DANISH MEDICAL JOURNAL

Protocol Article

Dan Med J 2021;68(5):A09200710

Intracorporeal versus extracorporeal anastomosis in right colectomy – a protocol for a randomised trial

Niclas Dohrn[1, 2], Mads Falk Klein[1] & Ismail Gögenur[2]

1) Department of Surgery, Copenhagen University Hospital – Herlev Hospital, 2) Department of Surgery, Zealand University Hospital, Denmark

Dan Med J 2021;68(5):A09200710

ABSTRACT

INTRODUCTION: A minimally invasive approach in colorectal surgery reduces surgical stress compared with open surgery. Today, the gold standard in the treatment of right-sided colonic cancer is a minimally invasive approach, which can be performed with either a "minimally invasive assisted" technique – a combination of open and minimally invasive surgery with an extracorporeal anastomosis (ECA) or with a "totally minimally invasive" technique with intracorporeal anastomosis (ICA). The prevailing technique is ECA, but there is no conclusive evidence on the superiority of one technique over the other, and randomised trials comparing ICA with ECA are warranted. We hypothesised that ICA will yield improved recovery compared with ECA.

METHODS: This is a triple blind, multicentre, randomised controlled trial comparing robotic right colectomy with ECA with robotic right colectomy with ICA. We plan to include 100 patients undergoing elective minimally invasive right colectomies in two colorectal centres in Denmark. The primary outcome is patient-reported post-operative recovery, and secondary outcomes are additional measures of post-operative recovery (pain, analgesics, nausea and vomiting, time to first flatus/bowel movement, length of hospital stay), operative time, intraoperative complications, conversions, readmissions, reoperations, 30- and 90-day morbidity and mortality.

CONCLUSION: The results of this randomised controlled trial will contribute with valuable knowledge on the best surgical management of right-sided colonic cancer.

FUNDING: The study has received unrestricted grants from the Louis-Hansen Foundation, Jacob & Olga Madsen's foundation, Trigon Foundation, Toyota Foundation, Dagmar Marshalls Foundation, Vissing Foundation, The Kjaer Foundation and the Nyegaard foundation.

TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT03130166.

The gold standard in the treatment of right-sided colonic cancer is minimally invasive right colectomy [1], but at present, no standardised technique exists for ileocolic anastomosis. Surgeons, therefore, perform the procedure according to local practices and experience. The procedure is performed as a "minimally invasive assisted" technique – a combination of open and minimally invasive surgery with an extracorporeal anastomosis (ECA) or a "totally minimally invasive" technique with intracorporeal anastomosis (ICA).

The possible advantages of ICA are 1) a suprapubic incision associated with a reduction in pain, fewer pulmonary and wound complications [2], 2) no externalisation of the intestines, and 3) less extensive mobilisation of the transverse colon. The combined effect is thought to mitigate the surgical stress response and improve short-term outcomes compared with ECA. The disadvantage of ICA is that it is perceived to be technically more challenging [3], possibly because it requires proficiency with intracorporeal suturing.

The prevailing technique is ECA. However, there is no conclusive evidence on the superiority of one technique over the other. Systematic reviews on the subject conclude that ICA results in faster post-operative recovery with a faster return of bowel function and a shorter length of stay and improved short-term outcomes [4-7]. However, the literature predominately consists of studies with either a retrospective or a prospective, non-randomised design and are thus subjected to the inherent biases of these approaches. Only three recently published randomised controlled trials [8-10] exist. No current studies have reported on patient-reported recovery outcome parameters.

The objective of this study was to compare ICA with ECA in robotic right colectomy. We hypothesise that ICA leads to an improved post-operative recovery compared with ECA.

METHODS

Study setting and population

This is a multicentre, triple-blind, randomised controlled trial comparing robotic right colectomy with ECA with robotic right colectomy with ICA. We plan to include 100 patients undergoing elective minimally invasive right colectomies in two colorectal centres in Denmark. Both centres are highly specialised in the treatment of colorectal cancer and competent in both techniques investigated in the study.

