Does Anesthesia influence Cancer recurrence?

Dr Ian McConachie FRCA FRCPC
London, ON, Canada
Factor influencing survival

- Cancer biology
- Location
- Local invasion
- Distant spread
- Early v late diagnosis / screening
- Genetics
- Comorbidities
- Complications
- Sarcopenia
- Age
Why did my cancer come back?

- Inadequate resection
- Micro metastases
- Lymph spread
- Tumour biology
- Immune system
- Genetics, sex, race, age?
- Blood transfusion
Why did my cancer come back?

- Inadequate resection
- Micro metastases
- Lymph spread
- Tumour biology
- Immune system
- Genetics
- Blood transfusion
- Anaesthesia and analgesia
Surgery and cancer progression and metastasis

**Surgical stress response and cancer**
Stress and surgical excision of the primary tumour can promote tumour metastasis

**Neuroendocrine system**
GA + surgical stress = immunity suppression

**Inflammatory system**
Promotion of cancer progression through immunosuppression via cytokines, chemokines, prostaglandins, COX

**Pain**
Suppression of NK cell activity and promotion of tumour development in animals

**Perioperative hypothermia**
Hypothermia leads to a reduction in cell-mediated immunity, particularly NK cells, and an increase in lung tumor retention and metastasis in rat
• Circulating tumor cells released during the surgical procedure may eventually lead to recurrence or metastases as they escape the immune surveillance.

• Concentrations of tumor-related anti-angiogenic factors (e.g., angiostatin and endostatin) are decreased while angiogenic factors such as vascular endothelial growth factor (VEGF) are increased.

• Surgery is also associated with release of transforming growth factor-beta (TGF-B) that plays a significant role in establishing tumor blood supply and cell proliferation.
Anaesthesia and cancer spread

- Immune modulation
- Pain
- Hypothermia
- Stress response
- Anesthesia
- Analgesia
- Regional blocks
Choice of Anaesthetic
Animal studies

“A peculiar thing in medicine is that we never believe anything unless it can be demonstrated in animals”

John Schindler MD

“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”
IV agents and NK cell activity

- In rats, all anesthetics, except propofol, significantly reduced NK activity and increased lung tumour retention or lung metastases.
- Ketamine promoted metastasis most.

Anesth Analg 2003; 97: 1331-9
Volatile anaesthetics and NK cell activity

• Volatile anesthetics inhibit NK cell activity dose dependently in vitro.
• Mechanism unclear but may induce CD8+ T cells which suppress the activation of NK cells.
• Depression of NK cell activity may also be associated with the activation of the Neuroendocrine System - changes in serum cortisol show an inverse relationship with NK cell cytotoxicity during and after surgery.
Volatile or Propofol?

- Volatile anesthesia suppresses neutrophil and lymphocyte function.
- Propofol has inhibitory effects on neutrophil, monocyte and macrophage functions but not on NK cell or lymphocyte functions.

NK cell cytoxicity in vitro

• 10 Breast surgery patients.
• Serum from patients receiving propofol/paravertebral block exhibited greater NK cell cytotoxicity in vitro than serum from patients receiving sevoflurane/opioid.

Br J Anaesth 2014; 113: i56-62

NK CD16 activating receptor
• Tumour cell proliferation, invasion and apoptosis are crucial steps in tumour metastasis.
• Patients randomly assigned to receive propofol and thoracic epidural or sevoflurane with opioid analgesia.
• Colon cancer cells were cultured with patient serum from both groups.
• Serum from epidural group inhibited proliferation and invasion of cancer cells and induced apoptosis in vitro more than sevoflurane group.

Anaesthesia 2016 ; 71 :147-54
Inhalational anesthesia v TIVA

- Cancer centre
- Retrospective study
- Volatile (INHA) v TIVA
- After propensity matching, 2607 in each group
- 22.8% mortality (INHA) v 15.6% (TIVA).
- INHA hazard ratio 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis of known confounders.

Anesthesiology 2016; 124:69-79
• Usefulness of propensity scoring matching in retrospective studies is limited by the fact that remaining unmeasured confounding may still be present.

• Even after propensity matching, there was a statistically significant difference in transfusion rates between groups, there being an almost 50% higher rate of blood transfusion in the group receiving a volatile anesthetic (150 vs. 110 patients, $P = 0.011$).
Inhalational anesthesia v TIVA 2

- 2838 patients in database undergoing breast, colon and rectal Ca surgery.
- Overall 1 and 5 year survival rates favoured propofol.
- The 1-year survival for patients operated for colon cancer almost 10% higher after propofol anaesthesia.
- However, after adjustment for several confounders, differences not statistically significant.

