An Update on Existing Ongoing Prospective Trials Evaluating the Effect of Anesthetic and Analgesic Techniques During Primary Cancer Surgery on Cancer Recurrence or Metastasis

Jonathan Royds, MB, BCh, BAO, BA, MRCS, FCAI
Abdul H. Khan, BA, MBBS, FRCS, FCAI
Division of Anaesthesia, School of Medicine, Mater University Hospital, University College Dublin, Ireland
Donal J. Buggy, MB, ChB, RCSI, MSc, MRCPI, MD
Department of Anaesthesia, Mater University Hospital, School of Medicine, University College Dublin, Ireland and Outcomes Research, Cleveland Clinic, OH

The influence of anesthesic and analgesic regimens on metastasis and recurrence of cancer remain controversial. A consensus statement in the British Journal of Anaesthesia (BJA) in 2014 noted that although there is a substantial signal from experimental and observational clinical studies, there was as yet no hard evidence to support any change in clinical practice. Collaboration with other specialists was advised in an attempt to study the link between anesthetic techniques and cancer outcomes in surgical oncology patients. It was acknowledged that definitive proof of a cause and effect relationship between anesthetic and perioperative interventions and cancer outcomes requires prospective, randomized trials. Specific recommendations for further evaluation included the use of regional anesthesia and analgesia, intravenous lidocaine, and nonsteroidal anti-inflammatory drugs on cancer recurrence and metastasis.
Our aim was to identify all prospective, randomized clinical trials currently registered on databases worldwide, which are investigating the effect of anesthesia and analgesia techniques during primary cancer surgery on recurrence or metastasis.

**Methods**

To identify the relevant trials in progress, 2 authors searched clinicaltrials.gov, the ISRCTN registry, the EU clinical trials register, the WHO trial search, the Australia New Zealand clinical trials registry, the UMIN clinical trials registry, and the clinical trials registry India. The key words used were “anesthesia” or “anaesthesia,” “analgesia,” “cancer,” “malignancy,” “recurrence,” “metastasis,” “lidocaine,” “NSAIDS,” and a combination of those. Where the estimated trial finish date had expired, an email was sent to the investigator to enquire if the trial was still ongoing. All the relevant data were extracted from the trial registry page on the website of the registries listed above.

**Results**

A total of 16 current trials were retrieved, 15 of which were interventional randomized controlled trials (RCTs) and 1 observational trial. Three of the trials had expired according to their estimated finish date; the authors were emailed, and 2 confirmed that the trials were still ongoing. A further trial is still listed as being in the recruitment stage. The primary endpoints in 9 of the trials were based on mortality and cancer recurrence ranging from 2 to 10 years. The other 7 trials focused on biomarkers and natural killer cell activity, with the patient follow-up ranging from 1 hour to 3 weeks.

We categorized these trials into 2 groups on the basis of their intervention: group 1 trials evaluated a volatile agent against propofol anesthesia (n = 6); group 2 (n = 10) consisted predominantly of trials comparing regional anesthetic-analgesic techniques and medications as adjuncts for anesthesia and postoperative analgesia.

The trials examining the effect of propofol against a volatile agent are summarized in Table 1. Five of the trials are using sevoflurane as their standard volatile agent; the choice of the agent was not specified in the other trial. In 3 of the trials, the primary endpoint focuses on recurrence and survival, whereas the other 3 are examining biological samples. Some of the secondary endpoints include T-helper cell activity, and CD39 and CD73 levels at 1 and 24 hours. One of the trials has an analgesic protocol involving the use of opioids in the perioperative period; none of the other studies in Table 1 have a similar
protocol declared. None of the trials in Table 1 included an analysis of their power calculation for the estimated enrollment.

There are 5 studies comparing epidural/paravertebral anesthesia with opioid analgesia during and after surgery (Table 2). The Mater University Hospital Dublin led breast cancer study, in collaboration with Cleveland Clinic, differs somewhat as propofol is used for the maintenance of anesthesia in the epidural/paravertebral group. Sevoflurane is being used in patients in the same study in the morphine analgesia group. Four of these studies are using opioid adjuncts in their epidurals; it was not described in the protocol of the other trial. There is 1 ongoing trial examining the difference between using epidural analgesia with and without fentanyl and its effects on natural killer cell activity. Two trials are comparing general and spinal anesthesia, one in patients having inguinal lymph node dissections for malignant melanoma. The other is undertaking a similar trial in primary liver cancer ablation.

