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The Effects of Epidural Analgesia on Cancer Recurrence and Long-term Mortality in Patients after Non-small-cell Lung Cancer Resection: A Propensity Score-matched Study

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Abstract

Objectives: Previous studies showed reductions in recurrence and mortality rate of several cancer types in patients receiving perioperative epidural analgesia. This study aimed to investigate the effects of thoracic epidural analgesia on oncologic outcomes after resection for lung cancer.

Design: Retrospective study using propensity score matching methodology.

Setting: Single medical centre in Taiwan.

Participants: Patients with stage I-III non-small-cell lung cancer undergoing primary tumour resection between January 2005 and December 2015 and had either epidural analgesia, placed preoperatively and used intra- and postoperatively, or intravenous analgesia were evaluated through May 2017.

Primary and secondary outcome measures: Primary endpoint was postoperative recurrence-free survival and secondary endpoint was overall survival.

Results: The 3-yr recurrence-free and overall survival rates were 69.8% (95% CI: 67.4 – 72.2%) and 92.4% (95% CI: 91 – 93.8%) in the epidural group and 67.4% (95% CI: 62.3 – 72.5%) and 89.6% (95% CI: 86.3 – 92.9%) in the non-epidural group, respectively. Multivariable Cox regression analysis before matching demonstrated no significant difference in recurrence or mortality between groups (adjusted hazard ratio: 0.93, 95% CI: 0.76 – 1.14 for recurrence; 0.81, 95% CI: 0.58 – 1.13 for mortality), similar to the results after matching

(hazard ratio: 0.97, 95% CI: 0.71 – 1.31; 0.94, 95% CI: 0.57 – 1.54). Independent risk factors for both recurrence and mortality were male, higher pretreatment carcinoembryonic antigen level, advanced cancer stage, poor differentiation, lymphovascular invasion, microscopic necrosis, and postoperative radiotherapy.

Conclusions: Thoracic epidural analgesia was not associated with better recurrence-free or overall survival in patients receiving surgical resection for stage I-III non-small-cell lung cancer.

Keywords: Epidural Analgesia; Cancer; Recurrence; Mortality; Non-small-cell Lung Carcinoma; Propensity Score

Article Summary

Strengths and limitations of this study

- Large sample size and long follow-up time were employed to evaluate the impacts of epidural analgesia on long-term outcomes after lung cancer surgery.
- Propensity score matching was used to deal with possible imbalances in collected variables.
- Epidural assignment was not randomized, clinical care was not standardized and potential selection bias cannot be ruled out.
- Effects of unmeasured confounders on outcomes after lung cancer surgery cannot be further evaluated.

Introduction

Lung cancer is the most commonly diagnosed malignancy worldwide, and its incidence continues to grow.[1] An estimated 1.8 million new cases of lung cancer were diagnosed and 1.59 million lung cancer deaths occurred globally in 2012.[1] Surgical removal of the primary tumour is the mainstay of treatment for patients with non-small-cell lung cancer staged I through IIIA.[2] However, surgical dissection and manipulation are associated with unintentional dispersal of cancer cells into the blood and lymphatic systems.[3] Whether the residual neoplastic cell would develop into a metastasis depends on the perioperative immune competence of the patient. Surgically induced stress hormone, as well as inhaled volatile anesthetics and systemic opioids, can diminish natural killer cell function, the primary defense against cancer cells.[4]

Opioids inhibit components of both cell-mediated and humoral immunity.[5] Morphine also has proangiogenic properties that may promote dissemination of angiogenesis-dependent tumours.[6] Inflammatory cytokines have been shown to regulate the expression of the mu-opioid receptor (MOR) gene, highlighting an interaction between the opioid and immune systems.[7] It is noted that the MOR is over-expressed in several types of lung cancer and it promotes opioid- and growth factor-induced proliferation and migration in human lung cancer cells.[8] Furthermore, silencing the MOR greatly reduced opioid-induced tumour growth and metastasis in vitro.[9]

Thoracic epidural analgesia has commonly been used for the management of postoperative pain after thoracic surgeries. Epidural analgesia may be beneficial through its opioid and general anesthetic sparing and surgical stress alleviating properties. For major thoracic surgeries, epidural analgesia reduced mortality, respiratory complications and opioid consumption and improved time to ambulation.[10] However, the effect of epidural analgesia on oncologic outcomes after lung cancer resection remains unclear, and only one retrospective study with limited sample size is available for this issue.[11] Therefore, we conducted this retrospective cohort study to investigate the relationship between perioperative thoracic epidural analgesia and cancer recurrence or overall survival in patients following surgical resection for non-small-cell lung cancer. The effects of other major prognostic factors were assessed as well to determine the significant predictors of oncologic outcomes after lung cancer resection.

Methods

Setting and patient selection

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH No. 2015-11-010CC) and written informed consent was waived. Patients undergoing surgical resection of pulmonary neoplasms between January 2005 and December 2015 at our hospital were retrospectively identified from the institutional electronic medical database. Patients with secondary lung cancer, small cell lung cancer, stage IV disease determined at the time of surgery, or missing data about demographics, pathologic details or postoperative analgesic were excluded from the study. (Figure 1) Patients were analysed in two groups: those receiving general anaesthesia with perioperative epidural analgesia and their counterparts receiving general anaesthesia without epidural analgesia.

Analgesia management

All patients undergoing open thoracotomy or video-assisted thoracoscopic surgery at our hospital were offered the choice of epidurals with preoperative catheter placement or intravenous analgesia with a demand pump. If epidural analgesia was selected, an epidural catheter was typically placed at a middle thoracic region (e.g., T6–T8) and assessed its function with a test dose of local anesthetic preoperatively. Epidural analgesia was started intraoperatively with local anesthetic (bupivacaine 0.25% or 0.5%) and continued postoperatively for 48 to 72 hours. Typically, patients undergoing lung cancer surgery

received fentanyl 50 to 150 µg for anesthetic induction. Patients with effective epidurals were rarely given additional opioids perioperatively. If patients refused epidurals or it was contraindicated, an intravenous patient-controlled analgesia was administered via an ambulatory infusion pump (Gemstar™ Yellow, Hospira, IL, USA) programmed to deliver morphine at a demand dose of 1 mg with a lockout time of 6 minutes.

Data retrieval

An electronic medical database was used to determine the baseline clinicopathologic risk factors for cancer recurrence and mortality. The following data were obtained from medical records: demographic characteristics; the Eastern Cooperative Oncology Group (ECOG) performance score;[12] co-existing diseases (chronic obstructive pulmonary disease, diabetes, chronic kidney disease, etc); preoperative pulmonary function (forced vital capacity and forced expiratory volume in one second); pretreatment carcinoembryonic antigen (CEA) level;[13] anaesthesia time, perioperative packed red blood cell (pRBC) transfusion;[14] pathologic features (tumour differentiation, microscopic necrosis,[15] lymphovascular invasion,[16] and perineural invasion);[17] whether preoperative or postoperative adjuvant chemotherapy or radiotherapy was used; and each patient's current status as determined by documentation of follow-up visits to the hospital's outpatient clinic or subsequent admissions. Tumour nodes metastasis (TNM) staging was also obtained from the record and translated into stage I to III according to the American Joint Committee on Cancer criteria (AJCC-7

staging system).[18] Adjuvant therapies given in the form of chemotherapy (cisplatin-gemcitabine, cisplatin-paclitaxel, cisplatin-docetaxel, or carboplatin-paclitaxel) or radiotherapy were at the discretion of surgeons and patients, and was defined as any therapy given within 90 days of surgery. The radiologists and thoracic surgeons of our hospital determined whether cancer recurred or not, which was mainly based on imaging studies (computed tomography, magnetic resonance imaging, bone scan, etc.) and defined by response evaluation criteria in solid tumours (RECIST) guidelines.[19] Pathology-proven second primary lung cancer was not considered as a recurrent disease. At our hospital, close surveillance was performed for survivors of lung cancer following definitive surgical therapy, including chest computed tomography every 6 months for at least the first 2 years, and annually thereafter. The follow-up rates of this cohort were 95.3%, 88.7%, and 78.8% in the end of the postoperative first, third, and fifth year, respectively. (Table S1) The date of death was determined based on medical records or death certificate.

Medical records of all the patients included were extracted by specialist anesthesiologists who were not involved in data analysis. The quality of the extracted data was verified through random sampling by the authors. Data were collected up to the end of May 2017.

The primary endpoint was recurrence-free survival, which was defined as time from the date of surgery to the date of cancer recurrence. The secondary endpoint was overall survival, defined as time from the date of surgery to the date of death. For those without the event of

cancer recurrence or death, their survival times were regarded as the corresponding censored observations with the last visit date used as the censored date.

Statistical analysis

The comparisons of patient characteristics between the epidural and non-epidural groups were performed using chi-square tests for categorical variables and either t tests or Wilcoxon rank sum tests for continuous variables, as appropriate. The Kaplan-Meier method and log rank test were used to compare recurrence-free and overall survival distributions between the two groups. Univariate Cox regression analysis was used to evaluate the effects of epidural analgesia and other variables collected in the study on recurrence-free or overall survival. Significant predictors of recurrence-free or overall survival in the univariate analysis were used as candidates for stepwise model selection processes in the following multivariable analysis. The entry and exit criteria of significance level were set at 0.05 and 0.1, respectively, to select factors associated with recurrence-free and overall survival in the multivariable analysis. Afterward the effects of epidural analgesia adjusted for the selected predictors in the multivariable analysis on recurrence-free and overall survival were further evaluated.