Inhalational anesthesia v TIVA 2

• 2838 patients in database undergoing breast, colon and rectal Ca surgery.
• Overall 1 and 5 year survival rates favoured propofol.
• The 1-year survival for patients operated for colon cancer almost 10% higher after propofol anaesthesia.
• However, after adjustment for several confounders, differences not statistically significant.

“Thus, the results of our study do not support conclusions of other studies, claiming that survival might be higher after propofol anaesthesia. Based on the current results, we have made a power analysis for a prospective study. It was found that we will need at least 3,000 patients with colon cancer.”
Analgesia
Analgesia

- NSAIDs
- Opioids
- LA (Block or epidural)
NSAIDs attenuate lung tumour retention and suppression of NK cell activity in rats

J Pain 2002; 3: 301-8
Breast CA mice model

- 2 weeks of morphine stimulates COX-2, PGE-2 and angiogenesis in breast tumours accompanied by increased tumour weight, increased metastasis and reduced survival.
- Addition of celecoxib resulted in prevention of tumour growth, angiogenesis, metastasis.
Breast CA mice model

- 2 weeks of morphine stimulates COX-2, PGE-2 and angiogenesis, increasing tumour growth, angiogenesis, and metastasis.
- Additional insult leads to increased susceptibility.

Celecoxib is approved by the FDA for the prevention of colorectal cancer in high-risk patients with preexisting susceptibility such as familial adenomatous polyposis.
Intraoperative Analgesics and Recurrence after Mastectomy

Intraoperative Analgesics and Recurrence after Mastectomy

Surgeons largely closed the door on NSAIDs for colorectal surgery in many centres. Shortsighted?

Kaplan-Meier recurrence-free survival estimated for 319 patients receiving (or not receiving) intraoperative analgesics.

The vexing problem of opioids

Pain bad

Are opioids good or bad?
The opioid dilemma

• Opioids inhibit cellular and humoral immune function in humans.
• Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity.
• Opioid-induced promotion and stimulation of angiogenesis.

• IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans.
• Inhibitory effects of morphine on tumor growth have been found in human and animal models

The opioid dilemma

- Opioids inhibit cellular and humoral immune function in humans.
- Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity.
- Opioid-induced promotion and stimulation of angiogenesis.
- IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans.
- Inhibitory effects of morphine on tumor growth have been found in human and animal models.
- Opioid/tumor interaction is complex, its mechanisms are not completely understood, and to a certain extent are contradictory. Dose may be important.

The opioid dilemma

- Opioids inhibit cellular and humoral immune function.
- Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity.
- Opioid-induced promotion and stimulation of angiogenesis.
- IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans.
- Inhibitory effects of morphine on tumor growth have been found in human and animal models.

Pain also increases “stress’ and acts as an immunosuppressant.

Opioids and NK cells

- Small study 40 patients undergoing surgery.
- Large dose Fentanyl suppressed NK cell activity for 48hrs compared to small dose Fentanyl.
- NB: 75-100 µg/kg v 1 µg/kg !!

Intraoperative Analgesics and Recurrence after Mastectomy

Kaplan-Meier recurrence-free survival estimated for 319 patients receiving (or not receiving) intraoperative analgesics.
Intraoperative Analgesics and Recurrence after Mastectomy

Direct anti cancer effect of LA?

- Lidocaine has cytotoxic effects on neoplastic cells in vitro.
  
  Eur J Anaesthesiol 2012; 29: 35-41

- At clinically relevant concentrations, lidocaine demethylates DNA of breast cancer cell lines in vitro.


- Amide LAs inhibit TNF mediated invasiveness of lung Adenocancer cells in vitro.

  Br J Anaesth 2015;115:784–91

Potential additional benefit of IV Lidocaine infusions?
Epidurals and immune function – practical aspects

• Epidural anaesthesia reduces the activation of the neuroendocrine system and thus prevents immunosuppression.

• The depression of NK cell activity with GA attenuated by Epidural anaesthesia.
Epidural benefit?

Is it avoidance of Opioids
  Or
Avoidance of GA (GA usually given as well)
  Or
Better analgesia
  Or
Sympathetic block
  Or
Direct effect of LA drugs
  Or
All or none of the above
Epidural benefit?

Is it avoidance of Opioids
Avoidance of GA (GA usually given as well)
Better analgesia
Sympathetic block
Direct effect of LA drugs
All or none of the above

The role of intrathecal and epidural opioids commonly used in regional analgesia and pain management has not been explored.
What is the evidence?