---

**Table 1. Trials Comparing Volatile and Propofol Anesthetics**

<table>
<thead>
<tr>
<th>Lead Institution</th>
<th>Intervention Investigated/Design</th>
<th>Condition</th>
<th>Primary Outcome</th>
<th>Estimated Enrollment</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peking University First Hospital</td>
<td>Anesthesia with propofol (BIS 40-60) vs. sevoflurane</td>
<td>Cancer</td>
<td>Survival at 3 y</td>
<td>1000</td>
<td>May 2020</td>
</tr>
<tr>
<td>University of Zurich</td>
<td>Anesthesia with propofol (TCI) vs. sevoflurane</td>
<td>Breast cancer</td>
<td>Circulating tumor cells at 3d</td>
<td>231</td>
<td>August 2017</td>
</tr>
<tr>
<td>Konkuk University Medical Center</td>
<td>Anesthesia with propofol vs. sevoflurane</td>
<td>Breast cancer</td>
<td>Natural killer cell activity at 1 &amp; 24 h</td>
<td>300</td>
<td>July 2020</td>
</tr>
<tr>
<td>Konkuk University Medical Center</td>
<td>Anesthesia with propofol vs. sevoflurane</td>
<td>Colon cancer</td>
<td>Natural killer cell activity at 1 &amp; 24 h</td>
<td>300</td>
<td>July 2020</td>
</tr>
<tr>
<td>Seoul National University</td>
<td>Volatile vs. intravenous anesthesia</td>
<td>Hepatocellular carcinoma</td>
<td>Recurrence of HCC at 2 y</td>
<td>413</td>
<td>September 2016</td>
</tr>
<tr>
<td>Uppsala University</td>
<td>Anesthesia with propofol vs. sevoflurane</td>
<td>Breast, colonic and rectal cancer</td>
<td>Overall survival at 5 y</td>
<td>2000</td>
<td>December 2022</td>
</tr>
</tbody>
</table>

BIS indicates bispectral Index; TCI, target controlled infusion; HCC, hepatocellular carcinoma; RCT, randomized controlled trial.
We could not find any studies evaluating IV lidocaine infusions, but a trial is evaluating the effect of peritumoral injection of lidocaine in breast cancer. The intervention group has the tumors injected with 60 mL of 0.5% lidocaine in 6 surfaces of the tumor and within the tumor. They then proceed with the operation after 7 minutes. Nonsteroidal anti-inflammatory drugs are being used alongside propranolol in a double-blinded RCT. Patients are given the medications or placebo 3 days before and 2 days after surgery for breast cancer. Natural killer cells and other biomarkers are designated as Table 2.

**Table 2. Trials Comparing Anesthetic and Analgesic Methods**

<table>
<thead>
<tr>
<th>Lead Institution</th>
<th>Intervention Investigated/Design</th>
<th>Condition</th>
<th>Primary Outcome</th>
<th>Estimated Enrollment</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mater University Hospital, Cleveland Clinic</td>
<td>Volatile anesthesia &amp; opioids vs. propofol &amp; paravertebral/epidural RCT</td>
<td>Breast cancer</td>
<td>Cancer recurrence (10 y)</td>
<td>1100</td>
<td>March 2019</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Anesthesia with opioids vs. anesthesia with epidural Double blinded RCT</td>
<td>Colon cancer</td>
<td>Cancer recurrence (5 y)</td>
<td>2500</td>
<td>December 2022</td>
</tr>
<tr>
<td>Orebro University</td>
<td>Epidural vs. opioid analgesia RCT</td>
<td>Colorectal cancer</td>
<td>Survival at 5 y</td>
<td>300</td>
<td>May 2018</td>
</tr>
<tr>
<td>Institute of Molecular and Translational Medicine, Czech Republic</td>
<td>Epidural vs. piritramide vs. morphine analgesia RCT</td>
<td>Colon cancer</td>
<td>Biomarkers at 5 y</td>
<td>60</td>
<td>December 2017</td>
</tr>
<tr>
<td>National Taiwan University Hospital</td>
<td>Epidural PCA vs. morphine PCA RCT</td>
<td>Pancreatic cancer</td>
<td>Biomarkers</td>
<td>150</td>
<td>August 2015</td>
</tr>
<tr>
<td>McGill University Health Center</td>
<td>Epidural with bupivacaine vs. bupivacaine and fentanyl Double blinded RCT</td>
<td>Hepatocellular carcinoma, colorectal cancer</td>
<td>Natural killer cell activity (24 h)</td>
<td>30</td>
<td>December 2014</td>
</tr>
<tr>
<td>Renji Hospital</td>
<td>Ablation using general vs. regional anesthesia RCT</td>
<td>Primary liver cancer</td>
<td>Cancer recurrence (3 y)</td>
<td>300</td>
<td>April 2019</td>
</tr>
<tr>
<td>University Hospital Muenster</td>
<td>General anesthesia vs. regional anesthesia Assessor blinded RCT</td>
<td>Malignant melanoma</td>
<td>Survival at 5 y</td>
<td>230</td>
<td>March 2019</td>
</tr>
<tr>
<td>Tata Memorial Hospital</td>
<td>Peritumoral lidocaine infiltration vs. no intervention RCT</td>
<td>Breast cancer</td>
<td>Cancer recurrence (5 y)</td>
<td>1600</td>
<td>December 2021</td>
</tr>
<tr>
<td>Kaplan Medical Center</td>
<td>Perioperative etodolac and propranolol vs. placebo Double blinded RCT</td>
<td>Breast cancer</td>
<td>Biomarkers</td>
<td>32</td>
<td>January 2016</td>
</tr>
</tbody>
</table>

