

Complete Mesocolic Excision With Central Vascular Ligation Produces an Oncologically Superior Specimen Compared With Standard Surgery for Carcinoma of the Colon

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ABSTRACT

Purpose

The plane of surgery in colonic cancer has been linked to patient outcome although the optimal extent of mesenteric resection is still unclear. Surgeons in Erlangen, Germany, routinely perform complete mesocolic excision (CME) with central vascular ligation (CVL) and report 5-year survivals of higher than 89%. We aimed to further investigate the importance of CME and CVL surgery for colonic cancer by comparison with a series of standard specimens.

Methods

The fresh photographs of 49 CME and CVL specimens from Erlangen and 40 standard specimens from Leeds, United Kingdom, for primary colonic adenocarcinoma were collected. Precise tissue morphology and grading of the plane of surgery were performed before comparison to histopathologic variables.

Results

CME and CVL surgery removed more tissue compared with standard surgery in terms of the distance between the tumor and the high vascular tie (median, 131 v 90 mm; $P < .0001$), the length of large bowel (median, 314 v 206 mm; $P < .0001$), and ileum removed (median, 83 v 63 mm; $P = .003$), and the area of mesentery (19,657 v 11,829 mm²; $P < .0001$). In addition, CME and CVL surgery was associated with more mesocolic plane resections (92% v 40%; $P < .0001$) and a greater lymph node yield (median, 30 v 18; $P < .0001$).

Conclusion

Surgeons in Erlangen routinely practicing CME and CVL surgery remove more mesocolon and are more likely to resect in the mesocolic plane when compared with standard excisions. This, along with the associated greater lymph node yield, may partially explain the high 5-year survival rates reported in Erlangen.

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INTRODUCTION

The introduction of total mesorectal excision (TME) for the surgical treatment of rectal cancer has been shown to significantly improve outcomes,¹⁻³ and in some countries the survival has now overtaken that of colonic cancer.^{4,5} TME surgery is based on the principle that dissection in the mesorectal plane produces an intact fascial-lined specimen which contains all the blood vessels, lymphatic vessels, and lymph nodes through which the tumor may disseminate,^{6,7} and also reduces the risk of an involved circumferential resection margin (CRM). The resulting plane of surgery can be graded by the pathologist and has been shown to be independently related to the risk of developing local disease recurrence.^{8,9}

There are approximately 36,700 new cases of colorectal cancer diagnosed annually in the United

Kingdom,¹⁰ and 147,000 in the United States,¹¹ of which approximately two thirds occur in the colon. The colonic mesentery or mesocolon contains the vascular and lymphatic drainage systems of the colon and therefore adequate clearance is likely to have the same oncologic benefit as TME surgery in the rectum. Similar to within the rectum, embryological tissue planes have been shown to exist in the colon.¹² We have previously demonstrated that meticulous mesocolic plane surgery (intact mesocolon) is associated with a 15% greater 5-year overall survival compared with cases where defects in the mesocolon reached down onto the muscularis propria.¹³

The additional benefit of complete mesocolic excision (CME) in the mesocolic plane with central vascular ligation (CVL) is currently unknown. This more radical operation attempts to remove the entire mesocolon and all potential routes of

