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Epidural Anesthesia–Analgesia and Recurrence-free Survival after Lung Cancer Surgery: A Randomized Trial

Zhen-Zhen Xu, M.D., Huai-Jin Li, M.D., Mu-Han Li, M.D., Ph.D., Si-Ming Huang, M.D., Xue Li, M.D., Qing-Hao Liu, M.D., Jian Li, M.D., Xue-Ying Li, M.Sc., Dong-Xin Wang, M.D., Ph.D., Daniel I. Sessler, M.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Regional anesthesia and analgesia reduces the stress of surgery and decreases the need for volatile anesthesia and opioids.
- Observational studies have reported mixed results with regard to the beneficial effects of regional anesthesia for cancer surgery. Recent trials have failed to demonstrate a benefit.

What This Article Tells Us That Is New

- In a randomized trial of adults scheduled for video-assisted thoracoscopic lung cancer resection comparing combined epidural–general to general anesthesia, there was no difference between groups in recurrence-free survival time.
- There was also no difference in overall survival.

ABSTRACT

Background: Regional anesthesia and analgesia reduce the stress response to surgery and decrease the need for volatile anesthesia and opioids, thereby preserving cancer-specific immune defenses. This study therefore tested the primary hypothesis that combining epidural anesthesia–analgesia with general anesthesia improves recurrence-free survival after lung cancer surgery.

Methods: Adults scheduled for video-assisted thoracoscopic lung cancer resections were randomized 1:1 to general anesthesia and intravenous opioid analgesia or combined epidural–general anesthesia and epidural analgesia. The primary outcome was recurrence-free survival (time from surgery to the earliest date of recurrence/metastasis or all-cause death). Secondary outcomes included overall survival (time from surgery to all-cause death) and cancer-specific survival (time from surgery to cancer-specific death). Long-term outcome assessors were blinded to treatment.

Results: Between May 2015 and November 2017, 400 patients were enrolled and randomized to general anesthesia alone (n = 200) or combined epidural–general anesthesia (n = 200). All were included in the analysis. The median follow-up duration was 32 months (interquartile range, 24 to 48). Recurrence-free survival was similar in each group, with 54 events (27%) with general anesthesia alone *versus* 48 events (24%) with combined epidural–general anesthesia (adjusted hazard ratio, 0.90; 95% CI, 0.60 to 1.35; $P = 0.608$). Overall survival was also similar with 25 events (13%) *versus* 31 (16%; adjusted hazard ratio, 1.12; 95% CI, 0.64 to 1.96; $P = 0.697$). There was also no significant difference in cancer-specific survival with 24 events (12%) *versus* 29 (15%; adjusted hazard ratio, 1.08; 95% CI, 0.61 to 1.91; $P = 0.802$). Patients assigned to combined epidural–general had more intraoperative hypotension: 94 patients (47%) *versus* 121 (61%; relative risk, 1.29; 95% CI, 1.07 to 1.55; $P = 0.007$).

Conclusions: Epidural anesthesia–analgesia for major lung cancer surgery did not improve recurrence-free, overall, or cancer-specific survival compared with general anesthesia alone, although the CI included both substantial benefit and harm.

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Cancer is the second leading cause of death worldwide and the leading cause of death in China. Lung cancer is among the most common cancers and remains the leading cause of cancer death.[1,2] For example, an estimated 2,094,000 new lung cancer cases were diagnosed in 2018, resulting in 1,761,000 deaths.[2] Surgical resection remains the primary treatment for early-stage non–small cell lung cancer. However, local cancer recurrence or metastasis remain common and are the main causes of death in patients with lung cancer.[3,4]

Development of cancer recurrences depends largely on the balance between the metastatic potential of malignant cells and the antimetastatic immune activity of the body.[5] However, both anesthesia and surgery impair host defense against cancer, especially natural killer cell function. For example, opioids and volatile anesthetics are immunosuppressive and may affect cancer cells in ways that promote

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cancer recurrence.[6] Surgical manipulation releases cancer cells into circulation,[7] and surgery-related stress responses impair cell-mediated immunity and promote cancer growth.[8] Epidural anesthesia and analgesia block afferent noxious stimuli and blunts the stress response and inflammation induced by surgery.[9] Furthermore, combined epidural–general anesthesia reduces the need for volatile anesthetics and opioids, both of which impair natural killer cell function.[10,11] Consistent with this theory, neuraxial anesthesia preserves cancer-related immune function and reduces metastasis in animals.[12,13]

Some observational analyses in cancer patients report beneficial effects of regional anesthesia,[14] whereas most others do not.[15] There are four *post hoc* analyses of trials with a total of 746 patients who were randomized to receive either general or combined epidural–general anesthesia for major abdominal cancer surgeries.[16–19] A meta-analysis of these trials did not find any advantage of regional anesthesia on overall or progression-free survival.[20] Two recent randomized trials investigated the effect of paravertebral block in breast cancer patients with cancer recurrence as the primary outcome.[21,22] One trial of just 180 patients was underpowered[21]; the other recruited 2,132 patients.[22] Neither identified a recurrence benefit from paravertebral blocks.[21,22]

To the extent that regional analgesia might preserve host defense against cancer, the benefit is most likely in patients having operations that cause considerable tissue injury and are painful. Lung cancer surgery is far more invasive than breast surgery and thus triggers a far greater stress response, and more opioids are generally needed. We therefore tested the primary hypothesis that combining epidural–general anesthesia with epidural analgesia improves recurrence-free survival compared with general anesthesia alone with intravenous analgesia in patients having potentially curative lung cancer surgery. Secondarily, we tested the hypotheses that combined epidural–general anesthesia prolongs overall and cancer-specific survival after surgery.

Materials and Methods

Study Design and Participants

This was a randomized controlled trial with two parallel arms. The study protocol was approved by the Clinical Research Ethics Committee of the Peking University First Hospital (2013[653]; principal investigator: Dr. Wang) on December 27, 2013. The latest version study protocol (V1.4) was approved on September 22, 2017 (Supplemental Digital Content 1, http://links.lww.com/ALN/C645). The study was registered *a priori* with the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR-TRC-14004136; January 2, 2014) and ClinicalTrials.gov (NCT 02801409; June 15, 2016).

This trial was initiated after the end of patient recruitment of our previous trial investigating the impact of epidural anesthesia–analgesia on postoperative delirium with a long-term follow-up.[23,24] The trial was conducted in Peking University First Hospital in Beijing, China, in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from participating patients or authorized surrogates. The effect of combined epidural anesthesia on tumor-infiltrating lymphocytes in lung adenocarcinoma has been previously reported in a subset of these patients.[25]

We enrolled adults aged 18 to 80 yr who were clinically diagnosed as lung cancer, were scheduled for radical surgery, and requested patient-controlled postoperative analgesia. Exclusion criteria were: (1) distant metastasis, malignant tumor in other organs, or preoperative chemotherapy, radiation therapy, or immune therapy; (2) comorbid autoimmune diseases, glucocorticoid use, or immunosuppressant therapy within 1 yr; (3) severe neurologic conditions, hepatic disease (Child–Pugh classification C), renal failure (serum creatinine greater than 442 $\mu mol \cdot l^{-1}$), renal replacement therapy, or American Society of Anesthesiologists (ASA) physical status classification of IV or higher; (4) history of anesthesia and/or surgery within 1 yr; (5) contradictions to epidural anesthesia, including spinal deformity, coagulation dysfunction, local infection, and history of spinal trauma/surgery; or (6) allergy to any trial-related medication.

