DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

Complete Mesocolic Excision with central vascular ligation in Comparison With Conventional Surgery for the right colon cancer: An Italian randomized trial.

Administrative and ID information.

Acronym.	CoME IN trial.
Protocol version number and current status.	23/01/2020
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Trial Sponsor	Università degli studi di Torino- Facoltà di Medicina e Chirurgia, Campus San Luigi Gonzaga. Regione Gonzole, 10 -10043 Orbassano (To). Italy
Contact name	Prof. Maurizio Degiuli Telephone: + 39 011 90261 E-mail: maurizio.degiuli@unito.it. https://www.oncology.unito.it/do/docenti.pl/Show?_id=mdegiuli
Ethics committee	Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga Tel. 011.9026204 – 011.9026506 ore 10 – 12 da lunedì a venerdì Fax 0119026791 E-mail: sperimentazioni@sanluigi.piemonte.it

TABLE OF CONTEST

1) ROLES

Chief Investigator (CI):	Maurizio Degiuli, MD
Trial Coordinator (TC):	Mario Solej, MD
Trial statistician (TS):	Monagheddu MD/ Ricceri MD. Ph.D.
Trial Management Group (TMG).	Mario Solej MD, Prof. Maurizio Degiuli MD; Rossella Reddavid, MD. H. Aridai Resendiz MD. Giulia Marchiori MD.
Clinical Monitor (CM):	Patrizio Mao. MD. Nirvana Maroni. MD. Letizia Spidalieri.MD.
Collaborators (Cols):	Section 19 (page 23)

Research Ethics Committee (REC): Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga and Ethics committee of each collaborator centre

Data coordinating centre (DOC): Università degli studi di Torino, Dipartimento di Oncologia, AOU San Luigi, Chirurgia Oncologica e Digestiva, Orbassano (TO)

2. ORGANIZATIONAL STRUCTURE AND RESPONSABILITIES.

Chief Investigator (CI) Responsibilities:
CI is responsible for the intellectual conception and of the administrative and ethical aspects of the research project. CI ensures that all investigators, research associates/assistants and students on the project are fully informed of relevant University policy and administrative procedures associated with the project, including intellectual property and confidentiality provisions, ethical and other clearances that are required and that the project is carried out in accordance with approved protocols and codes of good practice in research. CI is responsible for preparation of protocol and its revisions and progress and for final communication of any project outcomes.

Trial Coordinator (TC) Responsibilities:
Organization of steering committee meetings.
Design and conduct of the study.
Preparation of protocol and revisions.
Preparation of investigators brochure and Case Report Forms.

Trial Statistician (TS) Responsibilities:
Design of the study and statistical analysis.

Trial Management Group (TMG) Responsibilities:
Establishment and monitoring of participating centers recruitment.
Distribution and supply of data collection forms and other appropriate documentation for the trial.
Preparation of protocol and revisions.
Data collection and management.
Data entry and cleaning.
Data analysis.
Organising and servicing the Independent Data and Safety Monitoring Committee (IDSMC)

Clinical Monitor (CM) Responsibilities:
Assurance of data security and quality, and observance of data protection laws Assurance that the trial is conducted by the good clinical practice in research.
Revision and and approval of the Statistical Analysis Plan for the trial.
Revision of the trial progress and analysis of interim data.
As the only body with access to the unblinded comparative data, the IDSMC is responsible for monitoring these data and making recommendations to the TMG on whether there are any ethical or safety reasons why the trial should not continue or protocol should be amended. To determine if additional interim analyses of trial data should be undertaken.

Collaborators responsibilities:
Design and execution of the protocol in ethic and safe terms.
Data management and entry.
Drafting, revision and approval of the final manuscript.

Research Ethics Committee (REC) responsibilities:
REC ensures that the project is carried out following approved protocols and codes of good practice in research.

Data Coordinating Center (DOC) responsibilities:
Contribution to the development of the protocol, and to all study documentation including datasheets.
Design, production and regular update of all trial materials and arrangement of printing and

supply of trial documentation.
Monitoring of patient's recruitment and advice on remedial action if targets are not being met.
DOC uses all reasonable efforts to ensure that data collected and reported are accurate, complete and identifiable at the source; and that record-keeping and data transfer procedures adhere to the Data Protection law.

3. LIST OF ABBREVIATIONS/GLOSSARY

ASA SCORE.	The American Society of Anesthesiologists physical status classification system.
BMI.	Body Mass Index.
CEA.	Carcinoembryonic Antigen.
CI.	Chief Investigator.
CM.	Clinical Monitor.
CME.	Complete mesocolic excision.
COLS.	Collaborators.
CRFS.	The Case Report Forms.
CT.	Computed tomography.
CVL.	Central vascular ligation and apical lymphadenectomy.
DFS.	Disease-free survival
DOC.	Data coordinating center.
EORTC	European Organization for Research and Treatment of Cancer
GIA	Gastrointestinal anastomosis.
IDSMC.	Independent Data and Safety Monitoring Committee.
QLQ.	Quality of Life Questionnaire
QOL.	Quality of life.
LLQ	Left-lower-quadrant.
LN.	Lymph nodes.
LPS	Laparoscopic
LUQ	Left-upper-quadrant
MCA.	Middle Colic Artery.
MCV.	Middle Colic Vein.
OS.	Overall Survival
REC.	Research Ethics Committee.
SLUH.	San Luigi Universitari Hospital
SMA.	Superior mesenteric artery
SMV.	superior mesenteric vein.
TC.	Trial Coordinator.
TME.	Total mesorectal excision
TMG.	Trial Management Group.
TNM	The American Joint Committee on Cancer Staging
TS.	Trial statistician.
WHO	World health organization.

