University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Dubowitz, JA;Cata, JP;De Silva, AP;Braat, S;Shan, D;Yee, K;Hollande, F;Martin, O;Sloan, EK;Riedel, B;Hiller, J;Koldej, R;Leslie, K;Myles, P;Buggy, D;Wigmore, T;Gottumukkala, V;Sessler, DI

Title:
Volatile anaesthesia and peri-operative outcomes related to cancer: a feasibility and pilot study for a large randomised control trial

Date:
2021-09-01

Citation:
Dubowitz, J. A., Cata, J. P., De Silva, A. P., Braat, S., Shan, D., Yee, K., Hollande, F., Martin, O., Sloan, E. K., Riedel, B., Hiller, J., Koldej, R., Leslie, K., Myles, P., Buggy, D., Wigmore, T., Gottumukkala, V. & Sessler, D. I. (2021). Volatile anaesthesia and peri-operative outcomes related to cancer: a feasibility and pilot study for a large randomised control trial. Anaesthesia, 76 (9), pp.1198-1206. https://doi.org/10.1111/anae.15354.

Persistent Link:
https://hdl.handle.net/11343/298128

Check for updates

Article type : Original Article

Author Manuscript

Original Article

Volatile anaesthesia and peri-operative outcomes related to cancer (VAPOR-C): a feasibility and pilot study for a large randomised control trial

J. A. Dubowitz,[1] J. P. Cata,[2] A. P. De Silva,[3] S. Braat,[3] D. Shan,[4] K. Yee,[4] F. Hollande,[5] O. Martin,[6] E. K. Sloan,[7] B. Riedel[8] and the Global Onco-Anaesthesia Research Collaboration Group*

1 Specialist, 4 Trainee, 8 Professor and Director, Department of Anaesthesia, Peri-operative and Pain Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia

2 Assistant Professor, Department of Anesthesiology and Peri-operative Medicine, Division of Anesthesiology and Critical Care, University of Texas MD Anderson Cancer Center, Houston, TX, USA.

3 Research Fellow, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, 5 Professor, Department of Clinical Pathology and University of Melbourne Centre for Cancer Research, 6 Associate Professor, Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne Australia

7 Associate Professor, Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Parkville, Australia

*See Appendix 1

Correspondence to: J. A. Dubowitz

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ANAE.15354

This article is protected by copyright. All rights reserved

Email: julia.dubowitz@petermac.org

Keywords: anaesthesia; volatile; propofol; TIVA; intravenous anaesthesia; peri-operative outcomes; cancer

Author Manuscript

Summary

Published data suggest that the type of general anaesthesia used during surgical resection of cancer may impact on patient long-term outcome. However, robust prospective clinical evidence is essential to guide a change in clinical practice. We explored the feasibility of conducting a randomised controlled trial to investigate the impact of total intravenous anaesthesia with propofol vs. inhalational volatile anaesthesia on postoperative outcomes of patients having major cancer surgery. We undertook a randomised, double-blind feasibility and pilot study of propofol- total intravenous anaesthesia or volatile-based maintenance anaesthesia during cancer resection surgery at three tertiary hospitals in Australia and the USA. Patients were randomly allocated to receive propofol-total intravenous anaesthesia or volatile-based maintenance anaesthesia. Primary outcomes for this study were successful recruitment to the study and successful delivery of the assigned anaesthetic treatment as per randomisation arm. Of the 217 eligible patients approached, 146 were recruited, a recruitment rate of 67.3% (95%CI 60.6–73.5%). One hundred and forty-five patients adhered to the randomised treatment arm, 99.3% (95%CI 96.2–100%). Intra-operative patient characteristics and postoperative complications were comparable between the two intervention groups. This feasibility and pilot study supports the viability of the protocol for a large, randomised controlled trial to investigate the effect of anaesthesia technique on postoperative cancer outcomes. The volatile anaesthesia and peri-operative outcomes related to cancer (VAPOR-C) study that is planned to follow this feasibility study is an international, multicentre trial with the aim of providing evidence-based guidelines for anaesthetic management of patients requiring major cancer surgery.

Introduction

This article is protected by copyright. All rights reserved

Cancer is a leading cause of death worldwide. Surgical resection is common in the management of solid tumours, with two-thirds of cancer patients (currently about 10 million patients annually) requiring cancer surgery and hence exposure to anaesthesia [1].

Anaesthetic technique has been implicated in modulation of long-term outcomes in surgical cancer patients. Retrospective clinical trials point toward an increase in overall survival with the use of propofol-based total intravenous anaesthesia (propofol-TIVA) compared to inhalational volatile-based anaesthesia for major cancer surgery [2, 3], a finding which is summarised by a recent meta-analysis [4]. This is supported by preclinical studies that show a benefit of propofol-TIVA compared to volatile anaesthesia in reducing tumour cell proliferation, preserving peri-operative immune function and limiting metastasis in various cancer cell lines and in vivo models [5].