To account for the potential imbalance in measured confounders related to cancer recurrence or survival of lung cancer between epidural and non-epidural groups, propensity scores based on a collection of patient characteristics was developed to estimate the probability of receiving epidurals (Table S2). Propensity score matching was performed as the primary

analysis using a caliper with width equal to 0.2 of the standard deviation of the logit of the propensity score to ensure sufficient balance in collected variables between matching pairs.[20] For sensitivity analysis, all subjects were divided into five equal-size groups using the quintiles of the estimated propensity score and stratified Cox regression analysis was conducted to obtain a pooled hazard ratio across the five strata to ensure the consistency among different estimates of the effects of epidurals on cancer recurrence or overall survival. The significance level of all hypotheses was 0.05 for a two-sided test. IBM SPSS Statistics for Windows Version 22.0 (Armonk, NY: IBM Corp.) was used for all analyses.

Results

Total of 2191 patients were included in this study and 1799 (82.1%) of them received epidural analgesia. There were some differences in the distributions of baseline characteristics between groups, including larger forced expiratory volume in one second (p = 0.031) and less thoracoscopic surgery (p < 0.001) in epidural group. (Table 1) The rate of epidural replacement declined because more resections of lung cancer were done with thoracoscopic technique at our hospital in recent years. (Table S3) Those not receiving epidurals, as mentioned above, had intravenous patient-controlled opioid analgesia. The follow-up time was longer in epidural group, 43.5 months (interquartile range 25.3 – 72.4) versus 39.4 (21.9 – 59.9) in non-epidural group, respectively (p < 0.001). Table 2 shows the details of cancer stages and pathologic features of the two groups. The epidural group had higher rate of lymphocytic infiltration. After propensity score matching, the final sample of 372 matched pairs of patients was analysed, and no significant difference was found in demographic or pathologic characteristics between groups. (Table 1)

Association between Thoracic Epidural Analgesia and Recurrence-free Survival

The 3-yr and 5-yr recurrence-free survival were 69.8% (95% CI: 67.4 – 72.2%) and 64.4% (95% CI: 61.9 – 66.9%) in the epidural group and 67.4% (95% CI: 62.3 – 72.5%) and 62.8% (95% CI: 57.1 – 68.5%) in the non-epidural group, respectively. No significant difference in the distribution of recurrence-free survival after lung cancer surgery was noted when

comparing epidural with non-epidural group (p = 0.54 by log rank test, Figure 2A). Moreover, epidural analgesia was not associated with better recurrence-free survival in patients stratified by cancer stages (Figure. 2B).

The multivariable regression model indicated eight independent prognostic factors, including male (HR: 1.30), pretreatment CEA level (HR: 1.26, on base-10 logarithmic scale), cancer stage (II vs. I, HR: 1.93; III vs. I, HR: 2.85), tumour differentiation (moderate vs. good, HR: 3.75; poor vs. good, HR: 5.20), microscopic tumour necrosis (HR: 1.44), pathologic lymphovascular invasion (HR: 2.05), and postoperative chemotherapy (HR: 1.46) and radiotherapy (HR: 1.44). (Table 3) Adjusting for other covariates, the effect of epidurals on recurrence-free survival after lung cancer surgery was non-significant (HR: 0.93, 95% CI: 0.76 – 1.14, p = 0.47) in the multivariable analysis, similar to the results after propensity-score matching (hazard ratio: 0.97, 95% CI: 0.71 – 1.3, p = 0.82) and the quintile-stratified analysis (pooled HR: 0.94, 95% CI: 0.76 – 1.15, p = 0.53).

Association between Thoracic Epidural Analgesia and Overall Survival

The 3-yr and 5-yr overall survival were 92.4% (95% CI: 91 – 93.8%) and 85.8% (95% CI: 83.8 – 87.8%) in the epidural group and 89.6% (95% CI: 86.3 – 92.9%) and 84.3% (95% CI: 80 – 88.6%) in the non-epidural group.

No significant difference in the distribution of long-term mortality after lung cancer surgery was found between the epidural and non-epidural groups (Figure 2C, p = 0.13 by log rank

test). In addition, no significant difference in overall survival was noted between the two groups in the subgroup analysis for distinct cancer stages (Figure 2D).

Nine independent prognostic factors were identified after the multivariable analysis (Table 3), including male (HR: 1.97), ECOG performance score ≥ 1 (HR: 1.49), pretreatment CEA level (HR: 1.67), cancer stage (II vs. I HR: 2.06; III vs. I, HR: 2.96), perioperative pRBC transfusion (HR: 1.40), tumour differentiation (moderate vs. good, HR: 4.72; poor vs. good, HR: 6.17), microscopic necrosis (HR: 1.38), pathologic lymphovascular invasion (HR: 2.13), and postoperative radiotherapy (HR: 1.81). Multivariable analysis indicated no association between epidural analgesia and mortality in non-small-cell lung cancer after surgery (HR: 0.81, 95% CI: 0.58 – 1.13, $p = 0.21$). Propensity score matching generated similar results to the multivariable regression analysis (HR: 0.94, 95% CI: 0.57 – 1.54, $p = 0.8$) as well as the quintile-stratified (HR: 0.8, 95% CI: 0.58 – 1.1, $p = 0.17$) propensity score analyses.

Discussion

To our knowledge, this is the largest retrospective study applying propensity scoring methods to evaluate the impacts of epidural analgesia on oncologic outcomes after lung cancer surgery. We found no evidence that epidural analgesia was associated with improved recurrence-free survival or overall survival in patients following surgical resection of non-small-cell lung cancer. Major clinicopathologic prognostic factors were also taken into account in this study to estimate the adjusted effects of epidurals and avoid potential confounding effects from unbalanced distributions of important risk factors between the epidural group and its counterpart. From the perspective of methodology, we used propensity score matching to cancel out the potential imbalances in baseline characteristics and obtained similar results with those from traditional multivariable model. The combination of both analytical methods provided more persuasive proof than either of them did. Our study provided valuable information to reject the hypothesis of beneficial effect of epidurals on cancer recurrence or long-term survival after surgical resection of non-small-cell lung cancer with large sample size and considerable prognostic factors which were lacked in the previous survey.[11]

Perioperative immune function is an important determinant for metastases after cancer resection surgery. Anesthetic management of cancer patients could impact long-term outcome, and potentially beneficial interventions include minimizing the use of volatile anesthetics and blood transfusion, administration of cyclooxygenase antagonists and statin, and hypothermia

therapy.[21] However, whether regional analgesia reduces cancer recurrence after resection surgery remains inconclusive. The Cochrane review included four post-hoc analyses of previous controlled trials and indicated that current evidence for the benefit of regional anaesthesia on cancer outcome is inadequate due to limitations of study design and incomplete consideration of confounders.[22]

Although Cata and colleagues reported null results of epidural analgesia on recurrence-free and overall survival after lung cancer surgery,[11] they found an association between the intraoperative opioid consumption and recurrence-free survival or overall survival later only for stage I disease.[23] Our results did not support beneficial effects of epidural analgesia on oncologic outcomes in patients stratified by cancer stages. This may be attributed to the difference in distributions of patient attributes or treatment modality. Maher and co-workers reported an association between increased opioid doses during initial 96-hours postoperative period and higher recurrence rate of non-small-cell lung cancer within 5 years.[24] However, they found no difference in intraoperative opioid administration among those with or without recurrence of lung cancer at the 5 year follow-up. The effects of regional block and opioid doses on long-term cancer outcomes in early-stage lung cancer await further investigation.

Our results showed perioperative blood transfusion is a risk factor for all-cause mortality, in line with previous literature.[14] In addition to mortality, allogenic blood transfusion may be associated with increased risk of cancer recurrence.[25] Transfused leucocytes can lead to

immunomodulation, including changes in circulating lymphocytes, helper T-cell, suppressor T-cell ratios, and B-cell function.[25] The meta-analysis by Churchhouse and colleagues examined the effect of blood transfusion on cancer recurrence and overall survival in patients undergoing surgical resection of lung cancer in 5378 patients. Though no definitive conclusions could be drawn, there appeared to be a relationship between transfusion and reduction of disease-free survival.[26] In our analysis, the association between blood transfusion and recurrence was non-significant after adjustment for covariates. This finding may imply that the potential impacts of other important confounders (e.g., disease severity, presence of postoperative complications) may have a greater bearing on prognosis than the reception of blood itself.

Several limitations are inherent in this retrospective observational study. First, patients were not randomized and clinical care was not standardized, so that potential selection bias and effects from unmeasured confounders cannot be excluded. Second, relatively small percentage (17.9%) of the patients was cared for without epidural analgesia. Third, the rate of epidural replacement was lower in the latter years and this may result in longer follow-up period of epidural group. However, these imbalances have been cancelled out after propensity score matching. Fourth, it is difficult to determine the total narcotic consumptions for each patient due to the incompleteness of our electronic medical records.

In conclusion, our study rejected the association between epidural analgesia and cancer

recurrence or long-term mortality in patients after surgery for stage I through III non-small-cell lung cancer. Prospective randomized trials are warranted to confirm or refute causal relationships between epidural analgesia and the long-term outcomes after lung cancer surgery.

Footnotes

Author contributors: The author contributions were as follows: HLW and YHT contributed to data acquisition and manuscript drafting. MYT helped revise the manuscript. HHC contributed to study design and statistical analysis. KYC contributed to statistical review, manuscript revision, and final approval of the version to be published. All authors read and approved the final manuscript.

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Competing interests: None declared.

Patient consent: Not required.