4. INTRODUCTION

Colorectal cancer is the third most common malignant disease worldwide and its incidence is significantly higher in men than in women. In men, colorectal cancer is the third most commonly occurring cancer after prostate and lung cancers while it is the second most commonly occurring cancer in women after breast cancer [1]. Over 1.8 million new cases were diagnosed in 2018 according to the world cancer research foundation [2].
In Italy, it is the second most common tumor and leading cause of death [3] with approximately 53,000 new diagnoses of colorectal cancer estimated in 2017 [4].

Colorectal cancer is not a single type of tumor; its pathogenesis depends on the anatomical location of the tumor which differs between the right and the left side showing pathologic and molecular characteristics different between these tumor entities. Despite the location, surgical resection is the most effective procedure for its radical treatment at least in case of localized disease, and the long-term prognosis can be improved by improving surgical treatment without increasing perioperative mortality [5].

In general, standard oncologic resection of the colon refers to a wide resection of the tumor-bearing segment and the lymphatics draining along the named artery; recently, in case of right colon cancer, the application of the Complete mesocolic excision(CME) in addition with central vascular ligation (CVL) has been suggested to improve the oncological outcomes in analogy with total mesorectal excision(TME), which has been reported to enhance oncological results in patients with middle and low rectal cancer .

The CME + CVL emphasizes the sharp dissection along the mesocolic plane between the visceral and parietal fascia layers with true central ligation of the main arteries and veins at their roots with the principle of en-bloc resection in a horizontal, vertical, and circumferential directions of the primary tumor with regional lymph nodes (LN) and all grossly suspected or involved lesions removed during operation. Therefore, the CME may remove a larger specimen with free margins, more mesocolon tissues and free tumor cells on peritoneal surface and may reduce potential sources of disease recurrence.

5. BACKGROUND

Many changes have occurred over the last three decades in the management of patients with colorectal cancer: the advancements in imaging techniques, the setting of radiotherapy and the creation and development of multidisciplinary teams. But the most revolutionary contribution was the anatomic description of the mesorectum and the introduction of the total mesorectal excision (TME) supported by the concept of the "en-bloc clearance of the tumor's lymphatic drainage enveloped in the intact fascia of embryologic origin" by Heald et al. [6], in the 1980s.

Later, in 2009 Hohenberger et al [7] applied the same concept of the TME as a curative treatment in patients with other colon cancer locations resulting in the complete mesocolic excision (CME). which, to date, remains a hot topic in the medical community.

The pillars of the CME are sharp dissection of the anatomical leaves and dissection of the visceral plane from the parietal one, resulting in a higher quality of the specimen and in a higher number of LN harvested (Table 1), with no tears in the fascial leaf on each side of the mesocolon [7], with central division of the feeding arteries at their origins from the superior

mesenteric artery (SMA) in case of tumors of the right colon and from the inferior mesenteric artery (IMA) or the aorta in tumors of the left colon.

Hohenberger analyzed 1329 patients undergoing R0 resection with application of the CME concepts and showed that local recurrence rate decreased from 6.5% to 3.6% and 5-year cancer-related survival rate increased from 82.1% to 89.1% [7]. Furthermore, the study of West et al [8] compared the CME specimens with specimens of standard surgery with non-CME and observed that the CME surgery removed a greater area of the mesentery and achieved higher resection rates through the mesocolic plane when compared with standard non-CME surgeries.

Six years after the introduction of this technique, Bertelsen CA et al [9] in a retrospective study of DFS after CME showed that CME surgery yielded better 4year DFS rates when compared to conventional non-CME surgery for patients with stage I colon cancer [9].

Data from supplemental trials confirmed the favorable outcomes reported after open CME also after minimally invasive approach [10, 11]. Additionally, in a recent study performed by Spinoglio, et Al [12] both laparoscopic and robotic right colectomy with CME were reported to be safe and feasible and resulted unsuccessful survival.

At the moment, data from literature confirm that CME can guarantee:
- a superior quality of the specimen in terms of integrity of anterior and posterior leaves, area of the resected mesentery distance from the tumor center to ligation of ICA and MC. Table 1, Kim NK [16].
- A higher number of LN retrieved. Table 1, Table 2, Kim NK [16].
- A better disease-free survival at 3 years (Table 2. Kim NK [16] with a medium survival gain close to 8-10 %.
- A Lower local relapse.
- A better disease-specific survival at 5-year.
Table 3., Hohenberger [7], G. Galizia,[24].

