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Title:

Radiological and pathological evaluation of the level of arterial division after colon cancer surgery

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Abstract:

Aim: Complete mesocolic excision for colon cancer includes central division of the tumour feeding artery. The degree of central radicality is assessed by measuring the distance from the tumour to the artery ligation by the pathologist on the resected specimen. As the length of the artery is highly variable between individuals, this technique may not be the most accurate measure of radicality as it cannot assess the length of the artery left behind inside the patient. The aim was to visualize the length of the tumour feeding artery after surgery and compare the relationship to pathological measures.

Method: The length of the arterial stump was measured from the origin to the ligation point on a CT-scan two days post-operatively. This was done by a specialized radiologist who was blinded to operative procedure.

Results: 52 patients had the required CT images. The mean length of the residual arterial stump was 38 mm, which was significantly longer than the expected length of <10 mm ($p<0.0001$). On the right side, the mean length was 31 mm and independent of the relation to the superior mesenteric vein. On the left side, the mean length was 49 mm. There was no correlation between the residual arterial stump and the pathological measures of specimen radicality.

Conclusions: The residual arterial stumps measured by post-operative CT were longer than expected even on the right side where a CME was attempted.. Caution should be taken when using pathological measures as an estimation of a central ligation.

What does this paper add to the literature?

This is the first study that measures the length of the remaining arterial stump after colon cancer surgery in a prospective and consecutive cohort. Furthermore, the results are compared to the pathological measures of central radicality on the specimen resected and we found no correlation.

Introduction

Colon cancer is a common disease with a high rate of cancer-related mortality. In Denmark, the incidence is approximately 2,700 new cases per year and almost half of them will ultimately die from their disease [1]. Twenty years ago the prognosis for colon cancer was better than for rectal cancer, but this has reversed over recent years [2,3]. The introduction of standardized surgery for rectal cancer (total mesorectal excision (TME)) has improved survival for rectal cancer patients such that it now exceeds the survival for colon cancer [1,4,5].

The principles of TME surgery are now increasingly being used in colon cancer surgery (termed complete mesocolic excision (CME)) to improve the outcome. With this technique, the surgeon follows the embryological plane behind the mesocolon and ligates the tumour-feeding artery at its origin (central high tie). If the operation is performed correctly, this technique renders a specimen with no mesocolic defects and minimal potential exposure of tumour cells. By performing a central division of the supplying artery, all of the mesocolic lymph nodes that may potentially contain metastatic deposits should be removed. This technique is associated with significantly improved survival for colon cancer patients [7-9].

The principles for the optimal pathological evaluation of colon cancer specimens are also obtained from advances in the evaluation of rectal cancer specimens. To assess the degree of central radicality, pathologists measure the distance from the tumour feeding artery to the nearest bowel wall on the specimen. This is ideally performed on the fresh specimen prior to formalin fixation. This distance records the length of the main supplying vessel removed, which is known to be highly variable between individuals [10,11] and the technique cannot assess the length of the tumour feeding artery left behind inside the patient. A recent Norwegian study based on post-operative CT-scans following complications necessitating imaging demonstrated that a much longer stump of artery was left inside the patient than that expected [12]. With optimal CME surgery and high tie ligation we would expect the vessel to be no longer than 10 millimetres (mm).

The aim of this prospective study was to measure the length of the main tumour feeding artery left behind inside the patient after colon cancer surgery. Furthermore we will explore the relationship between the distance measured on the specimen and the actual length of the arterial stump. Finally, we will clarify whether there is a difference in arterial length according to the location of the tumour in the colon and to surgical technique.

Material and methods:

Patients:

All patients over the age of 18 years at diagnosis having elective surgery for colon cancer at Randers Regional Hospital (Jutland, Denmark) were included in the study. Exclusion criteria were: 1) patients with predicted T4 tumours on the preoperative CT scan as these patients often require more extensive surgery. 2) Tumours located in the transverse colon

or at the flexures as these are few in number, the debate regarding the division of the arteries in this area is even more controversial [13,14], and the treatment of these cancers are organised differently in our region. 3) Patients with benign tumours as the pathologists did not evaluate theses specimens according to CME guidelines.4) Patients with contrast allergy or decreased renal function. The inclusion period was between 7th May 2014 and 22th June 2015 with a short interruption between 5th March 2015 and 11th May 2015 due to financial restrictions. The population in the area of Randers and Aarhus is 570,000 and all surgery for non-advanced colon cancer is performed in Randers Regional Hospital.