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Tables

Table 1: Patient demographics

	Before matching			After matching		
	EA (n=1799)	**Non-EA (n=392)**	**SD**	**EA (n=372)**	**Non-EA (n=372)**	**SD**
Age, year	64 ± 11	64 ± 11	0.1	64 ± 12	64 ± 11	5.8
Sex, male	918 (51.0%)	194 (49.5%)	3.1	192 (51.6%)	183 (49.2%)	4.8
ASA physical status ≥ 3	424 (23.6%)	109 (27.8%)	9.7	104 (28.0%)	100 (26.9%)	2.4
ECOG PS ≥ 1	549 (30.5%)	130 (33.2%)	5.7	132 (35.5%)	117 (31.5%)	8.6
Comorbidities						
COPD	474 (26.3%)	107 (27.3%)	2.1	102 (27.4%)	100 (26.9%)	1.2
Diabetes	297 (16.5%)	56 (14.3%)	6.2	56 (15.1%)	52 (14.0%)	3.1
Coronary artery disease	171 (9.5%)	41 (10.5%)	3.2	41 (11.0%)	39 (10.5%)	1.7
Heart failure	74 (4.1%)	21 (5.4%)	5.9	15 (4.0%)	19 (5.1%)	5.2
Stroke	60 (3.3%)	18 (4.6%)	6.4	25 (6.7%)	17 (4.6%)	9.3
Chronic kidney disease	141 (7.8%)	35 (8.9%)	3.9	25 (6.7%)	31 (8.3%)	6.1
Pulmonary function test						
FVC, liter	2.88 ± 0.76	2.81 ± 0.73	9.5	2.83 ± 0.76	2.82 ± 0.73	1.9
FEV1, liter	2.22 ± 0.62	2.15 ± 0.60	12.3	2.17 ± 0.62	2.16 ± 0.59	2.8
Pretreatment CEA, μg·L^{-1}	2.4 (1.8 – 3.7)	2.6 (1.7 – 4.2)	8.5	2.5 (1.7 – 4.0)	2.6 (1.7 – 4.2)	2.0
Surgeon experience			1.2			0.6
Specialist < 20 years	701 (39.0%)	155 (39.5%)		141 (37.9%)	142 (38.2%)	
Specialist ≥ 20 years	1098 (61.0%)	237 (60.5%)		231 (62.1%)	230 (61.8%)	
Thoracoscopic surgery	1199 (66.6%)	322 (82.1%)	36.1	292 (78.5%)	305 (82.0%)	8.8
Anesthesiologist experience			3.9			10.8
Specialist < 15 years	810 (45.0%)	169 (43.1%)		183 (49.2%)	163 (43.8%)	
Specialist ≥ 15 years	989 (55.0%)	223 (56.9%)		189 (50.8%)	209 (56.2%)	
Anaesthesia time, min	315 (265 – 360)	300 (240 – 368)	8.4	300 (240 – 360)	300 (240 – 360)	1.4
pRBC transfusion	203 (11.3%)	52 (13.3%)	6.0	51 (13.7%)	49 (13.2%)	1.6
Year of Procedure			25.7			5.7
2005 – 2009	627 (34.9%)	69 (17.6%)		74 (19.9%)	67 (18.0%)	
2010 – 2012	517 (28.7%)	157 (40.1%)		148 (39.8%)	145 (39.0%)	
2013 – 2015	655 (36.4%)	166 (42.3%)		150 (40.3%)	160 (43.0%)	
Preoperative C/T ± R/T	77 (4.3%)	21 (5.4%)	5.0	17 (4.6%)	20 (5.4%)	3.7
Postoperative C/T	834 (46.4%)	163 (41.6%)	9.6	151 (40.6%)	158 (42.5%)	3.8
Postoperative R/T	98 (5.4%)	22 (5.6%)	0.7	26 (7.0%)	21 (5.6%)	5.5
Follow-up time, month	43.5 (25.3 – 72.4)	39.4 (21.9 – 59.9)	20.4	40.3 (24.4 – 62.2)	39.6 (21.9 – 59.8)	8.8

Values were mean ± SD, counts (percent), or median (interquartile range). Continuous variables are analysed with Wilcoxon rank-sum tests; categorical variables are analysed with Pearson chi-square tests. SD: standardized difference (imbalance is defined as absolute value greater than 20). ASA: American Society of Anesthesiologists; ECOG PS: Eastern Cooperative Oncology Group performance score; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; CEA: carcinoembryonic antigen; pRBC: packed red blood cell; C/T: chemotherapy; R/T: radiotherapy.

Table 2: Cancer stages and pathologic features

	Before matching			After matching		
	EA (n=1799)	**Non-EA (n=392)**	**SD**	**EA (n=372)**	**Non-EA (n=372)**	**SD**
AJCC stage			2.0			1.8
Stage I	1316 (73.2%)	289 (73.7%)		271 (72.8%)	276 (74.2%)	
IA	546 (30.4%)	116 (29.6%)		114 (30.7%)	110 (29.6%)	
IB	770 (42.8%)	173 (44.1%)		157 (42.2%)	166 (44.6%)	
Stage II	205 (11.4%)	52 (13.3%)		55 (14.8%)	48 (12.9%)	
IIA	106 (5.9%)	26 (6.6%)		32 (8.6%)	24 (6.5%)	
IIB	99 (5.5%)	26 (6.6%)		23 (6.2%)	24 (6.5%)	
Stage III	278 (15.5%)	51 (13.0%)		46 (12.4%)	48 (12.9%)	
IIIA	253 (14.1%)	46 (11.7%)		42 (11.3%)	44 (11.8%)	
IIIB	25 (1.4%)	5 (1.3%)		4 (1.1%)	4 (1.1%)	
Pathologic features						
Subtype			6.8			5.1
Adenocarcinoma	1511 (84.0%)	314 (80.1%)		292 (78.5%)	303 (81.5%)	
SCC	200 (11.1%)	54 (13.8%)		54 (14.5%)	46 (12.4%)	
Other	88 (4.9%)	24 (6.1%)		26 (7.0%)	23 (6.2%)	
Tumour differentiation			5.3			1.8
Good	181 (10.1%)	46 (11.7%)		39 (10.5%)	46 (12.4%)	
Moderate	1100 (61.2%)	215 (54.8%)		209 (56.2%)	201 (54.0%)	
Poor	516 (28.7%)	131 (33.4%)		124 (33.3%)	125 (33.6%)	
Microscopic necrosis	388 (21.6%)	77 (19.6%)	4.8	77 (20.7%)	71 (19.1%)	4.0
Lymphocytic infiltration	189 (10.5%)	27 (6.9%)	12.9	34 (9.1%)	27 (7.3%)	6.9
Lymphovascular invasion	497 (27.6%)	127 (32.4%)	10.4	115 (30.9%)	118 (31.7%)	1.7
Perineural infiltration	58 (3.2%)	12 (3.1%)	0.9	10 (2.7%)	11 (3.0%)	1.6

Values were counts (percent). Categorical variables are analysed with Pearson chi-square tests or Mann-Whitney U tests, as appropriate. SD: standardized difference (imbalance is defined as absolute value greater than 20). AJCC: American Joint Committee on Cancer; SCC: squamous cell carcinoma.

Table 3: Multivariable analysis for cancer recurrence and all-cause mortality after model selection

	Cancer recurrence			All-cause mortality		
	HR	**95% C.I.**	***p***	**HR**	**95% C.I.**	***p***
EA vs. non-EA	0.927	0.755 – 1.139	0.473	0.811	0.582 – 1.129	0.214
Sex (M vs. F)	1.297	1.026 – 1.642	0.030	1.969	1.344 – 2.882	0.001
Pretreatment CEA*	1.263	1.046 – 1.524	0.015	1.494	1.105 – 2.019	0.009
Postoperative C/T	1.456	1.187 – 1.786	<.001	1.672	1.221 – 2.290	0.001
Postoperative R/T	1.443	1.126 – 1.849	0.004	1.402	1.008 – 1.948	0.045
Stage			<.001	1.810	1.271 – 2.578	0.001
II vs. I	1.927	1.521 – 2.440	<.001			<.001
III vs. I	2.848	2.265 – 3.581	<.001	2.059	1.388 – 3.054	<.001
Tumour differentiation			<.001	2.964	2.032 – 4.323	<.001
Moderate vs. good	3.752	1.919 – 7.338	<.001			0.014
Poor vs. good	5.198	2.632 – 10.265	<.001	4.718	1.153 – 19.310	0.031
Microscopic necrosis	1.444	1.203 – 1.733	<.001	6.169	1.487 – 25.587	0.012
Lymphovascular invasion	2.053	1.717 – 2.456	<.001	1.378	1.037 – 1.831	0.027

HR: hazard ratio; EA: epidural analgesia; M: male, F: female; CEA: carcinoembryonic antigen; C/T: chemotherapy; R/T: radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance score; pRBC: packed red blood cell.

* On base-10 logarithmic scale

Figures and Legends

Figure 1: Flow diagram for patient inclusion.

Figure 2: Unadjusted Kaplan–Meier curves for recurrence-free and overall survival of epidural and non- epidural groups

No significant difference in recurrence-free survival (A and B) or overall survival (C and D) after surgery for non-small-cell lung cancer was noted when comparing epidural with non-epidural group as a whole or stratified by cancer stage.

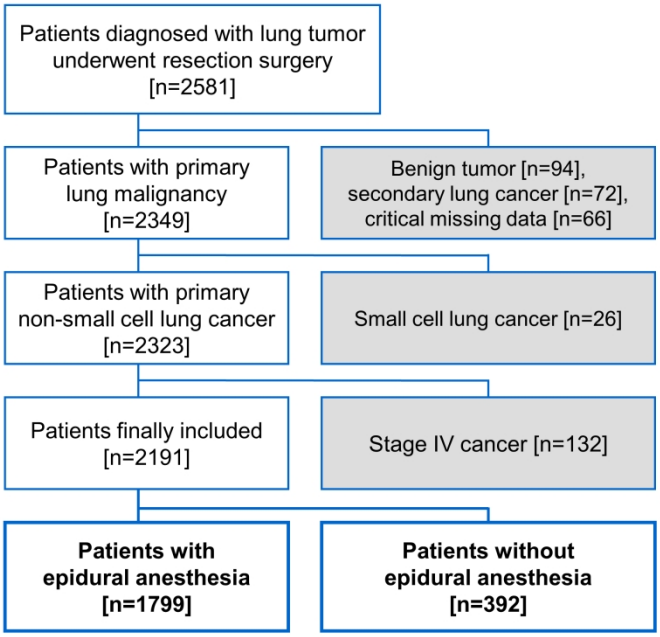

Figure 1: Flow diagram for patient inclusion.