Randomization

Random numbers were generated by a biomedical statistician using the SAS 9.2 software (SAS Institute, USA) with a block size of 4 and were concealed in sequentially numbered opaque envelops. The envelopes were opened by an investigator shortly before induction of anesthesia; allocation was thus concealed as long as was practical. During the study period, the enrolled patients were randomly allocated to receive either general anesthesia alone plus postoperative intravenous analgesia or combined epidural–general anesthesia plus postoperative epidural analgesia in a 1:1 ratio without stratification.

Procedures

No premedication was given. Routine intraoperative monitoring included electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, end-tidal concentrations of inhaled anesthetics and carbon dioxide, nasopharyngeal temperature, Bispectral Index, and urine output. Invasive arterial pressure and central venous pressure were monitored when necessary. In each case, surgery was video-assisted thoracoscopic tumor resection.

For patients assigned to general anesthesia alone, anesthesia was induced with propofol, sufentanil, and rocuronium, with or without midazolam. Anesthesia was maintained with propofol infusion and/or sevoflurane inhalation, with or without nitrous oxide inhalation, supplemented with opioids (remifentanil infusion and sufentanil infusion/injection) and muscle relaxants (rocuronium or cisatracurium).

Dexmedetomidine was given at the discretion of anesthesiologists. The target was to maintain a Bispectral Index between 40 and 60. A double-lumen endobronchial tube or a bronchial blocker was used to facilitate one-lung ventilation. A mixture of oxygen and air/nitrous oxide was provided during two-lung ventilation and also during one-lung ventilation as long as the pulse oxygen saturation was higher than 93%. After surgery, patient-controlled intravenous analgesia was provided for up to 3 days. The analgesic infusion was morphine 0.5 mg · ml^{-1}, and the pump was programed to deliver 2-ml boluses with a lockout interval of 8 min and a background infusion rate of 1 ml · h^{-1}.

For patients assigned to combined epidural–general anesthesia, an epidural catheter was inserted before anesthetic induction. The intervertebral space was selected according to the site of incision, usually between T5 and T8. A test dose of 2% lidocaine was injected to confirm the position of epidural catheter. Epidural anesthesia was maintained with intermittent boluses of 0.375% ropivacaine until the end of surgery. General anesthesia was induced and maintained as for patients assigned to general anesthesia alone, again titrated to a Bispectral Index between 40 and 60. After surgery, patient-controlled epidural analgesia was provided for up to 3 days. The analgesic solution was a mixture of 0.12% ropivacaine and 0.5 μg · ml^{-1} sufentanil. The pump was programed to deliver 2-ml boluses with a lockout interval of 20 min and a background infusion rate at 4 ml · h^{-1}. If an epidural catheter could not be inserted, patients were given general anesthesia and intravenous analgesia as above.

Low-dose glucocorticoids (usually 5 mg dexamethasone) were administered before anesthesia induction as prophylaxis against postoperative nausea and vomiting. Intraoperative hypotension was managed by reducing anesthetic depth, fluid infusion, and/or administration of vasopressors (ephedrine, phenylephrine, norepinephrine, dopamine, and/or epinephrine). Intraoperative bradycardia was managed with atropine and/or other chronotropic agents (dopamine, epinephrine, and/or norepinephrine).

Patients were monitored in the postanesthesia care unit for at least 30 min before being transferred back to their wards. Intensive care unit (ICU) beds were reserved for patients with preexisting conditions such as severe reduction in ventilatory and/or diffusion function, preexisting respiratory failure, or significant cardiovascular comorbidities, pneumonectomy, and advanced age.[26] However, their beds were released if they had smooth and uneventful anesthetics. Other patients were unexpectedly admitted to an ICU when they experienced massive intraoperative bleeding or unstable hemodynamic conditions or were difficult to extubate. Disposition decisions were made collaboratively by attending anesthesiologists and surgeons.

Patients with insufficient postoperative analgesia were initially managed with patient-controlled analgesia; supplemental analgesics including nonsteroidal anti-inflammatory drugs and other opioids were given when necessary. Per routine, pain management in the postanesthesia care unit was performed by anesthesia nurses and anesthesiologists and in the ICU by nurses and intensivists. In surgical wards, patient-controlled analgesia was guided by anesthesia nurses who evaluated patients twice daily; supplemental analgesics were prescribed by surgeons. The target was to maintain a numeric rating scale level (an 11-point scale where 0 = no pain and 10 = the worst pain) of pain at rest of 3 or lower.

Postoperative chest physiotherapy was performed routinely to improve ventilation and promote sputum clearance. Patients were encouraged to spend time out of bed within 24 h. Chest drainage tubes were removed when there was no longer an air leakage, atelectasis resolved, and drainage volume of less than 200 ml of clear fluid within 24 h.[27] Patients were usually discharged from the hospital a day after their chest tubes were removed.

Measurements and Endpoints

Anesthesiologists and patients were aware of group assignment, as were the investigators assessing immediate postoperative management (S.-M.H. and H.Kong). However, all long-term outcomes including cancer recurrence and mortality were performed by a separate group of investigators (Z.-Z.X., Q.-H.L., and X.-Q. Shang) who did not participate in anesthesia/surgery and had no knowledge of trial group assignment; those investigators were forbidden to discuss type of anesthesia with patients or other healthcare providers.

Baseline data included demographic and morphometric characteristics, preoperative surgical diagnosis, medical comorbidities, previous surgery, family history of cancer, personal history (smoking, drinking, and contact with potentially carcinogenic substances), laboratory and other examinations, as well as clinical pathologic type and tumor-node-metastasis stage if available. Intraoperative data were recorded by attending anesthesiologists and included type and duration of anesthesia, type and doses of anesthetics and other medications, volume of estimated bleeding, blood transfusion, fluid balance, vital signs (heart rate, blood pressure, and pulse oxygen saturation), and arterial blood gas results, as well as type, location, and duration of surgery.

Vital signs were monitored continuously in patients admitted to an ICU. On surgical wards, vital signs were evaluated noninvasively at 15- to 30-min intervals until the first postoperative morning and then once or twice daily until hospital discharge. Pain intensity at rest and with coughing was assessed with the 11-point numeric rating scale between 8 and 10 AM during the first 3 days; a minimum difference of 1 point was considered clinically meaningful.[28]

We recorded analgesics including opioids contained in patient-controlled analgesia infusions and rescue analgesics. Administered opioids were converted to intravenous morphine equivalents.[29] Postoperative complications were defined as new-onset medical conditions that were deemed

harmful and required therapeutic intervention (*i.e.*, grade II or higher on the Clavien–Dindo classification).[30] Duration of chest-tube placement and length of hospital stay were recorded. The results of pathologic examinations and tumor-node-metastasis staging[31] were documented.

