Effects of Anaesthetics on colorectal cancer outcomes

ENCORE Trial

The effects of anaesthetic techniques on time to start of adjuvant chemotherapy, and early and late outcomes following surgery for colorectal cancer: A prospective, multicentre, international, observational, pragmatic study

Study protocol

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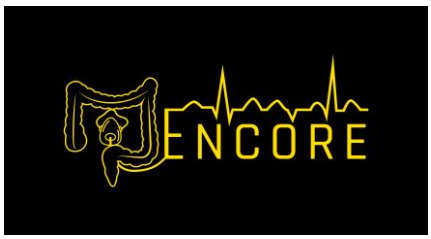

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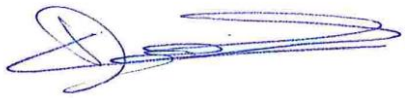

Local Principal Investigator

(Centre, Place, Date)

(Name, Signature)

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Synopsis

Principal Investigator	Prof. Max Bell, Karolinska University Hospital, Stockholm, Sweden
Title	Effects of aNaesthesia in COloREctal cancer outcome trial - ENCORE The effects of anaesthetic techniques on time to start of adjuvant chemotherapy, and early and late outcomes following surgery for colorectal cancer (Stage I - III)
Protocol Version	ENCORE, V1.0 21DEC20
Clinicaltrials.gov	NCT04493905
Background & Rationale	Colorectal cancer (CRC) is the third commonest cancer in the world with a high postoperative mortality (2 – 6%) as well as a low 5-year survival (60%). Despite advances in surgery and the use of minimally invasive laparoscopic surgery in recent years and adjuvant chemotherapy after surgery in stage III (and advanced stage II), long-term prognosis has only improved marginally. Epidural analgesia is commonly used as a part of the perioperative management of patients undergoing open, colorectal cancer surgery. Epidurals have been shown to reduce perioperative inflammation and preserve immunological function, which may be beneficial in perioperative tumorigenesis. In several retrospective studies, anaesthesia and choice of analgesia have shown to improve long-term survival, but no randomized studies have been published in the literature today. Similarly, the benefits of propofol anaesthesia in comparison to inhalational anaesthesia have recently been high-lighted in relation to cancer surgery, and many patients today request the use of epidurals, total intravenous anaesthesia and loco-regional anaesthetic technique during surgery, without clear evidence from prospective studies in the literature.
Primary objective	To investigate the effect of anaesthetic technique on: Short term: time to start of adjuvant chemotherapy in patients planned for RIOT Long term: Time to recurrence (TTR) at 3 years. (please see section 4.2 for details)
Secondary objectives	0-30-day postoperative morbidity Length of hospital stay and days at home for 30 days (DAH-30) Adverse events related to oncological treatment (chemotherapy, radiotherapy)
Study Subjects	Patients with stage I-III colorectal cancer (stratified to stage and type of cancer) scheduled for upfront curative surgery.
Study design	Prospective, multicentre, international, observational, pragmatic study
Planned sample size	10000 patients from > 200 centres (minimum 40 patients/centre)
Inclusion criteria	Age > 18 years ASA I-III Scheduled for elective (planned) colorectal cancer surgery for stage I-III (open or minimally invasive) Signed written informed consent when requested by the local Ethics committee
Exclusion criteria	Uncontrolled renal or liver disease, restrictive (limiting mobility) heart failure or ischemic heart disease (ASA IV-V) Speech, language or cognitive difficulties precluding signing informed consent to participate Stage IV colorectal cancer
Exposure	This is an observational study, so no intervention will be made. Type of regional anaesthesia (epidural vs. no epidural) or general anaesthesia (total intra-venous or inhalational) will be the exposure.

Primary Outcomes	Time to return to intended adjuvant (postoperative) chemotherapy (number of days after surgery) Time to recurrence (TTR) of cancer at 3 years (please see section 4.2 for details)
Secondary outcome	Percentage of complications within 30 days of surgery as graded by the Clavien-Dindo classification Other adverse events not included in the C-D classification within 30 days Length of hospital stay defined as days from index surgery to arrival at original living facility Days at home for 0-30 days (DAH-30) after index surgery Adverse events related to oncological treatment
Statistical Considerations	Start of adjuvant chemotherapy: Number of patients who can start chemotherapy for those who return to intended oncological therapy (RIOT) Previous studies have shown that approx. 15% patients cannot start adjuvant chemotherapy within 8 weeks after surgery. Our hypothesis is that the application of an epidural (vs. no-epidural) or the use of propofol (vs. inhalational anaesthesia) will decrease this to 10%. Therefore, we estimated that 1830 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the start of chemotherapy > 8 weeks from 15% in the No-epidural (or inhalational anaesthesia) group to 10% in the Epidural (or total intravenous anaesthesia) group. If 30% patients are Stage I cancers (no adjuvant chemotherapy required), the sample size will need to be increased by 30% to approximately 2500 patients for time to start of adjuvant chemotherapy (< or > 8 weeks) in patients who are expected to return to intended oncological treatment. The above data will be gathered as a continuous outcome (time to first start of intended chemotherapy after surgery in the subgroup of patients intended for RIOT)
Study timetable	First Subject In: Q3 2021 Last Subject In: Q2 2023

List of Abbreviations

ASA	American Society of Anaesthesiologists Physical status classification
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computerized tomography
CTN	Clinical Trial Network
EC	Ethics Committee
EDA	Epidural analgesia
ESAIC	European Society of Anaesthesiology and Intensive Care
FLOX	5-Flourouracil, leucovorin, oxaliplatin
FOLFIRINOX	folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (Camptosar), oxaliplatin (Eloxatin)
FOLFLOX	Folinic acid (leucovorin), Fluorouracil (5-FU) and Oxaliplatin (Eloxatin)
GCP	Good clinical practice
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
NC	National Coordinating Investigator
NRS	Numeric rating score
RIOT	Return to intended oncological therapy
SC	Steering Committee

1. Administrative Structure

1.1. Chief Investigator

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1.3 Sponsorship

ENCORE is entirely sponsored by a grant from the European Society of Anaesthesiology and Intensive Care Clinical Trial Network (ESAIC CTN). The aim of the European Society of Anaesthesiology and Intensive Care Clinical Trial Network is to provide an infrastructure for clinical research in the fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational European collaborative studies. No other institution or industrial company is or will be involved in financing, planning or conducting the ENCORE Trial. However, the submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the sponsor and the SC.

