Review

Roland S. Croner*, Henry Ptok, Susanne Merkel and Werner Hohenberger

Implementing complete mesocolic excision for colon cancer – mission completed?

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Abstract: The definition of complete mesocolic excision (CME) for colon carcinomas revolutionized the way of colon surgery. This technique conquered the world starting from Erlangen. Nevertheless, currently new developments especially in minimally invasive surgery challenge CME to become settled as a standard of care. To understand the evolution of CME, anatomical details occurring during embryogenesis and their variations have to be considered. This knowledge is indispensable to transfer CME from an open to a minimally invasive setting. Conventional surgery for colon cancer (non-CME) has a morbidity of 12.1–28.5% and a 3.7% mortality risk vs. 12–36.4% morbidity and 2.1–3% mortality for open CME. The morbidity of laparoscopic CME is between 4 and 31% with a mortality of 0.5–0.9%. In robotic assisted surgery, morbidity between 10 and 25% with a mortality of 1% was published. The cancer-related survival after 3 and 5 years for open CME is respectively 91.3–95% and 90% vs. 87% and 74% for non-CME. For laparoscopic CME the 3- and 5-year cancer-related survival is 87.8–97% and 79.5–80.2%. In stage UICC III the 3- and 5-year cancer-related survival is 83.9% and 80.8% in the Erlangen data of open technique vs. 75.4% and 65.5–71.7% for laparoscopic surgery. For stage UICC III the 3- and 5-year local tumor recurrence is 3.8%. The published data and the results from Erlangen demonstrate that CME is safe in experienced hands with no increased morbidity. It offers an obvious survival benefit for the patients which can be achieved solely by surgery. Teaching programs are needed for minimally invasive CME to facilitate this technique in the same quality compared to open surgery. Passing these challenges CME will become the standard of care for patients with colon carcinomas offering all benefits of minimally invasive surgery and oncological outcome.

Keywords: colon cancer; colorectal cancer; complete mesocolic excision; minimally invasive surgery; robotic.

***Corresponding author: Prof. Dr. Roland S. Croner,** Department of General-, Visceral-, Vascular- and Transplant Surgery, University Hospital Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany, E-mail: Roland.Croner@med.ovgu.de
Henry Ptok: Department of General-, Visceral-, Vascular- and Transplant Surgery, University Hospital Magdeburg, Magdeburg, Germany
Susanne Merkel and Werner Hohenberger: Department of Surgery, University Hospital Erlangen, Erlangen, Germany

Introduction

Colorectal cancer (CRC) is the third main frequent malignancy worldwide. In 2012 a global count of 14.1 million CRCs was estimated. Of these patients, 7.4 million were male and 6.7 million female. Recent ratings expect this number to increase to about 24 million in 2035. CRC is more frequent in so-called "more developed" countries (29.9/100.000 people) compared to "less developed" ones (11.7/100.000 people). This may reflect a specific lifestyle in developed countries which increases the risk for not only cancer but also other diseases related to affluent societies [1]. The realization of this fact led to the initiation of preventive colonoscopy programs. These screening programs reduced the CRC incidence by about 67% and the mortality by approximately 50% [2]. But it was not only screening programs that decreased CRC mortality. Also emerging multimodal, interdisciplinary new treatment algorithms influenced this development.

Surgery is a key player in CRC therapy and can therefore affect the outcome tremendously. Several new techniques such as total mesorectal excision, which was described by Heald, and cylindrical abdominoperineal excision, described by Holm, improved the outcome in rectal cancer [3–6]. In colon carcinomas the surgical technique of complete mesocolic excision (CME) that was published by Hohenberger in 2009 started in Erlangen then spread around the world [7]. Until today it influences the style of surgery in colon carcinomas and led to a survival benefit for patients [8]. Nevertheless, there are ongoing inventions in minimally invasive surgical procedures, and new adjuvant chemotherapies evolve. Behind these facts CME must find its place within this new setting and face current challenges.

Anatomical background of CME

CME follows the concept of tissue mobilization by releasing planes during dissection following the embryologic interphases between the parietal and the mesenteric fasciae. This avascular space develops during secondary attachment of the parietal and visceral fascia. The visceral mesenteric fascia covers the gastrointestinal tract like a continuously running plane and includes the visceral organs and the providing vessels with the draining lymph nodes. The parietal fascia covers the inner wall of the abdominal cavity. It received a variety of names, like Gerota's or Waldeyer's fascia. Even the Dennonvillieur's fascia is part of that. The visceral fascia of the ascending and descending colon attaches during embryogenesis to the parietal one. Hereby avascular spaces develop which can be divided by surgery through sharp dissection. The visceral and parietal planes, finally being a fascia covering all intra-abdominal organs on one side and the retroperitoneal ones on the other, are recognized as planes during this procedure along which the surgeon can find his guidance.

The colon-serving arteries and especially the veins exhibit several anatomical variations which have to be considered during surgery. For example, the right colic artery is not an anatomical constancy in all cases. At a maximum of 15% of cases, it arises from the mesenteric artery as a solitary branch (Hohenberger's experience). Most frequently, the ascending colon is supplied from the right branch of the middle colic artery. An accessory middle colic artery exists in 11.7%. The ileocolic and middle colic arteries are constant vessels arising from the superior mesentery artery in 100% of cases [9, 10]. The ileocolic artery can surround the superior mesenteric vein or arise beneath the ileocolic vein. This is an important variation and has to be recognized during the procedure of central vessel ligation.