An improved understanding of the impact of anaesthetic technique on cancer outcomes has the potential to significantly improve the prognosis of thousands of patients requiring cancer surgery worldwide [6]. However, clinical equipoise remains due to the heterogeneity and predominantly retrospective nature of the available data, with insufficient evidence to warrant a change in clinical practice [4]. Robust, prospective evidence is needed to identify the most appropriate anaesthetic technique for use during cancer resection surgery.

We hypothesised that propofol-based TIVA anaesthesia for major cancer resection surgery would improve disease-free survival and overall survival compared to volatile anaesthesia. To test this, we designed a double-blind randomised controlled trial to investigate the feasibility of a large, multicentre randomised controlled trial aimed at investigating the impact of propofol-TIVA vs. inhalational volatile-based anaesthesia (using sevoflurane) for patients requiring major cancer surgery for colon, rectal or non-small cell lung cancer.

Methods

All patients provided informed, written consent before recruitment to the study. Investigators, research nurses, scientists and authors were governed by the obligations of the declaration of Helsinki and the study results reported in accordance with the 2010 CONSORT guidelines.

This article is protected by copyright. All rights reserved

Author Manuscript

Patients eligible for inclusion were aged 18–80 years and scheduled for elective surgery for resection of solid cancers with curative intent, and not for palliative surgery. All had no documented allergy to anaesthetic agents and no documented history of severe postoperative nausea and vomiting, defined by a modified Apfel score > 3, where propofol-TIVA may be preferred [7].

This randomised, double-blind parallel-group study was conducted at three major tertiary medical centres in Australia and the USA. Using a randomisation list of permuted blocks computer-generated by an independent statistician, patients were randomly allocated on the day of surgery to receive either propofol-TIVA anaesthesia or inhalational volatile anaesthesia in equal groups, with the former delivered via target-controlled infusion pump (in Australia) or weight-based infusion (in the USA). Randomisation was stratified by cancer type (colorectal, lung, breast, melanoma, prostate and 'other') and by hospital site. The treating anaesthetist was unblinded to the treatment arm due to the need to deliver the anaesthetic, and all other peri-operative care was provided at their discretion, including the pragmatic use of propofol for induction within the volatile anaesthesia treatment arm. Investigators and statisticians remained blinded to the treatment arm.

Primary endpoints of this feasibility study were successful ability to recruit patients into the study and successful administration of randomised anaesthetic technique. The secondary (exploratory) endpoints included postoperative outcomes.

The following were recorded for each patient: baseline BMI; ASA physical status; presence of comorbid disease, measured by the Charlson Comorbidity Index [8]; assessment of cardiovascular fitness, measured by the Duke Activity Status Index (DASI) [9]; regular concomitant medication usage; cancer type; cancer stage; and any neoadjuvant oncological therapy.

Intra-operative data collected included: total dose of randomised anaesthetic agent administered; intra-operative analgesia use (opioid, and non-opioid); use of regional anaesthesia techniques; fluid administration; blood transfusion; and duration of surgery. Data on EEG-based depth of anaesthesia monitoring were not recorded in this study.

Presence of postoperative complications within the first 30 days were recorded by organ system according to the definitions of the validated postoperative morbidity survey (POMS) [10]. The Clavien-Dindo classification was used to document the severity of postoperative complications and it was dichotomised into minor complications, grades 1–2,

This article is protected by copyright. All rights reserved

Author Manuscript

not requiring surgical intervention or admission to ICU or severe complications grade 3 and above requiring surgical intervention or admission to ICU [11].

Measures of postoperative recovery were recorded, including: hospital length of stay; ICU length of stay; and days at home within 90 days of surgery [12]. The latter is a patient-centric metric that allows capture of any hospital re-admissions. Functional assessments of physical fitness using the DASI and patient-reported quality of life were performed at baseline and repeated at postoperative day 30. Data were recorded on successful return to adjuvant oncologic therapy (RIOT) in those patients that were recommended for adjuvant therapy by the treating surgical and/or medical oncologist. Return to adjuvant oncologic therapy was measured in the days from date of surgery to commencement of adjuvant oncological therapy. Biospecimens were collected for exploratory analyses, and these will be reported on elsewhere.

Participants were randomly allocated, study data collected and managed using REDCap electronic data capture tools (Research Electronic Data Capture, Vanderbilt University, TN, USA) hosted at the University of Melbourne.. All patients were monitored for adverse events.

Anticipating a 75% recruitment rate and using an exact method (Clopper-Pearson), a sample size of 200 eligible patients were required to provide a 95%CI of the true underlying recruitment rate of 68%–81%. Assuming 75 patients were recruited to each arm and anticipating a successful delivery rate of 91%, then a 95%CI of the true underlying successful delivery rate would be 82%–96%.