Surgery:

According to the operative notes, all patients underwent surgery with an intention to perform the CME technique with central ligation of the tumour feeding artery on the right side and a D2 resection on the left side. On the right side they aimed to divide the ileocolic artery (ICA) at its origin from the superior mesenteric artery (SMA). On the left side, the surgeons collectively aimed to ligate the inferior mesenteric artery (IMA) just after the departure of the left ileocolic artery (LCA) (D2 resection) in order to maintain sufficient blood flow to the left flexure [15,16]. Only certified colorectal surgeons perform colon cancer surgery at Randers Regional Hospital, and all surgeons were trained in the CME technique through on-site-visits by Professor Werner Hohenberger (University Hospital of Erlangen, Germany) and in laparoscopic CME by Professor Robin Kennedy (St. Marks Hospital, England). During the inclusion period we asked the surgeons to mark the point of ligation of the artery using a laparoscopic metal clip. This enabled the radiologist to locate the exact point of artery ligation on subsequent imaging. Unfortunately, not every patient received the clip during surgery.

Computed Tomography scans (CT-scans):

All patients diagnosed with colon cancer have a routine CT-scan of their chest, abdomen and pelvis before surgery in order to identify synchronous distant metastases using a multi-slice CT-scanner, Philips brilliance 64. The patients had a repeat abdominal CT-scan two days post-operatively prior to discharge from hospital to estimate the length of the residual vessel. Pre-operative scans were made with standard protocols for colon cancer and were used in comparison with the post-operative pictures. The postoperative scans were obtained with the following parameters: coll: 64x 0,625; increment: 1mm; pitch: 1,176; tabl.speed: 0,75; kV: 120; mAs: 250 (depending on the individual patient); dose modulation used: (D-dom). For contrast media administration (iomeron 300 mg/ml total 4 ml/kg max *180* ml followed by 50ml *s*aline) we used a power injector. Scans were obtained in the arterial and portovenous phase (scan delay for acquisition 15 sec. and 50 sec after bolus-threshold, Threshold 150HU). The postoperative scans were analysed immediately by local radiologists, to identify any clinically relevant issues prior to discharge.

Measurement of arteries:

The CT scan images were reviewed on a dedicated Philips CT workstation with 2D MPR (multi-planar reconstruction). The measurements of the arterial stump were done by one radiologist specialized in abdominal imaging (Mona Rosenkilde) and blinded to operative procedure but with knowledge of tumour location.

Concerning right hemicolectomies, the ICA was chosen as it is almost always present and for the left sided resections, the IMA was measured. Both arteries were measured from their origin to the ligation point, marked by the clip where used (Fig. 1). The ICA originates

from the SMA, and the IMA originates directly from the aorta. As the surgeons in this study chose to ligate the IMA distal to the LCA we included two measurements for the IMA: the distance from the ligation to the IMA origin (according to CME guidelines) and the distance from the ligation to the departure of the LCA (intention of the surgeons).

Validation of measurements:

We asked a second radiologist to review 20 CT-scans from the study and to measure the length of the arterial stump. We randomly selected 10 CT-scans after surgery on the right side (5 with clips and 5 without) and 10 CT-scans from the left side. These were selected by a person without any knowledge of CT-scan interpretations.

Pathology:

All standard pathological measurements taken from the specimen were recorded routinely in the pathology report. The specimens were fixed in formalin before measurements were performed. For each patient we collected: TNM-stage (version 5), distance from the high tie to the nearest bowel wall, distance from the high tie to the tumour, plane of resection (mesocolic, intramesocolic or muscularis propria), and the number of lymph nodes harvested.

Statistics:

Statistical analyses were performed with Stata IC 12 using the student *t*-test in univariate analyses. All data were demonstrated to follow a normal distribution. Spearman's rank correlation was calculated in order to identify any correlation between the variables. P values less than 0.05 were considered statistically significant.

