Anaesthetic interventions and long-term tumour recurrence

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Surgery is a major component of the treatment plan for patients with potentially curable solid tumours. The efficacy of surgery in preventing tumour recurrence is affected by several factors, including disease stage, adequacy of surgical tumour resection, and intrinsic antitumour immunity.[1] Although adequate intraoperative and postoperative pain control is an important component of optimum recovery after surgery, pain might also be another factor affecting the risk of long-term recurrence after cancer surgery.[1] Specifically, pain has both direct and indirect (ie, mediated via the surgical stress response) immunosuppressive effects,[2] as do some commonly used pain-control drugs (eg, inhaled general anaesthetics and opioids).[3]

Most evidence establishing a link between pain, anaesthetic technique, and tumour recurrence originates from animal and in-vitro studies,[4] and clinical data in patients are scarce and non-definitive. Several studies have examined the association of anaesthesia type and pain management technique with risk of tumour recurrence after cancer surgery, with mixed results.[5] Importantly, most previous studies in patients have been non-randomised in design and, therefore, severely limited by the many measured and unmeasured confounders that affect choice of anaesthesia type for major surgery.[6]

In *The Lancet*, Daniel Sessler and colleagues[7] present the results of a multicentre randomised controlled trial that assessed whether the combination of an intravenous anaesthetic agent (propofol) and regional anaesthesia technique (nerve block) in breast cancer surgery could prevent long-term tumour recurrence. Regional anaesthesia techniques mitigate the surgical stress response,[3] decrease pain intensity, preserve immune surveillance activity, and reduce exposure to possibly harmful drugs (eg, opioids),[8] while propofol has beneficial effects on systemic inflammation and immune function. After analysis of 2108 women younger than 85 years in the trial, the second interim analysis met prespecified futility criteria with respect to the primary endpoint of time to tumour recurrence over a median follow-up of 3 years.

Sessler and colleagues deserve credit for overcoming the logistical challenges of an 11-year recruitment period, a 6-year follow-up period, and implementation of a paravertebral nerve block procedure (blocking intercostal nerves innervating the breast) across many different anaesthesia providers at 13 study sites in eight countries. This clinically important trial has many strengths, including high methodological quality, a large sample size (n=2108) exceeding that of all previous similar trials combined, few crossovers (n=6 [0·3%]) in assigned anaesthetic technique, a high proportion of successful follow-up (97% [n=67 lost to follow-up]), a generalisable global population, and a pragmatic design consistent with usual clinical practice. Although the trial was terminated early, the estimated hazard ratio (HR) for time-to-recurrence had a 95% CI that excluded any moderate-sized treatment effect (HR 0·97, 95% CI 0·74–1·28). Therefore, a combination of paravertebral nerve block and intravenous propofol anaesthesia (by comparison with the typical clinical approach of general inhaled anaesthesia and opioid analgesia) is unlikely to reduce the risk of tumour recurrence in most patients having breast cancer surgery. These robust findings disprove earlier expectations and address relevant limitations noted previously.[5]

Some important issues should be considered when interpreting the results of this trial. First, although the sample was drawn from 13 hospitals in eight countries, almost 60% of participants were enrolled from one hospital in China. Furthermore, evidence was seen of effect modification based on surgery being done at this centre (p=0·039 for the interaction between Chinese

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and non-Chinese study sites), with a suggestion of a more beneficial effect of paravertebral nerve blocks and propofol anaesthesia on time-to-recurrence in patients from China (HR 0·77, 95% CI 0·55–1·09). Further research is needed to assess these subgroup effects, which might reflect a chance finding, genetic variations,[9] and differences in overall breast cancer care. Second, pain intensity and exposure to inhaled volatile general anaesthetic might have a dose–response relation with risk for tumour recurrence. In this study, the duration of surgery was, on average, only 1·3 h in both study groups. Thus, patients assigned to general anaesthesia and opioids received relatively low amounts of opioids in the perioperative period and had a relatively short exposure to inhaled general anaesthetic compared with the usual duration of most tumour resection surgeries. Therefore, it is plausible that the benefits of regional nerve block and propofol anaesthesia apply principally to patients undergoing prolonged procedures with more associated surgical pain (eg, colon cancer resection surgery).

The most striking finding of this trial could relate to the secondary outcome of chronic post-surgical pain. Contrary to previous promising data,[10] at 1 year after surgery, at least one in four participants in both study groups had persistent incisional pain, and one in 15 had developed neuropathic pain. These pain-related complications represent important long-term morbidities of breast cancer surgery. Further research is needed to ascertain if either improvements in the nerve block technique (eg, by use of ultrasound guidance) or addition of other analgesic agents[11] could help prevent this important and frequent cause of postoperative morbidity.

*Faraj W Abdallah, Duminda N Wijeysundera
Department of Anesthesiology and Pain Medicine, and the Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON K1H 8L6, Canada (FWA); Department of Anesthesia (FWA, DNW) and Institute of Health Policy, Management, and Evaluation (DNW), University of Toronto, Toronto, ON, Canada; and Li Ka Shing Knowledge Institute of St Michael's Hospital (FWA, DNW) and Department of Anesthesia, St Michael's Hospital (DNW), Toronto, ON, Canada
fabdallah@toh.ca

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What is the first choice for blood pressure treatment?