254x190mm (300 x 300 DPI)

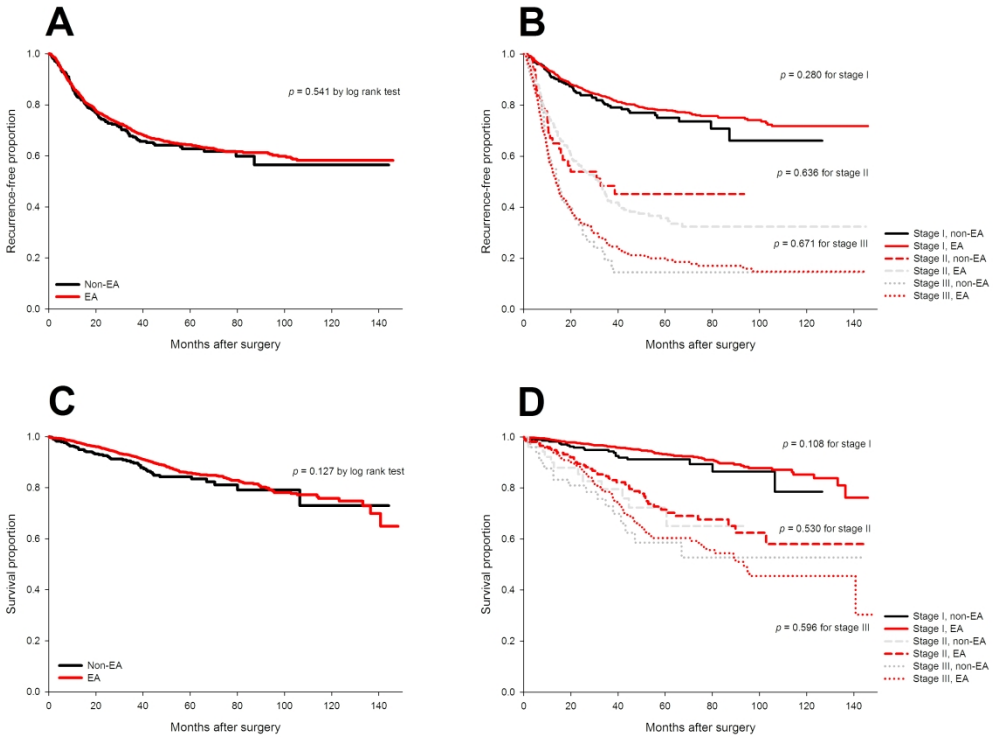

Figure 2: Unadjusted Kaplan–Meier curves for recurrence-free and overall survival of epidural and non-epidural groups

No significant difference in recurrence-free survival (A and B) or overall survival (C and D) after surgery for non-small-cell lung cancer was noted when comparing epidural with non-epidural group as a whole or stratified by cancer stage.

352x260mm (300 x 300 DPI)

Supplement Table 1: Postoperative follow-up in this study

Year after Surgery	No. of Patients under Follow-up	No. of Patients Lost to Follow-up*	No. of Mortality	No. of All Patients	Follow-up Rate (%)**
1st year	2031	103	57	2191	95.3
2nd year	1846	239	106	2191	89.1
3rd year	1400	196	134	1730	88.7
4th year	1066	238	163	1467	83.8
5th year	807	262	168	1237	78.8
6th year	589	262	151	1002	73.9
7th year	399	241	139	779	69.1
8th year	260	187	123	570	67.2
9th year	192	165	105	462	64.3
10th year	109	142	81	332	57.2
11th year	53	101	53	207	51.2
12th year	13	35	15	63	44.4

* Loss to follow-up is defined as lost contact beyond 3, 6, and 12 months in the first, second, and third year after surgery, respectively.

** Follow-up rate = (number of all patients – number of patients lost to follow-up) / number of all patients

Supplement Table 2: The result of logistic regression analysis for propensity score matching

	OR	95% C.I.	*p*
Age	1.015	1.001 – 1.029	0.036
Sex (F vs. M)	1.166	0.817 – 1.665	0.397
ASA physical status ≥ 3	0.834	0.618 – 1.125	0.235
ECOG PS ≥ 1	0.823	0.599 – 1.130	0.228
COPD	1.137	0.823 – 1.571	0.437
Diabetes	1.285	0.913 – 1.807	0.150
Coronary artery disease	0.990	0.653 – 1.500	0.961
Heart failure	0.942	0.539 – 1.644	0.832
Stroke	0.825	0.462 – 1.474	0.515
Chronic kidney disease	1.161	0.744 – 1.813	0.510
FVC	0.862	0.578 – 1.285	0.466
FEV1	1.649	1.016 – 2.678	0.043
Pretreatment CEA *	0.716	0.513 – 0.999	0.049
Thoracoscopic surgery	0.591	0.389 – 0.898	0.014
Anaesthesia time **	1.282	0.924 – 1.778	0.137
pRBC transfusion	0.739	0.507 – 1.079	0.117
Postoperative CT	1.269	0.957 – 1.682	0.098
Postoperative RT	0.879	0.513 – 1.508	0.640
Preoperative C/T ± R/T	0.722	0.405 – 1.286	0.269

OR: odds ratio; F: female, M: male; ASA: American Society of Anesthesiologists; ECOG PS: Eastern Cooperative Oncology Group performance score; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; CEA: carcinoembryonic antigen; pRBC: packed red blood cell; C/T: chemotherapy; R/T: radiotherapy. * On base-10 logarithmic scale; ** On base-2 logarithmic scale

Supplement Table 2 (continued)

	OR	95% C.I.	*p*
Cancer stage I (reference)			0.568
Cancer stage II	1.039	0.690 – 1.564	0.854
Cancer stage III	1.260	0.815 – 1.950	0.299
Well-differentiated tumour (reference)			0.078
Moderately-differentiated tumour	1.294	0.881 – 1.902	0.189
Poorly-differentiated tumour	0.965	0.622 – 1.498	0.875
Microscopic necrosis	1.247	0.890 – 1.749	0.200
Lymphocytic infiltration	0.995	0.628 – 1.578	0.985
Lymphovascular invasion	0.830	0.612 – 1.127	0.233
Perineural invasion	1.288	0.639 – 2.597	0.480
Surgeon (≥ 20 vs. < 20 years)	1.137	0.887 – 1.458	0.312
Anaesthesiologist (≥ 15 vs. < 15 years)	1.073	0.848 – 1.356	0.559
Year of procedure			0.001
2012 – 2010 vs. 2005 – 2009	0.455	0.295 – 0.701	< 0.001
2015 – 2013 vs. 2005 – 2009	0.621	0.388 – 0.996	0.048

OR: odds ratio.

Supplement Table 3: The frequency and proportion of epidural placement and thoracoscopic surgery

Year of Procedure	Epidural Analgesia		Thoracoscopic Surgery	
	Counts	Proportions	Counts	Proportions
2005	135 / 146	92.5%	8 / 146	5.5%
2006	130 / 139	93.5%	8 / 139	5.8%
2007	122 / 132	92.4%	9 / 132	6.8%
2008	108 / 124	87.1%	29 / 124	23.4%
2009	132 / 155	85.2%	78 / 155	50.3%
2010	166 / 221	75.1%	158 / 221	71.5%
2011	173 / 229	75.5%	210 / 229	91.7%
2012	178 / 224	79.5%	213 / 224	95.1%
2013	194 / 240	80.8%	234 / 240	97.5%
2014	236 / 297	79.5%	293 / 297	98.7%
2015	225 / 284	79.2%	281 / 284	98.9%
Overall	1799 / 2191	82.1%	1521 / 2191	69.4%

The proportion of epidural analgesia decreased as more thoracoscopic surgeries were performed in the tumour resection of lung cancer in the period of study.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	5-6
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	7
	#6b	For matched studies, give matching criteria and number of exposed and	7-9

		unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-10
Bias	#9	Describe any efforts to address potential sources of bias	17
Study size	#10	Explain how the study size was arrived at	12
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7, 10-11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10-11
	#12b	Describe any methods used to examine subgroups and interactions	10-11
	#12c	Explain how missing data were addressed	10-11
	#12d	If applicable, explain how loss to follow-up was addressed	10-11
	#12e	Describe any sensitivity analyses	10-11
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
	#13b	Give reasons for non-participation at each stage	12
	#13c	Consider use of a flow diagram	12
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12-14
	#14b	Indicate number of participants with missing data for each variable of interest	12-14
	#14c	Summarise follow-up time (eg, average and total amount)	12-14

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	12-14
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
	#16b	Report category boundaries when continuous variables were categorized	12-14
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12-14
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-18
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17-18
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

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BMJ Open

The Effects of Epidural Analgesia on Cancer Recurrence and Long-term Mortality in Patients after Non-small-cell Lung Cancer Resection: A Propensity Score-matched Study

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The Effects of Epidural Analgesia on Cancer Recurrence and Long-term Mortality in Patients after Non-small-cell Lung Cancer Resection: A Propensity Score-matched Study

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Abstract

Objectives: Previous studies showed reductions in recurrence and mortality rate of several cancer types in patients receiving perioperative epidural analgesia. This study aimed to investigate the effects of thoracic epidural analgesia on oncologic outcomes after resection for lung cancer.

Design: Retrospective study using propensity score matching methodology.

Setting: Single medical centre in Taiwan.

Participants: Patients with stage I-III non-small-cell lung cancer undergoing primary tumour resection between January 2005 and December 2015 and had either epidural analgesia, placed preoperatively and used intra- and postoperatively, or intravenous analgesia were evaluated through May 2017.

Primary and secondary outcome measures: Primary endpoint was postoperative recurrence-free survival and secondary endpoint was overall survival.

