Can regional anaesthetic techniques or local anaesthetic drugs during cancer surgery influence recurrence or metastases?

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&

Eccles Unit, National Cancer Control Programme

Dublin Ireland

And Anaesthesia….?

Cancer

- No.1 cause death jointly with cardiovascular
- Attributable to metastases
- Surgery main treatment
- Many patients have micrometastases at surgery
- Minimal Residual Cancer

Perioperative factors promoting cancer v. Perioperative factors resisting cancer

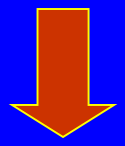
Catecholamines
Endogenous steroid excess

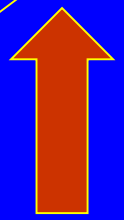
Surgery per se

Some GA agents per se

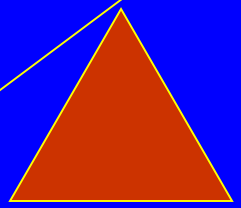
Pain

Opioids





Immunity: Natural Killer Cells
Direct effects: LA drugs



Proliferation Minimal Residual Cancer: Metastases

Countering Perioperative Risk Factors for Cancer Metastases

Anti-Tumour

- Immune Function
- Direct effects
- ?propofol
- Amide LA

Tumour-Promoting

- Stress Response
- Pain
- Opioids
- Volatile & Some IV Anesthetics

Neutral Effect

- Propofol

Regional Anaesthesia

Hypothesis

That certain bundled anaesthetic techniques and / or direct effect of amide LA during cancer surgery effects cancer outcome, i.e. risk of recurrence or metastases

So what’s the current evidence?

Existing evidence

Experimental cell culture

Live animal model

SIGNAL:
Anaesthetic technique might effect cancer outcome

Translational studies

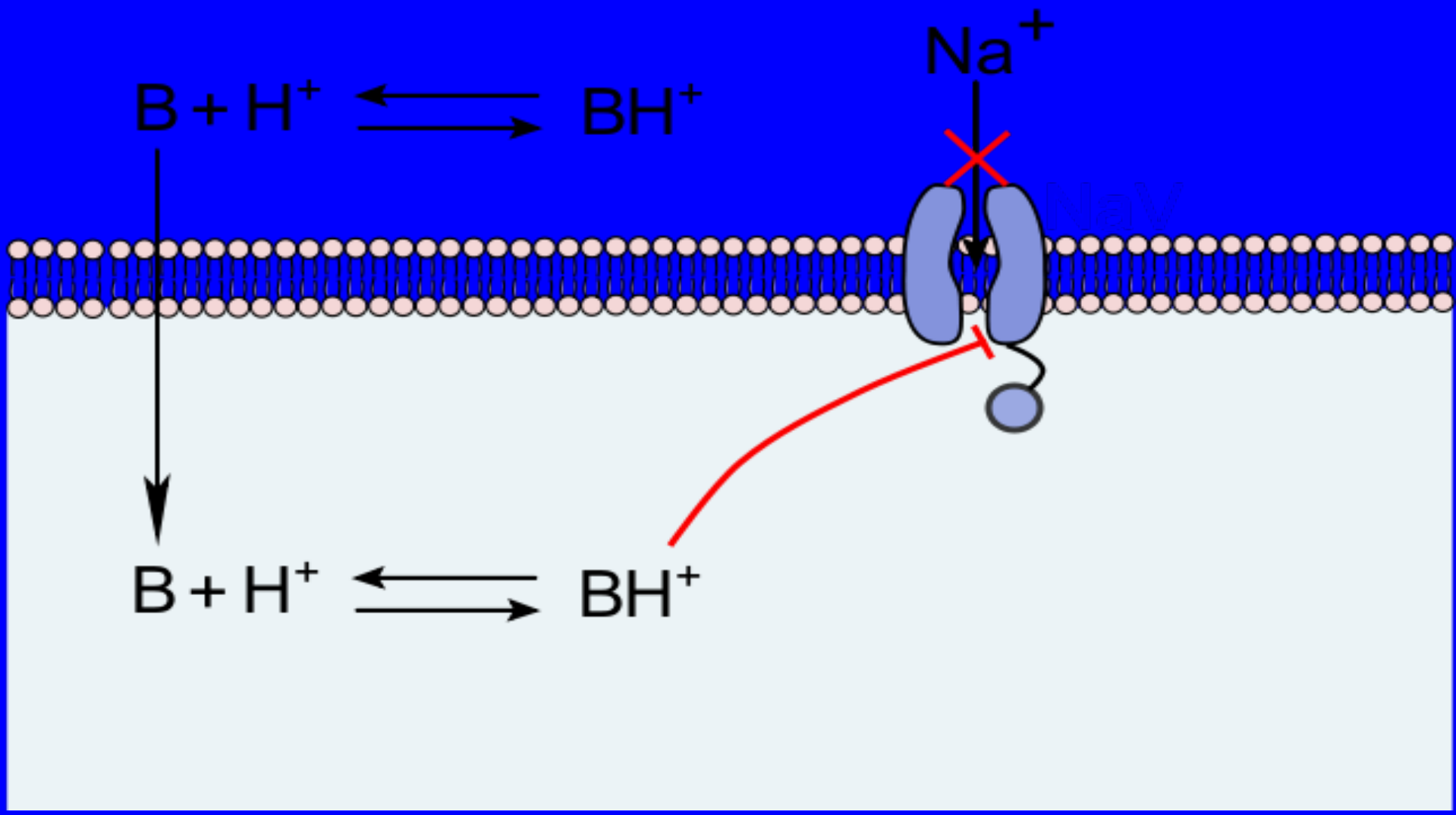
Retrospective clinical studies

Prospective RCT

Cell culture evidence

- Direct effect of drugs we use in regional
- Local anaesthetics

How do local anaesthetics work?



Useful not only for sensory nerves, but also blocks cancer cell invasion

Tumor and Stem Cell Biology

Cancer Research

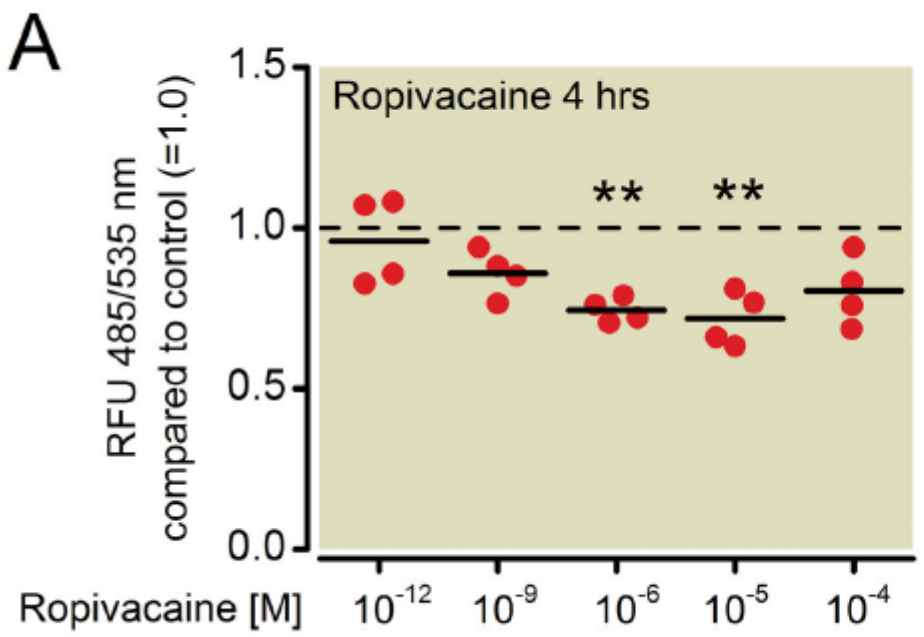
Voltage-Gated Na^+ Channel *SCN5A* Is a Key Regulator of a Gene Transcriptional Network That Controls Colon Cancer Invasion

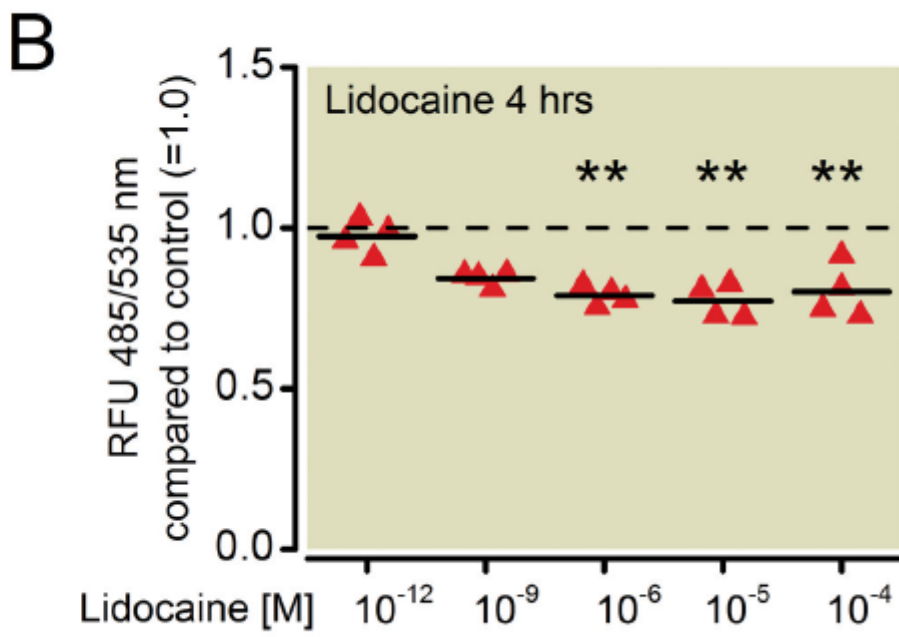
Carrie D. House[1], Charles J. Vaske[3], Arnold M. Schwartz[2], Vincent Obias[2], Bryan Frank[1], Truong Luu[1], Narine Sarvazyan[1], Rosalyn Irby[4], Robert L. Strausberg[5], Tim G. Hales[1], Joshua M. Stuart[3], and Norman H. Lee[1]

Experimental cell culture studies
Voltage gated sodium channel is indeed involved in colon cancer invasion