Inclusion criteria

Eligible are patients above 18 years of age, American Society of Anesthesiologists classification system (ASA) I-III, with verified or clinical suspicion of malignant epithelial colonic lesion proximal to mid-transverse colon scheduled for minimally invasive right colectomy or extended right colectomy with curative intent. Laparoscopic and robotic approaches are accessible in both centres. If patients are enrolled in the study, they are scheduled for a robotic approach. No other selection criteria for a robotic or laparoscopic approach apply. If logistic circumstances result in the robotic approach not being available on the day of surgery, the patient is not eligible but is registered in the screening log.

Exclusion criteria

Not eligible are patients undergoing an emergency procedure or major concomitant procedures and patients who are unable to comply with study requirements, provide informed consent, or have lesions located in the distal transverse colon or for whom a splenic flexure is planned for extended right colectomy. In case of protocol violations or withdrawal of consent, patients are excluded and a detailed description is published as part of the results of the study.

Randomisation

Patients are randomised in a 1:1 ratio to either ICA or ECA in robotic right colectomy. Randomisation is performed with a random sequence generator with random block sizes of 4-10. The randomised sequences are concealed in sequentially numbered, opaque envelopes by an independent member of staff with no further involvement in the study. When patients are recruited, they are assigned a unique study ID and the envelope with the corresponding number is opened at the time of randomisation.

Randomisation is done intraoperatively before mobilisation of the transverse colon. Randomisation will be completed only if both techniques are possible. A thorough description of the patients who are not randomised will be included in the final publication. After randomisation, data will be analysed according to the intention-to-treat principle.

Requirements to the surgeon

Only surgeons who are proficient in both techniques may contribute to the study. Proficiency is self-assessed and with no number of cases needed. Even so, surgeons are required to have performed both techniques routinely before contributing to the study. The number of cases for whom the surgeon has performed surgery is registered for each patient in order to assess any residual learning curve effect.

Surgical technique

Pneumoperitoneum is achieved by the method of choice of the operating surgeon. A camera port is placed close to the umbilicus, and three additional robotic ports are placed, one in the suprapubic area, one in the right iliac fossa, and one in the upper left quadrant. Finally, a 12-mm trocar for the assistant is placed in the left side of the abdomen. Additional assisting trocars may be placed in any number of locations as needed. An initial assessment is made by laparoscopy and the robot is docked.

A medial to lateral approach is applied. The ileocolic pedicle is isolated and ligated and the dissection is continued to the lateral-side wall. The right branch of the middle colic vessels is isolated and ligated. If an extended right colectomy is performed, the middle colic artery is isolated and ligated centrally. The gastrocolic ligament is taken down and the hepatic flexure is mobilised. Randomisation will be completed before mobilisation of the transverse colon. The rest of the procedure follows the description of either ICA or ECA.

Intracorporeal anastomosis

No further mobilisation is performed, and an appropriate site of transection of the transverse colon is identified in pursuance of the normal principles of oncological resection, visual inspection of colour change of the bowe, and a non-quantitative ICG perfusion test. A laparoscopic or robotic stapler is used to transect the transverse colon and terminal ileum, and the resected specimen remains inside the abdomen until the end of the procedure. The ileum and transverse colon are brought together and a stay suture may be applied at the surgeon's preference. An isoperistaltic side-to-side anastomosis is created through two small enterotomies on the antimesenteric sides of the transverse colon and ileum. A laparoscopic or robotic 45/60 mm linear stapler is applied with a jaw inserted in each enterotomy, and the residual defect is closed in a single layer by laparoscopically continuous suturing with a barbed suture. The specimen is removed with a wound protector in place through a suprapubic transverse incision – if suitable, by enlargement of the suprapubic port.

Extracorporeal anastomosis

Mobilisation of the transverse colon is completed, and the intestines are brought extracorporeally by a right-sided transverse subcostal incision with a wound protector in place and, if possible, with muscle preservation. An appropriate site of transection of the transverse colon is identified in pursuance of the normal principles of oncological resections, visual inspection of colour change of the bowel, and test for bleeding/pulsation of the marginal artery. The ileum and transverse colon are transected extracorporeally by sharp incision, and the specimen is removed from the operative field. The two ends of the bowel are aligned for ECA and an end-to-end hand-sewn anastomosis with continuous one-layer suturing is performed.