On the opposite a longer operative time has been observed in the majority of reports; Overall, all systematic reviews and metanalyses of CME report morbidity and mortality rates comparable to those observed after non-CME. A higher rate of intraoperative injuries to the superior mesenteric vein and spleen was showed only in one study, although it seems directly correlated with the surgeon experience, Table 3. G. Galizia,[24].

The importance of a higher number of LN harvest using the CME + CVL is supported by the research published by Jhonson PM et al.[26] who examined the number of negative and positive nodes of 20,702 specimens obtained from patients with stage IIIB and IIIC Colon Cancer and described the Disease-specific survival by substage according to the number of negative nodes identified and created a proportional hazards model to determine the effect of the number of negative nodes on survival ; In stage IIIB and IIIC patients, the Authors reported a significant decrease of disease-specific mortality as the number of negative nodes increased (P< .0001).

In patients with stage IIIC cancer with 13 or more negative nodes, the reported 5-year mortality was 42%as compared to 65% of those with three or fewer resected negative LN (P <.0001); In stage IIIA patients, there was no association between the number of negative nodes identified and the disease-specific survival.

Thereby, a higher number of negative nodes yielded is an important independent prognostic factor of DSS in patients with stage IIIB and IIIC colon cancer.

Table 1
Specimen quality after complete mesocolic excision (CME) surgery for colon cancer.

Author, year	N	Mesocolic plane[a] (%)	Specimen length (cm)	Tumor to high tie (mm)	Area of mesentery (mm^2)	Lymph nodes (number)
West 8 |, 2010	CME:49 Non-CME:40	NR	Rt colon = CME:34.8[b] Non-CME:24.4 Lt colon = CME:39.2[b] Non-CME:26.0	Rt colon = CME:129[b] Non-CME:81 Lt colon = CME:145[b] Non-CME:97	Rt colon = CME:16,770[b] Non-CME:8881 Lt colon = CME:24,128[b] Non-CME:13,166	CME:30[b] Non-CME:18
Bertelsen 22 , 2011	CME:93 Non-CME:105	CME:82 Non-CME:80	NR	CME:96[b] Non-CME:71	NR	CME:26.7[b] Non-CME:24.5

NR, not reported.
[a] The plane of surgery is classified into: (1) a muscularis propria plane means a poor plane of surgery; (2) an intramesocolic plane means a moderate plane of surgery; and (3) a mesocolic plane means a good plane of surgery.
[b] Statistically significant.

Table 2
Short-term and oncologic outcomes after extended lymphadenectomy including complete mesocolic excision (CME) for colon cancer.

Author, year	Study period	Characteristics	N	Colon cancer	OT (min)	Cx (%)	LN	AC (%)	Survival (%)
Galizia |(24), 2014	2004–2012	non-CME (NCME) vs. CME	NCME:58 CME:45	Rt	NCME:130[a] CME:178	NCME:12 CME:13	NCME:15[a] CME:20	NCME:25 CME:21	5year-CSS = NCME:74 vs. CME:90
Bertelsen (9) , 2015	2008–2011	non-CME (NCME) vs. CME	NCME:1031 CME:364	Rt,Lt	NR	NR	NCME:21[a] CME:37	(Stage III) NCME:70 CME:74	4year-DFS = NCME:75.9 vs. CME:85.8[a]

OT, operative time; Cx, postoperative complication; LN, number of lymph node examined; AC, adjuvant chemotherapy; NR, not reported; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival.
[a] Statistically significant.

Table 3 Analysis of end-points

	CME group 45 patients	Classic group 58 patients	*p* value
Operation time (min)[a]	178±21 (130–220)	130±20 (90–190)	**0.0001**[b]
Total intraoperative blood loss (mL)[a]	280±40 (200–400)	200±30 (120–280)	**0.0001**[b]
Length of resected bowel (mm)[a]	288±27 (250–360)	278±41 (190–360)	0.1106[b]
High tie (mm)[a]	106±13 (75–134)	87±17 (39–129)	**0.0001**[b]
No. of harvested nodes[a]	20±9 (8–45)	15±6 (5–30)	**0.0013**[b]
Recurrences			
No	39	44	0.2610[c]
Yes	6	14	
Local/distant	0/6	12/8	**0.0341**[c]
Disease-specific survival			
Alive	42	44	**0.0356**[c]
Dead	3	14	
Disease-specific survival (node positive)[d]			
Alive	19	13	**0.0187**[c]
Dead	2	11	

High tie indicates the shortest distance between tumor and point ligation of vessels supplying tumor
[a] Values are mean±SD (range)
[b] Student's *t* test
[c] Chi-square test
[d] Only node-positive tumors (15 pN0 plus six pN1c tumors in CMEgroup, and 22 pN0 plus two pN1c tumors in classic group)

One- to 5-year survival rate in node-positive right-sided colon cancers undergoing potentially curative surgery. CME group vs. classic group 2: HR=0.25 (95 % CI 0.11–1.02), p =0.05

