcome after CME, which limits external validity [118]. Because of this, comparison of results from these studies with the findings of article IV is difficult, but according to a meta-analysis the short-term mortality after CME seems not to be higher than for non-CME [101].

The reduction of 30-day mortality from 2008-9 to 2012-2013, as shown in the supplementary analyses in article IV, might be related to a potential learning phase, but other factors might be present. The number of colorectal surgeons was reduced during 2008-9, and better selection of patients fit for resection and excluding unfit patients from surgery might also have reduced the mortality. The reduction in short-term mortality during the study period is in accordance with the general improved short-term survival observed in Denmark [11].

Although pulmonary complications are the most common non-surgical ones [12, 100], the frequencies for both the CME and the non-CME group in article IV are higher compared with these large single-centre studies. The increased risk of respiratory failure or need of vasopressors associated with CME has not been reported by others. These increased risks after CME have to be reduced even though the mortalities from these complications were similar for the CME and the non-CME group. In approximately half of the cases, they were caused by anastomotic leakage, and a reduction might be obtained by ensuring sufficient perfusion of the anastomoses. When dividing IMA for left-sided CME resections, it is essential to divide the large bowel in the upper rectum and not at the rectosigmoid junction. This might not only reduce the number of leakages, but also the number of cases needing reoperations for anastomotic leakage, which were significantly larger in the CME group.

Other reasons for these two severe non-surgical complications could be related to the higher proportion of patients with ASA score III, more open resections and more extensive bowel resection in the CME group. The open approach was, during the study period, standard for all tumours located in the distal part of the ascending colon, the transverse colon, the flexures, or proximal descending colon. These resections can be performed laparoscopically, and the frequency of these complications might be reduced. It has been shown that the short-term mortality and morbidity are less when compared with open CME [119].

There is no evidence supporting better oncological outcome after right sided subtotal colectomies for tumours in the left third of the transverse colon, the splenic flexure, or proximal descending colon, when compared with segmental resections with division of the left branch of the MCA and the LCA at their bases, but with D3 excision performed around the central parts of the MCA and the IMA. The latter might be associated with less short-term mortality and morbidity and should be investigated further.

In article IV, peroperatively recognised injury to the SMV, to the spleen and to other segments of the colon was reported significantly higher during CME. A higher risk of injury to the SMV during CME was expected [95] because it is completely exposed by the D3 dissection performed along it. The experience was that injuries to the SMV are easily managed with haemostatic patches. Injury to the spleen is related to mobilisation of the flexure, which is needed to ensure the length of the oral colon to the anastomosis in sigmoid CME resections. The patients in the CME group underwent surgery during an implementation phase, during which the skills of the surgeons improved, so one might expect that the risk of both these injuries would be reduced with increasing experience and use of laparoscopic resections.

Gastrocolic ligament resection

The finding of gastroepiploic or infrapyloric LN+ in 4% of the patients (article III) is in accordance with the findings of the other articles investigating this issue [27, 79, 95, 96]. A possibly improved oncological outcome after GCL resection has never been investigated, but the reported risk of GCLN+ in 3-17% of patients with tumours located within the colon from the distal part of the ascending colon to the proximal descending colon, indicates that GCL resection should be performed as standard in all curative-intended resections for these tumour locations.

Methodological considerations

The concept of CME and quality of colon cancer surgery has some unsolved issues regarding validation of surgery performed. There is no gold standard whether or not the resections have been performed as CME, i.e. CVL and removal of the complete mesocolon related to the tumour. Several parameters have been proposed and are mostly based on the assessment of the specimens by pathologists i.e. mesocolic resection plane, morphometric characteristics as LN yield, distance from tumour to vascular division (high tie), length of bowel and calculated area of excised mesocolon [41, 120]. The question is whether these parameters really are useable to validate the surgical procedure performed and to label it as CME.

Mesocolic excision plane

Assessment of the mesocolic plane by the pathologist is limited by the fact that only the specimen, and not the intraabdominal result, is assessed.

The pathologist can only assess the specimens for visible muscularis propria close to the tumour and for tears and defects in the mesocolon. The interobserver agreement has been investigated only within expert pathology environments [25]. The differences reported in the annual reports of the DCCG 2011-3 [7, 121, 122] emphasise the issue of possible interobserver disagreement, as some centres achieved 95% mesocolic plane according to the pathologists. It was stated that regional and national training programmes are needed to ensure acceptable interobserver agreement, but the mesocolic plane will remain a pseudo-parameter because the pathologist can only assess the specimen.

