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The introduction and implementation of right colectomy with extended D3 mesenterectomy anterior and posterior to the mesenteric vessels

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Abbreviations

BVS – Bojan V. Stimec
3D – three-dimensional
2D – two-dimensional
cm – centimetre
CME – complete mesocolic excision
CVL – central vascular ligation
CT – computer tomography
FDA – Food and Drug Administration, USA
FTP – File Transfer Protocol
GTH – gastrocolic trunk of Henle
ICA – ileocolic artery
ICV – ileocolic vein
IV – intravenous
JJA – jejunal artery
JJV – jejunal vein
JMN – Jens Marius Nesgaard
JSCCR - Japanese Research Society for Cancer of the Colon and Rectum
LN – lymph node(s)
LtM – lateral to medial approach
MCA – middle colic artery
MDCT – multidetector computer tomography
MtL – medial to lateral approach
OS – overall survival
RCA – right colic artery
RCT – randomised controlled trial
RD3APM – right colectomy with extended D3 mesenterectomy anterior and posterior to the mesenteric vessels
SMA – superior mesenteric artery
SMV – superior mesenteric vein
TC – coeliac trunk
TME – total mesorectal excision
TNM staging system – a cancer staging system created and updated by Union for International Cancer Control and American Joint Committee on Cancer

List of papers

1

Nesgaard, J.M., Stimec, B.V., Soulie, P., Edwin, B., Bakka, A.O. and Ignjatovic, D. (2018). Defining minimal clearances for adequate lymphatic resection relevant to right colectomy for cancer: a post-mortem study. Surg Endosc., Sep;32(9):3806-3812.

2

Nesgaard, J.M., Stimec, B.V., Bakka, A.O., Edwin, B. and Ignjatovic, D. (2015). Navigating the mesentery: a comparative pre- and per-operative visualization of the vascular anatomy. Colorectal Dis., 17(9):810-818.

3

Nesgaard, J.M., Stimec, B.V., Bakka, A.O., Edwin, B. and Ignjatovic, D. (2016), Navigating the mesentery: Part II. Vascular abnormalities and a review of the literature. Colorectal Dis., 19(7):656-666.

4

Gaupset, R., Nesgaard, J.M., Kazaryan, A.M., Stimec, B.V., Edwin, B. and Ignjatovic, D. (2018). Introducing Anatomically Correct CT-Guided Laparoscopic Right Colectomy with D3 Anterior Posterior Extended Mesenterectomy: Initial Experience and Technical Pitfalls. J Laparoendosc Adv Surg Tech A. 2018 Oct;28(10):1174-1182

5

Nesgaard, J.M., Stimec B.V., Bakka A.O., Edwin, B., Bergamaschi, R., Ignjatovic, D. (2019). Right colectomy with extended D3 mesenterectomy: anterior and posterior to the mesenteric vessels. Surg Technol Int. 2019 Jun 25;35

6

Nesgaard, J.M., Stimec, B.V., Bakka, A.O., Edwin, B. and Ignjatovic, D. (2019). Vascular stumps and operative images for the evaluation of lymphadenectomy after Right Colectomy with Extended D3 Mesenterectomy anterior and posterior to the Mesenteric Vessels. European Surgery 2019 July 1-8

Thesis at a glance

Paper	Questions/Aims	Methods	Results	Conclusion
1	What are the minimal clearances for adequate lymphatic resection in right colectomy for cancer?	Central mesenteric lymph vessels, nodes, and blood vessels were dissected in 16 cadavers.	The cranial-caudal clearances were: 6.3±2.7 mm cranial to MCA, 5.7±1.9 mm caudal to ICA. Long lymphatic vessels approaching SMA crossing SMV anteriorly and posteriorly.	Cranial–caudal clearances determine the tissue to be resected superior/ inferior to colic artery origins. Long lymphatic vessels traverse the SMV on both sides approaching the SMA, placing the medial clearance on the left side of the SMA.
2	Are 3D reconstructions of abdominal CTs reliable? To register and classify normal vascular variations in the mesentery using 3D reconstructions.	Preoperative 3D reconstructions from 139 patients were compared to photos taken during RD3APM for cancer.	3D reconstructions have high specificity, sensitivity, accuracy and reliability when compared to findings during surgery. Vascular variations central in the mesentery were registered.	3D reconstruction can be used as a roadmap for surgery. Classification of relationship between SMA and SMV with branches was done.
3	Define, classify, and demonstrate the trajectories and to assess the clinical value of arterial and venous abnormalities in the central mesentery.	3D reconstructed abdominal CT scans from 340 patients were investigated for vascular abnormalities.	Arterial abnormalities were found in 28 (8%) and venous in 35(10%). The abnormalities were registered and classified.	Mesenteric vascular abnormalities are not rare. They can offer both benefits and inconveniences during surgery.
4	Is laparoscopic RD3APM for cancer feasible?	18 patients underwent laparoscopic	Median operative time was 276 min and blood	Laparoscopic RD3APM is feasible,

		RD3APM with the aid of 3D reconstructed abdominal CT scan	loss 200ml. 7 (39%) converted and 2 reoperations Median 40 harvested LN Median hospital stay was 5 days	associated with acceptable morbidity and fast recovery
5	To present open RD3APM with short term results	176 patients were operated using 3D reconstructed CT of the blood vessels in the mesentery as a road map.	Mean operating time was 200 min, blood loss 273 ml and length of stay 7.9 days. 15 reoperations and 9 anastomotic leakages. One vascular injury. Mean harvested LNs 40.9 comprising 13.8 LNs in the D3 volume.	This surgical procedure is feasible and safe. In this, all lymphatic tissue below LN station 214 (N4) is resected.
6	What is the extent and quality of lymphadenectomy after RD3APM?	Residual vascular stumps were measured, and the quality of central lymphadenectomy evaluated using 3D reconstructed vascular anatomy from follow up CT dataset and images taken during surgery in 31 patients.	Median vascular stump lengths measured on 3D reconstructed CT and images taken at surgery were: RCA: 0.0/ 0.0mm, ICA: 0. 0 /0.0mm, ICV: 0.0/ 0.0mm, MCA: 0.0/ 1.0mm and right branch of MCA: 0.0/0.0 mm. Extent of lymphadenectomy was judged acceptable in all patients.	Very short residual vascular stumps and acceptable lymphadenectomy signify superior lymphadenectomy in RD3APM.

Introduction

Cancer of colon and rectum, largely adenocarcinomas, is one of the most frequent cancers worldwide with an age-adjusted incidence of 24.4 /100 000. In 2012, there were 1.36 million new cases causing 694.000 estimated deaths. In Norway, colorectal cancer is the second most frequent cancer in women following breast cancer and the third most frequent cancer in men after lung and prostate cancer (1). In 2017 there were 3007 new cases of colon cancer in Norway, and this constitutes 9% of all the cancers in the country (1). The incidence has been increasing in the last 50 years, and this is expected to continue, more in Norway than in the other European countries. The incidence increases with age, the youngest being less than 20 years of age, but with the majority arising from 50-60 years and above.

Cancer on the right side of the colon constitutes 44% of all colon cancers (2) and it has poorer OS after treatment when compared to left-sided colon cancer (3).

Adenocarcinoma of colon develops in the mucosal layer of the bowel and may be disseminated through the bloodstream, the lymphatic system, intraperitoneally, or grow into a neighbouring organ.

Colon cancers are classified according to the TNM (4) and to the Dukes` staging system (5). T describes the depth of the primary tumour growth into the colonic wall (T1-T3) or beyond (T4). N points at regional lymph node status: N0 indicating no LN metastasis, N1 less than three LNs with metastases, and N2 more than three. M refers to distant metastasis, M0 indicating no metastasis and M1 the presence of metastasis.

When analysing the TNM classification, Stage I (T1-2, N0, M0) corresponds to Dukes A, Stage IIA (T3, N0, M0) and IIB (T4, N0, M0) correspond to Dukes B and Stage IIIA (T1-2, N1, M0), Stage IIIB (T3-4, N1, M0) and Stage IIIC (Tany, N2, M0) correspond to Dukes C. Stage IV (Tany, Nany, M1) is equal to Dukes D.

The relative five-year survival rates for colon cancer in Norway 2013-2017 for males/females are (1): for Stage I and II: 94.5% / 97.4%, Stage III: 81.6% / 83.0%, and Stage IV: 13.8% / 17.3%.

The Mesentery

The interface between colon and the rest of the body is the intersection between the mesentery and bowel characterized as a true intestinal hilum where blood vessels, lymphatic vessels, and nerves enter or leave the bowel (6). The mesentery is contiguous and spans from the duodenum to the rectum. Within the mesentery, blood and lymphatic vessels run together within a connective tissue lattice. Just below the peritoneal surface of the mesentery, there is a submesothelial monolayer of lymphatic vessels on the anterior (upper or peritoneal) surface of mesocolon measuring 10µm in diameter and typically located within 100 µm of the mesothelial surface (7). Besides the blood vessels, nerves, as well as lymphatic- and connective tissue, there is adipose tissue, which constitutes most of the mesentery volume. The lymphatic vessels and LNs are mostly localized along the arteries (8, 9).

Toldt`s and Fredet`s fasciae

The colon and its mesocolon, actually the whole gastrointestinal tract with mesentery distal to the duodenojejunal flexure, is an extraretroperitonel organ (6). The small bowel and the transverse and sigmoid colon are mobile, whereas the right and left colon with mesocolon is flattened against the posterior abdominal wall (6). Toldt`s fascia between the parietal and visceral peritoneal surfaces (from the early foetal period) of colon/ mesocolon and retroperitoneum consists of collagen tissue mainly holding together the two surfaces (7). Fredet`s fascia is collagen tissue between visceral peritoneum that covers of the duodenum and pancreas, and the ascending mesocolon (10). These fasciae play an essential role in CME, and other surgical procedures, as will be shown shortly.

Lymphatic tissue

Central dissemination of cancer in the lymphatic tissue

In 1906 Dr Jamison and Mr Dobson (11) were the first to report metastases to central lymph nodes surrounding the superior mesenteric vessels in colon cancer. They also disclosed that the “lymphatic glands” of the large bowel were scattered along the course of the blood vessels in groups not sharply defined from each other. The groups were named epicolic, paracolic, intermediate, and main groups. The epicolic LNs were positioned close to the intestinal wall and were characterized as numerous, small, and unimportant. The paracolic LNs were located near the vascular arcade along the gut. The intermediate LNs were situated approximately half-way between the arcades and the origins of the colic vessels. The main group LNs surrounded the stems of the colic vessels near their origin.

In 1977 the JSCCR published the first issue of “General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus” (12) containing the classification and a description of the LN distribution. The groups of LN had identical names and anatomical positions as described in Jamison and Dobson`s article. The JSCCR gave the LN groups an N number, which today is the conventional way to address the different LN groups: the epiploic and paracolic group being N1, the intermediate group N2 and the main group N3 (*Figs.1-3*). The corresponding LN group resections in surgery for colon cancer were initially named R1 to R3, later changed to level of dissection (D1 to D3). The position of the main group of LNs (N3) is described to be at the root of the corresponding colic artery (ICA, RCA, or MCA). The JSCCR has defined the main nodes for cecum, ascending and transverse colon as 203, 213 and 223 respectively, but it is stated in their publications (12), that the anatomical main group for the right colon is the superior mesenteric nodes at the root of the SMA (214).

Fig. 3 demonstrates that the areas for the main LNs (coded 203,213,223 after the JSCCR) cover most of the anterior aspect of SMA from caudal to the ICA origin to cranial to the MCA origin. One could get the impression that the N3 area constitutes more than just the LNs around the origin of the colic artery. In Sondenaa et al`s article (13) it is written: “According to European CME and Japanese guidelines the lymph nodes around the root of the feeding artery should be dissected away and removed *en bloc* with the specimen but there is a danger of damage to splanchnic nerves if the surgeon strips the root of the artery”. Because of the danger of injuring the splanchnic nerves, they advise to ligate 1 cm away from the origin of the artery. In the same

article (13) a Japanese investigation not published internationally is referred claiming that on the right side, the lymphatic drainage stops in front of SMV. Therefore, it is unnecessary to divide the artery behind the vein and the dissection is accomplished anterior to and along, the axis of the SMV. In other words, there is no agreement of the level of division of the colon arteries in D3 and CVL let alone defining a D3 area or volume (14). When dissecting posterior to the right colon mesentery in Toldt`s fascia lateral to medial, there is no anatomical border, so the dissection could continue unhindered behind SMV, SMA and the small bowel mesentery. The medial border of the mesentery needs to be established, but so far, there is no definition (15).
There has been little emphasis on the lymphatic tissue distribution around the mesenteric vessels (SMA and SMV). One cadaver study has shown LNs both anterior and posterior to the above-mentioned vessels (16). These findings coincide with JSCCR descriptions referred previously concerning the anterior aspect of SMA.
In a clinical study by Benz et al. (17), the number of LNs found along the central 4 cm of ICA/ICV amounted to 35% of the total number of LNs removed with right hemicolectomy with CME and CVL. In other words, there is abundant lymphatic tissue placed centrally in the mesentery.

Dissemination of cancer in the lymphatic system

The lymphatic flow needs to be continuous from the colon wall to the thoracic duct which drains into the venous system. The lymphatic spread of cancer (18) follows the lymphatic flow. Cancer cells can be implanted in LNs, producing LN metastasis but can also pass through LNs (18). Several studies have shown that cancer can bypass one or two N levels, e.g., bypass N1- and N2- level and implant directly to N3 LN. These are called skip metastases (19, 20). The LN stations (N1-3) are clusters of LNs, and there is basically no difference from one level of clusters to the next except for the distance from the cancer. The spread of cancer along the lymphatic system is probably not in any strict, orderly fashion moving from N1 to N2 and so on, but rather in a more stochastic manner (21), although more LN metastases occur in the lower LN stations than in the higher (22).

Longitudinal dissemination of cancer in the lymphatic tissue

According to Toyotas study (23) the rates of metastases to the epicolic and paracolic LNs in right colon cancer are 0.3 % 10 cm or more from the primary tumour in the proximal direction, and 0.9% in the distal direction. According to JSCCR (12), the LN stations along the right colon are classified as follows: LNs within 5 cm of the primary tumour being N1 level, and 5-10cm from the primary tumour being N2 level and more than 10 cm being N3 level. Due to this knowledge, many surgeons, especially in Asia, do resect only 10 cm of colon distal to the tumour. Term ileum is the proximal resection line in right hemicolectomy.

Other routes of lymphatic spread

In cancers of the right flexure and transverse colon, metastasis to the infra pyloric LN was found in 4% and to LN along the gastroepiploic arcade in 3% of the cases (23, 24).

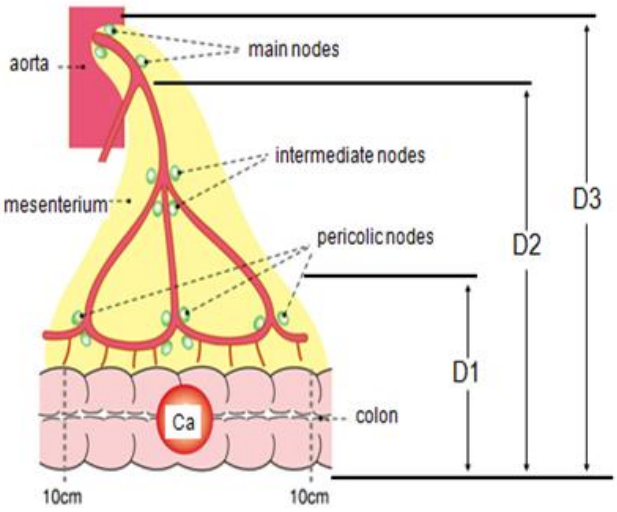

Figure 1:
Levels of dissection in colorectal cancer with D3 resection.
Ca – Cancer.