But amide LA also have non-Na+ channel mechanism of action

Piegeler et al. Page 22



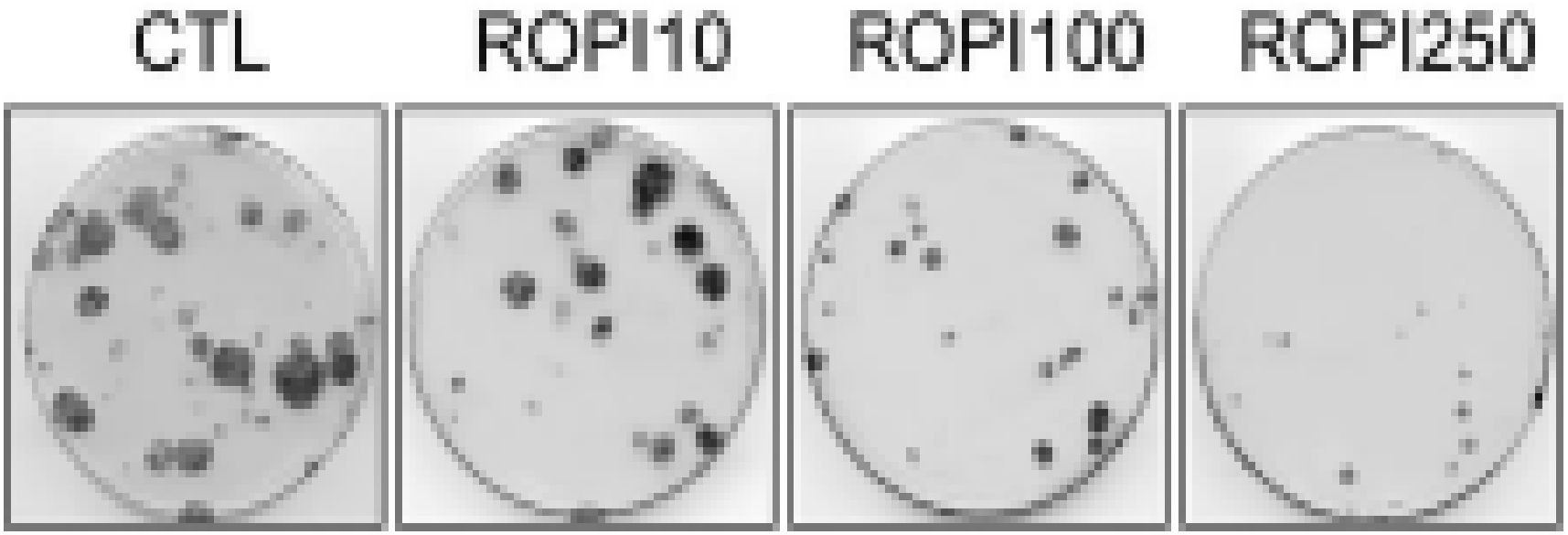


Amide LA inhibit TNF-α induced Src-activation and IAM phosphorylation

Stops cancer cell migration!

Antiproliferative Effects of Local Anesthetics on Mesenchymal Stem Cells

Potential Implications for Tumor Spreading and Wound Healing



British Journal of Anaesthesia **109** (2): 200–7 (2012)
Advance Access publication 27 April 2012 · doi:10.1093/bja/aes128

BJA

Lidocaine time- and dose-dependently demethylates deoxyribonucleic acid in breast cancer cell lines *in vitro*†

P. Lirk[1,2*‡], R. Berger[3‡], M.W. Hollmann[1] and H. Fiegl[3*]

[1] Department of Anaesthesiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

British Journal of Anaesthesia Page 1 of 7
doi:10.1093/bja/aeu201

BJA

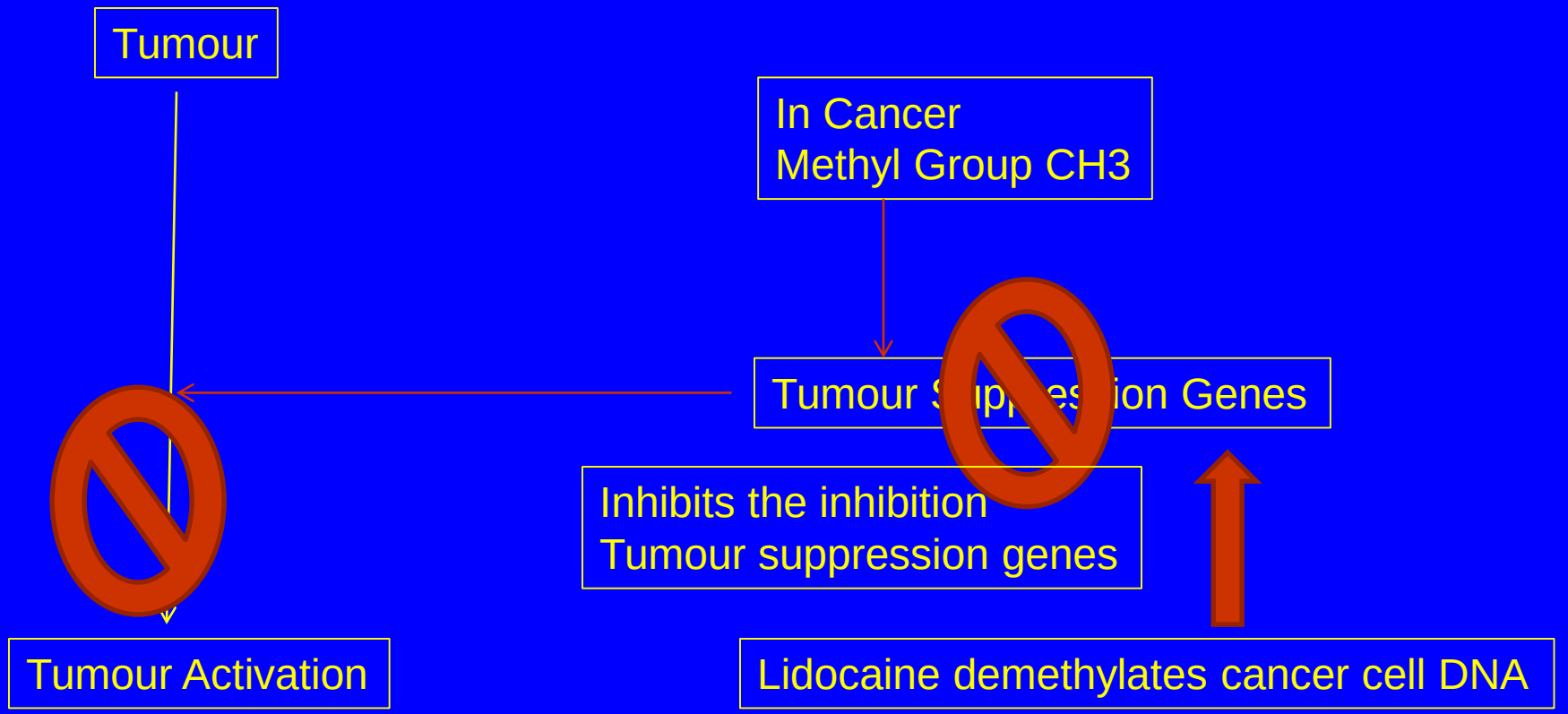
Lidocaine and ropivacaine, but not bupivacaine, demethylate deoxyribonucleic acid in breast cancer cells *in vitro*

P. Lirk[1*], M. W. Hollmann[1], M. Fleischer[2], N. C. Weber[1] and H. Fiegl[2*]

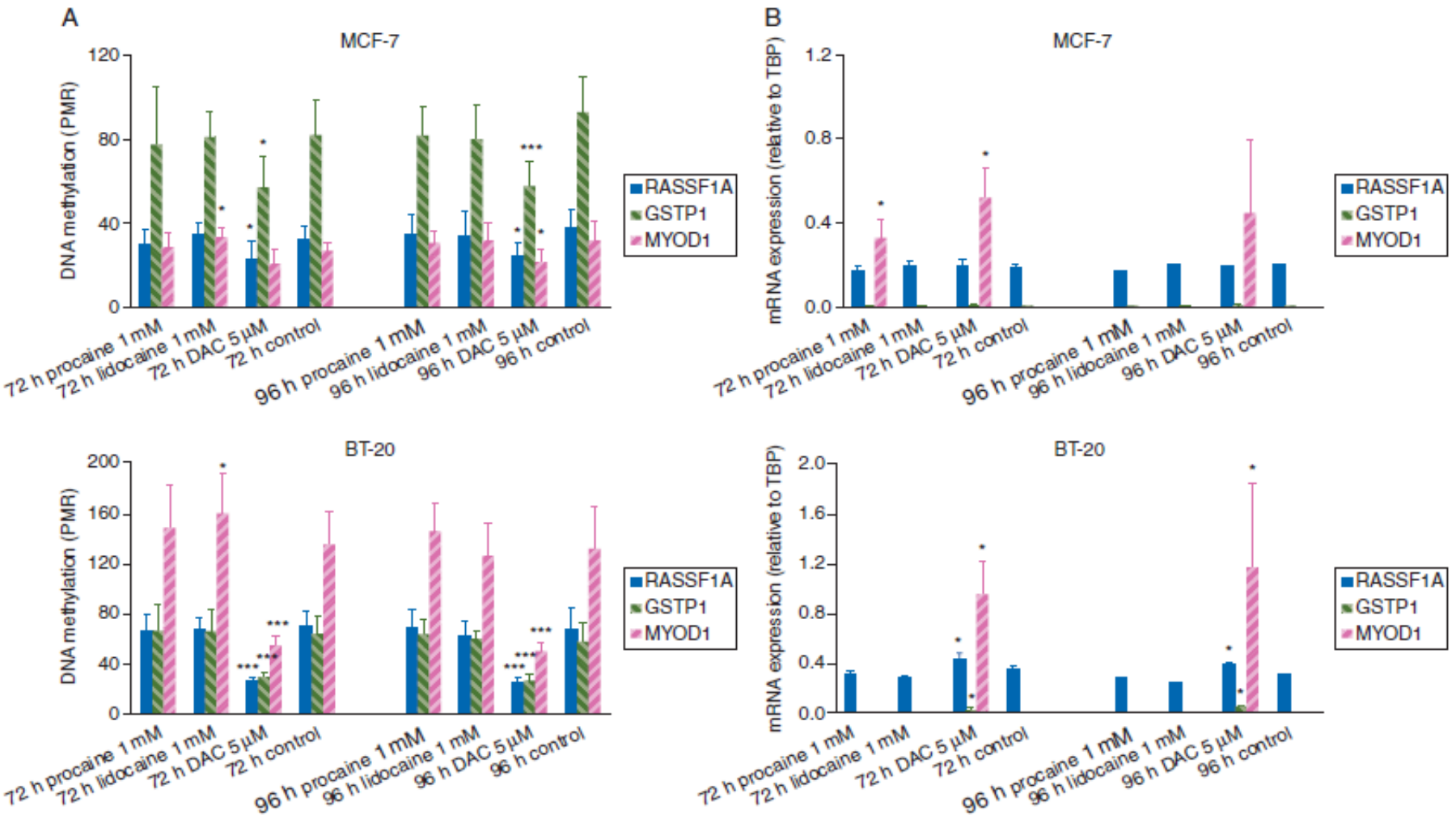
[1] Department of Anaesthesiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105AZ, The Netherlands
[2] Department of Gynaecology and Obstetrics, Innsbruck Medical University, Anichstr. 35, Innsbruck 6020, Austria