Performing mesocolic dissection and achieving the perfect specimen to present to the pathologist can be more difficult when performing central LN dissection than if the vessels are divided peripherally in the middle of the D2 segment. The specimen can be assessed as mesocolic resection plane, even if large parts of the mesocolon related to the tumour are not resected. Graspers used in laparoscopic resections, extraction of the colon though a too-small incision or handling large specimens in both open and laparoscopic colectomies can create tears and defects in the specimens. These injuries to the specimen can occur after the mesocolon is mobilised from the retroperitoneal fascia. The theoretical oncological impact of potential spillage of tumour cells have so far not been investigated, and a rejection of a null-hypothesis will probably be impossible because of a lack of study power. The assessment of the mesocolic resection plane contains both a surgeon and a pathologist factor, which currently reduce the validity of the mesocolic excision plane as a parameter to ensure that CME has been performed.

West et al [25] showed an association between mesocolic plane assessed by the pathologist and five-year overall survival after curative-intended resection without CVL for stage III colon cancer. If the specimen was assessed as mesocolic or intramesocolic the HRs for recurrence were 0.50 (95% CI 0.26-0.98, p=0.043) and 0.55 (95% CI 0.30-1.02, p= 0.059) respectively, when compared with muscularis propria plane. There was no difference for stage I-II tumours. The dissection around the tumour seems to be the most important issue in non-CVL resections, because no difference between mesocolic and intramesocolic resection plane was shown. Unfortunately, their multivariable analyses did not include microradicality. Resection plane was not included in the analyses for article V, because it was assessed in only 71% of the non-CME group and the validity was questionable as mentioned above. Microradicality, defined as 1 mm or less from tumour tissue to lateral resection margin at tumour site, was a significant factor of recurrence with an HR 3.74 (2.47-5.67, p<0.0001) for all patients in article V. The only other published study, investigating outcome associated with the mesocolic resection plane, reported, that five-year overall survival was higher for mesocolic plane (81.5%) than intramesocolic (72.2%) and muscularis propria plane (60%) [115].

Central lymph dissection

LN yield and number of LN+ detected contain the same issue of being related to both surgery and the pathological assessment. The surgical factor is related to the level of LN dissection (D1-D3) and contains an obvious risk of bias, making it difficult to compare studies or different groups. The pathology factor contains bias, because the resources and methods used to detect the LNs might differ between studies. Implementation of methods like ex-vivo methylene blue injection in the arteries increases LN yield and even seems to upstage early cancers [123]. The number of LN+ detected might be biased by the methods used. A single slice of haematoxylin-eosin staining is commonly used, but multiple slices outside the midline of the LN have been able to upstage pN0 in 32% of the patients, when including isolated tumours cells < 0.2 mm as pN+ [124]. The number of micrometastases increases with the use of immunohistochemistry and molecular methods [124-127]. Upstaging of stage I and II tumours has been shown to occur in 16% and 30% respectively with a total of 25% when the molecular method known as one-step nucleic acid amplification is used [128].

MR can be used to assess the completeness of the mesorectal resection after TME [129]. CT has been proposed as a method to investigate if CVL has been performed by assessing the length of the remaining part of the tumour-bearing arteries [130]. The arteries can be visualised years after surgery, but CT angiography does not assess if the central LNs are excised, so high tie remains a pseudo-parameter of CVL.

A valid gold standard is needed for assessing if CME is performed and just relying on the LN yield and resection plane assessed by the pathologist seems not to be adequate. A possible method might be blinded assessment of photographs of the retroperitoneal fascia, the tumour bed, and LN dissection including CVL. These can easily be supplemented by videos in case of laparoscopic resection. A validated assessment by pathologist can be added to ensure that CME has actually been performed according to the principles described by Hohenberger [12].

Randomised control trials

Conducting an RCT would be preferable, as it would make causal inference possible without the dependency of the observed, or the balance of both observed and unobserved parameters [93], but RCTs seem very difficult to perform. It would be impossible to define non-CME or “conventional” surgery for the control group, as in articles IV and V, where the control groups were considered to be a sample of the non-CME surgery performed in Denmark.

A randomisation between dissections in different planes will be impossible, as dissection in the muscularis plane would be associated with a great risk of non-radical resection. Similarly non-CME defined as D1 excision would be associated with a risk of not including LN+ in 8-50% of the cases [1]. An RCT between D2 and D3 resections defined by anatomical landmarks might be a possibility, but contain risk of bias, because trained CME-surgeons might unconsciously tend to perform more extensive resections in the non-CME group. A design with randomisation of referral to either a CME or non-CME centres would also contain bias. The non-CME surgeon would be aware of the study, and it would contain a risk of misclassification because non-CME surgeons might perform more central ligation within the prospective study design. This design would also be biased when comparing the short-term outcome, because the surgeon and postoperative care variables would not be randomised. Both variables might be an important risk factor for the short-term outcome, and the results might not be representative of the general population.