The right colic vein, the gastroepiploic vein, and the pancreatic veins do not regularly drain into the superior mesenteric vein separately. Their drainage is most frequently provided by a common vein, the trunk of Henle which can be found in around 88% of all cases [10, 11]. The drainage of these veins via the trunk of Henle or directly in the superior mesenteric vein underlies a variation which has to be considered by surgeons during mobilization of the hepatic flexure of the colon. There is no sex-dependent relation concerning the vein variability [10]. The exact knowledge of the vessels and the possible variations has to be recognized and studied by surgeons who attempt correct central vessel ligation. Only a sharp and correct central vessel ligation ensures the dissection and harvesting of the central proportion of the tumor-draining lymph nodes. This is important because it can influence the patients' prognosis.

History of CME

The concept of CME was developed and published by Hohenberger et al. [7]. He established this type of surgery which includes plane preservation and central lymph node dissection and is oriented along the avascular planes. Hereby the specimen can be harvested as a package which contains the tumor providing arteries, the draining vessels, the lymph nodes, and eventually other tumor deposits. This is important for the surgeon to guarantee the integrity of the visceral peritoneum around the specimen, to prevent tumor spread, and to harvest the tumor and its anatomical edges completely including the central proportion.

The particular features of the specimens harvested by CME were initially recognized by Quirke (Pathology and Tumour Biology, St James's University Hospital, Leeds, UK), who identified and described the specific items by pathological examinations. West (Pathology and Tumour Biology, Leeds Institute of Cancer and Pathology, School of Medicine, Leeds, UK) compared the CME specimens with colon resections harvested during conventional surgery and defined landmarks for morphometric evaluation of the resected specimens [12]. Hereby the pathologist can assess the quality of the removed tissue. This is an important tool, because it makes surgical quality measurable and comparable by objective parameters. Based on West's parameters, the difference between specimens harvested by CME and conventional surgery became obvious [12]. The first analysis of the Erlangen data elucidated that patients had a better outcome than other cohorts which did not undergo CME [7, 13]. This initiated the recognition of CME as a new surgical tool to improve patients' prognosis worldwide. Currently, CME is an established procedure in colon surgery for cancer with obvious prognostic benefit for the patients. But there are ongoing discussions if it should be used as standard of care for patients for morbidity concerns.

Surgical technique and pitfalls of CME

The key for the right CME dissection is the identification of the avascular planes between the parietal and the mesenteric fasciae [7]. In open surgery the direction is usually a lateral to medial approach (Figure 1). Once the right space has been established, it can be followed to the central vessels. Usually, the orientation during plane dissection can be carried out by following an obviously guiding line which is visible during a correct procedure. Losing the right way will result in bleeding and can damage retroperitoneal structures. To get the necessary access to the central vessels, it is important not only to mobilize the bowel involved with cancer but also to take down all embryologic adhesions by sharp dissection of the interphase between the parietal fascia and the mesenteric fascia, which was described by Toldt, already more than 100 years ago [14]. It includes a full Kocher maneuver for tumors of the right and transverse colon. These steps allow bringing the tumor with the adjacent bowel and its root in front of the abdominal wall with easy access and then to the central vessel. On the right side, the next step is to take down the duodenum with the pancreatic head from the ascending mesocolic fascia, again following the mesenteric plane, which is running continuously covering posteriorly the dorsal aspect of the pancreatic head, then becoming the duodenal fascia, which is commonly called "serosa", then continuing over the uncinated process of the pancreas and the ascending mesocolic fascia. To get access to the superior mesenteric vein and the artery afterwards, this fascia has to be split and dissected off the vein first. The vessels develop inside the layers of the visceral fascia during embryogenesis, and they supply and drain the colon. Only by opening the peritoneum around the vessels can the anatomy and the described variations be identified exactly. This is important because the central ligation of the vessels ensures the harvesting of all tumor-draining lymph nodes. Without correct vessel identification the risk of wrong dissection occurs, which can be very harmful for the patient. During the stepwise mobilization of the mesocolon between the fascia's layers, it is important to keep some traction on the specimen. Traction and countertraction facilitate a sharp dissection and opening