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2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The research project will be carried out in accordance with the research plan and the principles enunciated in the current version of the Declaration of Helsinki (amendment 2013) by the World Medical Association and the ICH-GCP Guidelines E6(R2). Specific national and local regulatory authority's requirements will be followed as applicable.

2.2 Risk categorisation

No research related interventions are anticipated, and all patients will receive routine care according to the standards laid out in each institution. Time to recurrence will be calculated as the reappearance of primary disease (CRC) assessed by CT/MRI scan. The former encompasses a dose of radiation. However, all patients are usually followed up by routine CT scans at definite time periods, varying from country to country. Although our plan is to follow the routines already existing in each hospital/country, we will request a CT/MRI scan performed after 2 years since the TTR (average) is about 21 months. If this is unavailable at this timepoint, the first CT/MRI scan after 2 years (± 3 months) will be used to determine recurrence. Considering the benefits of early detection of recurrence to the patients, the possible added radiation harm is small.

2.3 Institutional Review Board (IRB) and Competent Authorities (CA) or equivalent

The proposed study is an observational study. Therefore, no ethical concerns can be foreseen. Written, informed consent will be obtained from each patient prior to inclusion, if necessary.

In all cases, all participating centres must submit the study to the local Institutional Review Board (IRB) for ethical judgment and obtain document of proof that the trial has been subject to IRB/IEC review and given approval/favourable opinion.

If informed consent is not required by the local IRB, an explicit, written exemption must be obtained from the Institutional Review Board. This process should take place prior to initiation of the trial and in compliance with the applicable national regulatory requirement(s).

2.4 Participant Information and Informed Consent

If applicable, informed consent forms and any other written information to be provided to the patients as well as advertisement for subject recruitment (if used) should be subject to IRB/IEC review and given approval/favourable opinion. Informed consent will be obtained as follows: the patients will be presented with the IRB approved Patient Information Sheet to make an informed decision about their participation in the study, i.e. explaining the nature of the study, its purpose, the general lack of any procedures involved, the expected duration, the potential risks and benefits (see Appendix 2A Patient Information Sheet and Appendix 2B-2C Patient Information Sheet and Consent). Each participant will be informed that their participation in the study is voluntary and that he/she may withdraw from the study at any time and without explanation, that withdrawal of consent will not affect his/her subsequent medical assistance and treatment and that no further data will be collected, while already collected encoded data will be pseudonymised and analysis may be performed up to the point of data collection.

The participant will be informed that his/her medical records will be examined by authorised individuals other than their treating physician. The participant will read the statement and will have the opportunity to ask questions before signing and dating the ICF and will be given a copy of the signed document (when requested by the local ethics committee). Patients will confirm that they were given adequate time to reach a decision. The ICF must also be signed and dated by the investigator (or designee), when applicable, and it will be retained as part of study records.

The Sponsor provides an English version of the Patient Information Sheet and Patient Informed Consent Form (see ESAIC home page – ENCORE Trial). All translation and adaptation of the Appendices should be sent to ESAIC the Sponsor for validation. Guidance published by the Sponsor should be followed in this regard.

2.5 Participant privacy

The investigator affirms and upholds the principle of the participant's right to privacy and shall comply with applicable privacy laws. Specifically, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers and only pseudonymised data will be recorded in the central database.

For data verification purposes, authorised representatives of the sponsor or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.6 Early termination of project

ENCORE is an observational cohort study. Therefore, premature termination of the study resulting from ethical or safety concerns is most unlikely. In case of insufficient participant recruitment, the study period may be extended to reach the calculated sample size of 10,000 patients. After one year, if there are less than 10,000 patients enrolled, the study period can be extended to reach that goal.

2.7 Amendments, Changes

Only the steering Committee (SC) or persons delegated by the SC are entitled to amend the protocol. National Coordinating Investigators and Local Principal Investigators (PI) will receive timely notification of changes and will be required to submit amendments locally. Written documentation of the amendments' approval will be provided to the sponsor and substantial amendments of the protocol will be only implemented after approval of the responsible IRB. In consideration of the observational nature of the study, the necessity of protocol deviations to protect the rights, safety and well-being of human subjects without prior approval of the sponsor and the IRB appears remote. Such deviations must be documented and reported to the sponsor and the IRB as soon as possible.

All non-substantial amendments like administrative changes will be communicated to the IRB as necessary by the PI. It is the local PI responsibility to communicate with their IRB.

