The ROYAL MARSDEN
NHS Foundation Trust

Anaesthesia and Cancer

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Life demands excellence
NHS

ICR The Institute of Cancer Research

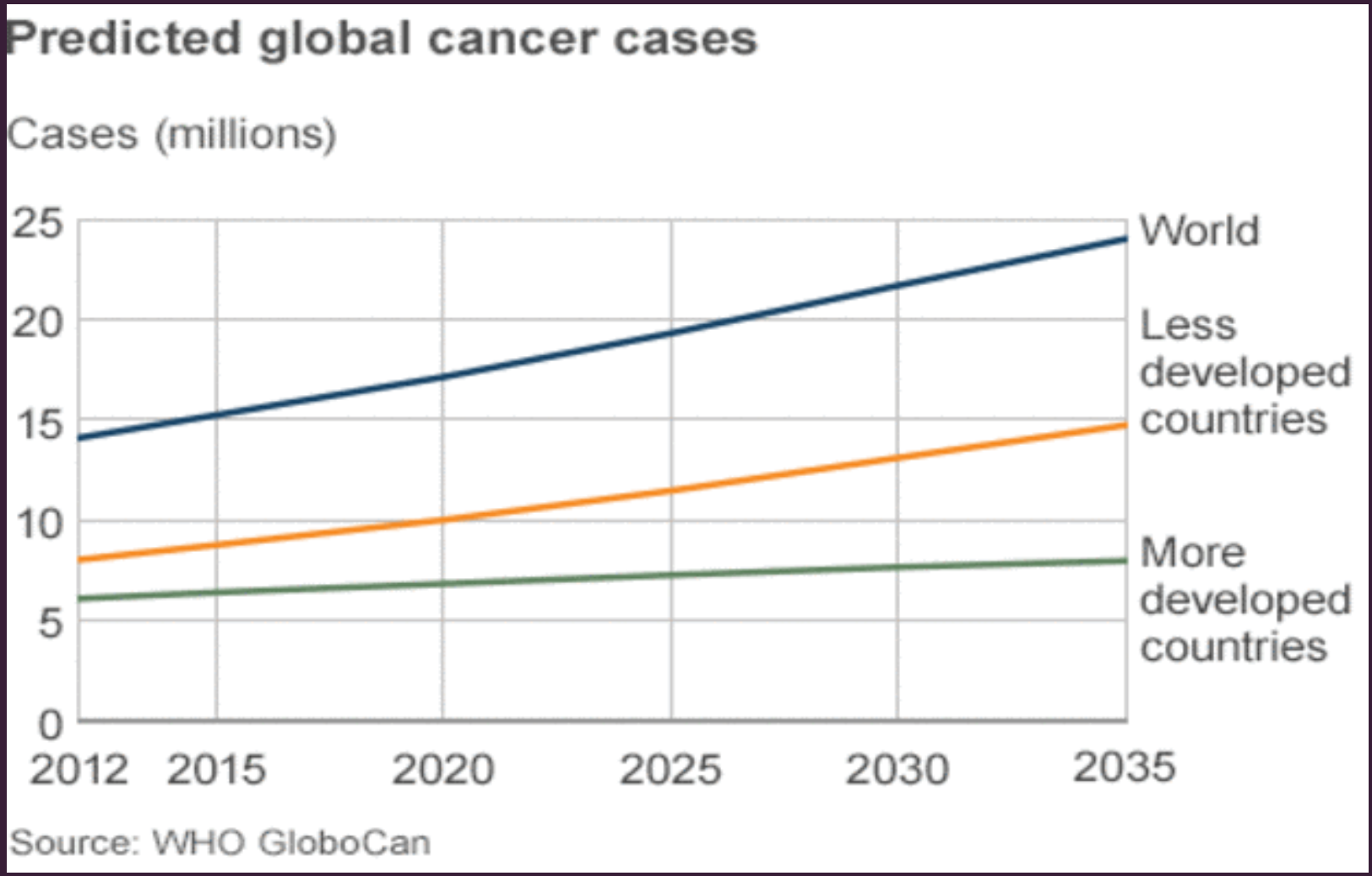

FOUNDED IN 1851 BY
WILLIAM MARSDEN MD

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

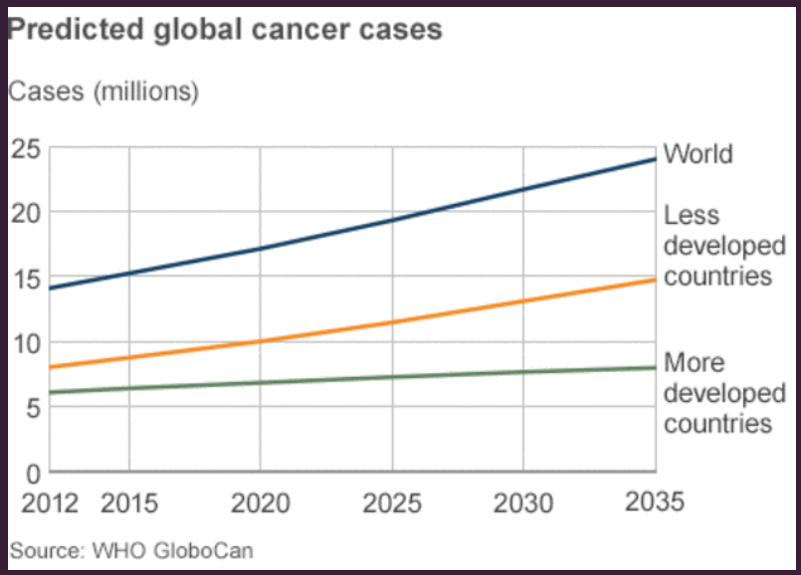
…to gas or not to gas (in cancer)…

Cancer – the burden



Cancer surgery

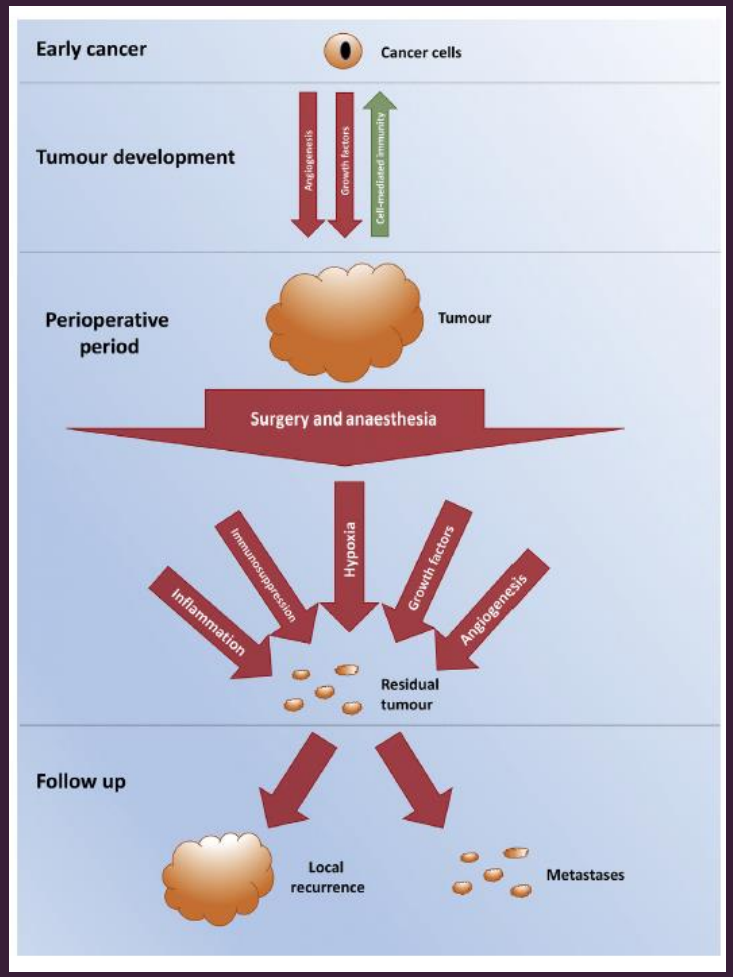
- 80% of patients require surgery
- Many multiple times



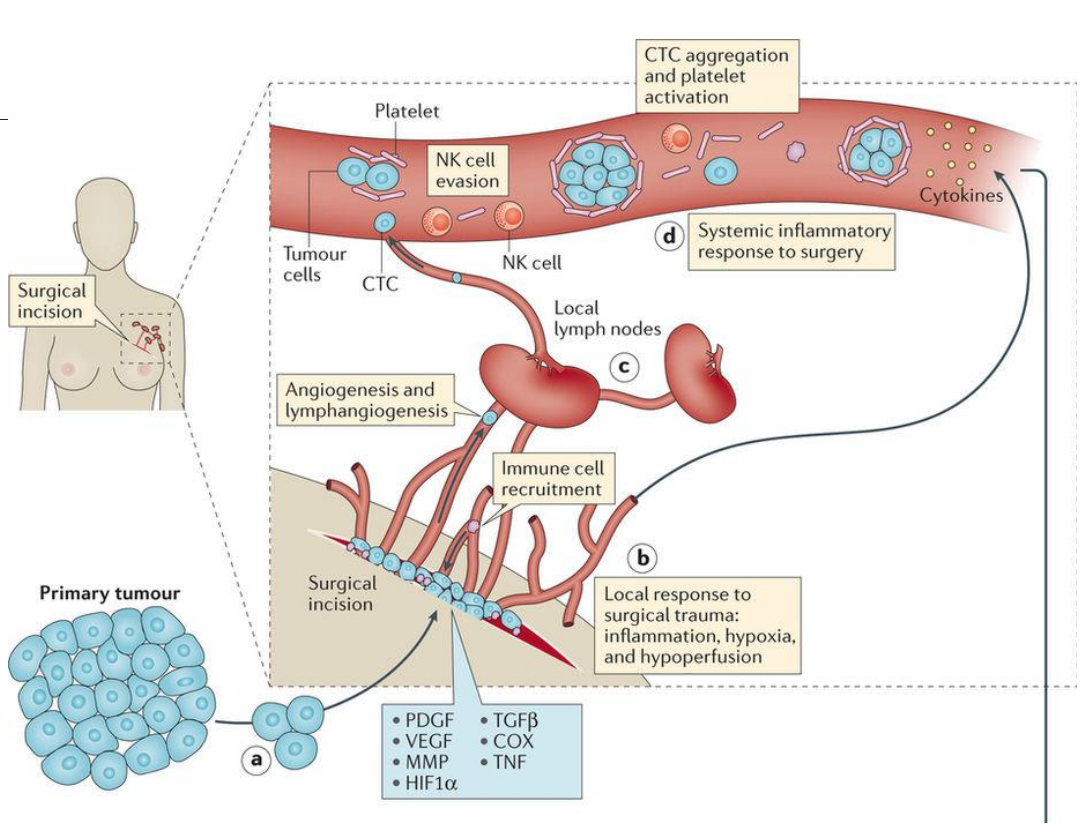
- By 2030, over 45 million cancer operations

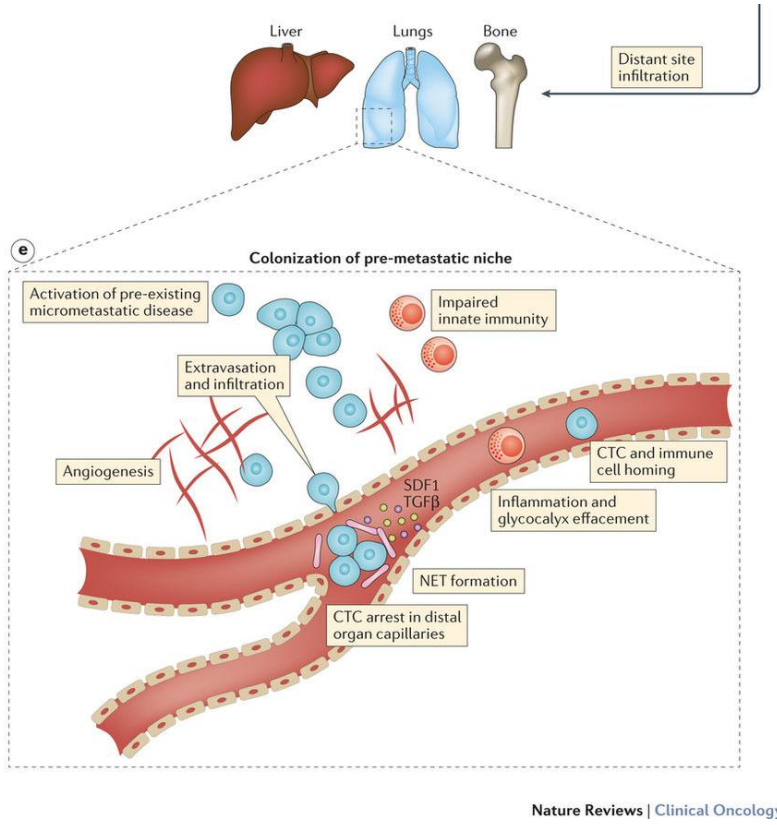
Cancer – metastases

- All patients have circulating tumour cells
- Tumour handling / surgery increases numbers