The analysis sample included all randomly allocated patients according to their randomised treatment arm. The proportion and corresponding two-sided 95%CI were obtained for the recruitment rate (defined as the proportion of eligible patients who consented to recruitment) and for the successful delivery rate (defined as the proportion of randomised patients who were successfully delivered the anaesthetic assigned, as per their allocated treatment group and without crossover to other anaesthetic technique during the operation).

Pre-operative and intra-operative characteristics and study outcomes were summarised by group (propofol-TIVA vs. inhalational volatile).

Intra-operative patient characteristics were compared between the two treatment groups using the Wilcoxon's rank sum test for the comparison of medians and the Pearson's

This article is protected by copyright. All rights reserved

Author Manuscript

chi-squared test for the comparison of proportions. To compare the study outcomes between treatment groups, we used a logistic regression model to examine the study outcome's RIOT and postoperative complications. A linear regression model was performed on natural log-transformed study outcomes (due to skewed data) for DASI at postoperative day 30 and time to RIOT. Ordinal logistic regression was performed on maximum severity of complications, negative binominal regression on hospital length of stay and POMS score at day 30. A quantile regression model with 100 bootstrap replications was fitted to the outcome data 90-days at home within 90 days of surgery. Each regression model was adjusted for hospital and cancer type and the model for DASI was adjusted for log-transformed baseline DASI values. Organ system complications, admissions to ICU and ICU length of stay were not compared between the treatment groups due to the rarity of these outcomes in this cohort. No adjustment for multiple testing was done due to the explorative nature of the secondary outcomes. All statistical analyses were conducted using Stata 15.0 (Stata Corp, College Station, TX, USA).

Results

This study was conducted over a 2-year period (August 2017 to September 2019; Fig. 1) during which 217 eligible patients were approached for recruitment. A total of 150 patients were recruited, with four patients withdrawing consent after recruitment but prior to randomisation. A total of 146 patients were recruited and randomly allocated to receive either propofol-TIVA or inhalational volatile anaesthesia, indicating a successful recruitment rate of 67.3% (95%CI 60.6–73.5%).

Of all the eligible patients, 10 (58.8%) aged < 40 years declined to participate, compared to 31 (38.3%) patients aged 40–60 years and 30 (25.2%) patients aged > 60 years. The recruitment rate at Peter MacCallum Cancer Centre (the primary recruitment site) was 77.3% (119 recruited out of a total 154 eligible patients); 5.5% of eligible males declined to participate, compared with 64.4% of eligible females ($p < 0.001$). When patients with sex-biased cancers (breast and prostate) were excluded, recruitment rates were comparable between sexes, with 28% of eligible males and 22% of eligible females declining to participate ($p = 0.55$). Twelve percent of eligible prostate cancer patients refused to participate compared with 32% of breast cancer patients ($p = 0.07$). Intra-operative failure of an anaesthetic machine led to one patient requiring anaesthetic management outside of

This article is protected by copyright. All rights reserved

Author Manuscript

the randomised arm, resulting in an adherence to randomisation of 99.3% (95%CI 96.2–100%) across all study patients that was similar between the groups. Complete 30-day follow up data were collected in 141 (96.7%) patients and 90-day follow up in 136 (93%).

Pre-operative characteristics across the study groups were balanced (Table 1). The most common cancer type recruited was prostate followed by colorectal. Presence of potential confounding factors, including lymphovascular space invasion (defined as the presence of malignant cells extending into the blood vessels and/or lymphatics on histology) was equally present between the two study arms. Neoadjuvant chemotherapy and radiotherapy treatment were 21.6% and 16.7% in the propofol-TIVA anaesthesia group, compared to 11.3% and 7.0% in the inhalational volatile group.

Intra-operative patient characteristics were comparable between the two treatment arms (Table 2). Median (IQR [range]) propofol total dose was 2503 mg (1990–3583 [303–9600 mg]) in the propofol-TIVA group, and total dose of volatile anaesthetic was 59.1 ml (29.5–106.5 [10.0–438.0 ml]) in the inhalational volatile group. Intra-operative opioid use, compared using oral morphine equivalent dosage, was similar at 60 mg (equivalent to 300 µg intravenous fentanyl) in both groups with comparable ranges. Intra-operative lidocaine was used in most patients, with 67.7% and 71.0% patients in each of the propofol-TIVA and volatile anaesthesia groups receiving intravenous lidocaine infusion, defined as a total dose of lidocaine greater than 1 $mg.kg^{-1}$. Data on lidocaine were missing in 19 patients. The median total dose of lidocaine administered in these patients was 3.5 $mg.kg^{-1}$ in both groups. Of note, a further 13 patients (10.2%) received a dose of lidocaine < 1 $mg.kg^{-1}$, given as a bolus dose at induction of anaesthesia.