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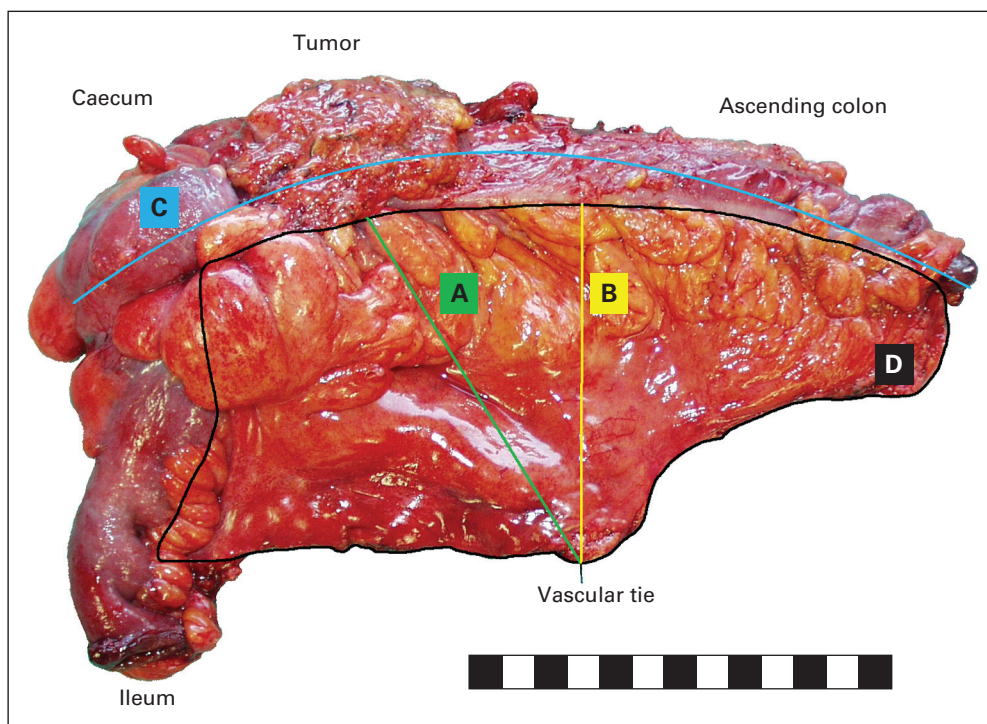


Fig 1. Method of morphometric quantitation including (A) distance from the tumor to the high vascular tie, (B) closest bowel wall to the high vascular tie, (C) length of the large bowel, and (D) area of mesentery.

metastatic tumor spread by carefully dissecting along embryologic tissue planes and transecting the supplying vessels at their origin.¹² For right-sided tumors, this involves division of the ileocolic vessels at their origin from the superior mesenteric artery and vein. In some patients a right colic artery may also be present which is similarly divided at its origin. For left-sided tumors, the root of the inferior mesenteric artery is divided. Surgeons in Erlangen, Germany, routinely practice this technique and report 5-year survival rates in potentially curative resections of higher than 89%.¹²

We aimed to further investigate the importance of CME and CVL surgery for colonic cancer by comparing a series of CME and CVL specimens from Erlangen to standard excisions from Leeds, United Kingdom. Lymph node yields, tissue morphometry, and grading the plane of surgery were used to investigate differences between the techniques that could potentially explain the relative differences in survival.

METHODS

Erlangen Patients

A consecutive series of 49 primary open resections for suspected colonic adenocarcinoma performed by nine surgeons between April 25, 2007, and October 29, 2008, were prospectively identified at the University Hospital of Erlangen, Germany. CME and CVL was attempted in all patients as described previously.¹² The unfixed specimens were immediately photographed by the surgical team after removal.

Leeds Patients

A series of 25 resections for colonic adenocarcinoma performed at the Leeds General Infirmary, United Kingdom, between April 2, 2008, and December 15, 2008, were prospectively identified and photographed by the pathology department in the unfixed state. In addition, the unfixed pictures from a further 15 resections performed between May 21, 1999, and September 12, 2003, were retrospectively identified from the departmental image archive. Neither were a consecutive series as specimens were not routinely photo-

graphed fresh. All were primary resections performed both open and laparoscopically by 10 surgeons (median, 3.5 cases per surgeon; interquartile range [IQR], 3.0 to 6.5). None of the surgeons were known to be routinely practicing CME and CVL. To ensure comparability of the data sets, three Leeds patients were excluded from lymph node retrieval, side of resection, length of large bowel, and area of mesentery analyses (two subtotal colectomies and one small wedge excision).