CONCLUSION

The primary finding of an association between improved disease-free survival and CME, when compared with conventional colon cancer surgery, shows that improved and more extended LN excision benefits the oncological outcome for colon cancer patients. The evidence from other studies supporting this finding contains some limitations in methodology including the issue of validation of CME surgery with parameters assessed by pathologist and not on standardised surgical parameters.

The risk of central mesocolic LN+ is reported to be 1-22% for right sided cancers and up to 12% in sigmoid cancers, with the risk associated with advanced T-stage. The higher disease-free survival after CME for stage III can be partly explained by the frequencies of central mesocolic LN+, but the difference between CME and non-CME was only 6% and lower than for stage I and II. The finding of gastroepiploic or infrapyloric LN+ in 4% of the patients supports the CME principle, although there is currently no evidence of better oncological outcome from this.

The distance from tumour to vessel ligation increased with the implementation of CME. The mesocolic resection plane was high even before implementation and did not improve.

Short-term outcome did not worsen during implementation, and short-term mortality was reduced, although not significantly, during the study period. CME was not associated with significantly increase risk of short-term mortality or surgical complications, but attention should be drawn to the findings of the higher risk of respiratory failure and need for vasopressors after CME. Although the risk of dying from non-surgical complications after CME was not increased, these complications must be reduced in Hillerød and when implementing CME at other centres. The increased use of laparoscopic resections and segmental CME resections for tumours in or close to the splenic flexure, instead of subtotal colectomies, might decrease the risk of these severe non-surgical complications. The preoperative morbidity measured as ASA score was the most important risk factor of short-term mortality, and the reduction during the study period in the CME group, and in Denmark in general, might be related to better selection of patients fit for colon cancer resection no matter if this is performed as CME or not.

PERSPECTIVE AND FUTURE STUDIES

Long-term and short-term outcomes

The impact of CME on the overall survival has to be investigated further as the follow-up of our population increases. This will make it possible to show, if the increased risk of recurrence in the non-CME group has impact on the overall mortality, as the potential effect of surgical treatment of recurrences and palliative chemotherapy expires.

As the risk of 30-day and 90-day mortality after CME in Hillerød has been reduced to a level comparable to other Danish and foreign centres [131], the main issue of further investigations is the association between the postoperative need for vasopressors and respiratory failure and CME observed in Hillerød. These increased risks were not reported by Hohenberger et al [12] and might be related to the patient factors, the surgeon, postoperative care or unknown causes. They might be reduced by changing the approach and extent of the resections without compromising the central LN dissection.

Laparoscopic surgery

A larger proportion of the patients in the CME group in article IV underwent open resections than in the non-CME group. This was mainly caused by the decision of the colorectal team to perform all extended right hemicolectomies and right-sided subtotal colectomies openly. These resections can be performed laparoscopically [77, 132]. Similarly, segmental resection of the transverse colon and the splenic flexure was often performed instead of right-sided subtotal colectomy in the non-CME group. These segmental resections can be performed with D3 dissection around MCA and IMA, where the IMA is spared by dividing the LCA at its origin [21, 133]. A larger proportion of laparoscopic resections and segmental resections with D3 resection might reduce the complications after CME for tumours in the transverse colon and in the flexures.

T1-2 tumours - Colorectal cancer screening

The finding in article V of better outcome in stage I tumours is important in the perspective of the national colorectal cancer screening programme which has been implemented in Denmark since 2014. It is expected to result in downstaging of the population with more pT1-2 tumours. Further studies are warranted to investigate the improved outcome of CME for these early cancers. The population of this thesis might add important information when the follow-up time of all the 455 patients with pT1-2 tumours in article IV is more than three years in 2017.

Functional outcome

The functional outcome after colon cancer surgery is important for the quality of life. Beside the long-term consequences of perioperative complications, bowel, urinary and sexual function can potentially be impaired by colorectal surgery, and even the improved oncological outcome might potentially be outweighed by an impaired quality of life.

Bowel dysfunction

The impact on both short- and long-term bowel function from colon cancer surgery, and CME especially, is unknown. CME might increase the length of stay from increased time to bowel function, gastroparesis, and other complications. As there are differences in the ERAS programmes between the centres in article IV e.g. use of epidural after laparoscopic resection, length of stay has not been compared. Impact of CME on length of stay seems to be of less importance from the patients' point of view than that of the administrations, especially with the already short length of stay in the centres in the Capital Region in mind [2, 82].

There might be potential increased risk of gastroparesis in the perioperative period after CME with GCL resection compared with operations without GCL resection. Gastroparesis might be associated with a risk of aspiration pneumonia. A study based on prospectively recorded data from Hillerød will be carried out during 2017.