Patients were advised to return to the hospital for evaluation every 3 months during the initial year, every 6 months during the second year, and yearly thereafter.[32] Patients with lymph node metastasis (tumor-node-metastasis stage II or higher) at the time of surgery were asked to return every 3 months throughout. Investigators contacted patients at the designated intervals to remind them to return and to ask about recurrence, cancer treatment, and vital status. Specific evaluations were prescribed by thoracic surgeons and usually included chest radiography, computed tomography scans, positron emission tomography scans, sputum cytology, and serum tumor markers.[32,33] Test results and clinical diagnoses were collected from our hospital's medical information system. Occasionally, patients were unable to return for a particular visit, in which case their medical records and examination results were requested from the relevant institution and when possible and then verified on subsequent visits to our hospital.

Data collected during each postoperative patient contact included the following: (1) Whether anti-cancer therapies were given. (2) Results of interval examinations. Cancer recurrence was defined as reappearance of the same cancer in the ipsilateral thorax, including lung and/or mediastinal/hilar lymph nodes. Metastases were defined as reappearance of the same cancer in any other part of the body. Cancer recurrence and/or metastasis was diagnosed by thoracic surgeons (and/or radiologists); time of the earliest diagnosis was recorded. For patients who had palliative resections or had unresectable cancers, cancer progression was defined by the first of an increase in tumor diameter of 2 mm or more, appearance of new metastatic foci, or death. (3) Vital status, including date of death. Cancer-specific death was defined as death fully attributable to lung cancer for which surgery was performed and usually occurred after cancer recurrence/metastasis after exclusion of other causes such as stroke, myocardial infarction, and accidents.

Among patients surviving 1 yr, metabolic equivalents (1 metabolic equivalent is equal to 3.5 $ml \cdot min^{-1} \cdot kg^{-1}$ resting oxygen consumption) during daily life activities were assessed. Full physical recovery was defined as engagement in moderately intense activity (3 to 5.9 metabolic equivalents) for at least 150 min a week.[34,35]

Our original primary outcome was cancer recurrence. However, during the follow-up period, we noted that some cancer patients died before recurrence/metastasis. Before analysis and without accessing trial data, we therefore changed the primary outcome to recurrence-free survival, defined as time from surgery to the earliest date of recurrence/metastasis or death from any cause, whichever came first. Simultaneously, we added recurrence-free, overall, and cancer-specific survival in patients with confirmed cancer. Secondary endpoints included overall survival and cancer-specific survival. Overall survival was defined as time from surgery to all-cause death. Cancer-specific survival was defined as time elapsed between surgery and cancer-specific death, with deaths from other causes being censored.

Other secondary endpoints included ICU admission, the incidence of postoperative complications, duration of chest tube placement, postoperative hospital duration, in-hospital mortality, and physical activity among 1-yr survivors. Other prespecified outcomes included pain intensity during the first 3 postoperative days. *Post hoc* subgroup analyses were performed as functions of age, sex, chronic smoking, ASA physical status, tumor-node-metastasis stage, and postoperative anticancer therapy.

Trial-related adverse events were evaluated from initiation of anesthesia until the 3rd postoperative day. Failed epidural catherization was identified by the responsible anesthesiologist. Intraoperative high airway pressure was defined by peak airway pressures greater than 30 cm H_2O unrelated to mechanical factors such as kinked or misplaced endotracheal tubes. Bradycardia was defined as heart rate less than 45 beats/min. Hypotension was defined as systolic blood pressure less than 90 mmHg or a decrease of more than 30% from individual preoperative ward values. Hypertension was defined as systolic blood pressure greater than 180 mmHg or an increase of more than 30% above preoperative ward values.

Statistical Analysis

Sample Size Estimation. In a previous study of patients who had complete resections for non–small cell lung cancer, one third had tumor recurrences within a median duration of 24 months.[36] In a pilot investigation in our institution, the hazard for recurrence within a year after lung cancer surgery was 48% lower in patients with combined epidural–general anesthesia compared with general anesthesia alone. We anticipated that patient recruitment would take 2 yr and planned to follow patients for at least 2 yr thereafter and that the 2-yr recurrence incidence would be 33% in patients with general anesthesia alone.

With the two-sided significance level set at 0.05 and power at 80%, an estimated sample size of 360 participants (180 per group) was required to detect a one-third reduction in recurrence. Considering a dropout rate of 8% and an epidural failure rate of 2% according to our own experience, we therefore planned to enrolled 400 patients without interim analyses. Sample size was estimated by log-rank test with PASS software (version 11.0, NCSS PASS, USA). Enrollment ceased when the target sample size was reached.

Outcome Analyses. Baseline balance was assessed with absolute standardized differences, which are defined as the absolute difference in means, mean ranks or proportions divided by the pooled SD and calculated using the

formula published by Austin.[37] Baseline data with an absolute standardized difference greater than or equal to 0.196 (i.e., $1.96\times\sqrt{(n1 + n2)/(n1 \times n2)}$) were considered imbalanced between groups.

Recurrence-free survival was analyzed using a Kaplan–Meier estimator with differences between groups assessed by log-rank test; a Cox proportional hazard model was used to adjust for factors predetermined according to clinical importance and included age, sex, chronic smoking, ASA physical status classification, tumor-node-metastasis stage, and postoperative anticancer therapy. Effect size was expressed as hazard ratio and 95% CI. The interactions between treatment effect and predefined factors as above were assessed separately with Cox proportional hazard models. Schoenfeld residual was used to test proportional hazard assumptions.

Secondary endpoints including overall and cancer-specific survival, as well as subgroup endpoints including recurrence-free, overall, and cancer-specific survival in cancer patients were analyzed using Kaplan–Meier estimators with differences between groups assessed by log-rank tests; the Cox proportional hazard models were used to adjust for the predetermined factors listed above.

For other outcomes, numeric variables were analyzed using independent-sample *t* or Mann–Whitney U tests; differences (and 95% CIs for the differences) between medians were calculated with Hodges–Lehmann estimators.