3. RATIONALE AND BACKGROUND

3.1. Rationale

Colorectal cancer (CRC) is the third most common cancer in the world with a high postoperative mortality (2 – 6%) as well as a low 5-year survival (60%). Despite advances in surgery and the use of minimally invasive laparoscopic surgery in recent years and adjuvant chemotherapy after surgery, long-term prognosis has only improved marginally. Epidural analgesia is commonly used as a part of the perioperative management of patients undergoing open, colorectal cancer surgery. Not only does it reduce pain and stress, epidurals have been shown to reduce perioperative inflammation and preserve immunological function, all of which may be beneficial in perioperative tumorigenesis. In several retrospective studies, anaesthesia and choice of analgesia have shown to improve long-term survival, but no randomized studies have been published in the literature today. Similarly, the benefits of propofol anaesthesia in comparison to inhalational anaesthesia have recently been highlighted in relation to cancer surgery, and many patients today request the use of epidurals, total intravenous anaesthesia and loco-regional anaesthetic technique during surgery, without clear evidence from prospective studies in the literature. Therefore, the question as to the real benefit of anaesthesia technique in postoperative outcomes and tumour recurrence remain unanswered, and scepticism abounds amongst both surgeons and anaesthesiologists. It is therefore important to study short- and long-term outcomes in patients undergoing CRC surgery, comparing epidural vs. no epidural or inhalational vs. total intravenous anaesthesia. However, prospective, randomized studies are costly, require many patients, and the benefits of choice of anaesthesia and analgesia on outcome remain uncertain from the current literature. There is a clear diffusion in practice across the world in the choice of anaesthesia for patients undergoing CRC surgery, a lack of evidence in the literature and an absence of, pragmatic study, with low costs, it will be possible to answer some of the important questions guidelines on best practice anaesthesia care. We believe that by performing a large, prospective, observational, international pertaining to the choice of anaesthesia and analgesia. Approximately 10,000 patients from around the world and from participating centres will be enrolled and followed up during a period of 3 years to determine outcome (start of adjuvant chemotherapy, 30-day morbidity, cancer recurrence and death). The Clinical Trials Network at the European Society of Anaesthesiology and Intensive Care will play an important role in ensuring quality, documentation, verification and follow-up.

3.2 Background

In the United States, as in most of the western world, colorectal cancer is the third deadliest of all cancers. In 2016 there were > 130,000 new colorectal cancer (CRC) cases with > 45,000 colorectal cancer deaths in the USA (American Cancer Society, homepage). Depending on the stage of the disease (Appendix 8), 5-year survival rates vary from 14% (distant metastases) to 90% (localized cancer) with an average of 63% survival for all stages taken together. The prognosis appears to be approximately the same for colon as for rectal cancer.

	3-year Survival Rate*	5-year Survival Rate**
Stage 1	95 – 99%	90%
Stage II	90 – 95%	75%
Stage III	75 – 80%	71%
Stage IV	20 - 30%	14%
All (combined)	65 – 70%	63%

*Table 1 : * Majana et al, Lancet Oncology 2019;20:74-87 ** American cancer society (www.cancer.org)*

An oncological surgical resection is the mainstay of treatment for potentially curable colon cancer. However, even in stage I and II colon cancers, 10–30% will develop recurrence of disease. It is known that, even with the best surgical technique, surgery for cancer is associated with release of tumour cells.

Early postoperative morbidity and mortality after CRC surgery varies between countries but has shown a steady improvement. In the UK, between 2003-2006, overall, 6.7% of the study population died within 30 days of surgery. There was significant variation across the population with post-operative mortality greater in the elderly, men, the socio-economically deprived, those with advanced stage disease at diagnosis or with additional co-morbidities and amongst those operated upon as an emergency. The 30-day mortality today is between 1 – 2.5% in the western world, showing a 3-fold reduction in the last 10 years. Re-operations, anastomotic leakage and infections are the commonest causes.

At the time of surgery, a large fraction of patients harbour minimal residual disease, although this may not be visible (1). Additionally, the surgical trauma itself induces immunosuppression (2) and may facilitate cancer recurrence and the formation of metastasis (3). Anaesthetic agents, both intravenous and inhalational, have been shown to affect immune cell function negatively in vitro and in vivo (4,5). Intravenous agents like propofol used during total intravenous anaesthesia may improve survival compared to inhalational anaesthesia with sevoflurane or desflurane (6). Opioids reduce activity of natural killer (NK) cells and promote tumour cell proliferation and angiogenesis (7,8). Therefore, neuraxial analgesic techniques where perioperative opioid consumption is minimized may also reduce the surgical stress response (9) and thus preserve postoperative immune function and prolong survival (10). In previous retrospective studies, the use of epidural anaesthesia in combination with general anaesthesia has been shown to be associated with improved survival in older patients with non-metastatic colon cancer undergoing colectomy (11). Christopherson et al. also found comparable results (12). Gottschalk et al., however, could not find an association between the use of epidural anaesthesia and a reduction in cancer recurrence after surgery for colorectal cancer but they did find a possible benefit of epidural anaesthesia in older patients (13). In a retrospective study, Gupta et al. showed that epidural anaesthesia reduced all-cause mortality after surgery for rectal but not for colon cancer (14). The surgical technique (laparoscopic or open surgery) is also believed to play a role in tumour recurrence and survival, with slightly better outcomes achieved during laparoscopic surgery (15).

Neoadjuvant chemotherapy and/or radiation therapy are sometimes administered preoperatively to decrease the size of the tumour, specifically in patients with rectal cancer. Recent studies suggest that neoadjuvant chemotherapy may avoid the need for adjuvant chemotherapy in CRC and therefore there may be a trend in using neoadjuvant rather than adjuvant chemotherapy in the future. Following successful surgery with the aim of removing macroscopic tumour, adjuvant chemotherapy (AC) is usually administered in stage II and III colorectal cancers. AC for colon cancer has been shown to significantly improve overall survival in stage III disease and a trend toward increased disease-free survival in selected patients with stage II disease at high risk of relapse. In these studies, the first cycle of chemotherapy was administered within 8 weeks of surgery. However, in routine clinical practice, AC cannot always be initiated within 8 weeks after surgery. Two recent meta-analyses studying time to adjuvant chemotherapy in colon cancer have shown that the survival benefit of AC diminishes with increasing waiting times after surgery (16,17). The greater the delay, the worse is the prognosis. Thus, the time to start of adjuvant chemotherapy may play an important role in outcome for patients with stage II/III CRC undergoing surgery with curative intent. The risk for cancer recurrence, metastasis and survival after primary surgery for cancer might be affected by several perioperative factors.