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Following the new definition in the 2017 American College of Cardiology/American Heart Association hypertension guideline, 103·3 million adults in the USA now have hypertension.[1] The majority of these people are candidates for pharmacological antihypertensive therapy. Health-care providers faced with the question of which medication to prescribe first for newly diagnosed patients get little help from current hypertension guidelines. These guidelines recommend multiple first-line drug classes, including thiazide or thiazide-like diuretics (THZs), angiotensin converting-enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs),[2,3] and, in some cases, β blockers.[4] Which of these medications should be preferentially initiated in newly diagnosed hypertensive patients remains undecided.[1,5]

The LEGEND-HTN study[6] attempts to answer this question, and is the largest and most comprehensive

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

*Daniel I Sessler, Lijian Pei, Yuguang Huang, Edith Fleischmann, Peter Marhofer, Andrea Kurz, Douglas B Mayers, Tanja A Meyer-Treschan, Martin Grady, Ern Yu Tan, Sabry Ayad, Edward J Mascha, Donal J Buggy, on behalf of the Breast Cancer Recurrence Collaboration**

Summary

Background Three perioperative factors impair host defence against recurrence during cancer surgery: the surgical stress response, use of volatile anaesthetic, and opioids for analgesia. All factors are ameliorated by regional anaesthesia-analgesia. We tested the primary hypothesis that breast cancer recurrence after potentially curative surgery is lower with regional anaesthesia-analgesia using paravertebral blocks and the anaesthetic propofol than with general anaesthesia with the volatile anaesthetic sevoflurane and opioid analgesia. A second hypothesis was that regional anaesthesia-analgesia reduces persistent incisional pain.

Methods We did a randomised controlled trial at 13 hospitals in Argentina, Austria, China, Germany, Ireland, New Zealand, Singapore, and the USA. Women (age <85 years) having potentially curative primary breast cancer resections were randomised by computer to either regional anaesthesia-analgesia (paravertebral blocks and propofol) or general anaesthesia (sevoflurane) and opioid analgesia. The primary outcome was local or metastatic breast cancer recurrence. The secondary outcome was incisional pain at 6 months and 12 months. Primary analyses were done under intention-to-treat principles. This trial is registered with ClinicalTrials.gov, NCT00418457. The study was stopped after a preplanned futility boundary was crossed.

Findings Between Jan 30, 2007, and Jan 18, 2018, 2132 women were enrolled to the study, of whom 24 were excluded before surgery. 1043 were assigned to regional anaesthesia-analgesia and 1065 were allocated to general anaesthesia. Baseline characteristics were well balanced between study groups. Median follow-up was 36 (IQR 24–49) months. Among women assigned regional anaesthesia-analgesia, 102 (10%) recurrences were reported, compared with 111 (10%) recurrences among those allocated general anaesthesia (hazard ratio 0·97, 95% CI 0·74–1·28; p=0·84). Incisional pain was reported by 442 (52%) of 856 patients assigned to regional anaesthesia-analgesia and 456 (52%) of 872 patients allocated to general anaesthesia at 6 months, and by 239 (28%) of 854 patients and 232 (27%) of 852 patients, respectively, at 12 months (overall interim-adjusted odds ratio 1·00, 95% CI 0·85–1·17; p=0·99). Neuropathic breast pain did not differ by anaesthetic technique and was reported by 87 (10%) of 859 patients assigned to regional anaesthesia-analgesia and 89 (10%) of 870 patients allocated to general anaesthesia at 6 months, and by 57 (7%) of 857 patients and 57 (7%) of 854 patients, respectively, at 12 months.

Interpretation In our study population, regional anaesthesia-analgesia (paravertebral block and propofol) did not reduce breast cancer recurrence after potentially curative surgery compared with volatile anaesthesia (sevoflurane) and opioids. The frequency and severity of persistent incisional breast pain was unaffected by anaesthetic technique. Clinicians can use regional or general anaesthesia with respect to breast cancer recurrence and persistent incisional pain.

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Introduction

Breast cancer is the most common cancer in women and the second leading cause of cancer death.[1] Mortality from breast cancer is usually attributable to distant organ metastasis despite surgical resection with curative intent. Surgery is the primary and most effective treatment for breast cancer, but residual disease in the form of scattered micrometastases and tumour cells is usually unavoidable.[2] Whether minimal residual disease results in clinical metastases is a function of host defence and tumour survival and growth.

At least three perioperative factors shift the balance towards progression of minimal residual disease. First, surgery depresses cell-mediated immunity, reduces concentrations of tumour-related antiangiogenic factors (eg, angiostatin and endostatin), increases concentrations of proangiogenic factors such as vascular endothelial growth factor, and releases growth factors that promote local and distant growth of malignant tissue.[3] Second, volatile anaesthetics such as sevoflurane impair many immune functions (eg, natural killer cells) and directly facilitate cancer cell growth.[4] Third, opioid analgesics

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*Listed in appendix

Department of Outcomes Research (Prof D I Sessler MD, Prof A Kurz MD, D B Mayers MD, M Grady MD, Prof S Ayad MD, E J Mascha PhD), **Department of General Anesthesiology** (Prof A Kurz), **Department of Regional Anesthesiology** (D B Mayers, M Grady, Prof S Ayad), **and Department of Quantitative Health Sciences** (E J Mascha), **Anesthesiology Institute and Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; Department of Anesthesiology, Peking Union Medical College Hospital, Beijing, China** (L Pei MD, Prof Y Huang MD); **Department of Anaesthesia, General Intensive Care and Pain Management, Medical University of Vienna, Vienna, Austria** (Prof E Fleischmann MD, Prof P Marhofer MD); **Department of Anesthesiology, University of Düsseldorf, Düsseldorf, Germany** (T A Meyer-Treschan MD); **Tan Tock Seng Hospital, Singapore, Singapore** (E Y Tan MD); **and Mater University Hospital, School of Medicine, University College Dublin, Dublin, Ireland** (Prof D J Buggy MD)

Correspondence to: Prof Daniel I Sessler, Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH 44195, USA **ds@or.org**

or

Prof Yuguang Huang, Department of Anesthesiology, Peking Union Medical College Hospital, Beijing, China **garybeijing@163.com**

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Research in context

Evidence before this study

The putative relation between regional analgesia and cancer recurrence is based on mechanistic and animal evidence, along with observational analyses. Surgical stress, volatile anaesthetics, and opioids all reduce resistance to cancer in rodents. Several small clinical trials have also been done in which patients were randomly allocated to regional analgesia for other reasons and were subsequently reanalysed for cancer recurrence. Clinical results have been contradictory, with some reporting fewer recurrences with regional anaesthestic but others not.