Results: The 3-yr recurrence-free and overall survival rates were 69.8% (95% CI: 67.4 – 72.2%) and 92.4% (95% CI: 91 – 93.8%) in the epidural group and 67.4% (95% CI: 62.3 – 72.5%) and 89.6% (95% CI: 86.3 – 92.9%) in the non-epidural group, respectively. Multivariable Cox regression analysis before matching demonstrated no significant difference in recurrence or mortality between groups (adjusted hazard ratio: 0.93, 95% CI: 0.76 – 1.14 for recurrence; 0.81, 95% CI: 0.58 – 1.13 for mortality), similar to the results after matching

(hazard ratio: 0.97, 95% CI: 0.71 – 1.31; 0.94, 95% CI: 0.57 – 1.54). Independent risk factors for both recurrence and mortality were male, higher pretreatment carcinoembryonic antigen level, advanced cancer stage, poor differentiation, lymphovascular invasion, microscopic necrosis, and postoperative radiotherapy.

Conclusions: Thoracic epidural analgesia was not associated with better recurrence-free or overall survival in patients receiving surgical resection for stage I-III non-small-cell lung cancer.

Keywords: Cancer; Epidural Analgesia; Mortality; Non-small-cell Lung Carcinoma; Propensity Score; Recurrence

Article Summary

Strengths and limitations of this study

1. Large sample size and long follow-up time were employed to evaluate the impacts of epidural analgesia on long-term outcomes after lung cancer surgery.
2. Propensity score matching was used to deal with possible imbalances in collected variables.
3. Epidural assignment was not randomized, clinical care was not standardized and potential selection bias cannot be ruled out.
4. Effects of unmeasured confounders on outcomes after lung cancer surgery cannot be further evaluated.

Introduction

Lung cancer is the most commonly diagnosed malignancy worldwide, and its incidence continues to grow.[1] An estimated 2.1 million new cases of lung cancer were diagnosed and 1.76 million lung cancer deaths occurred globally in 2018.[1] Surgical removal of the primary tumour is the mainstay of treatment for patients with non-small-cell lung cancer staged I through IIIA.[2] However, surgical dissection and manipulation are associated with unintentional dispersal of cancer cells into the blood and lymphatic systems.[3] Whether the residual neoplastic cell would develop into a metastasis depends on the perioperative immune competence of the patient. Surgically induced stress hormone, as well as inhaled volatile anesthetics and systemic opioids, can diminish natural killer cell function, the primary defense against cancer cells.[4]

Opioids inhibit components of both cell-mediated and humoral immunity.[5] Morphine also has proangiogenic properties that may promote dissemination of angiogenesis-dependent tumours.[6] Inflammatory cytokines have been shown to regulate the expression of the mu-opioid receptor (MOR) gene, highlighting an interaction between the opioid and immune systems.[7] It is noted that the MOR is over-expressed in several types of lung cancer and it promotes opioid- and growth factor-induced proliferation and migration in human lung cancer cells.[8] Furthermore, silencing the MOR greatly reduced opioid-induced tumour growth and metastasis in vitro.[9]

Anesthetic management in primary cancer surgery has been proposed to impact recurrence or metastases, including blood transfusion,[10] narcotics consumption,[11-13] and analgesic techniques.[14] Thoracic epidural analgesia, commonly used for the management of postoperative pain, has been shown to reduce mortality, respiratory complications and opioid consumption and improved time to ambulation in thoracic surgeries.[15] However, the effect of epidural analgesia on oncologic outcomes after lung cancer resection remains unclear. It is hypothesized that epidural analgesia may reduce tumour growth and spread through its opioid and general anesthetic sparing and surgical stress alleviating properties, but only one retrospective study with limited sample size is available for this issue.[16] Therefore, we conducted this retrospective cohort study to investigate the relationship between perioperative thoracic epidural analgesia and cancer recurrence or overall survival in patients following surgical resection for non-small-cell lung cancer. The effects of other major prognostic factors were assessed as well to determine the significant predictors of oncologic outcomes after lung cancer resection.

Methods

Setting and patient selection

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (IRB-TPEVGH No. 2015-11-010CC) and written informed consent was waived. Patients undergoing surgical resection of pulmonary neoplasms between January 2005 and December 2015 at our hospital were retrospectively identified from the institutional electronic medical database. Patients with secondary lung cancer, small cell lung cancer, stage IV disease determined at the time of surgery, or missing data about demographics, pathologic details or postoperative analgesic were excluded from the study. (Figure 1) Patients were analysed in two groups: those receiving general anaesthesia with perioperative epidural analgesia and their counterparts receiving general anaesthesia without epidural analgesia.

Analgesia management

All patients undergoing open thoracotomy or video-assisted thoracoscopic surgery at our hospital were offered the choice of epidurals with preoperative catheter placement or intravenous analgesia with a demand pump. If epidural analgesia was selected, an epidural catheter was typically placed at a middle thoracic region (e.g., T6–T8) and assessed its function with a test dose of local anesthetic preoperatively. Epidural analgesia was started intraoperatively with local anesthetic (bupivacaine 0.25% or 0.5%) with or without fentanyl 1–2 $\mu g \cdot mL^{-1}$ at an infusion rate of 5–10 $ml \cdot hour^{-1}$, continued postoperatively for 48 to 72

hours, and switched to oral acetaminophen or non-steroidal anti-inflammatory drugs thereafter. Typically, patients undergoing lung cancer surgery received intravenous fentanyl 50 to 150 μg for anesthetic induction. Patients with effective epidurals were rarely given additional opioids perioperatively. If patients refused epidurals or it was contraindicated, an intravenous patient-controlled analgesia was administered via an ambulatory infusion pump (Gemstar™ Yellow, Hospira, IL, USA) programmed to deliver morphine sulfate 1 $mg \cdot mL^{-1}$ in normal saline, at a demand dose of 1 mg with a lockout time of 6 minutes.

Data retrieval

An electronic medical database was used to determine the baseline clinicopathologic risk factors for cancer recurrence and mortality. The following data were obtained from medical records: demographic characteristics; the Eastern Cooperative Oncology Group (ECOG) performance score;[17] co-existing diseases (chronic obstructive pulmonary disease, diabetes, chronic kidney disease, etc); preoperative pulmonary function tests (forced vital capacity, forced expiratory volume in one second, and their predicted percentages); pretreatment carcinoembryonic antigen (CEA) level;[18] anaesthesia time, perioperative packed red blood cell (pRBC) transfusion;[19] pathologic features (tumour differentiation, microscopic necrosis,[20] lymphovascular invasion,[21] and perineural invasion);[22] whether preoperative or postoperative adjuvant chemotherapy or radiotherapy was used; and each patient's current status as determined by documentation of follow-up visits to the hospital's outpatient clinic or

subsequent admissions. Tumour nodes metastasis (TNM) staging was also obtained from the record and translated into stage I to III according to the American Joint Committee on Cancer criteria (AJCC-7 staging system).[23] Adjuvant therapies given in the form of chemotherapy (cisplatin-gemcitabine, cisplatin-paclitaxel, cisplatin-docetaxel, or carboplatin-paclitaxel) or radiotherapy were at the discretion of surgeons and patients, and was defined as any therapy given within 90 days of surgery. The radiologists and thoracic surgeons of our hospital determined whether cancer recurred or not, which was mainly based on imaging studies (computed tomography, magnetic resonance imaging, bone scan, etc.) and defined by response evaluation criteria in solid tumours (RECIST) guidelines.[24] Pathology-proven second primary lung cancer was not considered as a recurrent disease. At our hospital, close surveillance was performed for survivors of lung cancer following definitive surgical therapy, including chest computed tomography every 6 months for at least the first 2 years, and annually thereafter. The follow-up rates of this cohort were 95.3%, 88.7%, and 78.8% in the end of the postoperative first, third, and fifth year, respectively. (Supplementary Table 1) The date of death was determined based on medical record or death certificate.

Medical records of all the patients included were extracted by specialist anesthesiologists who were not involved in data analysis. The quality of the extracted data was verified through random sampling by the authors. Data were collected up to the end of May 2017.

The primary endpoint was recurrence-free survival, which was defined as time from the date

of surgery to the date of cancer recurrence. The secondary endpoint was overall survival, defined as time from the date of surgery to the date of death. For those without the event of cancer recurrence or death, their survival times were regarded as the corresponding censored observations with the last visit date used as the censored date.

Statistical analysis

The comparisons of patient characteristics between the epidural and non-epidural groups were performed using chi-square tests for categorical variables and either t tests or Wilcoxon rank sum tests for continuous variables, as appropriate. The Kaplan-Meier method and log rank test were used to compare recurrence-free and overall survival distributions between the two groups. Univariate Cox regression analysis was used to evaluate the effects of epidural analgesia and other variables collected in the study on recurrence-free or overall survival. Significant predictors of recurrence-free or overall survival in the univariate analysis were used as candidates for stepwise model selection processes in the following multivariable analysis. The entry and exit criteria of significance level were set at 0.05 and 0.1, respectively, to select factors associated with recurrence-free and overall survival in the multivariable analysis. Afterward the effects of epidural analgesia adjusted for the selected predictors in the multivariable analysis on recurrence-free and overall survival were further evaluated.

To account for the potential imbalance in measured confounders related to cancer recurrence or survival of lung cancer between epidural and non-epidural groups, propensity scores based

on a collection of patient characteristics was developed to estimate the probability of receiving epidurals (Supplementary Table 2). Propensity score matching was performed as the primary analysis using a caliper with width equal to 0.2 of the standard deviation of the logit of the propensity score to ensure sufficient balance in collected variables between matching pairs.[25] Imbalance of the distribution of baseline attributes between groups was measured by standardized difference (SD), the difference in mean, proportion or rank divided by the pooled standard error, expressed as percentage, and was defined as absolute value greater than 20.[26] For sensitivity analysis, all subjects were divided into five equal-size groups using the quintiles of the estimated propensity score and stratified Cox regression analysis was conducted to obtain a pooled hazard ratio across the five strata to ensure the consistency among different estimates of the effects of epidurals on cancer recurrence or overall survival. The significance level of all hypotheses was 0.05 for a two-sided test. IBM SPSS Statistics for Windows Version 22.0 (Armonk, NY: IBM Corp.) was used for all analyses.