Suggesting that LA destroys breast cancer cell replication

How lidocaine inhibits cancer cell DNA



Lidocaine demethylates cancer cell DNA



How Amide LA Inhibits Cancer Cells

- Amide LA (but not ester LA) inhibit lung cancer cell migration in vitro by inhibiting TNF-α induced Src signalling & IAM phosphorylation
- Amide LA induces demethylation of cancer cell DNA
- Not forgetting Na+ channel inhibition
  - Borgeat A et al Anesthesiology 2012
- Why not proceed to prospective, randomised trial?
- Lack of live animal data

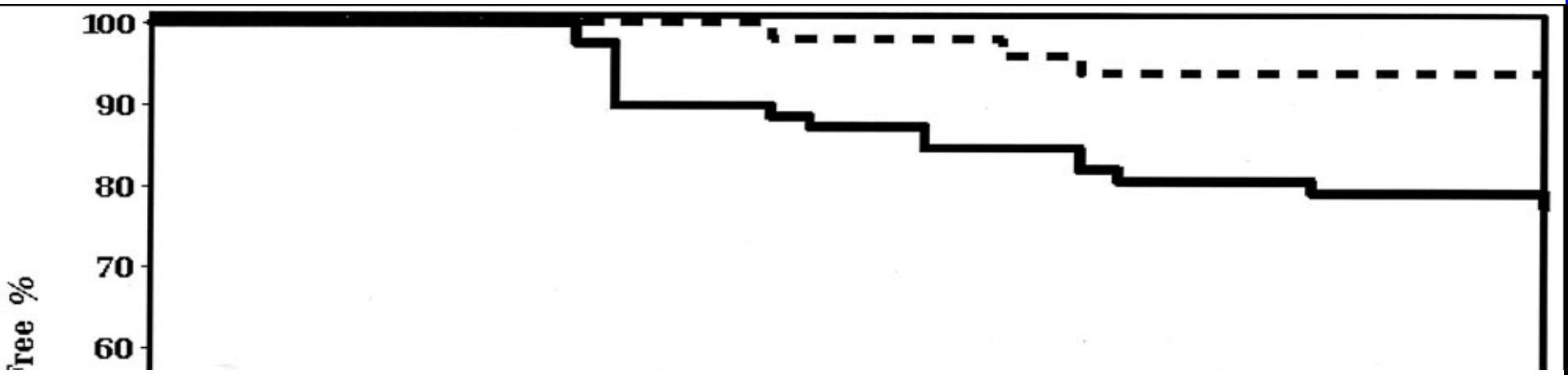
Any clinical studies?

- Yes
- Retrospective analysis
- Selection bias
- Can only show *associations* and generate hypotheses
- Cannot prove cause-and effect link

Anesthesiology 2006; 105:1–1

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

Aristomenis K. Exadaktylos, M.D.,* Donal J. Buggy, M.D., M.Sc., 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.‖

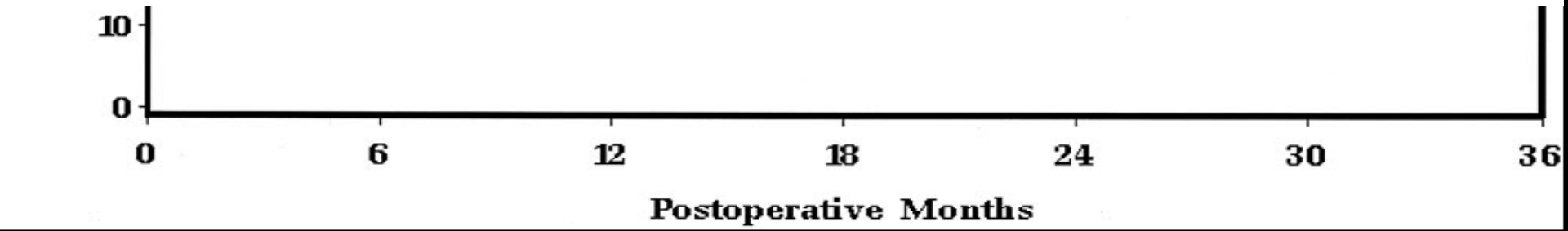


Anesthesiology 2008; 109:1–1

Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence

A Retrospective Analysis

Barbara Biki, M.D.,* Edward Mascha, Ph.D.,† Denis C. Moriarty, M.D.,‡ John M. Fitzpatrick, M.D.,§ Daniel I. Sessler, M.D.,‖ Donal J. Buggy, M.D., M.Sc., F.R.C.P.I., F.C.A.R.C.S.I., F.R.C.A.#



British Journal of Anaesthesia 107 (2): 164–70 (2011)
Advance Access publication 17 May 2011 · doi:10.1093/bja/aer100

BJA

CLINICAL PRACTICE

Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in Central Sweden

A. Gupta[1,2,5*], A. Björnsson[1,5], M. Fredriksson[3,5], O. Hallböök[4,5] and C. Eintrei[1,5]

[1] Department of Anaesthesiology and Intensive Care and [2] University Hospital, Örebro, Sweden
[3] Linköping Academic Research Centre, Faculty of Health Sciences, [4] Department of General Surgery and [5] University Hospital, Linköping University, Sweden

Swedish Data: Rectal Cancer

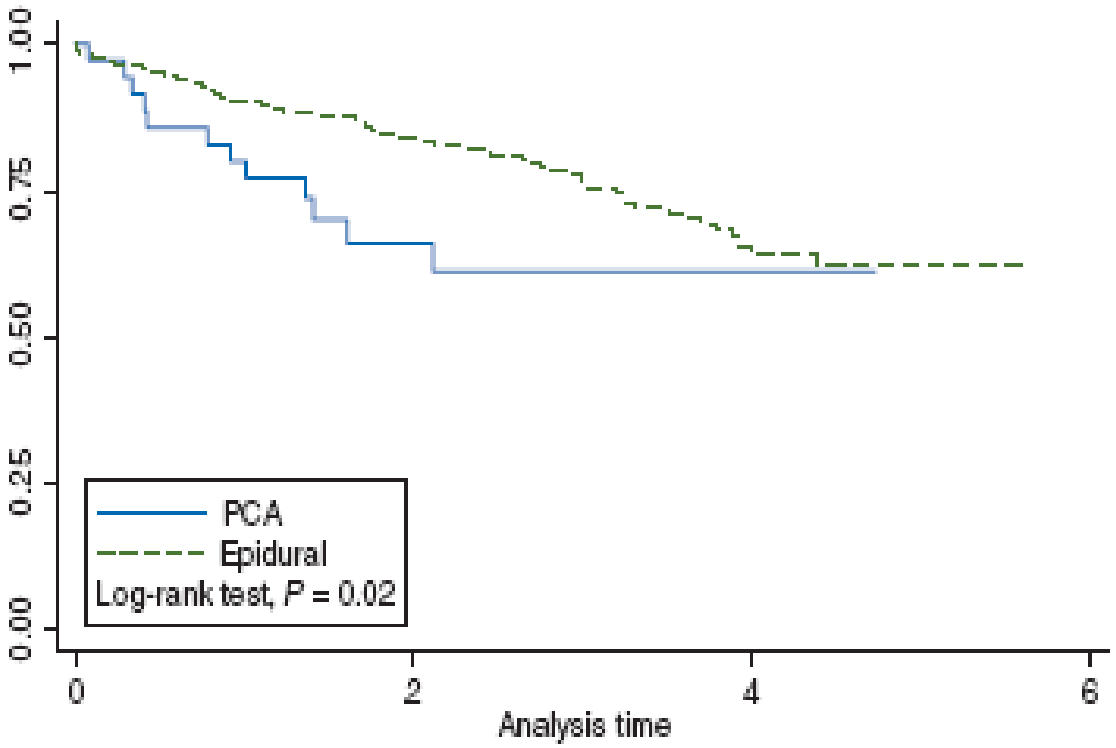


Fig 3 The Kaplan–Meier survival curves for patients with rectal cancer. PCA, patient-controlled analgesia. *X*-axis: number of years; *Y*-axis: proportion surviving.

Retrospective Studies: What's the Score?

Oh Yes It Does!

- Exadaktylos, Anesthesiology 2006 Breast
- Biki, Anesthesiology 2008: Prostate
- *Christopherson, FARCT: A & A 2008: Colorectal*
- Wuethrich, Anesthesiology 2010 Prostate
- Gupta A et al, Br J Anaesth 2011
  Rectal Yes Colon No
- Lin Br J Anaesth 2011 ovarian
- P Forget, M de Koch Anesth Analg 2011 NSAIDs Breast
- De Oliviera RAPM 2011 ovarian
- Gottschalk Br J Anaesth 2012 melanoma

Oh No It Doesn't!

- Gottschalk et al, Anesthesiology 2010
  Colorectal: But YES for Patients >64 yr!
- *Tsui (FARCT) Anesthesiology 2010*
  Major abdo colorectal:
  22% epidural vs.34% GA
- *Myles et al (FARCT) BMJ 2011*
  Major abdo; MASTER trial
- Ismail H et al, Br J Anaesth 2010
  (Brachytherapy cervical cancer)
- Lai Anesth Analg 2012 HCC
- *Fleischmann E: BMC Anesthesiology 2009*
  FARCT: N_2O not assoc colorectal
- Day Br J Anaesth 2012: Lap colorectal
- Cummings, Anesthesiology 2012
  Population: Survival yes, Recurrence No