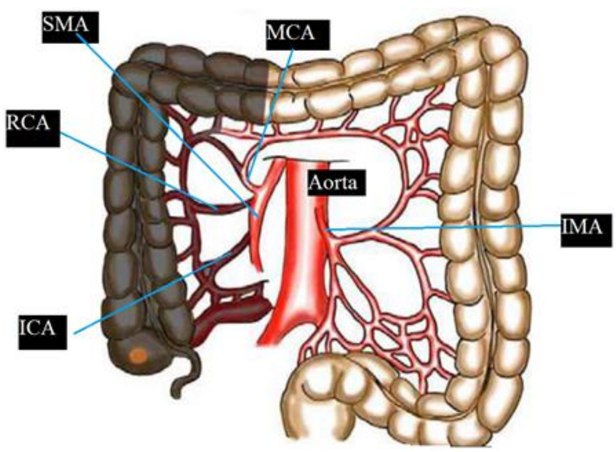

Figure 2:

A segment of the colon with blood vessels removed during D3 right colectomy. ICA: ileocolic artery, RCA: right colic artery, SMA: superior mesenteric artery, MCA: middle colic artery, IMA: inferior mesenteric artery

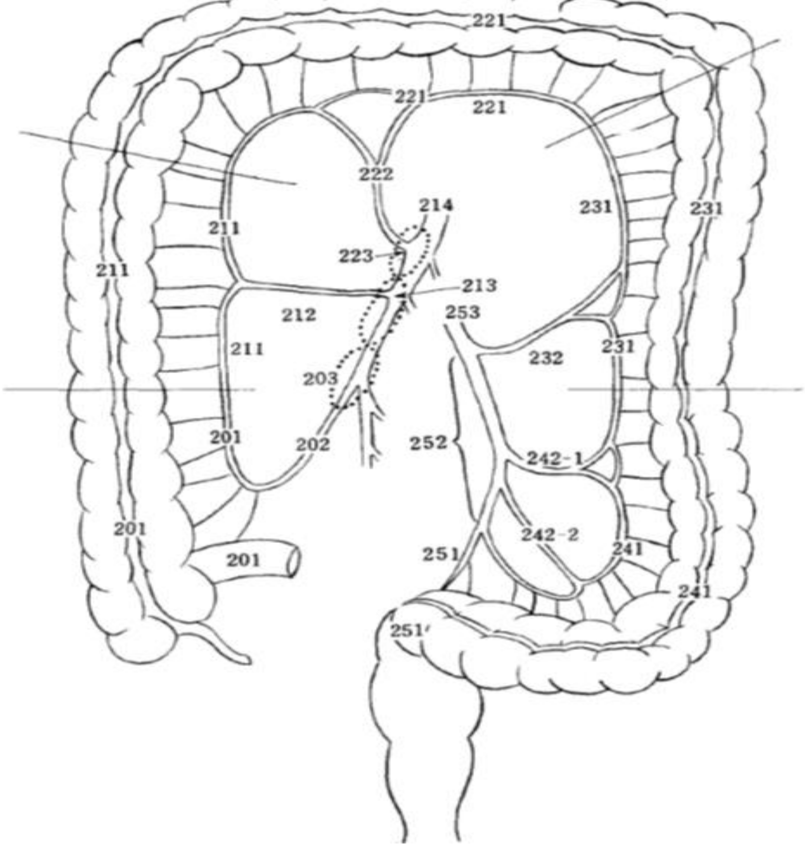

Figure 3:

Coding of LNs of the large bowel according to the JSCCRs definitions.
Copy from JSCCRs General rules (12)

Does removal of lymphatic tissue improve the survival rates?

Nobody disputes the possible spread of colon cancer through the lymphatic system or that the findings of LN metastasis worsen the prognosis of the disease. On the other hand, there are disagreements about the effect of removing these LNs. In most countries, colorectal surgeons remove lymphatic tissue believing that just this will improve the prognosis in the patients. Several studies have shown that the more LNs removed the better the prognosis (25-28). Another argument for LN removal is staging. The more LNs removed, the higher is the probability of correct staging. Adjuvant chemotherapy is given to patients with LN metastasis (stage III disease) in many countries. Evidence is provided in the literature that adjuvant therapy increases five years of survival with 7-8 % in stage III colon cancer (29). There are reports (30) that the removal of LN metastasis does not influence the disease outcomes, while others think that leaving LNs metastasis in situ will lead to a recurrence of cancer (31). Patients with LN metastases to N3 LNs have better prognosis after resection of the affected LNs than intuitively expected. This is shown in in the following three studies with hemicolectomies with D3 resections. Toyota et al. (23) presented that out of six patients with metastasis to N3 LNs, two patients survived longer than ten years and one patient longer than two years without recurrence (still alive when the article was published). Kotake et al. (32) presented a 5-year disease-free survival of 36.4% and in Liang et al. (33) 48.0% in patients with N3 LN metastasis. The prognosis in patients with LN metastasis is generally more dependent on the number of affected LNs (No, N1, N2 (TMN)) than the position of the affected LNs (N1-N3 (JSCCR)) (21). There have been several studies investigating sentinel nodes in colorectal cancer, and the results have been disappointing compared to findings in malignant melanoma and breast cancer. Poor concordance between LN metastases and sentinel node was found, and sentinel node mapping judged to be of little clinical value in colorectal cancer (34, 35).

Surgical issues

The distant spread of colon cancer is mainly through the blood or lymph. As far as we know, surgery is the only form of therapy that can provide a permanent cure for colon cancer. Both the extent of resection and surgical technique are of uttermost importance. Removing enough tissue, operating in the embryonic planes, not harming the mesocolic envelope, and handling the tumour with care to reduce dissemination into the circulation, are all essential factors. More than 50 years ago, Turnbull initiated the no-touch technique with ligation of the feeding artery and draining vein before the manipulation of the tumour, with good results in a non-randomized study (36). Later Slanetz (37) preformed ligature of the bowel in addition to the non-touch technique with excellent results. The concept was supported through animal studies (38), but later a randomized prospective trial (39) comparing no-touch with conventional surgery for colon cancer was not able to confirm the good results of earlier studies. Results after five years follow-up indicated a tendency towards a reduction in the number of liver metastases in the no-touch group (p=0.14), but overall survival did not differ significantly between the two groups even though results were in slight favour of the non-touch technique in every analysis.

The nomenclature of the surgical procedures for colon cancer (colectomy, hemicolectomy, etc.) is misleading. During a surgical operation for colon cancer, most of the time is spent disengaging the mesentery, which often is the most challenging part of the operation.

Possible lymphadenectomies for right-sided colon cancer are D1 to D3 resections. D1 resection is not accepted in surgical treatment with curative intent. D2 is the standard resection in most centres. D3 and more advanced forms of D2 resections are slowly getting more acceptance.

Jamison`s and Dobson`s description of operation for right-sided colon cancer from 1906 contains the following: ”stripping downwards the fatty tissue surrounding the vessels which contain the uppermost glands of the ileocolic chain and dividing the ICA and ICV close to the SMA” (11) indicating removal of the N3 LNs. After that, it seems that D2 resections have been the most used technique of lymphadenectomy in right-sided colon cancer surgery. The critical anatomical region for surgeons attempting D3 right colectomy lies in the root of the small bowel mesentery, where the SMV and SMA lie well hidden in the fatty tissue together with their variable branches. It seems that these complex anatomical relations are the crucial factors that govern the practice of vascular division on the right side of the SMV, resulting in D2 resections. In right hemicolectomy with D2 resection, the posterior dissection plane is usually along Toldt`s fascia. The mesentery with the colic arteries is divided to the right of SMV, and the procedure can be done either laparoscopically (40, 41) or as an open operation. Using the JSCCR definitions, there are some surgical procedures where the lymphadenectomy is somewhere between D2 and D3. In these techniques, the root of the mesentery to the right colon is divided anterior to SMV, not excising the D3 LNs but still removing more lymphatic tissue than with standard D2 resections. This is the case in Toyota`s article (23) where the following was expressed in the discussion: "Although the Japanese Rules define the main nodes as those situated at the roots of the ICA, RCA, and MCA, it is actually routine to dissect nodes situated anterior to the surgical trunk (42), i.e., the SMV between Henle's gastrocolic trunk and the ICV running along the right side of the SMA".

Right hemicolectomy with extended lymphadenectomies

In the last decades, the number of papers published on right hemicolectomy with D3 resections or CME has steadily increased. In the Far East, the extended lymphadenectomy is mostly called D3 resection. The comparable western surgical procedure is called CME with CVL. There are some differences, but they are becoming smaller. Hardly any of the publications of the various surgical procedures state the limits of the resection area/volume of the central mesentery, but they mostly refer to the level of ligation of colonic arteries (ICA, RCA, MCA) or use the JSCCRs definitions.

D3

Different surgical procedures with D3 resection are described as MtL, LtM, open or laparoscopic (43-46) (*Table 1*). Recently a new surgical procedure was published with beyond D3 LN dissection with a caudal to cranial approach (47). Most often, the dissection planes in relation to Toldt`s fascia are not stated in D3 resections, but some state that they do, e.g. D3 with CME (33, 48).

CME

The open surgical concept for CME described by Hohenberger (49) is the sharp dissection in Toldt`s fascia resulting in the complete mobilization of the mesocolon with an intact peritoneal surface, central ligation of the supplying artery and the extent of the surgical procedure determined by the location of the cancer. In addition, LNs along the greater curvature of the stomach are removed in tumours in the hepatic flexure and transverse colon. Hohenberger`s approach includes the Kocher manoeuvre for better control and visualization of proximal parts of SMA and SMV.

In laparoscopic CME (50-52), a different surgical technique (compared with the open Hohenberger`s) is employed using the SMV as a surgical landmark. In contrast to the open method the colic vessels are divided with CVL before dissecting in Toldt`s fascia MtL and mobilizing mesocolon, respecting the mesocolic envelope. No Kocher manoeuvre is performed.

The uncinated process first (53) is another laparoscopic CME approach. The dissection commences at the fourth part of the duodenum with MtL approach mobilizing the mesenteric root before getting access to the central parts of mesenteric vessels.

Robotic modified CME with CVL (54) has also been done upholding CME principles and with comparable results.

It is unlikely and not documented that the pioneers Jamison and Dobson (11) and Toyota (23), were dissecting in Toldt`s fascia, keeping the mesocolic envelope unharmed when performing extended lymphadenectomy for right-sided colon cancer. Nowadays, one gets the impression that most surgeons try to do a proper dissection in Toldt`s fascia. A comparison (55) using the resected specimen to judge the quality of the resections, showed very good results for both east and west with high mesocolic plane resection rates and long distances between the high tie and the bowel wall. There was shorter bowel resection in the eastern specimens as expected and in accordance with JSCCR rules (12).

Points of interest:

-A definition of the volume of lymphatic tissue with borders, that ought to be resected through a proper D3 lymphadenectomy is missing.

-All extended lymphadenectomies are surgically challenging and potentially dangerous operations, probably explaining the difference in frequency of D3 resections between right- and left-sided colon cancers.

-None of the above mentioned surgical procedures for extended lymphadenectomy for right-sided colon cancer has removed all N3 LNs as defined by JSCCR nor the LNs behind the mesenteric vessels (16).

-Outcome studies for D3 resections/CME are suboptimal and very few have examined the compliance with the surgical procedures in the central mesentery.

Aims of study/purpose

The main aim of this dissertation is to report on aspects of the introduction and implementation of right colectomy with D3 extended mesenterectomy anterior and posterior to the mesenteric vessels for cancer (RD3APM) and to evaluate the results of the operation, through the following specific aims:

-Define minimal clearances for adequate lymphatic resection relevant to anatomically correct D3 right colectomy for cancer.

-Does the 3D reconstructed vascular anatomy from CT scans provide reliable information about the relationship between SMA and SMV and their main branches in the central mesentery?

- Can the crossing pattern ICA predict the crossing pattern for JJV?

-Classify the vessel crossing pattern in the central mesentery important to surgery.

-Define, classify, demonstrate the trajectories, and assess the clinical value of arterial and venous abnormalities in the central mesentery.

-Establish, prove feasibility, and provide short-term outcomes data in 3D reconstructed CT guided open and laparoscopic anatomically correct RD3APM.

-Assess the impact of the open surgical procedure RD3APM on vessel stump lengths and the completeness of the lymphadenectomy.

Material and methods

The order of the papers presented is not chronological but is influenced by didactic objectives.

Material

In *paper 1*, an anatomical dissection study performed on cadavers is presented while *papers 2-6* present clinical research.

Sixteen fresh frozen bodies in the Anatomy Sector, Department of Cellular Physiology and Metabolism, Faculty of Medicine, University of Geneva, Geneva, Switzerland, were dissected. The bodies were donations based on anatomical gift statements, including informed consent, given during the lifetime of the donors. Under Swiss federal law (Human Research Act 810.30), no Institutional Review Board approval was mandatory, given the fact that the data were anonymous.

All the patients in the research presented in *papers 2- 6* were included in the trial "Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography (MDCT) Angiography" (http://clinicaltrials.gov/ct2/show/NCT01351714). They were treated in the following Norwegian hospitals: Akershus University Hospital, Lørenskog; The Vestfold Hospital Trust, Tønsberg; and Haukeland University Hospital, Bergen (only *paper 2*). Some of the patients were included in more than one study for this dissertation. The clinical data were registered in a prospectively maintained study database. All patients were required to sign an informed consent form at inclusion. The clinical study has been approved by the Regional Ethical Committee, South-East Norway no. 2010/3354.

Methods

The anatomical dissection study

A detailed macro- and microdissection of the central mesentery was carried out by JMN and BVS in the 16 specimens at the University of Geneva, Switzerland. The bodies were fresh frozen (-20 °C). After thawing the specimens consisting of the pylorus, duodenum, pancreas, proximal jejunum, cecum, ascending colon, and the transverse colon, together with their corresponding mesenteries were harvested *en bloc.* The specimens were immersed in 4% buffered formaldehyde for fixation after rinsing the bowel with running water. The borders of the dissected volume in the cadavers were 2 cm cranial to the origin of the MCA, the left side of the SMA, at least 3 cm right to the right side of the SMV, caudally 2 cm distal to the origin of the ICA, posteriorly along Toldt`s fascia and anteriorly at the peritoneal surface. These limits were chosen in order to include the complete N3 (12) volume with good margins. At each step of the dissection, photographs were taken. With the aid of a fluorescent ring light magnifying glass, forceps with curved sharp edges, micro-dissecting scissors, and small clamps, the minute dissection was started first removing the peritoneum over the central part of the mesentery. The fatty tissue was scraped off, leaving blood vessels, lymph vessels, and LNs behind. The SMA and SMV and their branches were identified and dissected free, representing anatomical landmarks for the overall arrangement of the lymph nodes and vessels. The extent of lymph vessels in the lympho-vascular bundles was measured with a digital Vernier electronic calliper (S-Cal Work 150 mm; Sylvac, Crissier, Switzerland) cranial and caudal to the origin of MCA, RCA, and ICA.

For further identification of lymphatic vessels, random samples of tissue from the dissected specimens underwent hematoxylin-eosin staining (H&E) and were examined in a light microscope to look for the presence of the perivascular lymphatic vessels, which were indirectly identified as thin-walled vessels with the presence of valvules. To confirm the identification of lymphatic vessels, immunohistochemical staining that specifically stain lymphatic endothelial cells (56) (Human LYVE-1 Antibody (R&D Systems, AF2089-SP) and Monoclonal Mouse Anti-Human Podoplanin Clone D2-40 (Dako, Aglient Technologies, Santa Clara, CA, USA) with the Ventana

Discovery automated staining system (Ventana Medical Systems, Tucson, AZ, USA)) was used.