Prospective, randomized, controlled studies looking at the impact of anaesthetic technique to CRC outcome are eagerly awaited but are difficult to perform, time- and resource- demanding, prohibitively expensive and require a very large number of patients to show survival benefits. However, pragmatic, observational studies where data is collected prospectively in an international, multicentre study are cost-effective, easily performed and can control for several factors that may affect outcome, using a factorial design.

3.3 Preliminary data

In a small prospective, randomised on-going study recruiting just 200 patients (EPICOL), preliminary data on recurrence of tumour (as observed by CT scan performed every year) and all-cause mortality appear to point towards a more favourable outcome in patients having an epidural analgesia as the primary method of pain management perioperatively as opposed to intravenous analgesia using morphine (Fig 1a and 1b). Although no statistically significant difference can be seen between the groups in this study, which is based on a small sample size and short follow-up period, there appears to be a separation between the groups on the Kaplan-Meyer curves after about 1 year. In a retrospective study from our group where we analysed > 600 patients in Sweden, we found statistical difference between the groups, in favour for epidural analgesia, in patients undergoing surgery for rectal but not colon cancer (14).

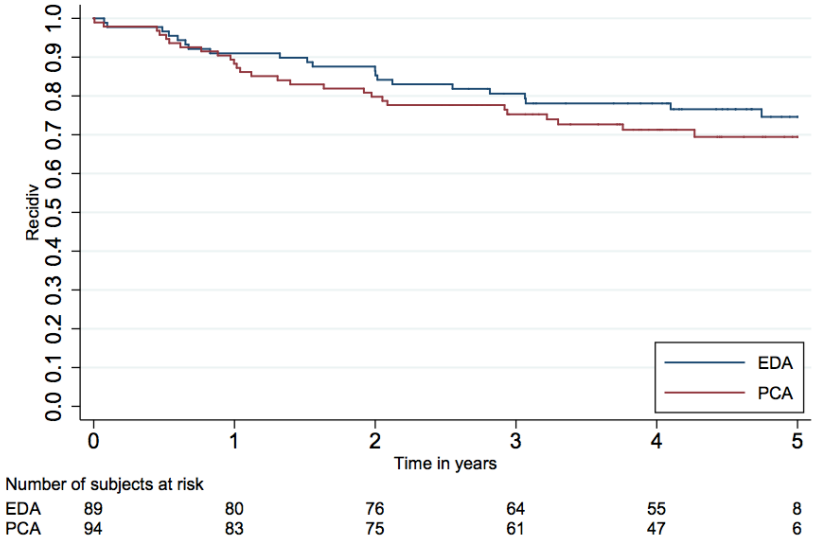


Fig 1a. Kaplan-Meier analysis for recurrence after CRC surgery (preliminary data)

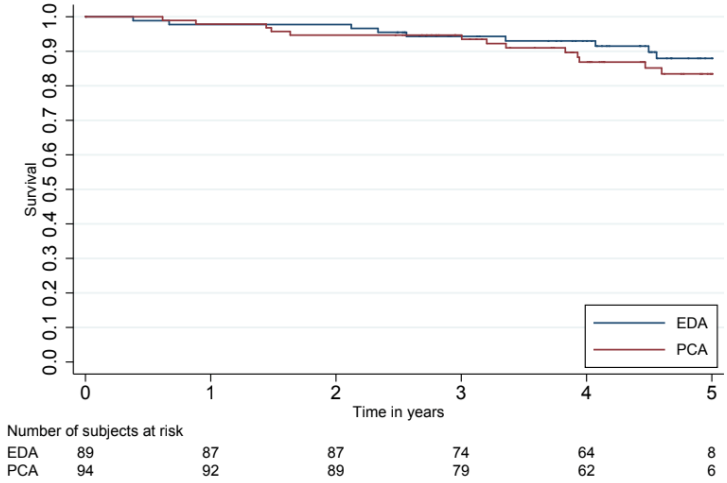


Fig 1b. Kaplan-Meier analysis for survival after CRC surgery (preliminary data)

4. OBJECTIVES AND OUTCOMES

4.1. Objectives

The main objective of this observational study is to investigate whether the choice of anaesthetic technique affects the time to start of adjuvant chemotherapy (for the sub-group intended to return to oncologic therapy (RIOT)) and 2/3-year recurrence. Secondary objectives are to determine incidence of postoperative complications (0 - 30 days), cancer recurrence at 3 years and cancer-related deaths following surgery for colorectal cancer.

4.2. Primary Outcomes

Short-term: Time to start of adjuvant chemotherapy (RIOT) in patients undergoing primary colon or rectal cancer surgery with curative intent, when it is intended to be give adjuvant chemotherapy (Primarily Stage III, and some Stage II CRC).
Long-term: Time to recurrence (TTR) of cancer determined at 3 years. Please see definition of TTR under "definitions", appendix 9)

4.3. Secondary Outcomes

- Percentage of adverse events related to surgery within 30 days of surgery as graded by the Clavien-Dindo classification (Appendix 10)
- Other adverse events not included in the C-D classification within 30 days
- Length of hospital stay defined as days from index surgery to arrival at original living facility
- Adverse events related to oncological treatment (please see section 4.4 for grading – Appendix 8)
- Days at home for 0-30 days (DAH-30) after index surgery

4.4. Other variables

Patient variables

Sex, Date of birth, Weight, Height, Tobacco/ alcohol use, Co-morbidity including ASA score (Appendix 11), MET and mDASI-4q score (see appendix 12), Lab tests (specifically Albumin, Hb, creatinine, CRP and neutrophil count) and others, as appropriate will be assessed. Carcinoembryonic antigen (CEA) value when available will be registered. If pre-habilitation programme was started before surgery.

