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Uppsala University

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Total intravenous or volatile anaesthesia and survival after colorectal cancer surgery: a Swedish National registry study

Statistical Analysis Plan (SAP)

1. **Introduction**

Inhalational anaesthesia has been gold standard worldwide for long. Propofol was introduced in Europe and the USA in late 80’s. Based on data from animal experiments, investigations on human cell-lines, and retrospective patient studies, we have a hypothesis that inhalational anaesthetics, which are time- and dose dependently affecting the immune system, and which upregulate Hypoxia-inducible factor in cancer cells, and which are also genotoxic in humans, presumably in a dose dependent way, may negatively affect patients’ survival after cancer surgery. Theoretically, the opposite may be the case for propofol. This is investigated in an on-going RCT, the Cancer and Anaesthesia study (CAN-study). So far, there are sparse with other adequately dimensioned RCT:s with this study question, and results will anyway be years away. Thus, we need complementary data. The retrospective study design has its draw-backs however, whereas population-based registries with prospectively collected data may offer a better complement to upcoming RCT:s.

1. **Study objectives**

To use national Swedish quality registries, known for their completeness and data quality, to compare survival for colon- and rectal cancer patients anaesthetized with an inhalational agent with those anaesthetized with propofol.

* 1. **Primary Objective**

The primary objective is to evaluate whether overall survival after radical colon- and rectal cancer surgery in general anaesthesia is significantly higher in patients given the intravenously administered hypnotic propofol than in patients given an inhalational agent (desflurane, isoflurane, or sevoflurane) during the period 2014-2019. The difference is seen as clinically relevant if the absolute difference is minimum five percentage points during the follow-up period up to the date for data extraction. We have not defined a minimum length for the clinically relevant difference.

* 1. **Secondary Objectives**

To complement overall survival with the point estimate for one and three-year overall survival.

**2.3 Exploratory Objectives**

To complement overall survival with disease free survival.

1. **Study design and data sources**

The Swedish perioperative register, SPOR, contains information on the anesthetic used during the individual surgical procedure, and the national colon rectal cancer registry, SCRCR, contains in addition to survival data also important supplementary information, e.g. cancer stage and other treatments (e.g. chemotherapy and radiation). By merging these registers with data from 2014 up to and including 2019, we can get almost 12,000 patients and in addition important demographic, anaesthesiological, surgical and oncological data to statistically adjust for known factors affecting survival.

1. **Sample size**

As an observational study, and not the least being a population-based study, a formal hypothesis is considered not to be of need. The estimated minimum of 12,000 patients is anyway considered to be statistically and epidemiologically robust.

1. **Study population**

Patients with surgical intervention for colon and rectal cancer in Sweden during 2014-2019, in where patients at their first colon and rectal surgery will be included.

1. **Variables to be collected**

The following variables will be extracted

Demographic variables including habits and general health

* Age, Gender
* Calendar year
* ASA-class

Anaesthesia related variables

* Volume of blood loss

Surgical and oncological variables

* Cancer location
* Date of surgery
* Laparoscopic surgery
* Acute or elective
* Stage at diagnosis

Outcome variable

* Overall survival and disease free survival

1. **Statistical analysis**
   1. **General statistical considerations**

All reported p values will be two-sided, and p<0.05 will be considered statistically significant. All data management and analyses will be performed using SAS 9.4 and R version 3.6.1. Secondary and subgroups analysis will not be adjusted for multiple comparisons and will be described and interpreted as exploratory analysis. Demographic, diagnostic, baseline, line of therapy and safety data will be presented using descriptive statistics. Continuous variables will be described by the number of patients with a recorded value, mean with standard deviation and when appropriate also 95% confidence interval (CI), median, upper and lower quartiles and maximum and minimum values. Categorical variables will be reported as number and percentages with 95% CIs. Differences between subgroups will be compared using chi-square tests, and Fisher’s test if few cases, for categorical variables and using t-test, and non-parametric statistics, for continuous variables. Missing data will be described in all summaries.

* 1. **Time to Event analysis**

The Kaplan-Meier (K-M) estimate will be used to measure the fraction of subjects living for a certain amount of time after surgery. The primary endpoints in the K-M analysis will be overall survival, with data presented at 3 year and 5-year with associated 95% CIs, and with number at risk over time, and compared using the log rank test. In addition, Hazard Ratios will be expressed using Cox regression models.

* 1. **Propensity Score Matching**

The propensity score matching approach will be used to balance the two groups in terms of demographics, anaesthesia, surgery and oncological variables using standardized mean differences with the nearest neighbor method with a threshold of 0.10.

1. **Tables and Graphs**
   * 1. **Table 1 -**. Baseline patient and clinical characteristics by choice of anaesthetic for colorectal cancer surgery in Sweden 2014-2019. Values are number (proportion), mean (SD) or median (IQR [range]).
     2. **Table 2 -** Patient and clinical characteristics by choice of anaesthetic for colorectal cancer surgery in Sweden 2014-2019 after propensity score matching. Values are number (proportion), mean (SD) or median (IQR [range]).
     3. **Table 3 -** One- and three-year survival rates for colorectal cancer patients by choice of anaesthetic in Sweden 2014-2019. Values are one- and three year estimates for survival with corresponding 95% confidence intervals.
     4. **Figure 1 -** Flow chart describing the study population.
     5. **Figure 2 -** Overall survival (Kaplan-Meier curve) by type of anaesthesia for matched pairs (1:2) from a full propensity score match of patients given propofol or an inhaled volatile anaesthetic for colon cancer surgery.
     6. **Figure 3** – Overall survival (Kaplan-Meier curve) by type of anaesthesia for matched pairs (1:2) from a full propensity score match of patients given propofol or an inhaled volatile anaesthetic for rectal cancer surgery.
     7. **Figure S1.** - Overall survival by type of anaesthesia in the unmatched cohort of colon cancer surgery. Blue = propofol, orange = inhaled volatiles.
     8. **Figure S2.** - Overall survival by type of anaesthesia in the unmatched cohort of rectal cancer surgery.
     9. **Figure S3. -** Disease-free survival by type of anaesthesia in the unmatched cohort of colon cancer surgery.
     10. **Figure S4.** - Disease-free survival by type of anaesthesia in the propensity score matched cohort of colon cancer surgery.
     11. **Figure S5.** - Disease-free survival by type of anaesthesia in the unmatched cohort of rectal cancer surgery.
     12. **Figure S6.** - Disease-free survival by type of anaesthesia in the propensity score matched cohort of rectal cancer surgery.