Table 4			
2015 Denmark	Bertelsen CA, et al. [9]	Retrospective study Left and right Colectomy	**CME, 364 pts, 4-year DFS 85·8%** **non-CME 1031 pts, 4-year DFS 75·9%** Multivariable Cox regression showed that CME surgery was a significant, independent predictive factor for higher DSF for all patients. After propensity score matching, DFS was significantly higher after CME, irrespective of UICC stage, **with 4-y DFS of 85·8% (95% CI 81·4–90·1) after CME and 73·4% (66·2–80·6) after non-CME (log-rank p=0·0014).**
2014 Italy	G. Galizia, et al [24]	Prospective study Right Colectomy	Number of harvested nodes and length of vascular ligation significantly better in CME ($p < 0.01$). A higher number of tumor deposits were harvested thus allowing chemotherapy in newly upstaged patients. Locoregional recurrences were never experienced in CME patients ($p = 0.03$). The risk of cancer-related death was reduced by over one half in all CME patients, and even by three quarters in node-positive tumors. The non-CME was significantly associated with poor outcome ($p < 0.01$).
2011 Denmark	Bertelsen CA, et al.	Prospective study Left and right Colectomy	198 patients divided into two groups, those treated before (93) and those after (105) June 2008 when CME was introduced as a standard procedure. The overall mean high tie increased from 7.1 to 9.6 cm (P 0.0001) the mean number of harvested LN from 24.5 to 26.7 (P=0.0095). the risk of complications was not statistically different. The median length of hospitalization increased from 4 to 5 days (P= 0.04).
2010 Greece	Pramateftakis MG.	Prospective study Right colectomy	CME and high ligation in 115 patients undergoing a right hemicolectomy. postoperative morbidity was 13.9% (16/115) the overall 5-year survival: 72.4% (55/76).

2010 UK	West NP et al.	Prospective/retrospective Left and right Colectomy	tissue morphometry and grading the plane of surgery in 49 CME + CVL specimens, and 40 standard specimens tissue was removed with CME and CVL compared with 'standard' surgery in terms of distance between the tumor and the high vascular tie, the length of large bowel and ileum removed and the area of mesentery. A greater LN harvest (median, 30 vs 18; P< 0.0001) and more accurate mesocolic plane resection (92% vs 40%; P < 0.0001) in CVL and CME. removal of an intact mesocolon in the mesocolic plane was oncologically superior implying a 15% overall survival advantage at 5 years
2009 Germany	Hohenberger W, et al.	Prospective study Left and right Colectomy	data analysis from 1329 pts with R0 resection after colon cancer surgery from 1978 to 2002. The 5- year recurrence rate was reduced from 6.5% to 3.6% the cancer-specific 5-year survival rate increased from 82.1% to 89.1%.

6. PURPOSE.

This study aims to compare the disease-free survival of the right hemicolectomy with CME+CVL with that of the standard non-CME right hemicolectomy in patients with stage II-IV a right colon cancer

7. GOOD CLINICAL PRACTICE

The trial will be carried out following the Declaration of Helsinki [17], after approval of the Ethics Committee of SLUH, Orbassano and afterwards by the Ethics Committees of each participating center.
The protocol, the final version of the Patient Information Sheet, Consent Form, and all written information given to trial subjects must be approved or given a favorable opinion in writing by an Ethics Committee as appropriate.

8. STUDY OBJECTIVES.

This is a National Multicenter Randomized Controlled Trial comparing two arms of treatment, the CME +CVL and the standard non-CME procedure in patients with right colon cancer.

The primary endpoint is:

- The 3-year DFS

The secondary endpoints are:

- Safety:
  - Operative time.
  - Intraoperative blood loss.
  - Intraoperative blood transfusion.
  - Intraoperative complications.
  - Early postoperative complications.
  - Late postoperative complication
  - Length of stay.
  - Postoperative mortality.

- Oncologic outcomes:
  - The number of positive, negative and total LN harvested.
  - 3- and 5-year Overall Survival.
  - 5-year DFS

- Quality of CME:
  - Area of the mesentery of the specimen
  - Integrity of the anterior and posterior leaves
  - Length from the tumor centre to the ligature of the ICA
  - Length from the tumour center to the ligature of the right branch or the main trunk of the MCA
  - Benz classification of the specimen quality

- Quality of life (QoL).

EORTC C-29/C-30

9.STUDY DESIGN

OVERVIEW OF THE STUDY DESIGN

This is a National multicenter randomized controlled trial in patients with a tumour of the right or proximal transverse colon as a primary diagnosis, requiring right hemicolectomy.
All patients who meet the inclusion/exclusion criteria and agree to sign the informed consent will be randomized to receive the CME + CVL or the standard non-CME procedure.

DURATION OF THE STUDY

Estimated start date: 3/2020
Estimated duration of the enrollment: according to the number of participants centres. (About 24 months)
Estimated duration of participation: 36 months.
Estimated duration of Follow-up: 60 months

STUDY SETTING

This is a Multicentre study conducted in Italian referral centres for colorectal cancer surgery and research coordinated by the Department of Oncology of SLUH, Turin, Italy.

CENTERS RECRUITMENT STRATEGY.