Patient and public involvement

This study is a retrospective analysis using the institutional medical database. There was no patient involved in the recruitment to and conduct of the study.

Results

Total of 2191 patients were included in this study and 1799 (82.1%) of them received epidural analgesia. There were some differences in the distributions of baseline characteristics between groups, including less thoracoscopic surgery (SD = 36.1) and longer follow-up time (SD = 20.4) in epidural group. (Table 1) The rate of epidural placement declined because more resections of lung cancer were done with thoracoscopic technique at our hospital in recent years. (Supplementary Table 3) Those not receiving epidurals, as mentioned above, had intravenous patient-controlled opioid analgesia. Table 2 shows the details of cancer stages and pathologic features of the two groups. The epidural group had higher rate of lymphocytic infiltration. After propensity score matching, the final sample of 372 matched pairs of patients was analysed, and no significant difference was found in demographic or pathologic characteristics between groups. (Table 1)

Association between Thoracic Epidural Analgesia and Recurrence-free Survival

The 3-yr and 5-yr recurrence-free survival were 69.8% (95% CI: 67.4 – 72.2%) and 64.4% (95% CI: 61.9 – 66.9%) in the epidural group and 67.4% (95% CI: 62.3 – 72.5%) and 62.8% (95% CI: 57.1 – 68.5%) in the non-epidural group, respectively. No significant difference in the distribution of recurrence-free survival after lung cancer surgery was noted when comparing epidural with non-epidural group ($p = 0.54$ by log rank test, Figure 2A). Moreover, epidural analgesia was not associated with better recurrence-free survival in patients stratified

by cancer stages (Figure. 2B).

The multivariable regression model indicated eight independent prognostic factors, including male (HR: 1.30), pretreatment CEA level (HR: 1.26, on base-10 logarithmic scale), cancer stage (II vs. I, HR: 1.93; III vs. I, HR: 2.85), tumour differentiation (moderate vs. good, HR: 3.75; poor vs. good, HR: 5.20), microscopic tumour necrosis (HR: 1.44), pathologic lymphovascular invasion (HR: 2.05), and postoperative chemotherapy (HR: 1.46) and radiotherapy (HR: 1.44). (Table 3) Adjusting for other covariates, the effect of epidurals on recurrence-free survival after lung cancer surgery was non-significant (HR: 0.93, 95% CI: 0.76 – 1.14, p = 0.47) in the multivariable analysis, similar to the results after propensity-score matching (hazard ratio: 0.97, 95% CI: 0.71 – 1.3, p = 0.82) and the quintile-stratified analysis (pooled HR: 0.94, 95% CI: 0.76 – 1.15, p = 0.53).

Association between Thoracic Epidural Analgesia and Overall Survival

The 3-yr and 5-yr overall survival were 92.4% (95% CI: 91 – 93.8%) and 85.8% (95% CI: 83.8 – 87.8%) in the epidural group and 89.6% (95% CI: 86.3 – 92.9%) and 84.3% (95% CI: 80 – 88.6%) in the non-epidural group.

No significant difference in the distribution of long-term mortality after lung cancer surgery was found between the epidural and non-epidural groups (Figure 2C, p = 0.13 by log rank test). In addition, no significant difference in overall survival was noted between the two groups in the subgroup analysis for distinct cancer stages (Figure 2D).

Nine independent prognostic factors were identified after the multivariable analysis (Table 3), including male (HR: 1.97), ECOG performance score ≥ 1 (HR: 1.49), pretreatment CEA level (HR: 1.67), cancer stage (II vs. I HR: 2.06; III vs. I, HR: 2.96), perioperative pRBC transfusion (HR: 1.40), tumour differentiation (moderate vs. good, HR: 4.72; poor vs. good, HR: 6.17), microscopic necrosis (HR: 1.38), pathologic lymphovascular invasion (HR: 2.13), and postoperative radiotherapy (HR: 1.81). Multivariable analysis indicated no association between epidural analgesia and mortality in non-small-cell lung cancer after surgery (HR: 0.81, 95% CI: 0.58 – 1.13, $p = 0.21$). Propensity score matching generated similar results to the multivariable regression analysis (HR: 0.94, 95% CI: 0.57 – 1.54, $p = 0.8$) as well as the quintile-stratified (HR: 0.8, 95% CI: 0.58 – 1.1, $p = 0.17$) propensity score analyses.

Discussion

To our knowledge, this is the largest retrospective study applying propensity scoring methods to evaluate the impacts of epidural analgesia on oncologic outcomes after lung cancer surgery. We found no evidence that epidural analgesia was associated with improved recurrence-free survival or overall survival in patients following surgical resection of non-small-cell lung cancer. Major clinicopathologic prognostic factors were also taken into account in this study to estimate the adjusted effects of epidurals and avoid potential confounding effects from unbalanced distributions of important risk factors between the epidural group and its counterpart. From the perspective of methodology, we used propensity score matching to cancel out the potential imbalances in baseline characteristics and obtained similar results with those from traditional multivariable model. The combination of both analytical methods provided more persuasive proof than either of them did. Our study provided valuable information to reject the hypothesis of beneficial effect of epidurals on cancer recurrence or long-term survival after surgical resection of non-small-cell lung cancer with large sample size and considerable prognostic factors which were lacked in the previous survey.[16]

Perioperative immune function is an important determinant for metastases after cancer resection surgery. Anesthetic management of cancer patients could impact long-term outcome, and potentially beneficial interventions include minimizing the use of volatile anesthetics and blood transfusion, administration of cyclooxygenase antagonists and statin, and hypothermia

therapy.[27] However, whether regional analgesia reduces cancer recurrence after resection surgery remains inconclusive. The Cochrane review included four post-hoc analyses of previous controlled trials and indicated that current evidence for the benefit of regional anaesthesia on cancer outcome is inadequate due to limitations of study design and incomplete consideration of confounders.[28]

Although Cata and colleagues reported null results of epidural analgesia on recurrence-free and overall survival after lung cancer surgery,[16] they found an association between the intraoperative opioid consumption and recurrence-free survival or overall survival later only for stage I disease.[11] Our results did not support beneficial effects of epidural analgesia on oncologic outcomes in patients stratified by cancer stages. This may be attributed to the difference in distributions of patient attributes or treatment modality. Maher and co-workers reported an association between increased opioid doses during initial 96-hours postoperative period and higher recurrence rate of non-small-cell lung cancer within 5 years.[12] However, they found no difference in intraoperative opioid administration among those with or without recurrence of lung cancer at the 5-year follow-up. The effects of regional block and opioid doses on long-term cancer outcomes in early-stage lung cancer await further investigation.

Our results showed perioperative blood transfusion is a risk factor for all-cause mortality, in line with previous literature.[19] In addition to mortality, allogenic blood transfusion may be associated with increased risk of cancer recurrence.[29] Transfused leucocytes can lead to

immunomodulation, including changes in circulating lymphocytes, helper T-cell, suppressor T-cell ratios, and B-cell function.[29] The meta-analysis by Churchhouse and colleagues examined the effect of blood transfusion on cancer recurrence and overall survival in patients undergoing surgical resection of lung cancer in 5378 patients. Though no definitive conclusions could be drawn, there appeared to be a relationship between transfusion and reduction of disease-free survival.[30] In our analysis, the association between blood transfusion and recurrence was non-significant after adjustment for covariates. This finding may imply that the potential impacts of other important confounders (e.g., disease severity, presence of postoperative complications) may have a greater bearing on prognosis than the reception of blood itself.

As a sided observation, in the study period, the use of epidurals gradually decreased with concomitant increasing uses of thoracoscopic surgery. Thoracoscopic pulmonary resection for primary lung cancer has been demonstrated to achieve less postoperative pain, faster recovery, shorter hospitalization, and long-term survival comparable to that of open thoracotomy.[31,32] In our analysis, the distributions of thoracoscopic surgery and year of surgery between groups have been balanced after propensity score matching and are therefore unlikely to affect the results.

Several limitations are inherent in this retrospective observational study. First, patients were not randomized and clinical care was not standardized, so that potential selection bias and

effects from unmeasured confounders cannot be excluded. Second, relatively small percentage (17.9%) of the patients was cared for without epidural analgesia. Third, the rate of epidural placement was lower in the latter years and this may result in longer follow-up period of epidural group. However, these imbalances have been cancelled out after propensity score matching. Fourth, it is difficult to determine the total narcotic consumptions for each patient due to the incompleteness of our electronic medical records.

In conclusion, our study rejected the association between epidural analgesia and cancer recurrence or long-term mortality in patients after surgery for stage I through III non-small-cell lung cancer. Prospective randomized trials are warranted to confirm or refute causal relationships between epidural analgesia and the long-term outcomes after lung cancer surgery.

Footnotes

Author contributors: The author contributions were as follows: HLW and YHT contributed to data acquisition and manuscript drafting. MYC helped in data verification. MYT helped revise the manuscript. HHC contributed to study design and statistical analysis. KYC contributed to statistical review, manuscript revision, and final approval of the version to be published. All authors read and approved the final manuscript.

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Competing interests: None declared.

Patient consent: Not required.

Ethics approval: The study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan.