The long-term bowel function might be impaired by malabsorption related to the length and site of resected bowel, and to injury to autonomic nerves. As the inferior mesenteric nerve plexus may be partly spared in conventional left sided resections, there might be a potentially better outcome in bowel function compared with CME. Similarly for right sided resection, the risk of injury to the superior mesenteric plexus might increase the risk of neurogenic diarrhoea. Impaired bowel function after right sided resection might also be caused by decreased bile acid absorption, as the distal part of the ileum is resected. This causes chronic diarrhoea from increased water secretion and motility in the colon [134]. These issues are going to be addressed in a nationwide questionnaire study, which will include more than 20,000 patients treated for colorectal cancer in Denmark from 2001-2014. Data from that study will be supplemented with data from article IV, and further clinical examinations of patients with impaired bowel function is planned.

Urinary and sexual dysfunction

There is a potential risk of urinary and sexual dysfunction after left sided colon resection, as the autonomic nerves might be injured. This has been reported after sigmoid and upper rectum cancer resection in male patients [135], but these patients underwent extramesocolic LN dissection (D4) which included paraaortic LN dissection from the level of the third portion of the duodenum and around the left renal vein to and along the common iliac artery and vein. This LN dissection is more extensive than performed during CME, as both the nerve plexus surrounding the aorta and the superior hypogastric nerve plexus were excised. The population-based questionnaire study after colorectal cancer surgery in Denmark mentioned above include data on urinary and sexual function, and subgroup analyses of the CME and non-CME groups from article IV will be performed during 2017. These studies might answer the question of a potentially increased risk of dysfunction associated with D3 dissection.

SUMMARY

Surgery is the most important factor for radical treatment of colon cancer, and the long-term prognosis can be improved by improving the surgical treatment without increased risk of perioperative mortality. Complete Mesocolic Excision (CME), in which more extensive lymph node (LN) dissection is performed, has been shown in single-centre studies with historical controls to be associated with better oncological outcome. However, better evidence is needed.

The main purpose of this Ph.D. thesis was to investigate whether CME could be implemented in a colorectal surgical department in Denmark, whether more extensive dissection could demonstrate LN metastases outside the mesocolon, and to demonstrate a possible association between CME and improved oncological results without increased risk of perioperative mortality.

This thesis includes five articles. Two articles (IV and V) are based on the population of patients undergoing elective resection for colon cancer in the Capital Region from June 2008 to December 2013. Two articles (II and III) are based on data from the local colon database in Hillerød, and the last article (I) is a systematic review concerning the risk of metastases from colon cancer to the central LNs in the mesocolon.

Article I found a risk of metastases in central LNs to be reported in 1-22% of the cases of right-sided colon cancers, and in up to 12% of the cases with sigmoid tumours. The populations included and methods used in the studies were very heterogeneous and no definitive conclusions can be drawn.

It was shown in article II that the surgical quality, i.e. quality of the specimens assessed by the pathologists, improved with implementation of CME in Hillerød. The vascular tie was higher, and the implementation was not associated with an increased risk of perioperative mortality.

Article III demonstrated a risk of LN metastases in the gastrocolic ligament along the stomach for tumours located in the transverse colon, in the ascending or descending colon close to or in the flexures. It occurred in 4% of all patients and 13% of the patients with LN metastases in mesocolon. Resection of these LNs seems advisable for these tumour locations.

Article IV showed no association between increased perioperative mortality and CME (n=529) when compared with non-CME (n=1,701). The 30-day mortality was 4.2% after CME compared with 3.7% after non-CME (p=0.605), and the 90-day mortalities were 6.2% and 4.9% (p=0.219) respectively. Odds ratios for 30-day and 90-day mortalities after CME were respectively 1.07 (95% confidence interval: 0.62-1.80) and 1.25 (0.77-1.94) in the multivariable logistic regression analyses. Postoperative respiratory failure and need for vasopressors were significantly more frequent in the CME group and, besides CME itself, could be associated with the fewer laparoscopic resections and more severe preoperative comorbidity in the CME Group.

Article V demonstrated an association between higher four-year disease-free survival for stage I-III tumours and CME (n=364) when compared with non-CME (n=1,031). Most notable was the difference for stage I and II cancers. The four-year disease-free survival for stage I was 100% in the CME group compared with 89.8% (83.1 to 96.6) in the non-CME group (p = 0.046). For stage II the disease-free survivals were 91.9% (87.2 to 96.6%) in the CME group and 77.9% (71.6 to 84.1%) in the non-CME group (p = 0.0033), and for stage III 73.5% (63.6 to 83.5) and 67.5% (61.8 to 73.2) (p = 0.13) respectively. In the multivariable Cox regression models, CME was a significant predictive factor for higher disease-free four-year survival for stage I-III patients with hazard ratios (HR) for CME of 0.59 (0.42 to 0.83, p = 0.0025). For stage II the HR was 0.44 (0.23 to 0.86, p = 0.018) and for stage III 0.64 (0.42 to 1.00, p = 0.048).

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