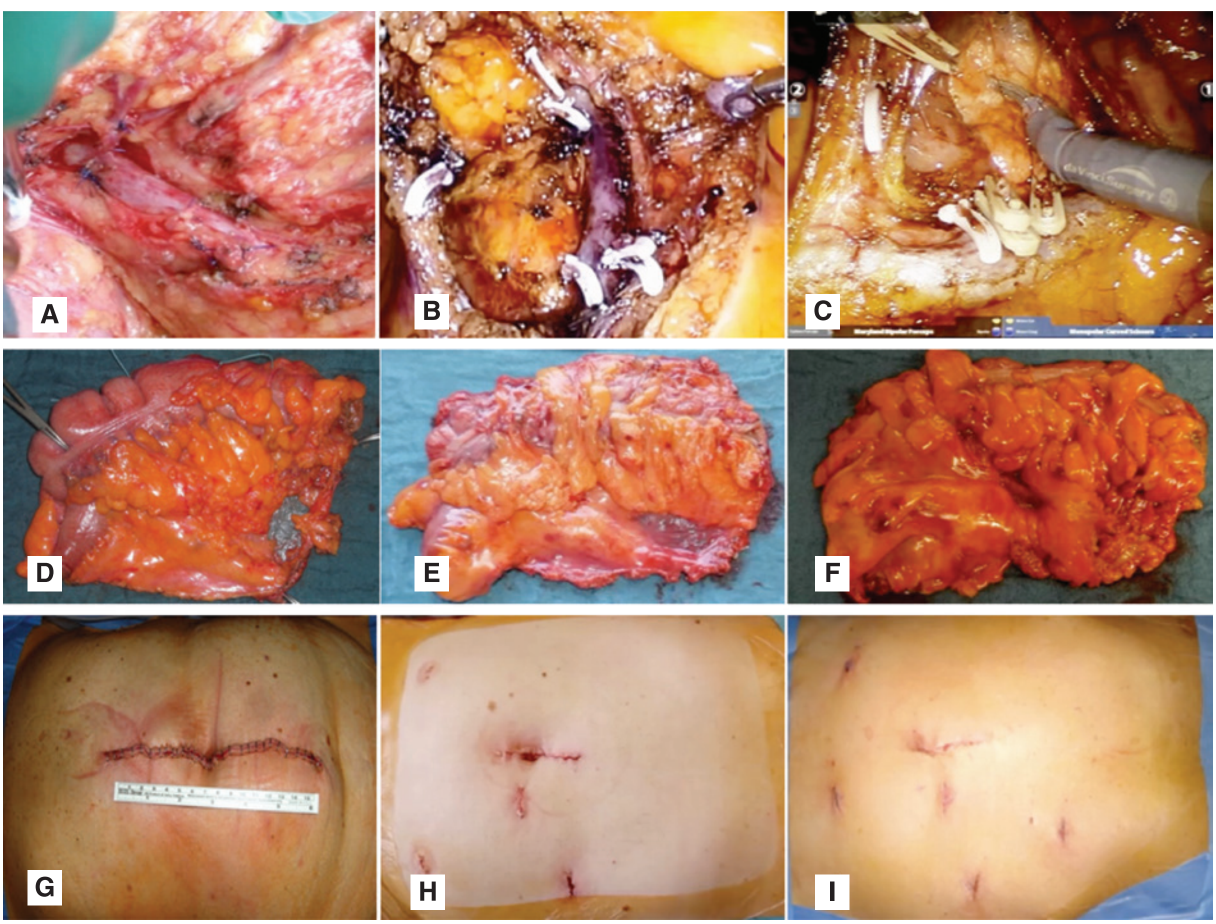


Figure 1: Central vessel dissection during complete mesocolic excision (CME) for right hemicolectomy by (A) open, (B) laparoscopic, and (C) robotic assisted CME.
Harvested specimens of the right colon by (D) open, (E) laparoscopic, and (F) robotic assisted CME. Postoperative abdomen after (G) open, (H) laparoscopic, and (I) robotic assisted CME.

of the necessary spaces. But this also takes the risk of damaging the veins by drawing too much tension on them.

Especially the small veins around the trunk of Henle can rupture and cause massive bleeding. Therefore, this region is also called the bleeding point, which means that special attention has to be drawn on this region during the preparation process. It has to be mentioned that especially the veins draining into the trunk of Henle show a brought variability. The right colic vein, the right gastro-epiploic vein, and the anterior pancreatic veins can drain to the trunk of Henle or lead separately to the superior mesenteric vein. They have to be separated and identified, because during right-sided CME usually only the right colic vein needs to be cut (Figure 1).

The right colic artery is present in less than half of all cases and is therefore not an anatomic constant landmark. The stem of the middle colic artery must be identified, because here the right branch is a part of the surgical specimen and needs to be cut in right hemicolectomy. The mobilization of the duodenum and the pancreatic head during open CME enables the ventralization of the vessels. It is a helpful procedure especially in obese patients. If bleeding especially at the veins occurs, the veins can be manually compressed by grabbing this mobilized region with a hand. Performing CME the correct way needs some training and a deep knowledge of the vessel anatomy. Otherwise there is a risk to increase morbidity.

Laparoscopic CME

CME can be carried out minimally invasively in the same quality compared to open procedures [15]. For laparoscopic CME various techniques are described to get access to the central portion of the vessels and to dissect the specimens along the right planes. A superior/inferior, retroperitoneal, and uncinate first approach are published [16–18]. Some authors prefer a medial to lateral, others a lateral to medial dissection of the avascular planes. Hereby especially in obese patients the main challenge is to identify the central portion of the vessels. Especially during the medial to lateral approach, the entrance directly to the superior mesenteric vein and artery can be problematic in patients with increased amounts of mesenteric fat. Intraoperative imaging tools like indocyanine green may be helpful to overcome this challenge in the future (Figure 2). Even single-port or hand-assisted procedures are discussed in the current literature [19–21]. No differences in morbidity and outcome between single-port and multiport laparoscopy for CME are described. The rates of 3-year disease-free and overall survival in single-port and multiport surgery are 95.5% and 91.3% ($p = 0.44$) and 100.0% and 98.7% ($p = 0.24$) [22]. The morbidity for the hand-assisted technique is quite low (6.4%) and may reflect good manual tissue and vessel control [19]. During laparoscopic CME all benefits of minimally invasive procedures can be added to the patients, but it needs advanced skills of the surgeon in this type of operation. The concept of traction and countertraction is even here necessary to identify the right dissection planes (Figure 1). But this offers the risk of venous bleeding by vessel damage caused by increased tension. Surgeons must be prepared for these pitfalls during conventional laparoscopy. Maybe the robot offers a better vessel control during its specific features.