Postoperative surgical complications were comparable between the two groups; 29.7% vs. 36.1% in the propofol-TIVA and inhalational volatile groups, respectively (Table 3), with a comprehensive complication index score of median (IQR [range]) 0 (0.0–9 [0–100]) in both groups. Of the 32 patients with a pre-operative plan for RIOT, 13 (81.3%) in the propofol-TIVA arm and 13 (81.3%) in the volatile arm returned to intended oncologic therapy. Time to RIOT for patients administered propofol-TIVA and inhalational volatile was median (IQR [range]) 44 days (34.5–80.0 [1–122 days]) and 41.5 days (33.0–57.0 [9–162 days]), respectively. The functional status measured in metabolic equivalents at postoperative day 30 was 5.1 (4.0–7.3 [2.7–9.9]) and 5.6 (4.5–7.0 [2.7–9.9]) for patients who

This article is protected by copyright. All rights reserved

Author Manuscript

had received propofol-TIVA and inhalational volatile anaesthesia, respectively, and had declined significantly from pre-operative values in both groups.

Discussion

This feasibility study demonstrated the ability to recruit and randomly allocate patients to propofol-TIVA vs. volatile anaesthesia and deliver the assigned anaesthetic technique during cancer resection surgery. This supports the practicality of our large international multicentre double-blind randomised controlled trial; volatile anaesthesia and peri-operative outcomes related to cancer (VAPOR-C). When planning the feasibility study, anticipated recruitment rate was set at 75% of patients. A slightly lower recruitment rate (67.3%) was achieved, that nonetheless enabled efficient recruitment of patients into the trial across our participating sites. Willingness to participate in the trial was higher amongst older patients, with rates of recruitment being highest in patients aged > 60 years and in those aged 40–60 years, compared to screened patients aged < 40 years. When sex-biased cancers were excluded, men and women agreed to participate in the study in equal proportions. A lower rate of participation amongst breast cancer patients compared to other cancer patients accounted for this difference. This raises the possibility of a recruitment bias that is worth considering when analysis of the main VAPOR-C trial is undertaken.

There was successful adherence to randomisation in 99.3% of cases, in excess of the anticipated 91%. This provides evidence for the feasibility to randomise treatment of patients to either inhalational volatile or propofol-TIVA anaesthesia for the subsequent prospective trial. Whilst anaesthetists are trained to administer TIVA and volatile-based anaesthesia, surveys of worldwide practice suggest that volatile-based inhalational anaesthesia remains the most common choice for anaesthetists [13, 14]. In this study, all patients in the propofol-TIVA arm were successfully managed with the allocated intervention. Successful adherence to the randomised treatment arm is in part dependent on access to equipment required for TIVA anaesthesia. Whilst in Australia access to programmed target-controlled infusion (Beckton Dickinson, Berkshire, UK) pumps is widespread, target-controlled infusion pumps are not approved for use in the USA by the US Food and Drug Administration. Despite this, there were no reported issues with delivery of propofol-TIVA using a weight-adjusted infusion protocol at the recruitment site in the USA,

This article is protected by copyright. All rights reserved

Author Manuscript

and only one case of failed adherence to the randomised treatment arm occurred due to equipment failure.

Anaesthetists used intravenous lidocaine infusion in 69.3% of patients in this trial, suggesting its clinical applicability as an intra-operative adjunct based on its analgesic and anti-inflammatory properties. In this study, patients received an average intravenous lidocaine infusion of 3.5 $mg.kg^{-1}$ intra-operatively, which is well within the reported safe dosing schedule for intravenous lidocaine infusion [15]. Intravenous lidocaine has anti-inflammatory activity [16] and preclinical evidence [17] suggests that lidocaine can reduce tumour growth and spread through Src kinase pathway inhibition, and may preserve immune cell function [18]. Consequently, it has a potential role in modulating the inflammatory response to cancer surgery and may improve long-term cancer outcomes. The role of intravenous lidocaine in reducing postoperative complications and facilitating return to adjuvant oncologic therapy has not been studied. Power analysis for the definitive trial indicates that an increase in sample size of only 10% is required to study propofol-TIVA vs. volatile anaesthesia and intravenous lidocaine. This has been incorporated into the design of the main VAPOR-C trial in the form of a 2 x 2 factorial design with sub-randomisation to intravenous lidocaine/placebo. Secondary endpoints in the confirmatory trial will also explore the role of lidocaine on chronic postoperative pain.

In the postoperative period, timely completion of intended adjuvant chemoradiotherapy has been identified as a key prognostic factor in patients undergoing surgical resection of cancer who have a disease stage that requires further therapy [19]. This has led to the concept of RIOT being regarded as a potential key performance indicator for institutions [20]. A major factor that contributes to failed RIOT is incomplete recovery from cancer surgery, with two major barriers being postoperative complications and patient frailty [19]. With an uneventful postoperative course devoid of postoperative complications, patients can return to baseline functional status earlier and be ready to receive adjuvant therapy in a timely manner. Using the approach of documenting clinician recommendations for adjuvant therapy at first postoperative review and calculating time from surgery to commencement of adjuvant therapy, we were able to accurately track patients' RIOT. This approach of measuring RIOT has been incorporated into the design of the confirmatory trial, and will be analysed in conjunction with postoperative complication rates to examine the relationship between postoperative course, RIOT and long-term cancer outcomes.