CRC-related variables

Position of primary tumour (Colon: appendix, right-sided, transverse, left-sided. Rectum: Distance from anal verge measured by rigid rectoscopy), Clinical TNM, Pathological TNM (Including circumferential resection margin, R-category and Extramural vascular invasion)

Treatment-related variables

- Oncology: Preoperative (Chemotherapy: Date of start and end, number of cycles, concomitant; Radiotherapy: Prescribed dose, date of end)
- Postoperative (Chemotherapy: Date of start and end, number of cycles; Radiotherapy: Prescribed dose, date of end)
- Surgery: Date of index surgery
- Technique (Minimal invasive: Laparoscopic, robotic; Conversion to open; open)
- Resected bowel segment (Appendectomy, ileocecal resection, right-sided colectomy, extended right-sided colectomy, transverse colectomy, left-sided colectomy, sigmoid resection, colectomy, PME, TME, intersphincteric APE, extralevator APE, proctocolectomy, Multivisceral resection)
- Reconstruction (Primary anastomosis, De-functional anastomosis, Permanent ostomy)
- Duration of surgery and anaesthesia
- Total blood loss and Blood transfusion (ERC, Plasma, thrombocytes, other blood products)
- Anaesthesia: Type (GA, Epidural + GA, Spinal + GA, other), Method (TIVA, Inhalation, combination)

- Postoperative analgesia: Epidural/spinal block, multi-modal analgesia with PCA, others

Chemotherapy-related adverse events

	Grade 1	Grade 2	Grade 3
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self-care ADL

Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.

Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL

Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.

Paraesthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL

Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth.

The patient grades each symptom as better or worse after anaesthesia/surgery according to PROM (Patient reported outcome measure).

5. PROJECT POPULATION

5.1 Inclusion Criteria

- Age > 18 years
- ASA I-III
- Scheduled for elective (planned) colorectal cancer surgery for stage I-III (open or laparoscopic)
- Signed written informed consent (unless the Ethics committee gives a waiver)

5.2 Exclusion Criteria

- Uncontrolled renal or liver disease, restrictive (severely limiting mobility) heart failure or ischemic heart disease (classified as ASA IV-V)
- Speech, language or cognitive difficulties precluding signing informed consent to participate
- Stage IV colo-rectal cancer

5.3. Criteria for withdrawal / discontinuation of participants

Due to the observational nature of the study, the protocol does not define any withdrawal/discontinuation criteria. Patients electing to withdraw from the study may do so at any

point. In this case, no further data will be collected, while already collected, encoded data will be pseudo-anonymised and analysis may be performed up to the point of data collection.

6. METHODS

6.1. Study design

This is a prospective, multicentre, international, pragmatic, observational study.

6.2. Setting and participants

All adult patients (> 18 years) in participating hospitals and diagnosed with colorectal cancer without distant metastasis at the time of diagnosis and undergoing elective primary curative surgery using laparoscopic or open technique during Q3 2021- Q2 2023 will be included. The study may be terminated earlier if 10,000 patients are included, or prolonged if this is not the case. Patients undergoing palliative surgery, or surgery for recurrence of primary (previously operated) colorectal cancer or those needing emergency surgery will be excluded.
Participating hospitals will be provided with a pre-study questionnaire (appendix 3) that enables standardized screening of surgical volume.

6.3. Anaesthetic management

The anaesthetic technique used at each centre will be based on local practices. Some centres use epidurals, others use spinals as a part of the regional anaesthetic technique. Similarly, different epidural/spinal opiates are used for pain management during and after surgery at different centres, some starting at the end of surgery, other using epidurals during surgery. Even anaesthetic techniques vary, some using inhalation with or without remifentanil, others total intravenous. Combination of different regional and general anaesthetic techniques is also used. No change in local practice will be done but centres will be requested to document the specific technique used in each patient using the to capture all events and techniques. At the end of the study, depending on the number of patients in each group, and following a discussion within the SC, specific groups and sub-groups of patients may be analysed.

6.4. Surgical management

The precise surgical procedure undertaken in each patient, depending on tumour characteristics will be recorded. The method of surgery, open or laparoscopic, will be left to individual surgeon competence and routines at each hospital. The surgical decision as to methodology, invasiveness of surgery etc will be final and non-negotiable after recruitment. Whether the laparoscopic procedure is subsequently converted to open will be left to the discretion of the individual surgeon. Data analysis for these patients will be done separately but as this is a pragmatic trial, these patients will also be assessed as being in the group they finally belonged i.e. converted patients will be analysed in the group ‘open surgery’.

6.5. Oncological management

Chemotherapy will be prescribed according to local practices and protocols and may include:

- FOLFOX (standard)
- FLOX (in patients with concomitant heart disease)
- FOLFIRINOX (for the young, with aggressive tumour.)

This is usually given in cycles, a total of 12 cycles, either as neoadjuvant therapy (before surgery) or after (adjuvant therapy). Variations in these standard methods will be acceptable, according to local hospital routines. Data on the precise start of the neo-adjuvant or adjuvant therapy will be recorded. The attending Oncologist who will decide on start of chemotherapy (before and after surgery) will be blinded to the anaesthesia technique. The exact date for start of chemo- or radiotherapy (when applicable) will be recorded. Surgeons, oncologists and radiotherapists often make up a team that decides on the precise management in each individual patient (multi-disciplinary team). The decision to start chemotherapy will be stated as pre-operative decision (intended to start adjuvant chemotherapy or not) or post-operative decision (based on tumour characteristics and patient tolerance/frailty etc.)