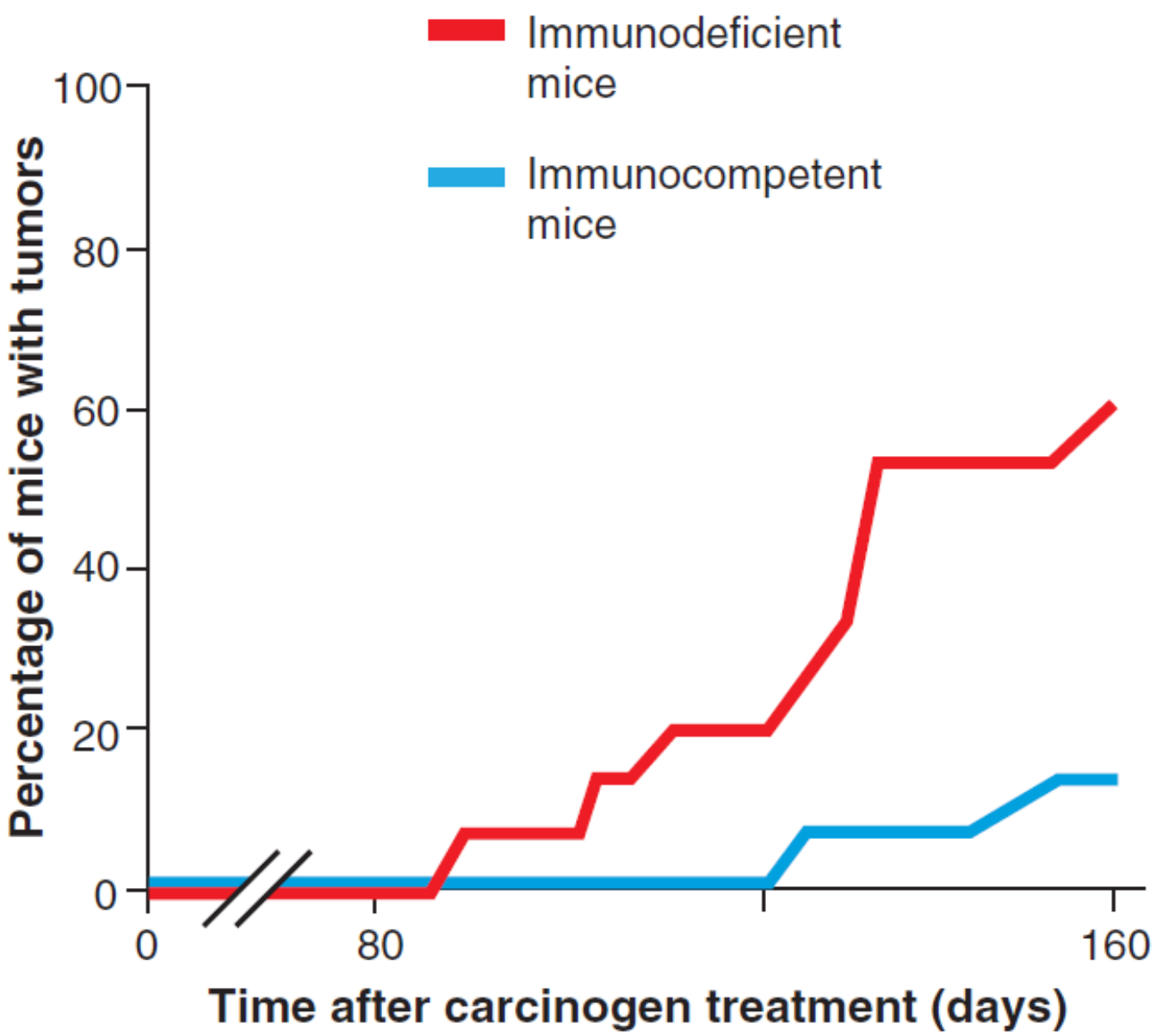


Surely surgery is curative….





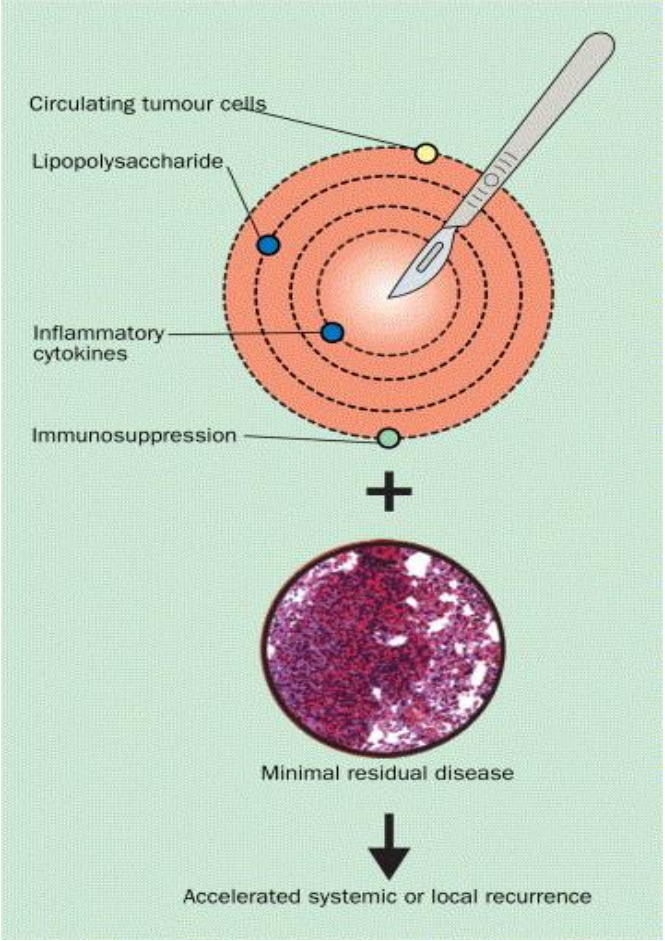
Hiller J*, Perry N* et al *Nat Rev Clin Onc* 2018



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)

Anaesthesics & the Cancer Cell

Anesthetic Drugs Accelerate the Progression of Postoperative Metastases of Mouse Tumors

Mouse lungs 15 days after IV injection of 1 x 10^6 T10 sarcoma cells

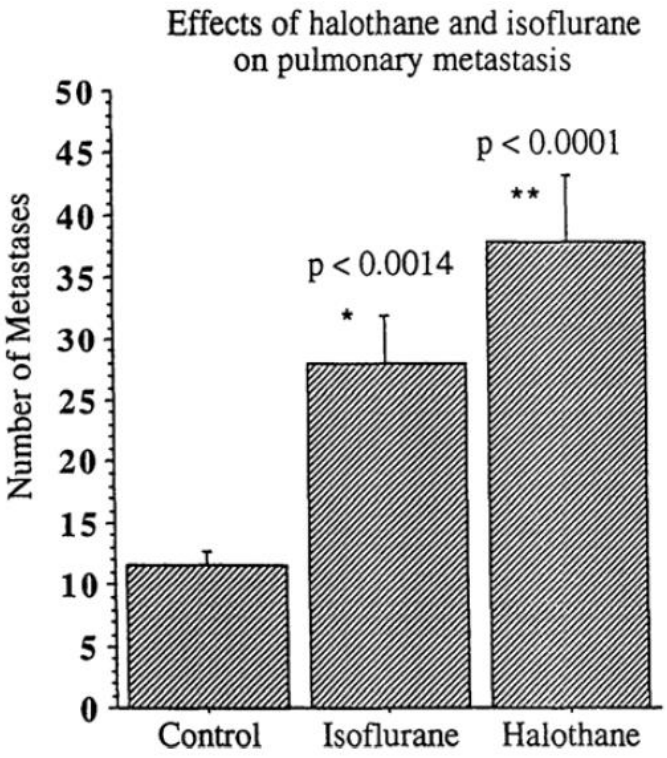
no anaesthetic

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.

Shapiro *et al. J. Clin. Invest. 1981*

Anaesthesia.....



Moudgil CJA 1997

Anesthesiology 2006; 105:660–4

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

Aristomenis K. Exadaktylos, M.D., Donal J. Buggy, M.D., M.Sc., D.M.E., F.R.C.P.I., F.C.A.R.C.S.I., F.R.C.A.,† Denis C. Moriarty, F.C.A.R.C.S.I.,‡ Edward Mascha, Ph.D.,§ Daniel I. Sessler, M.D., Ph.D.‖*

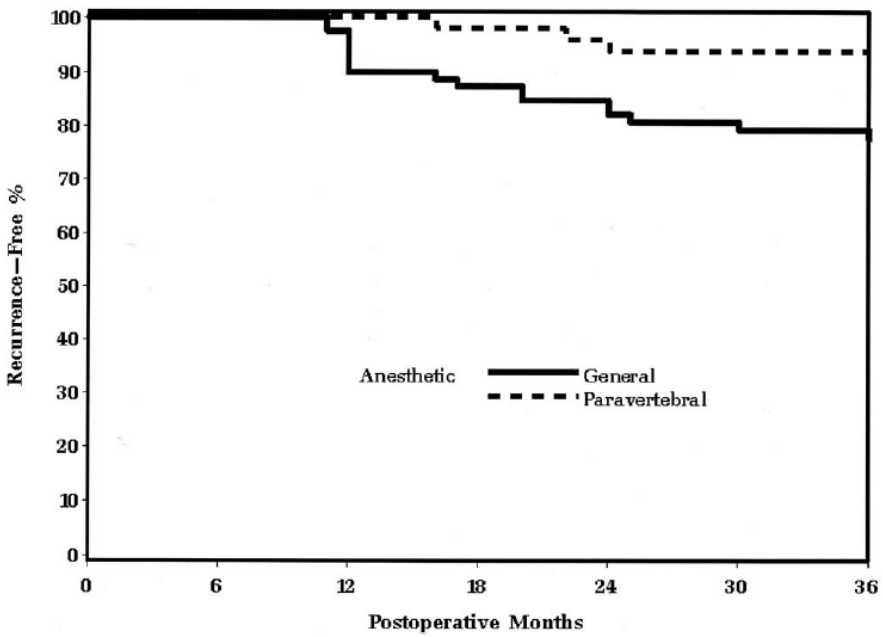
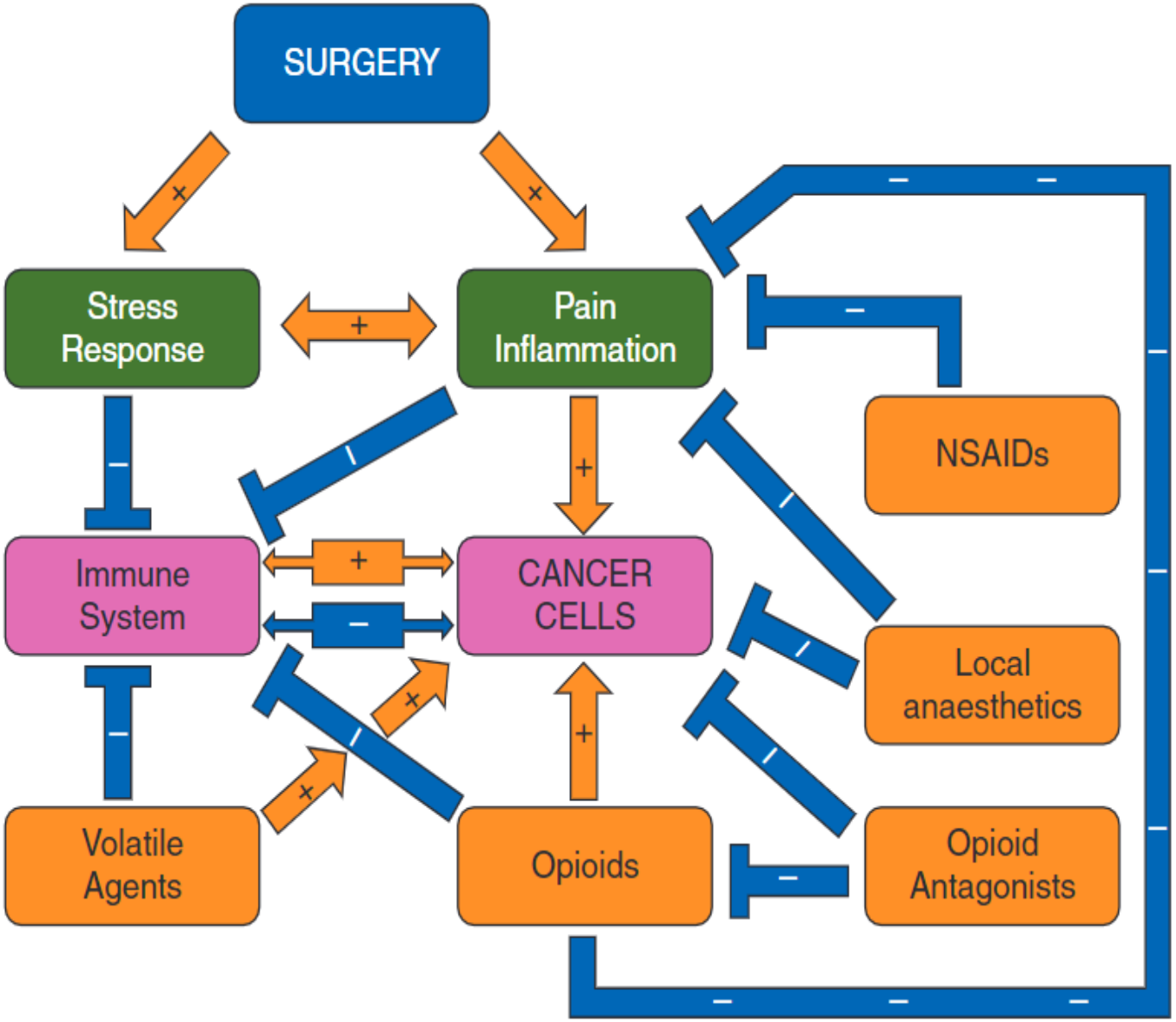


Fig. 1. Univariable association between paravertebral block and cancer recurrence, $P = 0.013$ log-rank test. The association remained significant ($P = 0.012$) in a multivariable model adjusting for histologic grade and number of axillary nodes.