Ethics:

The project was approved by The Central Denmark Region Committees on Health Research Ethics (J.nr. 1-10-72-333-13). Every patient provided written informed consent prior to participating in the project.

Results:

A total of 183 patients underwent surgery for non-advanced colon cancer at Randers Regional Hospital during the study period. After exclusions, 52 patients had the required CT images, which could be used for the study (Fig. 2). Patient characteristics of the study population are listed in table 1.

Radiology:

Overall: The mean length of the residual arterial stump following surgery was 38 mm, which was significantly longer than the expected length of 10 mm or less ($p<0.0001$)(Tab. 2a). The surgical technique (open vs. laparoscopic) did not influence stump length, and there was no difference in the mean stump length for cases with or without clips or according to the plane of surgery.

Right colon: The mean length of the arterial stump on the right side was 31 mm (Tab 2a). In 69 % of cases, the ileocolic artery passed posteriorly to the superior mesocolic vein, but there was no association between the length of the arterial stump and the position of the ileocolic artery (posterior: 29 mm, 95% CI (23 to 36 mm) vs. anterior: 34 mm, 95% CI (20 to 48 mm), $p= 0.47$).

Left: The mean length of the left arterial stump was 49 mm if measured to the origin of IMA (Tab 2a), but only 14 mm if measured to the origin of the LCA (Tab 2b). The measurement to the origin of the LCA was not significantly greater than the expected length of one centimetres (p=0.26).

Pathology:

Overall the mean distance from the tumour to the arterial tie on the specimen was 97 mm (95 % CI 89 to 105 mm), the mean distance from the nearest bowel wall to the arterial tie was 77 mm (95 % CI 71 to 83 mm) and the mean number of lymph nodes harvested was 27 (95 % CI 24 to 31).The correlation between these pathological measurements and the length of residual arterial stump are shown in figure 3a-c. Although we found at tendency towards a negative correlation, none of the results were statistically significant.

Comparison between radiologists:

Two competent radiologists measured the length of the arterial stump on 20 CT-scans. We found no difference between the two observers (mean 37 mm, 95% CI (26 to 47 mm) vs. 40 mm, 95% CI (30 to 49 mm) (p=0.34)).

Discussion:

Using post-operative CT scanning, we attempted to measure the length of the residual arterial stump following colon cancer resection. We were able to demonstrate that there is still a substantial length of arterial stump left behind after surgery that is reported to follow the principles of CME. This suggests that a central vascular ligation is still not routinely performed in our institution despite several years of focus on optimising colon cancer

outcomes including a CME training program. On both the left and right side of the colon, the residual arterial stump was much longer than expected.

CME is essentially an old concept [17] that has recently been rediscovered and proposed to be the optimal way to improve outcomes through standardized colon cancer surgery. However, not all surgeons routinely perform this operation. There is general consensus in the western world that the resection should be performed in the mesocolic (embryological) plane, but it is the importance of central ligation of the tumour feeding vessel that is still debated [18]. Concerns have also been raised about potentially increased morbidity from high ligation [16,19]. According to the descriptions by Hohenberger and Danish guidelines, the tumour feeding vessel should be ligated at its origin if the surgeon intend to perform CME surgery [7,20]. That is comparable to the Japanese D3 resection, which is mandated in all but the earliest colon cancers in Japan [21].

The strength of this study is the fact that it was performed prospectively and all patients included had a second CT-scan two days after surgery. We also validated the measures of the radiologist by comparing the results from two specialised radiologists and found no difference. This result supports that our approach to the measure of the arterial stump is objective. The introduction of clips at the ligation point of the vessel for some of the patients indicated the exact point of ligation. The finding of no difference in the mean length of residual arterial stump for the patients with and without clips implies that the radiologists were able to correctly identify the arterial stump without being impeded by thrombosis.

The limitations of the study were the high number of patients who did not participate during the study period and the 22 patients included that did not have a CT scan after surgery. This was mainly due to the fact that the main author was unable to ensure that all of the

necessary departments were aware of the project. We do not believe that this slip in continuity affects our results in the study.