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Tables

Table 1: Patient demographics

	Before matching			After matching		
	EA (N=1799)	**Non-EA (N=392)**	**SD**	**EA (N=372)**	**Non-EA (N=372)**	**SD**
Age, year	64 ± 11	64 ± 11	0.1	64 ± 12	64 ± 11	5.8
Sex, male	918 (51.0%)	194 (49.5%)	3.1	192 (51.6%)	183 (49.2%)	4.8
ASA physical status ≥ 3	424 (23.6%)	109 (27.8%)	9.7	104 (28.0%)	100 (26.9%)	2.4
ECOG PS ≥ 1	549 (30.5%)	130 (33.2%)	5.7	132 (35.5%)	117 (31.5%)	8.6
Comorbidities						
COPD	474 (26.3%)	107 (27.3%)	2.1	102 (27.4%)	100 (26.9%)	1.2
Diabetes	297 (16.5%)	56 (14.3%)	6.2	56 (15.1%)	52 (14.0%)	3.1
Coronary artery disease	171 (9.5%)	41 (10.5%)	3.2	41 (11.0%)	39 (10.5%)	1.7
Heart failure	74 (4.1%)	21 (5.4%)	5.9	15 (4.0%)	19 (5.1%)	5.2
Stroke	60 (3.3%)	18 (4.6%)	6.4	25 (6.7%)	17 (4.6%)	9.3
Chronic kidney disease	141 (7.8%)	35 (8.9%)	3.9	25 (6.7%)	31 (8.3%)	6.1
Pulmonary function test						
FVC, liter	2.88 ± 0.76	2.81 ± 0.73	9.5	2.83 ± 0.76	2.82 ± 0.73	1.9
% predicted	87.6 ± 15.7	85.9 ± 15.6	10.8	87.1 ± 16.3	86.1 ± 15.6	6.4
FEV1, liter	2.22 ± 0.62	2.15 ± 0.60	12.3	2.17 ± 0.62	2.16 ± 0.59	2.8
% predicted	86.3 ± 16.4	83.8 ± 16.6	15.5	85.4 ± 16.3	84.1 ± 16.4	7.8
Pretreatment CEA, μg·L^{-1}	2.4 (1.8 – 3.7)	2.6 (1.7 – 4.2)	8.5	2.5 (1.7 – 4.0)	2.6 (1.7 – 4.2)	2.0
Surgeon experience			1.2			0.6
Specialist < 20 years	701 (39.0%)	155 (39.5%)		141 (37.9%)	142 (38.2%)	
Specialist ≥ 20 years	1098 (61.0%)	237 (60.5%)		231 (62.1%)	230 (61.8%)	
Thoracoscopic surgery	1199 (66.6%)	322 (82.1%)	36.1	292 (78.5%)	305 (82.0%)	8.8
Anesthesiologist experience			3.9			10.8
Specialist < 15 years	810 (45.0%)	169 (43.1%)		183 (49.2%)	163 (43.8%)	
Specialist ≥ 15 years	989 (55.0%)	223 (56.9%)		189 (50.8%)	209 (56.2%)	
Anaesthesia time, min	315 (265 – 360)	300 (240 – 368)	8.4	300 (240 – 360)	300 (240 – 360)	1.4
pRBC transfusion	203 (11.3%)	52 (13.3%)	6.0	51 (13.7%)	49 (13.2%)	1.6
Year of Procedure			25.7			5.7
2005 – 2009	627 (34.9%)	69 (17.6%)		74 (19.9%)	67 (18.0%)	
2010 – 2012	517 (28.7%)	157 (40.1%)		148 (39.8%)	145 (39.0%)	
2013 – 2015	655 (36.4%)	166 (42.3%)		150 (40.3%)	160 (43.0%)	
Preoperative C/T ± R/T	77 (4.3%)	21 (5.4%)	5.0	17 (4.6%)	20 (5.4%)	3.7
Postoperative C/T	834 (46.4%)	163 (41.6%)	9.6	151 (40.6%)	158 (42.5%)	3.8
Postoperative R/T	98 (5.4%)	22 (5.6%)	0.7	26 (7.0%)	21 (5.6%)	5.5
Follow-up time, month	43.5 (25.3 – 72.4)	39.4 (21.9 – 59.9)	20.4	40.3 (24.4 – 62.2)	39.6 (21.9 – 59.8)	8.8

Values were mean ± SD, counts (percent), or median (interquartile range). Continuous variables are analysed with Wilcoxon rank-sum tests; categorical variables are analysed with Pearson chi-square tests. SD: standardized difference is the difference in mean, proportion or rank divided by the pooled standard error, expressed as percentage; imbalance is defined as absolute value greater than 20 (small effect size). ASA: American Society of Anesthesiologists; ECOG PS: Eastern Cooperative Oncology Group performance score; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; CEA: carcinoembryonic antigen; pRBC: packed red blood cell; C/T: chemotherapy; R/T: radiotherapy.

Table 2: Cancer stages and pathologic features

	Before matching			After matching		
	EA (N=1799)	**Non-EA (N=392)**	**SD**	**EA (N=372)**	**Non-EA (N=372)**	**SD**
AJCC stage			2.0			1.8
Stage I	1316 (73.2%)	289 (73.7%)		271 (72.8%)	276 (74.2%)	
IA	546 (30.4%)	116 (29.6%)		114 (30.7%)	110 (29.6%)	
IB	770 (42.8%)	173 (44.1%)		157 (42.2%)	166 (44.6%)	
Stage II	205 (11.4%)	52 (13.3%)		55 (14.8%)	48 (12.9%)	
IIA	106 (5.9%)	26 (6.6%)		32 (8.6%)	24 (6.5%)	
IIB	99 (5.5%)	26 (6.6%)		23 (6.2%)	24 (6.5%)	
Stage III	278 (15.5%)	51 (13.0%)		46 (12.4%)	48 (12.9%)	
IIIA	253 (14.1%)	46 (11.7%)		42 (11.3%)	44 (11.8%)	
IIIB	25 (1.4%)	5 (1.3%)		4 (1.1%)	4 (1.1%)	
Pathologic features						
Subtype			6.8			5.1
Adenocarcinoma	1511 (84.0%)	314 (80.1%)		292 (78.5%)	303 (81.5%)	
SCC	200 (11.1%)	54 (13.8%)		54 (14.5%)	46 (12.4%)	
Other	88 (4.9%)	24 (6.1%)		26 (7.0%)	23 (6.2%)	
Tumour differentiation			5.3			1.8
Good	181 (10.1%)	46 (11.7%)		39 (10.5%)	46 (12.4%)	
Moderate	1100 (61.2%)	215 (54.8%)		209 (56.2%)	201 (54.0%)	
Poor	516 (28.7%)	131 (33.4%)		124 (33.3%)	125 (33.6%)	
Microscopic necrosis	388 (21.6%)	77 (19.6%)	4.8	77 (20.7%)	71 (19.1%)	4.0
Lymphocytic infiltration	189 (10.5%)	27 (6.9%)	12.9	34 (9.1%)	27 (7.3%)	6.9
Lymphovascular invasion	497 (27.6%)	127 (32.4%)	10.4	115 (30.9%)	118 (31.7%)	1.7
Perineural infiltration	58 (3.2%)	12 (3.1%)	0.9	10 (2.7%)	11 (3.0%)	1.6

Values were counts (percent). Categorical variables are analysed with Pearson chi-square tests or Mann-Whitney U tests, as appropriate. SD: standardized difference is the difference in mean, proportion or rank divided by the pooled standard error, expressed as percentage; imbalance is defined as absolute value greater than 20 (small effect size). AJCC: American Joint Committee on Cancer; SCC: squamous cell carcinoma.

Table 3: Multivariable analysis for cancer recurrence and all-cause mortality after model selection

	Cancer recurrence				All-cause mortality		
	HR	**95% C.I.**	***p***		**HR**	**95% C.I.**	***p***
EA vs. non-EA	0.927	0.755 – 1.139	0.473	**EA vs. non-EA**	0.811	0.582 – 1.129	0.214
Sex (M vs. F)	1.297	1.026 – 1.642	0.030	**Sex (M vs. F)**	1.969	1.344 – 2.882	0.001
Pretreatment CEA*	1.263	1.046 – 1.524	0.015	**ECOG PS ≥ 1**	1.494	1.105 – 2.019	0.009
Postoperative C/T	1.456	1.187 – 1.786	<.001	**Pretreatment CEA***	1.672	1.221 – 2.290	0.001
Postoperative R/T	1.443	1.126 – 1.849	0.004	**pRBC transfusion**	1.402	1.008 – 1.948	0.045
Stage			<.001	**Postoperative R/T**	1.810	1.271 – 2.578	0.001
II vs. I	1.927	1.521 – 2.440	<.001	**Stage**			<.001
III vs. I	2.848	2.265 – 3.581	<.001	II vs. I	2.059	1.388 – 3.054	<.001
Tumour differentiation			<.001	III vs. I	2.964	2.032 – 4.323	<.001
Moderate vs. good	3.752	1.919 – 7.338	<.001	**Tumour differentiation**			0.014
Poor vs. good	5.198	2.632 – 10.265	<.001	Moderate vs. good	4.718	1.153 – 19.310	0.031
Microscopic necrosis	1.444	1.203 – 1.733	<.001	Poor vs. good	6.169	1.487 – 25.587	0.012
Lymphovascular invasion	2.053	1.717 – 2.456	<.001	**Microscopic necrosis**	1.378	1.037 – 1.831	0.027

HR: hazard ratio; EA: epidural analgesia; M: male, F: female; CEA: carcinoembryonic antigen; C/T: chemotherapy; R/T: radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance score; pRBC: packed red blood cell.
* On base-10 logarithmic scale

Figures and Legends

Figure 1: Flow diagram for patient inclusion.

Figure 2: Unadjusted Kaplan–Meier curves for recurrence-free and overall survival of epidural and non- epidural groups

No significant difference in recurrence-free survival (A and B) or overall survival (C and D) after surgery for non-small-cell lung cancer was noted when comparing epidural with non-epidural group as a whole or stratified by cancer stage.