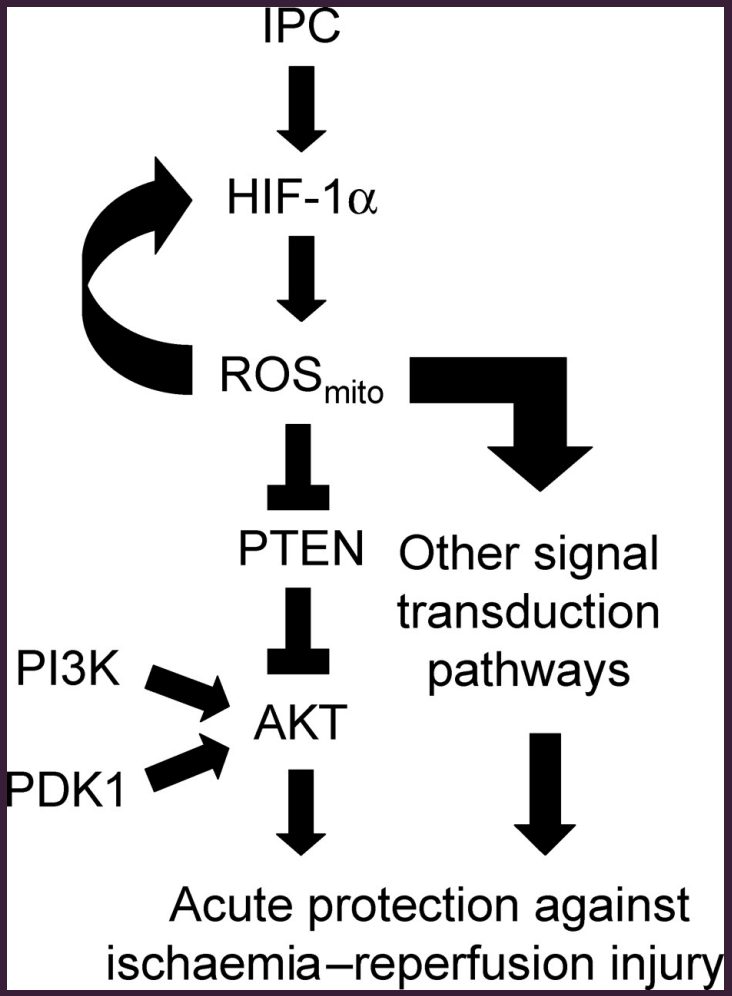


British Journal of Anaesthesia, 115 (S2): ii34–ii45 (2015)

Volatile vs propofol anaesthesia

Propofol vs volatile - science

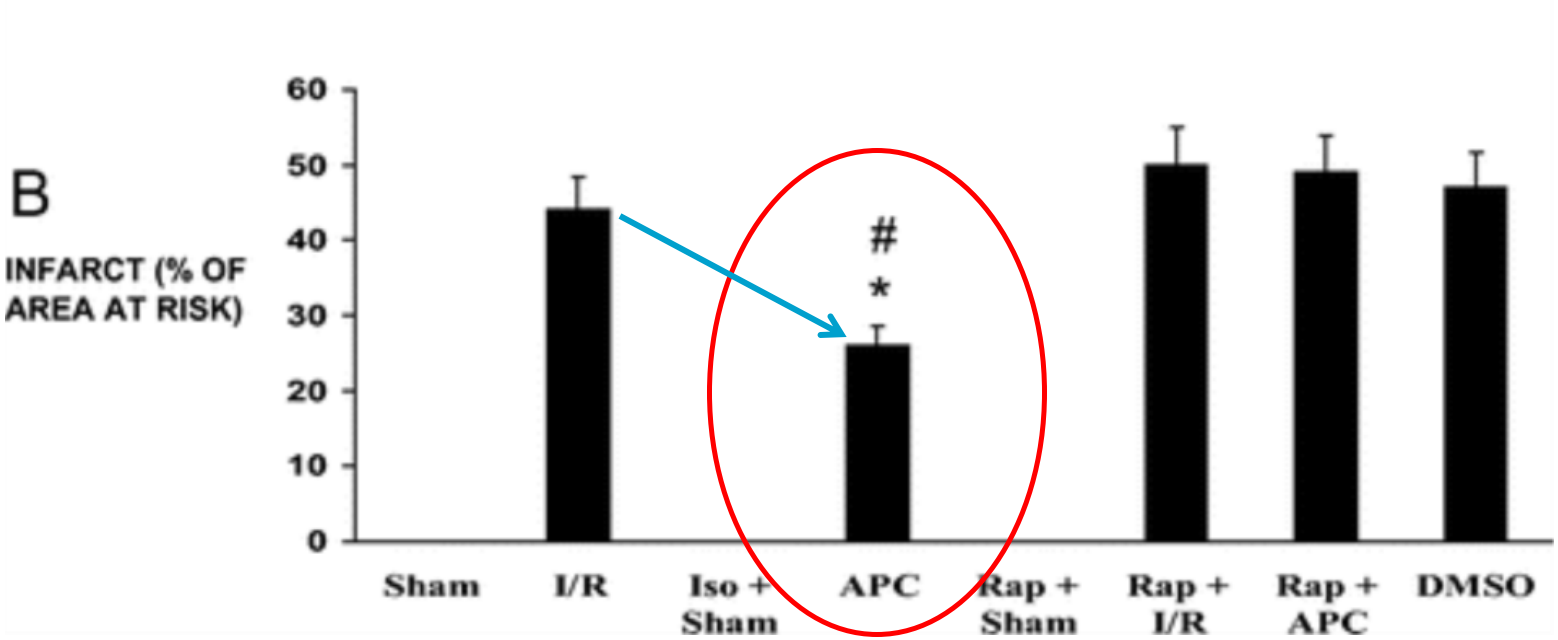
Ischaemic preconditioning

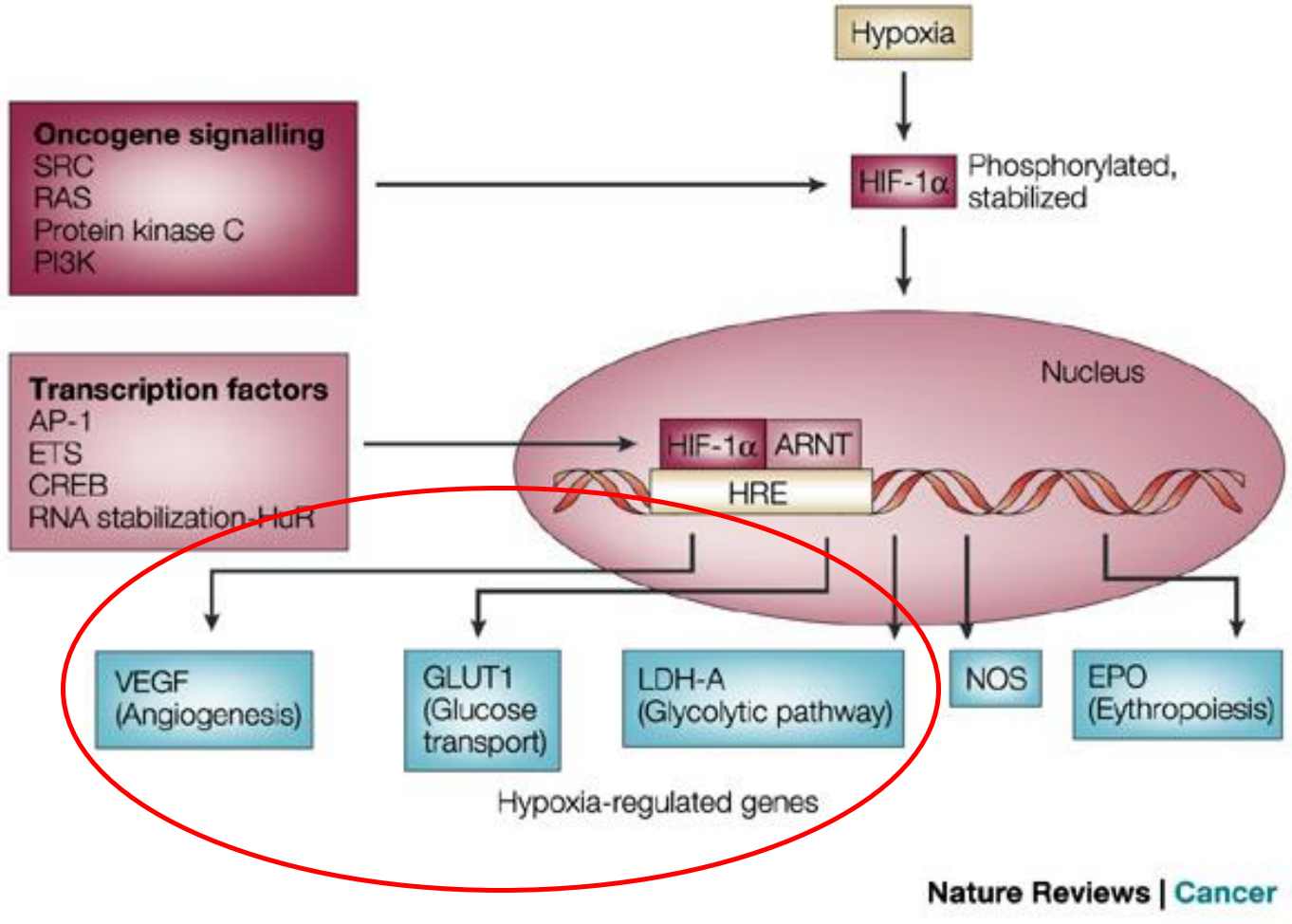


Anesthesiology 2008; 108:415–25

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., Zhiyi Zuo, M.D., Ph.D.,† Suzan Abedat, M.Sc.,‡ Ronen Beeri, M.D.,§ Yaacov Gozal, M.D.‖*





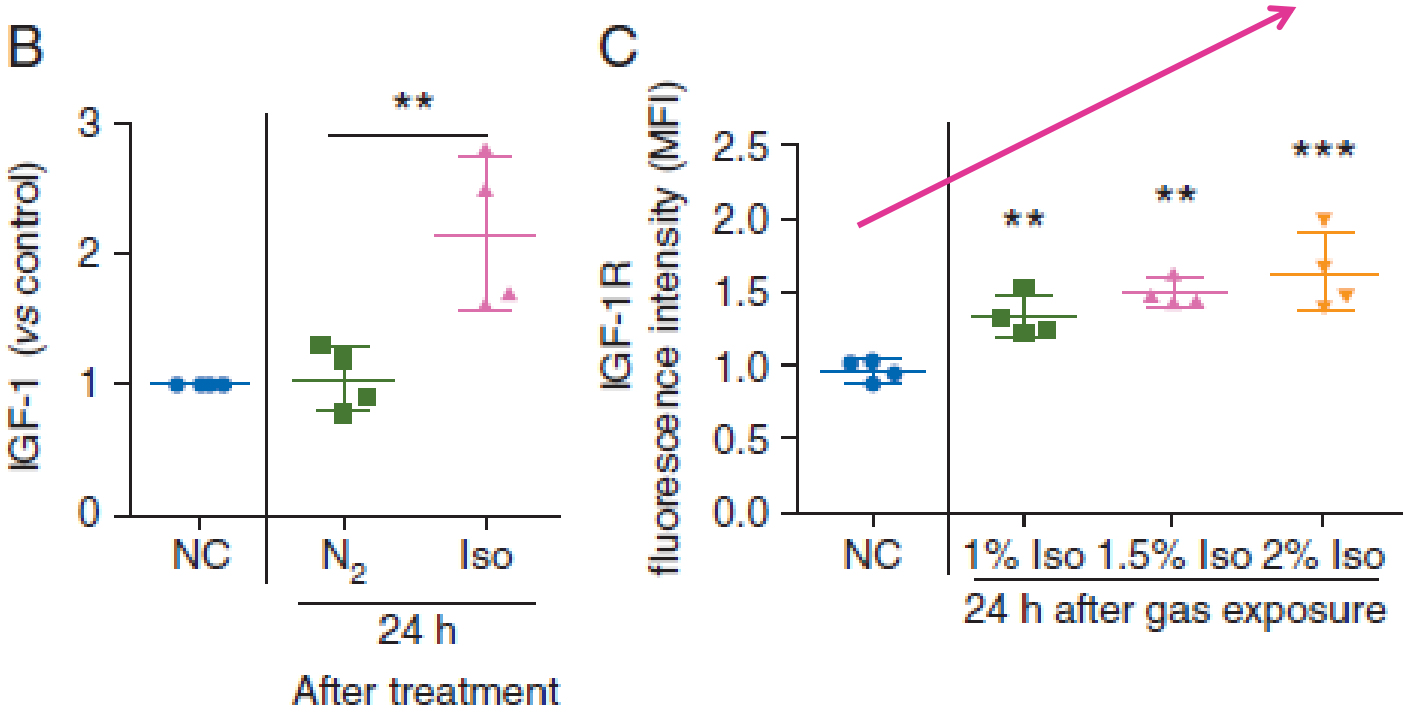
Harris. Nature Reviews Cancer 2002

British Journal of Anaesthesia **114** (5): 831–9 (2015)
Advance Access publication 13 December 2014 · doi:10.1093/bja/aeu408