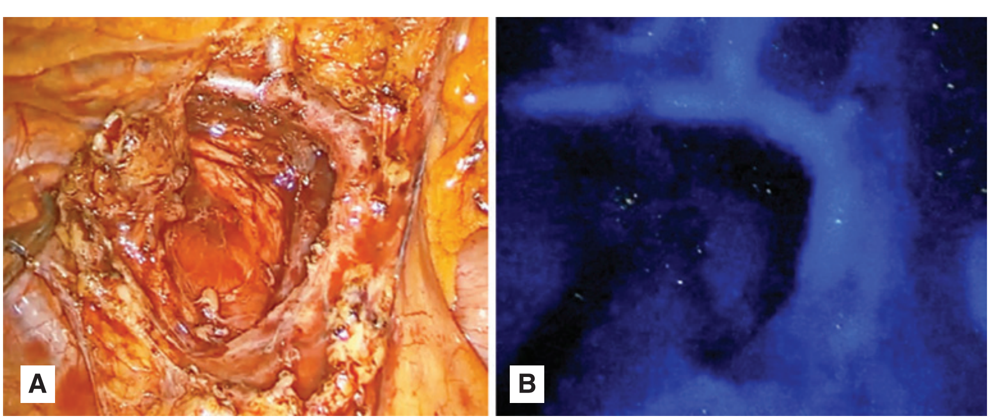


Figure 2: During the minimally invasive medial to lateral approach of right sided complete mesocolic excision (CME) for colon cancer, the median colic artery and vein are dissected (A).
The left and right braches are visible. After indocyanine green application (B) the median colic artery and their branches are visualized by fluorescence imaging.

Robotic assisted CME

The robot offers new technological possibilities for minimally invasive procedures. The three-dimensional visualization and magnification offers an excellent view to the operation field. The camera is controlled and handled by the surgeon, which makes the setting very stable during surgery. The EndoWrist (Intuitive, CA, USA) of the instruments' tip enable more dimensions of mobility in various directions. This is very important during vessel dissection and central ligation in CME. Vessels can be controlled and isolated very preciously. Sewing is more comfortable with the robot by using the EndoWrist (Intuitive, CA, USA) function. During robotic assisted surgery three instruments can be controlled by the surgeon, and a further instrument can be added with an assistant port which is run by an assistant surgeon on one side of the patient. This number of tools is very useful to handle and control challenging situations during the procedure. Taken together, the robotic features are an "add on" to conventional laparoscopy. The achievements of this technology will push forward minimally invasive procedures in the future. Especially in teaching programs, robotics will find its position. The learning curve for complex procedures seems to be decreased by robotics compared to conventional laparoscopy [23]. This is important because the aim must be to combine the oncological benefits of CME with the benefits of minimally invasive surgery. Only when surgeons overcome the learning curve with a marketable amount of patients will minimally invasive CME be spread out into clinical routine. CME is possible with the robot in the same quality compared to open procedures regarding the harvested specimens (Figure 1). Currently, there are only a few studies published which describe techniques (e.g. a suprapubic approach) and results for CME by robotic assisted surgery [24]. The morbidity of robotic procedures ranges from 10 to 25% with a mortality of 1% with a 3-year disease-free survival in stage UICC III of 78.2% and a cancer-related survival of 89.3% (Tables 1 and 2) [24, 38]. Further prospective studies are necessary to elucidate the benefits of robotic procedures.

Morbidity and mortality of CME

Comparison of morbidity rates of different cohorts is not without difficulties. They are influenced by the interpretation of postoperative complications. A standardized assessment, such as proposed by Dindo et al. [39], will help to characterize morbidity in a more objective manner but is not accessible throughout all studies.

During CME there are several steps of risk which can induce reasonable morbidity. Conventional colon resections without using the technique of CME have a 12.1–28.5% morbidity and a 3.7% mortality risk [25, 26]. In open CME procedures an overall morbidity of 12–36.4% with a mortality of 2.1–3% is described [19, 27–29]. The differences between non-CME and open CME seem not to be significant. The morbidity of laparoscopic CME lies between 4 and 31% with a mortality of 0.5–0.9%. In robotic assisted approaches morbidity between 10 and 25% with a mortality of 1% is described (Table 1) [17, 19, 27–37]. The morbidity and mortality seems to be less in minimally invasive procedures, but statistically significant differences have been found in only a few studies (Table 1).

In the Erlangen cohort between 2003 and 2012 (n = 596) a total morbidity of 21.1% was identified. This cohort is part of a recently published series [40]. The surgical morbidity was 12.4% including impaired wound healing (3.2%), anastomotic leakage (3.4%), bleeding (0.8%), fistula (pancreas, chylus, and small intestine 1%), abscess (0.8%), postoperative ileus (1.3%), peritonitis (0.7%), sepsis (1.2%) and pancreatitis (0.7%). Non-surgical postoperative complications were identified in 10.2%, with pulmonary (3.4%), urological (3.7%), nephrologic (1.2%), cardiac (2.2%), and neurologic (1.2%) manifestations. Reoperation was necessary in 4.4% (Table 2). It should be mentioned, however, that in this material about 10% of all cases were emergencies, which were mostly operated as radical as elective cases. Screening the literature, various surgical and nonsurgical postoperative complications are described with no specific correlation to the procedures. Anastomotic leakage in non-CME is described as 5.2%.

