ESAIC – ENCORE Study – Statistical Analysis Plan

Primary outcome

Short-term: Time to start of adjuvant chemotherapy (RIOT) in patients undergoing primary colon or rectal cancer surgery with curative intent, when adjuvant chemotherapy is intended to be given (Primarily Stage III, and some Stage II CRC). Time will be measured in days after primary surgery.

Long-term: Time to recurrence (TTR) of cancer determined at 3 years.

Table 1. Secondary outcomes and hypotheses of interest.

Hypothesis	Variable
Adverse events following surgery and during hospital stay differ depending on choice of anaesthetic	Percentage of adverse events related to surgery within 30 days of surgery as graded by the Clavien-Dindo classification (Appendix 10)
Adverse events not included in the C-D classification differ depending on choice of anaesthetic technique	Other adverse events not included in the C-D classification within 30 days
The duration of stay in the hospital after primary surgery differs between the groups depending on choice of anaesthetic technique	Length of hospital stay defined as days from index surgery to arrival at original living facility
Adverse events of oncological treatment differ between groups depending on choice of anaesthetic technique	Adverse events related to oncological treatment (please see section 4.4 for grading – Appendix 8)
The total duration of stay at home and within the first 30 days after primary surgery differs between the groups depending on choice of anaesthetic technique	Days at home for 0-30 days (DAH-30) after index surgery

NB. Not clearly written or defined in the protocol (and may be considered *post hoc*) but it is intended to separate colon and rectal cancers because management and prognosis of both cancer forms (colon and rectal cancer) differ considerably and it is difficult (in hindsight) to pool the results. Pooled analysis may be performed but implications of anaesthetic technique on outcomes for these may differ, as shown in at least one retrospective study, previously.

Study population for analysis regarding short term outcome

Adjuvant chemotherapy is recommended to colon cancer with pathological stage III and colon cancer p stage II with risk factors. These risk factors are grouped in low, intermediate and high risk factors. For the analysis, it can be assumed that colon cancer p stage II with pT4 and/ or number of examined regional nodes less than 12 should be treated with chemotherapy.

The Foxtrot study has introduced a new regimen for chemotherapy in colon cancer by dividing chemotherapy into pre- and postoperative chemo. This regimen has not been adopted worldwide but is spreading and used at Karolinska (Sweden). Patients with advanced clinical stage based on preoperative imaging are selected. In this case, the p stage represents the native colon cancer + potential downstaging. So, colon cancer with preoperative chemotherapy should also complete with adjuvant chemotherapy.

Adjuvant chemotherapy is also given in rectal cancer but the evidence is lower compared to colon cancer and often applied in extrapolation. At Karolinska (Sweden), rectal cancer treated with preoperative radiotherapy (RT) will not get adjuvant chemotherapy. In many countries, high rectal cancer (10 to 15cm from the anal verge) is treated like colon cancer, which means very rarely preoperative radiotherapy and adjuvant chemotherapy.

Of course, analysis could be limited to RIOT in all patients (colon + rectal cancer) that in fact got adjuvant chemo. By doing so, some patients could be missed, those who should have got chemotherapy but didn't due to prolonged recovery as the effect of adjuvant chemo only is seen, if chemo can be started before 10 weeks postoperatively have expired. Apart from prolonged recovery, advanced age or co-morbidity can be factors to avoid adjuvant chemotherapy but we do not have information on that in the CRF. Adjuvant chemotherapy is less/ not effective in CRC with deficient mismatch repair (dMMR) and these patients get immunotherapy. This regimen is currently introduced in clinical praxis and was not available when ENCORE started.

The study population for the RIOT analysis should be as followed:

- Colon cancer p stage III
- Colon cancer p stage II + pT4 and/ or less than 12 examined lymph nodes
- Colon cancer with preop cx and p stage any
- High rectal cancer without preop RT and p stage III
- High rectal cancer without preop RT and p stage II + pT4 and/ or less than 12 examined lymph nodes

Patients eligible to adjuvant chemotherapy according to the criteria above but not treated with adjuvant chemo could be seen as failure and might differ between our groups of exposure.

The secondary outcomes listed above can be seen as proxy for prolonged recovery (AE, lengt of stay, return home..) and should not be included in adjusted analyses with RIOT as outcome.