BJA

Impact of isoflurane on malignant capability of ovarian cancer *in vitro*‡

X. Luo[1,3†], H. Zhao[3†], L. Hennah[3], J. Ning[3], J. Liu[1], H. Tu[2] and D. Ma[3*]



FULL PAPER

BJC

British Journal of Cancer (2014) 111, 1338–1349 | doi: 10.1038/bjc.2014.426

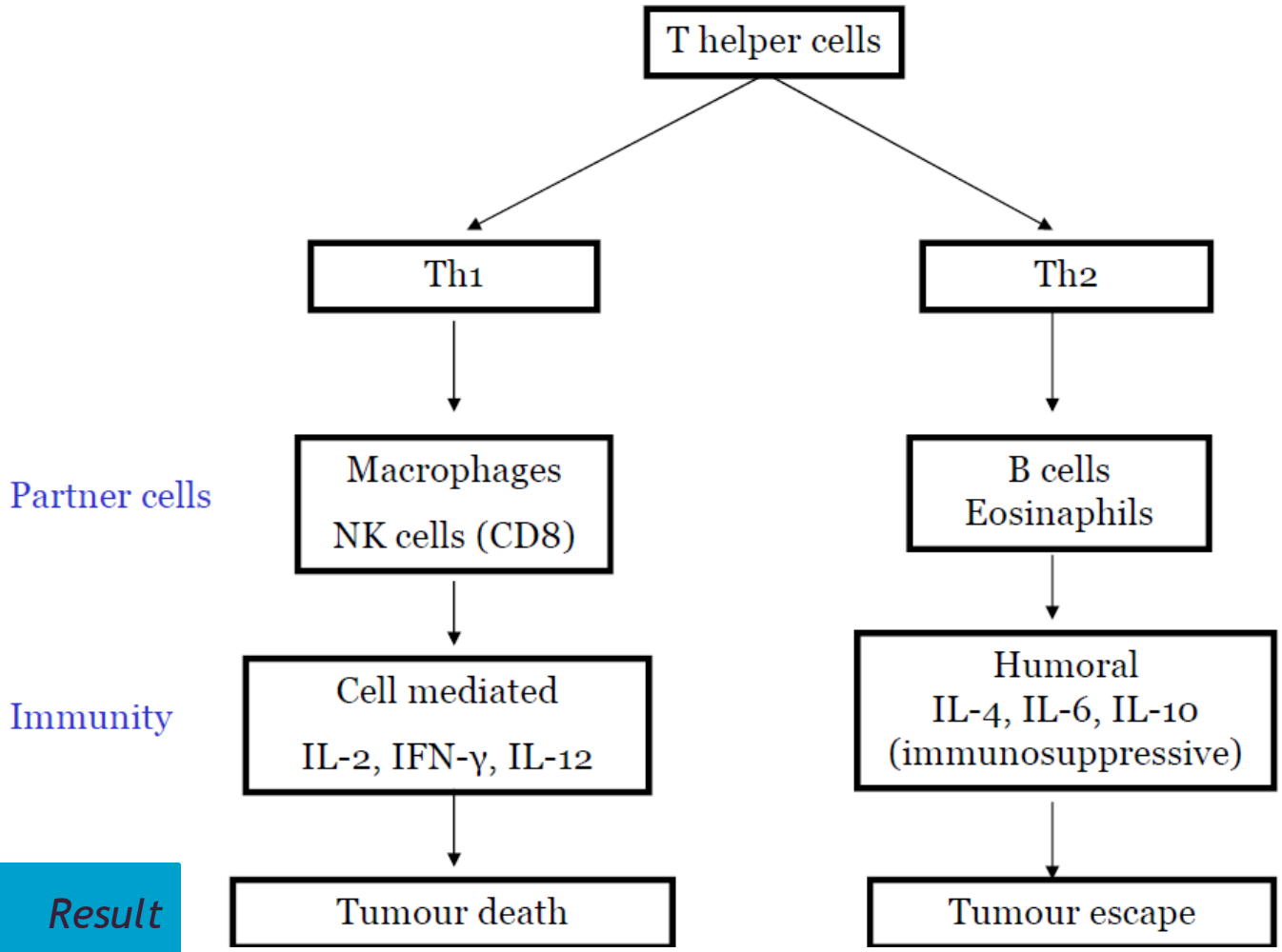
Keywords: prostate cancer; isoflurane; propofol; cancer cell malignancy

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

H Huang[1,2,4], L L Benzonana[1,4], H Zhao[1,4], H R Watts[1], N J S Perry[1], C Bevan[3], R Brown[3] 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 $CoCl_2$. Propofol also prevented isoflurane-induced HIF-1α activation, and partially reduced cancer cell malignant activities.

Cell mediated immunity vs humoral



Propofol ↑TH1… Iso ↓Th1

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

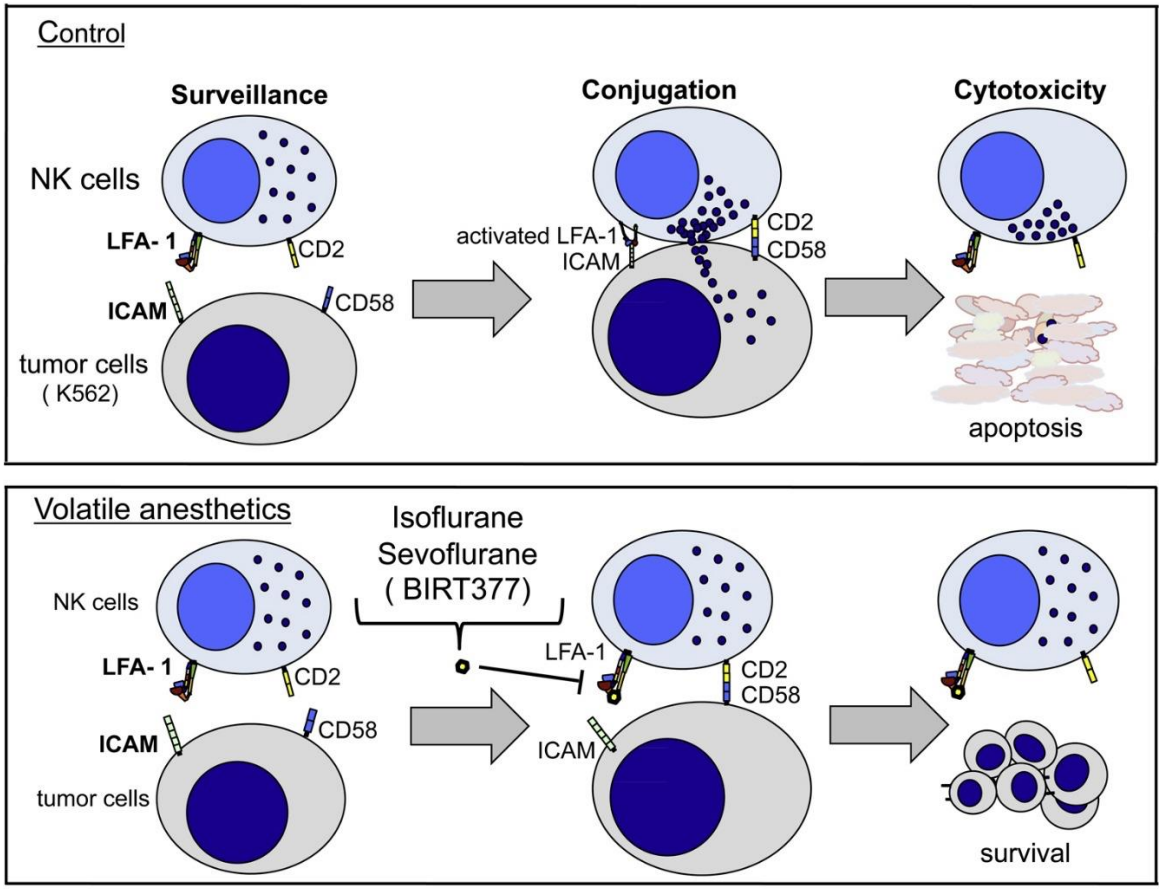
	Propofol (n = 9)	Isoflurane (n = 9)
Before induction of anaesthesia	2.4 (2.2–2.9 [1.8–3.1])	2.6 (2.5–3.1 [2.3–3.4])
1st postoperative day	2.0 (1.8–2.4 [1.1–2.9])	1.2 (0.9–1.9 [0.2–2.8])
3rd postoperative day	2.4 (2.0–2.5 [1.4–3.0])	1.1 (0.9–1.4 [0.7–3.7])
5th postoperative day	2.4 (2.1–2.8 [1.2–3.1])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

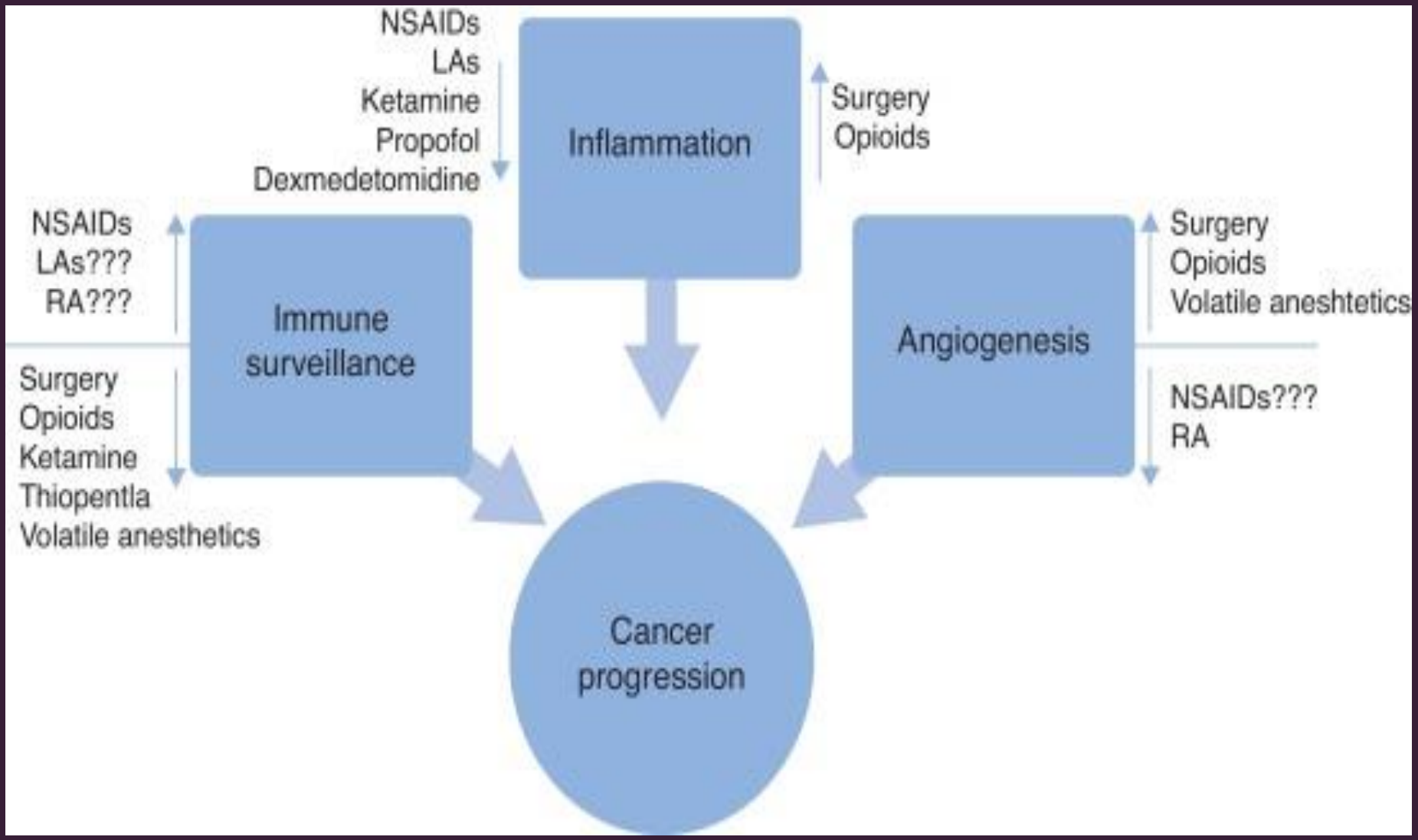
*Comparison between values before induction of anaesthesia and the mean postoperative values. Area under the curve for Th1/Th2 ratio was smaller in the isoflurane group than in the propofol group (p = 0.009).

The effect of different anesthetics on tumor cytotoxicity by natural killer cells

Kazumasa Tazawa[a,c], Sophia Koutsogiannaki[a,b], Matthew Chamberlain[a], Koichi Yuki[a,b,*]

[a] *Department of Anesthesiology, Perioperative and Pain Medicine, Cardiac Anesthesia Division, Boston Children's Hospital, Boston, MA 02115, USA*
[b] *Department of Anaesthesia, Harvard Medical School, Boston, MA 02115, USA*
[c] *Department of Anesthesia, Saitama Medical School, Saitama 350-8550, Japan*





BJA: British Journal of Anaesthesia, Volume 115, Issue suppl_2, December 2015, Pages ii34–ii45

To gas or not to gas?

Clinical evidence?

Propofol vs volatile – clinical data

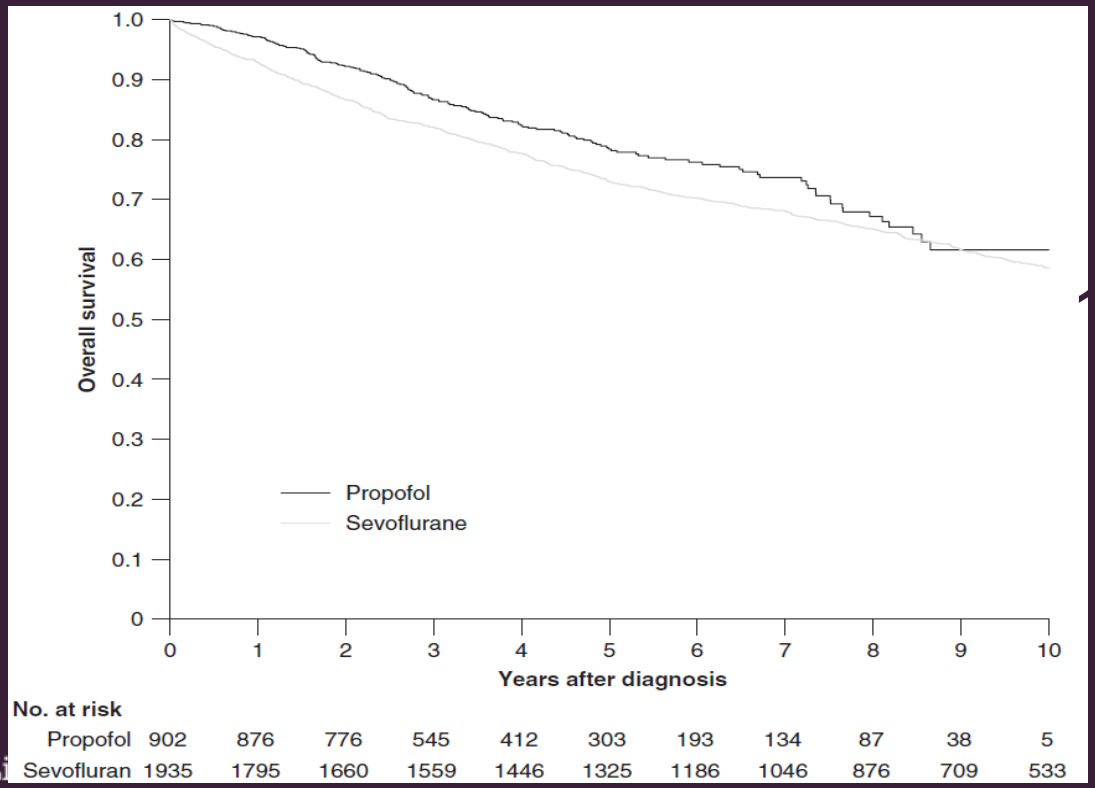
Upsala Journal of Medical Sciences. 2014; 119: 251–261

informa
healthcare

ORIGINAL ARTICLE

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

MATS ENLUND[1], ANDERS BERGLUND[3], KALLE ANDREASSON[2], CATHARINA CICEK[2], ANNA ENLUND[1] & LEIF BERGKVIST[2]



2500 pts
years inclusion
Non-sig after
adjustment

Long-term Survival for Patients Undergoing Volatile *versus* IV Anesthesia for Cancer Surgery

A Retrospective Analysis

Timothy J. Wigmore, M.A., F.R.C.A., F.F.I.C.M., F.C.I.C.M., Kabir Mohammed, M.Sc., Shaman Jhanji, Ph.D., M.R.C.P., F.R.C.A., F.F.I.C.M.