Added value of this study

We did a randomised controlled trial in women having potentially curative primary breast cancer resections. Our study was designed specifically to ascertain whether regional anaesthesia-analgesia with paravertebral blocks and propofol sedation reduces breast cancer recurrence compared with general anaesthesia with the volatile anaesthetic sevoflurane and opioid analgesia.

Implications of all the available evidence

The results of our large trial allowed us to make a fairly strong conclusion that regional anaesthesia-analgesia with paravertebral blocks and propofol sedation does not reduce recurrence of breast cancer. Additional trials are needed to assess potential benefits of regional analgesia in patients having larger operations that provoke more surgical stress, cause more pain, and require more opioid analgesia.

inhibit both cellular and humoral immune function in humans, increase angiogenesis, and promote breast tumour growth in rodents.[5]

Regional analgesia (eg, paravertebral block or epidural analgesia) attenuates or prevents the immune and angiogenic effects of surgery and anaesthesia by moderating the neuroendocrine surgical stress response, thereby eliminating or reducing the need for volatile anaesthetic and minimising opioid requirements.[6] Moreover, by contrast with the volatile anaesthetic sevoflurane, the intravenous anaesthetic propofol has anti-inflammatory properties and preserves immune function.[7] Combined regional analgesia and propofol thus might resist metastatic tumour cell survival. The theory is supported by findings of studies showing that serum from women given regional analgesia and propofol promoted helpful immune responses, whereas serum from women given a volatile anaesthetic degraded cancer-related immune function.[8,9] The results of retrospective comparisons between regional and volatile anaesthetic approaches have been variable.[10] Yet, cohort data suggest that an intravenous anaesthetic might be preferable to volatile anaesthetics.[11] Therefore, we did a randomised controlled trial to test the primary hypothesis that local or metastatic recurrence after potentially curative breast cancer surgery is reduced in women randomly allocated to regional anaesthesia-analgesia (paravertebral block and propofol) than in those assigned to general anaesthesia with the volatile anaesthetic sevoflurane and opioid analgesia.

Persistent incisional pain is common after breast cancer surgery.[12,13] Persistent pain results, at least in part, from activation of central re-entrant pathways that amplify pain and remain active long after the peripheral stimulus resolves. Regional analgesia might attenuate development of persistent pain by effectively disconnecting the CNS from peripheral stimuli during the period of most intense surgical pain. Consistent with this theory, findings of small studies suggest that optimising acute pain relief, including use of regional blocks, reduces the incidence and severity of persistent pain after breast surgery.[14] Therefore, we tested the secondary hypothesis that regional anaesthesia-analgesia reduces incisional pain at 6 months and 12 months.

Methods

Study design and participants

We did a randomised controlled trial at 13 hospitals in Argentina, Austria, China, Germany, Ireland, New Zealand, Singapore, and the USA (appendix p 2). We enrolled women younger than 85 years with primary breast cancer without known extension beyond the breast and axillary nodes (ie, believed to be tumour stage 1–3, nodes 0–2) who were scheduled either for unilateral or bilateral mastectomy, with or without implants, or for wide local excision with node dissection. We excluded women who had previous surgery for breast cancer (we allowed diagnostic biopsies and guide-wire insertion), had inflammatory breast cancer, were scheduled for free-flap reconstruction, had American Society of Anesthesiologists (ASA) physical status of IV or higher, had contraindications to either anaesthetic approach, or had other cancer not in long-term remission.

The study rationale[15] and methodology[16] have been published elsewhere, and the full protocol including statistical analysis plan is available in the appendix (pp 4, 5). The only substantive protocol change was designating persistent pain rather than mortality as the secondary outcome in April, 2011. The change was made without examining any accrued data; at that time, only 446 women (21% of the total) had been enrolled. Acute pain with propofol and volatile anaesthetic use has been previously reported in a subset of randomised patients.[17] Cancer biomarkers have also been published in a subset of patients.[18]

The trial was done in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and relevant regulatory requirements.

The Institutional Review Board at every study site approved the trial, and informed consent was obtained from all participants. The Department of Outcomes Research at the Cleveland Clinic (Cleveland, OH, USA) developed the protocol, managed conduct of the trial, obtained and managed study data, and did the statistical analysis.

Randomisation and masking

Patients were randomly assigned to either regional anaesthesia-analgesia with combined paravertebral blocks and propofol or general anaesthesia with the volatile anaesthetic sevoflurane and opioid analgesia, as previously described.[16] Computer-generated randomisation was in a 1:1 ratio stratified by study site with random blocking. The allocation was concealed until shortly before surgery when site investigators accessed a web-based system. All follow-up contact with patients, families, and caregivers was done by investigators who were unaware of patients' random assignments and intraoperative management.

Procedures

Procedures varied by study site; typically, paravertebral blocks were ultrasound-guided at T1–T5, using 5 mL concentrated long-acting local anaesthetic at each level.[19] Blocks could be supplemented with low-dose sevoflurane as necessary. Wounds were not infiltrated with local anaesthetic in either study group. Morphine was the first-line postoperative analgesic in both study groups. After approximately 24 h, patients in both study groups were transitioned to paracetamol, tramadol, non-steroidal anti-inflammatory drugs, or a combination of these analgesics; oral opioids were also permitted if necessary. We recorded the volatile anaesthetic dose in minimum alveolar concentration hours, which is a standard unit of anaesthetic potency, along with details of other anaesthetic and surgical management.