6.6. Postoperative Care

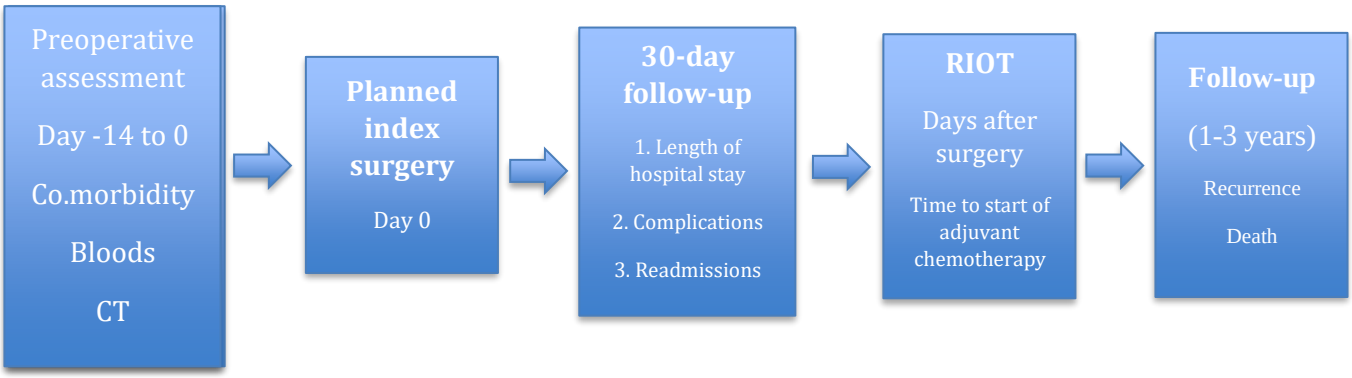
Postoperative care will be according to local practices. All complications within 30 days after surgery will be recorded according to Clavien-Dindo classification (Appendix 10). Furthermore, those patients who are admitted to the intensive care or high-dependency unit (as opposed to postoperative ward), will be documented in the eCRF. Analgesic consumption (morphine equivalents) will be recorded during the period 0 - 48 h after surgery. All other medical complications will also be recorded during the period 0-30 days after surgery (Appendix 13: Postoperative complications). The number of days at home (original place of stay) during 0-30 days after surgery will be registered and the time to start of adjuvant oncological treatment in patients intending to start chemotherapy will be determined. Any death occurring during the first 30 days will be recorded.

6.7. Follow-up

Patients will be followed up by the surgical and oncological departments according to local routines. At 3 years, data recorded in the medical records during the previous 3 years will be extracted and will include, amongst others, death (when applicable), cancer recurrence as determined by CT/MR or clinical examination and the dates as well as CEA (if taken) along with the dates. After 3 years, no further follow-up is anticipated.

6.8. Procedures

Figure 1: Protocol Flowchart: schematic diagram of trial design, procedures and stages.



The following data will be collected:

	Before day -	Day of surgery (t = 0)	Postoperative Day 1	Before home discharge	90 days follow-up	3 years follow-up
Consent (if needed)	X					
Neoadjuvant therapy	X					
Preoperative assessment	X					
Blood tests/CT/MRI	X		X			
Peroperative data		X				
Postoperative data		X	X			
Postoperative complications				X	X	
Adjuvant therapy					X	
CT/MRI						X
Recurrence/death						X

6.9. Expected duration of subject participation

The study is preliminarily planned to start in Q3, 2021 after receiving permission from the Ethics Committee. Data collection will then continue for 3 years or until a total of minimum 10,000 patients are recruited (please see "7.1 Study size" under Statistical method section below). Patients will be followed up until discharge from the hospital and at home by telephone at 30 days (± 2 weeks) and at

years (± 3 month). Any readmission due to complications will be recorded (for definitions, please see Appendix 13).

6.10. Intervention

This is a pragmatic, observational study and therefore no intervention will be made. Patients included into the study will be followed up according to hospital norms. However, data will be extracted from patient records and entered into a standardized case record form (CRF) (Appendix 5) after anaesthesia and surgery.

6.11 Participating Centres and role of local and National PIs

6.11.1 Pre-study questionnaire

Before inclusion of the first patient, each institution will fill in a site pre-study questionnaire regarding the hospital demographics, local standard of care for patients, number of cases/year and surgeon experience in performing open and laparoscopic surgery. The contents of this questionnaire are listed in the Appendix 3. In the one-two years anticipated recruitment period, data will be collected from each centre and the goal would be to include 40 patients per centre. It is planned that all centres that would like to participate in the study will be enrolled, with a maximum of 250 centres. Each centre will have a Local Principal Investigator, and a National Coordinating Investigator will be in contact with the participating centres in his/her country to ensure that Ethics committee approval is obtained as well as to clarify doubts arising during patient recruitment. The Steering Committee will provide guidance at all stages of patient recruitment.

6.11.2 National Coordinating Investigators (NC)

National coordinating investigators are anaesthesiologists or Surgeons appointed by ESAIC and the Steering Committee to lead the project within individual nations and:

- Identify local participating centres and recruit local principal investigators in participating hospitals
- Assist in the translation of study documents - upon needs
- Ensure necessary country or regional regulatory approvals are in place prior to start of patient inclusion
- Assist and train the Local Principal Investigator and monitor the conduct of the study according to good clinical practice (ICH-GCP guidelines)
- Ensure good communication with ESAIC headquarter and the participating sites in his/her countries (e.g. At data cleaning NC will cascade the information/requests to the relevant sites and assist when necessary).

6.11.3 Local Principal Investigators

Local Principal Investigators are Anaesthesiologists or Surgeons in each participating institution who will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory/ethical approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving

- Ensure timely completion of eCRF and follow up data; Local Principal Investigator is the main responsible for ensuring integrity of data collection. By signing the data on eCRF Local Principal Investigator confirms the data integrity
- Communicate with ESAIC headquarter and the relevant National Coordinating Investigator

7. STATISTICAL METHODS

7.1. Study size

Primary outcome: Start of adjuvant chemotherapy (data collected as number of days after surgery). For statistical calculations, the data will be dichotomised as number of patients who can start chemotherapy in < 8 weeks or > 8 weeks. Previous studies have shown that approx. 15% patients cannot start adjuvant chemotherapy within 8 weeks after surgery. Our hypothesis is that the application of an epidural (vs. no-epidural) or the use of propofol (vs. inhalational anaesthesia) will decrease this to 10%. Therefore, we estimated that 1830 patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the start of chemotherapy > 8 weeks from 15% in the No-epidural (or inhalational anaesthesia) group to 10% in the Epidural (or total intravenous anaesthesia) group. If 30% patients are Stage III cancers (adjuvant chemotherapy is standard of care), the sample size required will be approximately 2500 patients for time to start of adjuvant chemotherapy (< or > 8 weeks) in patients who are expected to return to intended oncological treatment (RIOT). Therefore, we intend to recruit 2500 patients in Stage III and a total of 10000 patients into the study.