Patient Demographics and Pathologic Data

Demographic and pathologic staging data were obtained from a combination of the hospital records and the histopathology reports. The reporting pathologists performed routine diagnostic examinations and were unaware of the study. Lymph node dissection was performed by the local pathologist without additional node enhancing or fat clearance techniques.

Grading the Plane of Surgery

The plane of surgery was graded from the specimen photographs by two independent observers (N.P.W., P.Q.) using a method described previously.¹³ Grading was dependent on the plane of mesocolic dissection and was classified into the muscularis propria plane, intramesocolic plane, or mesocolic plane. In right hemicolectomy specimens, a thin translucent peritoneal window is often seen in the right mesocolon formed by a bilayer of fused peritoneum with no intervening fat. Isolated disruption of this window did not downgrade the specimen from the mesocolic plane. Any differences between the grades were discussed before a final plane was agreed on.

Tissue Morphometry

The photographs received were all high-resolution digital color images taken of the front and back of the unfixed, unopened specimen placed alongside a metric scale. In all cases the mesentery was laid out flat without stretching, and the site of the tumor and high vascular ties (HVT) were identifiable. The distance from the tumor and the closest bowel wall to the HVT, the length of the large and small bowel, and the area of mesentery resected was accurately quantified (Fig 1) using the CellD image analyzer (Olympus, Tokyo, Japan).

Statistical Analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Institute, Chicago, IL). Comparisons between clinicopathologic variables were performed with the Fisher's exact, Mann-Whitney U, or the Kruskal-Wallis

Table 1. Clinicopathologic Data for Patients From Erlangen and Leeds

Characteristic	Erlangen		Leeds		P
	No.	%	No.	%	
Sex					
Male	24	49	19	48	.890
Female	25	51	21	53	
T stage					
T0	2	4	0	0	.565
T1	2	4	1	3	
T2	3	6	7	18	
T3	34	69	21	53	
T4	8	16	11	28	
N stage					
N0	29	59	20	50	.464
N1	10	20	11	28	
N2	10	20	9	23	
M stage					
M0	38	78	39	98	.006
M1	11	22	1	3	
Extramural vascular invasion					
No	45	92	27	68	.004
Yes	4	8	13	33	
WHO differentiation grade					
1	0	0	2	5	< .0001
2	26	55	35	88	
3	21	45	3	8	
NA	2				
Resection margin status					
R0	43	94	34	85	.221
R1	2	4	6	15	
R2	1	2	0	0	
NA or unknown	3		0		
Side of resection					
Right	30	61	16	40	.026
Left	19	39	21	53	
Other	0	0	3	8	

NOTE. Both raw numbers and valid percentages are shown. Percentages are rounded to the nearest whole number. Abbreviation: NA, not available.

test as appropriate. Correlation analyses were performed on all variables that fell within three standard deviations of the mean using Spearman's rho. Analyses where the *P* value was less than .05 were considered to represent statistical significance.

Ethical Approval

Individual patient consent was not needed for this study. Ethical approval was granted by the Northern and Yorkshire Research Ethics Committee, Jarrow, United Kingdom (unique reference number 07/MRE03/24).

RESULTS

Patient Characteristics

Patient clinicopathologic data are presented in Table 1 and lymph node retrieval data are presented in Table 2. There was no significant difference in histopathologic staging between the groups. The Leeds patients were older (median, 76 years; IQR, 67 to 80) compared with Erlangen patients (median, 68 years; IQR, 60 to 79), but this did not reach significance (*P* = .052). Significantly more lymph nodes were identified in excisions from Erlangen compared with Leeds (Table 2). This was true for both right-sided (median 32 v

23; *P* = .004) and left-sided resections (median, 29 v 14, *P* < .0001). Right-sided resections contained significantly more lymph nodes compared with left-sided resections in Leeds (*P* = .0009), but not in cases from Erlangen (*P* = .97).