We took measurements for prognostic factors related to the risk of breast cancer recurrence, including tumour size, grade, type, and oestrogen receptor status, based on pathology reports. We similarly gauged the extent of axillary nodal disease. We recorded whether preoperative or postoperative adjuvant chemotherapy and radiotherapy were used. For staging, we used 2005 National Cancer Institute TNM (Tumor, Node, Metastasis) definitions. Additionally, we calculated the Nottingham Prognostic Index, which is a score for breast cancer prognosis based on variables including tumour size, histological grade, and lymph-node involvement.[20] A score less than 3·4 suggests a good prognosis, whereas a score between 3·4 and 5·4 suggests intermediate prognosis. We also recorded whether resection margins were clear of tumour.

Outcomes

The primary outcome was local or metastatic breast cancer recurrence. Cancer recurrence was assessed by contacting patients, health-care providers, or both at 6-month intervals until recurrence was reported, 5–6 years had elapsed, or study enrolment ended. Cases of apparent recurrence were adjudicated at the trial coordinating site (Cleveland Clinic), using all available laboratory and clinical evidence, by investigators who were unaware of patients' random assignments.

The secondary outcome was incisional pain at 6 months and 12 months after the index surgery. To assess chronic pain we administered the modified Brief Pain Inventory (mBPI)[21] and the Neuropathic Pain Questionnaire Short Form.[22] We assessed quality of life with the Short Form-12 Health Survey (SF-12).[23] Tertiary outcomes were hospital length of stay, postoperative 48 h morphine equivalents, and postoperative nausea, vomiting, or both in the recovery room and on postoperative days 1 and 2. The only explicit safety outcome was occurrence of pneumothorax.

Statistical analysis

Full details about sample size considerations and interim analyses are provided in the appendix (pp 4, 5). Briefly, the study was designed with 85% power to detect a 30% reduction in cancer recurrence while adjusting for interim analyses, 3% dropout, and 5% crossovers. Interim analyses for efficacy and futility were planned at every 25% of the maximum number of required recurrences. Boundaries were not statistically binding, but the results were considered in the decision making of the Executive Committee (DIS, DJB, and AK). The statistical plan was completed before data were analysed. We used published work[24] to estimate the hazard function (risk of recurrence) over time. Baseline variables with an absolute standardised difference (ASD) of 0·085 or greater were considered imbalanced, and we adjusted for these variables in all analyses, using the formula published by Austin.[25]

The primary analysis was assessed by intention-to-treat principles. Patients who were lost to follow-up were censored at the time of last contact. Our primary analysis was a Cox proportional hazards model adjusted for predetermined factors including clinical centre, TNM stage, age, race, type of surgery, oestrogen receptor status, and whether adjuvant cancer treatment was given. We further tested for interactions between the treatment effect and preselected covariables, including China (the country with most enrolled patients) versus all others. The assumption of proportional hazards was assessed using the treatment group-by-time interaction.

We assessed secondary outcomes using Wilcoxon rank sum tests. We dichotomised the mBPI into no pain versus any pain. The effect of anaesthetic type on presence of any pain (yes *vs* no) over time was assessed using generalised estimating equation (GEE) models with logit link. The effect on quality of life was assessed using a linear mixed-effects model.

For assessment of tertiary outcomes, we used a univariable Cox proportional hazards model to compare groups

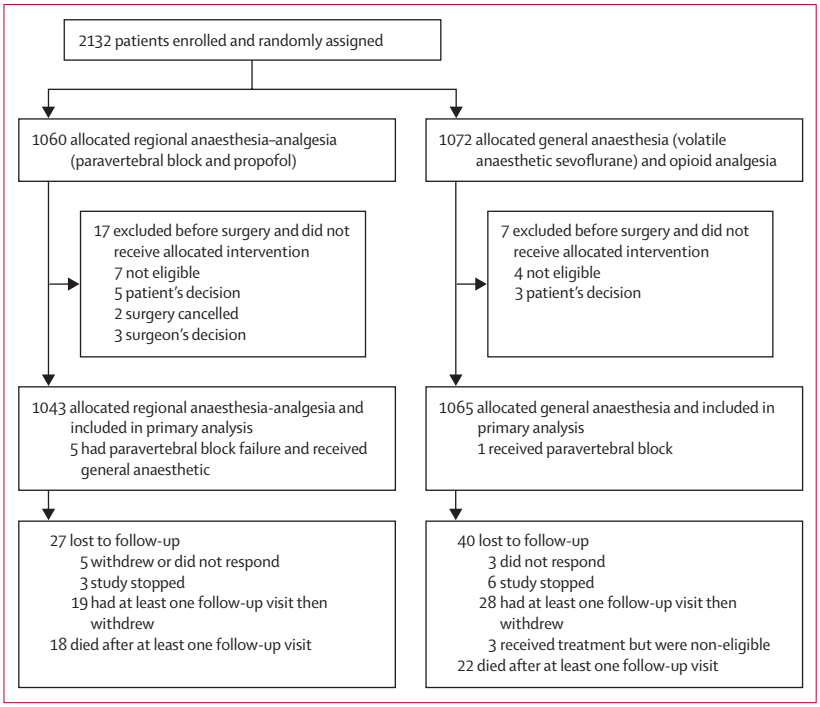

Figure 1: **Trial profile**

with respect to hospital length of stay. A Wilcoxon rank sum test was used for postoperative 48 h morphine equivalents. We used a GEE model with logit link to assess postoperative nausea, vomiting, or both.

For each hypothesis, we set the significance level (ie, type I error) at 0·05. Multiple comparisons within a hypothesis (eg, comparisons at various timepoints) were corrected to maintain the overall significance level. A threshold of 0·10 was used to define the significant level of the treatment-by-covariate interaction in pre-defined subgroup analyses. We used SAS version 9.4 for all statistical analyses.