3D reconstruction of abdominal CT scans and perioperative photos

The reconstructions were produced from the staging abdominal CT scan done prior to the operation. The patients in *paper 6*, in addition to the staging CT, had additional 3D reconstructions from an oncological follow-up CT. These CT scans were standard workup before the operation and standard follow-up in accordance with the Norwegian guidelines (57). Our studies did not generate any extra CT scans for the patients.

The CT datasets from the hospitals were sent via the FTP server to the study-coordinating centre at the Faculty of Medicine, University of Geneva, where the 3D reconstruction was accomplished, and the anatomy analysed. In Geneva, the CT datasets were partly manually recreated (BVS) using 2D multiplanar reconstruction with maximum intensity projection and a 3D volume rendering technique using Osirix v. 3.9 64-bit image processing application (58); FDA approved. The root of the mesentery and the adjacent structures were precisely depicted by means of the region of interest (ROI), repulsor tool, and/or 3D growing region. The curved structures were identified in the appropriate oblique planes through the 3D-curved multiplanar reconstruction and measured with the aid of open polygon tool. The identification, calibre, and course of the vascular structures within the root of the mesentery were analysed in accordance with the postulates for CT angiography of mesenteric vessels (59). In cases of ambiguous or indistinct findings by Osirix, the datasets were additionally analysed by manual segmentation, using the medical image processing software Mimics® ver. 14.12 for Intel X86, Platform V14.1.2.8, Materialise n.v., Leuven, Belgium, including the thresholding, dynamic region growing, 3D LiveWire, and the Boolean operation tools. The 3D object masks for superior mesenteric arteries and veins were achieved after minute single and multiple slice editing with interpolation.

The reconstructions and descriptions were returned to the hospitals with email as video clips with a 180 degrees rotation in vertical and horizontal planes, images, and written reports. The following information was in the report:

-Distances measured between origins of blood vessels in the reconstructions: ICV-GTH (measured at the right border of SMV), the intercolic artery distance (ICA-RCA-MCA measured at the anterior border of SMA).

-Distance from the origin to the first division of MCA.
-Crossing lengths anterior or posterior to SMV for MCA, RCA, and ICA.
-Calibres of MCA, RCA, ICA, all JJAs and JJVs.
-Description of trajectories and the internal relationship of and between MCA, RCA, MCA, SMV, JJAs, and JJVs.
-The cranial-caudal relationship between the origins of MCA and GTH.
-Distance between the origins of MCA and GTH in the cranial-caudal direction.

Photos were taken of the D3 area during RD3APM. Colic vessels` presence and internal relationships were recorded in the photos and in the 3D reconstructions. Agreement between the two techniques was investigated. The internal relationships in question were: ICA, RCA, and MCA to SMV, and JV and JA to SMA. The normal variations in the crossing patterns between ICA and SMV, and between JVs and SMA were mapped out in the same population. These crossing patterns were classified into four groups, with two subgroups (*paper 2*). Three-D reconstructions were used to map out and classify venous and arterial abnormalities central in the mesentery (*paper 3*). The same technique was used to find and measure the length of residual vascular stumps after right colectomy with D3 resection together with measurements of vascular stumps on photos taken during surgery (JMN). To measure the lengths of the vascular stumps on the photos, ImageJ (version 1.51j8, National Institute of Health, USA) was used. ImageJ was calibrated using a ruler placed in the operating field. On the same photos, the quality and the extent of the mesenterectomies were evaluated in conformity with our own criteria (*paper 6*).

Surgical procedure

The surgical procedures were done by JMN and surgeons at the other cooperating hospitals. Both open and laparoscopic approaches entail the same intra-abdominal procedure with dissection central in the mesentery with devascularisation first. The D3 volume is as described in *paper 2* supported by the cadaver study (*paper 1*). The detailed borders of the D3 volume are set in one of the following chapters "Discussion of main findings". Using these borders, all the tissue in front and behind SMV and SMA was resected, removing virtually all lymphatic tissue below the N4 level (LN station 214 in the JSCCR classification *Fig. 3*). In these techniques, we respect the mesenteric envelope, avoiding injury to the anterior and posterior peritoneal coverings.

Statistics

Descriptive statistics for continuous data were presented by median (range) and mean (±SD). Spearman`s correlation coefficient and logistic regression were used to assess the significant correlation between categorical- and continuous data in *paper 1*. Cohen kappa coefficient was used to show the level of agreement between two observations for binary variables in article 2. In *paper 6*, the Shapiro-Wilk test was used to investigate whether the measured values had a normal distribution or not. Wilcoxon Signed Rank Test was used as a nonparametric test comparing measurements of the same vascular stumps with two different methods. All analysis was done using the Statistical Package for Social Sciences (SPSS ver.20).

Results/summary of papers

In the cadaver study, tracing the lymph vessels draining the right colon, the borders for the tissue needed to be resected in RD3APM were attained. The "watershed" between lymphatics draining the right colon and the small bowel was mostly situated in front of SMA (in 14 of 16 cadavers, in front of SMV in 2 of 16). In accordance with these findings, the medial border ought to be along the left side of SMA. By measuring the width of lymphatic tissue in the lympho-vascular bundle of the colic arteries (ICA, MCA), the cranial border was set to be 1 cm above the origin of MCA and caudal border 1 cm below the root of ICA. Long lymphatic vessels were found traversing both anterior and posterior to the SMV and continuing in front of SMA. Preoperative 3D reconstruction from abdominal CT of the vascular anatomy central in the mesentery of the right colon was found to have high specificity and sensitivity as well as high accuracy and reliability when compared to the anatomy found at surgery, making the 3D reconstructions reliable "roadmaps" for surgical procedures in the central mesentery.

Registration of different crossing patterns between ICA and SMV, and JV and SMA using the anatomy found in the 3D reconstructions showed no regularity that could be of any benefit to the surgeon preparing surgery in the central mesentery of the right colon. In other words, we were unable to predict the crossing pattern between JVs and SMA if ICA relation to SMV (crossing SMV anteriorly or posteriorly) was known.

The registration of different crossing patterns (ICA in relation to SMV and JV in relation to SMA) resulted in a classification with four main groups and two subgroups (*paper 2*). Patients in one of these groups may *a priori* be more or less demanding to operate than patients in other groups. This issue was also investigated by comparing lengths of vascular stumps after the operation of patients in varying groups with different crossing patterns (*paper 6*). There was no difference in vascular stump lengths or the extent of mesenterectomy, but these subgroups were too small to allow a definitive conclusion.

We found arterial abnormalities in 28 (8%) and venous abnormalities in 35 (10%) of 340 investigated patients using 3D reconstructed abdominal CTs demonstrating that vascular abnormalities are not uncommon. The investigations led to a classification of the different abnormalities taking into account the potential harm or benefit these abnormalities could cause during surgery. Analysing the different groups in the arterial classification only abnormalities constituting shunts between or within the vascular territories of TC and SMA, had caused unexpected bleeding during RD3APM. This group consisted of 11 (3%) patients. Venous abnormalities caused no unfavourable events during operations in our patients. Once the abnormalities were identified in 3D reconstructions, they were quite manageable during surgery.

Surgical procedures

A new surgical procedure RD3APM, is described with open and laparoscopic approach with borders for the D3 volume like earlier defined. The laparoscopic procedure is described in a step by step fashion with elucidation of technical pitfalls. The first 18 patients were investigated, and the approach was found to be feasible, although seven (39%) of the operations had to be converted to open procedures, and two of the patients had to be re-operated. These results were from all the intended laparoscopic operations from the very first and onwards and consequently included the learning curve. The median LN harvest was 40, and the median hospital stay was five days.

Our study started with the first open surgical procedure in 2011, some years in advance of the first laparoscopic operation, which was in 2013. In the 176 patients with the open procedure, the mean operating time was 200 minutes, blood loss 273 ml, and length of stay 7.9 days. There were 15 reoperations and nine anastomotic leaks. One patient required a more extensive small bowel resection due to a slipped ligature at the ICA origin requiring repair of the SMA. The total number of harvested lymph nodes was mean 40.9 per specimen. The mean lymph node numbers were 27.1 in the D1-2 and 13.8 in

D3 volume, respectively. The open surgical procedure is feasible and with good short-term results.

***Evaluation of the surgical procedure*.**

The surgical procedure was evaluated measuring the lengths of vascular stumps on 3D reconstructions and on photographs taken at surgery, and the lymphadenectomy reviewed on the same photos in 31patients operated with open RD3APM. The lengths of the vascular stumps of ICA, ICV, RCA, MCA, and right branch of MCA were measured. The residual vascular stumps were very short, less than 10 mm on average. The lymphadenectomies were evaluated to be sufficient in all the patients relative to our own criteria in the photos. The criteria were: both SMA and SMV should be skeletonized from the level 1cm distal of the stumps of the ICA and ICV to 1 cm cranial to the origin of MCA with a medial border along the left side of SMA. The photo documentation and finding of very short residual vascular stumps on 3D reconstructed CT provided objective evidence of sufficient lymphadenectomy. There was no significant difference between average stump lengths measured on 3D reconstructed abdominal CTs and photographs taken at surgery.

Discussion of main findings

Based on the results presented in our cadaver study, we defined the minimal clearances required for adequate lymphatic resection in the treatment of right sided colon cancer (RD3APM). As described earlier, we have traced lymph vessels draining the right colon to the central mesentery. Lymph vessels stretch from the periphery, either as an integral part of the lymphovascular bundles or as separate long lymphatic vessels on their way to SMA. These findings, with the exception of the long lymphatic vessels, are consistent with the anatomical positions of lymph vessels and LNs in Atlas of lymphography (60). The JSCCR general rules do neither describe nor depict lymph vessels (12), but the distribution of N3 LN stations (203,213,223) almost exclusively covers the front of the SMA on their illustration *Fig.3*.

In a previous cadaver study in our group, LNs were found both anterior and posterior to SMV and SMA. It was stated in the abstract that the LNs posterior to the superior mesenteric vessels did not necessarily have any clinical relevance (16). The function of these LNs is still not clear. With the findings in *paper 1*, we can speculate that the long lymphatic vessels crossing posterior to SMV are connected to the LN posterior to the SMA and SMV. In that respect, might these LNs have a clinical relevance in being able to receive metastatic cancer cells. These LNs may also drain the small bowel lymph as well as the LN in front of SMA and SMV. Lymph vessels from the right colon and small bowel seem to converge in common LNs in front of SMA or SMV linked together with lymph vessels in what is characterized as the watershed in *paper 1*. This row of LNs along the anterior side of SMA or SMV seems to continue cranially both in our study and other studies (23, 60).

In the first definition of the D3 area in our group, the colic and mesenteric blood vessels were used as landmarks (61). These definitions did partly rest on anatomical findings of LNs anterior and posterior to the mesenteric vessels (16). After experience from a number of operations with RD3APM, the caudal border was expanded with 5mm (*paper 2*).   The findings in *paper 1* supported the caudal borders from *paper 2* and in addition, lead to an increment in the cranial border to 1 cm. The width of the measured lymphatic tissue surrounding the origin of ICA caudally and MCA cranially were 5.7 ± 1.9 mm and 6.3 ± 2.7 mm respectively. Taking into account the shrinkage of the tissues under the influence of formalin and the fact that these borders were going to be applied in surgery, 1 cm was found to be a suitable length. The median border from earlier definition concurred with the finding of the watershed in front of SMA in 14 of 16 cadavers. The lymphatic tissue at the watershed possibly draining both the right colon and the small bowel can be regarded as the most medial part of the lymphatic tissue draining the right colon. With the medial border of the D3 volume on the left side of SMA, all of the lymphatic tissue at the watershed will be resected.

The right side of SMV has been used as the medial border in right hemicolectomy with D2 resection (40). In the study where the residual vascular stumps were measured after right colectomy with D2 resection (62), the medial resection line of the mesentery was found to be approximately 1 cm lateral to SMV. We decided to use the same border for our lateral border of the D3 area.

To be more precise, a tissue volume rather than an area will better characterize what needs to be removed with RD3APM.

The D3 volume will have the following borders:

Medial: a line running along the left side of SMA.

Cranial: a line running 1 cm cranial to the line between the origins of MCA and GTH

Caudal: a line running 1 cm caudal to the line between the origins of ICA and ICV

Lateral: a line running 1 cm lateral to the right side of SMV

Posterior: Toldt`s and Fredet`s fascia

Anterior: peritoneum of the mesentery

This is probably one of the first definitions of the D3 volume. So far, the descriptions of extended lymphadenectomy in right-sided hemicolectomy have related to the level of division of colic vessels (ICA, RCA, MCA, or right branch of MCA), e.g., in D3 resection, the N3 LNs at the origin of the colic vessels are resected. Others have defined an area like Strey et al. (63) who in an endeavour of standardization right hemicolectomy with CME, used target criteria of CME for oncologic radicality to define what ought to be resected during surgery. Their target criteria of CME for oncologic radicality were:
(a) Preservation of visceral fascia without injuring the mesocolon.
(b) Complete removal of the regional lymphatic vessels and lymph nodes.
(c) Division of the supplying arteries close to their origin (ileocolic artery (ICA), right colic artery, right branch of the middle colic artery).
(d) Complete removal of the lymphatic tissue along the right side of the superior mesenteric vein (SMV) from approximately 3 cm distal to the ileocolic vein (ICV).

Their target criteria were extracted from a review of unspecified literature, contrasted to our definitions, which now are founded on anatomical findings in cadaver studies.

With the borders defining the D3 volume, the weight of lymphatic resection will crucially be placed on the mesenteric tissue and not on the level of vessel division. A high tie can be accomplished without resecting the lymphatic tissue around the artery, especially if the area is approached from the lateral side. A clamp can easily be slid along the artery achieving a high tie but leaving D3 LNs in the patient.

The finding of the long lymphatic vessels traversing independently between the lymphovascular bundles, crossing SMV both anteriorly and posteriorly, has as far as we know, not been described earlier. The long lymphatic vessels had very few connections to the LNs, and cancer cells could, in theory, travel a fairly long distance before being exposed to a LN i.e. crossing more than one N station. These vessels could be an anatomical prerequisite for skip LN metastases. One could speculate that the long lymphatic lymph vessels may be an explanation of the stochastic spread of LN metastasis to different N stations experienced in colorectal cancer. The same mechanism could also be the reason for the lack of success with sentinel node biopsies (35). Malignant cells may travel with the flow in the long lymphatic vessels to a higher N level while the indicator for sentinel node might end up in nearby LNs.

3D CT reconstruction

Had arterial and venous branching patterns within the root of the mesentery been more predictable, surgery in this area would have been easier. This lack of regularity makes the preoperative 3D reconstruction important as an aid to surgery in an area with variable and challenging anatomy. The 3D reconstructed abdominal CTs function as a roadmap for surgery, showing clearly the mesenteric blood vessels, the colic arteries and veins with their internal relations, and allow accurate length measurements. In our and others experience, using the 3D reconstructions as a surgical roadmap facilitates the surgery in the central mesentery while making it safer. Shorter operating times and fewer vascular complications were found in a study using 3D reconstructed abdominal CT in one group compared to another group without any roadmap (64).

Anatomists have conducted cadaver studies on anatomical variations of vasculature over the last several hundred years (65, 66), and some of these studies have been observations during surgery (67). After the onset of extended lymphadenectomy for right-sided colon cancer, a renewed interest has appeared (68), and the importance of knowing the incidence and variations of the vascular anatomy centrally in the mesentery pointed out. In our study (*paper 2*) 3D reconstructed abdominal CT was used to examine the anatomical variations of blood vessels in the central mesentery. There was no relationship between the crossing pattern of ICA with SMV and of JV with SMA, and the crossing pattern of ICA could not be used to predict the crossing pattern of the

JV. However, just the knowledge of different anatomical variations may be of great help during surgery in many surgeon's opinions (65). Different types of crossing patterns depending on the relations between the ICA and the SMV, as well as those between the JV and the SMA were classified, resulting in four main groups and two subgroups. Patients from different groups were compared regarding operating times, vascular events, etc. (69). *A priori*, the complexity of surgery would probably vary due to the different types of vascular crossings. In this study, no difference in blood loss and LN yield between patients within the different groups was found. These results are indicative of a smoothening effect of the road map emphasizing the use of reconstructed CTs as a guide in all these operations.