Plane of Surgery

There was moderate correlation between the two scorers with agreement in 78% of cases (κ = 0.425; 95% CI, 0.204 to 0.647). Significantly more mesocolic plane excisions were seen in Erlangen compared with Leeds, and there was no significant change from the retrospective to the prospectively collected Leeds cases (Fig 2). There was a trend toward better planes with left-sided resections but this was not statistically significant for either Leeds (*P* = .323) or Erlangen (*P* = .100).

Tissue Morphometry

Surgeons in Erlangen removed significantly more tissue than surgeons in Leeds across all patients (Fig 3), which was independent of the side of resection (Table 3). A greater area of mesentery was removed with left-sided resections compared with right-sided resections

Table 2. Lymph Node Retrieval Data for Patients From Erlangen and Leeds

Parameter	Erlangen	Leeds	P
Median No. of lymph nodes retrieved	30	18	< .0001
IQR	23-39	12-24	
Positive nodes retrieved			
All patients			
Median	0	1	.241
IQR	0-2	0-3	
N1/2 patients			
Median	4	3	.923
IQR	1-6	1-6	
Negative nodes retrieved			
All patients			
Median	28	16	< .0001
IQR	21-38	10-22	
N1/2 patients			
Median	26	12	< .0001
IQR	18-33	5-17	
Lymph node ratio			
All patients			
Median	0	3	.110
IQR	0-6	0-29	
N1/2 patients			
Median	10	27	.019
IQR	4-24	8-53	

NOTE. Positive nodes are those containing histologic evidence of metastatic carcinoma. Negative nodes show no evidence of metastatic spread. Lymph node ratio is the percentage of lymph nodes retrieved that contain metastatic carcinoma. Abbreviation: IQR, interquartile range.

in both Erlangen ($P = .011$) and Leeds ($P = .047$). In addition, there was a greater distance from the tumor to the HVT ($P = .020$) and the closest bowel wall to the HVT ($P = .044$) in left-sided resections compared with right-sided resections from Leeds, and also a greater

length of large bowel in left-sided resections compared with right-sided resections from Erlangen ($P < .0001$).

Across all patients, there was a significant correlation between the number of lymph nodes retrieved and the distance from the tumor to the HVT ($r = 0.305$; $P = .006$), the distance from the closest bowel wall to the HVT ($r = 0.241$; $P = .033$), the length of the large bowel ($r = 0.307$; $P = .006$), and the area of mesentery ($r = 0.374$; $P = .001$).

Less tissue was removed by muscularis propria plane surgery compared with mesocolic plane surgery in the Leeds patients although the differences were not statistically significant: distance from the tumor to the HVT (median, 77 v 87 mm; $P = .850$), distance from the closest bowel wall to the HVT (median, 78 v 79 mm; $P = .777$), length of the large bowel (median, 171 v 249 mm; $P = .299$), and area of mesentery (median, 6,731 v 13,166 mm²; $P = .186$).

It appeared that more tissue was removed in the prospectively collected cases from Leeds compared to the retrospective cases although the differences were not statistically significant: distance from the tumor to the HVT (median, 95 v 81 mm; $P = .303$), distance from the closest bowel wall to the HVT (median, 86 v 73 mm; $P = .252$), length of the large bowel (median, 209 v 200 mm; $P = .567$), and area of mesentery (median, 13,095 v 11,013 mm²; $P = .690$).

DISCUSSION

While the optimal operative technique, avoidance of CRM involvement and the influence of the plane of surgery in rectal cancer are well established, the evidence for a similar effect in colon cancer is less accepted. We have previously shown that removal of an intact mesocolon in the mesocolic plane is an oncologically superior operation inferring a 15% overall survival advantage at 5 years compared with