Outcomes

The primary outcome is patient-reported post-operative recovery measured by the "Quality of Recovery – 15

Danish" (QoR-15D) questionnaire (**Table 1** and **Table 2**). The QoR-15 is a validated, patient-reported outcome measure of post-operative quality of recovery on a scale ranging from 0 to 150 [11-13].

TABLE 1 Definition of post-operative recovery, intraoperative and post-operative outcomes.

Outcome	Definition
Post-operative recovery	
Quality of Recovery 15 – Danish: primary outcome	A measure of patient-reported quality of post-operative recovery based on the patient's physical and mental well-being after surgery: 0-150 range
Pain: at rest and during movement	A measure of patient-reported level of pain relying on a VAS: 0-100 range
Analgesic usage	Dosage of non-opioid and opioid analgesics administered as registered in the electronic patient chart each post-operative day
Mobilisation	Mobilisation at 6 h post-operatively: yes/no
Intestinal recovery	Time to 1st flatus/bowel movement: h since skin closure
Nausea	A measure of patient-reported level of nausea on a VAS: 0-100 range
Vomiting	Event with involuntary expulsion of the contents of the stomach: yes/no
Antiemetics usage	Dosage of antiemetics administered as registered in the electronic patient chart each post-operative day
Length of hospital stay	Total length of hospital stay starting from the 1st post-operative day[a] until discharge
Intraoperative outcome	
Operative time for total procedure	Min. from skin opening to skin closure
Operative time for anastomosis	Min. from 1st enterotomy/incision until the last knot is tied
Intraoperative complications	Various intraoperative complications specifically registered by the surgeon in surgeon's CRF: yes/no and specification, e.g. hollow organ perforation or bleeding
Blood loss	Blood loss in ml as registered by the operating surgeon in surgeon's CRF
Conversions to open surgery	Any unplanned abdominal incision or the performance of any unplanned step of the procedure at the extracorporeal site
Conversion to laparoscopic surgery	Any unplanned step of the procedure performed laparoscopically
Length of incision	Cm of skin incision at the extraction site measured at skin closure with measuring tape
Number of harvested lymph nodes	Number of lymph nodes in specimen as registered in the pathology report
Quality of specimen	Complete, near complete or incomplete mesocolic excision as registered in the pathology report.
Radicality of operation	R0, R1, R2 as registered in the pathology report
Post-operative outcome	
30- and 90-day morbidity	30- and 90-day morbidity are defined as a surgical complication within 30 and 90 days, respectively A complication is defined as any deviation from the normal post-operative course All individual complications are graded according the required treatment by the CDC and overall morbidity is rated on a 0-100 scale by the CCI Minor complications are defined as CDC < IIIb and major complications are defined CDC ≥ IIIb
Anastomotic leakage	Defined as a defect of the intestinal wall integrity at the ileocolic anastomotic site leading to communication between intra- and extraluminal compartments or abscess formation in proximity of the anastomosis [2, 3]: yes/no, and severity grading of the anastomotic leakage by CDC and A-B-C-grading according to the International Study Group for Rectal Cancer
Pulmonary complication	Defined as a composite outcome of any deviation in pulmonary function from the normal post-operative course regardless of aetiology or pneumonia visualised on radiological exam and/or positive outcome of a sputum culture and requiring antibiotic treatment
Post-operative ileus	Nausea, vomiting and the absence of stools within 72 h post-operatively
Bowel obstruction	Radiological signs of bowel obstruction on CT
Intestinal ischaemia	Ischaemia of the small or large intestines, visualised by abdominal CT or colonoscopy requiring intervention
Surgical site infection	Superficial skin infection or deep wound infection at surgical site, defined by redness, pain, drainage of cloudy fluid or localised swelling at surgical wounds requiring antibiotic treatment
Urinary tract infection	Clinical symptoms in combination with positive urine sediment or urine culture requiring antibiotic treatment
30- and 90-day mortality	Death within 30 or 90 days post-operatively
Reoperation	Surgical intervention in the abdominal region within 30 days after index surgery
Readmission	Readmission to hospital within 30 days after the index surgery
Pathophysiological outcome	
"Timed-Up-and-Go" test	A measure of mobility and balance by the number of sec. it takes to rise from a chair, walk 3 m, turn around, walk back to the chair and sit down
Spirometry	A measure of post-operative lung capacity: FEV1, FVC and FEV1/FVC-ratio
Peak expiratory flow	A measure of post-operative lung function
Pulse oximetry	A continuous 1-Hz measure of respiratory function 48 h post-operatively
Orthostatic hypotension test	A test of imbalance of the autonomic nervous system in response to surgical stress defined as a fall in systolic blood pressure of ≥ 20 mmHg or in diastolic blood pressure of ≥ 10 mmHg or an increase in heart rate of 30 bpm from supine to standing
Heart rate variability	A continuous 1,000-Hz measure of the variation in time between each heartbeat controlled by the autonomic nervous system in response to surgical stress intraoperatively and 48 h post-operatively
Quantitative indocyanine green test	A measure of anastomotic blood perfusion after confectioning of the anastomosis In ECA, q-ICG is performed immediately after suturing of the fascia and in ICA, q-ICG is performed immediately after confectioning of the anastomosis
Laboratory blood analysis	For exploratory analyses of the surgical response, plasma cytokine measurement and mRNA multiplex transcriptional profiling will be performed, among others, in order to describe the adaptive and innate immune response