- All elective cases June 2010 to May 2013 (11716 cases)
- 3316 individual patients inhalational only
- 3714 patients TIVA only

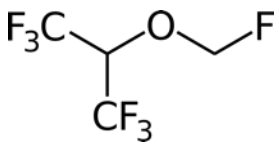
Long-term Survival for Patients Undergoing Volatile *versus* IV Anesthesia for Cancer Surgery

A Retrospective Analysis

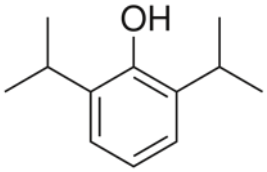
Timothy J. Wigmore, M.A., F.R.C.A., F.F.I.C.M., F.C.I.C.M., Kabir Mohammed, M.Sc., Shaman Jhanji, Ph.D., M.R.C.P., F.R.C.A., F.F.I.C.M.

- Outcome – Survival at censure date (31/10/14)
- Cox proportional hazard regression model (uni)
- Propensity score for baseline characteristics

Inhalational *versus* intravenous anaesthesia

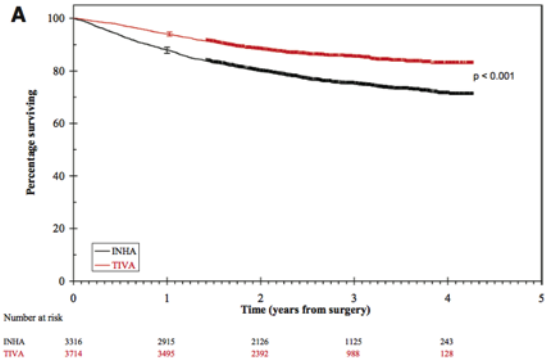


Sevoflurane

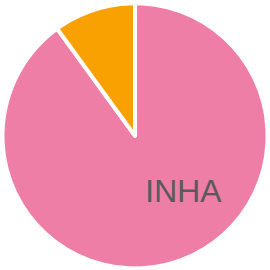


Propofol

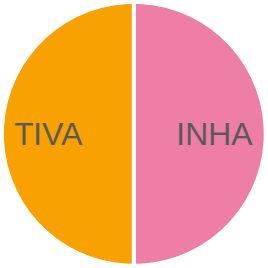
Overall



TIVA / other



United Kingdom



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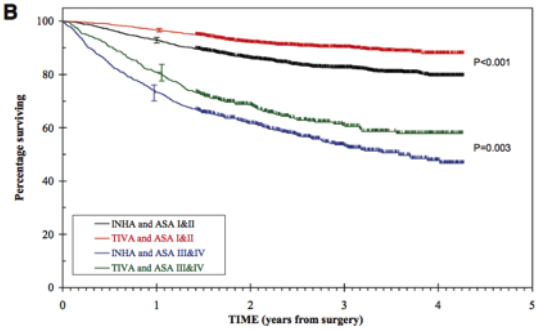
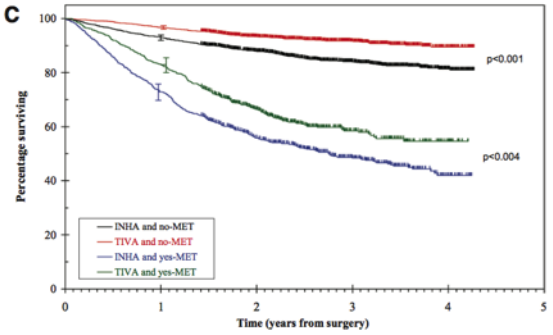
By co-morbid status (ASA score)

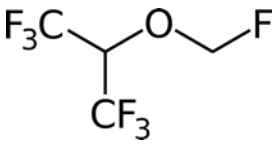


By presence/absence of metastases

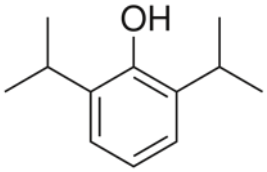


Wigmore, T., Mohammed K., Jhanji, S. Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery. *Anesthesiology* 2016

Inhalational *versus* intravenous anaesthesia

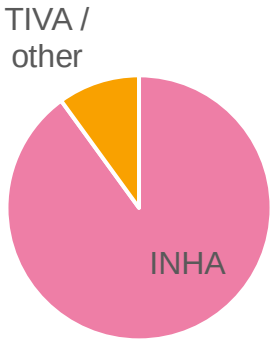


Sevoflurane

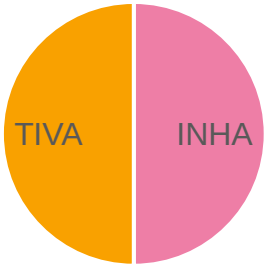


Propofol

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



United Kingdom



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BJA

British Journal of Anaesthesia, 115 (S2): ii34–ii45 (2015)

doi: 10.1093/bja/aev375
Regional Anaesthesia

Regional anaesthesia and analgesia: relationship to cancer recurrence and survival

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BJA
British Journal of Anaesthesia

Volume 113, Number S1, July 2014

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

EDITORIAL

Special issue on anaesthesia and cancer

D. J. Buggy[1]* and H. C. Hemmings[2]

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[2] Weill Cornell Medical College, New York, USA
*Corresponding author: E-mail: donal.buggy@ucd.ie

SCIENTIFIC REPORTS

OPEN

Impact of anesthetic agents on overall and recurrence-free survival

PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

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

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

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"

in partnership with

Elucidate impact of inhalational versus intravenous anaesthesia upon:

1) Cancer cell phenome

2) Cancer cell molecular signalling and metabolism

In order to:

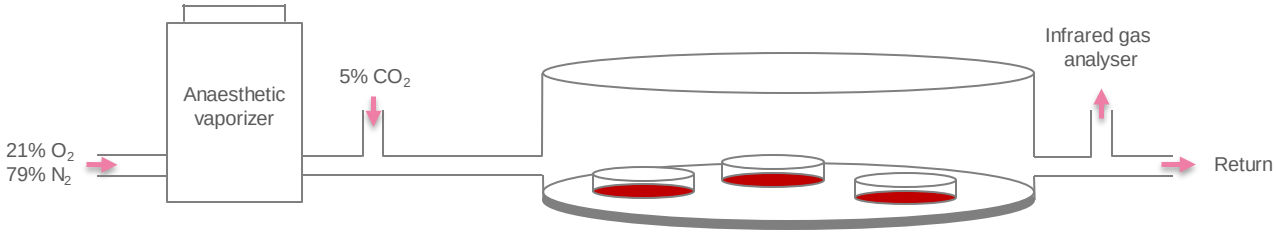
1) Identify specific vulnerabilities to postoperative cancer progression

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

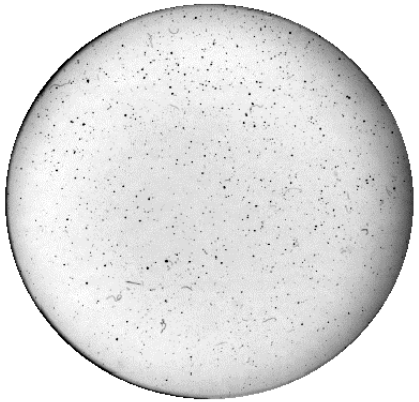
- 2.2% and 3.6% sevoflurane
- 1.4% and 2.0% isoflurane
- 2 – 8 µg/ml propofol (lipid emulsion)

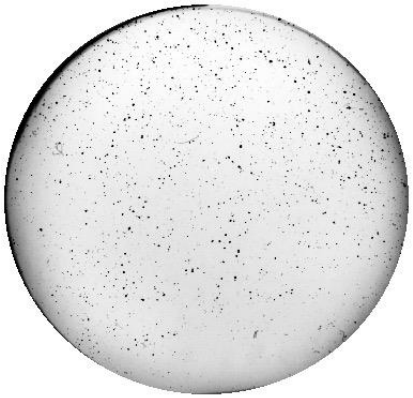
Duration

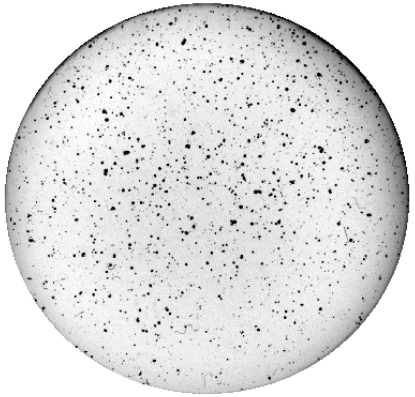
- 2 - 6 hours to reflect typical duration of surgery

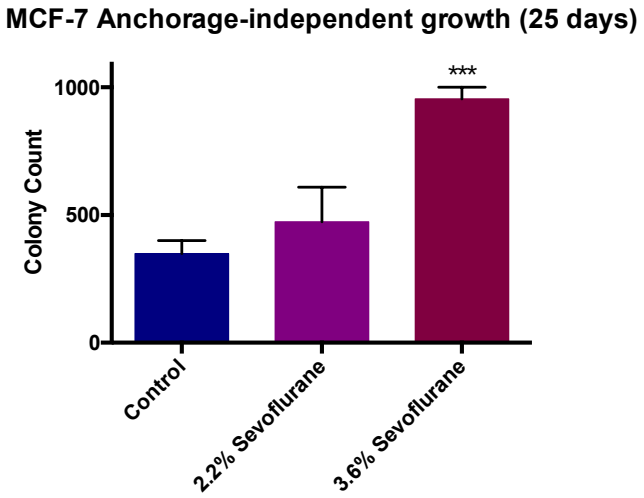
Sevoflurane increases colony formation

MCF-7 (anchorage independent)