7.2 Data processing

Data will be collected at each centre, pseudo-anonymised, and entered into a bespoke electronic case report form (eCRF). Completed forms will be submitted to the sponsor, ESAIC Clinical Trials Network (ESAIC CTN), in Brussels, Belgium.

7.3 Planned analyses

7.3.1 Main analysis

Descriptive statistics such as mean (SD), median [interquartiles, range] and frequencies (%) will be presented as appropriate. The precision of the estimates will be reported with 95% confidence intervals to show the prevalence and incidence rates of major adverse events and complications.

The primary outcome measure is time to initiation of adjuvant chemotherapy in patients intended for RIOT. This will be on a continuous scale (0 days - 120 days) but dichotomized to >/< 8 weeks for the primary outcome measure and analysed by chi-2 statistics. Median time to start of adjuvant chemotherapy will be calculated for each group and compared using Mann-Whitney U-test.

Time to recurrence (TTR) will be measured in each group dichotomized to Yes/No and analysed by Kaplan-Meier plot and Cox-regression.

Secondary outcomes include:

- Clavien-Dindo scale for postoperative surgical complications will be measured on a scale 1-5 and presented as median for each group, analysed by Chi-2 or Fishers test as appropriate.

- 30-day mortality, length of hospital stay, DAH-30 and 1-year mortality will be measured and analysed appropriately.

Univariate analyses will be used to help identify variables of potential interest for multivariable analyses, in addition to stepwise selections. Specific factors, or subsets of interest, will be investigated further using linear mixed models. Binary and categorical outcomes will be analysed using multivariable logistic regression, survival analysis and Cox proportional hazards regression as appropriate.

7.3.2 Datasets to be analysed

Data from all participants will be analysed with respect to completeness of data entry for all variables in an pseudonymised format. Patients will be nested within centre and stratified by country for relevant epidemiological purposes.

7.3.3 Handling of missing data

If the patient withdraws consent during the study, data until that time point will be included in the analyses. Patients will not be completely withdrawn from the study if some data points are missing. Instead, appropriate statistical tests will be used in case of missing data.

7.3.4 Deviations from the original statistical plan

Any deviations from the initial statistical analysis plan will be identified and explained in any reports. It is expected that such additional analyses will be reported in the Discussion only as post hoc and not in Results, as appropriate.

8. GDPR, DATA AND QUALITY MANAGEMENT

8.1 Data quality

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirements.

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly, including written SOP (in English for all countries) for data collection and entry, automated consistency checks, and training of National Coordinating Investigator and local PI. It will be responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PI. Local PI will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local PIs to conduct periodic and random checks to ensure data quality in her/his centre. The sponsor will make random assessments of centres in order to confirm that there are no improper and incorrect data entered into the eCRF. On-site monitoring visits by the sponsor are not planned.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Any agreements,

made by the sponsor with the investigator/institution and any other parties involved with the study, will be in writing, as part of the protocol or in a separate agreement. The PI is required to sign and date the protocol to confirm receipt and also their agreement to work to and uphold the current version of the protocol. No fee or financial compensation is given to PI and/or participating institution for patient recruitment.

8.2 Data handling and record keeping / archiving

The hospital will also be provided with a logsheet (appendix 6) that will contain the patient's name and hospital specific identification number and help sites to link patient with ID number.

Data will be then be collected in individual centres on paper case report forms (CRFs) (appendix 5). CRF are identified through a Patient Identification Number and shall not include any names, patient initials or local hospital patient numbers.

Local investigators will then transcribe all collected data from the data acquisition sheet (CRF) onto an internet-based electronic CRF. Data are thus first collected on paper CRF then entered into the electronic Case Report Form (eCRF) by the site staff pseudo-anonymously using only the specific patient identification number (PIN).

Paper and electronic CRF will be in English for all centres involved in this trial. Paper CRFs will be stored within a locked cabinet/office in accordance with local and national regulations until the Sponsor has agreed to archive the Study.

Access to the data-entry system is protected by a personalized and confidential username and password.

No names, patient initials or local hospital patient numbers are collected or are kept on the data acquisition forms, nor electronically in the eCRF. Each centre will keep a confidential patient log sheet, which matches each CRF/eCRF, through their PIN, to the individual patient. The log sheet will be stored behind a lock, together with the data acquisition forms. Data will be handled confidentially, and all data will be stored for the length of the study and for at least 10 years or longer if locally required, for further publication. Each centre will maintain an Investigator File including: protocol, IRB judgment, EC approval (if applicable), local investigator delegation log, local translation of informed consent form (if applicable), signed informed consent forms (if applicable), etc.

Pseudonymized data will be analysed at the study statistician's institution (Stockholm, Sweden). This institution will keep data until publication of the material. After completed publication, data must be sent for storage to ESAIC headquarters located in Brussels and destroyed at the statistician's site. A respective document signed and dated by the study statistician and the chief investigator will be sent to ESAIC headquarters. ESAIC also declares to respect the data protection laws of the participating European countries. All handling of personal data will comply with the GCP Guidelines. All collected data will remain the property of the Sponsor.

Sponsor and centres will maintain and update their trial master files according to the recommendation of the ICH-GCP Guidelines E6(R2).