In our study, the RCA originating directly from SMA was found in 17 (12%) of 139 patients at surgery. Our number is small compared to 32% in a study of 600 specimens (70). According to Haywood et al. (71), RCA can be a branch of MCA, ICA or SMA. In their study, 25 cadavers were dissected: RCA originated from the right branch of MCA in 9, the root of MCA in 3, the ICA in 3 or the SMA in 8 of the cadavers. The RCA was absent in two specimens. The RCA nourish the ascending colon and the lymph tissue draining the same area would go along RCA wherever the RCA originates. In the case of RCA originating from the root of MCA central ligation of the MCA should be the considered.

In our *paper 2* study, there were multiple MCAs in 10 (7.2%) of the patients; triple in one and double in nine patients. All the extra MCA originated cranial to the origin of the main MCA, and they all supplied the left side of the transverse colon. In extended right hemicolectomy with central ligation of MCA, the extra MCA/MCAs will supply the remaining part of the transverse colon.

Vascular abnormalities

In our studies, we found a high frequency of vascular abnormalities: 8,2% arterial and 10,3% venous. In a search for other studies, based on dissections and radiological investigations, about the same high level of occurrence of arterial abnormalities were found (66, 72-78). On the other hand, not all the arterial variations we had defined in our study were reported by the authors of the other studies. The results of this comparison should therefore be interpreted with caution. Many of these abnormalities were not clinically relevant to extended lymphadenectomy, but arterial shunts in the D3 volume and most of the venous abnormalities were. During surgery, we have had unexpected bleedings from injured arterial shunts. The shunts can bleed significantly, having a calibre of approximately 2 mm (ICA has a calibre of approx. 3.5 mm measured in the same way). If one is not aware of the shunt, the bleeding is unanticipated and comes from an unexpected angle. Our shunt bleedings presented themselves before we were fully aware of these abnormalities. If the reconstructed CTs are investigated carefully, these shunts are detectable before the operation. A bifid SMV is the most frequent venous abnormality found and is most often an advantage rather than a problem. If one of the SMVs in a bifid SMV has to be sacrificed due to, as examples, invading cancer or injury, the remaining SMV will have the capacity for the necessary drainage, avoiding stasis in the small bowel.

Surgery

Several studies have shown favourable oncological outcomes after operations for colon cancer with extended lymphadenectomy (D3, CME, CVL) compared to conventional surgery (D2- resection) (32, 49-51, 79-81). However, many of these studies have been criticized for suboptimal design being mostly retrospective. So far, no RCT has been published (82, 83). In a Danish study (79), even patients with stage I and II cancer (no LN metastasis with the ordinary pathological investigation) benefited from CME. At first glance, these results would be hard to explain, if the LN examination was thorough and correct. On the other hand, this phenomenon could be accounted for if there were micro-metastasis in LNs. Micro-metastasis are generally not discovered during standard pathological examination.

Faerden et al. (84) showed that in patients with colon cancer and no LN metastasis found by standard pathological examination, but still had micro-metastasis or isolated tumour cells in LN detected by complementary examinations, gained 5-year disease-free survival of 75%. The 5-year relative survival for Stage III cancer was 69%. The real "Stage I-II," *i.e.*, no micro-metastasis or isolated tumour cells in LNs, had a 93% 5- years disease-free survival. Many studies (25-28) have shown that the more LN removed the better oncological outcome. In summary, an explanation could be that LNs with micro-metastasis were removed with an extensive lymphadenectomy taking away cancer cells that otherwise would have been left behind in the body with a less extensive removal of LNs.

There are several surgical procedures for right colectomy with extended lymphadenectomy (43-53, 85, 86), as already described in the introduction. Their extent of lymphatic resection differs. In some of these procedures, the colic arteries (ICA and RCA) and the mesentery are divided at a level anterior to SMV, while in others, at the level of origin of the colic arteries. In almost all D3 surgical procedures, lymph tissue anterior to SMV is removed. Some divide the colon only 10 cm from the tumour in both directions while others do a formal right or extended right colectomy.

The novelty with our surgical procedure both open and laparoscopic is that all the lymphatic tissue both in front and behind SMV and SMA is resected. The resection is tailored for the individual patient by resecting the D3 volume with borders specified by the patient's anatomy, e.g. the cranial border: a line running 1 cm cranial to the line between the origins of MCA and GTH (*see above for borders of the D3 volume*). As far as we know, there is no other centres doing lymphadenectomy to the same extent. Practically all the lymphatic tissue draining the right colon caudal LN station 214 (*Fig. 3*) is removed.

From our operations (*paper 4 and 5*), the number of LN extracted were median 40 in the laparoscopic patients and mean 40.1 in the open operated patients. One would expect that our patients had the highest number of resected LNs since our D3 volume is larger than in right hemicolectomy with D3 resection or CME. It turns out to be a higher total number of resected LNs in Lee`s patients (43) (*Table 1*). However, in their study, nine of 44 patients had cancer in hepatic flexure or proximal transverse colon, leading to extended right hemicolectomy where the greater omental attachments were dissected from the gastric edge. This extra dissection, which we have not done in our patients with extended hemicolectomy, would add to the number of resected LNs and could explain the difference. In Petz study (87) (*Table 1*), it is nearly the same number of resected LNs as in ours. In their article, they describe resection of the tissue in front of SMA and SMV comparable to our technique, explaining the similarity in numbers of LNs. The rest of the extended lymphadenectomies in *Table 1* shows a lower number of resected LNs than in our material, as expected. However, the number of extracted LNs might be a debatable parameter for deeming the extent of lymphadenectomy. Omitting the surgeon's contribution, the most important factor affecting the LN count is probably the pathologist`s experience and interest. Besides, other factors like age and sex of the patient, primary tumour size and location, immunological status, etc. (88) will also affect the number of LNs.
The median number of LNs in the D3 volume was 11.5 (range 4-35) in the laparoscopic operated patients and mean 13.8 (SD 16.9) in the open operated patients in our studies. These numbers are comparable with Wu`s figures (89) (*Table 1*) although the D3 area in that study seems to be smaller than defined in our study. In their surgical technique documented with photos and morphometric measurements, all tissue in front of SMV with a medial border along the right side of SMA, was removed. According to the description, their D3 volume is missing the posterior flap and having a smaller anterior flap

compared to the D3 volume defined earlier in the dissertation. Liang (33) and Han (46) (*Table 1*) have both a lower number of LNs in the D3 area compared to Wu (89), even though they seem to have the same surgical procedure. It is peculiar that Liang (33) has such a low number of D3 LNs in spite of a high number of total LNs: 34.4. One could suspect that their lateral, superior, and inferior borders could vary. Their medial border seems to be the principal LNs as defined by JSCCR. As it turns out, none of the authors has defined the D3 area/volume in their articles, and a difference in the size of the D3volume would, of course, explain the differences in the number of LNs.

Evaluation of lymphadenectomy

When introducing a new surgical procedure, short-term outcomes are usually reported. It is also important to evaluate the accomplishment of the procedure itself to ascertain satisfactory implementation and to control that the participating surgical teams perform as planned. In *paper 6*, we have evaluated 31 patients from two hospitals after RD3APM. Our results were sufficient with short vascular stumps (< 10 mm) and acceptable lymphadenectomy.

In a Danish study (90) evaluating right hemicolectomy with CME, using CT scans taken two days after the operation for the measurement of the vascular stump of ICA, long vascular stumps not consistent with proper CME with CVL were revealed. The average ICA stump length was 31mm and should have been less than 10 mm as recommended in the CME guidelines. This stump length was longer than the mean stump length of 28 mm found in an earlier study in our group (62), where the patients had had standard right hemicolectomy (D2).

When comparing colonic resection for cancer with extended lymphadenectomy with a hitherto standard procedure, it is of uttermost importance, with respect to oncologic outcomes, to know if the quality and extent of the lymphadenectomy is adequate. There must be no doubt about the compliance with the surgical procedure in such studies. In future research, an evaluation of the procedure as described above, should be mandatory.

Methodological considerations

In the methodological considerations of the lymph vessels dissections in *paper 1* there was a challenge with the distinction between lymph vessels and fine nerves, connective tissue, and small blood vessels in the central mesentery of the right colon. To overcome this challenge, a minute dissection technique with special attention to differentiate between these structures using course, consistency, and relation to the lymph nodes to discriminate. There was no dye injection, and this technique is also used by others (91, 92). To fortify the findings of lymph vessels, random samples of tissue from dissected specimens underwent hematoxylin-eosin staining (H&E) and light microscopy to confirm the presence of the perivascular lymphatic vessels. Immunohistochemical staining (Human LYVE-1 Antibody and Monoclonal Mouse Anti-Human Podoplanin for lymphatic endothelial cells) were also used to verify the identification of lymphatic vessels.

It would have been of great interest to find the trajectories of the lymph vessels not only anterior to SMA but also posterior. The rationale for removing the posterior flap is the finding of LNs posterior to SMA (16). In the present study, lymph vessels crossing posterior to SMV were found, but the dissection sadly did not continue behind SMA. As far as we know, the lymph vessel trajectories posterior to SMA have not been investigated.

3D Reconstruction

The clinical accuracy of MDCT is proven beyond doubt in most fields, including angiographies of abdominal blood vessels. Traditional 2D CT images of blood vessels have been challenging to interpret for surgeons and physicians. It is difficult to imagine the trajectories and internal relationships of the mesenteric vessels and their branches. The radiologists, on the other hand, have developed the geometrical skills and the visual capacity needed to build 3D mental models of the anatomy from sequences of 2D images (93). With these features in mind and the desire to do anatomical studies on blood vessels central in the mesentery with MDCT, we have used post-processing tools on CT datasets to create 3D images and videos. When image processing programs are used to process CT data to yield 3D image (i.e., volume rendering programs), there is a possibility of systematic errors. In addition, random errors should be considered when measurements are made by human observers (94).

We have tested the accuracy of the 3D reconstructions. FDA approved Osirix MD v. 9.0.2 64-bit image processing application (Pixmeo, Bernex, Switzerland) was used via its 2D multiplanar reconstruction (MPR) with maximum intensity projection (MIP) and a 3D volume rendering technique (58). For blood vessels with larger calibre (ICA, MCA, and JV), there was no disagreement between the 3D reconstructed image and measurements on photos taken during the surgery in our study even when 5 mm MDCT slices were used for reconstruction.

In experimental studies using pig knees (94), a difference between exact measurements on the pig and the 3D reconstructed CT using OsiriX software was mean 0.1 mm (maximum 0.3 mm) in high-quality MDCT. In another study comparing three software programs (Osirix, CTTRY, and Advantage Workstation Volume Share 4) for 3D graphics imaging compared to operative findings during lung resection (95), all the software programs produced 3D images that facilitated the understanding of vascular supply. The 3D images of blood vessels at the subsegmental level (blood vessels less than 1.5 mm in diameter) in lung resections lacked accuracy when compared with operative findings. When validating 3D-reconstructed computed tomography images using OsiriX software for pre-transcatheter aortic valve implantation, aortic annulus sizing (96) measurements were accurate and reproducible. Compared to 2D CT, the mean difference was 0.4 ± 2.2 mm.

The CT dataset was analysed by manual segmentation using Mimics Medical® image processing software in cases of indistinct or ambiguous findings by Osirix. Studies have shown that linear measurements with Mimics

Medical® compared to direct measurements on foam pelvises (97) or human dry skulls (98) are accurate, valid, and reliable.

In our study, the vertical relationship between the MCA origin and the GTH termination level differed on 3D reconstructed preoperative CT and at photos taken during surgery. The 3D reconstructions of the blood vessels in the mesentery can be positioned in a uniform orientation, making consistent and reliable measurements of the vertical relationship between MCA and GTH. Even though we intended to take the photos at 90 degrees angle to the operating field and mesenteric vessels, it was difficult to accomplish. That could explain some of the differences. The GTH confluences and MCA origins were situated in the cranial part of the operating fields in most cases. When taking the photos, the middle part of the wound was focused, leading to slightly distorted images concerning the vertical relationships.

There were also some other discrepancies between findings at CT and surgery. For the RCA there were three false negative and one false positive on 3D reconstructions in 139 patients. All the false negatives for RCA were found in reconstructed images from 3 mm slice CTs. Of the preoperative MDCTs, 48% had 1mm, 47% had 3 mm, and 5% had 5 mm slices. Other explanations for the false negative and positive findings were poorly filled arteries and our experience that blood vessels were hard to find and track in areas with little surrounding fat and in near location to other blood vessels. This anatomical consideration was more pertinent to RCA than ICA. RCA had an average calibre of 3,5 (SD 0.6) mm and ICA 3.6 (SD 0.6) mm (62), so the size of the vessel did not explain the difference of detection of the two vessels. The ICA was found in all the reconstructions, including the ones with poor resolution (3- and 5- mm slices).

The most time-consuming part of making 3D reconstructions from CT scans is the manual segmentation that takes two to three hours per patient. There exists a variety of segmentation techniques, which can be categorised as fully automated segmentation, semi-automated segmentation and manual segmentation. Manual segmentation is used in all the 3D reconstructions used in our studies, and it would be tempting to use fully automated or semi-automated segmentation to save the doctor`s time. Some in our group have studied the anatomical completeness of models produced by semi-automatic and manual segmentation (99). They concluded that 3D reconstruction generated from semi-automated segmentation could cause considerable confusion at surgery. For the time being, there is no alternative to manual segmentation.

Surgical procedures

In our open and laparoscopic surgical techniques (*paper 4 and 5*) , the approach to the mesentery and its content is safe, incising the peritoneum and mesentery from outside the D3-volume caudally, medially, and cranially. In that way, the anterior flap of the mesentery covering the SMA and SMV is dissected from the blood vessels with a minimal division of lymph vessels draining the right colon. After raising the anterior flap, the colic arteries and veins can be divided at their origin inside the vascular sheath again, keeping the division of lymph vessels to a minimum and thereby reducing the likelihood of spillage of lymphatic fluid possibly containing cancer cells. With RD3APM with the help of a roadmap, it is easier to find and divide the colic vessels at their origin compared to other techniques. With SMA not visible and few anatomical landmarks, it is difficult to do CVL. Prevot et al. (100) found a low correlation between intraoperative estimation done by the surgeon and CT findings of the level division of inferior mesenteric artery in 60% of the patients operated for sigmoid cancer. 70% of these surgeons overestimated their division, thinking their ligature was higher up than it really was. The long arterial stumps found after CME with CVL in the Danish study (101) could also be due to difficult navigation with missing landmarks. The identification of the vessel origin seems to be necessary for the correct judgment of the level of vessel ligation, as well as a complete lymphadenectomy.

One of the major objections to central vascular ligation in D3 resection for right-sided colon cancer is the risk of accidental injury of mesenteric vessels (102). One patient in our material had serious bleeding from ICA after a ligature slipped. Freund et al. (103) have found a frequency of 1,6% of serious injuries to SMV in right side colectomies with CME and CVL. To our best knowledge, there is no documentation of arterial lesions during right hemicolectomy in the literature. These injuries are rare, and they are seldom reported.

There has been concern about the consequences of injuring the sympathetic nerves surrounding SMA during dissection inside the vascular sheath in RD3APM. Thorsen et al. (104) showed no significant difference in bowel function or Gastrointestinal Quality of Life Index six months after this operation except not significant tendency of increased bowel-movement frequency.