Survival after non-CME and CME with different techniques

The 3- and 5-year overall survival of patients (stage UICC I–III) who underwent open CME is 79.3–85.5% and 78.5% vs. 83.7–94.5% and 70.4–83% for laparoscopic cases. The 3-year overall survival after robotic assisted CME is 90.3%. The cancer-related survival after 3 and 5 years for open surgery is 91.3–95% and 90% vs. 87.8–97% and 79.5–80.2% for laparoscopic procedures. In stage UICC III the 3- and 5-year cancer-related survival is 83.9% and 80.8% in the Erlangen data of open technique (2003–2012) vs. 75.4% and 65.5–71.7% for laparoscopic surgery described in the literature. For non-CME the 3- and 5-year cancer-related

Table 1: Morbidity and mortality after complete mesocolic excision (CME) for colon carcinomas.

Author	Year	Study	Approach/method	Period	Tumor site	n	Morbidity (%)	p-Value	Mortality (%)	p-Value
Erlangen	2017	R	Open CME	2003–2012	m	596	21.1	–	2.1	–
Galizia et al. [25]	2014	R	n-CME CME vs. open CME	2004–2007	r	58 (n-CME)	12.1	0.914	–	–
				2008–2012		45 (open CME)	13.3		–	
Bertelsen et al. [26]	2016	R	n-CME vs.	2008–2013	m	1.701 (n-CME)	28.5	0.351	3.7	0.605
			laparoscopic + open CME			529 (laparoscopic + open CME)	30.6		4.2	
Huang et al. [27]	2015	R	Open CME vs.	2012–2013	r	49 (open CME)	12	0.222	–	–
			laparoscopic CME			53 (laparoscopic CME)	4		–	
Kim et al. [28]	2016	R	Open CME vs.	2008–2013	r	99 (open CME)	36.4	0.036	3.0	0.241
			laparoscopic CME			116 (laparoscopic CME)	23.3		0.9	
Storli and Eide [29]	2016	P	Open CME vs.	2007–2004	t	23 (open CME)	36.4	0.02	–	–
			laparoscopic CME			33 (laparoscopic CME)	15.2		–	
Sheng et al. [19]	2017	R	Open CME vs. HAL CME	2012–2014	r	72 (open CME)	15.3	0.079	–	–
						78 (HAL CME)	6.4		–	
Adamina et al. [30]	2012	R	Laparoscopic CME	2005–2010	r	52	31	–	–	–
Feng et al. [17]	2012	R	Laparoscopic CME	2010–2011	r	32	8.6	–	–	–
Han et al. [31]	2013	R	Laparoscopic CME	2003–2010	r	177	13	–	–	–
Siani et al. [32]	2017	R	Laparoscopic CME	2008–2015	r	600	35.5 (90 days)	–	0.5 (90 days)	–
Mori et al. [33]	2015	R	Laparoscopic CME	2010–2013	r	31	9.7	–	–	–
Takahashi et al. [34]	2016	R	Laparoscopic CME	2008–2014	r	202	10	–	–	–
Mori et al. [35]	2017	R	Laparoscopic CME	2011–2016	l	60	10	–	–	–
Wang et al. [36]	2017	R	Laparoscopic CME	2010–2015	r	172	16.3	–	–	–
Xie et al. [37]	2017	P	Laparoscopic CME	2014–2015	r	36	19	–	–	–
Spinoglio et al. [38]	2016	R	Robotic assisted mCME	2005–2013	r	100 (mCME)	25	–	1	–
Petz et al. [24]	2017	R	Robotic assisted CME	06–12/2016	r	20 (CME)	10	–	–	–

Study: R, Retrospective; P, prospective. Approach: HAL, hand-assisted laparoscopy; mCME, modified CME; nCME, no CME. Tumor site: r, right colon; t, transverse colon; l, left colon; m, multiple sites.

Table 2: Surgical and non-surgical morbidity and mortality after complete mesocolic excision (CME) for colon carcinomas.

Author	Approach	n	Surgical postoperative complications [n (%)]							Non-surgical postoperative complications [n (%)]		
			Anastomotic leakage	Anastomotic bleeding	Hemoperitoneum	Chylus leakage, fistula	Prolonged bowel paralysis/ileus	Wound infection	Intra-abdominal abscess	Pneumonia/pulmonary infection	Respiratory failure	Cardiac failure
Erlangen[a]	Open CME	596	20/585 (3.4)	–	5 (0.8)	6 (1)	8 (1.3)	19 (3.2)	5 (0.8)	–	20 (3.4)	13 (2.2)
Galizia et al.[25][b]	n-CME vs. open CME	58	3 (5.2)	–	–	–	1 (1.7)	2 (3.4)	–	1 (1.7)	–	–
		45	2 (4.4)				2 (4.4)	1 (2.2)		1 (2.2)		
Huang et al. [27][b]	Open CME vs. lap. CME	49	–	0	–	–	–	4 (8.2)	–	2 (4.1)	–	–
		53		1 (1.9)				0		1 (1.9)		
Kim et al. [28][b]	Open CME vs. lap. CME	99	0	–	2 (2.0)	5 (5.0)	7 (7.1)	15 (15.2)	4 (4.0)	–	5 (5.0)	–
		116	2 (1.7)		1 (0.9)	3 (2.6)	6 (5.2)	10 (8.6)	0		6 (5.2)	
Sheng et al. [19][b]	Open CME vs. HAL CME	72	–	–	–	1 (1.4)	2 (2.8)	5 (6.9)	–	1 (1.4)	–	–
		78				1 (1.3)	2 (2.6)	1 (1.3)		0		
Adamina et al. [30][b]	Lap. CME	52	2 (3.8)	2 (3.8)	–		–	1 (1.9)	–	–	1 (1.9)	3 (5.8)
Feng et al. [17][b]	Lap. CME	32	–	–	1 (3.1)	1 (3.1)	–	–	–	1 (3.1)	–	–
Han et al. [31][b]	Lap. CME	177	7 (4.0)	–	–	4 (2.3)	3 (1.7)	3 (1.7)	–	2 (1.1)	–	–
Siani et al. [32][b]	Lap. CME	600	15 (2.5)	–	–	–	9 (1.5)	63 (10.5)	–	59 (9.8)	–	–
Mori et al. [33][b]	Lap. CME	31	-	1 (3.2)	–	–	1 (3.2)	–	–	–	–	–
Takahashi et al.[34][b]	Lap. CME	202	1 (0.5)	–	1 (0.5)	–	4 (2.0)	–	1 (0.5)	1 (0.5)	–	1 (0.5)
Spinoglio et al. [38][b]	Robotic assisted mCME	100	1 (1.0)	2 (2.0)	1 (1.0)	–	9 (9.0)	5 (5.0)	–	2 (2.0)	2 (2.0)	2 (2.0)
Petz et al. [24][b]	Robotic assisted CME	20	–	2 (10.0)	–	–	–	–	–	–	–	–