Our study shows that surgeons may not always follow CME guidelines when they are reportedly undertaking CME surgery, and there appears to be room for improvement regarding central ligation. We systematically performed a CT scan on patients two days following colon cancer surgery and found that the mean length of the residual tumour feeding artery was 38 mm, which was significant longer than expected. The cut-off of 10 mm was an estimated ideal length of the remaining arterial stump, as a flush with the aorta may cause damage to the hypogastric nerves and a long arterial stump will risk leaving important lymph nodes behind.

Several aspects should be taken into consideration when determining the acceptable residual stump length following CME surgery for colon cancer.
On the right side there is significant variation in the anatomy of the vessels supplying and draining the large bowel. The ileocolic artery often passes posteriorly to the superior mesocolic vein [22-24], which theoretically should result in a longer residual stump as a central tie is more difficult to achieve and surgeons often choose to divide the vessel after the crossing of the vein. In our series, the ileocolic artery passed posterior to the superior mesocolic vein in 69% of cases but surprisingly did not result in a longer stump length probably because the superior mesocolic vein was never exposed. This is a potential issue as the area behind the vein is considered to a part of the mesocolon [24] and it is possible to find lymph node metastases in that area[25]. This emphases the fact, that the SMA should be divided at its origin no matter how it crosses the vein.

On the left side, the inferior mesenteric artery almost always exists and according to the principles of CME it should be divided at its origin. The superior hypogastric plexus of nerves is close to the origin of the IMA and damage to these nerves can cause severe urological and sexual dysfunction [19]. In spite of these argumentations a systematic review has shown that central ligation of the IMA should be safe [26]. However, at our institution it has been standard practice for the surgeons to ligate the vessel distal to the LCA ensuring sufficient blood supply to the left colic flexure even though there is no convincing evidence in the literature that supports this practice. This technique resulted in a significantly longer stump length on the left side compared to the right side and it should be an oncological concern that on average 40 mm of artery with its associated lymph nodes is left behind inside the patient. If the surgeon is concerned that the blood flow to the left flexure may be compromised, it could be considered to perform a D3 resection of the mesocolon but stripping this from the vessel and sparing the IMA.

On the left side we modified our analysis to additionally assess the residual stump length with respect to the origin of the LCA and showed that this was still in excess of the expected 10 mm. Our findings are similar to earlier studies that also found a much longer residual arterial stump length than would be expected [12,27].

The theory behind central ligation of the tumour feeding artery is to remove as many lymph nodes as possible and therefore any intranodal and intravascular tumour deposits that could give rise to tumour recurrence. All the lymph nodes draining the tumour-area are located within the mesocolon, mainly along the large vessels as they run centrally [28,29].

The nodes can be subdivided into pericolic (running close to the bowel wall), intermediate (running along the feeding artery) and central (at the origin of the main vessel). The number of harvested lymph nodes in this study was high even though a true CME was not performed. This number also is influenced by several factors including patient factors (age and gender), tumour factors (tumour biology, tumour stage), surgery (length of bowel resected, length of the high tie) and the scrutiny of the pathologist [31]. Only a small number of additional lymph nodes can be found at the high tie. However, there is a 10 % risk of D3 metastases hence it is worth considering the removal of these nodes[25,30]. If central tie is not performed, these nodes will be left behind and may give rise to tumour recurrence. In accordance with this we found a strong tendency to a greater number of lymph nodes harvested if the residual arterial stump length was short.

The pathological evaluation of colon cancer specimens is important for the purpose of giving feedback to the surgical team regarding surgical quality. The description of the plane of surgery provides feedback as to how well the surgeons were able to dissect in the mesocolic plane. The degree of central radicality is assessed by measuring the distance between the vascular tie and the nearest bowel wall and tumour. However, due to the marked inter-population differences that exist in these measures, it cannot accurately be determined whether a true central ligation has occurred on an individual patient basis. The pathologist can only comment on the amount of material resected, not on the amount of material that has been left behind in the patient. In our study we found no significant correlation between the length of vessel on the specimen and the residual arterial stump length on left sided specimens, which indicates that clinical teams should be careful when using these measurements as a surrogate for the radicality of surgery. While CT scans of

the residual stump length may be the ideal way to monitor central radicality, this may be difficult to implement as standard in many centres due to the cost of an additional scan and the increased dose of radiation. Another potential method is to use photo documentation during surgery to demonstrate central ligation of the artery, but this procedure is very dependent on the compliance of the surgeon. At the present time we do not have a validated method for the evaluation of the level of artery division but recent unpublished evidence from our group indicates that undertaking measurements of the residual stump length on the routine CT-scan after one year is feasible.