This protocol has been presented, discussed and accepted in several colorectal cancer network meetings of the Italian Society of Surgical Oncology (SICO). Only national referral centres for colorectal cancer surgery and research with at least 30 procedures/year for right colon cancer will be registered as enrolling centres in this trial.

Each participating centre will be provided with a master video explaining the correct technique of CME and non-CME. A Scientific Committee will prepare these videos. The Scientific Committee includes the coordinating centre and two of all participating centres, chosen by the highest number of CME performed together with the highest H-index score of the participating centre PI.

This Scientific Committee (also called Expert Panel) will evaluate the adequacy of all the steps of the technique performed in each participating centre through unedited movies prepared and sent by each centre. Additional pictures of the specimens at the end of the procedure will allow assessing each specimen according to the classification of S. BENZ et Al., which directly reflects the quality of the procedure [27].

Provisions for treating and/or compensating subjects who are harmed as a consequence of their participation in the study have been defined. The policy will be released to each ethic committee of the participant centers after the protocol approval. (Please find the quote policy by MEDICAL & COMMERCIAL INTERNATIONAL (ON BEHALF OF CERTAIN UNDERWRITERS AT LLOYD'S) 4TH FLOOR 33 GRACECHURCH STREET LONDON EC3V 0BT UNITED KINGDOM in the annexes documents).

STUDY POPULATION

Patients are eligible to be included in the trial if they meet the following criteria:

Inclusion criteria:
Age > 18,
ASA score I to III,
Right colon cancer T2-T4a, any N. (*The right-sided location of the cancer is defined as the location from the caecum up to the proximal third of the transverse colon)
N positive, any T

*All patients will be staged by computed tomographic scan and will have an endoscopically and histologically proven malignant colon cancer.

Exclusion criteria:
Age > 85 years old.
T1, N0
T4b, any N
BMI > 30.
Metastatic disease (Abdominal and chest CT scan will be mandatory to exclude distant metastasis.)
ASA IV.
History of previous cancer, in the past 5 years.
Need for Emergency surgery,
Infectious disease requiring treatment.
Pregnancy.
Use of systemic steroids.
No history of familial adenomatous polyposis, ulcerative colitis or Crohn's disease.

10. ENROLLMENT, RANDOMIZATION AND ALLOCATION.

The Investigator(s) must obtain the informed consent and the consensus for the treatment of sensitive data (according to the Regolamento Europeo sulla Protezione dei Dati (GDPR) n. 679/2016a partire dal 19 settembre c.a., del D.Lgs n. 101 del 10 agosto 2018 pubblicato sulla Gazzetta Ufficiale del 04 settembre c.a.) of the patient or his/her designee before any procedures.
Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time and choosing not to participate will not affect the care or the treatment of their disease.
Subjects will be told about alternative treatments available if they refuse to take part in the study and that such refusal will not prejudice future treatment.
The subject or legally acceptable representative will be given enough time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded through either the subject's or his/her legally acceptable representative's dated signature.
A copy of the signed informed consent form must be given to the subject.
If the subject or legally acceptable representative is unable to read or write, an impartial

witness should be present for the entire informed consent process (which includes reading and explaining all written information) and personally date and sign the informed consent form after the oral consent of the subject or legally acceptable representative is obtained.

The original consent form signed and dated by the patient and by the person consenting the patient before the patient's entry into the study must be maintained in the Investigator's study files and a copy given to the patient.

Besides, if a protocol is amended and it impacts on the content of the informed consent, the informed consent must be revised. Patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent.

RANDOMIZATION

All included patients will be randomized with a 1:1 ratio between the two treatments CME + CVL vs. standard non-CME right colectomy. All surgical approaches (open, LPS or Robotic) are allowed.
The randomization sequence will be generated centrally by a computed algorithm and kept concealed to investigators.
The random assignment will be continuously available on a dedicated web-based platform.

11. TREATMENT.

PREOPERATIVE PREPARATION.

Patients with colon cancer do not receive any mechanical bowel preparation and oral antibiotics and fast only from midnight of the night before the surgery.
The first-generation cephalosporin are used as a prophylactic antibiotic and administered just before the start of surgery and during the first postoperative day.
If necessary, low molecular weight heparin is administered for thromboprophylaxis.

GENERALITIES

A video session will be prepared by the CI explaining the optimal technique of CME with CVL.

CME

A proper CME+CVL technique must include:

1) Separation of the visceral fascia from the parietal fascia by sharp dissection leaving intact mesocolon coverage. Eventual defects of the anterior and posterior leaves will be annotated as percentage of the integrity (up to 100%) in the quality assessment measurements.

2) Transecting the supplying vessels at their origin from the main vessels, in particular:

- The Ileocolic Vein and Artery at their origin from the Superior Mesenteric Vessels. In particular, the SMV should be cleared from all adipose tissue all along its anterior surface until its intrapancreatic entrance.

- The Right Colic Vein and Artery at their origin from SMV or Gastrocolic Trunk of Henle (GCTH) and from SMA,

- The superior right colic vein (when present) at its origin from the GCTH

- The Right branches of the Middle Colic Vein (MCV) and of the Middle Colic Artery (MCA) at their origin from the main branches of the MCV and the MCA.