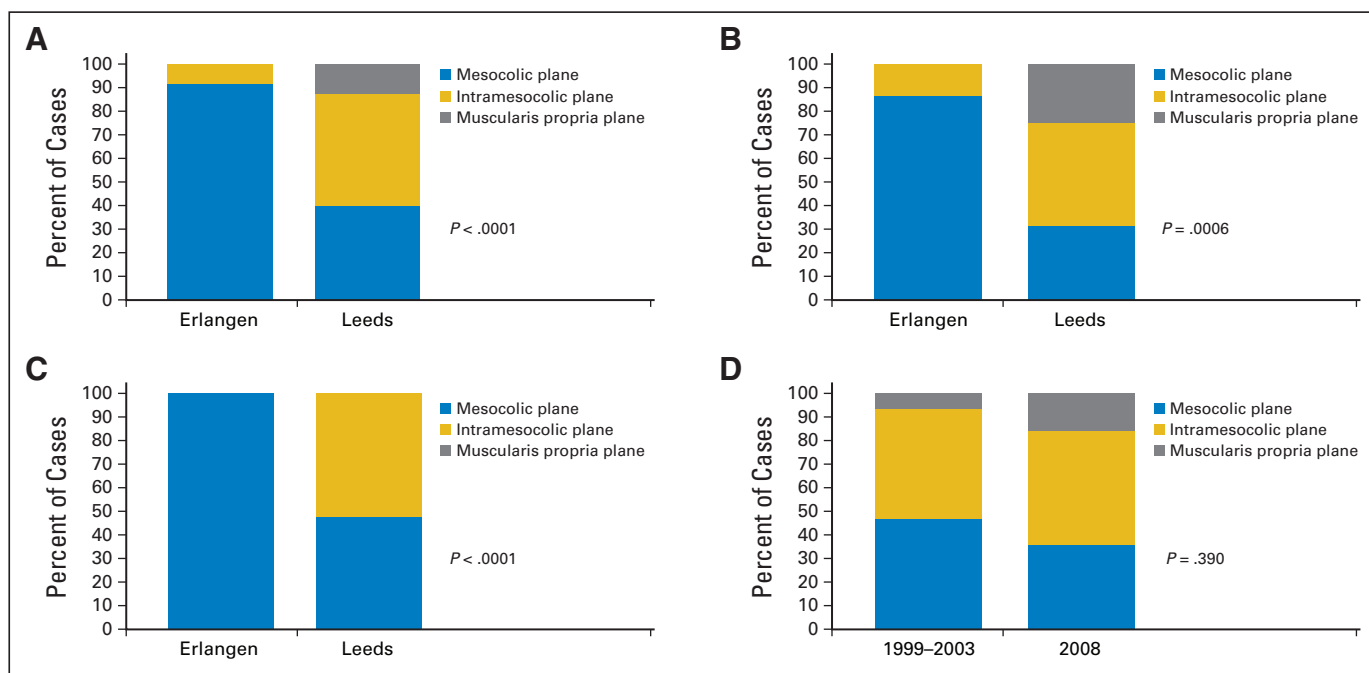


Fig 2. Percentage distribution of the plane of surgery (mesocolic, intramesocolic, or muscularis propria) according to institution or time period for (A) all patients, (B) right-sided resections, (C) left-sided resections, and (D) Leeds patients collected retrospectively (1999-2003) and prospectively (2008).