CCI = Comprehensive Complication Index; CDC = Clavien-Dindo classification; CRF = case report form; ECA = extracorporeal anastomosis; FEV1 = forced expiratory volume in 1st second; FVC = forced vital capacity; ICA = intracorporeal anastomosis; q-ICG = quantitative indocyanine green test; VAS = visual analogue scale.
a) The day after index surgery.

TABLE 2 Blinding and timing of primary and secondary outcomes.

			Post-operatively							
	Blinded outcome	Baseline	6 h	day 1	day 2	day 3	day 14	day 30	day 90	continuous measurement
Primary outcome										
Quality of Recovery 15 – Danish	Yes	x	x	x	x	x	x			
Secondary outcome										
Pain	Yes	x	x	x	x	x	x			
Analgesic usage	Yes	x	x	x	x	x	x			
Nausea and vomiting	Yes	x	x	x	x	x	x			
Antiemetic usage	Yes	x	x	x	x	x	x			
Time to 1st flatus/bowel movement	Yes									x
Length of hospital stay	No									x
Morbidity: CDC and CCI	No							x	x	
Mortality	No							x	x	
Reoperation	No							x		
Readmission	No							x		
Laboratory blood tests	Yes	x		x	x		x			
"Timed-Up-and-Go" test	Yes	x	x	x	x		x			
Spirometry	Yes	x	x	x	x		x			
PEF	Yes	x	x	x	x		x			
Pulse oximetry	Yes									x: 48 h
Orthostatic hypotension	Yes	x	x	x	x		x			
Heart rate variability	Yes									x: 48 h

CCI = Comprehensive Complication Index; CDC = Clavien-Dindo classification; PEF = peak expiratory flow.

Secondary outcomes are additional measures of post-operative recovery, intraoperative outcomes, post-operative outcomes, and pathophysiological tests (Table 1 and Table 2).

Timing of the assessments and blinding of the outcomes are listed in Table 2. Patients will be followed until 90 days after surgery, during which period medical records will be evaluated for morbidity, readmittance, reinterventions, and mortality.

Blinding

Only the operating surgeons and other staff members present at the operating theatre are knowledgeable about the actual intervention performed. The surgeons will describe all procedure-related details in a separate "surgeon's case report form" document, which is stored in an opaque, sealed envelope, and no information related to the anastomosis is available in the patient chart. Treatment assignment will be revealed after completion of all study-related questionnaires and tests on post-operative day (POD) 14. If it is not possible to maintain blinding until completion of all study-related questionnaires or tests on POD 14, this is reported.