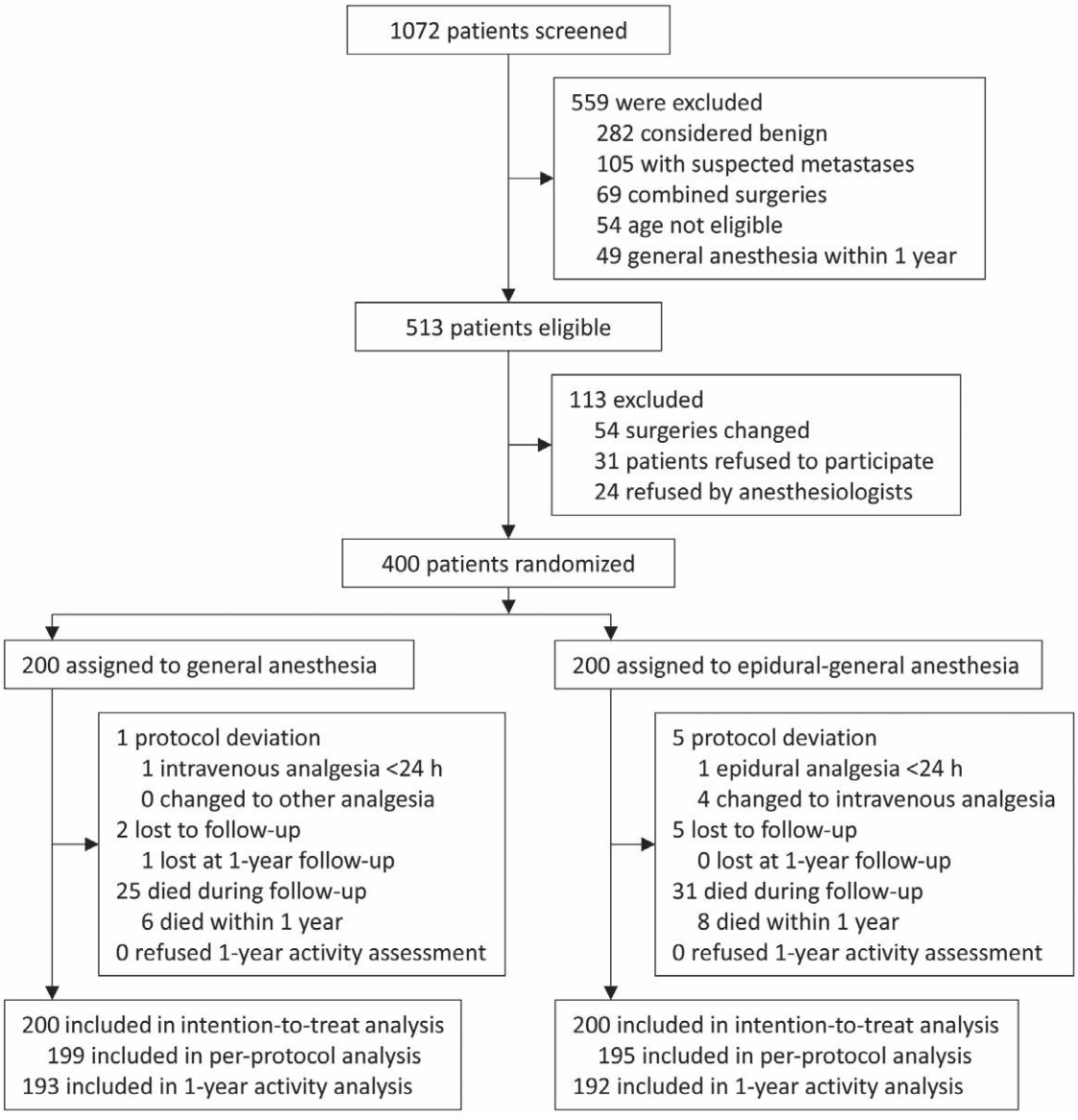


Fig. 1. Trial diagram.

Categorical variables were analyzed with the chi-square tests, continuity correction chi-square tests, or Fisher exact tests. Other time-to-event variables such as duration of chest tube drainage and duration of postoperative hospitalization were analyzed with Kaplan–Meier estimators, with differences between groups assessed with the log-rank tests. Ordinal variables such as pain scores at rest and with cough were analyzed with Mann–Whitney U test.

Outcome analyses were performed in the intent-to-treat population. A per-protocol analysis was also performed for

Table 1. Baseline Data

	General Anesthesia Alone (n = 200)	Combined Epidural–General Anesthesia (n = 200)	Absolute Standardized Difference
Age, yr	61 ± 10	60 ± 10	0.192
Male sex, n (%)	101 (50.5)	110 (55.0)	0.090
Body mass index, kg · m^{-2}	24.3 ± 3.5	24.6 ± 7.5	0.047
Comorbidity, n (%)			
Stroke/transient ischemic attack	13 (6.5)	7 (3.5)	0.138
Hypertension	62 (31.0)	63 (31.5)	0.011
Coronary heart disease	16 (8.0)	14 (7.0)	0.038
Arrythmia*	9 (4.5)	5 (2.5)	0.109
Diabetes	34 (17.0)	27 (13.5)	0.097
Chronic bronchitis	1 (0.5)	2 (1.0)	0.058
Emphysema	1 (0.5)	2 (1.0)	0.058
COPD	5 (2.5)	1 (0.5)	0.165
Asthma	1 (0.5)	1 (0.5)	0.000
Renal dysfunction†	4 (2.0)	1 (0.5)	0.135
Thyroid disease‡	7 (3.5)	5 (2.5)	0.059
Cancer history in first-degree relatives, n (%)	10 (5.0)	13 (6.5)	0.064
Chronic smoking, n (%)§	62 (31.0)	74 (37.0)	0.127
Smoking index‖	600 (400, 900)	600 (400, 800)	0.041
Alcoholism, n (%)#	14 (7.0)	21 (10.5)	0.124
Harmful exposure, n (%)**	4 (2.0)	4 (2.0)	0.000
ASA classification, n (%)			0.165
I	55 (27.5)	41 (20.5)	
II	138 (69.0)	151 (75.5)	
III	7 (3.5)	8 (4.0)	
Laboratory tests			
Hemoglobin, g · l^{-1}	137 ± 14	139 ± 16	0.090
Leukocyte, 10^9 · l^{-1}	6.2 ± 1.7	6.2 ± 1.8	0.039
Platelet, 10^9 · l^{-1}	217 ± 66	225 ± 78	0.115
Albumin, g · l^{-1}	41.9 ± 3.6	42.3 ± 3.8	0.102
Creatinine, μmol · l^{-1}	79.8 ± 17.7	80.2 ± 16.2	0.025
Maximum tumor diameter, cm	2.5 ± 2.2 [37]	2.5 ± 1.6 [34]	0.036
Pathologic type, n (%)			0.133
Noncancer	34 (17.0)	30 (15.0)	
Adenocarcinoma	127 (63.5)	138 (69.0)	
Squamous carcinoma	29 (14.5)	25 (12.5)	
Small cell cancer	4 (2.0)	2 (1.0)	
Other non–small cell lung cancers††	6 (3.0)	5 (2.5)	
Tumor-node-metastasis stage, n (%)‡‡			**0.272**
0§§	56 (28.0)	41 (20.5)	
1	99 (49.5)	114 (57.0)	
2	17 (8.5)	18 (9.0)	
3	27 (13.5)	22 (11.0)	
4	0 (0.0)	3 (1.5)	
x‖‖	1 (0.5)	2 (1.0)	

The data are given as mean ± SD, n (%), or median (interquartile range). The numbers in square brackets indicate patients with missing data. An absolute standardized difference greater than or equal to 0.196 (shown in bold) was considered unbalanced between the two groups.

*Included paroxysmal or persistence atrial fibrillation, sick sinus syndrome (pacemaker implantation), atrial premature beat, ventricular premature beat, and completed right bundle branch block. †Calculated glomerular filtration rate less than 60 ml·min^{-1}·1.73 m^{-2} according to the Cockcroft–Gault method. ‡Included Hashimoto's thyroiditis, subhypothyroidism, and thyroidectomy. §Defined as smoking of at least 100 cigarettes; does not include smoking cessation for over 10 yr. ‖Defined as the average number of cigarettes smoked per day multiplied by years of smoking. #Defined as alcohol consumption of more than 80 g/day for men or 40 g/day for women. **The existence of silicon, dust, graphite, coral, asbestos, or benzenes in the working or living environment. ††Included neuroendocrine tumor, malignant mesenchymal tumor, and atypical carcinoid. ‡‡According to the 8th edition International Association for the Study of Lung Cancer and the American Joint Committee on Cancer tumor-node-Metastasis classification. §§Included noncancer, preinvasion lesion (carcinoma *in situ* or atypical adenomatous hyperplasia), and microinfiltrating carcinoma. ‖‖Unable to classify stage in three cases because of (1) unresected small cell lung cancer confirmed by fast-frozen pathologic results, (2) unable to report size (T stage) due to irregular shape of cancer foci, or (3) second-station lymph node sampling without lobectomy.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

the primary endpoint. For all hypotheses, two-tailed *P* values <0.05 were considered statistically significant. For interactions between treatment effect and predefined factors, *P* values <0.10 were considered statistically significant. Multiple testing for secondary endpoints increases the risk of type I error, but we did not correct for multiplicity.