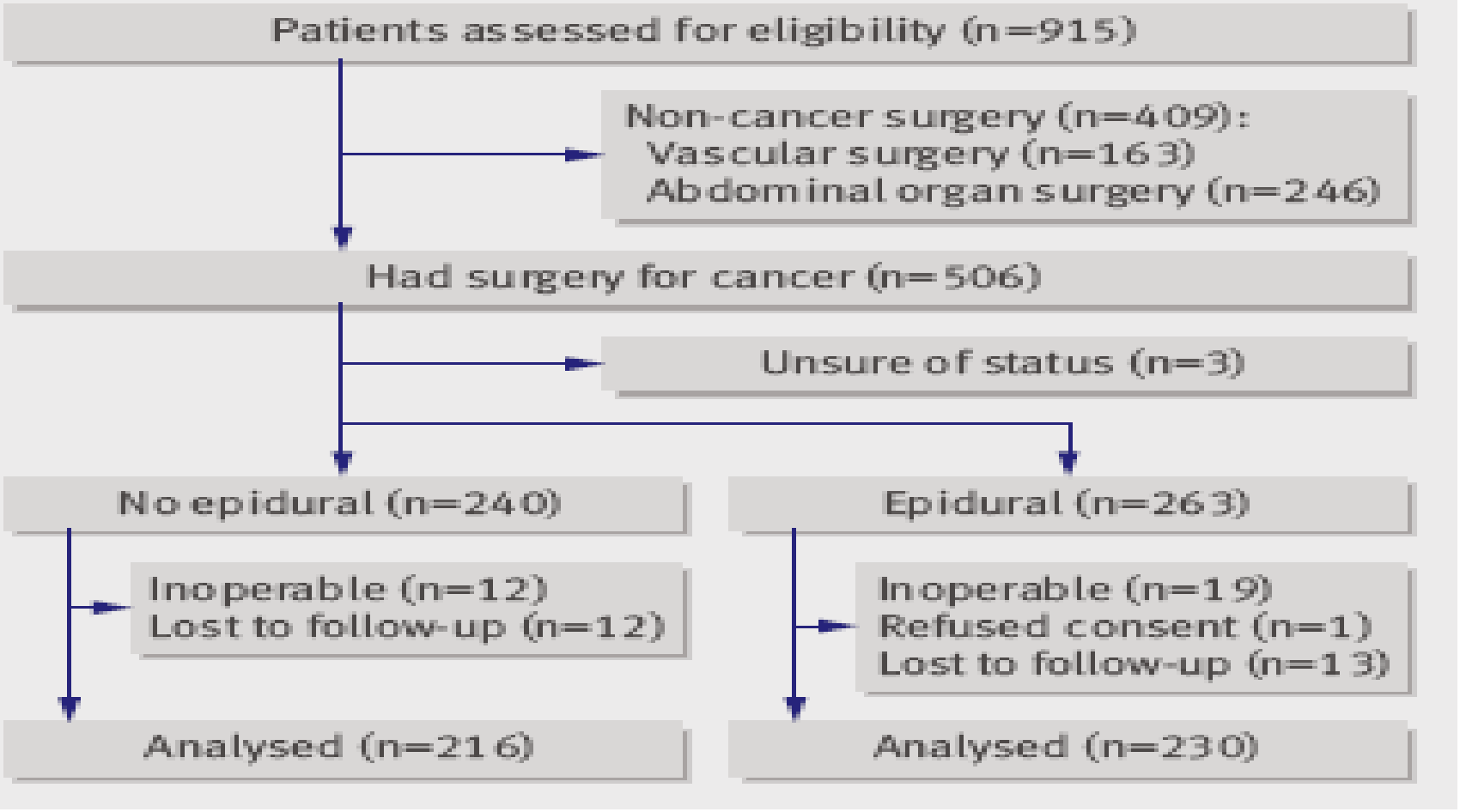
BMJ

RESEARCH

Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial

Paul S Myles, professor,[1] director,[2] Philip Peyton, consultant,[3] Brendan Silbert, consultant,[4] Jennifer Hunt, research coordinator,[1] John R A Rigg, retired consultant,[5] Daniel I Sessler, professor and chair[6] for the ANZCA Trials Group Investigators

Follow-up analysis of previous RCT MASTER Trial (Lancet 2000)



Myles P et al BMJ 2011

Follow-up RCT: No difference with epidural

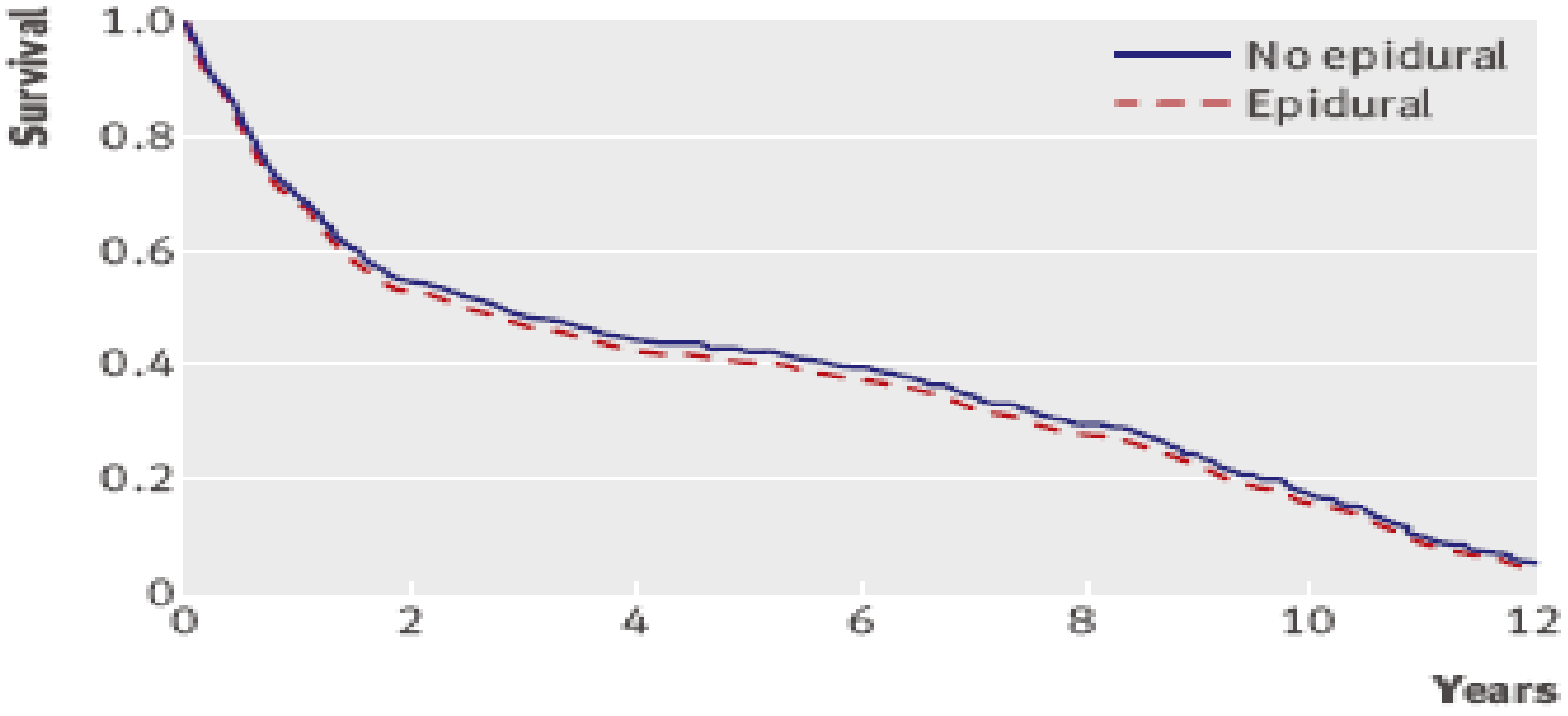


Fig 2| Recurrence-free survival after cancer surgery by group (log rank P=0.61)

Myles P et al BMJ 2011

Prospective Randomised Clinical Trials

- Only method of evaluating a causal link between anaesthesia drug or technique and cancer
- 9 registered trials
- Require large numbers of patients
- Difficult to acquire large scale funding
- Demanding follow up of patient outcomes
- Takes a long time!
- Meantime, in vitro cell cultures, live animal models, translational data and retrospective clinical data is all we have got!

Breast Cancer Study Power NCT 418457

20% recurrence originally anticipated

- 20% treatment effect
- 3% drop out rate
- Type 1 error 0.05,Type 2 error 0.1:Power 90%
- Need 2,700 patients!
- 30% treatment effect
- Type 2 error 0.15 (power 85%)
- Need 1,100 patients
- We have n=1300 but actual recurrence <10%!
- Still need nearly 3,000 patients!

Propofol/ Paravertebral Group

- Paravertebral catheter
- Ipsilateral T2-3
- 20-ml bolus 0.25% levo-bupivacaine
- GA propofol TCI
- Continuous paravertebral analgesia
- Catheter removed 24 hr

Balanced GA

- Induction
  - Fentanyl 1-3 mcg/kg
  - Propofol 2-4 mg/kg
- Maintenance
  - Sevoflurane (ET 1-3%)
  - Air/O_2
- Intraoperative analgesia
  - Morphine 0.1-0.15 mg/kg iv
- Postoperative analgesia
  - PCA morphine

So must we wait for results of RCT?

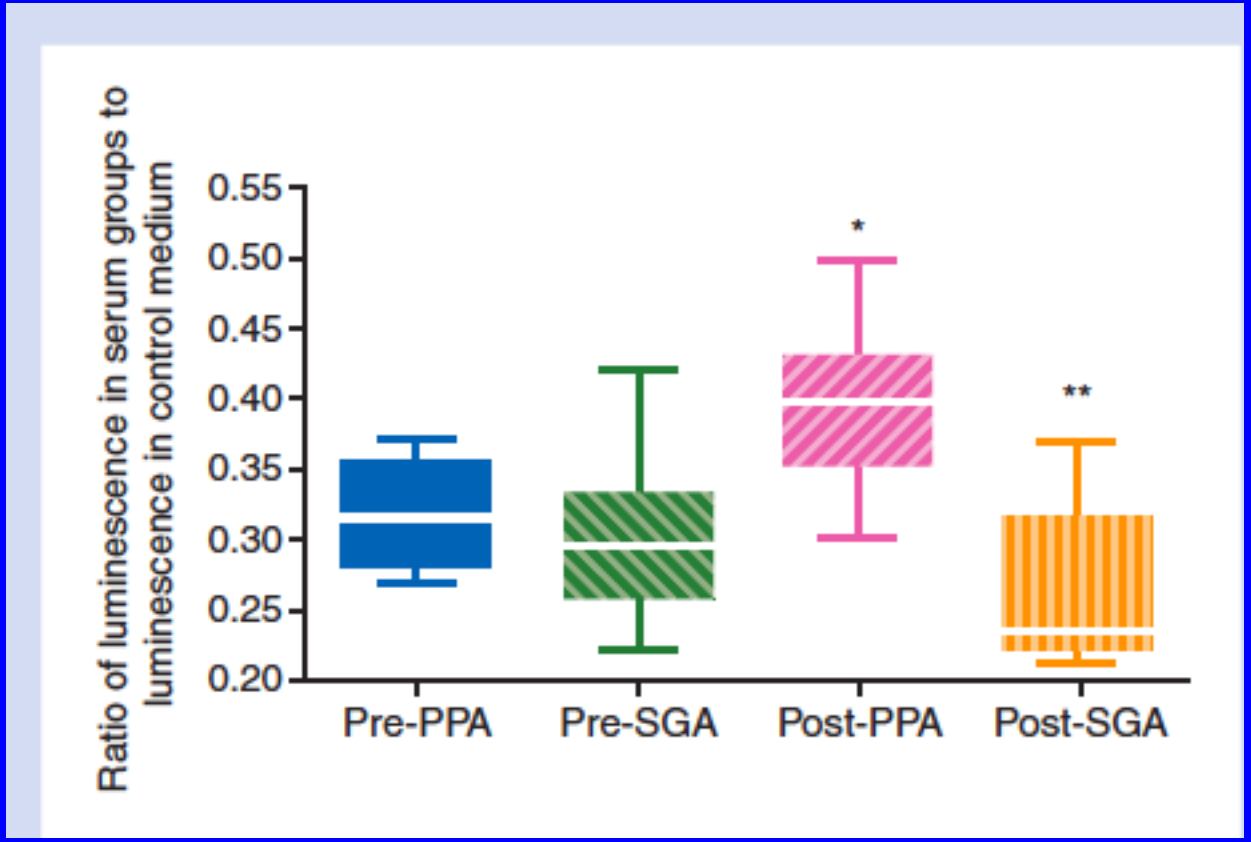
Yes

But there are small translational studies based on the ongoing RCT

How to evaluate if overall anaesthetic technique is influencing breast cancer function in vitro?