This trial is registered at ClinicalTrials.gov, number NCT00418457.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to trial data and jointly chose to submit for publication. The corresponding authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 30, 2007, and Jan 18, 2018, 2132 patients were enrolled to the study, of whom 1060 were randomly allocated to regional anaesthesia-analgesia and 1072 were assigned to general anaesthesia (figure 1). 17 patients assigned to regional anaesthesia-analgesia and seven patients allocated to general anaesthesia

	Regional (n=1043)	General (n=1065)	ASD*
Demographics			
Age (years)	53 (12)	53 (11)†	0·023
Body-mass index (kg/m²)	25 (5)†	26 (6)†	0·091
Ethnic origin	..	..	0·038
Asian	639 (61%)	641 (60%)	..
Native Hawaiian or other	2 (<1%)	2 (<1%)	..
Black or African American	7 (1%)	5 (<1%)	..
White	326 (31%)	341 (32%)	..
Unknown	69 (7%)	76 (7%)	..
Hispanic or Latino	..	..	0·018
Yes	3 (<1%)	4 (<1%)	..
No	972 (93%)	989 (93%)	..
Unknown	68 (7%)	72 (7%)	..
ASA physical status	..	..	0·097
I	585 (57%)‡	548 (53%)‡	..
II	388 (38%)	444 (43%)	..
III	46 (5%)	46 (4%)	..
Tumour information			
Tumour site	..	..	0·040
Left	515 (50%)†	513 (49%)†	..
Right	506 (49%)	524 (50%)	..
Bilateral	15 (1%)	20 (2%)	..
Tumour findings	..	..	..
Microcalcification	323 (33%)§	309 (31%)§	0·041
Parenchymal distortion	97 (10%)§	109 (11%)§	0·034
Mass	757 (77%)§	771 (77%)§	0·004
Other	54 (5%)§	61 (6%)§	0·027
Oestrogen receptor	800 (78%)†	834 (79%)†	0·030
Resection margins (mm)	5 (2–10)¶	5 (2–10)¶	<0·001
Pathology stage, tumour	..	..	0·054
TX	3 (<1%)†	2 (<1%)†	..
T0	6 (1%)	7 (1%)	..
Tis	17 (2%)	15 (1%)	..
T1	581 (56%)	605 (58%)	..
T2	378 (37%)	370 (35%)	..
T3	44 (4%)	45 (4%)	..
T4	5 (<1%)	8 (1%)	..
Pathology stage, nodes	..	..	0·007
NX	7 (1%)†	7 (1%)†	..
N0	600 (58%)	611 (58%)	..
N1	252 (24%)	255 (24%)	..
N2	81 (8%)	81 (8%)	..
N3	98 (9%)	101 (10%)	..
Pathology stage, metastasis	..	..	0·030
MX	93 (9%)†	89 (8%)†	..
M0	940 (91%)	959 (91%)	..
M1	5 (<1%)	7 (1%)	..

(Table 1 continues on next page)

	Regional (n=1043)	General (n=1065)	ASD*
(Continued from previous page)			
Tumour TNM stage	..	..	0·057
0	24 (2%)†	19 (2)†	..
1	394 (38%)	421 (40%)	..
2	423 (41%)	418 (39%)	..
3	190 (18%)	194 (18%)	..
4	5 (<1%)	7 (1%)	..
Nottingham Prognostic Index	4·1 (1·3)‖	4·1 (1·2)‖	0·015
Preoperative treatment			
Previous radiation	5 (<1%)	2 (<1%)	0·050
Previous chemotherapy	62 (6%)	72 (7%)	0·034
Preoperative drugs			
β blocker	42 (4%)†	44 (4%)‡	0·007
COX2 inhibitor	9 (1%)†	19 (2%)†	0·082
Surgical information			
Surgical duration (h)	1·3 (1·0–1·7)†	1·3 (1·0–1·7)	<0·001
Surgery type	..	..	0·025
Simple mastectomy	109 (11%)†	111 (11%)†	..
Modified radical	492 (47%)	490 (46%)	..
Wide local excision with node dissection	339 (33%)	357 (34%)	..
Other	98 (9%)	98 (9%)	..
Regional block level	..	..	..
Left upper	524 (52%)‡	NA	NA
Right upper	506 (50%)‡	NA	NA
Left lower	510 (50%)‡	NA	NA
Right lower	486 (49%)§	NA	NA
Year of surgery	..	..	0·028
2007–09	155 (15%)	166 (16%)	..
2010–12	122 (12%)	127 (12%)	..
2013–15	514 (49%)	511 (48%)	..
2016–18	252 (24%)	261 (25%)	..
(Table 1 continues in next column)			

	Regional (n=1043)	General (n=1065)	ASD*
(Continued from previous column)			
Intraoperative variables			
Crystalloid (L)	1 (1–1·5)†	1 (1–1·5)†	0·13
Colloid (L)	0 (0–0)†	0 (0–0)†	0·019
Blood loss (mL)**	100 (10–250)†	50 (10–200)†	0·12
Allogeneic blood (mL)	0 (0–0)	0 (0–0)†	0·03
MAP (mm Hg)	77 (9·9)†	75 (9·2)‡	0·20
Heart rate	73 (11)†	69 (9)‡	0·35
Bispectral index	51 (13)¶	55 (13)¶	0·32
Core temperature (°C)	36·1 (35·9–36·5)†	36·2 (36·0–36·5)†	0·17
Sevoflurane (MAC h)	0 (0–0)†	0·9 (0·7–1·5)†	1·95
Sevoflurane (any)	176 (17%)†	1027 (97%)†	2·71
Sevoflurane amount, if received (MAC h)	1·3 (0·8)	1·1 (0·7)	0·21
Ondansetron (mg)	4 (0–4)	4 (4–4)	0·10
Propofol (mg)	525 (377–809)	120 (100–150)	2·13
Midazolam (mg)	1 (1–2)	1 (1–2)	0·15
Lidocaine (mg)	0 (0–0)	0 (0–30)	0·11
Neostigmine (mg)	0 (0–1)	1 (0–1)	0·09
Rocuronium (mg)	20 (0–30)	20 (0–30)	0·05
Ephedrine (mg)	0 (0–10)	0·0 (0–12)	0·08
Atropine (mg)	0 (0–0·5)	0·5 (0–0·5)	0·09
Fentanyl (μg)	100 (50–100)	200 (100–250)	1·4
Intraoperative morphine equivalents (mg)	10 (5–10)	20 (15–25)	1·8
Postoperative treatment			
Radiation	437 (42%)†	428 (40%)†	0·032
Chemotherapy	582 (56%)†	567 (54%)†	0·05