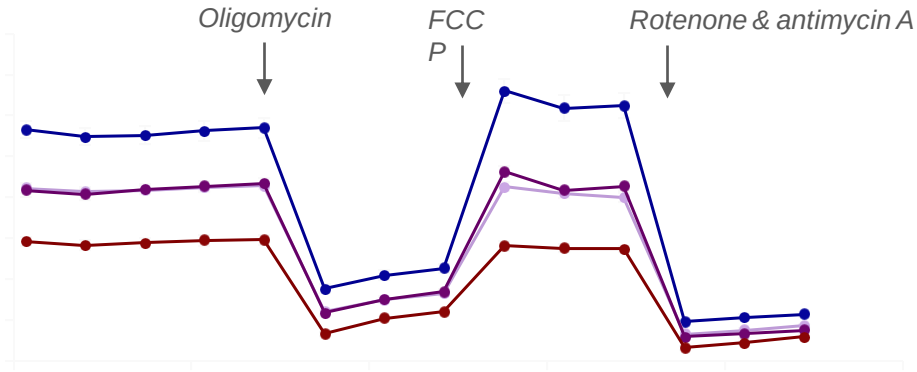


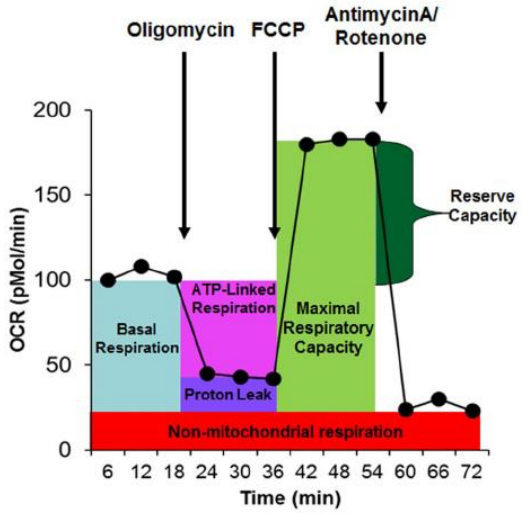


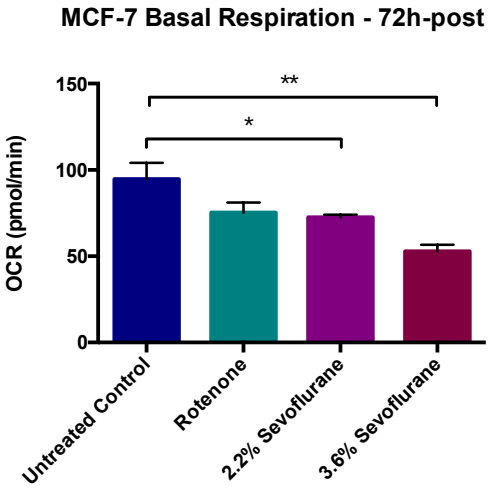


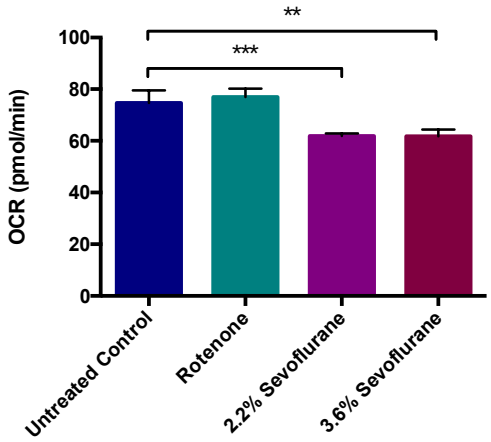


Respiration impaired and **phenotype persists**

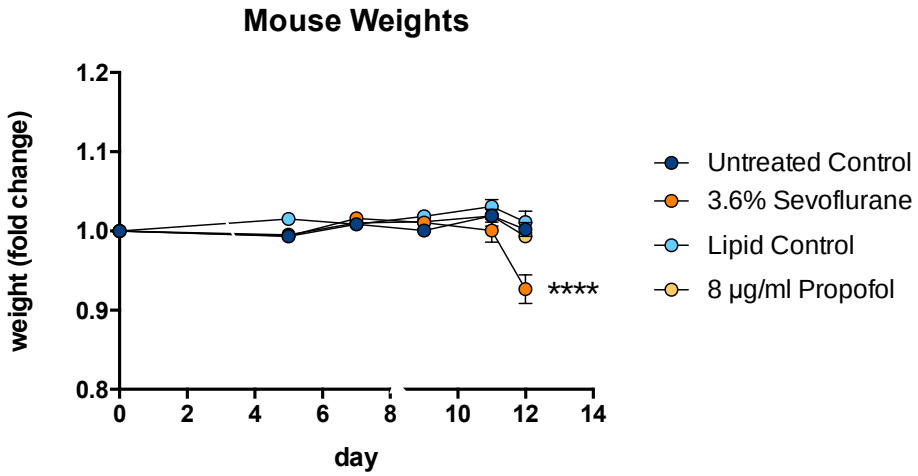


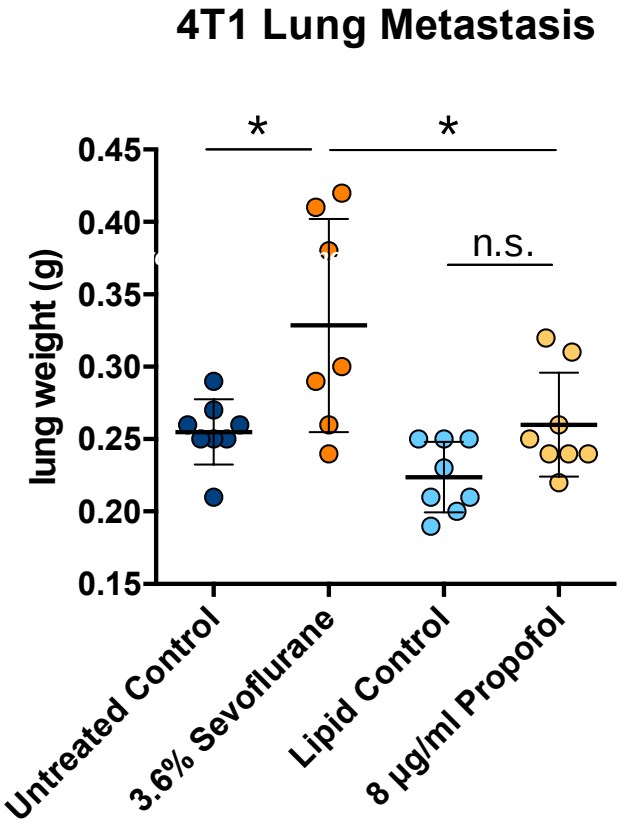




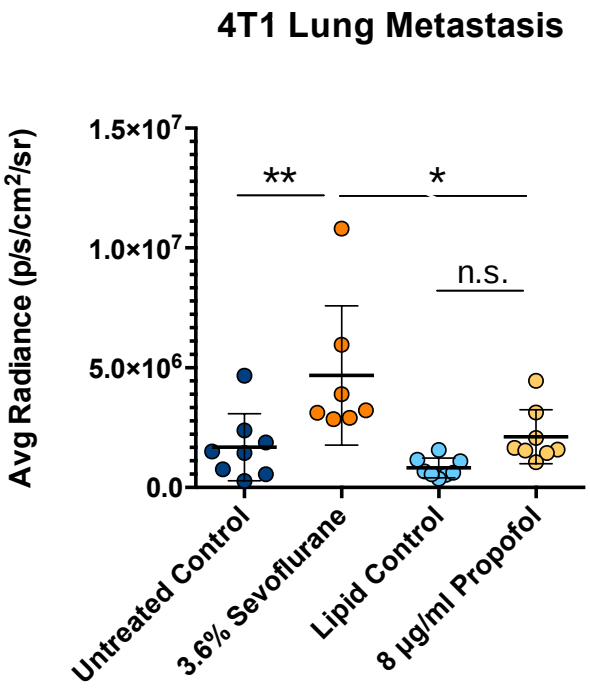


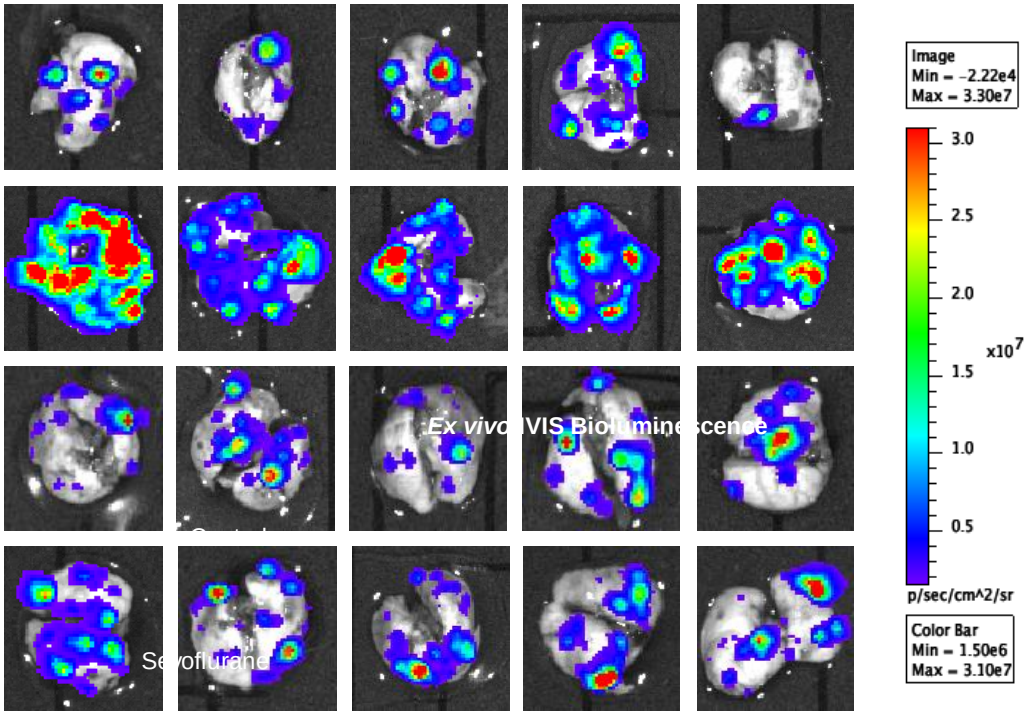
Sevoflurane increases 4T1 lung metastasis in Balb/c tail vein inoculation model





Sevoflurane increases 4T1 lung metastasis in Balb/c tail vein inoculation model





ARTICLES | VOLUME 394, ISSUE 10211, P1807-1815, NOVEMBER 16, 2019

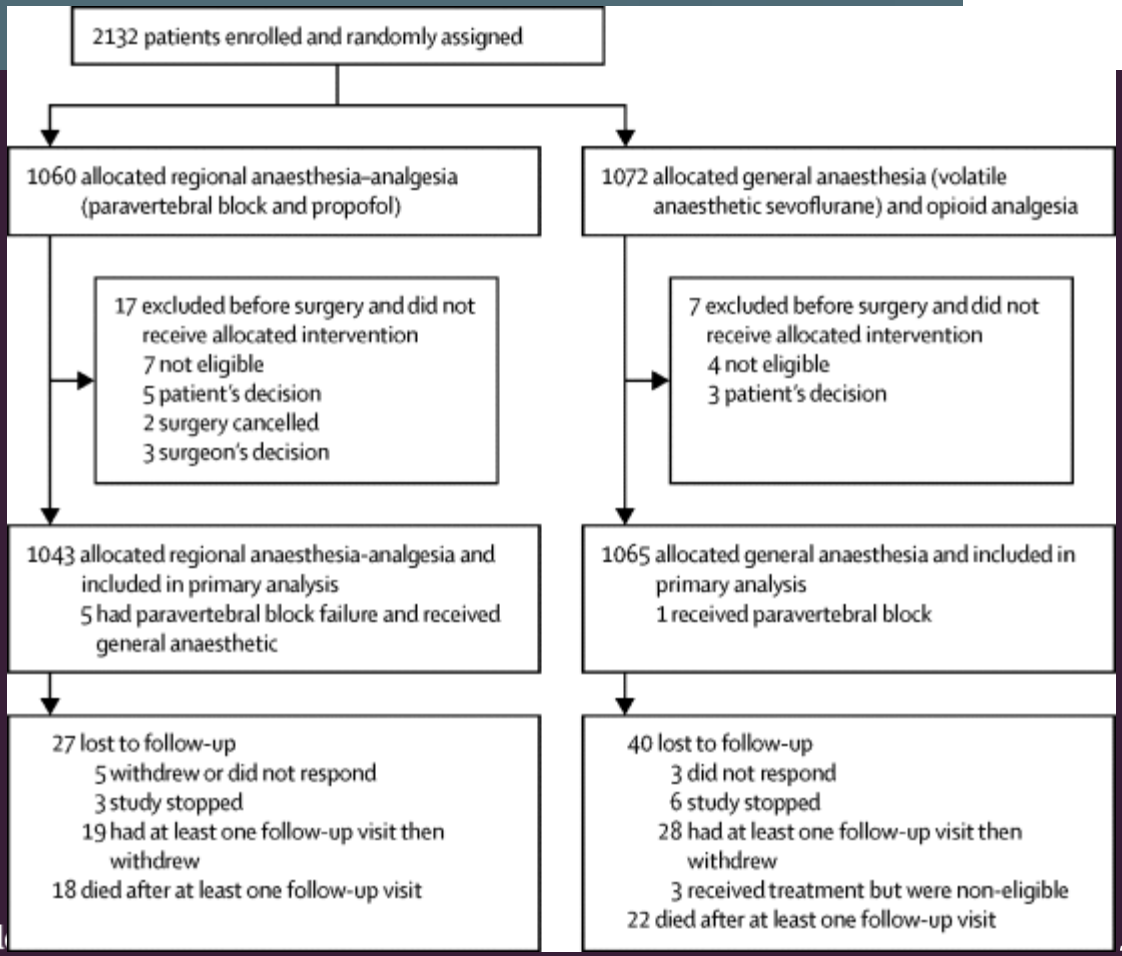
Purchase Sub

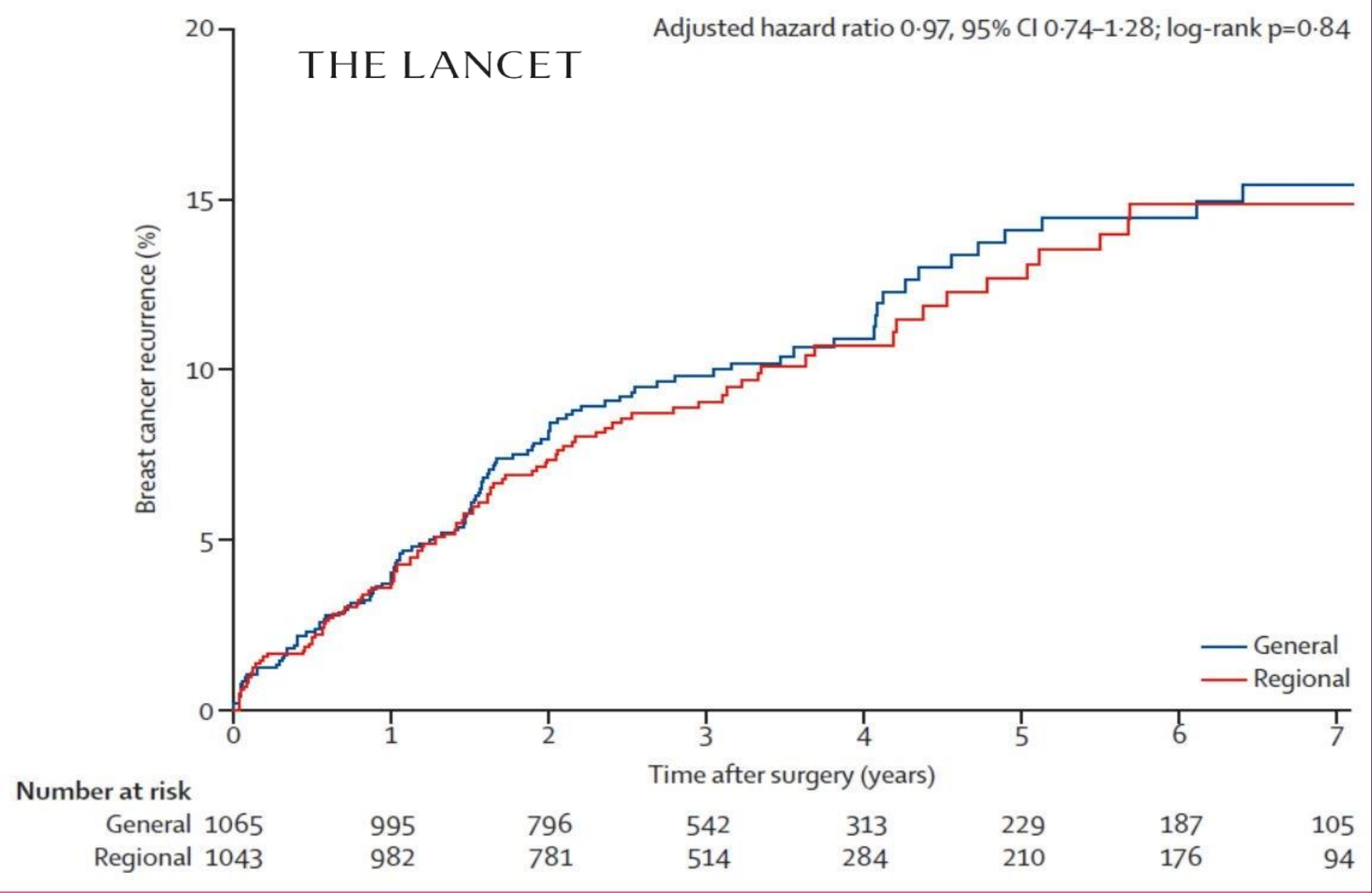
Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial

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. Show all authors • Show foo

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

THE LANCET




THE LANCET
Adjusted hazard ratio 0·97, 95% CI 0·74–1·28; log-rank p=0·84
Breast cancer recurrence (%)
20
15
10
5
0
0
1
2
3
4
5
6
7
Time after surgery (years)
General
Regional
Number at risk
General 1065 995 796 542 313 229 187 105
Regional 1043 982 781 514 284 210 176 94

Does anaesthesia make a difference?