- Use Serum from patients given different anaesthetic techniques
- Preop and 24 hr postop samples
- Existing randomized study
- Propofol-Paravertebral
- Sevoflurane-Opioid
- Compare effect diluted serum on breast cancer cell line function *in vitro*

Sevo-Opioid GA serum decreased apoptosis in breast cancer cells



Anesthesiology 2010; 113:1118–25

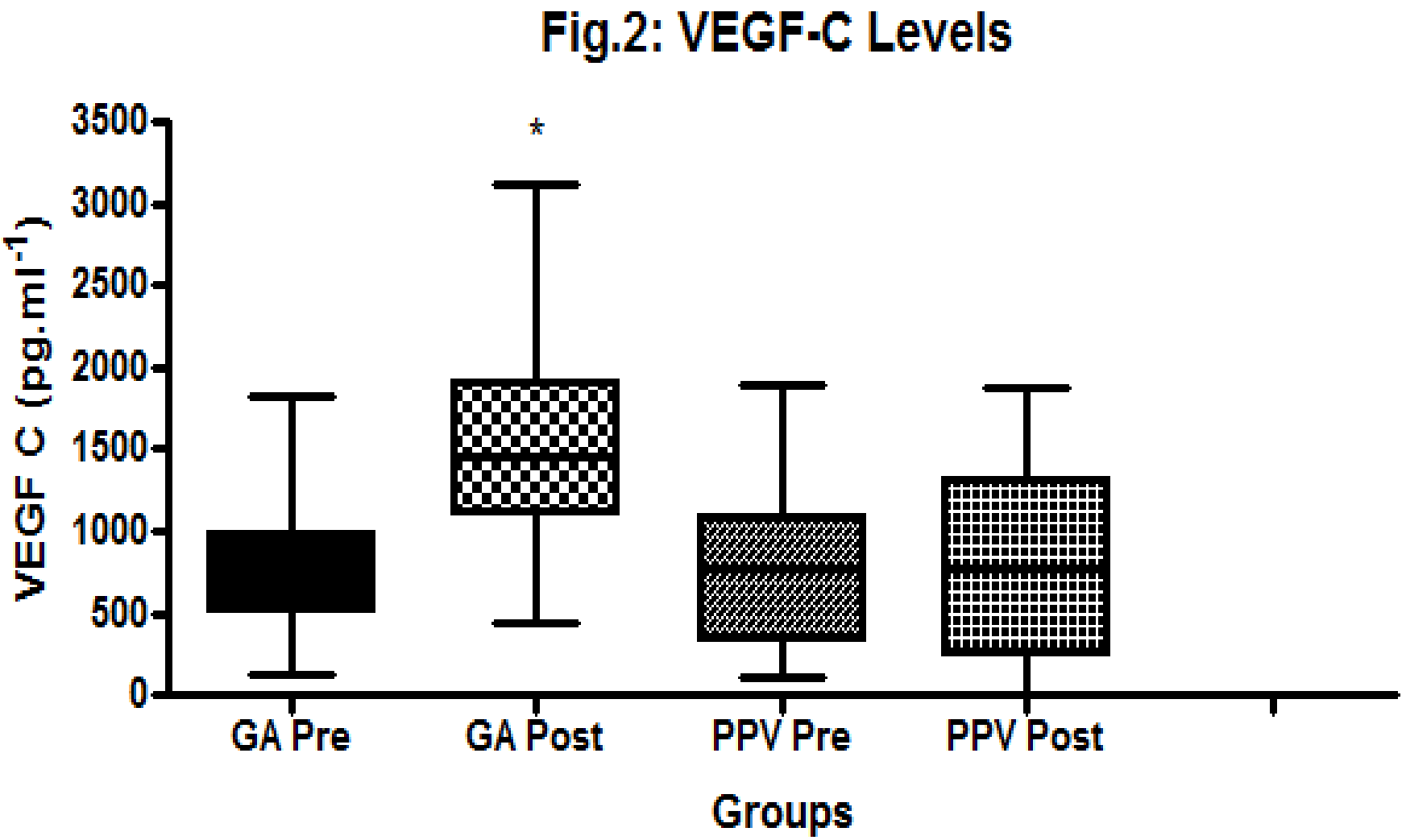
Effect of Anesthetic Technique on Serum Vascular Endothelial Growth Factor C and Transforming Growth Factor • in Women Undergoing Anesthesia and Surgery for Breast Cancer

Micheal Looney, F.C.A.I.,* Peter Doran, Ph.D.,†
Donal J. Buggy, M.D., M.Sc., D.M.E., F.R.C.P.I., F.C.A.I., F.R.C.A.‡

Effect anaesthetic technique on angiogenesis promoting factors

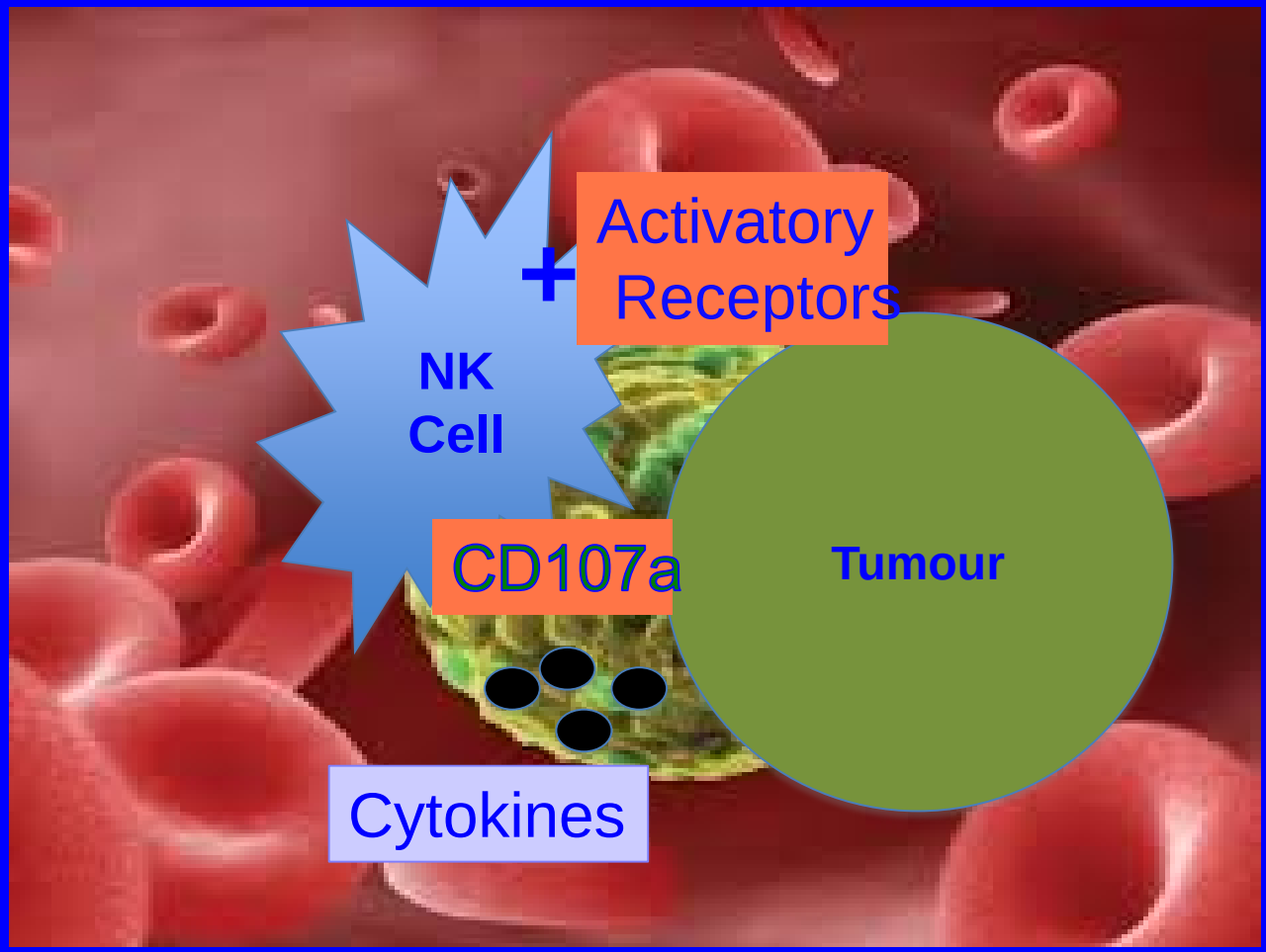
- VEGF-C essential for breast cancer angiogenesis
- May be stimulated by surgical stress response or direct effect of opioids
- Tested hypothesis that propofol-paravertebral technique would reduce VEGF-C postop vs. standard GA
    - Looney M et al Anesthesiology 2010

Effect anaesthetic technique on VEGF-C



Any immunological studies?

