Anaesthesia and Cancer

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Outline

– Cancer surgery and metastases
– Pathophysiology of cancer metastases
– Intravenous vs inhalation anaesthesia
– Opioids, regional anaesthesia and cancer
– Current and future research
– Modern anaesthesia and cancer care

...to gas or not to gas (in cancer)...

Life demands excellence

The ROYAL MARSDEN
NHS Foundation Trust
Cancer - the burden

Predicted global cancer cases

Source: WHO GloboCan
Cancer surgery

• 80% of patients require surgery
• Many multiple times

By 2030, over 45 million cancer operations

Sullivan et al. Lancet Oncology. 2015
Cancer - metastases

- All patients have circulating tumour cells
- Tumour handling / surgery increases numbers
Surely surgery is curative….
Schreiber et al. 2011, Science
The hypothesis...

- Surgery releases cancer cells into the circulation
- Stress response can modify immune activity
- Anaesthesia / surgery can simultaneously...
  - Directly affect cancer cells
  - Modify immune activity
Drugs in anaesthesia

- Oxygen, Air and Nitrous oxide ✗
- Inhalation and intravenous anaesthetics
- Opioids
- Muscle relaxants ✗
- Anti emetics
- Local anaesthesia/regional anaesthesia
- Vasopressors ✗
- Other adjuncts (alpha agonists, NSAIDS, Heparin)
Anesthetic Drugs Accelerate the Progression of Postoperative Metastases of Mouse Tumors

Mouse lungs 15 days after IV injection of $1 \times 10^6$ T10 sarcoma cells

no anaesthetic  

pentothal sodium

Although we found that anesthetic drugs strongly accelerated metastasis, we cannot at this stage attribute the activity of these drugs to an effect on a defined target cell, let alone on a defined cellular component.

Can Anesthetic Technique for Primary Breast Cancer Surgery Affect Recurrence or Metastasis?


Effects of halothane and isoflurane on pulmonary metastasis

![Graph showing effects of halothane and isoflurane on pulmonary metastasis]

- Control
- Isoflurane
- Halothane

Number of Metastases

- 50
- 45
- 40
- 35
- 30
- 25
- 20
- 15
- 10
- 5
- 0

p < 0.0001

p < 0.0014

p < 0.0014

Moudgil CJA 1997

Fig. 1. Univariable association between paravertebral block and cancer recurrence, \( P = 0.013 \) log-rank test. The association remained significant \( (P = 0.012) \) in a multivariable model adjusting for histologic grade and number of axillary nodes.
Volatile vs propofol anaesthesia
Propofol vs volatile - science

Ischaemic preconditioning

- IPC
- HIF-1α
- ROS_{mito}
- PTEN
- PI3K
- AKT
- PDK1

Other signal transduction pathways

Acute protection against ischaemia–reperfusion injury
**Isoflurane Preconditioning Decreases Myocardial Infarction in Rabbits via Up-regulation of Hypoxia Inducible Factor 1 That Is Mediated by Mammalian Target of Rapamycin**

Jacob Raphael, M.D.,* Zhili Zuo, M.D., Ph.D.,† Suzan Abedat, M.Sc.,‡ Ronen Beeri, M.D.,§ Yaakov Gozal, M.D.||
Harris. Nature Reviews Cancer 2002
Impact of isoflurane on malignant capability of ovarian cancer in vitro
d
X. Luo¹,³†, H. Zhao³†, L. Hennah³, J. Ning³, J. Liu¹, H. Tu² and D. Ma³*

B

C

IGF-1R
fluorescence intensity (MFI)

24 h after gas exposure

NC 1% Iso 1.5% Iso 2% Iso

24 h after treatment

NC N₂ Iso

IGF-1 (vs control)

0 1 2 3

NC N₂ Iso
Prostate cancer cell malignancy via modulation of HIF-1α pathway with isoflurane and propofol alone and in combination

H Huang¹,²,⁴, L L Benzonana¹,⁴, H Zhao¹,⁴, H R Watts¹, N J S Perry¹, C Bevan³, R Brown³ and D Ma*,¹

Results: We demonstrated that isoflurane, at a clinically relevant concentration induced upregulation of HIF-1α and its downstream effectors in PC3 cell line. Consequently, cancer cell characteristics associated with malignancy were enhanced, with an increase of proliferation and migration, as well as development of chemoresistance. Inhibition of HIF-1α neosynthesis through upper pathway blocking by a PI-3K-Akt inhibitor or HIF-1α siRNA abolished isoflurane-induced effects. In contrast, the intravenous anaesthetic propofol inhibited HIF-1α activation induced by hypoxia or CoCl₂. Propofol also prevented isoflurane-induced HIF-1α activation, and partially reduced cancer cell malignant activities.
Cell mediated immunity vs humoral immunity

T helper cells

Th1
- Macrophages
- NK cells (CD8)
- Cell mediated
  - IL-2, IFN-γ, IL-12
  - Tumour death

Th2
- B cells
- Eosinaphils
- Humoral
  - IL-4, IL-6, IL-10 (immunosuppressive)
  - Tumour escape

Partner cells

Immunity

Result
Propofol ↑TH1... Iso ↓Th1

Table 2  Th1/Th2 ratio in patients undergoing craniotomy under propofol or isoflurane anaesthesia. Values are median (interquartile range [range]).