This article is protected by copyright. All rights reserved

Author Manuscript

Rate of postoperative complications in this study was in keeping with published rates for other major surgery [21]. No difference in rates of postoperative complications between the treatment arms was found, which supports the safety of the trial design. We collected data on postoperative complications using the definitions from the validated POMS survey. Whilst this tool is validated to provide a snapshot of early postoperative complications that delay hospital discharge [22], it was not detailed enough to provide a complete description of the number and severity of complications experienced by each patient. By reporting on the site of complication as well as severity (using the Clavien-Dindo severity of postoperative complication grading system) and incorporating these data into a composite measure (the complication index score) we were able to more accurately compare the clinical burden of complications encountered by each patient. The complication index score will be used to compare postoperative complications within 30 days in the confirmatory trial.

Strengths of this feasibility and pilot trial include the randomised, controlled, multicentre, double-blinded study design. In addition, the study was designed to estimate primary outcomes of rate of randomisation and adherence to treatment arm and was able to complete prolonged follow-up of enrolled patients. The pragmatic study design enabled recruitment to the trial whilst reflecting real life clinical practice amongst anaesthetists across different healthcare systems (Australia and USA).

In conclusion, the findings of this feasibility study support the conduct of our planned confirmatory randomised control trial that is designed to provide a definitive answer to whether anaesthesia technique impacts cancer outcomes. We are currently recruiting for this trial.

Acknowledgements

The authors would like to thank E. Crone and K. Coleman for assistance with patient recruitment and data collection. This study obtained ethics approval from the institutional review boards at Peter MacCallum Cancer Centre, Australia and University of Texas M.D. Anderson Cancer Center, USA. This trial was prospectively registered with ANZCTR (ACTRN12617001065381) and ClinicalTrials.gov (NCT04316013. The work was funded by the Australian and New Zealand College of Anaesthetists Anaesthetists Foundation and the National Health and Medical Research Council. These funding bodies played no other role in

This article is protected by copyright. All rights reserved

Author Manuscript

the study. JD is funded by Monash University PhD and ANZCA scholarships. No other competing interests declared

Author Manuscript

References

1. Sullivan R, Alatise OI, Anderson BO, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncology* 2015; **16**: 1193-224.
2. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic—sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis. *Uppsala Journal of Medical Sciences* 2014; **119**: 251-61.
3. Wigmore T, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery. A Retrospective Analysis. *Anesthesiology* 2016; **124**: 69-79.
4. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. *Canadian Journal of Anaesthesia* 2019; **66**: 546-61.
5. Dubowitz JA, Sloan EK, Riedel BJ. Implicating anaesthesia and the perioperative period in cancer recurrence and metastasis. *Clinical and Experimental Metastasis* 2018; **35**: 347-58.
6. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncology* 2011; **12**: 933-80.
7. Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. *British Journal of Anaesthesia* 2002; **88**: 234-40.
8. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American Journal of Epidemiology* 2011; **173**: 676-82.

This article is protected by copyright. All rights reserved

9. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391**: 2631-40.

10. Bennett-Guerrero E, Welsby I, Dunn TJ, et al. The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery. *Anesthesia and Analgesia* 1999; **89**: 514-9.

11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004; **240**: 205-13.

12. Bell M, Eriksson LI, Svensson T, et al. Days at Home after Surgery: An Integrated and Efficient Outcome Measure for Clinical Trials and Quality Assurance. *EClinicalMedicine* 2019; **11**: 18-26.

13. Lim A, Braat S, Hiller J, Riedel B. Inhalational versus propofol-based total intravenous anaesthesia: practice patterns and perspectives among Australasian anaesthetists. *Anaesthesia and Intensive Care* 2018; **46**: 480-7.

14. Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: protocol, methods, and analysis of data. *British Journal of Anaesthesia* 2014; **113**: 540-8.

15. Weibel S, Jokinen J, Pace NL, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *British Journal of Anaesthesia* 2016; **116**: 770-83.

16. Hollmann Markus W, M.D, Durieux Marcel E, M.D., Ph.D. Local Anesthetics and the Inflammatory Response: A New Therapeutic Indication? *Anesthesiology* 2000; **93**: 858-75.

17. Chamaraux-Tran T-N, Piegeler T. The Amide Local Anesthetic Lidocaine in Cancer Surgery-Potential Antimetastatic Effects and Preservation of Immune Cell Function? A Narrative Review. *Frontiers in Medicine* 2017; **4**: 235.