Research staff are blinded to the intervention. Research staff assist patients with questionnaires, assess post-operative recovery (gastrointestinal function, post-operative pain, post-operative nausea and vomiting, and mobilisation), and perform pathophysiological tests. As the specimen extraction sites in ICA and ECA are different, blinding of these groups is maintained by applying large abdominal wound patches covering both potential specimen extractions sites immediately after surgery. The operating surgeons do the daily rounds including an assessment for post-operative complications and of the wounds with replacement of the abdominal wound patch in case of permeation.

Patients are blinded to the intervention. Obviously, patients only feel discomfort from one site, but specifically, they are not informed about which incision relates to ICA and ECA.

A blinded data analyst with no relation to any other parts of the study will perform the statistical analyses.

Perioperative care

The operation is performed under general anaesthesia and all patients are managed according to the anaesthetic protocol regardless of the intervention (**Table 3**). All doses of administered medicine and violations of the anaesthetic protocol are registered.

TABLE 3 Anaesthetic protocol[a].

Administered medicine	Dosage
IV propofol	Initially 1-3 mg/kg followed by 5 mg/kg/h
IV remifentanil	Initially 50 µg/kg/h followed by 25-50 µg/kg/h
IV oxycodon	0.3 mg/kg 20 min. before extubation
IV paracetamol	1,000 mg 20 min. before extubation
IV ondansetron	4 mg 20 min. before extubation
SC ropivacain	4 mg/kg injected at around the skin incisions at skin closure

IV = intravenous; SC = subcutaneous.
a) No steroids, non-steroidal anti-inflammatory drugs or regional analgesic blockade is allowed.
Neuromuscular blockage is administered at induction followed by a continuous infusion.
Ephedrine and phenylephrine may be administered if needed.
All doses are registered.

Irrespective of the intervention performed, patients are managed with an enhanced recovery after surgery (ERAS) protocol following the "ERAS society colorectal guidelines" [14] implemented at both centres.

Discharge criteria are pre-specified as 1) adequate pain relief on oral analgesia regimen, 2) tolerance of oral intake, 3) return of bowel function/flatus and 4) absence of unmanaged complications.

Timeline

Enrolment was initiated in the first centre in May 2018 and in the second centre in September 2019. Completion is expected in January 2021.

Study size

Following our power calculation, we plan to enrol 100 patients in the study. The power calculation was based on QoR-15D data from patients who underwent minimally invasive colonic resections with a standard deviation (SD) of 23 at baseline and an assumption that a decline of 10% (15 units) from baseline to POD 2 is clinically significant. At a power of 0.80 and a two-sided alpha significance level of 0.05, 42 patients are required in each study arm. Based on a dropout rate (conversions, exclusions, etc.) of 20%, we plan to include 50 patients in each arm.

Statistical analysis plans

All statistical analyses will be conducted by a blinded biostatistician after data collection has been completed in accordance with the current statistical analysis plan.

Primary analysis

For the primary outcome of QoR-15D, we plan to conduct a mixed analysis of variance (ANOVA) with a between-subjects factor with two levels (treatment: ICA or ECA) and a within-subjects factor with six levels (time: baseline, six hours post-operatively, POD 1, POD 2, POD 3, and POD 14) provided the assumptions of sphericity and approx. normal distribution are met.

With a median length of stay of 2-3 days in patients undergoing minimally invasive right colectomy in centres with a high adherence to ERAS protocols, the post-operative recovery on POD 2 is of particular clinical interest. Hence, we will conduct a separate analysis of covariance (ANCOVA) on the specific difference in QoR-15D from baseline to POD 2 with the baseline value of QoR-15D as an independent variable.

A post-hoc sensitivity analysis with consideration of "as-treated" analysis, subgrouping, definitions, statistical assumptions, missing data strategy, etc., will be applied with guidance from the results of the primary analysis. A two-sided alpha value of < 0.05 will be considered significant.