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 9)</th>
<th>Isoflurane (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before induction of anaesthesia</td>
<td>2.4 (2.2–2.9 [1.8–3.1])</td>
<td>2.6 (2.5–3.1 [2.3–3.4])</td>
</tr>
<tr>
<td>1st postoperative day</td>
<td>2.0 (1.8–2.4 [1.1–2.9])</td>
<td>1.2 (0.9–1.9 [0.2–2.8])</td>
</tr>
<tr>
<td>3rd postoperative day</td>
<td>2.4 (2.0–2.5 [1.4–3.0])</td>
<td>1.1 (0.9–1.4 [0.7–3.7])</td>
</tr>
<tr>
<td>5th postoperative day</td>
<td>2.4 (2.1–2.8 [1.2–3.1])</td>
<td>0.8 (0.8–1.9 [0.4–3.5])</td>
</tr>
<tr>
<td>7th postoperative day</td>
<td>2.6 (2.0–3.0 [1.3–3.9])</td>
<td>1.0 (0.9–1.4 [0.5–3.0])</td>
</tr>
<tr>
<td>Mean value 1st–7th postoperative day</td>
<td>2.4 (2.1–2.6 [1.3–2.9])</td>
<td>1.0 (0.9–1.6 [0.5–3.2])</td>
</tr>
<tr>
<td>p = 0.14*</td>
<td></td>
<td>p = 0.011*</td>
</tr>
</tbody>
</table>

*Comparison between values before induction of anaesthesia and the mean postoperative values. Area under the curve for Th1/Th2 ratio was smaller in the isoflurane group than in the propofol group (p = 0.009).
The effect of different anesthetics on tumor cytotoxicity by natural killer cells

Kazumasa Tazawa\textsuperscript{a,c}, Sophia Koutsogiannaki\textsuperscript{a,b}, Matthew Chamberlain\textsuperscript{a}, Koichi Yuki\textsuperscript{a,b,*}

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\textsuperscript{b} Department of Anesthesia, Harvard Medical School, Boston, MA 02115, USA
\textsuperscript{c} Department of Anesthesia, Saitama Medical School, Saitama 350-8550, Japan
To gas or not to gas?

Clinical evidence?
Propofol vs volatile - clinical data

The choice of anaesthetic—sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis

MATS ENLUND, ANDERS BERGLUND, KALLE ANDREASSON, CATHARINA CICEK, ANNA ENLUND & LEIF BERGKVIST

2500 pts
12 years inclusion
Non-sig after adjustment
Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery

A Retrospective Analysis


• All elective cases June 2010 to May 2013 (11716 cases)

• 3316 individual patients inhalational only

• 3714 patients TIVA only
Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery

A Retrospective Analysis


- Outcome - Survival at censure date (31/10/14)
- Cox proportional hazard regression model (uni)
- Propensity score for baseline characteristics
Inhalational *versus* intravenous anaesthesia

Sevoflurane

Propofol

Overall

By co-morbid status (ASA score)

By presence/absence of metastases

Wigmore, T., Mohammed K., Jhanji, S. Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery. *Anesthesiology* 2016
Inhalational *versus* intravenous anaesthesia

Inhalational anaesthesia mortality: 22.8%
Propofol anaesthesia mortality: 15.6%
Hazard ratio: 1.46
Confidence interval: 1.29 – 1.66

Wigmore, T., Mohammed K., Jhanji, S. Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery. *Anesthesiology* 2016
Regional anaesthesia and analgesia: relationship to cancer recurrence and survival

T. Tedore*
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*E-mail: tft9001@med.cornell.edu

British Journal of Anaesthesia, 113 (S1): i1–i3 (2014)
doi: 10.1093/bja/aeu261

EDITORIAL

Special issue on anaesthesia and cancer

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Impact of anesthetic agents on overall and recurrence-free survival

ABSTRACT

Background: The association between type of anesthesia used and recurrence of cancer remains controversial. This retrospective cohort study compared the influence of total IV anesthesia and inhalation anesthesia on the primary outcome of recurrence-free survival after breast cancer surgery.