Data are n (%), mean (SD), or median (IQR). ASD=absolute standardised difference. ASA=American Society of Anesthesiologists. TNM=Tumor, Node, Metastasis. COX2=cyclo-oxygenase 2. NA=not available. MAP=mean arterial pressure. MAC h=minimum alveolar concentration hours. *We considered variables with ASD ≥0·085 to be unbalanced.[25] †1–19 missing datapoints. ‡20–39 missing datapoints. §40–69 missing datapoints. ¶>150 missing datapoints. ‖90–120 missing datapoints. **Blood loss was consistently not reported at Chinese sites for these surgeries (because of relative low amounts); estimated blood loss is reported for non-Chinese sites.

Table 1: **Demographic and clinical characteristics of participants**

were excluded before surgery because they were judged not eligible or decided not to participate. Therefore, the population included in the primary analysis comprised 1043 patients assigned to regional anaesthesia-analgesia and 1065 allocated to general anaesthesia. Among these patients, 1253 (59%) were from Beijing, 404 (19%) were from Dublin, and 170 (8%) were from Vienna (appendix p 2). Paravertebral blocks failed in five patients, who converted to general anaesthesia; one patient assigned general anaesthesia received a paravertebral block. 27 patients assigned regional anaesthesia-analgesia and 40 allocated general anaesthesia were lost to follow-up; reasons for loss to follow-up are shown in figure 1. Both groups had a median follow-up of 36 (IQR 24–49) months.

Baseline demographics, medical comorbidity, tumour grade and stage, and surgical management variables were well balanced between study groups (table 1), with the exception of body-mass index (ASD=0·091) and ASA status (ASD=0·097), which were both slightly above our ASD threshold of 0·085. However, since the recorded imbalance was not clinically meaningful, we did not adjust for these variables in our multivariable models. No substantive complications were attributed to paravertebral blocks. Patients assigned to regional anaesthesia-analgesia were given more intraoperative propofol and less sevoflurane and opioid, which was as expected (table 1).

The second of four preplanned interim analyses was initiated after 180 recurrence events had been reported in 2076 patients. During the period of data processing, integrity checks, and analysis for this interim analysis,

32 additional patients underwent randomisation and 33 further recurrences were reported. The Executive Committee, thus, considered all 213 recurrences (61% of the maximum 351 planned) in 2108 patients in the second interim analysis, comprising the cohort included in this report. At this second interim analysis, the futility boundary was crossed (appendix p 6) and the Executive Committee decided to halt the trial.

Cancer-free survival did not differ by type of anaesthesia (figure 2). Among 1043 women assigned to regional anaesthesia-analgesia, 102 (10%) recurrences were reported, compared with 111 (10%) among 1065 women who were allocated to general anaesthesia (multivariable adjusted hazard ratio [HR] 0·97, 95% CI 0·74–1·28; p=0·84; table 2). No violation of the proportional hazard assumption was recorded (p=0·82). In a sensitivity analysis adjusting for the imbalanced baseline factors (body-mass index and ASA status), the estimated HR was 0·96 (95% CI 0·73–1·26; p=0·75). In another sensitivity analysis including only the Chinese study site, the interim-adjusted HR was 0·77 (95% CI 0·55–1·09; p=0·15). Among the 213 patients with recurrence events, median recurrence-free survival was 15 (IQR 7–26) months for patients assigned regional anaesthesia-analgesia versus 17 (7–24) months for patients allocated general anaesthesia.

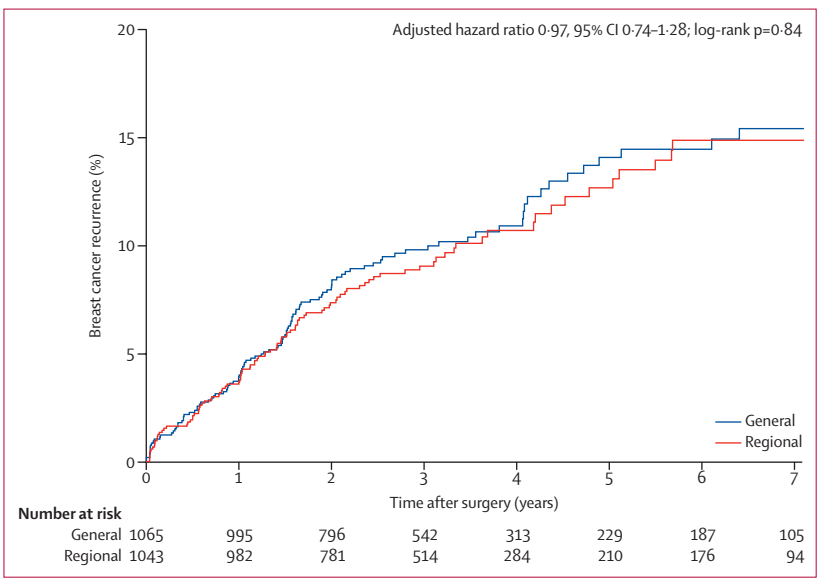

Figure 2: Kaplan-Meier estimates of recurrence among patients who were given regional or general anaesthesia
Multivariable Cox proportional hazards model adjusted for study site, age, ethnic origin, preoperative chemotherapy and radiotherapy, type of surgery, oestrogen receptor status, tumour stage, and postoperative chemotherapy and radiotherapy.