Evaluation of lymphadenectomy (*paper 6*)

Measurements of vascular stumps in photos taken at surgery were done using ImageJ software (version 1.51j8, National Institute of Health, USA). ImageJ is a reliable method for measuring distances at images (105). On the other hand, there could be some inaccuracy in the measurements due to the inability to take the photos in 90 degrees angle to all the measured objects due to the size of the photographed area. Furthermore, the depth of the wound would imply that some of the measured vascular stumps were situated at a different level of depth compared to the level of the ruler used for the calibration of ImageJ. Depending on this relation, the measurements would be too long or too short compared to the real distance. These erroneous measured values would be quite small since the size and depth of the surgical wound needed for these operations is moderate, and the minute inexactness will not alter the results with short vascular stumps of ICA smaller than 10 mm.

The photos taken during surgery were also used to evaluate the extent of lymphadenectomy applying the criteria stated in *paper 6*. The same method is used in a large Japanese multicentre study (106), including 1057 patients, to control the quality of D3 resections. This is a robust method. It is easy to detect tissue that should have been resected, in front of the mesenteric vessels.

The general accuracy of 3D reconstructed CT measurements was as described above, but in measuring the vascular stumps, there were specific challenges. Finding vascular stumps could be difficult. They could be small and hardly visible. After removing connective tissue, fat, and lymphatic tissue during operation, the blood vessels could take a new position. The 3D reconstructions, both from before and after surgery were used to find the spot coinciding with the vascular stump. The distance from divisions/origins of vessels and relations to other blood vessels like JAs facilitated the identification of the vessel stumps.

Further on, the 3D reconstructions could be rotated in all directions making the measurements of the lengths of the stumps very accurate. Thrombosis of vascular stumps could have been a source of inaccuracy. In a Danish study (101) measuring vascular stumps after CME using the two-dimensional multi-planar reconstructions of abdominal CT, some of the surgeons had used metal clips visible on CT for ligation. There was no difference in mean stump length between patients with or without clips implying that, the radiologists correctly identified the arterial stump without being hindered by thrombosis (101). The same patients were re-examined after one year using a routine follow up abdominal CT, and the investigations were done by the same radiologists (107). In 81% of the patients, the residual artery stumps were found and could be measured. Of these stumps, 66% appeared normal, 21% as a fibrotic line, and the rest were thrombosed. The thrombosed and fibrotic stumps were on average 4,5 mm shorter after one year. These stumps were mean 38 mm two days after the operation. In a study by Kaye et al. (108) vascular stumps were found many months (on average over two years) after surgery. The stumps were mostly thrombosed but visible on 3D reconstructed routine follow-up

CTs. Both studies support the accuracy of measuring vascular stumps. Thrombosis or not does not seem to alter the results. Comparing our two methods of measuring stump lengths also support the accuracy of measurements in both methods.

There have been other ways to evaluate CME and CVL. LN yield has often been used, but as pointed out earlier, many confounders make this parameter imprecise. West et al. (55) introduced tissue morphometry and classification of grading the plane of mesocolic dissection. The findings were used to judge the quality of CME and the height of CVL, among other objectives. In the Danish study mentioned above (101), there was no correlation between the distance from the tumour or nearest bowel wall to the vascular tie in morphometry, and the length of arterial stumps found on CT.

The grading of the plane of mesocolic dissections is pertinent and a good method to assess the quality of the surgery. It seems to be an overall survival advantage doing mesocolic plane surgery instead of surgery in the muscularis propria plane (109). This is a simple way to evaluate an important part of the procedure just by inspecting the specimen.
The level of vascular ligation is a surrogate for lymphadenectomy. It is possible to achieve a CVL without removing the lymphatic tissue surrounding the artery and its origin. This practice would be revealed on photos taken during surgery, but not by measuring vascular stumps on 3D reconstructed CT.

Study (ref)	year	n	Surgical procedure	CVL	Laparo-scopic	Stage UICC	LN tot	LN D3
An (50)	2018	34	CME H	Y	Y	I-III	30±11	NA
He (110)	2017	72	CMAP	Y	Y	I-III	20.6 ± 7.7,	NA
Lee (43)	2009	42	D3 MtL	Y	Y	I-III	45 (r:18–92)	NA
Liang (33)	2015	244	D3 with CME	Y	Y	II-III	34.4 ± 8.4	6.4 (4–16)
Petz (87)	2017	20	CME	N	Robot		40 (19-67)	NA
Zurleni(81)	2018	97	CME	Y	N	I-III	33	NA
Toyota (23)	1995	275	D3	N	N	I-III		
Han (46)	2012	177	D3	Y	Y	I-III	15.2 ± 10.1	4.1 ± 5.1
Xie (111)	2015	36	D3 + CME	Y	Y	NA	20 IQR 14.8-27	NA
Wu (89)	2017	31	CME/ D3, HA	Y	Y		34 (r 18-91)	13 (r 3-28)
Park (112)	2010	14	CME	Y	Y		36	NA
Adamin(113)	2012	52	CME	Y	Y		22	NA
Feng (52)	2012	35	CME	Y	Y		19	

Table 1

Different surgical procedures for right colectomy with extended lymphadenectomy

n: number, **CVL**: central vascular ligation, **LN tot**: total number of LN resected, **LN D3**: mean (SD) or median (range) number of LNs in the D3 area, CME: complete mesocolic excision, CME H: complete mesocolic excision am Hohenberger, CMAP: completely medial access by page-turning approach with CME, MtL: medial to lateral approach, HA: Hand assisted, NA: Not applicable, Y: Yes, N: No, r: Range

Conclusion & implications

The content of the papers in this thesis has provided the logical basis for, supported, described, and quality assured lymphadenectomy in RD3APM for right-sided colon cancer. With this surgical procedure respecting the mesenteric envelope, more lymphatic tissue is removed central in the mesentery than with any of the other known surgical procedures for right sided colon cancer. So far, the complications and adverse effects of this procedure seem to be comparable with those of other procedures.

Cancer-specific and overall survival after this procedure is an important outcome. Our study (114) is a case-control study requiring a large number of included patients to get enough power for significant results and, combined with five years of observation after surgery, renders the research long-lasting. None of the other centres doing extended lymphadenectomy for colon cancer has done randomized controlled studies (82, 83). However, they have shown better oncological outcomes compared to D2 resections (33, 45, 49, 51, 79). Nonetheless, it is of utmost importance for the patients and the surgical community to be able to clarify the, by our opinion, highly probable oncological benefit of extended lymphadenectomy in an indisputable way.

Most of our included patients were operated with an open approach. Among the patients operated with a laparoscopic approach, 39% were converted to open procedures (*paper 4*), possibly reflecting the early learning curve. However, this is and will be a very challenging procedure. It might be easier to do robot-assisted RD3APM. Surgeons in our group have done such introductory operations with Da Vinci Xi robot (115). Their impression was that the degree of difficulty was at the same level as an open operation. In the future, the 3D reconstructed CT presently used as a roadmap for surgery could most likely be integrated into the robot console making the use of the map more convenient (116). Some investigators in our group are working with different ways to present the CT data (117) of the mesenteric blood vessels integrated into screens used at surgery (laparoscopy or robot). 3D reconstructed CTs has helped us making challenging surgery less difficult and safer. The reconstructions could be used in other parts of the body where the vasculature could pose a problem either because of complicated anatomy or considerable variation of the anatomy.

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Errata list

Cor -correction

Page	**Line**	**Original text**	**Correction type**	**Corrected text**
3	1	Innhold	Cor	Contents
13	23	*Fig. 1*	Cor	*Fig.3*
14	6	posterior the right	Cor	posterior to the right
32	12	*Fig. 1*	Cor	*Fig. 3*

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Defining minimal clearances for adequate lymphatic resection relevant to right colectomy for cancer: a post-mortem study

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Abstract

Background There has been a lengthy discussion on the extent of lymphatic resection for right-sided colon cancer and the central borders of the mesentery that are not yet defined. The objectives of this study are to define minimal clearances for adequate lymphatic resection in regard to colic artery origins and the superior mesenteric artery (SMA) and vein (SMV) relevant to right colectomy.

Methods Central mesenteric lymph vessels, nodes, and blood vessels were dissected in 16 cadavers. Cranial–caudal clearances were defined as distances between an individual colic artery origin (ileocolic, right colic, and median colic artery) and the outermost lymphatic vessel within its lymphovascular bundle, cranial and caudal along the SMA. Long lymphatic vessels crossing the SMV between arterial bundles were counted and they constituted the medial clearances. An arbitrary watershed between small bowel and colonic lymph was localized. Immunohistochemistry was performed to histologically verify lymphatic vessels.

Results Cranial–caudal clearances were ileocolic 3.6 ± 1.9 and 5.7 ± 1.9; right colic 2.8 ± 1.6 and 3.3 ± 1.0; middle colic artery bundle 6.3 ± 2.7 and 5.9 ± 2.4 mm, respectively. Long lymphatic vessels crossing the SMV between arterial buntles and approaching the SMA were found in all cadavers (antero/posteriorly in 12, only anteriorly in 4), median 3.5 (1–7) long lymphatic vessels anteriorly, and 1.5 (0–5) posteriorly per cadaver.

Conclusions Right colonic lymphovascular bundles are volumes of mesenteric tissue that surround the superior mesenteric vessels anteriorly and posteriorly. Long lymphatic vessels traverse the superior mesenteric vein anteriorly/posteriorly approaching the superior mesenteric artery between arterial bundles and placing the medial clearance on the left side of the artery. These do not correlate to arterial crossing patterns. Cranial–caudal clearances determine the tissue to be removed superior/inferior to arterial origins together with long lymphatic vessels transversing independently between the lymphovascular bundles placing the weight of lymphatic resection on the mesenteric tissue and not on the level of vessel division (High tie).

Keywords Right colectomy · Mesenteric lymph vessel · Post-mortem study · Colonic neoplasm/surgery

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According to Culligan et al. [1], the lymphatic system of the mesentery is twofold. A fine network of lymphatic vessels associated with the mesothelium constitutes the first, superficial group of lymphatics. These vessels are found within 100 µm of the mesothelium surface. The second group comprises long vessels located within the body of the mesentery. A lymphovascular bundle is defined as a number of collecting lymph vessels accompanying or adjunct to a blood vessel, running together within a connective tissue lattice, which in turn separates the surrounding adipose compartments. However, it is not yet clear if all vessels adhering to the latter group inhabit these lymphovascular bundles, or not. These vessels are of paramount importance for lymphatic drainage of the bowel, contrary to the former, and should therefore be taken into consideration when defining the extent of lymphatic resection.

A lengthy discussion in the literature on the extent of lymphadenectomy for right-sided colon cancer started in 1909. Dr. Jamison and Mr. Dobson [2] were the first authors to report metastases to central lymph nodes surrounding the superior mesenteric vessels. Since then many prominent surgeons have contributed to the understanding of the principles and the improvement of surgical procedures in the area [3–5]. Despite proper training in the technique of complete mesocolic excision (CME), a recent study [6] has shown mean residual colonic artery stump lengths to be 31 mm (95% CI 25–37) indicating less radical surgery than expected (D2). Contemporary authors concur that the medial borders of the right mesocolon are still not defined [7]. Several articles describe subserosal or colonoscopic injection of various dyes in order to depict the extent of mesenterectomy at surgery with more or less success [8–11]. It does, however, seem that this 100-year-old discussion should come to its natural end when the macro-anatomy of right colonic lymphovascular bundles is fully described.

The aim of this study is to define minimal clearances for adequate lymphatic resection in regard to colic artery origins, present the macro-anatomy of lymphovascular bundles, and demonstrate lymph vessel trajectories relevant to right colectomy for cancer.

Materials and methods

The detailed macro- and micro-dissections were carried out at the Anatomy Sector, Department of Cellular Physiology and Metabolism, Faculty of Medicine, University of Geneva, Geneva, Switzerland. Sixteen fresh frozen (− 20 °C) bodies were used for the study. All donations were based on anatomical gift statement, including the informed consent, given during the lifetime of donors. Given the fact that data were anonymous, no Institutional Review Board approval was mandatory under Swiss federal law (Human Research Act 810.30). After thawing, the abdominal cavity was opened via a large incision, and the specimen consisting of the pylorus, duodenum, pancreas, proximal jejunum, cecum, ascending colon, and the transverse colon, together with their corresponding mesenteries was harvested en bloc, respecting the cleavage plane formed by Treitz and Toldt's fusion fascias, up to the coeliac mesenteric axes [12]. After rinsing the intestines with running water, the whole specimen was immersed in 4% buffered formaldehyde for fixation.

The minute anatomical dissection of the excised specimen was accomplished (JMN and BVS) using forceps with curved sharp edges, micro-dissecting scissors, and small clamps, with the aid of a fluorescent ring light magnifying glass for very fine structures. After identifying the ileocolic fold as a basic landmark, the dissection began by removing the peritoneum over the central part of the mesentery of the small bowel and the right colon using sharp dissection. The fatty tissue was scraped off with tweezers, medical wooden spatulas, and scissors, leaving lymph vessels and nodes behind. The dissection was done in stages, each time comprising one lymph node and its corresponding vessels, respecting a stratigraphic approach. At each phase of the dissection, the serous membranes and subserosal connective tissue were moisturized by a phenol solution to facilitate observation. Particular attention was devoted to distinguishing lymph vessels from the fine nerve fibers and connective tissue, with regard to their course, consistence, and relation to the lymph nodes. The superior mesenteric artery (SMA) and vein (SMV) and their branches were identified and dissected free without damaging the lymphatic tissue in their vicinity, representing anatomical landmarks for the overall arrangement of the lymph nodes and vessels. The limits of the main area of interest were as follows: 2 cm cranial to the origin of middle colic artery (MCA), the left side of the SMA, at least 3 cm right to the right side of the SMV, and caudally 2 cm distal to the origin of the ileocolic artery (ICA). In an earlier publication [13], our group has defined the N3 area of the right colon. The limits of the main area of interest in the present study are chosen in order to include the complete N3 area with good margins. The relationships between the SMV and the colic vessels: ICA, right colic artery (RCA), and MCA were noted. Photographs were taken at each step of the dissection.

Cranial–caudal and medial lymphatic clearances

Cranial–caudal clearances to arterial origins along the SMA are defined as distances between an individual colic artery origin (ICA, RCA, MCA) and the outermost lymphatic vessel within its lymphovascular bundle, cranial and caudal along the SMA (Fig. 1). These distances were measured with a digital Vernier electronic caliper (S-Cal Work 150 mm; Sylvac, Crissier, Switzerland) and constitute the extent of lateral dissection required to achieve complete lymphatic resection.

Medial clearances are defined through lymphatics that cross the SMV (anterior and/or posterior) not belonging to the above-mentioned lymphovascular bundles. They were counted separately and determine the extent medial dissection towards the left required to achieve complete lymphatic resection (Fig. 1). These lymphatics approach the SMA. Some connect to small bowel lymphatics (see *the watershed* below) while others enter lymph nodes along the SMA.