8.3 Confidentiality, Data Protection

To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification code and identifiable patient data will be stored separately in a locked cabinet accessible to authorised personnel only and corresponding electronic files will be protected by personalised and confidential usernames and passwords. eCRF are identified through the patient identification code and will not include any names, initials, date of birth or local hospital patient numbers; therefore, no patient identifiable data will be directly accessible from the eCRF. Data protection will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Further, only encrypted data will be stored centrally. The database will be hosted on servers physically located in the European Union and data can only be transferred to servers located in member States of the European Union or in other countries where the level of personal data protection has been determined as adequate by the European Commission on the basis of the General Data Protection Regulation (GDPR, Article 45).

Open direct access to all relevant study information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections to the sponsor, national coordinators, IRB, or regulatory authorities. All handling of personal data will comply with the GCP Guidelines and follow strictly the legal and national requirements of GDPR. For any additional question please contact the ESAIC Data Protection Officer at privacy@ESAIC.org or 24, Rue des Comédiens 1000 Brussels, Belgium.

Please see Appendix 15 - Data Protection Overview is destined to any person involved in the ENCORE study to have a better understanding of the data flow and data storage of the study.

Please see Appendix 16– Lawfulness of processing of data – GDPR can be used to give an overview to the patients of the processing of the patient's data. The first part of the document details the information that can be given to the patient while the second part explains the situation to the Local Investigator.

9. PUBLICATION AND DISSEMINATION POLICY

9.1 Publication of results

Data collected from this project can be used for publication of one or more studies in a peer-reviewed international journal of high quality and presented at Euroanaesthesia and at international and national meetings. Members of the Steering Committee and other particularly committed investigators (see below) that fulfil those criteria will be part of the Writing Group. The members of the Writing group and the "ENCORE Investigators" will be authors of the publications derived from ENCORE. When submitting a manuscript, the corresponding author will specify the group name as "ENCORE Investigators". As recommended by the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html; accessed July 12th 2020), authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, and submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. According to the recommendations issued by the International Committee of Medical Journal Editors, the byline of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the byline. To ensure that MEDLINE will list the names of individual group members who are authors, there will be a note associated with the byline clearly stating that the individual names are elsewhere in the paper and that those names are authors. All collaborators will be detailed in the manuscript appendix and can be tracked via PubMed (in accordance with the Journal authorship policy – Appendix 14). Local Principal Investigator will be asked to submit names of staff actively involved from their institution in the End of Study Reporting Form (Appendix 7). If the number of recruited patients from a country/centre is too low to justify sufficient active involvement, the steering committee will decide on the legitimacy of authorship. The final decision will be left to the decision of the Chief Investigator in consultation with the ESAIC and members of the steering committee and in line with journal policy. In general, each participating centre including at least 40 patients can designate two investigators to be mentioned in the publication. The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. This is described in Table 2 below.

Table 2: Number of investigators named according to number of patients enrolled:

Number of patients completed	Number of investigators at that centre
15-39	1
40-70	2
71-100	3
>100	4

Presentation at international meetings will be restricted to the members of the SC or their delegates. National Coordinators will qualify for presentation at national meetings after approval by the SC and the sponsor. ESAIC Clinical Trial Network will be acknowledged in all publications and presentations.

9.2 Secondary analyses, nested sub-studies, and data sharing

After publication of the pooled results, centres will be allowed to use their own pseudonymised data for local presentation and publication. Duplicate data publication is not permitted.

The pseudo-anonymised pooled dataset may be available for secondary analyses upon specific request in form of a detailed study proposal (including authorship rules) to the SC. The final approval of these potential secondary analysis rests with the SC. Prior to journal submission, any paper originating from the pooled data will be reviewed by the SC that is also entitled to require revisions. Authorship of any publication derived from the pooled data set will include the group name “ENCORE Investigators” and the names of the SC who have worked on the particular manuscript with a byline clearly stating that the individual names are elsewhere in the paper and specifying whose individual names refer to authors and to collaborators, respectively. For transparency, the original paper must be referenced to in all articles of secondary analyses. Requests for data sharing for individual-level

meta-analyses are to be addressed to the Sponsor and SC. The sponsor of the study (ESAIC CTN) can use pseudonymised pooled data for internal analyses and educational purposes.

10. FUNDING AND SUPPORT

ENCORE is sponsored by a grant from the European Society of Anaesthesiology and Intensive Care Clinical Trial Network (ESAIC CTN). The submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the sponsor and the SC. The SC members declare not to have any conflicts of interest (a declaration of conflict of interest will be signed by each SC member and kept by the Sponsor).

11. INSURANCE

ENCORE is a negligible-risk, observational study. Insurance might be required based upon individual agreement between local Principal Investigator and the relevant institutional legal department. The ESAIC has Public Liability insurance in place to cover the legal liability of the ESAIC as Sponsor in the eventuality of harm to a research participant arising from management of the research by the ESAIC. This does not in any way affect the responsibility of a Centre for any clinical negligence on the part of its staff.

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13. LIST OF APPENDICES

Appendix 1 – Study Synopsis

Appendix 2 – Patient information Sheet and Consent - generic

Appendix 2A – Patient Information Sheet – Legitimate interest

Appendix 2B – Patient Information Sheet and Consent – Legitimate interest

Appendix 2C – Patient information sheet and consent – Consent

Appendix 3 - Site pre-study questionnaire for participation in the ENCORE trial

Appendix 4 – Approval Documentation Coversheet

Appendix 5 – Case Report Form

Appendix 6 – Confidential Patient Logsheet

Appendix 7 – End of Study Reporting Form

Appendix 8 – Staging of Colorectal Cancer

Appendix 9 – Definitions

Appendix 10 – Clavien Dindo Classification

Appendix 11 – ASA-Physical Status classification

Appendix 12 - mDASI - q4

Appendix 13 – Postoperative complications

Appendix 14 – Authorship Policy

Appendix 15 – Data Protection Overview

Appendix 16 – Lawfulness of processing data – GDPR