Findings of predefined subgroup analyses showed that the effect of regional anaesthesia-analgesia versus general anaesthesia on cancer recurrence depended on ethnic origin (Asian *vs* non-Asian; interaction p=0·043) and study site (Chinese *vs* non-Chinese; interaction p=0·039), but not on other predefined factors. Additionally, no effect of regional anaesthesia-analgesia versus general anaesthesia was detected within any subgroups of these factors (figure 3).

In a post-hoc analysis, we compared breast cancer recurrence in patients who were (n=1203) and were not (n=901) given sevoflurane, ignoring group allocation and excluding four patients with missing sevoflurane, and no association was recorded (log-rank p=0·78). Results were similar comparing patients assigned to regional anaesthesia-analgesia who used (n=176) and did not use (n=865) sevoflurane (log-rank p=0·88).

Chronic pain did not differ between the study groups at 6 months and 12 months, as measured by mBPI scores (appendix pp 7, 8). At 6 months, incisional pain was reported by 442 (52%) of 856 patients assigned regional anaesthesia-analgesia and 456 (52%) of 872 patients allocated general anaesthesia; at 12 months, 239 (28%) of 854 patients and 232 (27%) of 852 patients, respectively, reported pain (overall interim-adjusted odds ratio [OR] 1·00, 95% CI 0·85–1·17; p=0·99). Chronic persistent neuropathic pain was reported by 87 (10%) of 859 patients assigned regional anaesthesia-analgesia and 89 (10%) of 870 patients allocated general anaesthesia at 6 months, and by 57 (7%) of 857 patients and 57 (7%) of 854 patients, respectively, at 12 months. Quality of life—as assessed by scores on SF-12—did not differ between groups (appendix pp 7, 8).

Postoperative nausea was reported in the recovery room by 79 (8%) of 1039 patients assigned regional anaesthesia-analgesia and 213 (20%) of 1045 patients allocated general anaesthesia (OR 0·32, 98·3% CI 0·23–0·45; p<0·0001; appendix p 9). At postoperative day 1, the prevalence

	Recurrence	Follow-up (months)	Unadjusted HR (95%CI)*	p value (log rank)	Adjusted HR (95%CI)*†	p value (adjusted)*†
Regional	102/1043 (10%)	36 (24–49)	0·94 (0·72–1·23)	0·67	0·97 (0·74–1·28)	0·84
General	111/1065 (10%)	36 (24–49)	Ref	..	Ref	..
Sensitivity analysis: China only						
Regional	60/624 (10%)	36 (24–49)	0·83 (0·59–1·17)	0·27	0·77 (0·55–1·09)	0·15
General	72/629 (11%)	36 (24–49)	Ref	..	Ref	..

Data are n/N (%) or median (IQR), unless otherwise stated. HR=hazard ratio. *Interim-adjusted α=0·049 for all analyses. †Multivariable Cox proportional hazards model adjusted for study site, age, ethnic origin, preoperative chemotherapy and radiotherapy, type of surgery, oestrogen receptor status, tumour stage, and postoperative chemotherapy and radiotherapy. p=0·18 for treatment × site interaction in adjusted model. No violation of the proportional hazard assumption (p=0·82).

Table 2: **Comparison of randomised groups (regional *vs* general anaesthesia) on breast cancer recurrence**

of nausea remained higher with general anaesthesia compared with regional anaesthesia-analgesia (OR 0·47, 98·3% CI 0·37–0·60; p<0·0001) but, by postoperative day 2, prevalence was much diminished and similar between study groups (0·81, 0·53–1·24; p=0·23; appendix p 9). A strong interaction was noted between study group and time with respect to incidence of nausea and vomiting (p=0·00020). The median duration of hospitalisation (4 [IQR 3–5] days) and postoperative 48-h morphine equivalents (0 [0–0] mg) were the same with each anaesthetic approach (appendix p 9).

No serious adverse events were attributed to regional anaesthesia-analgesia and no cases of pneumothorax were reported. 40 patients died during the study (figure 1).

Discussion

Our randomised trial shows that, compared with general anaesthesia with the volatile anaesthestic sevoflurane and opioids for analgesia, regional anaesthesia-analgesia using paravertebral block and propofol does not reduce breast cancer recurrence. Before our trial began, in-vitro and in-vivo evidence suggested that the combination of paravertebral block and propofol anaesthesia might be protective for cancer recurrence compared with general anaesthesia with sevoflurane and opioid analgesia.[4–9] Scant (and inconsistent) evidence in patients also suggested potential benefit.[26,27] In fact, in our study, little sign of an effect was recorded: patients randomly assigned regional anaesthesia-analgesia had cancer recurrences recorded at almost the same rate as did those allocated general anaesthesia with sevoflurane and opioid analgesia, with the estimated treatment effect ranging from about a 26% reduction to a 28% improvement and crossing a futility boundary. Our study comprised 2108 patients with 213 cancer recurrences, and it seems highly unlikely that we missed any clinically important benefit of regional anaesthesia-analgesia on cancer recurrence. Nonetheless, paravertebral block not only almost eliminates the need for general anaesthesia with a volatile anaesthetic but also reduces opioid use and enhances analgesia, each of which is valuable in its own right.[17] Regional analgesia also markedly reduces nausea and vomiting.

Several analyses of cancer recurrence have been done in patients who were randomly allocated for other reasons to general anaesthesia versus general and regional anaesthesia or to general anaesthesia alone versus regional anaesthesia. Only one study was specific to breast cancer,[26] a trial of 180 patients who were randomly assigned to general anaesthesia or general anaesthesia combined with paravertebral blocks for breast cancer surgery. The findings of this study accord with ours in that no apparent protective effect of regional analgesia was seen, but the analysis in that study was underpowered.