PCA indicates patient controlled analgesia; RCT, randomized controlled trial.

We could not find any studies evaluating IV lidocaine infusions, but a trial is evaluating the effect of peritumoral injection of lidocaine in breast cancer. The intervention group has the tumors injected with 60 mL of 0.5% lidocaine in 6 surfaces of the tumor and within the tumor. They then proceed with the operation after 7 minutes. Nonsteroidal anti-inflammatory drugs are being used alongside propranolol in a double-blinded RCT. Patients are given the medications or placebo 3 days before and 2 days after surgery for breast cancer. Natural killer cells and other biomarkers are designated as Table 2.
the primary endpoint with the 5-year survival being the secondary endpoint.

Power calculations were described in 3 of the 10 studies in Table 2 to justify enrollment numbers.8,13,17

**Discussion**

After the consensus statement in the BJA, it is encouraging to see 8 trials powered to cancer recurrence and mortality examining various methods of anesthesia and analgesia.3,7–10,14–16,18 The other 7 trials may produce further translational evidence delivering mechanistic data on how perioperative interventions might influence the cancer outcome and justify more RCTs powered to cancer recurrence in the future.4–6,11–13,17

The studies examining volatile and propofol anesthetics have so far focused on the immune function and their biological effect on malignant tumors.1,19–25 Evidence from RCTs on long-term survival is lacking, with data confined to retrospective reviews.26,27

There is some evidence that regional anesthesia reduces metastatic cancer dissemination and attenuates the neuroendocrine stress response.1,28,29 Clinical evidence for regional anesthesia and analgesia as an independent variable for cancer recurrence has been examined in the follow-up analysis of previous RCTs designed to evaluate a very different primary endpoint in colorectal and prostate surgery. They found no association between epidural anesthesia and an improved cancer outcome, although one did in a subset of patients above 64 years old.30–32 These trials also raise the question on the use of opioids in cancer surgery, and their effect on angiogenesis and tumor development.33,34

There are many retrospective reviews comparing regional techniques and opioids, with conflicting evidence on many different cancers.1 Two trials listed in this review are investigating this, with cancer recurrence being the primary outcome.8,9 The breast cancer study has another variable to consider as it is using propofol for the maintenance of anesthesia in the regional analgesia group.8 The concurrent use of opioids in some of the studies where epidurals are being utilized may appear to be conflicting.9–12 Although the doses are low, they will be absorbed into systemic circulation.35

The efficacy of local anesthetics alone on tumor recurrence is unclear.1 Various studies have shown reduced mesenchymal stem cell proliferation and alteration in DNA methylation in breast cancer cell lines.36,37 A current trial will test this hypothesis, which has as its endpoint recurrence at 5 years.16 Their method involves infiltrating
lidocaine to attenuate the dissemination of cancer cells before commencing surgery.

The long-term use of COX inhibitors has been shown to reduce the risk of developing breast cancer in a systematic review. Although COX 2 is expressed in breast cancer and prostaglandins have been shown to promote cancer cell adhesion, causation cannot be confirmed without a RCT. A population-based study analyzing breast cancer in patients taking β-blockers showed that patients taking propranolol were less likely to have tumor invasion at presentation. A double-blind RCT combining both of these medications during the perioperative period is ongoing.

The existence of these prospective randomized clinical trials investigating the effect of anesthesia and analgesic techniques on cancer recurrence and metastasis is promising. Only this arduous and long-term study design will provide definitive evidence as to whether there is truly a cause-and-effect link between the anesthetic-analgesic technique and the cancer outcome, and address this urgent clinical question.

D.J.B. is an editor for *British Journal of Anaesthesia and International Anesthesiology Clinics*. The remaining authors declare that they have nothing to disclose.

### References


11. The Institute of Molecular and Translational Medicine, Czech Republic, Berta E. Effects of different types of perioperative analgesia on minimal residual disease development after colon cancer surgery. Available at: https://clinicaltrials.gov/show/NCT02314871. Accessed December 1, 2014.