Author Manuscript

This article is protected by copyright. All rights reserved

18. Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. *Regional Anesthesia and Pain Medicine* 2015; **40**: 43-8.

19. Kim BJ, Caudle AS, Gottumukkala V, Aloia TA. The Impact of Postoperative Complications on a Timely Return to Intended Oncologic Therapy (RIOT): the Role of Enhanced Recovery in the Cancer Journey. *International Anesthesiology Clinics* 2016; **54**: e33-46.

20. Aloia T, Zimmitti G, Conrad C, Gottumukalla V, Kopetz S, Vauthey J. Return to intended oncologic treatment (RIOT): a novel metric for evaluating the quality of oncosurgical therapy for malignancy. *Journal of Surgical Oncology* 2014; **110**: 107-14.

21. The International Surgical Studies Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *British Journal of Anaesthesia* 2016; **117**: 601-9.

22. Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of Clinical Epidemiology* 2007; **60**: 919-28.

Author Manuscript

Figure Legends

Figure 1 Consort diagram showing the number of subjects screened, enrolled, randomised, and included in the primary analysis.

Table 1 Pre-operative baseline and clinical characteristics. Values are number (proportion), median (IQR [range]) or mean (SD).

	Propofol-TIVA	**Volatile**
	n=74	**n=72**

This article is protected by copyright. All rights reserved

Male sex; n	50 (67%)	54 (75%)
Age; year	62.8 (55.6–70.3 [30.3–80.5])	64.0 (56.9–69.1 [31.5–76.9])
BMI; $kg.m^{-2}$	28.4 (7.3)	27.7 (4.5)
ASA score		
1	3 (4%)	3 (4%)
2	40 (54%)	44 (61%)
3	31 (42%)	25 (35%)
4	0	0
Cancer type		
Breast	7 (10%)	7 (10%)
Colorectal	16 (22%)	17 (24%)
Prostate	32 (43%)	31 (43%)
Melanoma	6 (8%)	4 (6%)
Lung	1 (1%)	0
Other*	12 (16%)	13 (18%)
Evidence of LVSI		
Negative	46 (62%)	46 (64%)
Positive	10 (14%)	9 (13%)
Unknown	18 (24%)	17 (24%)
AJCC Cancer stage		
0	3 (4%)	2 (3%)
1	17 (24%)	16 (24%)
2	21 (30%)	29 (43%)
3	23 (33%)	17 (25%)
4	6 (9%)	3 (5%)
Neoadjuvant therapy		
Chemotherapy	16 (22%)	8 (11%)
Radiotherapy	12 (17%)	5 (7%)
Immunotherapy	3 (4%)	2 (3%)
Hormone therapy	3 (4%)	4 (6%)

Author Manuscript

This article is protected by copyright. All rights reserved

Steroids	5 (7%)	5 (7%)
Regular medication		
Beta-blocker	12 (16%)	4 (6%)
NSAID	1 (1%)	2 (3%)
Charlson Comorbidity Index	4 (3–5 [2–12])	4 (3–5 [2–9])
Duke Activity Status Index at baseline (METS)	9.0 (6.6–9.9 [2.7–9.9])	9.0 (8.0–9.9 2.7–9.9])

TIVA, total intravenous anaesthesia; AJCC, American Joint Committee on Cancer; LVSI, lymphovascular space invasion; NSAID, non-steroidal anti-inflammatory drug; METS, metabolic equivalent of task (1 MET = 3.5ml.kg^{-1}min^{-1})

A cancer stage of 0 was recorded for breast cancer patients with ductal carcinoma in-situ (DCIS).

* Other cancers included squamous cell carcinoma (n=13), sarcoma (n=2), liver (n=1), lung (n=1), endometrial (n=3), thyroid (n=1), pancreas (n=1), bladder (n=1), urothelial (n=1), carcinoma of unknown origin (n=1).

Missing data

AJCC cancer stage: propofol-TIVA (4/74, 5.4%); Volatile (5/72, 6.9%).

Chemotherapy = volatile (1/72, 1.4%).

Radiotherapy: propofol-TIVA (2/74, 2.7%); Volatile (1/72, 1.4%).

Immunotherapy: propofol-TIVA (2/74, 2.7%); Volatile (1/72, 1.4%).

Hormone therapy: TIVA (3/74, 4.1%).

Steroids: propofol-TIVA (2/74, 2.7%); Volatile (2/72, 2.8%).

Table 2 Intra-operative patient characteristics. Values are number (proportion) or median (IQR [range]).