Lap., Laparoscopic; n-CME, non-CME; HAL, hand-assisted laparoscopy; mCME, modified CME. [a]CME multiple sides. [b]CME right colon.

Table 3: Oncological outcome after complete mesocolic excision (CME) for colon carcinomas.

Author	Year	Study	Approach	Period	Tumor site	n	3 year OAS	5 year OAS	3 year DFS	5 year DFS	3 year CRS	5 year CRS	p-Value
Erlangen	2017	R	Open CME	2003–2012	m	590	85.6% UICC I: 95.2% II: 86.6% III:75.4%	78.5% UICC I: 88.6% II: 78.1% III: 69.9%	–	–	92.8% UICC I: 99.4% II: 94.8% III: 83.9%	89.9% UICC I: 98.1% II: 91% III:80.8%	–
Galizia et al. [25]	2014	R	n-CME vs. open CME	2004–2007 2008–2012	r	58 (n-CME) 45 (open CME)	–	–	–	–	87% 95%	74% 90%	0.13
Bertelsen et al. [26]	2016	R	n-CME vs. laparoscopic + open CME	2008–2013	m	1701 (n-CME) 529 (laparoscopic + open CME)	–	–	–	–	–	–	CSS: 0.846
Storli and Eide [29]	2016	P	Open CME vs. laparoscopic CME	2007–2014	t	23 (open CME) 33 (laparoscopic CME)	–	–	–	–	91.3%[a] 97.0%	–	0.42
Kim et al. [28]	2016	R	Open CME vs. laparoscopic CME	2008–2013	r	99 (open CME) 116 (laparoscopic CME)	79.3% UICC I: 100% II: 86.9% III: 70.2% 94.5% UICC I: 100% II: 95.5% III: 90.7%	–	75.3% UICC I: 100% II: 84.5% III: 64.2% 82.0% UICC I: 100% II: 84.8% III: 68.9%		–	–	DFS: 0.125 OAS: 0.011
Han et al. [31]	2013	R	Laparoscopic CME	2003–2010	r	177	83.7% UICC I: 95.6% II: 86.8% III: 73.9%	70.4% UICC I: 85.0% II: 71.1% III: 60.9%	–	–	87.8% UICC I: 100% II: 92.7% III: 75.4%	80.2% UICC I: 94.1% II: 86.3% III: 65.6%	–
Siani et al. [32]	2014	R	Laparoscopic CME	2008–2015	r	600	–	83% UICC I: 97.3% II: 88.7% IIIA/B:72.4%	–	78.3% UICC I: 98% II: 87.8% IIIA/B: 70.5%	–	79.5% UICC I: 97.3% II: 87.8% IIIA/B: 71.7%	–
Wang et al. [36]	2017	R	Laparoscopic CME	2010–2015	r	172	89.1% UICC I: 100% II: 100% III: 80.8%	–	81.7% UICC I: 100% II: 94.6% III: 71.8%	–	–	–	–

Table 3 (continued)

Author	Year	Study	Approach	Period	Tumor site	n	3 year OAS	5 year OAS	3 year DFS	5 year DFS	3 year CRS	5 year CRS	p-Value
Spinoglio et al. [38]	2016	R	Robotic assisted mCME	2005–2013	r	100	90.3% UICC I: 95% II: 91.7% III: 86.3%	–	91.4%[a] UICC I: 100% II: 94.3% III: 78.2%	–	94.5%[a] UICC I: 100% II: 97.1% III: 89.3%	–	–