- The MCV and MCA at their origin from the SVM (or the GCTH) and the SMA, in case of cancer of the hepatic flexure or of the very proximal third of the transverse colon, as well as The Right Gastroepiploic Vein and artery at their origin from the GCTH and the gastroduodenal artery

NON-CME

A standard non-CME procedure entail:

- Transecting the Ileocolic Vein and Artery close to the Superior Mesenteric Vessels without clearing the SMV from the adipose tissue all along its anterior and medial surface

- Transecting the Right Colic Vein and Artery peripherally, not at their origin from SMV or Gastro colic Trunk of Henle (GCTH) and from SMA,

- Transecting the superior right colic vein (when present) peripherally, not at its origin from the GCTH

- Transecting the Right branches of the Middle Colic Vein (MCV) and of the Middle Colic Artery (MCA) peripherally, not at their origin from the main trunk of the MCV and the MCA or anyway without clearing the main trunk of the MCV and of the MCA

- The Right Gastroepiploic Vein and artery are never transacted.

Both open and minimally invasive (laparoscopic and robotic) approaches can be used.

Despite the surgical approach and the type of procedure adopted, the operation should be strictly conducted following the general rules for colorectal oncologic resection (See, for example, “Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020 Jan); 25(1): 1-42. Doi: 10.1007/s10147-019-01485-z. Epub 2019 Jun 15 “) particularly as concerns proximal and distal margins length and lymph node retrieval.

A side-to-side anastomosis is usually performed, although an end-to-side anastomosis is also fashioned, particularly during the extracorporeal procedure. End-to-end anastomosis is rarely performed.

The enterotomy is often hand-sutured, although its mechanical closure has been described and it's performed in few centers.

Therefore, during minimally invasive procedures, both intracorporeal and extracorporeal anastomosis may be considered in this setting, with either side-to-side or end-to-side fashioning. Closure of the enterotomies may be performed either manually or mechanically (linear staplers), according to the surgeons' preference.

Manual Reinforcement of a mechanical anastomosis is left to the surgeons' choice.

In open surgery, totally hand-sewn anastomosis is still performed in some centres and therefore can be performed as an alternative to stapled anastomosis depending on each surgeon's custom.

12. SCHEDULE OF CLINICAL ASSESSMENT AFTER TREATMENT.

Postoperative months	1	3	4	6	9	12	18	24	30	36
DFS						**x**		**x**		**x**
Postoperative mortality	**x**									
EORTC C-29/C-30 and SF36			**x**			**x**				
Clinical assessment		**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
CT				**x**		**x**		**x**		**x**
CEA		**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Colonoscopy						**x**				
Overall Survival										**x**

13. EFFICACY AND SAFETY MEASUREMENTS

The primary aim is to describe the DFS of the CME + CVL procedure in patients with a malignant tumor of the right or proximal transverse colon, and to compare it with that of the standard non-CME operation.
DFS is defined as the length of time (months) after randomization (and surgical treatment, CME or non-CME) that the patient survives without any signs or symptoms of colon cancer. [Time frame: at 12 36 months after surgery].

*Patients who are lost to follow-up will be censored at their last assessment date.

An absolute improvement of 0.10 of the 3-years DFS (from 0.70 to 0.80) is considered clinically promising the experimental treatment.

The secondary aims are:

1) To compare the safety of CME in terms of:
- Operative time
- Intraoperative blood loss
- Intraoperative blood transfusion
- Intraoperative Complications
- Early postoperative complications
- Late postoperative complication
- Length of stay
- Postoperative mortality

OPERATIVE TIME. Total time from incision to skin closure expressed in minutes.
[Time frame: after the intervention has ended]

INTRAOPERATIVE BLOOD LOSS. Defined by the volume drained in cm2 into aspiration systems and weight of gauzes, calculated, subtracting the weight of the dry gauzes and volume of saline solution used for irrigation.
[Time frame: after the intervention has ended]

INTRAOPERATIVE BLOOD TRANSFUSION. Defined as the number of red blood cells units, platelets or plasma transfused during surgery and up to 24 h thereafter
[Time frame: at 24 of the postoperative periods]

INTRAOPERATIVE COMPLICATIONS. Defined as any deviation from the ideal intraoperative course occurring between skin incision and skin closure according to the Intraoperative Adverse Event Severity Classification [19]
[Time frame: after the intervention has ended].

EARLY POSTOPERATIVE COMPLICATIONS. Defined as any event untoward correlated with the intervention within 30 days after surgery according to the Clavien-Dindo classification [20].
[Time frame: at 30 days]

LATE POSTOPERATIVE COMPLICATIONS. Defined as any event untoward correlated with the intervention 30 days before surgery according to the Clavien-Dindo classification [20].
[Time frame: at 3 months after intervention]

LENGTH OF STAY. A term defined as the length of an inpatient episode of care, calculated from the day of operation to the day of discharge and based on the number of nights spent in

the hospital.
[Time frame: ate the patient discharge]

POSTOPERTIVE MORTALITY. Defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital.
[Time frame: at 30 posts surgical day]

2) To compare the CME+CVL with standard non-CME treatment in terms of:

- Positive, negative and total LN harvest
- 5-year DFS
- 3- and 5-year Overall Survival
- Quality of life (QoL)

OVERALL SURVIVAL (OS). Defined as the time from random assignment to the date of death due to any cause.
[Time frame at 36 and 60 months] or to the date of censoring at the last time the subject was known to be alive in intention-to-treat populations.