Cell mediated immunity



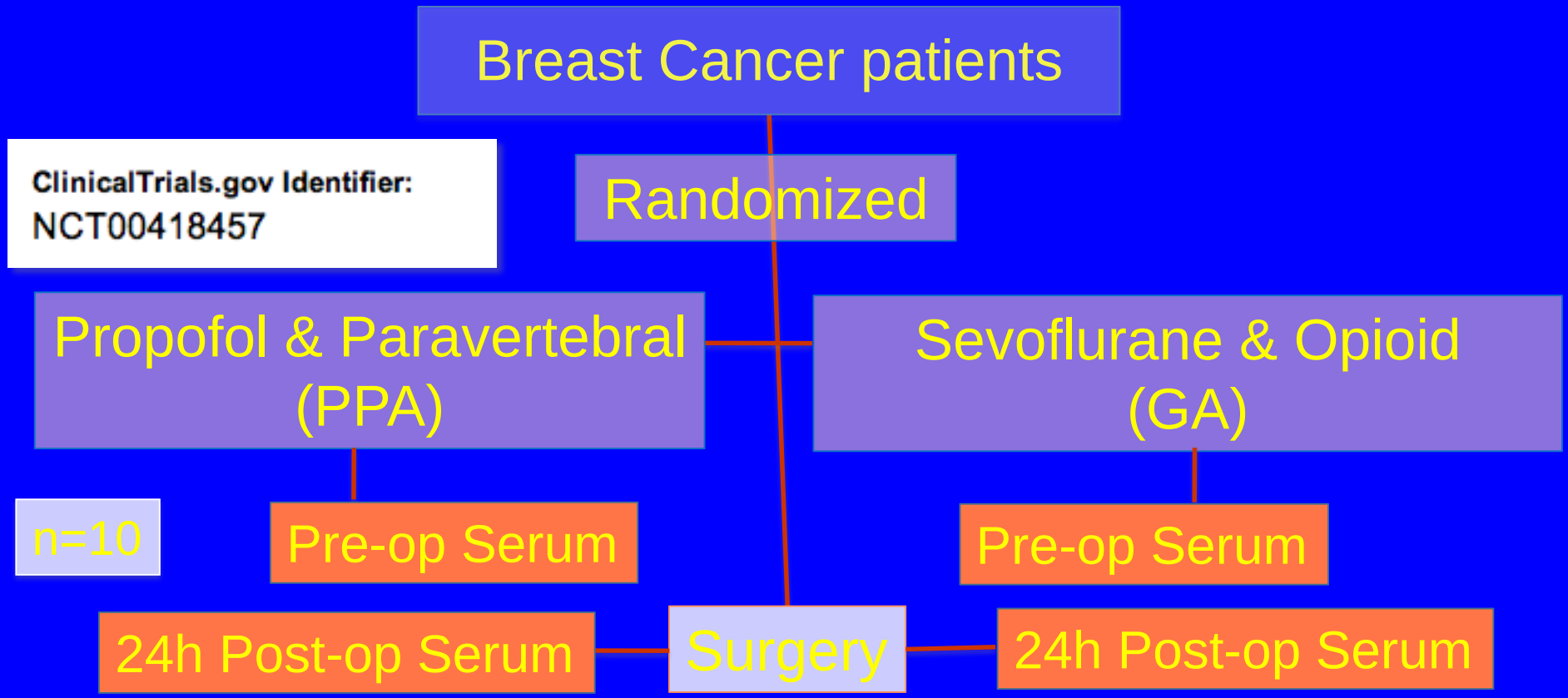
British Journal of Anaesthesia **113** (S1): i56–i62 (2014)
Advance Access publication 9 July 2014 · doi:10.1093/bja/aeu200

BJA

Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study

A. Buckley[1*], S. McQuaid[2], P. Johnson[2] and D. J. Buggy[1,3,4]

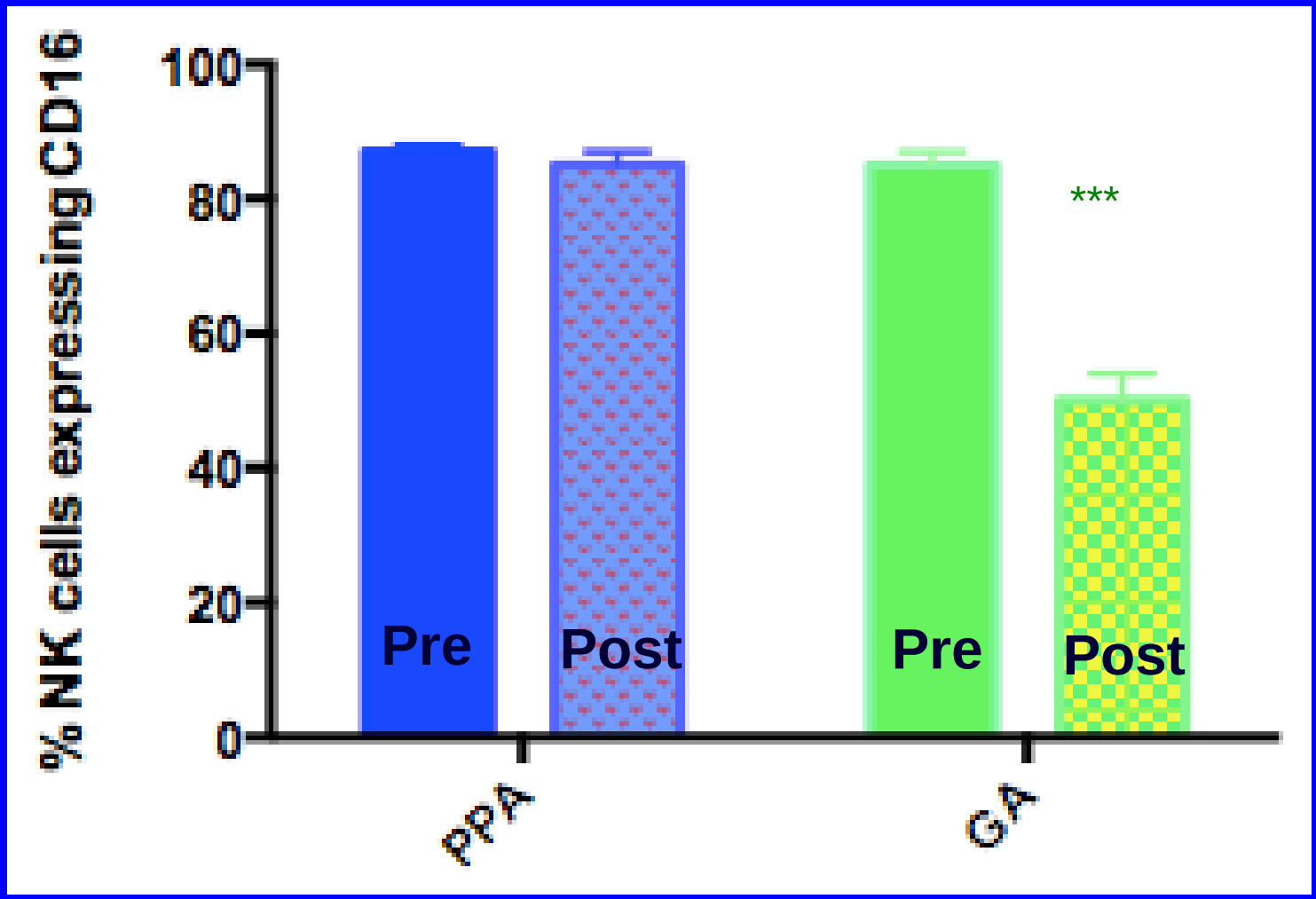
[1] Department of Anaesthesia, Mater Misericordiae University Hospital, Dublin, Ireland
[2] Department of Immunology, Dublin City University, Dublin, Ireland
[3] School of Medicine & Medical Science, University College Dublin, Dublin, Ireland



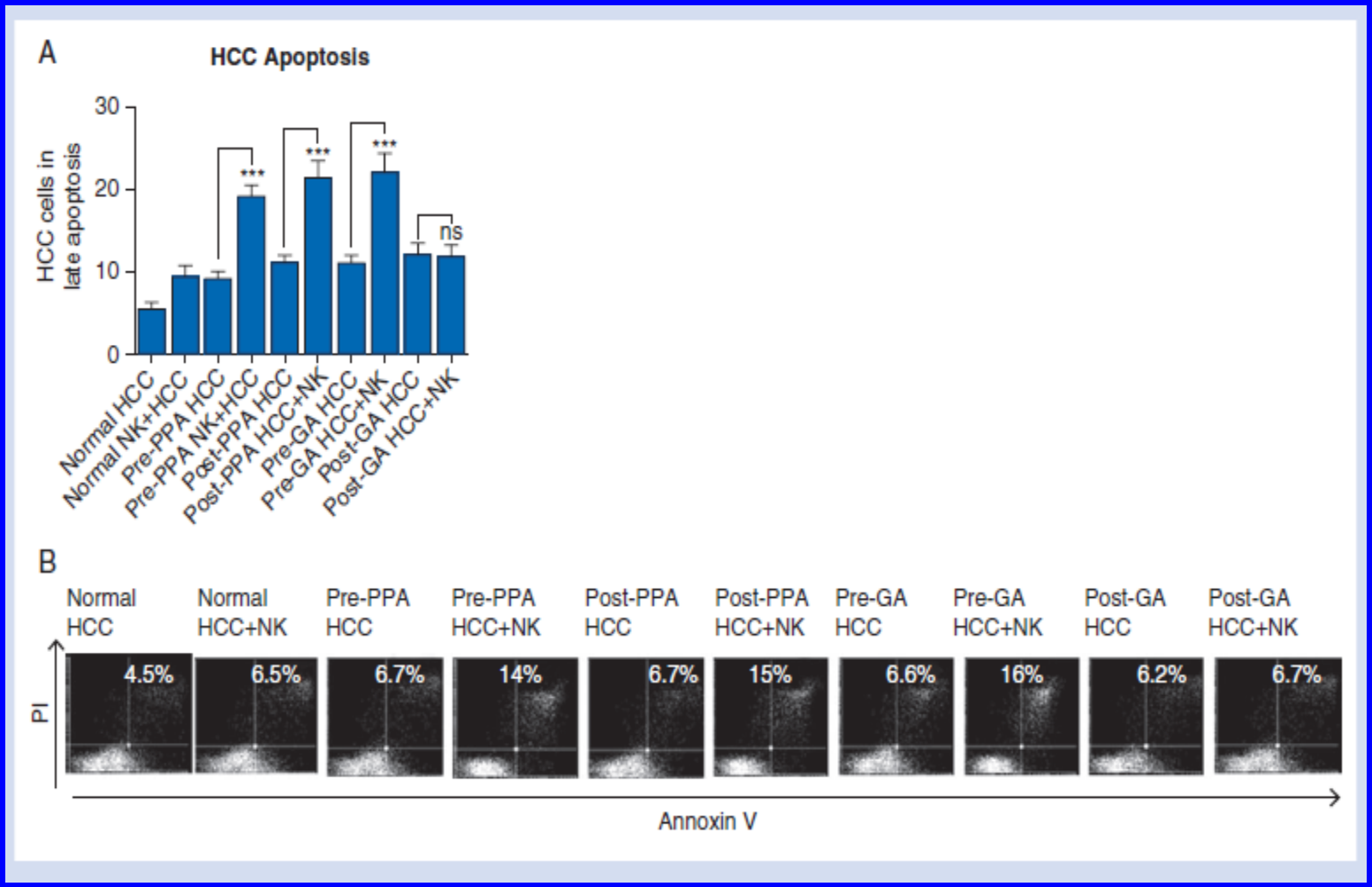
Healthy NK cells:

1. Activatory Receptors
2. Cytokines
3. Cytotoxicity
4. Apoptosis of ERPR+ breast cancer cell line (HCC1500)

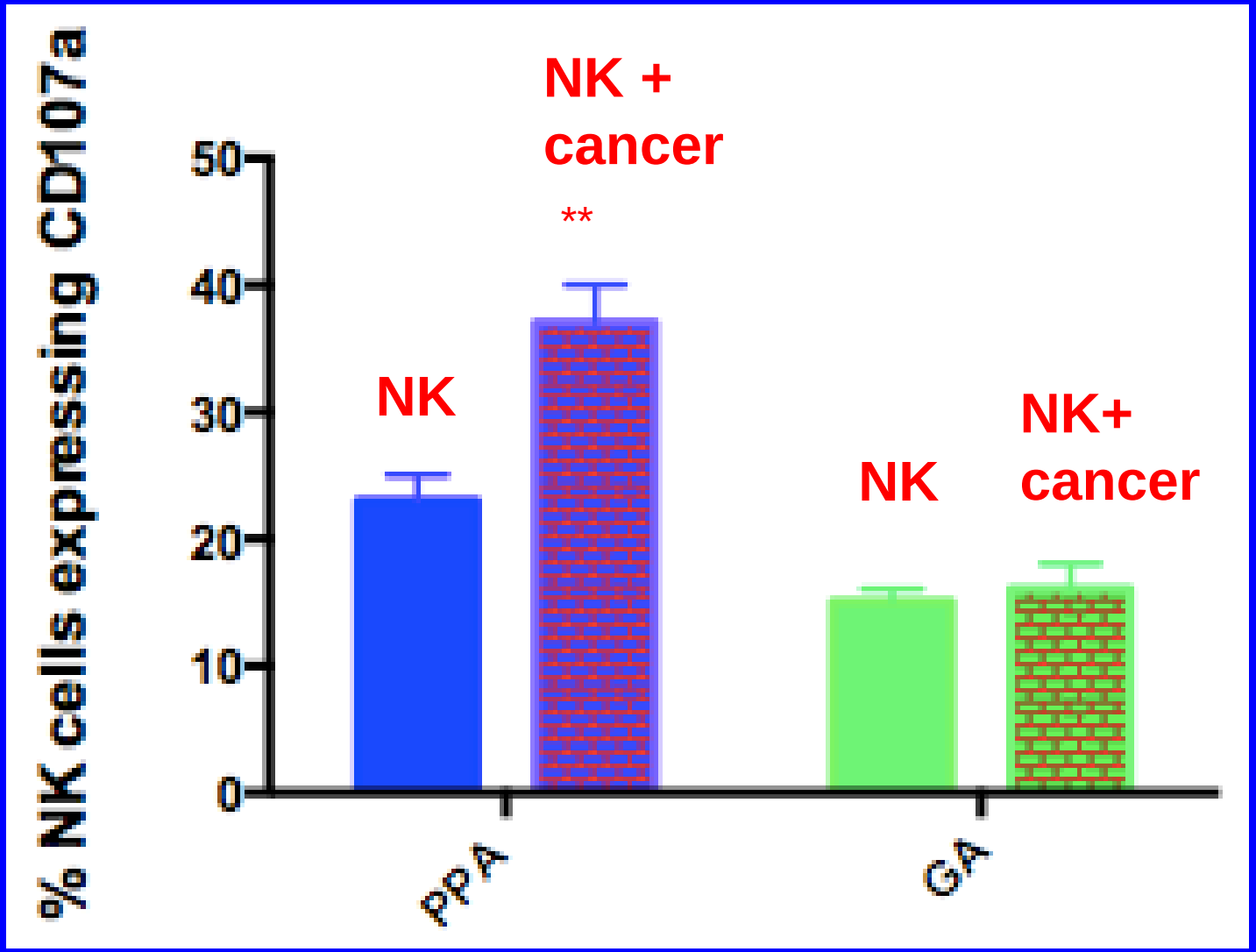
Activatory receptors: CD16



PPA serum increases cancer cell apoptosis



NK cell cytotoxicity



Breast prospective trial CJA

Can J Anesth/J Can Anesth (2015) 62:241–251
DOI 10.1007/s12630-014-0285-8

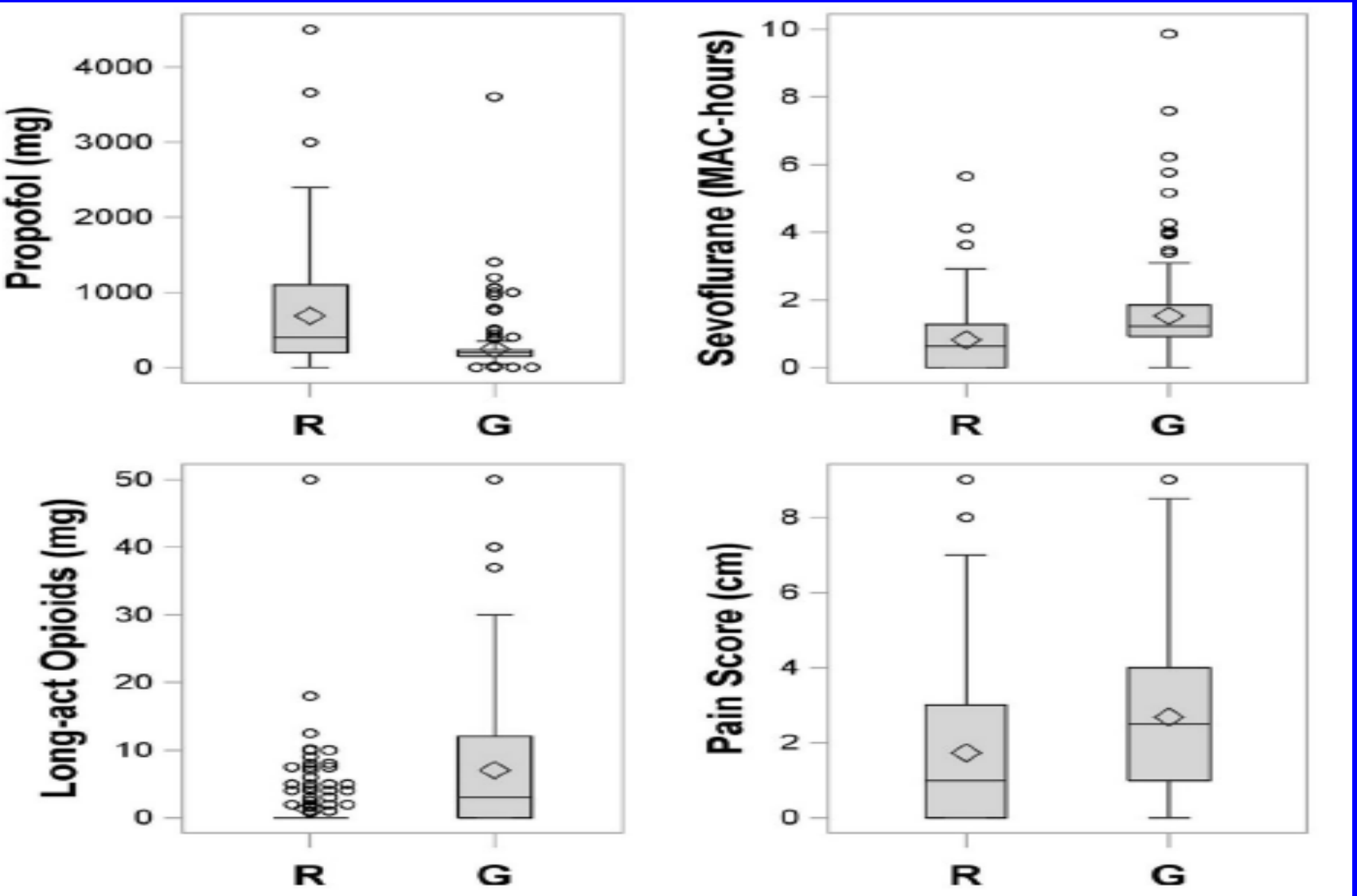
REPORTS OF ORIGINAL INVESTIGATIONS

Thoracic paravertebral regional anesthesia improves analgesia after breast cancer surgery: a randomized controlled multicentre clinical trial

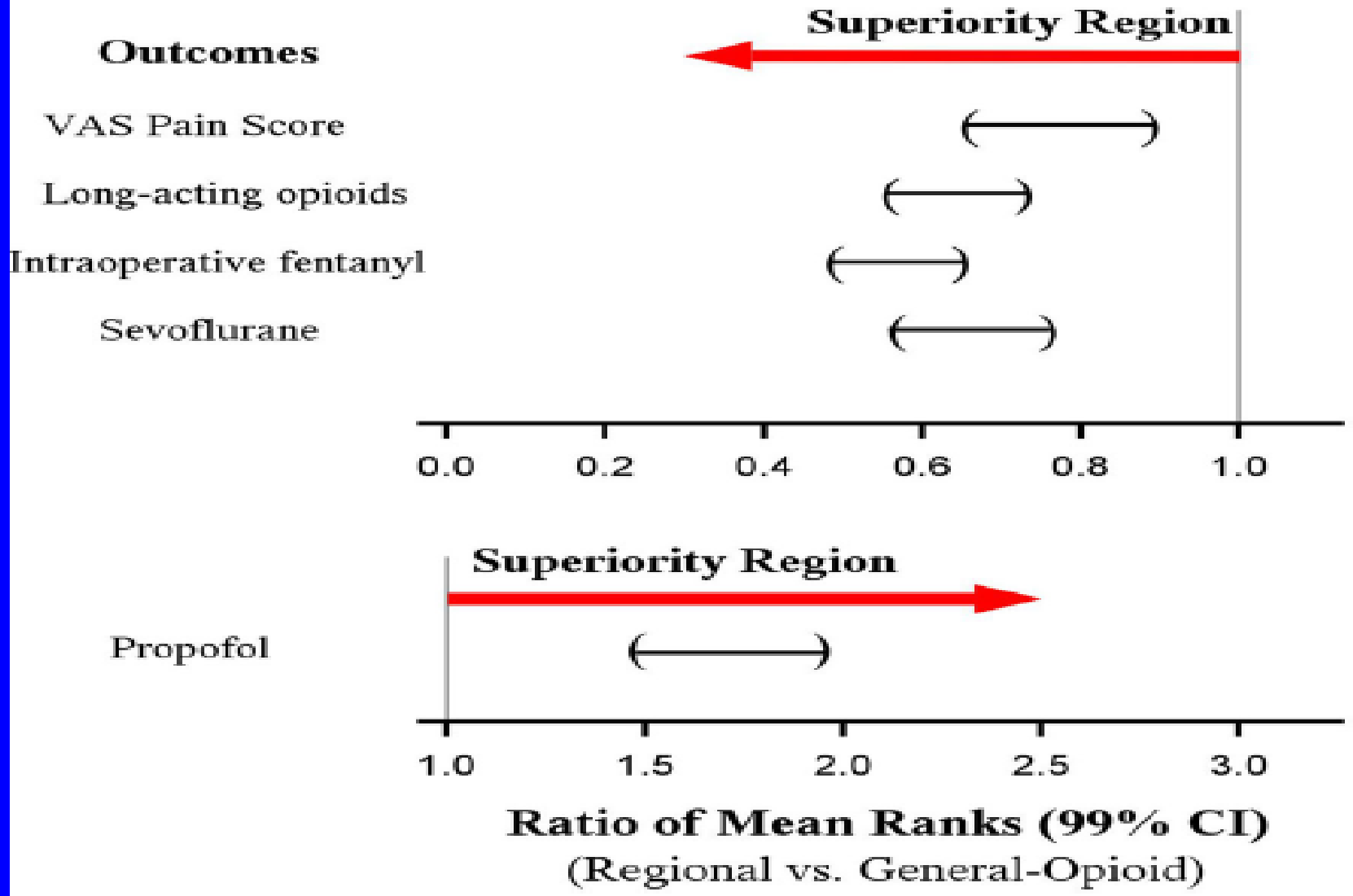
L'anesthésie régionale paravertébrale thoracique améliore l'analgésie après chirurgie pour cancer du sein: essai clinique multicentrique randomisé contrôlé