Methods: The authors reviewed the electronic medical records of patients who had breast cancer surgery at a tertiary care teaching hospital between January 2005 and December 2013. The patients were grouped according to whether IV or inhalation anesthesia was used for surgery. Propensity score matching was used to account for differences in baseline characteristics. Kaplan–Meier survival curves were constructed to evaluate the influence of type of anesthesia on recurrence-free survival and overall survival. The risks of cancer recurrence and all-cause mortality were compared between each type of anesthesia.

Results: Of 7,678 patients who had breast cancer surgery during the study period, data for 5,331 patients were available for analysis (IV group, n = 3,085; inhalation group, n = 2,246). After propensity score matching, 1,766 patients remained in each group. Kaplan–Meier survival curves showed that there was no significant difference in recurrence-free survival or overall survival between the two groups, with 5-yr recurrence-free survival rates of 86.7% vs 87.8%, and 84.2% vs 84.2% for the IV and inhalation groups, respectively.

Total Intravenous Anesthesia versus Inhalation Anesthesia for Breast Cancer Surgery

A Retrospective Cohort Study

Seokha Yoo, M.D., Han-Byoel Lee, M.D., Wonshik Han, M.D., Ph.D., Dong-Young Noh, M.D., Ph.D., Sun-Kyung Park, M.D., Won Ho Kim, M.D., Ph.D., Jin-Tae Kim, M.D., Ph.D.

Anesthesiology 2019; 130:31–40
Hypothesis

“That the type of general anaesthetic drug used during cancer surgery impacts upon the metabolic physiology, survival adaptations and metastatic potential of malignant cells, with implications for post-operative disease progression”
Elucidate impact of inhalational versus intravenous anaesthesia upon:

1) Cancer cell phenome
2) Cancer cell molecular signalling and metabolism

In order to:

1) Identify specific vulnerabilities to postoperative cancer progression
2) Inform design and focus of future Randomised Controlled Trials
Our pilot data

• Breast cancer models

• ER+ve / triple negative to start with

• Concentrating on metastatic pathways (alongside hypothesis of spread perioperatively)

• Apoptosis + colony formation / metabolism
Treatment Methodology

**Dose**
- 2.2% and 3.6% sevoflurane
- 1.4% and 2.0% isoflurane
- 2 – 8 μg/ml propofol (lipid emulsion)

**Duration**
- 2 - 6 hours to reflect typical duration of surgery
Sevoflurane increases colony formation
MCF-7 (anchorage independent)
Respiration impaired and phenotype persists

MCF-7 Basal Respiration - 72h-post Rx

![Graph showing OCR (pmol/min) for MCF-7 with untreated control, rotenone, and sevoflurane treatments.]

MDA-MB-231 Basal Respiration - 72h-post Rx

![Graph showing OCR (pmol/min) for MDA-MB-231 with untreated control, rotenone, and sevoflurane treatments.]

**Oligomycin**

**FCC P**

Rotenone & antimycin A
Sevoflurane increases 4T1 lung metastasis in Balb/c tail vein inoculation model

Mouse Weights

4T1 Lung Metastasis

* * n.s.

Untreated Control
3.6% Sevoflurane
Lipid Control
8 µg/ml Propofol
Sevoflurane increases 4T1 lung metastasis in Balb/c tail vein inoculation model
Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial

Prof Daniel I Sessler, MD  Lijian Pei, MD  Prof Yuguang Huang, MD  Prof Edith Fleischmann, MD
Prof Peter Marhofer, MD  Prof Andrea Kurz, MD  et al.

Published: October 20, 2019  DOI: https://doi.org/10.1016/S0140-6736(19)32313-X

2132 patients enrolled and randomly assigned

1060 allocated regional anaesthesia-analgesia (paravertebral block and propofol)

17 excluded before surgery and did not receive allocated intervention
  7 not eligible
  5 patient’s decision
  2 surgery cancelled
  3 surgeon’s decision

1043 allocated regional anaesthesia-analgesia and included in primary analysis
  5 had paravertebral block failure and received general anaesthetic

27 lost to follow-up
  5 withdrew or did not respond
  3 study stopped
  19 had at least one follow-up visit then withdrew
  18 died after at least one follow-up visit

1072 allocated general anaesthesia (volatile anaesthetic sevoflurane) and opioid analgesia

7 excluded before surgery and did not receive allocated intervention
  4 not eligible
  3 patient’s decision

1065 allocated general anaesthesia and included in primary analysis
  1 received paravertebral block

40 lost to follow-up
  3 did not respond
  6 study stopped
  28 had at least one follow-up visit then withdrew
  3 received treatment but were non-eligible
  22 died after at least one follow-up visit
Breast cancer recurrence (%) vs. Time after surgery (years)

- General: 1065, 995, 796, 542, 313, 229, 187, 105
- Regional: 1043, 982, 781, 514, 284, 210, 176, 94

Adjusted hazard ratio 0.97, 95% CI 0.74-1.28; log-rank p=0.84
Does anaesthesia make a difference?