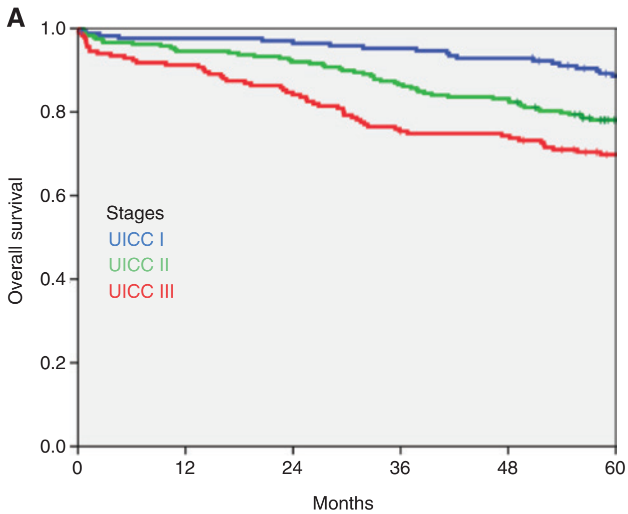
Study: R, Retrospective; P, prospective; OAS, overall survival. Approach: HAL, hand-assisted laparoscopy; DFS, disease-free survival; mCME, modified CME; CRS, cancer-related survival. Tumor site: r, right colon; t, transverse colon; l, left colon; m, multiple sites. [a](4-year survival rate). UICC, stage UICC.

survival is 87% and 74% [25, 26, 28, 29, 31, 36, 38, 41–43] (Table 3 and Figure 3). Local recurrence after 3 and 5 years is 1.8% and 2.2% for patients receiving open surgery in the Erlangen cohort. For stage UICC III the 3- and 5-year local tumor recurrence is 3.8% for both time intervals in the Erlangen data. These patients developed distant metastases in 11.9% after 3 years and 13.5% after 5 years including stage UICC I–III. For stage UICC III 22.8% and 25.5% distant metastases after 3 and 5 years are described (Figure 4). In summary, the data elucidate a 16% 5-year survival benefit for open CME compared to non-CME surgery.

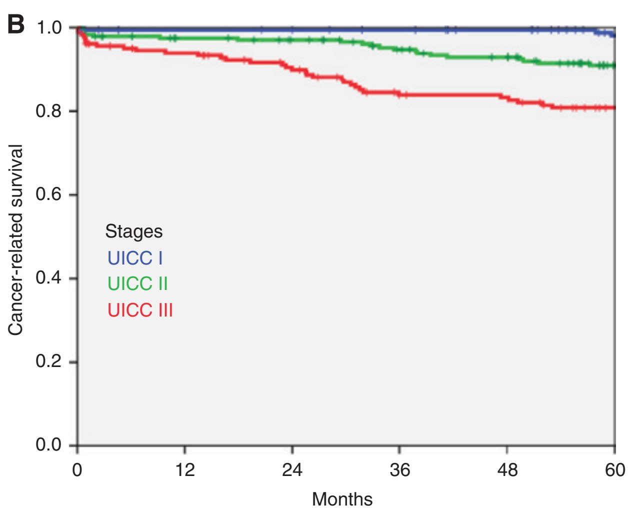
Discussion

In the meanwhile CME is accepted worldwide. It is an established technique for colon cancer patients. It has really influenced the type of surgery for colon carcinomas. However, its correct implementation is not yet completed, by far. Mainly, the definition of a central tie is not realized, which finally is the transection of the supplying arteries of the bowel involved with cancer flush with the main vessel. Its need is frequently questioned, although in the meanwhile there is abundant literature to support that essential [44–47].

The data from the literature and Erlangen demonstrate that it has no increased morbidity and mortality compared to non-CME techniques. Screening the literature, minimally invasive procedures like laparoscopy or robotic assisted surgery seems to have even less morbidity and mortality [17, 31, 33–38, 42, 48]. Behind these facts the ongoing discussion that CME cannot be accepted as standard technique of care for the reason of increased morbidity and mortality is not verified. Nevertheless, especially the sharp central vessel dissection needs experienced skills of anatomy and surgery because of the risk of causing injuries of the central vessels, which, however, can always be supplied in experienced hands. Furthermore, the entrance to the dissection planes must be recognized prior to the beginning of CME. Here are specific teaching programs necessary to reduce surgeons' reservations for the use of CME and to prevent the spread of so-called "modified CME" [38]. The technique of CME can even be carried out minimally invasively as a safe procedure. But the currently published oncological outcomes, especially in stage UICC III, seem to be behind open techniques, especially when compared to the Erlangen data. Various techniques for laparoscopic CME are described. Here a standardization is needed, which enables central vessel and lymph node dissection in the same way compared to the open procedure and for which surgeons can

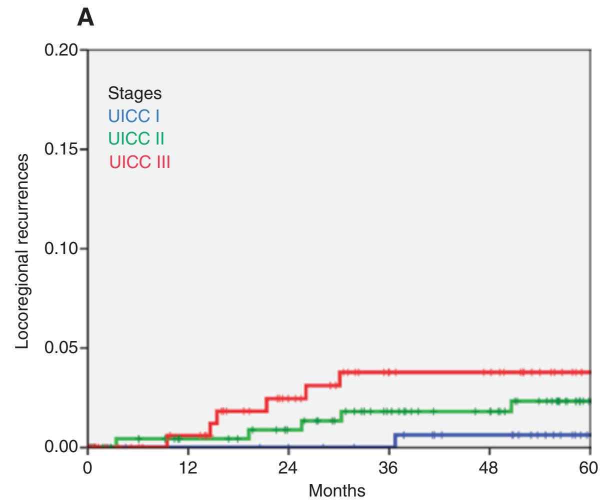


	n	3-year rate/SE	5-year rate/SE	p
Stage I	169	95.2/1.6	88.6/2.5	
Stage II	238	86.6/2.2	78.1/2.7	0.014
Stage III	183	75.4/3.2	69.9/3.4	0.283