The watershed between the small bowel and right colon lymphatics is arbitrarily defined through the points of confluence of lymph vessels draining the respective areas. These points were counted and their positions in relation to SMA

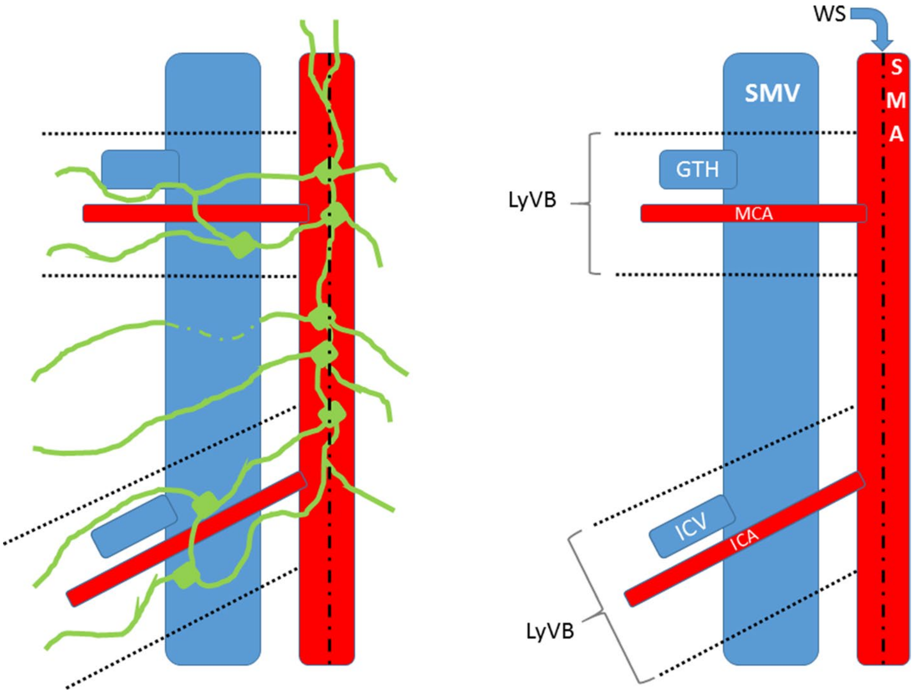

Fig. 1 A simplified representation of cranial–caudal and medial clearances, and the watershed (WS). Lymphovascular bundles (LyVB) of the ileocolic (ICA) and middle colic artery (MCA) are defined through dotted lines depicting the outermost lymph vessel within the lymphovascular bundle. Long lymph vessels cross the superior mesenteric vein (SMV) both anteriorly and posteriorly approaching the superior mesenteric artery (SMA) in between the lymphovascular bundles. *GTH* the gastro colic trunk of Henle, *ICV* ileocolic vein

or SMV noted. An arbitrarily straight vertical line between the points of confluence was drawn and its position in relation to SMA or SMV noted in each cadaver (Fig. 1). Due to the limitations of the dissection area (the left side of the SMA), these points of confluence were registered only on the anterior aspect of superior mesenteric vessels (SM).

Immunohistochemical staining

Random samples of tissue from dissected specimens underwent hematoxylin-eosin staining (H&E) and light microscopy in order to confirm the presence of the perivascular lymphatic vessels. Lymphatic vessels were indirectly identified on H&E sections as thin-walled vessels with the presence of valves (when visible). The absence of erythrocytes in the lumen compared to erythrocytes-filled blood vessels could not be used as a criterion in this study because of the long time body preservation in formol bath. To confirm the identification of lymphatic vessels, immunohistochemical staining that specifically stain lymphatic endothelial cells [14] was used. Four-µm-thick tissue sections from formalin-fixed paraffin-embedded samples were analyzed using Human LYVE-1 Antibody (R&D Systems, AF2089-SP) and Monoclonal Mouse Anti-Human Podoplanin Clone D2-40 (Dako, Aglient Technologies, Santa Clara, CA, USA) with the Ventana Discovery automated staining system (Ventana Medical Systems, Tucson, AZ, USA). Ventana reagents for the entire procedure were used. For anti-LYVE-1 and D2-40 antibodies, antigen retrieval pretreatment was required (P1 or CC1st). After automatic deparaffinization and pretreatment, slides were incubated 30 min at 37 °C with primary antibodies diluted at 1/100 (LYVE-1) or 1/50 (D2-40) in antibody diluent from Dako (S2022). Then secondary antibodies were applied at dilution 1/250 (anti-goat (LYVE-1) and anti-mouse (D2-40) biotinylated, Dako). Detection of secondary antibodies was carried out using the DabMap kit (Ventana Medical Systems), based on conversion of diaminobenzidine to a dye with multimeric horseradish peroxidase (HRP).

Statistical analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS ver.21 64-bit edition, Chicago, Ill., USA) software. Descriptive statistics for continuous data are presented by median (range) and mean (± SD). Lymph vessel ratios were calculated by dividing the number of lymph vessels crossing anteriorly with the total number of lymph vessels crossing the SMV. Spearman's correlation coefficient and logistic regression were used to assess significant correlation between categorical and continuous data.

Results

A total of 16 cadavers (11 females, aged 83.9 ± 9.2 years [mean ± SD]) were included. According to the available medical histories and macroscopic findings, there were no cases of abdominal pathology or prior surgery, which altered the lymphatic anatomy in question. The ICA and

Table 1 Cranial–caudal clearance

	MCA	RCA	ICA
Distance to outermost lymphatic (cranial)	6.3 ± 2.7	2.8 ± 1.6	3.6 ± 1.9
Distance to outermost lymphatic (caudal)	5.9 ± 2.4	3.3 ± 1.0	5.7 ± 1.9

Cranial–caudal clearance from arterial origins [ileocolic (ICA), right colic (RCA) when present and the middle colic artery (MCA)] to outermost cranial/caudal lymphatic within the lymphovascular bundles. Values are in millimeters ± SD

Table 2 Long lymphatic vessels crossing the superior mesenteric vein

	ICA posterior to SMV	ICA anterior to SMV
Lymph vessel ratio	0.59	0.70
Lymph vessels anterior (n)	19 (41.3%)	14 (29.8%)
Lymph vessels posterior (n)	27 (58.7%)	33 (70.2%)
Σ	46 (100%)	47 (100%)

The table presents numbers of long lymphatic vessels crossing the superior mesenteric vein (SMV) and approaching the superior mesenteric artery either/or anteriorly or posteriorly in relation to the crossing pattern of the ileocolic artery (ICA). Lymph vessel ratio was calculated by dividing the number of lymph vessels crossing SMV anteriorly with the total number of lymph vessels crossing the SMV

MCA were present in all 16 cadavers, the MCA crossing anterior to the SMV in all cases. Eight cadavers had an ICA crossing the SMV posteriorly. The RCA was present in three (18.8%) cadavers, crossing the SMV posteriorly in two of them.

Cranial–caudal and medial lymphatic clearances

Cranial–caudal clearances

Anatomical dissection revealed multiple long lymphatic vessels within the lymphovascular bundles of all arteries. Mean distances from the outermost cranial and caudal lymph vessels to the center of the arterial origins of ICA, MCA, and RCA along the SMA are presented in Table 1 and Fig. 1.

Medial clearances

Long lymphatic vessels crossing the SMV, not belonging to the lymphovascular bundles of colic arteries were found in all cadavers (anteriorly and posteriorly in 12, only anteriorly in 4), median 3, 5 (1–7) lymph vessels anteriorly, and 1, 5 (0–5) posteriorly per cadaver (Table 2).

In order to see if there was a correlation between the lymph vessel ratio and the position of ICA in relation to SMV, the Spearman's correlation coefficient (r_s) was calculated. There was poor correlation (r_s = 0.36) between lymph vessel ratio and the crossing pattern of ICA with an OR = 32, p = 0.145 for a lymph vessel on the opposite side of the ICA (Figs. 2, 3).

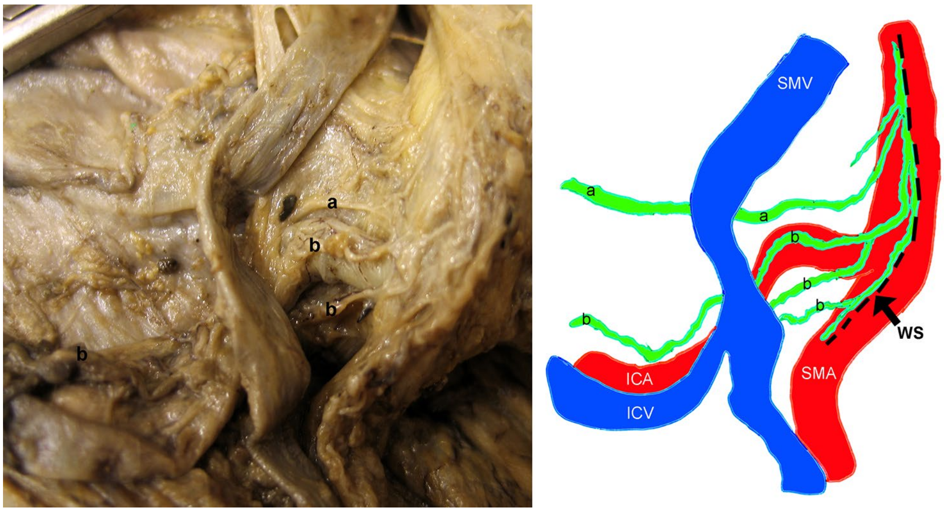

Fig. 2 Left panel: anatomical dissection of formaldehyde-fixed cadaver. Right panel: a sketch delineating structures of interest. After freeing from the surrounding connective tissue, the superior mesenteric vein's (SMV) surgical trunk has been drawn to the right, allowing the dissection of numerous lymph vessels that cross it posteriorly, either in the intercolic space as long lymph vessels (a) or adjoining the ileocolic artery (ICA) as parts of lymphovascular buntle (b). These vessels unite within a collective trunk lying in front of the superior mesenteric artery (SMA), constituting the watershed (WS) between small bowel and colon lymph drainage; Ileocolic vein (ICV)

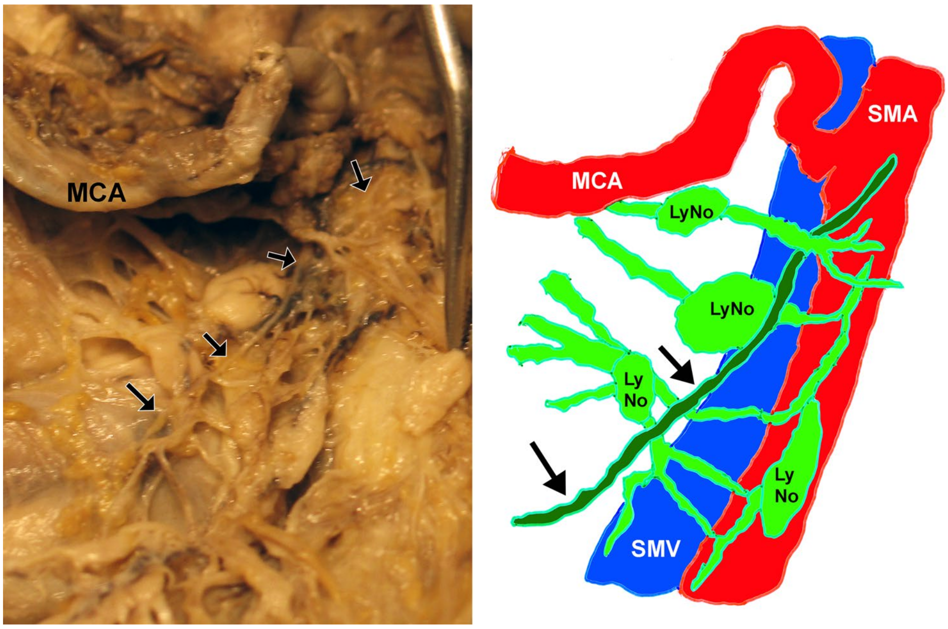

Fig. 3 Left panel: anatomical dissection of formaldehyde-fixed cadaver. Right panel: a sketch delineating structures of interest. Dissection of the upper portion of the superior mesenteric vein and artery. Lymph nodes (LyNo) and short lymphatic vessels inter-connecting them (light green) stemming from the right colon. The arrows point to a long lymphatic vessel (dark green) crossing the superior mesenteric vein (SMV) anteriorly and approaching the superior mesenteric artery (SMA) at the origin of the middle colic artery (MCA) without interruption in any of the central lymph nodes

The watershed

The arbitrary watershed was found over SMV in two cadavers and over SMA in 14 cadavers (Fig. 2).

Histopathology

Depending on specimen preservation, immunostaining was not always detectable. However, when detectable, LYVE-1 and D2-40 expressions were mainly observed in thin-walled (i.e., lymphatic) vessels. Lymphatic sinusoids of lymph nodes present in the sections were stained with LYVE-1 antibody, conferring an internal positive control [15]. Endothelial cells of high-walled vessels (i.e., blood vessels) were not stained. Lymphatic vessels were observed in the perivascular tissue of veins and arteries of all the stained samples.

Discussion

The most important find in this article is represented through the actual distances to the outermost lymph vessel within the colic artery lymphovascular bundle. When analyzing the measured values, shrinkage due to the formol fixation of the bodies should be taken into account. These values actually imply volumes of mesenteric tissue surrounding vessel origins. Moreover, the possibility for overlapping of the individual volumes can create a common central lymph node dissection area for the right colon (distances between arterial origins: ICA to MCA: 25.2 ± 11.3, ICA to RCA: 15.7 ± 4.7 a,nd RCA to MCA: 21.7 ± 11.1 mm [13]).

Accepting the region of central lymphatic resection as a volume is crucial. Previous representations of the lymph drainage (Jamison and Dobson's paper already in 1909 [2] and Viamonte and Rüttimann atlas from 1980 [16]) show lymph vessels in front of colic arteries (ICA, RCA) and continuing cranially along the anterior aspect of the SMA. Toyota et al.'s paper [4] depicts lymph vessels in front of the colic arteries, but continue along the anterior of the SMV. We found only two publications that do address the region as a volume [17, 18], demonstrating lymph nodes both anterior and posterior to the SMV/SMA. Insufficient knowledge and consciousness on the three-dimensional structure of the central mesentery has made a definite imprint on contemporary and past surgical practice, i.e., removing only the mesenteric tissue anterior to the SMV and omitting the resection of lymphatics anterior to the SMA and those posterior to the SMA/SMV [4]. Lymph nodes have demonstrated a significant correlation to the crossing pattern of the colic arteries [17]. The initial interpretation of this fact implied a sufficient lymphatic resection is one where all the mesenteric tissues were removed from the side of the colic artery crossing. The results of the current study invalidate such a conclusion. To our knowledge, ours is the first description of long lymph vessels not adhering to colic artery lymphovascular bundles that cross both anterior and posterior to the superior mesenteric vessels and approach nodes at the superior mesenteric artery. These vessels are noted in all specimens, in both positions with no correlation to the arterial crossing pattern. The importance of these vessels for the spreading of cancer to the central lymph nodes (e.g., skip metastasis) remains to be determined, despite the fact that their trajectory points in the correct direction. Such a pattern of lymphatic vessels traversing independently between the lymphovascular bundles of the colic arteries seems also to imply that mesenteric tissue both anterior and posterior to SMV and SMA should be removed regardless of the colic artery crossing pattern and cancer position, e.g., cancer cells even from cecum could theoretically end up near the MCA origin using the long independent lymphatic vessels for conveyance. When the medial border of this now established volume is concerned, two factors should be included in the equation. The first are the long vessels between lymphovascular bundles that approach the SMA directly, indicating that the left edge of the SMA should represent the medial border. This statement is even more fortified through the location of the lymphatic watershed between the right colon and the small bowel. When this superficial lymphatic network is removed [1], the findings of this article show the watershed position most often anterior to the SMA, and are in complete accordance with the sketches presented in the Atlas of Viamonte and Rüttimann [16].