Jiang Wu, MD · Donal Buggy, MD · Edith Fleischmann, MD · Ivan Parra-Sanchez, MD · Tanja Treschan, MD · Andrea Kurz, MD · Edward J. Mascha, PhD · Daniel I. Sessler, MD

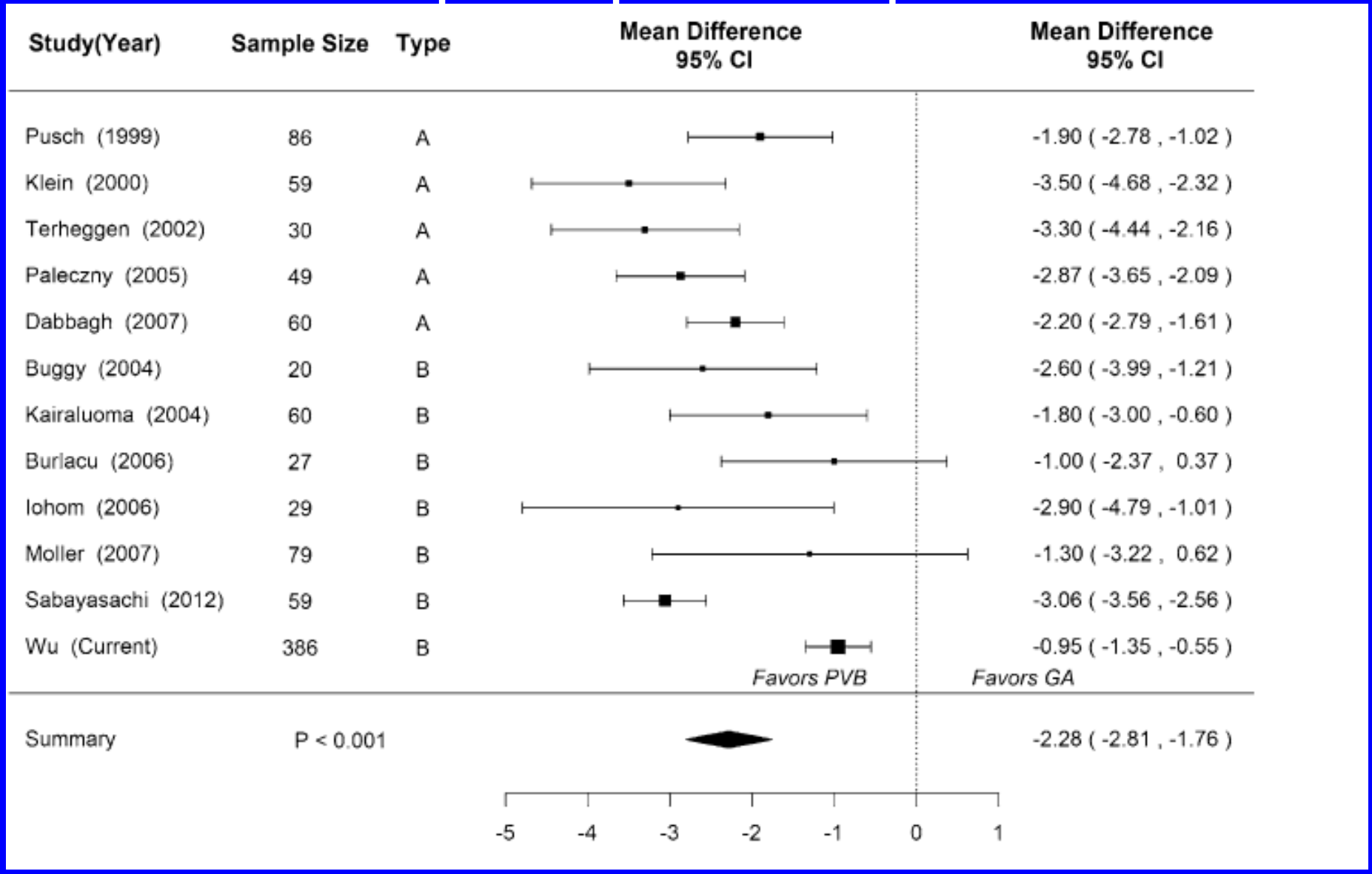
Breast RCT pilot data: use of different drugs between the groups



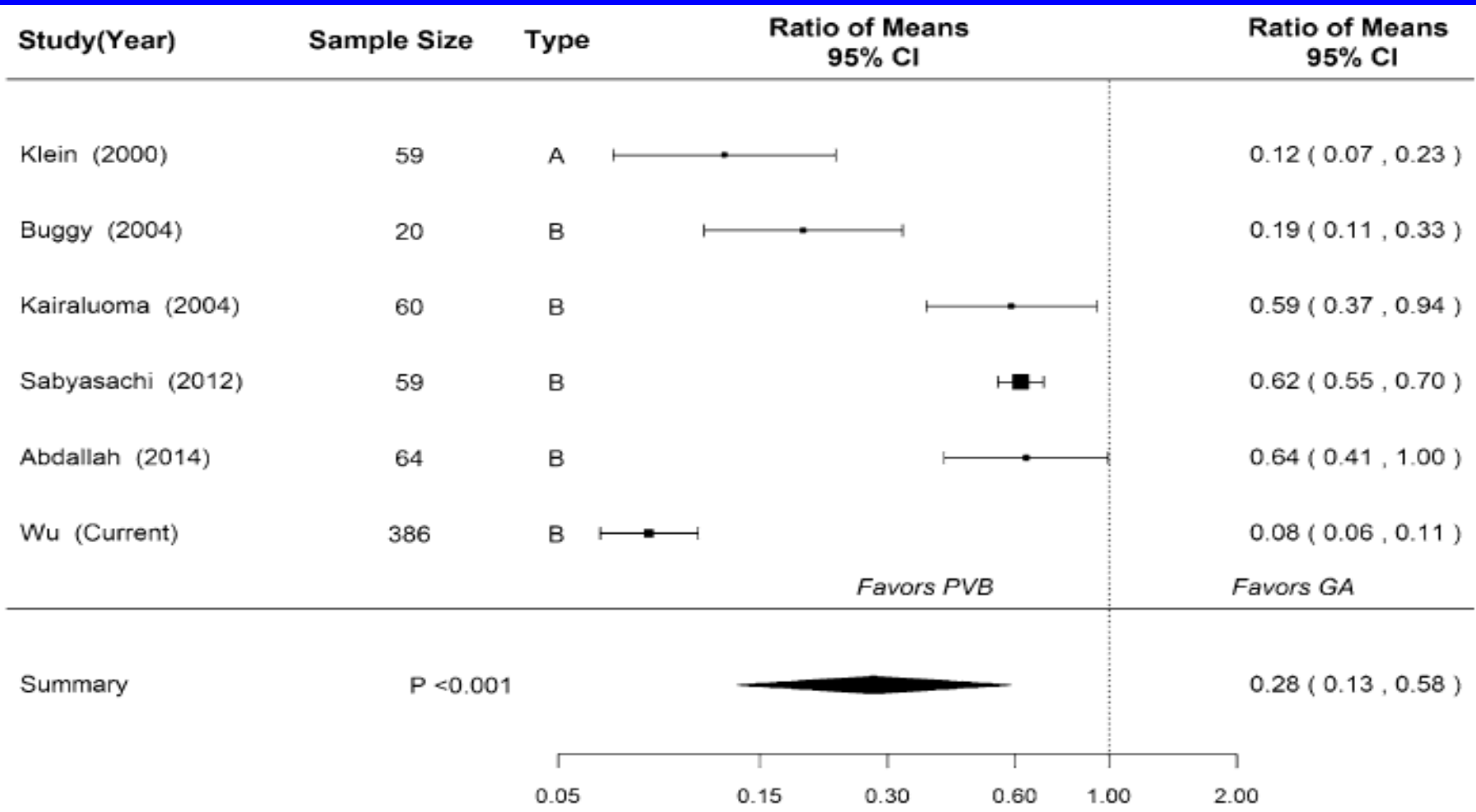
Breast RCT pilot data



Meta-analysis paravertebral-propofol vs GA for postop breast pain



Meta-analysis of PPA vs GA for opioid consumption



Centres

- Mater Dublin
- Cleveland Clinic
- Louisville
- Vienna
- Dusseldorf
- Beijing
- ?Your centre

Negative Conclusions!

- Anaesthetics don’t cause cancer
- Anaesthetics, not even local anaesthetics or regional techniques, will never CURE cancer
- I don’t have a cure for cancer!


?Anaesthesia &
Peroperatve Interventions
Radiotherapy
Chemo & Endocrine Therapy
Surgery

Can anaesthetic technique during primary breast cancer surgery influence cancer outcome?

Professor Donal Buggy,
Mater Misericordiae University Hospital
&
Eccles Unit, National Cancer Control Programme,Dublin, Ireland