- Looking primarily today at survival free recurrence.
- Overall survival, though obviously important, has so many influences and does not directly address the main question we are asking today.
Retrospective studies
Problems with retrospective studies

- Analysing preexisting data with multiple potential biases.
- Unknown and uncontrolled confounders eg were epidural patients younger or older ? Blood transfusion ?
- Reasons for epidural unknown eg different incisions ?
- Contraindications for epidural insertions unknown and uncontrolled eg coagulopathies, sepsis ?
- How effective were the epidurals ? Total opioid dose ?
- Concerns re adequacy of data collection.
- Often historical patient care being studied. Surgical and anesthetic care has improved overall.
Breast Cancer

Retrospective study 126 breast cancer patients
Paravertebral+GA group:
• Lower pain scores.
• Less tumour recurrence.
• Slower time to tumour recurrence.

Anesthesiology 2006; 105: 660-4
Prostate Cancer

- Retrospective review 225 patients after radical open prostatectomy.
- Endpoint was PSA level postop.
- After adjusting for confounders, the epidural plus GA group had an estimated 57% lower risk of recurrence compared with GA + opioids group.

Anesthesiology 2008;109:180-7
Prostate Cancer

- Retrospective review 225 patients after radical open prostatectomy.
- Endpoint was PSA level postop.
- After adjusting for confounders, the epidural plus GA group had an estimated 57\% lower risk of recurrence compared with GA + opioids group.

“Typically, it is offered in combination with general anesthesia to patients undergoing radical prostatectomy.”

Choice of epidural reasons?

225 patients January 1994 and December 2003

- We do over 250 per year

Anesthesiology 2008;109:180-7
Prostate Cancer 2

• Retrospective study of 261 patients over 6 years.
• GA with epidural analgesia associated with a reduced risk of clinical cancer progression.
• No difference on biochemical recurrence free survival, cancer specific survival, or overall survival.

Anesthesiology 2010; 113:570 – 6
Prostate Cancer 2

- Retrospective study of 261 patients over 6 years.
- GA with epidural analgesia associated with a reduced risk of clinical cancer progression.
- No difference on biochemical recurrence free survival, cancer specific survival, or overall survival.

Anesthesiology 2010; 113:570 – 6
Ovarian Cancer

- 182 patients.
- 127 no epidural. 29 epidurals only postoperatively. 26 intraoperative and postoperative.
- Cancer recurrence was documented in 121 patients.
- Intraoperative but not postoperative use of epidural anaesthesia was associated with an increased time to tumor recurrence after surgery.

Gastric cancer

- Medicare database.
- 2745 patients, 766 of whom had epidural.
- Patients receiving epidurals were more likely to have regional disease, be white, and live in areas with relatively high socioeconomic status.
- No difference survival or cancer recurrence.

Colorectal cancer 1

- 256 patients with compared with 253 without epidural in retrospective analysis.
- Overall, no association between epidural use and recurrence ($P = 0.43$).
- In *post hoc* analyses, epidural use was associated with a lower cancer recurrence in older patients.

Anesthesiology 2010; 113:27–34
Colorectal cancer 2

- Case cohort study of 42151 patients undergoing colectomy.
- 22.9% epidurals.
- Survival improved in epidural group but not cancer recurrence.
- Reasons/exclusions for epidural not stated.

Anesthesiology 2012; 116: 797-806
Liver resection for colorectal Ca metastases

- Retrospective review.
- 390 patients in epidural group and 120 in IV analgesia group.
- There was an association between epidural and improved recurrence free survival but not overall survival.

Ann Surg Oncol 2016; 23:1003–1011
Prospective studies
Prospective studies
- retrospective analyses of prospective data collected to answer a different question
Prostate Cancer

• Secondary analysis of previously conducted trial.
• 50 (GA) & 49 (GA+epidural).
• Clinical or biomarker recurrence (PSA)
• No benefit from Epidural.

Can J Anaesth 2010; 57: 107-12
Ovarian Cancer

- 80 patients with advanced ovarian cancer.
- After PS matching and weighting, no benefit in overall survival or time to recurrence in patients with advanced ovarian cancer from the use of epidurals during and after tumor debulking surgery.
- “Patients were identified from a prospective clinical registry.”

Anesth Analg 2013;117:653–60
Colorectal cancer 1

• Long term follow up of previous multicentre, prospective VA study published in 2001.
• No data on cause of death. (!)
• Epidurals had no effect on survival with metastases.
• Patients with epidural had better early survival. However the benefit was lost after 1.5–2.0 years.
• Patients surviving beyond 1.46 years, not receiving epidural appeared associated with lower risk but not statistically significant.