Guidelines often recommend division of colic arteries at their origin [3, 5]. Terminology used to depict extent of lymphatic resection should not be based on surrogate endpoints since it is possible to perform a high tie and not remove any lymph nodes. The present data in these articles imply that a lymphovascular bundle should not be dissected into in order to approach the artery since this would lead to division of the lymphatic vessels within the bundles and possible cancer cell spillage. When lymph vessel trajectories are taken into account, it seems appropriate to approach the area of dissection from the left side of the superior mesenteric artery and initially release the anterior flap of mesenteric tissue anterior to the SMV and SMA. After the superior mesenteric vessels are dissected free and the colic arteries divided, removal of the lymphatic tissue posterior to the SMV and SMA between the origins of colic arteries is made possible in a fashion that would not sever these lymphatic vessels. This approach also takes into account the small lymphatic vessels associated with mesothelium surfaces previously mentioned [1]. Placing the medial incision of the right colon mesentery along the left side of SMA at surgery allows for the removal of tissue both anterior and posterior to the SMA without harming the mesenteric envelope. When mobilizing the right colonic mesentery, the peritoneum anteriorly and fascia posteriorly should remain intact as described in CME [5, 19]. This operative technique [13] incorporates complete and coherent colic-mesocolic excision for colon cancer, adding the extended mesenterectomy posterior and anterior to the superior mesenteric vessels.

The surgical approach described above is currently performed in our ongoing prospective multicenter trial "Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography (MDCT) Angiography" registered at http://clinicaltrials.gov/ct2/show/NCT01351714 and ethically approved by Regional ethical committee, South-East Norway (REK Sør-Øst) no. 2010/3354. A 3-dimensional vascular anatomical roadmap derived from the staging CT is used to plan and accomplish the surgery. Surgery being performed both through open [13] and laparoscopic access [20].

The question of potential damage to the superior mesenteric nerve plexus while using this technique has been addressed in a previous publication from our group [21]. The results show no significant difference in bowel function or Gastrointestinal Quality of Life Index six months after surgery, with the exception of a somewhat increased bowel movement frequency

Conclusion

Lymphovascular bundles of the right colonic arteries represent volumes of fatty and lymphatic tissue that overlap and spread both anterior and posterior to the superior mesenteric vessels. Long lymph vessels traverse the SMV/SMA anteriorly and posteriorly between the right colonic artery lymphovascular bundles, without correlating to arterial crossing patterns, in this way placing the medial edge for resection on the left side of the SMA (medial clearance). Cranial–caudal clearances will determine the amount of mesenteric tissue to be removed cranial and caudal to arterial origins together with long lymphatic vessels traversing independently between the lymphovascular bundles of the colic arteries placing the weight of lymphatic resection on the mesenteric tissue and not on level of vessel division (high tie).

Compliance with ethical standards

Disclosures Jens Marius Nesgaard, Bojan V. Stimec, Bjørn Edwin, Pricilla Soulie, Arne O. Bakka, and Dejan Ignjatovic have no conflict of interest.

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CT and operative images for evaluation of right colectomy with extended D3 mesenterectomy anterior and posterior to the mesenteric vessels

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Summary
Background Surgical techniques like complete mesocolic excision (CME) and D3 mesenterectomy, D3 refering to the N3 lymph node groups central in the mesentery removed at surgery, were introduced without proper evaluation of the lymphadenectomy. The aim of this study was to measure the vascular stumps and evaluate the extent and quality of lymphadenectomy after right colectomy with extended D3 mesenterectomy anterior/posterior to the mesenteric vessels. We also compared the investigation methods.
Methods Residual vascular stumps were measured using three-dimensional (3D) reconstructed anatomy from follow-up computed tomography (CT) datasets and images taken during surgery. The quality of central lymphadenectomy was evaluated on the images.
Results In total, 31 patients (15 females), median age 67 years (50–78), with stage I ($n=7$), stage II ($n=13$), and stage III ($n=11$) disease, were operated. Tumor locations were: 14 (45%) in the cecum, ten (32%) in the ascending colon, three (10%) in the hepatic flexure, and four (13%) in the transverse colon. The middle colic artery (MCA) was divided at its origin (13 patients) or its right branch (18 patients). Median lengths (range) of residual vascular stumps measured on 3D reconstructed CT and photographic images taken during surgery were: right colic artery: 0.0 mm (0.0–1.8)/0.0 mm (0.0–1.1), ileocolic artery: 0.0 mm (0.0–7.2)/0.0 mm (0.0–3.0), ileocolic vein: 0.0 mm (0.0–7.5)/0.0 mm (0.0–0.0), MCA: 0.0 mm (0.0–18.1)/1.0 mm (0.0–8.0), and right branch of the MCA: 0.0 mm (0.0–1.8)/0.0 mm (0.0–2.0). There was no significant difference between average lengths measured with the two techniques. The extent of lymphadenectomy was deemed acceptable in all patients. No differences in stump lengths were found in patients with different vascular crossing patterns in the central mesentery and presumably different degree of difficulty at surgery.
Conclusion The results demonstrate very short residual vascular stumps and together with operative photographs provide objective evidence for superior lymphadenectomy in right colectomy with extended D3 mesenterectomy.

Keywords Right colectomy · Colonic neoplasm/surgery · Mesentery/blood supply · Digestive arteries · D3 resection

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This paper's novel aspects

The current literature demonstrates 3–5-cm-long vascular stumps after complete mesocolic excision. In this study, evaluation of lymphadenectomy after right colectomy with extended D3 mesenterectomy anterior and posterior to the mesenteric vessels using postoperative three-dimensional reconstructed computed tomography scans and images taken during surgery to measure the stump lengths revealed 0.9–3.5-mm-long stumps, showing the feasibility of thoroughly complete mesocolic excision.

Introduction

After the introduction of total mesorectal excision (TME) for treatment of rectal cancer, survival rates improved and local recurrence rates dropped [1]. The TME concept was transferred to complete mesocolic excision (CME) [2] keeping the mesocolic envelope intact and including central vascular ligation (CVL). Several centers reported favorable survival and low local recurrence rates after introducing CME [2, 3]. There is a general acceptance for respecting the embryonic planes, aiming for unharmed mesocolic fascia in surgery. However, when central lymphadenectomy in right colectomy is concerned, several approaches with a varying extent of mesenterectomy have been reported in the literature [2, 4–6]. The complex anatomical relationship between major blood vessels and their branches hidden in the fatty tissue of the central mesentery is challenging for surgeons [7, 8] and might explain the different approaches.

Two anatomical studies have recently contributed to a deeper understanding of the lymphatics draining the right colon. Long lymphatic vessels from the colon perimeter have a trajectory directly toward the superior mesenteric artery, bypassing some lymph nodes [9], while central lymph nodes were found both posterior and anterior to the superior mesenteric vessels [10]. In right colectomy with extended D3 mesenterectomy anterior/posterior to the superior mesenteric vessels [7], these anatomical findings are respected by removing tissue both anteriorly and posteriorly to the mesenteric vessels. D3 refering to N3 lymph node groups central in the mesentery removed at surgery.

Two studies [11, 12] have reported unexpected long vascular stumps after right-sided colectomy for cancer. A number of articles have been published stating that vascular stumps can be found on postoperative computed tomography (CT) scans, and their lengths measured (as a surrogate for the extent of lymphadenectomy; [11–14]).

In the present study, we evaluated the extent of lymphadenectomy in our patients operated on via right colectomy with extended D3 mesenterectomy anterior/posterior to the mesenteric vessels through establishing the level of vascular division on follow-up CT scans and on photographs taken at surgery. We also evaluated the CT findings by comparing them with the photographs.

Patients and methods

The study comprised a cohort of consecutively included patients to the "Safe Radical D3 Right Hemicolectomy for Cancer Through Preoperative Biphasic Multi-detector Computed Tomography (MDCT) Angiography" trial (http://clinicaltrials.gov/ct2/show/NCT01351714), from September 2014 to May 2017. The patients had operative photographs and a postoperative abdominal CT already taken. Clinical data were retrieved from the prospectively maintained study database and the data for this cohort were not published earlier. The patients were recruited from two Norwegian hospitals: Vestfold Hospital Trust, a central hospital, and Akershus University Hospital, a university hospital and operated on by dedicated surgeons all of whom were involved in the aforementioned trial. The patients were stratified into four anatomical groups and two subgroups according to the crossing pattern of the superior mesenteric artery and vein branches within the D3 volume (Fig. 1) as previously described [7].

All patients were required to sign an informed consent form at inclusion. Ethical approval was obtained from the regional ethics committee, South-East Norway (REK Sør-Øst) no. 2010/3354. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Surgery

The open surgical technique through a midline incision has been previously described [7]. In short, preoperatively reconstructed three-dimensional (3D) images from staging CT are used as a roadmap for surgery. A transverse incision is made in visceral peritoneum over the terminal ileal vessels 1 cm caudal to the origin of the ileocolic artery. After opening the vascular sheaths, the terminal ileal vessels are secured in vessel loops. The anterior flap of mesenteric tissue along the left side of the superior mesenteric artery (SMA) is developed and the surgical specimen is devascularized (ileocolic artery [ICA], right colic artery [RCA] and, middle colic artery [MCA] or its right branch are divided at their origin). The surgical specimen is fully mobilized in order to provide access to the posterior flap of mesenteric tissue. The medial border of the posterior flap, behind the superior mesenteric vein (SMV) and SMA, is divided along a line parallel to the left border of the SMA from the level of the origin of the ICA to the level of origin of the MCA after the SMV is gently "rolled" toward the left and its vascular sheath together with the vascular

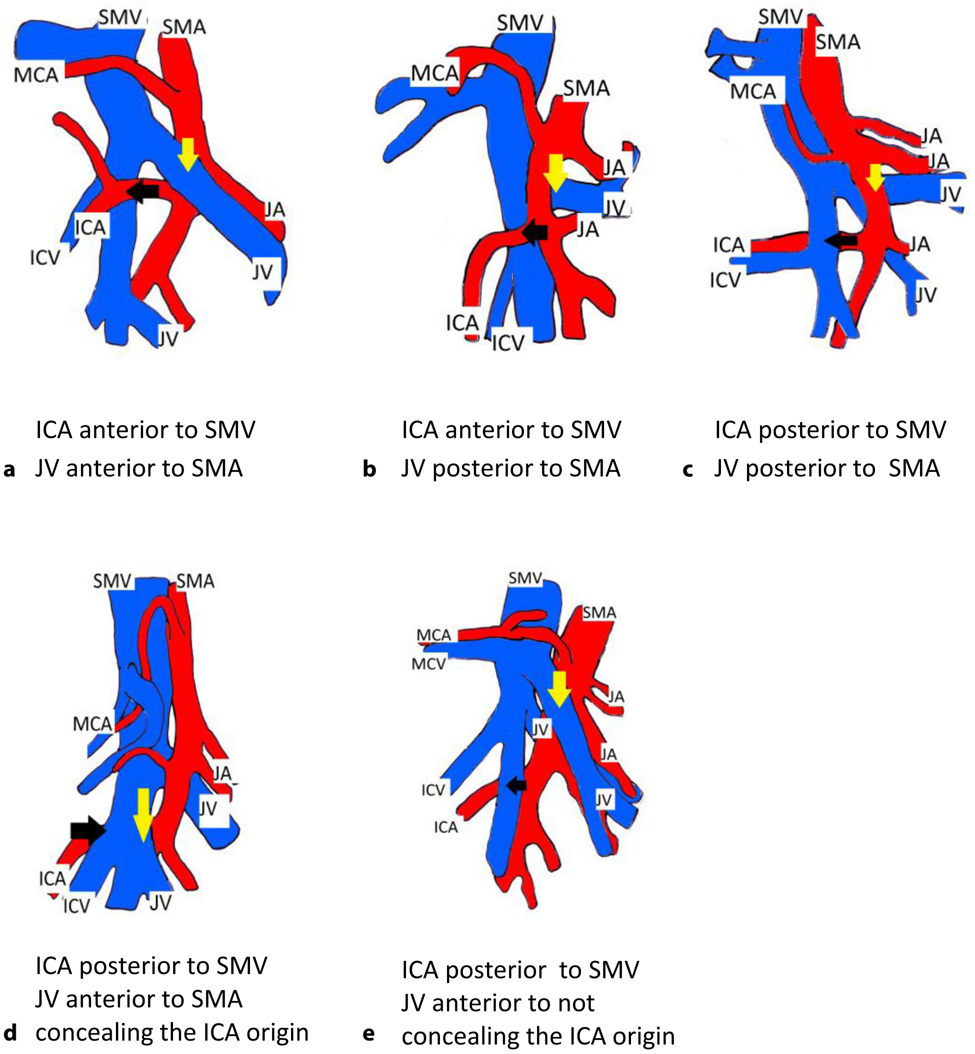

Fig. 1 Classification of vascular patterns in the D3 area. **a** Type I: *n* = 9 (6.5%), ICA anterior to SMV, JV anterior to SMA. **b** Type II: *n* = 44 (31.7%), ICA anterior to SMV, JV posterior to SMA. **c** Type III: *n* = 27 (19.4%), ICA posterior to SMV, JV posterior to SMA. **d** Type IVa: *n* = 30 (21.6%), ICA posterior to SMV, JV anterior to SMA concealing the ICA origin. **e** Type IVb: *n* = 9 (20.8%), ICA posterior to SMV, JV anterior to not concealing the ICA origin. *Black arrow*: the relationship between ICA and SMV. *Yellow arrow*: the relationship between JV and SMA. *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *ICA* ileocolic artery, *ICV* ileocolic vein, *MCA* middle colic artery, *MCV* middle colic vein, *JV* jejunal vein, *JA* jejunal artery

sheath of the SMA divided, removing complete arterial stumps. In this manner all tissue, both anterior and posterior to the mesenteric vessels, is removed en bloc with the specimen containing the central lymph nodes and vessels, the D3 volume. All surgical specimens are divided along a line parallel to and 1 cm lateral to the right side of the SMV in order to investigate the D3 volume for lymph node metastasis separately.

CT reconstruction

All evaluated patients had staging CT of the abdomen before surgery and a follow-up CT at 6 months after surgery in accordance with the Norwegian guidelines for standard treatment and follow-up after radical surgery for colon cancer [15]. A diagnostic CT scan in the early postoperative period due to postoperative complications was used when available. The MDCT datasets (preoperative and postoperative) were analyzed by means of manual and semimanual segmentation and subsequent 3D volume rendering (Fig. 2). This was accomplished by three software packages: FDA approved Osirix MD v. 9.0.2 64-bit image processing application (Pixmeo, Bernex, Switzerland), Mimics Medical image processing software, ver. 20.0, and 3-matic Medical software, ver. 12.0, both Windows 7 ultimate edition x64 2017 (Materialise NV, Leuven, Belgium). In short, the segmentation involved outlining the region of interest on each slice and achieving a clear 3D mask, as previously explained in detail [16]. All the measurements were performed on the 3DVR mask, using the Length and Distance tools. The reasoning behind this approach (in contrast to the plain two-dimensional CT) is in the more realistic presentation of vascular structures, in finding the adequate viewpoint easier, and in the frequent curviness or tortuosity of the said structures, requiring a stepwise measurement.