All statistical analyses were performed with SPSS 25.0 software (IBM SPSS, USA) and statistical packages R (http://www.r-project.org; Mirrors https://mirrors.tuna.tsinghua.edu.cn/CRAN/; version 3.6.1, Austria).

Results

Between May 25, 2015, and November 11, 2017, 400 patients were enrolled and randomly assigned to either general anesthesia alone (n = 200) or combined epidural–general anesthesia (n = 200). All were included in the intent-to-treat analysis. There were six protocol deviations (two had postoperative analgesia less than 24 h because of severe postoperative nausea and vomiting, and four changed from epidural to intravenous analgesia because of inadequate analgesia or massive bleeding), leaving 394 patients in the per-protocol analysis. One year after surgery, one patient was lost to follow-up and fourteen patients died; others completed activity assessment. At completion of the follow-up period (median, 32 months; interquartile range, 24 to 48 months), 7 patients (1.8%) were lost to follow-up (fig. 1). Follow-up ended November 30, 2019.

Among all enrolled patients, 84% (336 of 400) had histologically confirmed lung cancer. Baseline characteristics were generally comparable in the randomized groups. However, the percentage of patients with tumor-node-metastasis stage 0 and negative anaplastic lymphoma kinase gene detection were slightly lower in patients assigned to combined epidural–general anesthesia, whereas the percentage with mild ventilatory function reduction was slightly higher (table 1; tables S1 and S2 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646).

As expected, patients in the combined epidural–general anesthesia group were given less opioid and had lower mean arterial pressures during surgery. They received epidural sufentanil per protocol but were given less intravenous morphine over the initial 3 postoperative days. Total perioperative opioid consumption was about 8% less in patients assigned to combined epidural–general anesthesia (table 2; table S3 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646).

Only four deaths occurred before confirmed cancer recurrence. Specifically, one patient assigned to general anesthesia alone died from chemotherapy-related toxicity during the initial postoperative month; three others with combined epidural–general anesthesia died from chemotherapy-induced toxicity, severe brain injury, and acute myocardial infarction; none had evidence of cancer recurrence/metastasis, although all four had histologically confirmed lung cancer during their index operations. The two deaths caused by chemotherapy without recurrence/metastasis were judged to be cancer-related (table S4 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646). In our patients, recurrence-free survival was thus equivalent to being recurrence-free.

Primary and Secondary Outcomes

Recurrence-free survival did not differ between the two groups (fig. 2). When follow-up ended, there were 54 events (recurrence or death) among the 200 patients (27%) randomized to general anesthesia alone, compared with 48 events in the 200 patients (24%) given combined epidural–general anesthesia during a median 32-month period (adjusted hazard ratio, 0.90; 95% CI, 0.60 to 1.35; $P = 0.608$). The proportional hazard assumption was not violated ($P = 0.168$). Per-protocol analysis also showed no differences with 54 events in 199 patients (27%) assigned to general anesthesia alone *versus* 47 events in 195 patients (25%) given combined epidural–general anesthesia (adjusted hazard ratio, 0.92; 95% CI, 0.61 to 1.39; $P = 0.688$; table 3; table S5 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646). No subgroup interactions were statistically significant (fig. 3).

There were no statistically significant or clinically meaningful differences in overall and cancer-specific survival between the two groups (table 3; table S5 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646). In the subgroup of patients with confirmed lung cancer, there were no significant differences in recurrence-free, overall, or cancer-specific survival between the two groups (table S6 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646).

Patients assigned to combined epidural–general anesthesia were less likely to be admitted to the ICU after surgery (relative risk, 0.200; 95% CI, 0.044 to 0.901; $P = 0.032$) and had chest tubes removed earlier (hazard ratio, 1.23; 95% CI, 1.00 to 1.50; $P = 0.019$) and shorter postoperative hospitalization (hazard ratio, 1.29; 95% CI, 1.06 to 1.58; $P = 0.004$). Pain scores recorded on the first three postoperative mornings at rest (median difference, −1 to 0 points; all $P < 0.001$) and during coughing (median difference, −1 point; all $P < 0.001$) were significantly lower in patients with combined epidural–general anesthesia than in those with general anesthesia alone (table 4; tables S7 and S8 in Supplemental Digital Content 2, http://links.lww.com/ALN/C646).

Safety Outcomes

Epidural catheter insertion failed in 3 of 200 patients (1.5%). Patients assigned to combined epidural–general anesthesia had less intraoperative high airway pressure, bradycardia, and hypertension and required less treatment for hypertension.

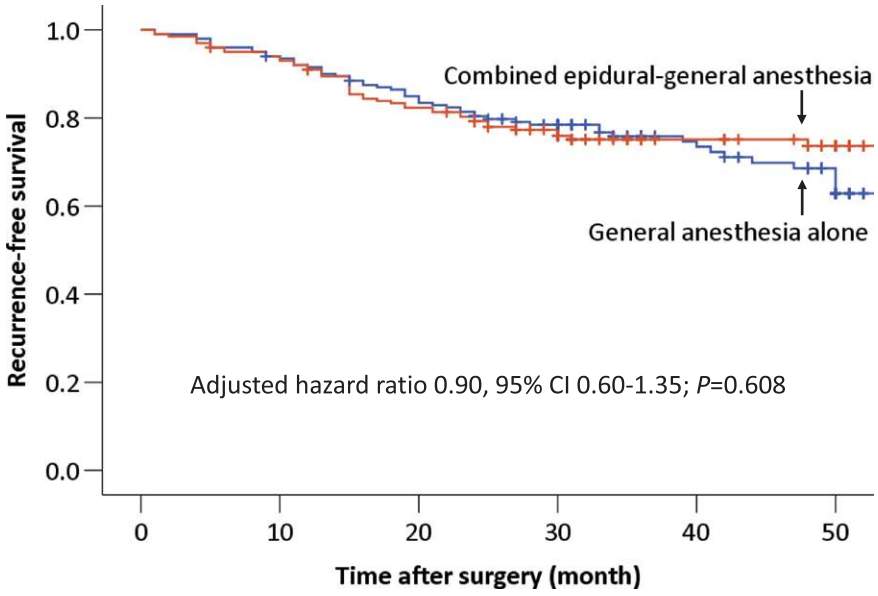
Table 2. Perioperative and Follow-up Data