	Propofol-TIVA n=74	**Volatile n=72**	**p value**

This article is protected by copyright. All rights reserved

Author Manuscript

Adherence to allocated anaesthetic arm of trial	74 (100%)	71 (99%)	
Oral morphine equivalent opioid dose; mg	60.0 (30.0–80.0 [0–110])	60.0 (36.3–79.0 [0–130])	0.97
Regional anaesthesia	22 (30%)	16 (22%)	0.30
Epidural	7 (19%)	2 (3%)	0.09
Spinal	15 (20%)	11 (15%)	0.43
Paravertebral	0	1 (1%)	0.31
Transverse abdominis plane	0	3 (4%)	0.08
Intercostal catheter	1 (1%)	0	0.32
Intravenous lidocaine	44 (67%)	44 (71%)	0.69
Total lidocaine dose; $mg.kg^{-1}$	3.5 (2.3–4.8 [1.0–9.9])	3.5 (1.9–4.2 [1.1–16.6])	0.48
Medication; n			
Dexamethasone	53 (72%)	60 (85%)	0.06
Beta-blocker	3 (4%)	5 (7%)	0.43
NSAID	21 (28%)	20 (28%)	0.98
Ketamine	9 (12%)	9 (13%)	0.93
Blood transfusion			
Number of patients	5 (7%)	4 (6%)	0.78
Number of units	1 (0.0–2.0 [0–7])	1 (0.0–3.5 [0–5])	0.90
Total fluids; $ml.kg^{-1}.h^{-1}$	4.7 (3.2–7.3 [0.0–16.3])	4.9 (3.6–6.7 [0.0–22.2])	0.79
Duration of surgery; min	195 (160–270 [40–905)	210 (160–270 [27–1327)	0.82

NSAID, non-steroidal anti-inflammatory drugs

Analyses for intravenous lidocaine are restricted to patients who were administered a lidocaine dose >1 $mg.kg^{-1}$.

Missing data for each outcome

Intravenous lidocaine: TIVA (9/74, 12.2%); volatile (10/72, 13.9%).

This article is protected by copyright. All rights reserved

Author Manuscript

Medication: propofol-TIVA (0/74, 0%); volatile (1/72, 1.4%).

Total fluids: propofol-TIVA (7/74, 9.5%); volatile (6/72, 8.3%).

Duration of surgery: propofol-TIVA (0/74, 0%); volatile (1/72, 1.4%).

Author Manuscript

Table 3 Comparison of postoperative outcomes between the two study arms. Values are median (IQR [range]) or number (proportion).

	Propofol-TIVA n=74	**Volatile n=72**	**p value**
Clinical outcomes			
POMS within 30 days	0.0 (IQR 0.0–1.0 [2.7–9.9])	0.0 (IQR 0.0–1.0 [0.0–7.0])	0.71
Postoperative complications within 30 days	22 (230%)	26 (36%)	0.31
Pulmonary	1 (1%)	1 (1%)	
Infectious	9 (12%)	11 (15%)	
Renal	6 (8%)	3 (4%)	
Gastro-intestinal	12 (16%)	6 (8%)	
Cardiovascular	4 (5%)	7 (10%)	
Neurological	2 (3%)	2 (3%)	
Haematological	1 (1%)	2 (3%)	
Wound	0	6 (8%)	
Pain	1 (1%)	0	
Maximum severity of complications within 30 days (as per Clavien-Dindo classification); n = 48			0.10
1	12 (55%)	8 (31%)	
2	8 (36%)	14 (54%)	
3	1 (5%)	4 (15%)	
4	0	0	
5	1 (5%)	0	
Comprehensive complication index; n=144	0 (0.0–9 [0–100])	0 (0.0–9 [0–44])	0.37

This article is protected by copyright. All rights reserved

DASI at day 30 (METS); n=146	5.1 (4.0–7.3 [2.7–9.9])	5.6 (4.5–7.0 [2.7–9.9])	0.58
RIOT achieved; n =32	13 (81%)	13 (81.3%)	0.62
Time to RIOT; days, n=32	44.0 (34.5–80.0 [1–122])	41.5 (33.0–57.0 [9–162])	0.62
Logistical outcomes			
Hospital length of stay; days; n=144	1.0 (1.0–6.0 [0–22.0])	2.0 (1.0–5.0 [0–20.0])	0.49
Unplanned admission to ICU; n =3	2 (4%)	1 (1.4%)	
ICU length of stay; days; n=3	2.5 (1.0–4.0 [1.0–4.0])	1.0 (1.0–1.0 [1.0–1.0])	
Days at home at 90 days; days; n=33	82 (78–88 [0–89])	83 (78–86 [64–89])	1.00

POMS, postoperative morbidity survey; DASI, Duke Activity Status Index; METS, metabolic equivalent of task (1 MET = 3.5ml.kg^{-1}min^{-1}); RIOT, return to intended oncologic treatment; Time to RIOT, received postoperative oncological therapy when indicated by treating team.

Organ system complications, unplanned admissions to ICU and ICU length of stay were not compared between propofol-TIVA and volatile due to rarity of these outcomes.