This study shows that even after several years of focussing on CME surgery there is still plenty of room for improvement. It is therefore crucial that surgical departments have a continuous focus on quality control through post-operative evaluations of surgery and post-graduate training.

In conclusion, we have demonstrated that it is possible to measure the residual arterial stump length following colon cancer surgery using post-operative CT-scans. We found no correlation between the level of arterial division and pathological measures. Furthermore even for right sided tumours where CME was attempted we found a surprisingly long residual tumour feeding artery suggesting that CME principles had not been strictly followed.

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Tables and figures

Table 1: Patients characteristics

Characteristics	No	%
Age, years		
Median	71	
IQR	(67 - 72)	
Sex		
Male	28	54
Female	24	46
Side of tumor		
Right (caecum and ascending colon)	32	62
Left (descending colon and sigmoid)	20	38
Type of surgery		
Open (including 4 conversions)	12	23
Laparoscopic	40	77
Plane of surgery		
Mesocolic	40	77
Intramesocolic	12	23
Muscularis propria	0	0
pT stage		
pT1	8	15
pT2	11	21
pT3	28	54
pT4	5	10
pN stage		
pN0	35	67
pN1	9	17
pN2	8	16
M stage		
M0	49	94
M1	3	6
Total lymph nodes		
Median	25	
IQR	20 - 33.5	
Number of lymph node metastases		
Median	0	
IQR	0 - 2	

Abbreviation: IQR: interquartile range

Tab 2a: Length of artery (mm) assessed by postoperative CT angiography
Intention for left side resections: ligation at the origin of the inferior mesocolic artery

	No	Mean length (mm)	95% CI	P
Total	52	38	(33 - 43)	
Right	32	31	(25 - 37)	
Left (Inf. Mesenteric artery)	20	49	(40 - 57)	
Surgical technique				
Open	12	37	(24 - 49)	
Laparoscopic	40	38	(32 - 44)	0.79
Clips				
No	39	38	(31 - 44)	
Yes	13	38	(27 - 49)	0.96
95% CI: 95% confidence interval				

Tab 2b
Intention for left side resections: ligation of the inferior mesocolic artery just after the origin of left colic artery

	No	Mean length (mm)	95% CI	P
Total	52	24	(19 - 29)	
Right	32	31	(25 - 37)	
Left (Left colic artery)	20	14	(7 - 21)	
Surgical technique				
Open	12	31	(17 - 44)	
Laparoscopic	40	23	(17 - 28)	0.18
Clips				
No	39	27	(21 - 32)	
Yes	13	18	(5 - 32)	0.15
95% CI: 95% confidence interval				

Legends:

Figure 1: CT-scan with the visualization of the inferior mesenteric artery with a clip at the ligation. The departure of the left colic artery is also visible.

Figure 2: Flow chart of exclusions

Figure 3a: Correlation between the distance “tumour to high tie” vs. the length of arterial stump. Correlation coefficient -0.13 (95% CI (-0.31; 0.05)) P=0.18

Figure 3b: Correlation between the distance “nearest bowel wall to high tie” vs. the length of arterial stump. Correlation coefficient -0.13 (95% CI (-0.38; 0.11)) P=0.28

Figure 3c: Correlation between the “number of lymph nodes harvested” vs. the length of arterial stump. Correlation coefficient -0.16 (95% CI (-0.33; 0.004)) P=0.06

Table 1: Patients characteristics

Tab 2a: Length of artery (mm) assessed by postoperative CT angiography
Intention for left side resections: ligation at the origin of the inferior mesocolic artery

Table 2b: Length of artery (mm) assessed by postoperative CT angiography
Intention for left side resections: ligation of the inferior mesocolic artery just after the origin of left colic artery