	General Anesthesia Alone (n = 200)	Combined Epidural–General Anesthesia (n = 200)	*P* Value
Duration of anesthesia, min	315 (265, 373)	321 (267, 380)	0.717
Intraoperative medication			
Glucocorticoids, n (%)*	188 (94.0)	183 (91.5)	0.335
Dexamethasone equivalent, mg†	5 (5, 5)	5 (5, 5)	0.417
Propofol, mg	1,052 (826, 1,459)	1,070 (770, 1,400)	0.803
Sufentanil, μg	56 (35, 89)	30 (20, 40)	**< 0.001**
Remifentanil, μg	620 (0, 1,378)	333 (0, 767)	**0.013**
Rocuronium, mg	50 (50, 50)	50 (50, 50)	0.202
Cisatracurium, mg	15 (9, 22)	14 (9, 20)	0.377
Ropivacaine, mg	0 (0, 0)	105 (85, 150)	
Use of midazolam, n (%)	50 (25.0)	54 (27.0)	0.648
Use of sevoflurane, n (%)	43 (21.5)	30 (15.0)	0.092
Sevoflurane, MAC·h‡	0.0 (0.0, 10.8)	0.0 (0.0, 9.0)	0.090
Use of nitrous oxide, n (%)	108 (54.0)	100 (50.0)	0.423
Nitrous oxide, MAC · h	0.9 (0.0, 1.6)	0.2 (0.0, 1.6)	0.382
Use of dexmedetomidine, n (%)	69 (34.5)	53 (26.5)	0.082
Use of tranexamic acid, n (%)	39 (19.5)	31 (15.5)	0.292
Use of NSAIDs, n (%)			0.710
None	44 (22.0)	51 (25.5)	
Paricoxib	37 (18.5)	35 (17.5)	
Flubiprofen axetil	119 (59.5)	114 (57.0)	
Total fluid infusion, ml	1,600 (1,100, 2,075)	1,600 (1,100, 2,075)	0.986
Crystalloid fluid	1,600 (1,100, 1,800)	1,600 (1,100, 1,600)	0.578
Artificial colloid	0 (0, 238)	0 (0, 500)	0.238
Estimated bleeding, ml	100 (50, 200)	100 (50, 200)	0.617
Urine output, ml	400 (250, 600)	400 (200, 600)	0.819
Blood transfusion, n (%)	3 (1.5)	4 (2.0)	> 0.999
Mean arterial pressure, mmHg§	79 ± 7	77 ± 7	**0.001**
Average heart rate, beats/min§	62 ± 7	61 ± 6	0.111
Duration of surgery, min	213 (171, 271)	218 (170, 285)	0.773
Right-side surgery, n (%)	110 (55.0)	120 (61.2)	0.209
Type of resection, n (%)			0.189
Lobectomy	144 (72.0)	141 (70.5)	
Wedge resection/sublobectomy	39 (19.5)	33 (16.5)	
Pneumonectomy	4 (1.5)	3 (1.0)	
Bilobectomy, right	12 (6.0)	19 (9.5)	
Bilateral lobectomies	1 (0.5)	0 (0.0)	
Palliative resection/unresectable	0 (0.0)	4 (2.0)	
PCA after surgery, n (%)			0.123
Completed	199 (99.5)	195 (97.5)	
Early termination, less than 24 h‖	1 (0.5)	1 (0.5)	
Changed analgesia#	0 (0.0)	4 (2.0)	
Postoperative NSAIDs, n (%)**	179 (89.5)	171 (85.5)	0.210
Postoperative opioids, within 3 days			
Epidural sufentanil, μg	0 (0, 0)	87 (62, 125)	**< 0.001**
Intravenous morphine, mg	42 (37, 48)	0 (0, 0)	**< 0.001**
Others††	75 (37.5)	58 (29.0)	0.071
Total morphine equivalent, mg‡‡	168 (130, 221)	155 (114, 209)	**0.033**
Thoracic drainage			
Within 24 h, ml	150 (80, 250) [2]	188 (85, 278)	0.165
Total volume, ml	735 (390, 1,398) [2]	735 (460, 1,160)	0.564
Postoperative anticancer therapy, n (%)	19 (9.5)	30 (15.0)	0.093
Radiotherapy, n (%)	1 (0.5)	5 (2.5)	0.215
Chemotherapy, n (%)	18 (9.0)	25 (12.5)	0.258
Targeted drugs, n (%)	3 (1.5)	4 (2.0)	> 0.999
Duration of follow-up, month§§	32 (24, 48)	31 (24, 48)	0.610

The data are given as median (interquartile range), n (%), or mean ± SD, unless otherwise indicated. The numbers in square brackets indicate patients with missing data.

*Included dexamethasone, hydrocortisone, and methylprednisolone. †100 mg hydrocortisone = 3.75 mg dexamethasone; 40 mg methylprednisolone = 7.5 mg dexamethasone. ‡The data are given as median (full range). §From the start of epidural block (for patients with combined epidural–general anesthesia) or anesthetic induction (for patients with general anesthesia alone) to the end of surgery. Mean arterial pressure = 1/3 systolic blood pressure + 2/3 diastolic blood pressure. ||Because of severe postoperative nausea and vomiting or epidural catheter dislodge. #Changed from epidural analgesia to intravenous analgesia because of failure of epidural block. **Included flubiprofen axetil. ††Included oxycodone and tramadol. ‡‡Calculated as intravenous morphine equivalent. Included intraoperative and postoperative opioids: 30 mg of morphine (*per os*) = 10 mg morphine (intravenously [IV]) = 10 μg sufentanil (IV) = 100 μg remifentanil (IV) = 100 mg tramadol (IV) = 200 mg tramadol (*per os*) = 20 mg oxycodone (*per os*).[28] §§From date of surgery to November 30, 2019.

MAC · h, minimum alveolar concentration × hours; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia.



Number at risk						
Combined epidural-general	200	187	168	119	63	24
General anesthesia alone	200	187	162	111	58	24

Fig. 2. Kaplan–Meier estimate of recurrence-free survival. Multivariable Cox proportional hazards model adjusted for age, sex, smoking history, American Society of Anesthesiologists physical status, tumor-node-metastasis stage, and postoperative anticancer therapy. *Crosses* indicate censored patients.

However, they more often experienced intraoperative hypotension and were more often given vasopressors. One patient in the combined epidural–general anesthesia group developed severe ischemic–hypoxic brain injury, which was attributed to severe intraoperative hypotension caused by pulmonary artery rupture and massive bleeding that was deemed unrelated to the trial; the patient died 5 months after surgery (table 5).

Table 3. Long-term Survival

		Unadjusted Values		Adjusted Values	
	Events, n (%)	Hazard Ratio (95% CI)*	*P* Value	Hazard Ratio (95% CI)†	*P* Value
Primary endpoint					
Recurrence-free survival‡					
General anesthesia alone, n = 200	54 (27.0)	Reference		Reference	
Combined epidural–general anesthesia, n = 200	48 (24.0)	0.92 (0.62–1.36)	0.670	0.90 (0.60–1.35)	0.608
Recurrence-free survival, events (per-protocol analysis)					
General anesthesia alone, n = 199	54 (27.1)	Reference		Reference	
Combined epidural–general anesthesia, n = 195	47 (24.6)	0.94 (0.63–1.38)	0.736	0.92 (0.61–1.39)	0.688
Secondary endpoints					
Overall survival§					
General anesthesia alone, n = 200	25 (12.5)	Reference		Reference	
Combined epidural–general anesthesia, n = 200	31 (15.5)	1.29 (0.76–2.18)	0.350	1.12 (0.64–1.96)	0.697
Cancer-specific survival‖					
General anesthesia alone, n = 200	24 (12.0)	Reference		Reference	
Combined epidural–general anesthesia, n = 200	29 (14.5)	1.26 (0.73–2.15)	0.416	1.08 (0.61–1.91)	0.802

*Survival analysis and log-rank test. †Multivariable Cox proportional hazards model adjusted for age (less than 65 yr *vs.* 65 yr or more), sex (male *vs.* female), chronic smoking (no *vs.* yes), American Society of Anesthesiologists classification (I *vs.* II + II), tumor-node-metastasis stage (0 *vs.* 1 *vs.* 2 + 3 + 4 + x), and postoperative anticancer therapy (no *vs.* yes). ‡Endpoint events include all-cause death, recurrence, or metastasis, whichever came first. §Endpoint event is all-cause death. ||Endpoint event is cancer-specific death.