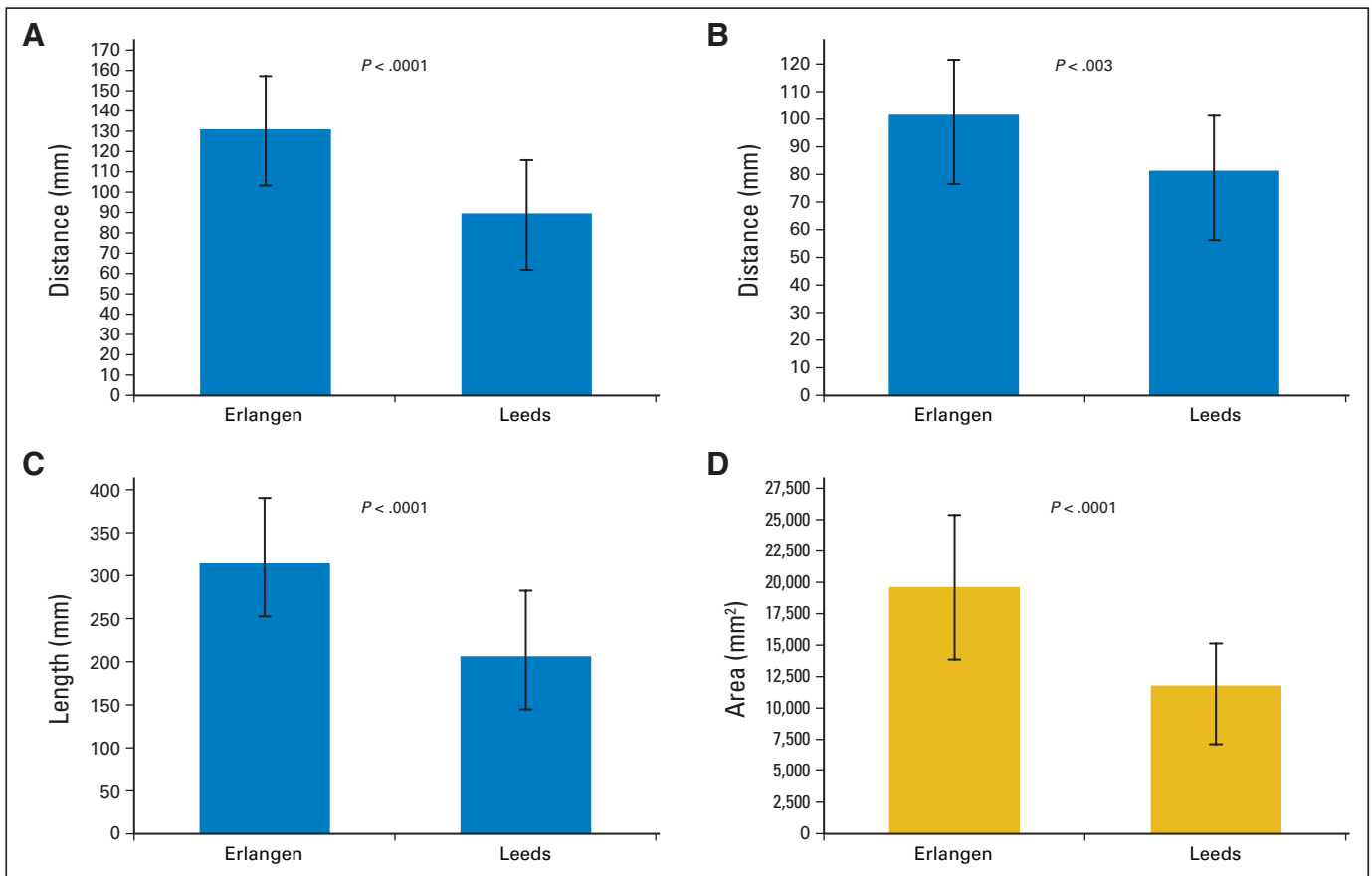


Fig 3. Median tissue morphometry measurements for patients from Erlangen and Leeds including (A) distance from the tumor to the high vascular tie, (B) closest bowel wall to the high vascular tie, (C) length of the large intestine, and (D) area of mesentery. Error bars signify the interquartile range.

surgery with large defects onto the muscularis propria.¹³ Others have also shown that consistent radical colonic cancer surgery is associated with improved outcomes.^{14,15} Surgery in the mesocolic plane forms an intact peritoneal and fascial-lined package of mesentery containing all potential routes of metastatic tumor spread. By contrast, surgical disruption of this plane risks tumor spillage into the peritoneal cavity, particularly in patients with advanced disease. We have shown that surgeons from Erlangen are more likely to produce a mesocolic plane

resection than surgeons from Leeds, which presumably reflects the more consistent use of embryological tissue planes when performing CME and CVL surgery. The agreement between the two scorers for the plane of surgery in this series was 78% compared to the previously reported 85% (κ from 0.76 to 0.84) obtained using cross-sectional slices in addition to whole specimen photographs.¹³ This provides further evidence that grading the plane of dissection in colon cancer may be a valid and reproducible method of specimen assessment and could be used as a marker of surgical quality.