Measurement of vascular stumps

Measurements on CT

The analysis of the postoperative MDCT mainly focused on possible stumps of relevant arteries and veins (e.g., ileocolic vein [ICV], ICA, RCA, MCA, and MCA right branch). In order to identify their location

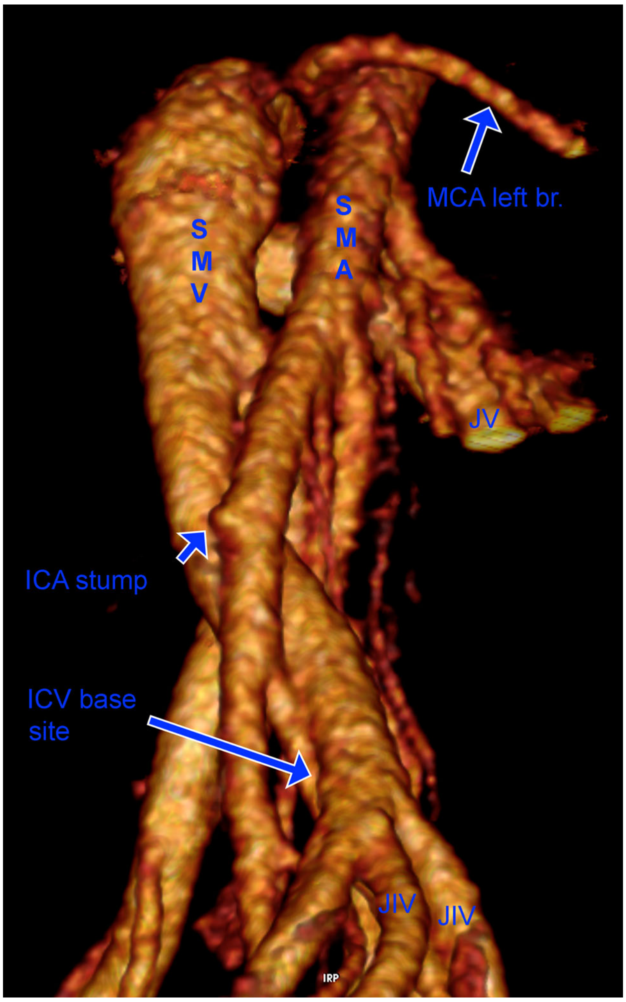

Fig. 2 A 3D volume rendering Osirix reconstruction of the follow-up CT showing the central mesentery after right colectomy with extended D3 mesenterectomy anterior/posterior to the mesenteric vessels. *ICA* ileocolic artery, *ICV* ileocolic vein, *MCA left br.* middle colic artery left branch, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *JV* jejunal vein, *JIV* jejunoileal vein

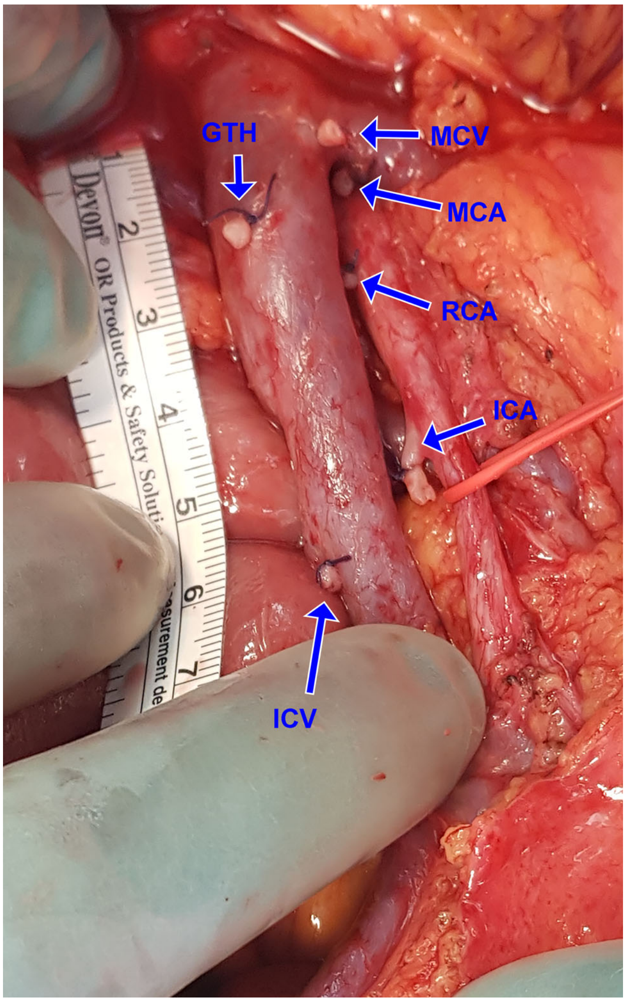

Fig. 3 Photograph taken after right colectomy with extended D3 mesenterectomy anterior/posterior to the mesenteric vessels. *ICA* ileocolic artery, *ICV* ileocolic vein, *MCA* middle colic artery, *MCV* middle colic vein, *RCA* right colic artery, *GTH* gastrocolic trunk of Henle

as precisely as possible, we used the following landmarks: number, caliber and level of origin of jejunal arteries; pattern and level of crossing of jejunal veins, and their caliber; length of the MCA common stem until its bifurcation; relation between the middle colic vein and gastrocolic trunk of Henle; and finally the termination of the inferior mesenteric vein. We have particularly taken into account the possible mutual shifting of blood vessels after operative dissection and liberation of the adjacent supporting connective tissue. To this end, the most valuable parameter for identifying the level of the ICA, RCA, and MCA stump from the SMA was their preoperatively ascertained relation to the scalariform jejunal arteries. The length of the residual vascular stumps of the ICA, ICV, RCA, MCA, and right branch of the MCA in the 3D masks was measured by one of the authors (BV). Care was taken to rotate the 3D image and erase the possible shielding elements in order to obtain a clear peripheral view of the stump for accurate identification, form evaluation (scar, dimple, tubular), and length measurement.

Measurements on operative images

Lengths of vascular stumps were measured on operative images using ImageJ software (version 1.51j8, National Institute of Health, USA) by one author (JMN). Images were taken at a 90 degrees angle to the vessels after the dissection of the anterior flap was finished, the colic vessels ligated and a cm scale in view. ImageJ was calibrated using the cm scale on the photo. Stumps of ICA, ICV, RCA, MCA and right branch of MCA were measured.

Evaluation of extent of lymphadenectomy

The measurement of vascular stumps is a surrogate for the extent of lymphadenectomy. In order to confirm the extent and completeness of the lymphadenectomy, photos of the central mesenteric blood vessels after the dissection of the anterior flap were examined. These photos demonstrated whether any significant mesenteric tissue (lymphatic and fatty tissue) was left behind. Photographs for quality control taken during surgery has also been used in other studies [17]. The mesenterectomy was deemed acceptable if both the SMA and SMV were skeletonized from the level 1 cm distal of the stumps of the ICA and ICV to the origin of the MCA with a medial border along the left side of the SMA on the photographs taken during surgery (Fig. 3).

Statistical analysis

Analysis was done using the Statistical Package for the Social Sciences (SPSS ver. 20). Descriptive statistics for continuous data are presented by median (range). The Shapiro–Wilk test was used to investigate whether the measured values had a normal distribution or not. Wilcoxon's signed rank test was used as a nonparametric test comparing measurements of the same vascular stumps with two different methods.

Results

In total, 31 patients (15 females) with a median age 67 years (50–78) were operated on via right colectomy and D3 extended mesenterectomy anterior/posterior to the mesenteric vessels. There were no secondary thrombosis, stenosis, or bypass circulation in the SMA or SMV due to dissection around the vessels. The median time from surgery to follow-up CT was 172 days (3–701). The ICA, ICV, and RCA were ligated at their origin. In 13 patients, the MCA was ligated at its origin while in 18 patients the MCA's right branch was ligated. Tumor locations were: 14 (45%) in the cecum, 10 (32%) in the ascending colon, three (10%) in the hepatic flexure, and four (13%) in the transverse colon. Seven patients had Dukes A, 13 Dukes B, and 11 Dukes C cancer. See Table 1 for TNM classification. The median number of lymph nodes harvested was 38 (17–75) in total and 11 (3–25) in the D3 volume. Two patients had lymph node metastasis in the D3 volume, and in one of these patients it was the only lymph node metastasis in the whole specimen (skip metastasis). There was no statistical difference between the median lengths of residual vascular stumps measured on images taken during surgery and the 3D reconstructions (Table 2) using the related samples Wilcoxon signed rank test for nonparametric data. The Shapiro–Wilk test confirmed the non-normal distribution of the data for all parameters: ICA in images $p=0.000$, MCA in images $p=0.004$, right branch of MCA in images $p=0.000$, ICA in CT $p=0.000$, ICV in CT $p=0.000$, MCA in CT $p=0.000$ and, right branch of MCA in CT $p=0.000$. It was not possible to calculate the ICV in images because of the invalid range (all values are 0). The p value is less than 0.05, i.e., the null hypothesis that the data are normally distributed is rejected and the data were not proven to have normal distribution. Measurements on images were missing in one patient; photographs were taken before ligating the vessels but after dissecting the D3 volume.

The extent and quality of mesenterectomy was deemed acceptable in all patients.

When the patients were reclassified according to vascular anatomy groups (Fig. 1), no difference in stump lengths between the different groups was shown (Table 3).

Table 1 TNM stage criteria for colorectal cancer (6th edition from the American Joint Committee on Cancer)

Stage		T1	T2	T3	T4	No.
Stage I	(N0)	1	6	–	–	7
Stage IIA	(N0)	–	–	12	–	12
Stage IIB	(N0)	–	–	–	1	1
Stage IIIA	(N1)	1	–	–	–	1
Stage IIIB	(N1)	–	–	7[a]	2	9
Stage IIIC	(N2)	–	–	1[b]	–	1
No.		2	6	20	3	31

[a]Skip metastasis to D3 volume
[b]Metastasis to D3 volume

Table 2 Median [range] lengths of vascular stumps measured on 3D reconstructed CT and images taken during surgery

Vascular stumps	3D CT stumps (mm)	Pts. no./total no.	Image stumps (mm)	Pts. no./total no.	*p*
ICA	0.0 [0.0–7.2]	31/31	0.0 [0.0–3.0]	30/31	0.08*
ICV	0.0 [0.0–7.5]	31/31	0.0 [0.0–0.0]	30/31	0.11*
MCA	0.0 [0.0–18.1]	13/14	1.0 [0.0–8.0]	12/14	0.17*
R. branch MCA	0.0 [0.0–9.0]	17/17	0.0 [0.0–2.0]	16/17	0.29*
RCA	0.0 [0.0–1.8]	3/3	0.0 [0.0–1.1]	3/3	n. a.

* Retain the null hypothesis; the significance level is 0.05
Related samples Wilcoxon signed rank test where the null hypothesis is as follows: The median of differences between vascular stumps lengths (ICA, ICV, MCA, and right branch of MCA) in CT and operative images equals 0
n. a. Not applicable owing to small number of cases, *ICA* indicates ileocolic artery, *ICV* ileocolic vein, *MCA* middle colic artery, *R.* right, *RCA* right colic artery

Table 3 Median lengths of vascular stumps with different vascular anatomy pattern

Anatomy type	Frequency $n = 31$	CT ICA (mm)	Image ICA (mm)	CT ICV (mm)	Image ICV (mm)
Type 1	3	2.9 [3.3]	0.0 [3.0]	0.0 [1.8]	0.0 [0.0]
Type 2	13	0.0 [7.2]	0.0 [2.0]	0.0 [1.6]	0.0 [0.0]
Type 3	6	0.7 [2.1]	0.0 [1.0]	0.0 [0.0]	0.0 [0.0]
Type 4a	6	0.0 [0.0]	0.0 [2.0]	0.0 [7.5]	0.0 [0.0]
Type 4b	3	1.6 [2.2]	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]

Median [range] lengths of ileocolic artery (*ICA*) and vein (*ICV*) stumps measured on 3D reconstructed CT and operative images in patients with different vascular anatomy patterns (Type 1–4b) in the central mesentery

Discussion

The most important finding in this study is the short residual arterial/venous stumps and acceptable extent and quality of mesenterectomy in patients operated on via extended D3 mesenterectomy anterior and posterior to the mesenteric vessels. Measurements on both surgical photographs and anatomical 3D reconstructed CT were used to document this level of vascular division. There was no statistical difference between the median lengths of residual vascular stumps measured with the two methods, and both methods can be used to measure vascular stumps with precision. This procedure entails that all tissue positioned anterior and posterior to the superior mesenteric vessels draining the right colon [9, 10] is resected en bloc with the specimen, rendering CVL itself a surrogate marker for the level of lymphadenectomy. We have also performed this procedure through laparoscopy [18]. In the present study, we chose to include patients operated on via open access in order to reach a large enough number of patients.

The results presented with regard to different anatomy groups indicate that the complexity of the anatomy does not present a limitation for the CVL and extent of mesenterectomy, even though the subgroups were too small to allow for a definitive conclusion (Table 3). In another study by our group [19], no difference in blood loss and lymph node yield was found between the anatomy groups. The mean operating time and number of vascular events were higher in the groups expected to be more challenging for operation. In spite of demanding anatomy, the end results were comparable.

In the present study there were no vascular events in spite of extensive resections of mesenteric tissue both anterior and posterior to the SMA and SMV. Using the preoperative 3D reconstructed abdominal CT as a road map makes the dissection safe and quite straightforward. We did not observe any thrombosis or stenosis dissecting near the SMA and SMV in the cohort in this study or in any of the other patients operated on in the "Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multidetector Computed Tomography (MDCT) Angiography" trial. The SMA and SMV have large calibers and high flow.

The operative photographs are crucial for demonstrating the extent of the lymphadenectomy, simultaneously excluding the option of sliding forceps along the artery in order to achieve a CVL without actually removing the lymphatic tissue surrounding the vessel origins. This might have been the case in a previous study [14] where no difference in lymph node harvest was found regardless of the level of vessel ligation.

The method used to measure residual arterial stumps was first described in patients with anastomotic leak after right colectomy in 2010 (average lengths of residual stumps were ICA: 28 mm, RCA: 37 mm; [12]) before the introduction of CME [2]. Later, Kaye et al. [13] demonstrated that ileocolic arterial stumps were still present on average 2 years after cancer resection using routine portal venous CT datasets. These findings strongly suggest the use of a standard postoperative follow-up CT scan as an in vivo marker for evaluating the length of the residual vascular stumps. The same technique showed an average length of 31 mm (95% CI: 25–37) for ICA stumps in patients who had undergone right colectomy after adopting the principles of CME with ligation of the ICA at its origin from the SMA by surgeons trained in the CME technique [11]. The CME guidelines recommend that ICA stumps should be 10 mm or less. A correlation between the level of ligation of the inferior mesenteric artery assessed by the surgeon and the length of residual vessel stumps found in postoperative CT datasets was seen in only 41% of patients undergoing sigmoidectomy for cancer [14], demonstrating again that the surgeon's judgment of the level of ligation of the feeding artery is difficult and unreliable. It seems that approaching the vessel origin is a prerequisite for the correct judgment of the level of vessel ligation, as well as a complete lymphadenectomy. An alternative method for evaluating the extent of lymphadenectomy through measuring vessel lengths on the side of the surgical specimen [20] has turned out to be ineffective [11].

Having this in mind, evaluation of the extent and quality of CME (extended lymphadenectomy) should not be underestimated. Since the introduction of CME or extended lymphadenectomy (D3), there has been conflicting evidence for an oncological benefit [21, 22]. Although many studies have shown favorable results with extended lymphadenectomy [2–4, 23], randomized controlled studies are missing. It would seem that the proper way to conduct trials with this aim is to use one or both methods to evaluate the quality and extent of lymphadenectomy to make sure that a proper lymphadenectomy is performed in CME or extended lymphadenectomy [11].

The strength of our present study lies in the two modalities used to evaluate (3D CT reconstruction and images taken during surgery) the level of vascular division and the quality of lymphadenectomy. A further strength lies in the availability and the use of the preoperative 3D CT reconstructions to accurately locate the vascular stumps on the postoperative 3D CT reconstructions as well as the lack of statistically significant difference between measurements performed on 3D CT reconstructions and on operative images for all vascular stumps measured. The possible repositioning of blood vessels after operative dissection and liberation of the adjacent supporting connective tissue, and a possible slight shortening of the vascular stumps due to thrombosis, could be a further limitation of the study.

Conclusion

The results presented here demonstrate very short residual vascular stumps of vessels. Beside this, the operative photographs provide further objective evidence for superior lymphadenectomy when performing right colectomy with extended D3 mesenterectomy. Future trials evaluating survival rates after surgery for colon cancer based on the extent of lymphadenectomy should employ at least one of these methods in order to achieve reliable results.

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Conflict of interest J.M. Nesgaard, B.V. Stimec, B. Edwin, A.O. Bakka, and D. Ignjatovic declare that they have no competing interests.

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