**Effect of anesthetic agents, propofol vs inhalation anesthetics,**

**on long-term survival after surgery for cancer:**

**a population-based registry study**

*Background*

Retrospective patient studies have shown that different anesthetic agents can lead to differences in survival after cancer surgery[1-11]. Biologically plausible explanations are available[12-38]. The differences in survival seen in retrospective studies are of an order of magnitude that exceeds the effects of chemotherapy. However, there are reasons to believe that different organs have different sensitivities to the effects of anesthetics. There is probably no difference between the drugs in survival for breast cancer[39-41].

A prospective, randomized, controlled trial (RCT; the "CAN trial") is run by the applicant[42]. This includes patients with breast or bowel cancer. There will probably not be that many more RCTs, which is why, from the perspective of evidence-based medicine, large observational studies need to be carried out as a supplement. We have recently conducted a relatively large retrospective study with a total of 6,305 patients with breast cancer, which makes the study the largest to date[43]. However, the main finding became an illustration of the inherent flaws of the retrospective design and that the way of analysis is critical. We therefore want to use Swedish quality registers with prospectively collected data at the population level to hopefully increase reliability, e.g., through reduced selection bias and thus obtain safer outcomes.

The Swedish Perioperative Register (SPOR) contains, among other things, information about which anesthetic was used in the individual operations, and the Regional Cancer Center's (RCC) register contains, in addition to survival data, important supplementary information, e.g., cancer stage and other treatment (e.g., chemotherapy and radiation). By combining these registers with data from 2014 up to latest available date (minimum six years for the first studies), we can obtain large materials and in addition important demographic, anesthesiology, surgical and oncology data to statistically adjust for known factors that affect survival.

For the breast and bowel cancer locations, we have approvals ready. Covid-19 has delayed the work, but at the time of writing it looks like we can start with continued work within soon. This application concerns cancer of either the brain, lungs, esophagus, stomach, gall bladder/biliary tract, pancreas, liver, kidneys, bladder, prostate, uterus, cervix, or ovaries.

It is important to get clarity on the effects of anesthetics on long-term survival for various forms of cancer. Is there a difference at all? If not, the result has great significance for the clinics, as sevoflurane dominates globally, you do not need to "reset" your anesthetic technique with demands for investment in infrastructure and training of personnel. If a clinically significant difference can be established, it has major implications primarily for patients, provided that the research results are implemented.

*Purpose*

To compare the one- and five-year survival in Sweden for cancer in listed organs depending on the anesthetic method during surgery from the year 2014 until the latest available date (minimum six years for the first studies).

*Question statement*

Does propofol-based anesthesia result in higher survival than sevoflurane-based anesthesia after adjustment for important confounders and effect modifiers?

*Hypothesis*

This study is exploratory and aims to determine the one- and five-year survival rates for cancer using registry data.

In a retrospective journal review (Dnr 2008/350), which became the first published retrospective study, included just under 3,000 patients[1]. After adjustment for confounding factors and effect modifiers and propensity matching, significance fell, HR = 0.72-1.00 for propofol versus sevoflurane (P=0.051). In the second retrospective study, conducted in London with mixed tumor sites, the number of patients was just over 7,000 and resulted in a statistically significant difference in one-year survival of just over 6 percentage points (P<0.001), and the HR for inhaled anaesthetics versus propofol was in propensity matching 1.30-1.95 (P<0.001)[2].

The hypothesis of the CAN study is that propofol-based anesthesia results in at least 5% units higher one- and five-year survival than sevoflurane-based anesthesia for planned surgery of breast or colorectal cancer.

*Method*

Cohort study based on national register data in RCC's database and SPOR. During autumn/winter 2020, the patients will be identified in the RCC databases for the years 2014 up to and including 2019 (and thereafter up to the latest available date). Data will be sent to UCR (Uppsala Clinical Research Center) which is responsible for SPOR. UCR adds its data to the files from RCC and de-identifies the final file (with key), before sending it encrypted to the principal responsible (the applicant) at the Center for Clinical Research (CKF) in Västerås.

Causative variable: drug given for maintenance of anesthesia, propofol or inhalational agent (desflurane, isoflurane or sevoflurane).

Control variables: age, weight/BMI, smoking, ASA class (functional assessment with a clear relationship to risk), clinic/hospital, perioperative lowest blood pressure measured, bleeding, any blood transfusion, any intra- and postoperative complication, type of surgical intervention, cancer classification (according to TMN), histopathology, adjuvant or neoadjuvant therapy (chemo-, radio-, endocrine- and/or antibody therapy).

The main analysis will be a comparison of total survival with multiple regression analysis ad modum Cox between patients who underwent inhalational anesthesia and intravenous anesthesia with

propofol and adjustment for demographic, oncological and other data according to control variables above.

We can adjust for a high number of prospectively collected important confounding factors and effect modifiers, and the hope is that we can get a result that, as reasonably as possible with a retrospective design, indicates possible differences in survival for cancer in several organs in addition to those already under investigation, i.e., breast and colorectal cancer.

Specifically, said data will be obtained from RCC and SPOR according to variable descriptions in the appendix, data that will thus be de-identified for us. All units involved, RCC, UCR, and CKF have the highest standard for data protection according to Swedish regulations on data security. All units have physical high-quality doors and windows, all with alarms adapted and connected to protective measures in the event of an alarm. For CKF, there is intermittent patrolling by guards at night. In addition to high-class firewalls, all computers are "styled" and monitored by the respective IT department. The data handling is logged. The transfer of data between the devices is encrypted. For CKF, data is stored on a special server to which only the research group has double password-protected access.

*Timetable*

The process for each separate registry study is time-consuming. Based on the time required for the first cancers studied (breast and colorectal cancer), we will at most be able to carry out three, or possibly four studies per year.

*Funding*

Fees for EPM and data retrieval from RCC and SPOR for the first two studies are covered by grants for the CAN study and a separate grant for the third registry study. Continued applications to both larger and smaller grant providers are planned.

The time for the applicant is financed by Region Västmanland (50% research position).

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