While the advantages of mesocolic plane surgery appear obvious, the optimal extent of mesenteric dissection has been debated for decades. Some studies have shown an advantage to central ligation,¹⁶⁻¹⁹ while others have been unable to show improved outcomes when compared with standard techniques.²⁰⁻²³ We believe this could be due to a failure to standardize the plane of surgery in these studies, with the potential advantage of CVL being lost by coexisting intraoperative disruption of the mesocolon and associated spread of the tumor.

Recognition that CVL may provide optimal lymphovascular clearance was first recognized 100 years ago.²⁴ Colonic lymph nodes tend to follow the arterial supply; hence central ligation will remove the highest draining nodes that may harbor occult metastases. This principle was strictly adhered to by Enker and colleagues¹⁹ who published their outcome data in 1979 where they reported 5-year disease-free survival rates of up to 70% in stage III. Surgeons in

Table 3. Median Tissue Morphometry Measurements for Patients From Erlangen and Leeds According to Side of Resection (right or left)

Resection by Side	Erlangen	Leeds	P
Right			
Tumor to HVT, mm	128.7	81.4	$< .0001$
Normal bowel to HVT, mm	101.6	72.4	.007
Length of large bowel, mm	264.9	183.2	.002
Length of small bowel, mm	83.3	60.3	.003
Area of mesentery, mm ²	16,769.6	8,881.0	$< .0001$
Left			
Tumor to HVT, mm	145.0	97.0	.001
Normal bowel to HVT, mm	107.6	85.1	.044
Length of large bowel, mm	392.2	260.3	$< .0001$
Area of mesentery, mm ²	24,127.5	13,166.2	$< .0001$

Abbreviation: HVT, high vascular ties.

Erlangen have routinely practiced CME and CVL for a number of years and have reported greater 5-year survival rates than standard mesocolic plane excisions for potentially curative colon cancer resected in Leeds.^{12,13} In addition, the Japanese Society for Cancer of the Colon and Rectum advocates recording the lymph node groups removed and would only consider a complete dissection of all regional nodes if the specimen contained the central (D3) nodes.²⁵ Japanese surgeons utilizing this technique report overall 5-year survival rates of up to 76% in stage III disease (K. Sugihara, personal communication, December 2008) and can produce similar lymph node yields to those seen in Erlangen, although we recognize that stage migration may confound the results.²⁶

We have confirmed that CME and CVL surgery removes significantly more tissue than standard excisions in terms of the distance from the tumor to the HVT, the distance from the closest bowel wall to the HVT, the length of the large bowel, length of the ileum (where present), and the area of mesentery. The distance from the tumor to the HVT was also measured in the Medical Research Council CLASICC (Conventional Versus Laparoscopic-Assisted Surgery in Colorectal Cancer) trial,²⁷ in which 794 patients were randomly assigned between open and laparoscopic surgery. Four hundred thirteen patients had colonic cancer resections and the median distance from the tumor to the HVT was 90 mm in open surgery (IQR, 70 to 110 mm) and 80 mm in laparoscopic surgery (IQR, 65 to 100 mm), providing evidence that the surgery in Leeds (median distance, 90 mm; IQR, 67 to 111 mm) is similar to that within a national United Kingdom trial.