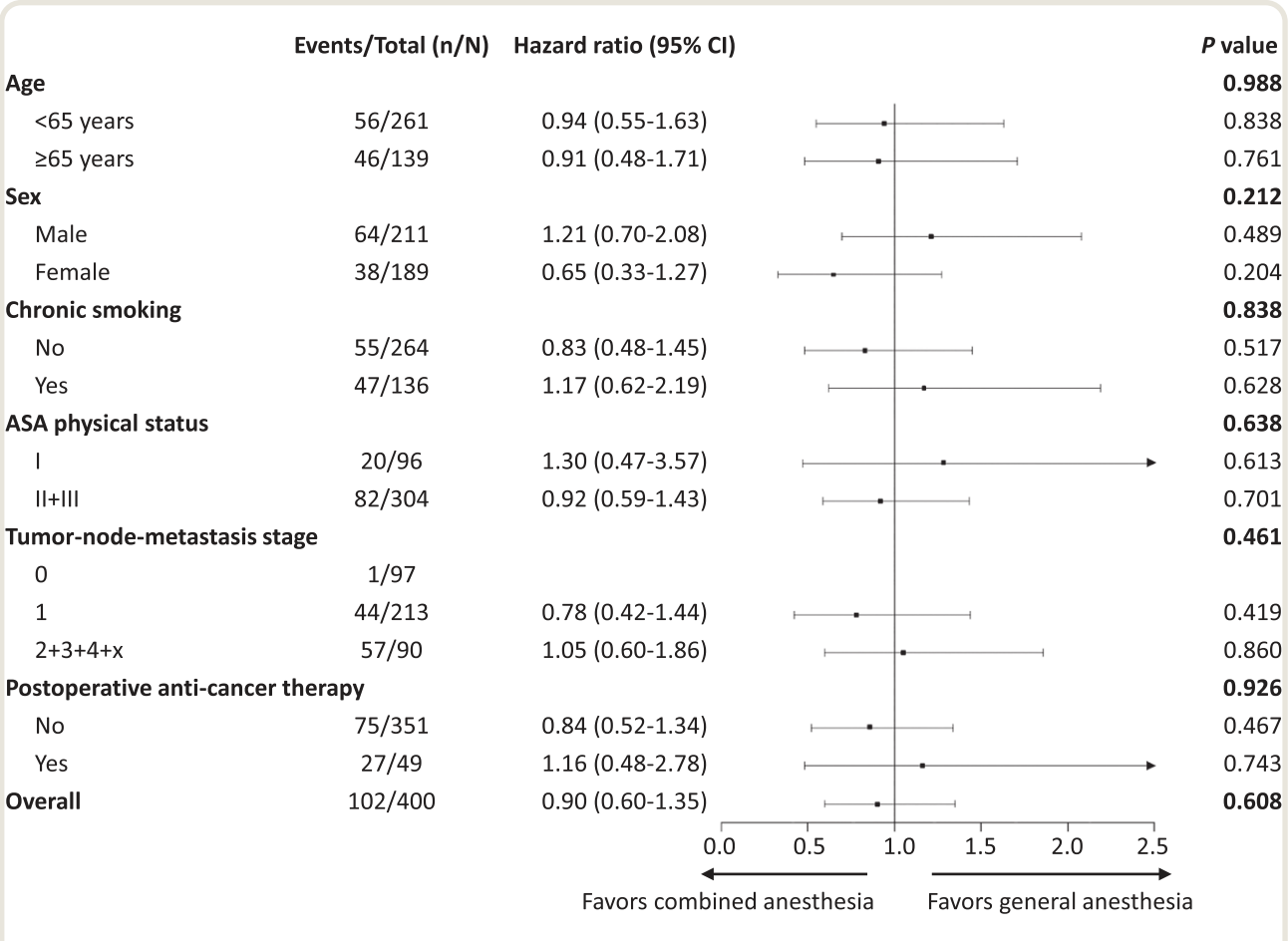


Fig. 3. Forrest plot assessing interaction between preselected baseline factors and the effect of combined epidural–general anesthesia *versus* general anesthesia alone on recurrence-free survival. The estimated overall hazard ratio was derived from a multivariable Cox proportional hazards model adjusted for age, sex, smoking history, American Society of Anesthesiologists (ASA) physical status, tumor-node-metastasis stage, and postoperative anticancer therapy. For the subgroup analyses, we assessed the treatment-by-covariate interaction on the primary outcome, adjusting for the same baseline variables.

Discussion

Combined epidural–general anesthesia with epidural analgesia did not improve recurrence-free survival compared to general anesthesia with opioid analgesia, nor did it improve other survival outcomes in the entire population or in patients with confirmed lung cancer. The only previous robust trial evaluating the effect of regional analgesia on cancer recurrence was for breast cancer, a far less invasive procedure. The breast cancer trial enrolled more than 2,100 patients, whereas we recruited 400 lung cancer patients considering that lung cancer recurs far more often. Although we reached the target number of outcome events, the CI for recurrence-free survival ranges from a 40% reduction in the hazard to a 35% increase. It therefore remains possible that regional anesthesia and analgesia reduces lung cancer recurrence by amounts that are clinically meaningful. Nonetheless, available evidence does not support the theory that regional anesthesia–analgesia reduces cancer recurrence in humans, despite strong *in vitro* and animal support.

As might be expected, most deaths were cancer-specific, usually resulting from cancer recurrence or metastasis. Our recurrence rate was lower than previously reported,[36,38] possibly because tissue diagnoses are rarely available before lung cancer surgery. We thus enrolled patients *believed* to have potentially resectable lung cancer. In fact, 16% of our patients turned out to have noncancer diseases. When noncancer patients were excluded, 32% of our patients had a recurrence within a median of 32 months, which is similar to previously reported results (33% within a median of 24 months).[36]

Epidural block is generally safe in patients without contraindications and usually successful. Epidural catheterization failed in only 3 of 200 (1.5%) patients, which was lower than previously reported results (6.1%).[39] Severe adverse events were rare, and none was attributed to epidural block

Table 4. Perioperative and Other Long-term Outcomes

Secondary Endpoints	General Anesthesia Alone (n = 200)	Combined Epidural–General Anesthesia (n = 200)	RR or HR (95% CI)*	*P* Value
ICU admission, n (%)	10 (5.0)	2 (1.0)	RR = 0.200 (0.044–0.901)	**0.032**
ICU admission with intubation, n (%)	6 (3.0)	1 (0.5)	RR = 0.167 (0.020–1.372)	0.122
Postoperative complication, n (%)	49 (24.5)	42 (21.0)	RR = 0.86 (0.60–1.23)	0.404
Duration of chest tube drainage, days	5 (3, 7)	5 (3, 6)	HR = 1.23 (1.00–1.50)	**0.019**
Length of hospital stay after surgery, days	6 (4, 8)	5 (4, 7)	HR = 1.29 (1.06–1.58)	**0.004**
In-hospital mortality, n (%)	0 (0.0)	0 (0.0)		
Full physical recovery in 1-yr survivors†	105 (54.4) [7]	119 (62.0) [8]	RR = 1.14 (0.96–1.35)	0.132

The data are given as n (%) or median (interquartile range). The numbers in square brackets indicate patients with missing data.