QUALITY OF LIFE (QoL).
Defined as the overall satisfaction with life, or, a sense of personal psychological, physical and social well-being in being self-determining, independent and satisfied with control of disease processes using the punctuation of the EORTC C-29/C-30 and SF36
[time frame: at 4 and 12 months after the treatment.]

3) To describe the Quality of CME as performed in participating centers, by

- Measuring the specimen ‘s area of the mesentery (cm2)
- Defining the integrity of its anterior and posterior leaves (% with respect to a 100 pc of integrity)
- Measuring the length from the tumor centre to the ligature of the ICA (cm)
- Measuring the length from the tumor centre to the ligature of the right branch or the main trunk of the MCA (cm)
- Assessing the Benz classification score to each specimen quality (0 to 3) [27].

14. STATISTICAL CONSIDERATIONS

STUDY DESIGN

This is a national, multicenter, randomized, controlled, parallel-groupie trial in patients with malignant tumor of the right or proximal transverse colon as a primary diagnosis, requiring right hemicolectomy.

SAMPLE SIZE CALCULATION

Parameter specifications can be as follows:

The study sample size has been calculated according to primary efficacy endpoint (DFS).

An absolute improvement of 0.10 of the 3-years DFS (from 0.70 to 0.80) is considered clinically promising the experimental treatment.

According to a single-stage (fixed sample size) design provided by Formula of Schoenfeld, Biometrika, Schoenfeld DA. Sample size formula for the proportional-hazards regression model. Biometrics 1983; 39:499-503, with 24 months of enrollment and 36 months of minimum follow-up, a total of 416 patients (208 each arm) are required to detect an increase in the 3-years DFS from 0.70 to 0.80 assessed with an alpha error of 5% (two tails) and a statistical power of 80% considering the 10% of follow up lost.

Reference: Schoenfeld DA. Sample size formula for the proportional-hazards regression model. Biometrics 1983; 39:499-503.

STATISTICS ANALYSIS

Demographic and baseline characteristics will be presented for all patients. Discrete variables will be summarized by frequencies and percentages. Continuous variables will be summarized by use of standard measures of central tendency and dispersion (mean and standard deviation or median).

Descriptive analyses will be performed using absolute frequencies and percentages for qualitative variables and means and standard deviations or medians and interquartile ranges for quantitative variables, depending on the normality of the distributions that will be tested using the Kolmogorov-Smirnov test.

The univariate analysis will consider comparison between the two groups for all the relevant variables, using the appropriate tests (chi-square test for qualitative variables, t-test for quantitative normally distributed variables, and Wilcoxon sum rank test for quantitative not-normally distributed variables).

All outcomes (primary and secondary) will be compared between the two groups using the aforementioned tests.

To control for confounders, multivariable semi-parametric Cox models will be performed, adjusting for all the relevant confounders (identified both biologically and from univariate analysis). Follow-up time will be defined as the time from recruitment to end of follow-up, death, loss-to-follow-up, or events occurrence (when the event is not death), whichever occurs first.

To control for proportionality of hazards, Schoenfeld residuals will be considered.

All analyses will be performed using STATA v15.

After 12 months, the outcomes will be analyzed in order to evaluate advantages/disadvantages of the study, to perform pertinent amendments or end the study prematurely.

15. VARIABLES

Demographic variables. (See the Trial CRF for more details)

- Age
- Gender

Clinical and preoperative variables.

- ASA score
- BMI
- Comorbidities
- Preoperative Carcinoembryonic Antigen (CEA) serum level
- Tumor size
- Tumor location
- Grading

Surgical characteristics.

- Operative time
- Intraoperative blood loss
- Intraoperative transfusion
- Intraoperative complications
-Type of approach
- Anastomosis type
- Drain placement
- Vascular ligature
- Lymphadenectomy characteristics

Postoperative characteristics

- Postoperative blood loss (drain output within 72 hours)
- Postoperative transfusion
- Bowel movements
- Return to oral feeding
- Drain removal
- Length of stay
- Early complications type
- Early complications by Clavien-Dindo Classification
- Late complications type

- Late complications by Clavien-Dindo Classification
- Postoperative mortality.

Pathological characteristics.

- Resection margins
- Length of the specimen
- Distance of the tumor from thee vascular ties (ICA, MCA)
- Area of the resected mesocolon
- WHO histological classification.
- TNM staging
- Total number of LN retrieved
- Number of positive LN retrieved
- Number of positive LN specifically recruited in LN station during CME procedure (optional, but recommended) (at the proper origins of the ileocolic vessels, the right colic vessels, the gastroepiploic vein, the right branch of the middle colic vessels or the main trunk of middle colic vessels)
- Status till the last follow-up.