Post-hoc analyses of several other trials have shown cancer recurrence after surgery. The first and largest study was a reanalysis of the MASTER trial[27] in which almost 500 patients with abdominal cancer were randomly assigned to epidural analgesia or general anaesthesia. Epidural analgesia had no perceptible effect on cancer recurrence in that study. By contrast, in a randomised trial of 132 patients undergoing abdominal surgery for cancer,[28] a non-significant improvement in cancer-free survival was noted with epidural analgesia (43% *vs* 24%), although that study was underpowered to detect clinically important effects. A benefit of epidural analgesia was also reported in a randomised study of 177 patients with colon cancer,[29] but only during the initial 1·5 years after surgery. Finally, in a small study of 99 patients randomly allocated either general anaesthesia alone or general anaesthesia combined with epidural analgesia,[30] epidural analgesia did not reduce cancer recurrence (HR 1·33, 95% CI 0·64–2·77; p=0·44). Our trial is larger than all these previous studies combined, and is the only one designed specifically to assess cancer recurrence.

Our trial results are generalisable to other settings because we enrolled study participants from 13 hospitals in eight countries worldwide. However, our study period was 12 years' duration, during which time treatment for breast cancer improved greatly. Moreover, because our trial was pragmatic, we obtained scant information about genetic and other characteristics that potentially could affect cancer recurrence, and some factors or

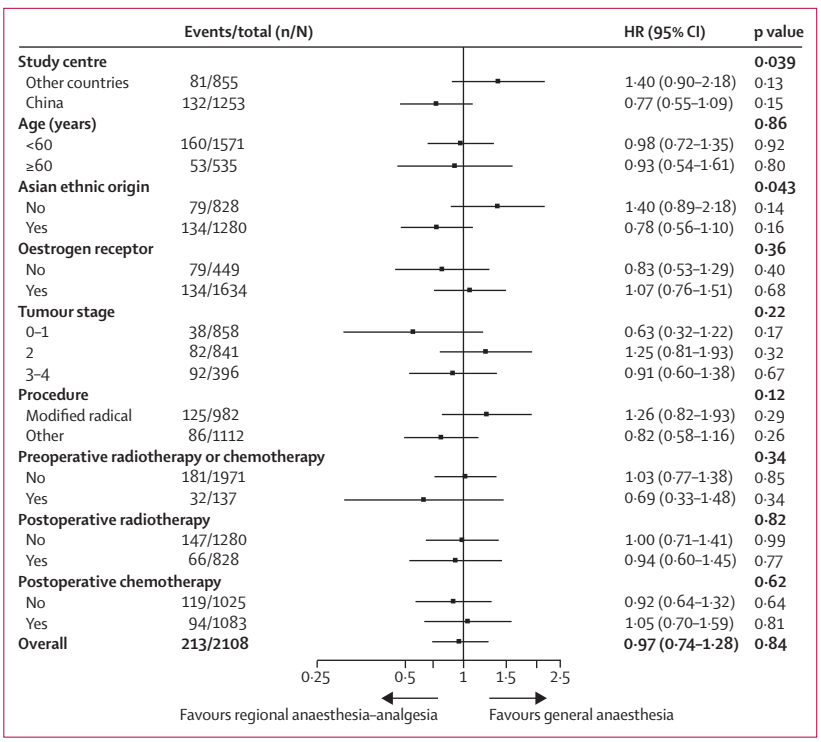

Figure 3: **Forest plot assessing interactions between prespecified baseline factors and the effect of regional versus general anaesthesia on breast cancer recurrence**

HRs and interim-adjusted 95% CIs are shown. The estimated overall HR was derived from a multivariable Cox proportional hazards model adjusted for predefined factors of study site, age, ethnic origin, preoperative chemotherapy and radiotherapy, type of surgery, oestrogen receptor status, tumour stage, and postoperative chemotherapy and radiotherapy. For the subgroup analyses, we assessed the treatment-by-covariate interaction on the primary outcome, adjusting for the same baseline variables. HR=hazard ratio.

features were not routinely available for screening or known about when our trial started. However, aside from *BRCA1* and *BRCA2* mutations (population average, 5%) and mismatch repair deficiency or high microsatellite instability (<2%), genetics do not typically alter management. Similarly, we have scant information about preoperative and postoperative radiation and chemotherapy. Yet, by virtue of the randomisation process, important baseline characteristics were presumably evenly distributed between treatment groups. Although the possibility remains that there are subpopulations of patients who might benefit disproportionately from regional analgesia, no apparent benefit was seen in any subpopulations we considered, including age, oestrogen receptor status, tumour stage, and cancer treatment.

A strong association has been noted between severe acute postoperative pain and persistent pain across many types of surgery.[31,32] In a previous report of a subset of our study population,[17] regional analgesia significantly reduced acute pain after breast surgery, although pain scores were low in both study groups. Regional analgesia might also prevent development of central re-entrant pathways that are thought to maintain pain well after the peripheral stimulus abates. Although the possibility remains that regional analgesia reduces persistent pain after more extensive surgery, or after surgery in other locations, our results suggest that interventions other than regional analgesia will be needed to prevent persistent incisional pain. Patients or responsible caregivers were contacted at 6-month intervals throughout the follow-up period. Surely we missed some cases, but there is no reason to believe that missingness would be anything other than random.

In summary, regional anaesthesia-analgesia by paravertebral blocks and propofol did not reduce breast cancer recurrence after potential curative surgery compared with general anaesthesia with the volatile anaesthetic sevoflurane and opioids for analgesia. The incidence and severity of persistent incisional breast pain was unaffected by anaesthetic technique. Future trials should address larger operations that provoke more surgical stress and require more postoperative opioid administration.

Contributors

DIS, DJB, and EJM contributed to study design. DIS, DJB, LP, YH, EF, AK, DBM, TAM-T, MG, EYT, PM, and SA contributed to data acquisition. EJM contributed to data analysis. DIS and DJB wrote the report. All authors reviewed the report and approved it for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified patient-level data will be shared for collaborative analyses on request to Daniel I Sessler (email: DS@OR.org) shortly after publication. The data dictionary and statistical tables and code will be provided as appropriate; a data-sharing contract will be required. The protocol is available by request.

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