YES

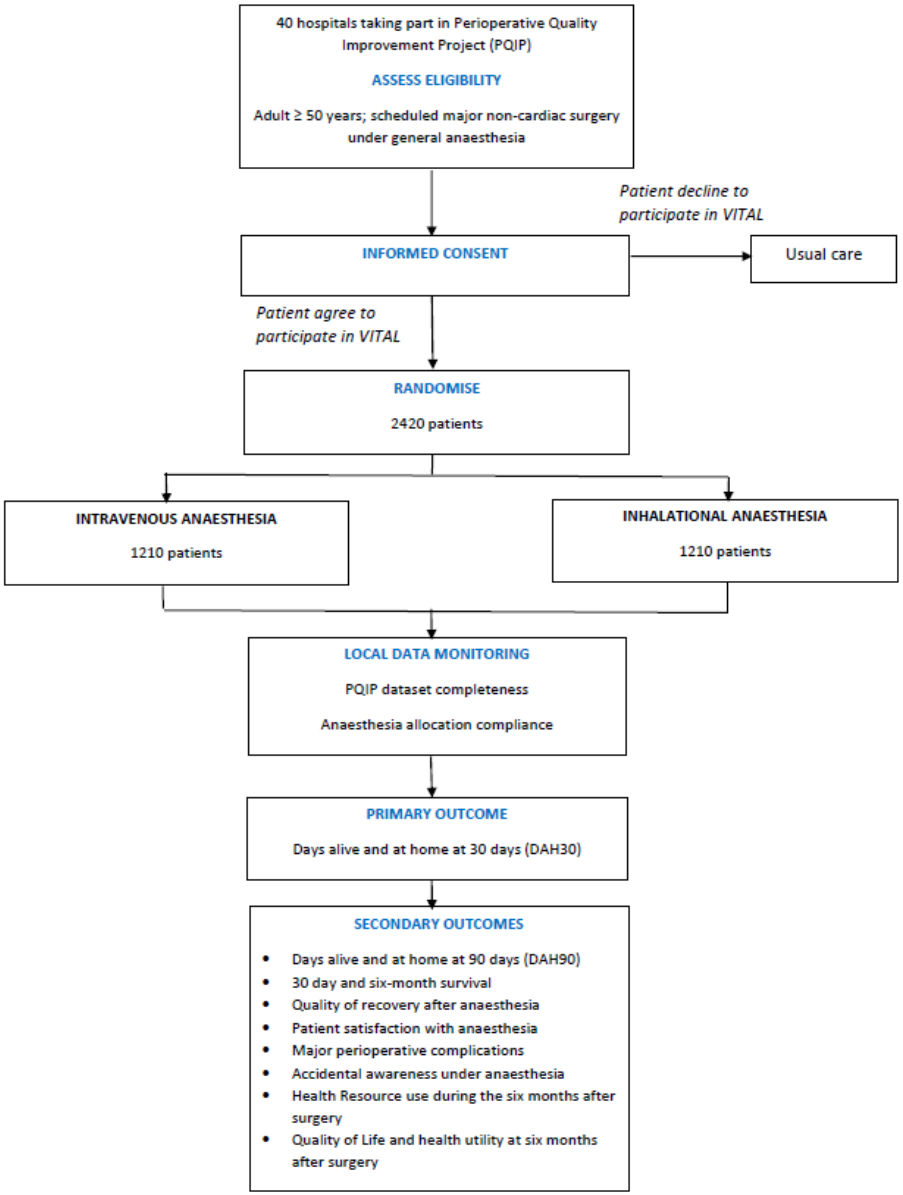
NO

MAY BE!

UK PERIOPERATIVE MEDICINE
CLINICAL TRIALS NETWORK

What next ?

NHS
National Institute for Health Research

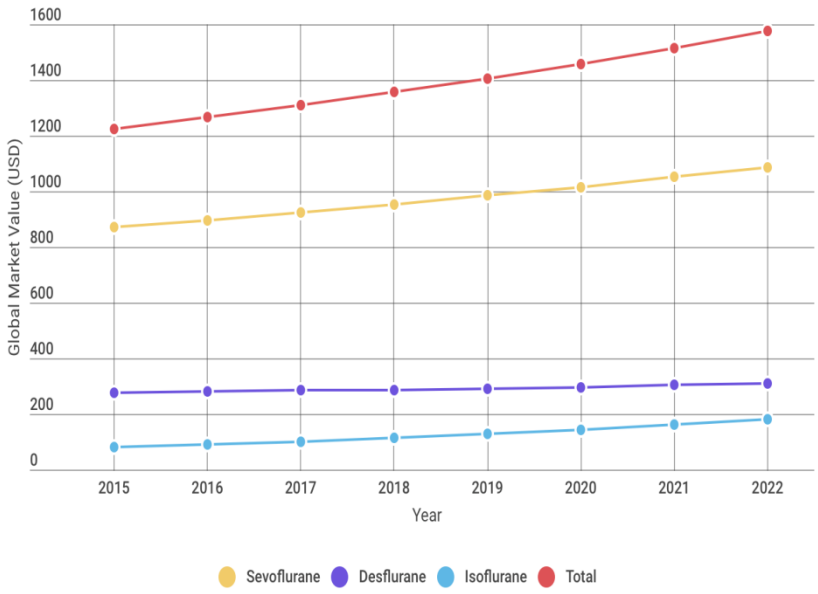


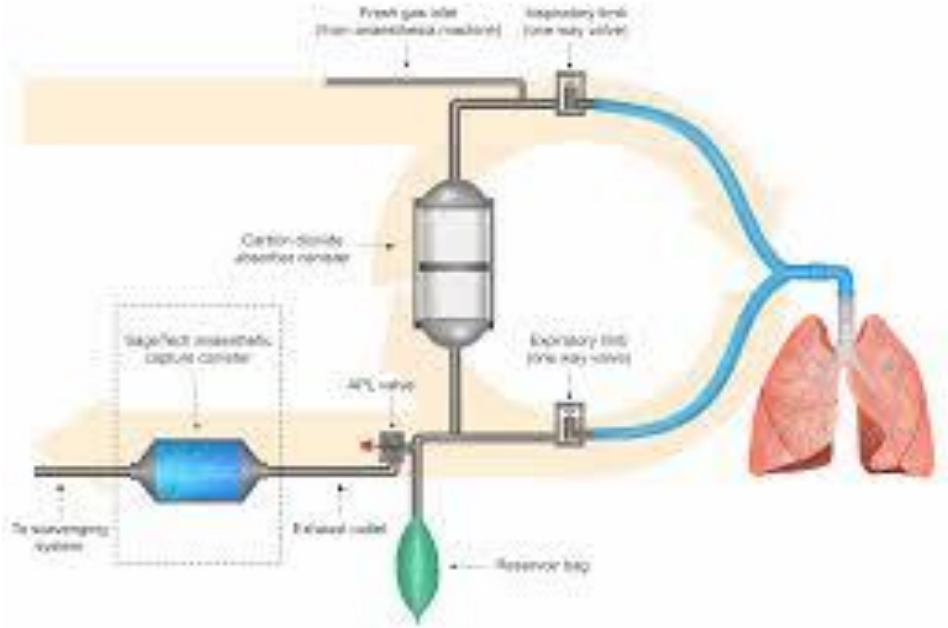
Award for Innovation in Anaesthesia, Critical Care and Pain 2020 – winner announced

Friday 10 January 2020

The Association of Anaesthetists has announced the winner for its annual 2020 Award for Innovation in A
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.





Life demands excellence

SAGETECH MEDICAL EQUIPMENT

Opioids and Cancer

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

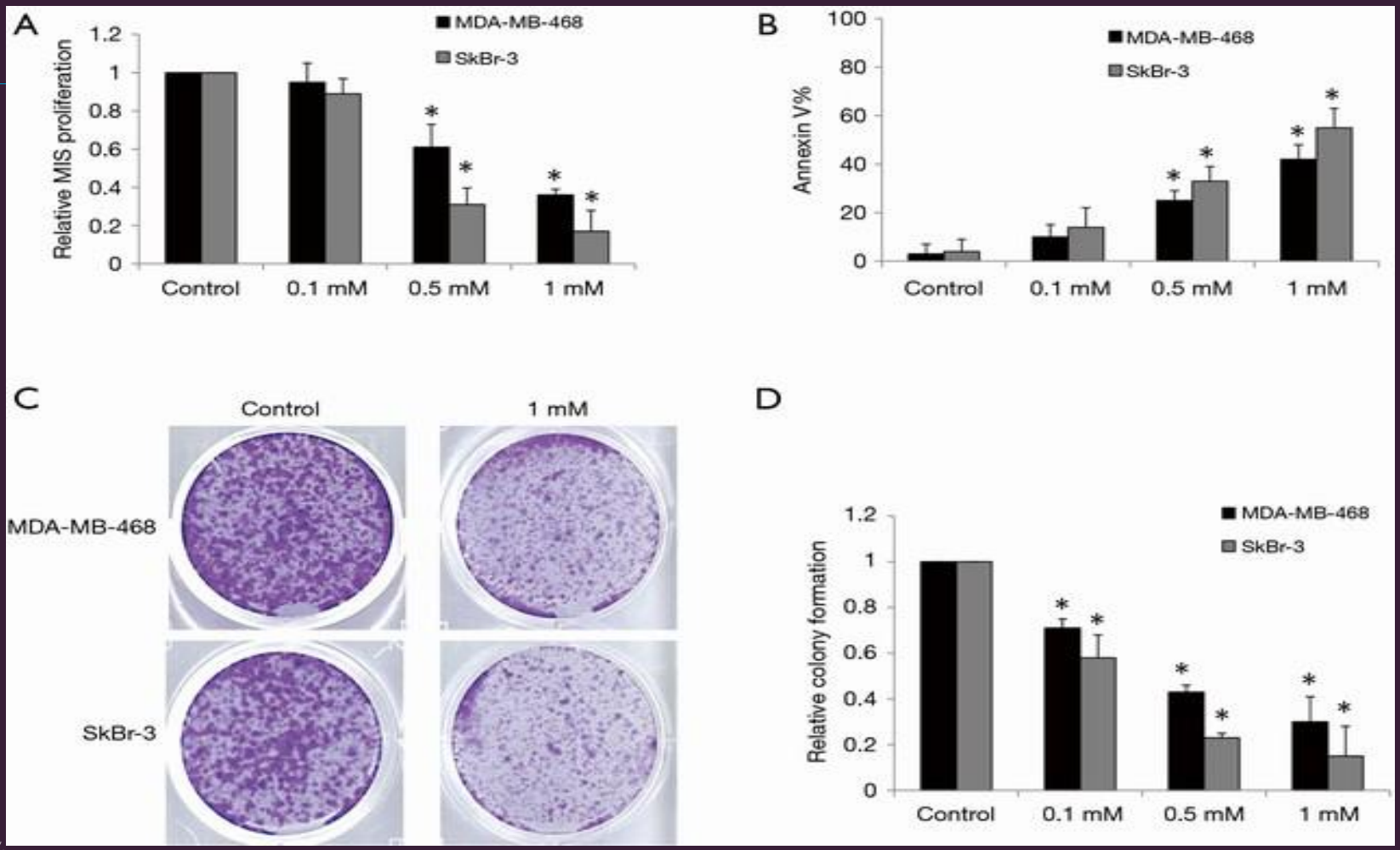
RFS: recurrence free survival, PFS: progression free survival.

Cancer Cell & Microenvironment 2016; 3: e1159.