YES

NO

MAY BE!
What next?

40 hospitals taking part in Perioperative Quality Improvement Project (POQP)

**ASSESS ELIGIBILITY**
- Adult ≥ 50 years; scheduled major non-cardiac surgery under general anaesthesia

**INFORMED CONSENT**
- Patient decline to participate in VITAL
- Patient agree to participate in VITAL

**RANDOMISE**
- 2420 patients

**INTRAVENOUS ANAESTHESIA**
- 1210 patients

**INHALATIONAL ANAESTHESIA**
- 1210 patients

**LOCAL DATA MONITORING**
- POQP dataset completeness
- Anaesthesia allocation compliance

**PRIMARY OUTCOME**
- Days alive and at home at 30 days (DAH30)

**SECONDARY OUTCOMES**
- Days alive and at home at 90 days (DAH90)
- 30 day and six-month survival
- Quality of recovery after anaesthesia
- Patient satisfaction with anaesthesia
- Major perioperative complications
- Accidental awareness under anaesthesia
- Health Resource use during the six months after surgery
- Quality of Life and health utility at six months after surgery
Award for Innovation in Anaesthesia, Critical Care and Pain 2020 – winner announced

Friday 10 January 2020

The Association of Anaesthetists has announced the winner for its annual 2020 Award for Innovation in Anaesthesia, Critical Care and Pain:

- SageTech Automated Extraction Machine - A unique process to capture, extract and purify inhalational anaesthetics such that they can be placed back on the market under licence. This will create the first ever circular economy for a pharmaceutical product in the UK. SageTech’s technology will reduce both the cost and the environmental pollution of anaesthesia.
## Opioids and Cancer

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>In vitro</th>
<th>In vivo animal</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung adenocarcinoma</td>
<td>Increase in proliferation and invasion. Stimulation of EMT transformation</td>
<td>Tumor growth increase after short-term exposure but decrease after long-term treatment</td>
<td>Decrease in RFS and OS in patients undergoing surgery and those with metastatic disease</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Pro- and antitumoral effects</td>
<td>Mixed findings</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Antiproliferative effects in some cell lines</td>
<td>No studies available</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>Predominant antiproliferative effects in oesophageal and gastric cells. No effect on liver and pancreatic cell lines.</td>
<td>Inhibition of tumor growth in gastric cancer mouse model.</td>
<td>Mixed findings</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>No effect on cell proliferation</td>
<td>No studies available</td>
<td>Association between the use of regional intraoperative anaesthesia and low opioid consumption, and longer PFS</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Antiproliferative effects</td>
<td>Inhibition of tumor growth</td>
<td>No studies available</td>
</tr>
</tbody>
</table>

RFS: recurrence free survival, PFS: progression free survival.
Local and regional anaesthesia in cancer

- Anti-inflammatory
- No evidence of cancer recurrence (animal models)
- Opioids in regional anaesthesia - ? Safe
- Regional with TIVA - probably best technique
Suppression of mitochondrial respiration with local anesthetic ropivacaine targets breast cancer cells
Glucocorticoids are widely used for prevention of chemotherapy-induced nausea and vomiting and as adjuvant therapy for pain control in patients with known metastatic cancer, without concern for worsening disease.

Dexamethasone for PONV - inconclusive evidence

Muscle relaxants - No clinical trials

Beta blockers - inconclusive evidence
Fig 2 Summary of the potential impact of commonly used anaesthetic agents upon cancer progression, metastasis and recurrence.
Can anaesthetists make a difference in cancer care ....

YES!
Pre-assessment unit – Royal Marsden
Patient, Time Specific, Evidence Based Interventions – Key 5 Pre Op Elements + 2 extra

Preoperative Anaemia among the elderly undergoing major abdominal surgery (PANAMA) study: Protocol for a single-center observational cohort study of preoperative anaemia management and the impact on healthcare outcomes.

Iron and cancer

GLU
Cystine
Cysteine
Glutamate
Glutathione
PUFAs-OH
PUFAs-OCH

STEAP3
DMT1
Fe3+
Fe2+

Lipid peroxidation
FERROPTOSIS
ROS

‘only OXYGEN can carry you to the top of the Everest’