Appendix 1. Global Onco-Anesthesia Research Collaboration Group Collaborators.

J. Hiller, Peter MacCallum Cancer Centre, University of Melbourne and Monash University, Australia.

R. Koldej, Peter MacCallum Cancer Centre and University of Melbourne, Australia.

K. Leslie, Royal Melbourne Hospital and University of Melbourne, Australia.

This article is protected by copyright. All rights reserved

Author Manuscript

P. Myles, Alfred Health and Monash University, Australia.

D. Buggy, Mater University Hospital, University College Dublin, Ireland.

T. Wigmore, Royal Marsden NHS Trust, London, England.

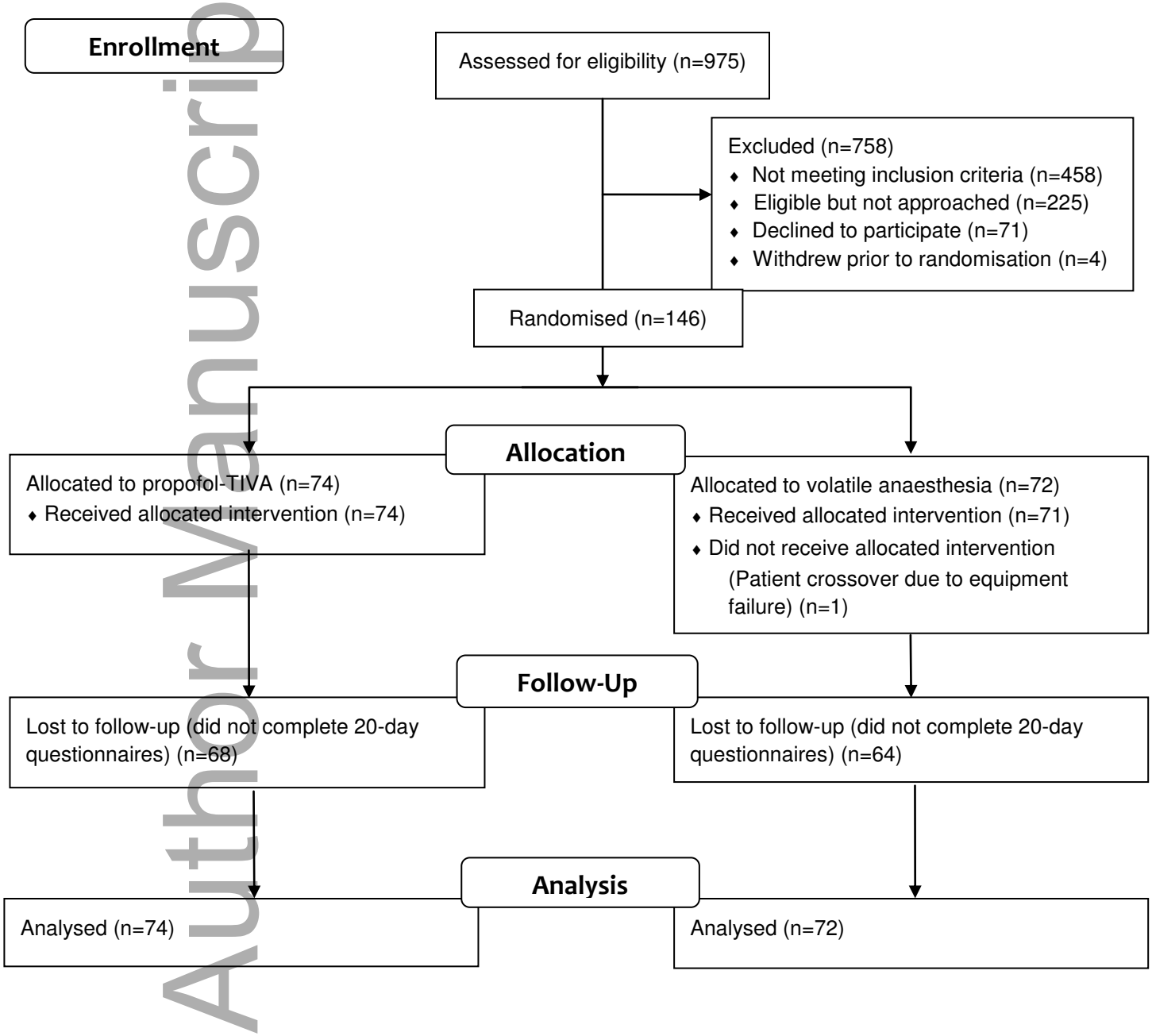
V. Gottumukkala, University of Texas MD Anderson Cancer Centre, Houston, TX, USA.

D. I. Sessler, Cleveland Clinic, Cleveland, OH, USA.

Author Manuscript

This article is protected by copyright. All rights reserved

Author Manuscript



This article is protected by copyright. All rights reserved