Anesth Analg 2008;107:325–32
Colorectal cancer 1

- No data on cause of death.
- Epidurals had no effect on survival with metastases.
- Patients with epidural had better early survival. However, the benefit was lost after 1.5–2.0 years.
- Patients surviving beyond 1.46 years, not receiving epidural appeared associated with lower risk but not statistically significant.

Early but not later survival in epidural group not strongly supportive of beneficial effect on cancer recurrence.

Anesth Analg 2008;107:325–32
Colorectal cancer 2

- Retrospective analysis of previous prospective patient data – published in 1993!!
- Trend but no statistical significance for recurrence free survival in Epidural group.

Colorectal cancer 3

• Long term follow up of abdominal cancer patients (mainly colorectal) in multicentre, prospective MASTER trial from 1990s.

• No difference in recurrence free survival in epidural group.

BMJ 2011;342:d1491
Meta Analyses
Cochrane review

No advantage for overall survival, progression-free survival or time to tumour progression.

Quality of evidence low for overall survival and very low for progression-free survival and time to tumour progression.

Currently, evidence for the benefit of regional anaesthesia techniques on tumour recurrence is inadequate.

Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD008877. DOI: 10.1002/14651858.CD008877.pub2
Cochrane review

No advantage for overall survival, progression-free survival or time to tumour progression.

Quality of evidence low for overall survival and very low for progression-free survival and time to tumour progression.

Currently, evidence for the benefit of regional anaesthesia techniques on tumour recurrence is inadequate.

All 4 studies (746 patients) were secondary data analyses of previously conducted prospective RCTS.

Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD008877. DOI: 10.1002/14651858.CD008877.pub2
Meta Analysis general cancer surgery

- A meta-analysis in 2013 demonstrated epidurals associated with improved survival.
- A significant positive association between epidural analgesia and improved overall survival was shown in the subgroup analysis for colorectal cancer.
- No association between epidural anesthesia and cancer recurrence.
- Lack of association of epidurals and cancer free survival or recurrence, retrospective nature of most studies and very large between-study heterogeneity highlights the need for large prospective randomised studies.

Latest Meta Analysis

• 21 studies.
• There was an association between neuraxial anesthesia and improved overall survival.
• Most of the benefit for overall survival was in colorectal cancer.
• There was a significant association between neuraxial anesthesia and improved recurrence free survival.

Oncotarget 2016; 7: 15262–15273
Latest Meta Analysis

- 21 studies.
- There was an association between neuraxial anesthesia and improved overall survival.
- Most of the benefit for overall survival was in colorectal cancer.
- There was a significant association between neuraxial anesthesia and improved recurrence free survival.

Oncotarget 2016; 7: 15262–15273

Beware !!
This journal included in Beall’s list of Predatory Journals.
Fee per paper $2850.
Danger

Concerns re opioid drugs and cancer recurrence could lead to denial of pain relief after cancer surgery (which itself would be detrimental)
Danger

Concerns re opioid drugs and cancer recurrence could lead to denial of pain relief after cancer surgery, which itself would be detrimental.

Good Pain Management Vital
“Abandoning a highly effective analgesic without a replacement is both inhumane and likely to be self defeating given the very significant adverse influence of pain and stress on cancer progression.”

What about steroids?

Dexamethasone common perioperative antiemetic – especially in women.

- No association between perioperative systemic dexamethasone administration and ovarian cancer recurrence after primary cytoreductive surgery.
  
  Anesth Analg 2014; 118: 1213-8

- Dexamethasone administration was not associated with an increased risk of recurrence in women having surgery for endometrial cancer.

  Curr Med Res Opin 2016; 33: 453-8
Keep a sense of perspective

- One hundred years of surgical history suggests this is *small print stuff* for the majority of our patients.
- Cancer outcomes are at an all time high.
- Surgical outcomes are at an all time high.
- Anaesthetic outcomes are at an all time high.
Trends in colorectal cancer mortality

Decreasing mortality despite increasing incidence

Gut 2016
Don’t Panic!

If the cancer has undergone a curative resection then it is still probably cured - regardless of the anaesthetic.
Bottom line

Surgical technique, chemo and radiotherapy and tumour biology are still the most significant factors in cancer survival.
Research challenges

- In an area of research where the primary outcome might be expected to occur several years after the recruitment of the 1st patient, conclusive trials will take a decade.
- Large number of confounding variables.
- Studies must control for age, patient comorbidities, underlying genetic predisposition, neoadjuvant chemo-radiotherapy, tumour staging and lymphovascular space invasion, clinical care providers, effective regional anaesthesia, choice of anesthesia, blood transfusion, temperature control and a range of perioperative pharmacology.
• Previous studies suggest that if a correlation between epidurals and cancer recurrence really exists, it will require the inclusion of many patients for a study to reach statistical significance.