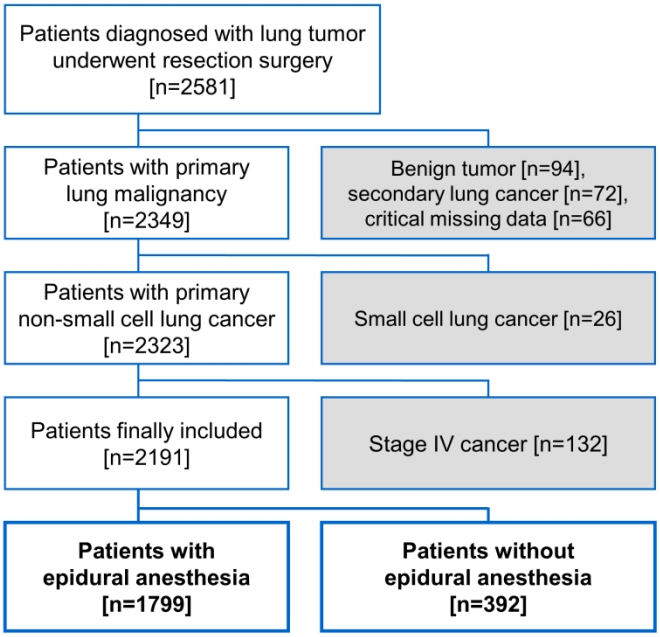

Figure 1: Flow diagram for patient inclusion.

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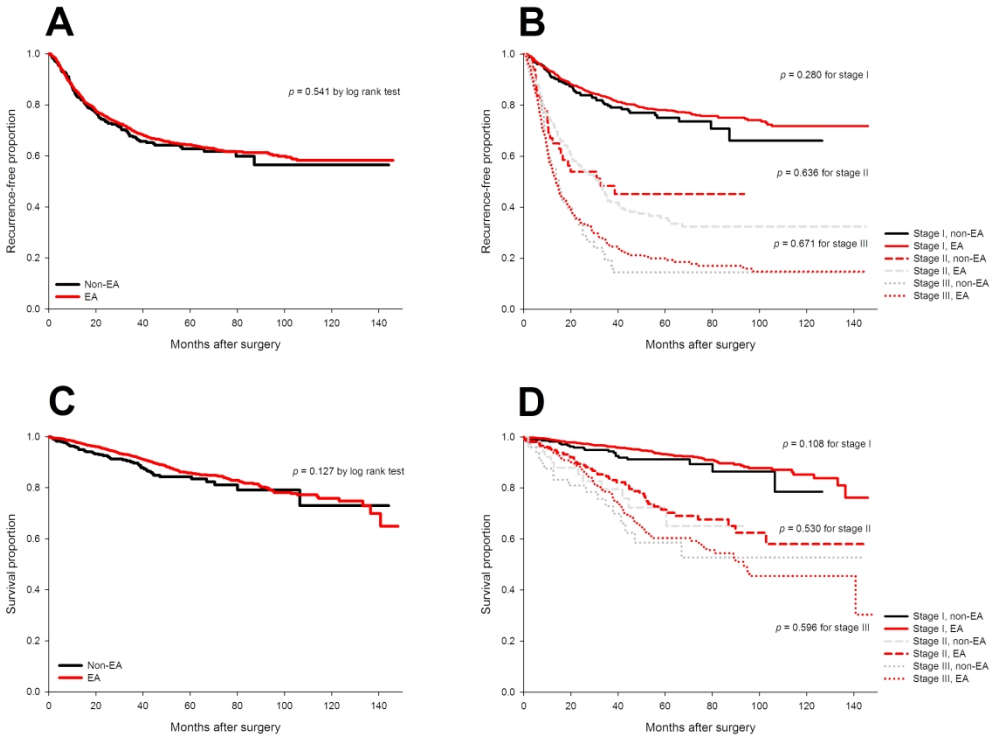

Figure 2: Unadjusted Kaplan–Meier curves for recurrence-free and overall survival of epidural and non-epidural groups

No significant difference in recurrence-free survival (A and B) or overall survival (C and D) after surgery for non-small-cell lung cancer was noted when comparing epidural with non-epidural group as a whole or stratified by cancer stage.

352x260mm (300 x 300 DPI)

Supplementary Table 1: Postoperative follow-up in this study

Year after Surgery	No. of Patients under Follow-up	No. of Patients Lost to Follow-up*	No. of Mortality	No. of All Patients	Follow-up Rate (%)**
1st year	2031	103	57	2191	95.3
2nd year	1846	239	106	2191	89.1
3rd year	1400	196	134	1730	88.7
4th year	1066	238	163	1467	83.8
5th year	807	262	168	1237	78.8
6th year	589	262	151	1002	73.9
7th year	399	241	139	779	69.1
8th year	260	187	123	570	67.2
9th year	192	165	105	462	64.3
10th year	109	142	81	332	57.2
11th year	53	101	53	207	51.2
12th year	13	35	15	63	44.4

* Loss to follow-up is defined as lost contact beyond 3, 6, and 12 months in the first, second, and third year after surgery, respectively.

** Follow-up rate = (number of all patients – number of patients lost to follow-up) / number of all patients

Supplementary Table 2: Logistic regression analysis for propensity score matching

	OR	95% C.I.	*p*
Age	1.015	1.001 – 1.029	0.036
Sex (F vs. M)	1.166	0.817 – 1.665	0.397
ASA physical status ≥ 3	0.834	0.618 – 1.125	0.235
ECOG PS ≥ 1	0.823	0.599 – 1.130	0.228
COPD	1.137	0.823 – 1.571	0.437
Diabetes	1.285	0.913 – 1.807	0.150
Coronary artery disease	0.990	0.653 – 1.500	0.961
Heart failure	0.942	0.539 – 1.644	0.832
Stroke	0.825	0.462 – 1.474	0.515
Chronic kidney disease	1.161	0.744 – 1.813	0.510
FVC	0.862	0.578 – 1.285	0.466
FEV1	1.649	1.016 – 2.678	0.043
Pretreatment CEA *	0.716	0.513 – 0.999	0.049
Thoracoscopic surgery	0.591	0.389 – 0.898	0.014
Anaesthesia time **	1.282	0.924 – 1.778	0.137
pRBC transfusion	0.739	0.507 – 1.079	0.117
Postoperative CT	1.269	0.957 – 1.682	0.098
Postoperative RT	0.879	0.513 – 1.508	0.640
Preoperative C/T ± R/T	0.722	0.405 – 1.286	0.269
Cancer stage I (reference)			0.568
Stage II	1.039	0.690 – 1.564	0.854
Stage III	1.260	0.815 – 1.950	0.299
Well-differentiated tumour (reference)			0.078
Moderately-differentiated tumour	1.294	0.881 – 1.902	0.189
Poorly-differentiated tumour	0.965	0.622 – 1.498	0.875
Microscopic necrosis	1.247	0.890 – 1.749	0.200
Lymphocytic infiltration	0.995	0.628 – 1.578	0.985
Lymphovascular invasion	0.830	0.612 – 1.127	0.233
Perineural invasion	1.288	0.639 – 2.597	0.480
Surgeon (≥ 20 vs. < 20 years)	1.137	0.887 – 1.458	0.312
Anaesthesiologist (≥ 15 vs. < 15 years)	1.073	0.848 – 1.356	0.559
Year of procedure			0.001
2012 – 2010 vs. 2005 – 2009	0.455	0.295 – 0.701	< 0.001
2015 – 2013 vs. 2005 – 2009	0.621	0.388 – 0.996	0.048

OR: odds ratio; F: female, M: male; ASA: American Society of Anesthesiologists; ECOG PS: Eastern Cooperative Oncology Group performance score; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; CEA: carcinoembryonic antigen; pRBC: packed red blood cell; C/T: chemotherapy; R/T: radiotherapy. * On base-10 logarithmic scale; ** On base-2 logarithmic scale

Supplementary Table 3: Frequency and proportion of epidural placement and thoracoscopic surgery in each year of procedure

Year of Procedure	Epidural Analgesia		Thoracoscopic Surgery	
	Frequency	**Proportion**	**Frequency**	**Proportion**
2005	135 / 146	92.5%	8 / 146	5.5%
2006	130 / 139	93.5%	8 / 139	5.8%
2007	122 / 132	92.4%	9 / 132	6.8%
2008	108 / 124	87.1%	29 / 124	23.4%
2009	132 / 155	85.2%	78 / 155	50.3%
2010	166 / 221	75.1%	158 / 221	71.5%
2011	173 / 229	75.5%	210 / 229	91.7%
2012	178 / 224	79.5%	213 / 224	95.1%
2013	194 / 240	80.8%	234 / 240	97.5%
2014	236 / 297	79.5%	293 / 297	98.7%
2015	225 / 284	79.2%	281 / 284	98.9%
Overall	1799 / 2191	82.1%	1521 / 2191	69.4%

The proportion of epidural analgesia decreased as more thoracoscopic surgeries were performed in the tumour resection of lung cancer in the period of study.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	5-6
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	7
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	7-10
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources /	#8	For each variable of interest give sources of data and details of methods of assessment	8-11

measurement		(measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	17-18
Study size	#10	Explain how the study size was arrived at	12
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7, 10-11
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	10-11
	#12b	Describe any methods used to examine subgroups and interactions	10-11
	#12c	Explain how missing data were addressed	10-11
	#12d	If applicable, explain how loss to follow-up was addressed	10-11
	#12e	Describe any sensitivity analyses	10-11
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
	#13b	Give reasons for non-participation at each stage	12
	#13c	Consider use of a flow diagram	12
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	12-14
	#14b	Indicate number of participants with missing data for each variable of interest	12-14
	#14c	Summarise follow-up time (eg, average and total amount)	12-14
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	12-14
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
	#16b	Report category boundaries when continuous variables were categorized	12-14
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14

Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12-14
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17-18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-18
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17-18
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19