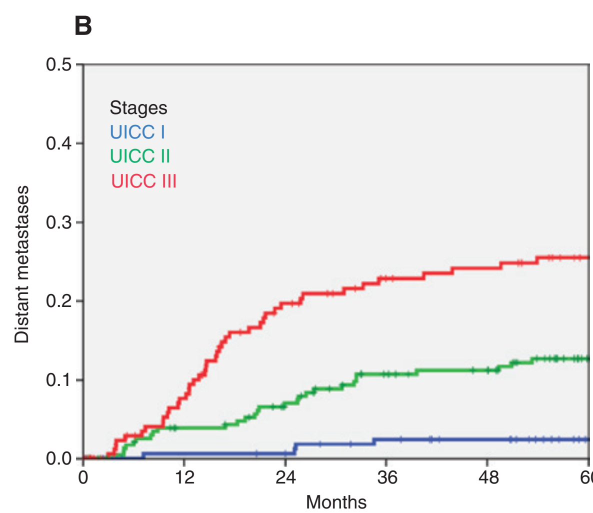


	n	3-year rate/SE	5-year rate/SE	p
Stage I	169	99.4/0.6	98.1/1.1	
Stage II	238	94.8/1.5	91.0/1.9	<0.001
Stage III	183	83.9/2.8	80.8/3.0	0.022

Figure 3: Overall and cancer-related survival rates.
(A) Overall survival (%) and (B) cancer-related survival (%) of patients which underwent open complete mesocolic excision (CME) between 2003 and 2012 at the Department of Surgery, University Hospital Erlangen, Germany, n = 590; SE, standard error.



	n	3-year rate/SE	5-year rate/SE	p
All	590	1.8/0.6	2.2/0.6	
Stage I	169	0	1.6/0.6	
Stage II	238	1.8/0.9	2.3/1.0	0.188
Stage III	183	3.8/1.5	3.8/1.5	0.237



	n	3-year rate/SE	5-year rate/SE	p
All	590	11.9/1.4	13.5/1.5	
Stage I	169	2.5/1.2	2.5/1.2	
Stage II	238	10.7/2.1	12.7/2.2	0.001
Stage III	183	22.8/3.3	25.5/3.4	0.002

Figure 4: Local recurrence and distant metastases rates.
(A) Local recurrence (%) and (B) distant metastases (%) of patients which underwent open complete mesocolic excision (CME) between 2003 and 2012 at the Department of Surgery, University Hospital Erlangen, Germany, n = 590; SE, standard error.

be trained. Only hereby can the benefits of minimally invasive surgery be combined with the oncological benefits of CME. Maybe the robot which has less learning curve and has a lot of new technical features can be a useful tool in this scenario [38, 48]. One main challenge is the identification of the central vessels especially in obese patients. This is necessary during the medial to lateral approach to figure out the correct entrance to the medial dissection line. New intraoperative imaging modalities with indocyanine green may facilitate this. During CME specimens with enhanced quality including more lymph nodes can be harvested which generates an obvious survival benefit for the patients [41]. The quality of specimens can be measured and documented which makes them comparable throughout the procedures. CME can be carried out with the same quality minimally invasive technique compared to the open technique. It is not acceptable that the prognostic benefits of CME cannot be added to all patients. The main reason for the unrestricted acceptance for CME is morbidity concerns. Therefore, stepwise teaching programs are needed to settle it, ideally for minimally invasive techniques. Furthermore, all specimens have to undergo morphometry as described by West during routine praxis to score the quality of surgery routinely [12].

The mission of CME implementation as started in 2009 was to develop a new concept for colon cancer surgery which may improve patients' outcome. The Erlangen data show that this can be provided by this type of surgery. But currently, many variations of CME are performed which all are named CME. Therefore, more qualified teaching programs for surgeons and detailed pathological examination protocols are needed to maintain the standard and quality of CME. These are main challenges for the future. Summarizing the facts, it becomes obvious that CME is the technique of choice for surgery in patients with colon carcinoma. But the mission to gain its acceptance as standard of care has not yet been completed. New surgical techniques and tools challenge this method. It is the surgeons' responsibility to offer the patients the best treatment possibility for a specific disease. For colon carcinomas this means CME in a minimally invasive approach. But until this has not been brought to an unrestricted acceptance, the mission is still not completed. The triple H (Hohenberger, Holm, and Heald) have guided a way of colorectal cancer surgery which improves the patients' prognosis. It depends on the surgeons to implement this knowledge into clinical routine practice.

Author Statement
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Author Contributions
Roland Croner: conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft. Henry Ptok: data curation; resources; validation; writing – review and editing. Susanne Merkel: resources; validation; writing – review and editing; statistical analysis. Werner Hohenberger: project administration; validation; writing – review and editing.

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Supplemental Material: The article (https://doi.org/10.1515/iss-2017-0042) offers reviewer assessments as supplementary material.

Reviewer Assessment

Roland S. Croner*, Henry Ptok, Susanne Merkel and Werner Hohenberger

Implementing complete mesocolic excision for colon cancer – mission completed?

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***Corresponding author: Prof. Dr. Roland S. Croner,** Department of General-, Visceral-, Vascular- and Transplant Surgery, University Hospital Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany, E-mail: Roland.Croner@med.ovgu.de

Reviewers' Comments to Original Submission

Reviewer 1: Ayhan Kuzu

Nov 21, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	90
Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
I would like to thank the authors for this good quality presentation.
There is a significant variation from one surgeons to another and even more from one unit to another unit results - oncological outcomes varies significantly in colon cancer treatment.
This review explains the technique and the results in an elegant way.