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



J Thorac Dis 2018;10(5):2804-2812

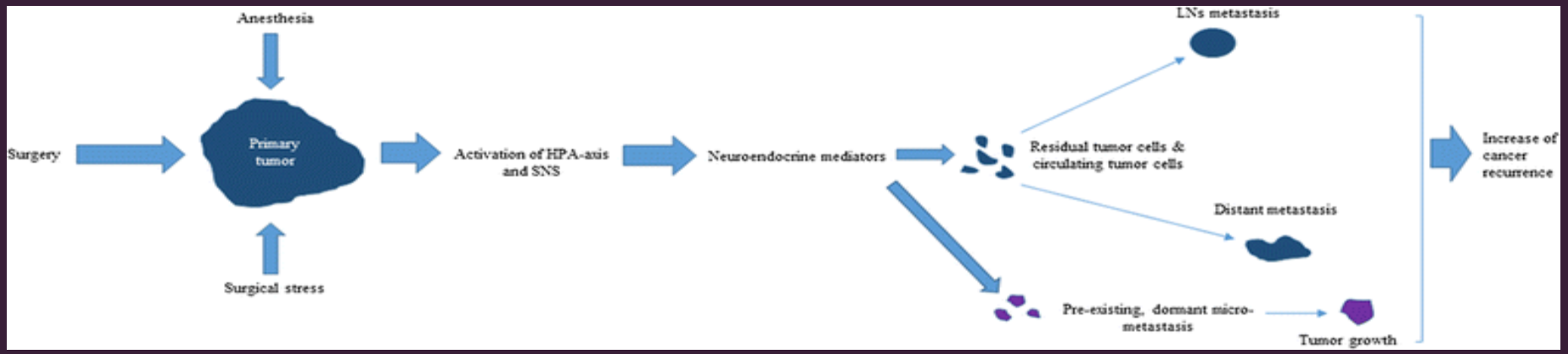
Anaesthesi adjuncts and cancer

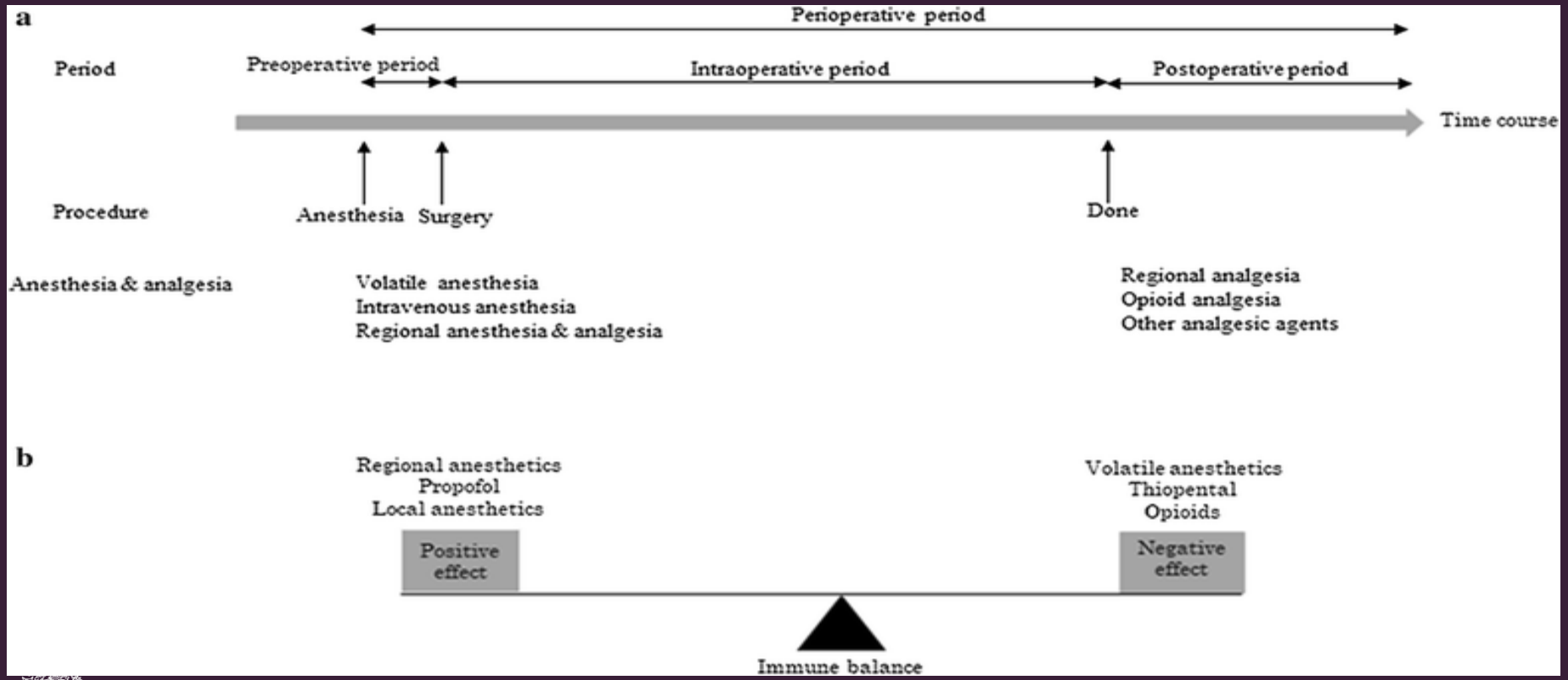
Glucocorticoids are widely used for prevention of chemotherapy-induced nausea and vomiting and as adjuvant therapy for pain control in patients with known metastatic cancer, without concern for worsening disease.

Dexamethasone for PONV - inconclusive evidence

Muscle relaxants - No clinical trials

Beta blockers - inconclusive evidence





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NHS

BJA 2015:115(52); ii35-ii45.

The ROYAL MARSDEN
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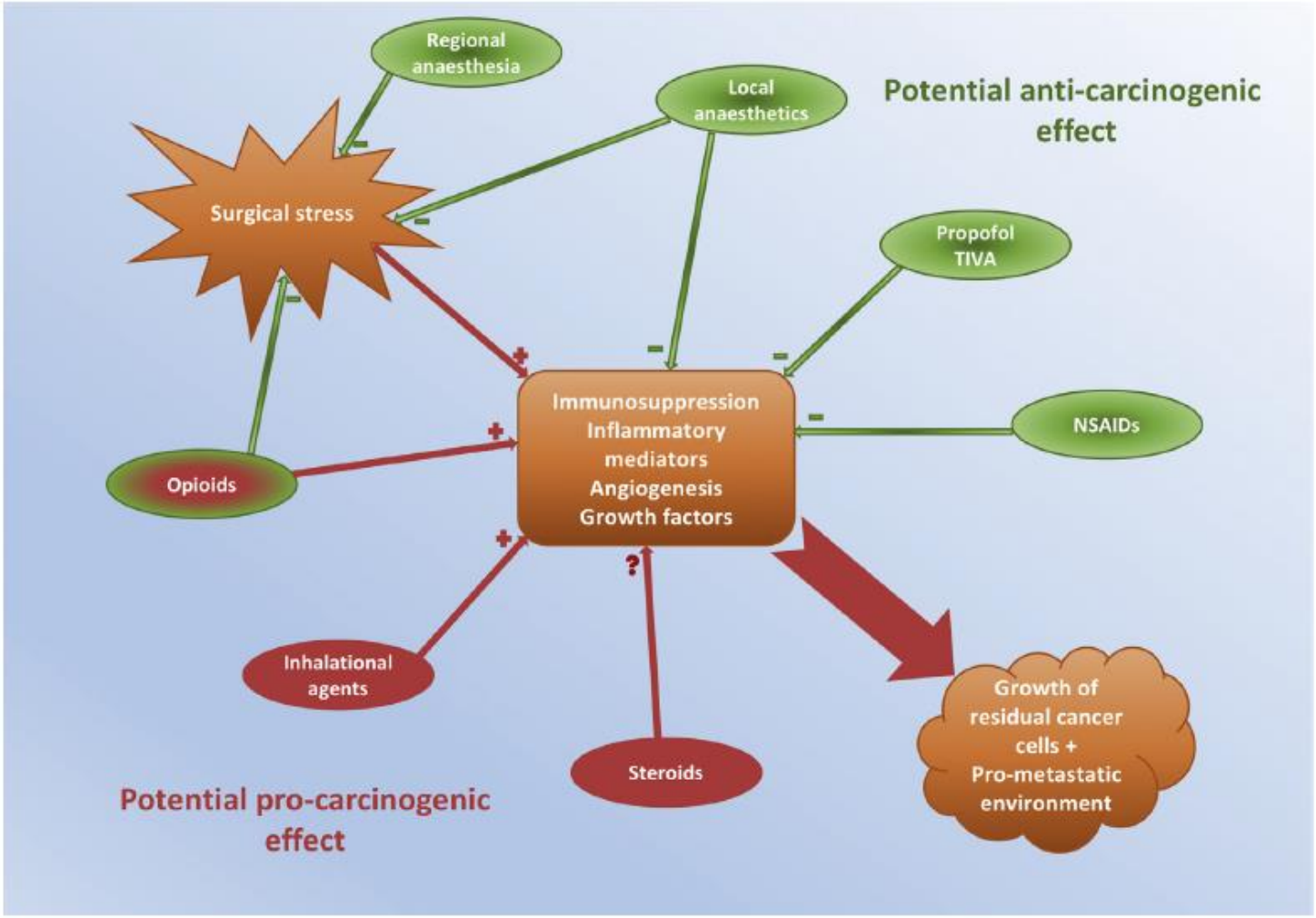

Fig 2 Summary of the potential impact of commonly used anaesthetic agents upon cancer progression, metastasis and recurrence.

Can anaesthetists make a difference in cancer care ….

YES!

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Pre-assessment unit – Royal Marsden

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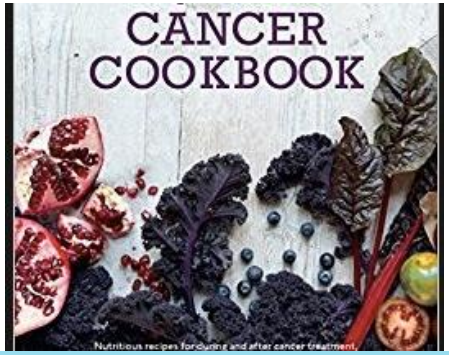
Patient, Time Specific, Evidence Based Interventions – Key 5 Pre Op Elements + 2 extra



Pre op Dietary Improvement

Prehabilitation

Pre op OT assessment

Pre op complex discharge planning

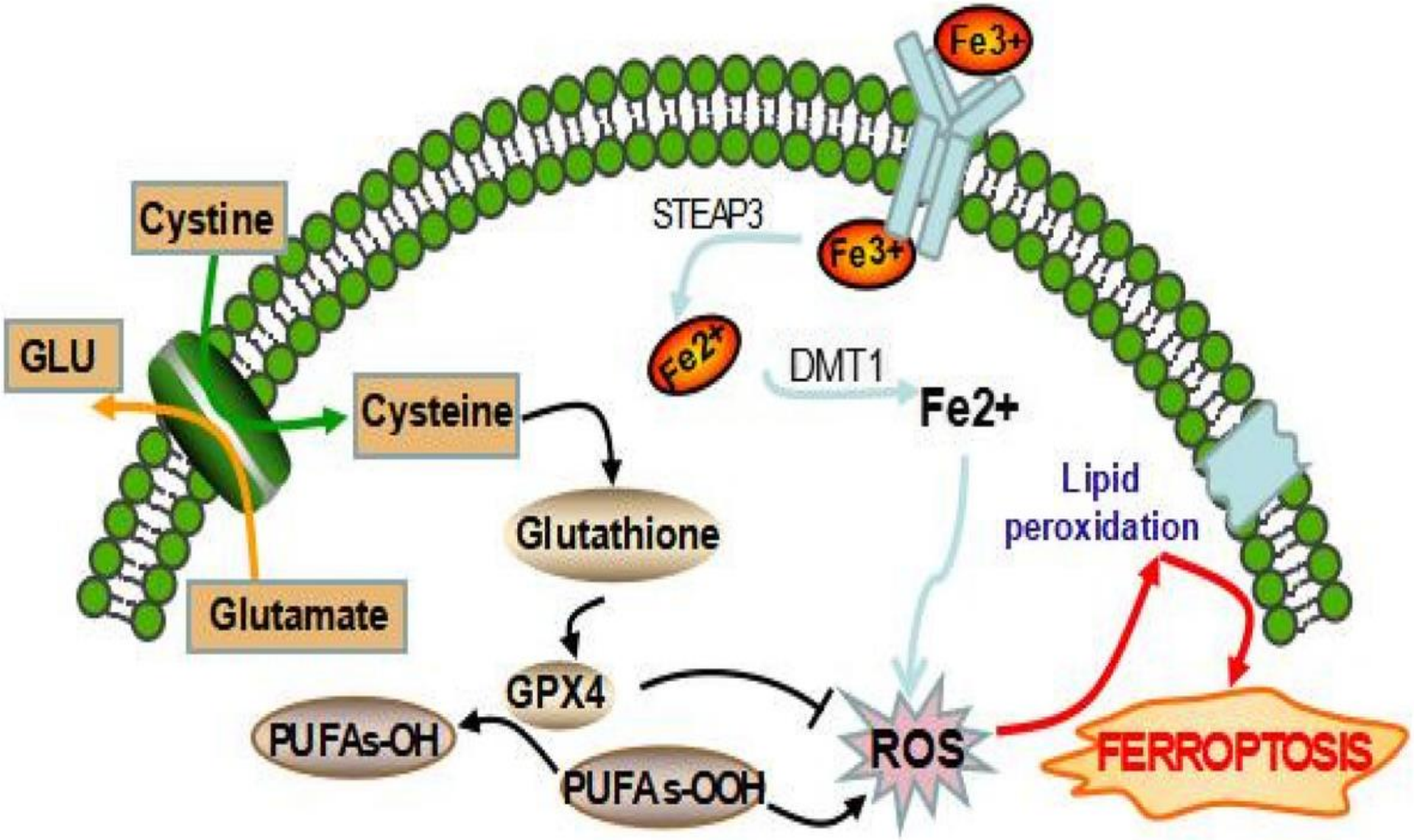
Polypharmacy optimisation

High Risk Patient MDT

Pre op Anaemia correction

Preoperative ANemiA among the elderly undergoing major abdominal surgery (PANAMA) study: Protocol for a single-center observational cohort study of preoperative anemia management and the impact on healthcare outcomes. Medicine. 2018 May;97(21):e10838.

Iron and cancer



Journal of Hematology & Oncology 12: 34 (2019)

Ravishankar.raobaikady@rmh.nhs.uk

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