Lymph node yields have previously been shown to be dependent on both the surgeon and the pathologist,²⁸ which could potentially bias the results in a two-center observational study. However, the median node yield in Leeds is well above the United Kingdom minimum standard,²⁹ as is the identification of extramural vascular invasion which can both be used as indirect markers of pathological quality. We believe that the difference in lymph node yields across all excisions and for both right- and left-sided resections are too great and must reflect the increased amount of tissue removed both longitudinally and centrally. This is confirmed by the significant correlations between greater lengths and areas with higher lymph node yields. In particular there was an increase in the number of negative lymph nodes with CME and CVL surgery which has been linked to improved survival in both lymph node-negative cases^{30,31} and stage III disease.³²

It is expected that the biggest survival advantage for patients undergoing CME and CVL surgery will be seen in stage III disease. CVL may result in down staging by converting what would otherwise have been a Dukes C2 case with standard surgery into a Dukes C1 case. The plane of surgery is also likely to be of great importance for stage III patients. We have previously shown in Leeds that potentially curative stage III disease resected in the mesocolic plane can expect a 5-year overall survival of 58% compared with just 35% if resected in the muscularis propria plane.¹³ Unfortunately it is not yet possible to accurately identify involved lymph nodes in colon cancer using radiologic imaging before surgical excision. We therefore must strive to achieve the optimal resection for all suitable patients, as around 50% of these will turn out to have stage III disease after formal high quality histopathologic staging.

While a relationship between the quality of rectal cancer surgery and local recurrence is established,⁹ the evidence for a similar effect in

colon cancer is lacking, apart from in the Medical Research Council CLASICC trial.³³ Due to the small numbers involved in our study and the prospective nature of data collection, it is neither possible nor appropriate to assess for local recurrence at this stage. During the resection of colon cancer, surgical resection margins are created in both the right colon (retroperitoneal margin) and distal left colon (top of the mesorectal circumferential margin). We have demonstrated a higher rate of incomplete tumor removal in resections from Leeds compared with Erlangen, but this was not significant, probably due to the relatively small number of cases investigated. Earlier data from Leeds suggested that retroperitoneal margin involvement in the right colon is associated with advanced tumor stage and therefore adjuvant radiotherapy may not offer the same degree of benefit as in rectal cancer.³⁴ The effect of both local recurrence and surgical resection margin involvement in colon cancer is currently under investigation in the prospective United Kingdom National Cancer Research Institute FOxTROT (Fluoropyrimidine, Oxaliplatin and Targeted Receptor Pre-Operative Therapy for Colon Cancer I) trial.

Some questions around the potential uses of CME and CVL surgery in colonic cancer remain unanswered. The utilization of laparoscopic techniques in colorectal surgery continues to rise and the feasibility of accessing the correct tissue planes is not fully understood, although some studies suggest that it is possible.²⁶ Additionally it remains unclear whether a more radical excision is associated with greater morbidity and mortality. Unfortunately due to the prospective nature and size of this study, relationship to these factors was not possible. However, studies performed in Erlangen have demonstrated an uneventful postoperative recovery in 80% of patients and a mortality rate during hospitalization of around 3%.¹² Others have suggested an increase in genitourinary complications for left-sided resections following CVL.²⁶ We understand that aggressive surgery may not be appropriate in patients with major comorbidities and the importance of extensive surgery in advanced disease remains unproven.

We have been able to demonstrate for the first time that CME and CVL surgery removes more tissue around the tumor and is more likely to be resected in the mesocolic plane, resulting in a maximal lymph node harvest. In a small comparative series, it is not possible to determine the absolute benefit of such surgery to patients and the relative importance of the extent of mesocolic dissection, the plane of surgery, the lymph node yield or other factors. The importance of the plane of surgery in colon cancer is currently under study in the NCRI FOxTROT trial, however, further studies are required and we wholly agree that a clinical trial using standardized mesocolic plane surgery with a random assignment between CVL and standard vascular ligation is urgently needed.³⁵ Understanding the variation in surgical practice in rectal cancer has led to major improvements in survival in Sweden,¹ the Netherlands,² Norway,³ the United Kingdom, and elsewhere. We believe that we have demonstrated in this article and previously¹³ that variation exists in colonic cancer surgery and equivalent benefits may be achievable by improvements in the plane of surgery accompanied by a quality assurance program. Such programs are very cost effective compared with interventions such as chemotherapy and need to be urgently explored in surgery for colon cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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