**Supplement 2**

For: Zhen-Zhen Xu, Huai-Jin Li, Mu-Han Li, et al. Epidural anesthesia-analgesia and recurrence-free survival after lung cancer surgery: A randomized controlled trial

**Contents**

[Authors’ affiliations 3](#_Toc71296787)

[Table S1. Baseline laboratory tests and instrumental examinations 4](#_Toc71296788)

[Table S2. Pathological results and gene expression 6](#_Toc71296789)

[Table S3. Intraoperative data 8](#_Toc71296790)

[Table S4. Cancer recurrence/metastasis during long-term follow-up 9](#_Toc71296791)

[Table S5. Exploratory analysis of long-term survival 10](#_Toc71296792)

[Table S6. Prespecified long-term survival analyses in cancer patients 11](#_Toc71296793)

[Table S7. Pain intensity during the first 3 postoperative days 12](#_Toc71296794)

[Table S8. Individual complications during hospital stay after surgery 13](#_Toc71296795)

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# Table S1. Baseline laboratory tests and instrumental examinations

|  |  |  |  |
| --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | **ASD** |
| Arterial blood gas (breathing air) | (n=159) | (n=164) |  |
|  PaO2, mmHg | 85 ± 14 | 85 ± 13 | 0.043 |
|  PaCO2, mmHg | 40 ± 5 | 39 ± 4 | 0.111 |
|  SaO2, % | 96 ± 3 | 96 ± 2 | 0.006 |
| