European Society of Anaesthesiology and Intensive Care

ENCORE Appendix 1 - Effects of Anaesthetics on colorectal cancer outcomes

ENCORE Trial – Study Synopsis

Chief 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	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 considered to 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