Secondary analyses

Continuous variables will be expressed as means ± SD and categorical data as frequencies. Distributional assumptions of normality of continuous data will be assessed through visual inspection of histograms and Q-Q plots or Shapiro-Wilk tests. Normally distributed and not-normally distributed data will be analysed with parametric and non-parametric tests, respectively. Dichotomous and categorical data will be analysed with Fisher's exact test and χ^2 test, respectively. If applicable, we plan to conduct a mixed ANOVA on clinical outcomes with repeated measurements and an ANCOVA on the specific difference from baseline to POD2 (e.g., post-operative pain, blood test analysis, etc.) in accordance with the clinical justification in the primary analysis.

Data sharing statement

Researchers who provide a methodologically sound proposal will be able to attain the de-identified individual participant data that underlie the results reported in the final article (text and tables) for any purpose.

Trial registration: Prior to commencement, this study was registered with Clinicaltrials.gov (ID NCT03130166).

DISCUSSION

The continuous striving to minimise the impact of surgery on patients together with the increased adoption of robotic surgical systems have revived the interest in the ICA technique. The present study will contribute with valuable knowledge on the best surgical management of right-sided colonic cancer.

Correspondence *Niclas Dohrn.* E-mail: niclas.dohrn@regionh.dk

Accepted 13 April 2021

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

REFERENCER

1. Arezzo A, Passera R, Ferri V et al. Laparoscopic right colectomy reduces short-term mortality and morbidity. Results of a systematic review and meta-analysis. Int J Colorectal Dis 2015;30:1457-72.
2. deSouza A, Domajnko B, Park J et al. Incisional hernia, midline versus low transverse incision: what is the ideal incision for

specimen extraction and hand-assisted laparoscopy? Surg Endosc 2011;25:1031-6.
3. Swanstrom L. Evaluating the degree of difficulty of laparoscopic colorectal surgery - invited critique. Arch Surg 2008;143:768.
4. Selvy M, Mattevi C, Slim K et al. Intra-versus extracorporeal anastomosis in laparoscopic right colectomy: a meta-analysis of 3699 patients. Int J Colorectal Dis Int J Colorectal Dis 2020;35:1673-80.
5. van Oostendorp S, Elfrink A, Borstlap W et al. Intracorporeal versus extracorporeal anastomosis in right hemicolectomy: a systematic review and meta-analysis. Surg Endosc 2017;31:64-77.
6. Milone M, Elmore U, Vignali A et al. Recovery after intracorporeal anastomosis in laparoscopic right hemicolectomy: a systematic review and meta-analysis. Langenbecks Arch Surg 2018;403:1-10.
7. Emile SH, Elfeki H, Shalaby M et al. Intracorporeal versus extracorporeal anastomosis in minimally invasive right colectomy: an updated systematic review and meta-analysis. Tech Coloproctol 2019;23:1023-35.
8. Bollo J, Turrado V, Rabal A et al. Randomized clinical trial of intracorporeal versus extracorporeal anastomosis in laparoscopic right colectomy (IEA trial). Br J Surg 2020;107:364-72.
9. Allaix ME, Degiuli M, Bonino MA et al. Intracorporeal or extracorporeal ileocolic anastomosis after laparoscopic right colectomy. Ann Surg 2019;270:762-7.
10. Mari GM, Crippa J, Costanzi ATM et al. Intracorporeal anastomosis reduces surgical stress response in laparoscopic right hemicolectomy. Surg Laparosc Endosc Percutan Tech 2018;28:77-81.
11. Kleif J, Edwards HM, Sort R et al. Translation and validation of the Danish version of the postoperative quality of recovery score QoR-15. Acta Anaesthesiol Scand 2015;59:912-20.
12. Kleif J, Waage J, Christensen KB et al. Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth 2018;120:28-36.
13. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score. Anesthesiology 2013;118:1332-40.
14. Gustafsson UO, Scott MJ, Hubner M et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. World J Surg 2019;43:659-95.