*Calculated as combined epidural–general anesthesia *versus* or *minus* general anesthesia alone. †Engagement of moderate-intensity activity (3 to 5.9 metabolic equivalents; 1 metabolic equivalent = 3.5 ml · min^{-1} · kg^{-1} resting oxygen consumption) for at least 150 min a week or above.[34,35]

HR, hazard ratio; ICU, intensive care unit; RR, relative risk.

per se. However, patients with epidural anesthesia had a 22% higher incidence of intraoperative hypotension and therefore the need for vasopressors, a well known consequence of combining epidural and general anesthesia.[40] Intraoperative hypotension is associated with adverse events including delirium,[41] myocardial injury,[42] acute kidney injury,[43] and mortality.[44] Our trial was not powered for specific organ injuries, although we evaluated a composite of serious complications and mortality. We were therefore unable to fully evaluate the overall risks and benefits of intraoperative epidural anesthesia.

Unsurprisingly, epidural anesthesia required about 46% less intraoperative opioid; epidural analgesia also provided superior postoperative pain relief, with a median 1 point lower on our 0- to 10-point pain scale. Overall, epidural anesthesia–analgesia consumed about 8% less opioid, which

Table 5. Adverse Events

	General Anesthesia Alone (n = 200)	Combined Epidural–General Anesthesia (n = 200)	*P* Value
Epidural puncture related			
Accidental epidural puncture, n (%)		0 (0.0)	
Failed epidural catherization, n (%)		3 (1.5)	
Intraoperative period			
Supraventricular tachycardia, n (%)*	3 (1.5)	4 (2.0)	> 0.999
Atrial fibrillation, n (%)†	2 (1.0)	2 (1.0)	> 0.999
Atrial/ventricular premature beat, n (%)	9 (4.5)	8 (4.0)	0.804
Ventricular fibrillation, n (%)‡	1 (0.5)	0 (0.0)	> 0.999
High airway pressure, n (%)§	17 (8.5)	7 (3.5)	**0.035**
Continuous positive airway pressure to nonventilating lung, n (%)‖	4 (2.0)	5 (2.5)	> 0.999
Bradycardia, n (%)#	19 (9.5)	3 (1.5)	**< 0.001**
Sinus tachycardia, n (%)**	5 (2.5)	7 (3.5)	0.558
Hypotension, n (%)††	94 (47.0)	121 (60.5)	**0.007**
Treatment for hypotension, n (%)‡‡	88 (44.0)	117 (58.5)	**0.004**
Hypertension, n (%)§§	55 (27.5)	20 (10.0)	**< 0.001**
Treatment for hypertension, n (%)‖‖	36 (18.0)	11 (5.5)	**< 0.001**
Massive blood loss (> 800 ml), n (%)	8 (4.0)	5 (2.5)	0.398
Postoperative period			
Dislodged epidural catheter, n (%)		3 (1.5)	
Postoperative nausea and vomiting, n (%)	23 (11.5)	20 (10.0)	0.628
Dizziness, n (%)	4 (2.0)	5 (2.5)	> 0.999
Severe ischemic-hypoxic brain injury, n (%)##	0 (0.0)	1 (0.5)	> 0.999

The data are given as n (%).

*Terminated after stopping surgical stimulation and/or elevating blood pressure. †One case required cardioversion and amiodarone therapy; the other three cases required β-blockers. ‡Caused by electric cauterization on pericardium; resuscitated successfully without sequelae. §Airway peak pressure greater than 30 cm H_2O after correcting other factors (tube position, muscle relaxation, secretion suction). ‖Applied to relieve desaturation (oxygen saturation measured by pulse oximetry less than 88%) during one-lung ventilation. #Heart rate less than 45 beats/min. **Heart rate greater than 100 beats/min. ††Systolic blood pressure less than 90 mmHg or a decrease of greater than 30% from baseline value before surgery. ‡‡Included ephedrine, phenylephrine, norepinephrine, dopamine, and epinephrine. §§Systolic blood pressure greater than 180 mmHg or an increase of greater than 30% above baseline value before surgery. ‖‖Included urapidil and nicardipine. ##Resulted from intraoperative massive bleeding and persistent hypotension.

is consistent with previous results.[45,46] The difference was smaller than might be expected because the epidural infusion included the opioid sufentanil per clinical routine.

Better analgesia and less opioid consumption likely explain other short-term benefits consequent to epidural–general anesthesia. For example, good analgesia might have improved the patients' ability to cough and recover good lung function, thereby allowing chest tubes to be removed earlier. Similarly, 80% fewer patients given epidural analgesia required postoperative ICU admission, possibly because pain was well controlled with less opioid. Shortened hospitalization (median 1 day shorter, corresponding to a 17% decrease) may have been a natural consequence in patients randomized to epidural–general anesthesia given earlier chest tube removal[47] and fewer ICU admissions.[48]

An important limitation is that clinical teams could not be blinded to analgesic strategy. Clinician expectations may thus have influenced the ICU admission, timing of chest tube removal, and discharge decisions. Although it seems unlikely that all apparent benefit and harm were due to clinician bias, some presumably was. Pain was assessed only once daily, starting the first postoperative morning. Furthermore, a difference of 1 point is of marginal clinical importance,[28] although we might have missed greater differences that are usually apparent during the initial postoperative hours.

As might be expected in a moderate-sized randomized trial, baseline balance was good. However, there were slight imbalances in tissue diagnoses and tumor extent. We therefore included cancer stage and other factors in a multivariable model for correction and performed a subgroup analysis in patients with confirmed cancer, which confirmed the primary results. With a total of 102 outcome events, we had reasonable power for identifying moderate treatment effects. However, it remains possible that regional anesthesia and analgesia reduces recurrence by amounts that might be considered clinically meaningful. Our single-center approach reduces generalizability of our findings. Nonetheless, our anesthetic approach was fairly routine and not overly proscriptive. Given our equivocal results, it seems unlikely that findings would much differ with any similar approach, even in another institution.

In summary, combined epidural anesthesia–analgesia for lung cancer surgery did not improve recurrence-free, overall, or cancer-specific survival compared to general anesthesia alone. Our trial was powered to detect a relative reduction in cancer recurrence of about a third, but was underpowered for smaller effects that might still be clinically meaningful. Combined epidural anesthesia–analgesia remains a reasonable alternative for major lung cancer, although it should not be expected to reduce the risk of lung cancer recurrence.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: dxwang65@bjmu.edu.cn. Raw data available at: dxwang65@bjmu.edu.cn.

Correspondence

Address correspondence to Dr. Wang: Peking University First Hospital, Beijing 100034, China. dxwang65@bjmu.edu.cn. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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