*For both groups the vessels ligated, and the level of these ligation will be recorded (ileocolic, right colic, gastroepiploic, the right branch of the middle colic, the origin of the middle colic vessels).

*For the case-control group the same variables (with the exclusion of the number and the positivity of LN in nodal stations specifically recruited in the CME procedure) will be analyzed.

16. REPORTS, DISSEMINATION, PUBLICATION AND CONFIDENTIALITY.

DISSEMINATION

The results of the trial will be reported first to trial collaborators during the meeting of the Colorectal Cancer Network of the Italian Society of Surgical Oncology.
Individual unit data will be presented at local meetings. The main report will be drafted by the trial coordinating team, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the collaboration.
The trial will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org). [2]

Overall collective data will be published in peer-reviewed journals and presented at relevant surgical meetings.

PROTOCOL AMENDMENTS

Any modifications to the protocol which may impact on the conduct of the study, a potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment

will be agreed and approved by the Ethics Committee before implementation and notified to the health authorities following local regulations.

DECLARATION OF INTEREST

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

ACCESS TO DATA

All Principal Investigators will be given access to the cleaned data sets.

CONFIDENTIALITY.

Participants' study information will not be released outside of the study without the written permission of the participant, except as necessary for monitoring by the country government and regulatory authorities.
For protecting confidentiality and anonymity will be mandatory the employ of study codes on data documents (CRF) and keep a separate document that links the study code to subjects' identifying information locked in a separate location.
All participant information will be stored in locked file cabinets in areas with limited access and all local databases will be secured with password-protected access systems.
Forms, lists, logbooks, appointment books, and any other listings will be stored in a separate, locked file in an area with limited access (only allowing primary investigators access).

All the Investigators must respect the treatment of sensitive data according to the Regolamento Europeo sulla Protezione dei Dati (GDPR) n. 679/2016 a partire dal 19 settembre c.a., del D. Lgs n. 101 del 10 agosto 2018 pubblicato sulla Gazzetta Ufficiale del 04 settembre c.a.) of the participants.

17. END OF TRIAL

The trial will be stopped prematurely if recommended by the Ethics Committee; by the IDSMC.
The trial will be stopped prematurely after 12 months of enrolment in the absence of a clear advantage of the CME intervention at interim data analysis.
The trial Ethics Committee will be notified in writing if the trial has been concluded or prematurely terminated .

18. COLLABORATORS

CENTRE	Surgeon	Contact E- Mail	Address
Università Federico II di Napoli	Francesco Corcione. Umberto Bracale	francesco.corcione@unina.it umbertobracale@gmail.com	Corso Umberto I 40 - 80138 Napoli
ASST Nord Milano - P.O. SSG	Gianandrea Baldazzi. Diletta CassiniI.	gbaldazzi@hotmail.com diletta_cassini@yahoo.it	P.O. “Citta” di Sesto San Giovanni Via Matteotti 83 – Sesto San Giovanni
Ospedale E. Agnelli Pinerolo	Andrea Muratore.	amuratore@aslto3.piemonte.it	Via Brigata Cagliari, 39, 10064 Pinerolo TO
Azienda Usl Toscana sud est	Paolo Pietro Bianchi.	bianchippt@gmail.com	Via Curtatone, 54, 52100 Arezzo AR
Struttura di chirurgia HPB e Colorettale di Candiolo	Giuseppe Spinoglio. Dario Ribero.	gspinoglio@icloud.com dario.ribero@ircc.it	SP142, km 3,95, 10060 Candiolo TO
AUSL Bologna	Elio Jovine. Raffaele Lombardi	elio.jovine@ausl.bologna.it	Via Castiglione, 29, 40124 Bologna BO
Università degli Studi di Ferrara	Gabriele Anania.	g.anania@unife.it	Dipartimento di Scienze mediche Corso Giovecca 203 44121 - Ferrara
Policlinico A. Gemelli Roma	Domenico D’Ugo Alberto Biondi	Biondi.alberto@gmail.com	Sede Operativa Largo Agostino Gemelli 8, 00168 Roma
AOU G. Martino - Messina	Giuseppe Navarra	gnavarra@unime.it	Via Consolare Valeria 1 - 98124 Messina (ME)
IRCCS Policlinico San Martino Genova	Stefano Scabini	stefanoscabini@libero.it	Largo Rosanna Benzi, 10, 16132 Genova GE
Tor Vergata Roma	Giuseppe Sica	sigisica@gmail.com	PTV, viale Oxford 81, 00133 Roma piano I TORRE 9, studio 19
Ospedale S. Andrea La Spezia	Stefano Berti Andrea Gennai	stefano.berti@asl5.liguria.it andrea.gennai@asl5.liguria.it	Via Vittorio Veneto, 197, 19121 La Spezia SP
Istituto Europeo di Oncologia	Fumagalli Romario Uberto Adamoli Laura	uberto.fumagalliromario@ieo.it laura.adamoli@ieo.it	Via Ripamonti, 435 - 20141 Milano

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