• This suggests a minor influence (compared to eg absence of residual disease or staging ) and may limit clinical consequences on an individual basis.
Answers no time soon!

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 RCT</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 Double blinded RCT</td>
<td>Breast cancer</td>
<td>Circulating tumor cells at 3 d</td>
<td>281</td>
<td>August 2017</td>
</tr>
<tr>
<td>Konkuk University Medical Center</td>
<td>Anesthesia with propofol vs. sevoflurane Investigator blinded RCT</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 Investigator blinded RCT</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 Retrospective, observational study RCT</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 Subject blinded RCT</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.
Answers no time soon!

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</td>
<td>Anesthesia with propofol (BIS 40-60) vs. sevoflurane</td>
<td>Cancer</td>
<td>Survival at 3 y</td>
<td>1800</td>
<td>May 2020</td>
</tr>
<tr>
<td>First Hospital</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Zurich</td>
<td>Anesthesia with propofol (TCI) vs. sevoflurane Double blinded RCT</td>
<td>Breast cancer</td>
<td>Circulating tumor cells at 3 d</td>
<td>281</td>
<td>August 2017</td>
</tr>
<tr>
<td>Konkuk University</td>
<td>Anesthesia with propofol vs. sevoflurane Investigator blinded RCT</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>Medical Center</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konkuk University</td>
<td>Anesthesia with propofol vs. sevoflurane Investigator blinded RCT</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>Medical Center</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seoul National University</td>
<td>Volatile vs. intravenous anesthesia Retrospective, observational</td>
<td>Hepatocellular carcinoma</td>
<td>Recurrence of HCC at 2 y</td>
<td>413</td>
<td>September 2016</td>
</tr>
<tr>
<td>University</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uppsala University</td>
<td>Anesthesia with propofol vs. sevoflurane Subject blinded RCT</td>
<td>Breast, colonic and rectal cancer</td>
<td>Overall survival at 5 y</td>
<td>200</td>
<td>December 2022</td>
</tr>
</tbody>
</table>

BIS indicates bispectral Index; TCI, target controlled infusion; HCC, hepatocellular carcinoma; RCT, randomized controlled trial.
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 anesthetics &amp; opioids vs. propofol &amp; paravertebral epidural RCT</td>
<td>Breast cancer</td>
<td>Cancer recurrence (10 y)</td>
<td>1000</td>
<td>March 2019</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Anesthesia with opioids vs. anesthesia with epidural RCT Double blinded RCT</td>
<td>Colon cancer</td>
<td>Cancer recurrence (3 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 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 remifentanil and fentanyl RCT</td>
<td>Hepatic recurrence, 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>Double blinded RCT Ablation using general 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>Perioperative infiltration vs. no intervention RCT</td>
<td>Breast cancer</td>
<td>Cancer recurrence (3 y)</td>
<td>1600</td>
<td>December 2021</td>
</tr>
<tr>
<td>Kaplan Medical Center</td>
<td>Perioperative oxycalc 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.

Int Anesthesiol Clin 2016 ; 54 :e76-83
Answers no time soon!

<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>1000</td>
<td>March 2019</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Anesthesia with opioids vs. anesthesia with epidural 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>Epidual vs. epidural analgesia Double blinded 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>Epidual 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>Epidual 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>Epidual withropivicaine vs. ropivicaine and fentanyl RCT</td>
<td>Hepatic recurrence, colorectal cancer</td>
<td>Natural kill cell activity (24 h)</td>
<td>30</td>
<td>December 2014</td>
</tr>
<tr>
<td>Renji Hospital</td>
<td>Double blurred RCT Ablation using gener vs. regional anesesthesia RCT</td>
<td>Primary liver cancer</td>
<td>Cancer recurrence (5 y)</td>
<td>300</td>
<td>April 2019</td>
</tr>
<tr>
<td>University Hospital Muenster</td>
<td>General anesthesia vs. regional anesthesia Ablation 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>1000</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.
Modern cancer anaesthetic?

• Decrease neuroendocrine stress response.
• Avoid proinflammatory agents.
• TIVA v inhalational technique?
• Caution with opioids – opioid sparing techniques.
• Regional blocks – may need to be started before incision for optimal inflammatory modulation.
• Good analgesia.
One size may not fit all

- Different chemotherapy regimes for different cancers
- Anaesthesia effects on cancer may not be the same for all cancers
- There may not be one “cancer anaesthetic”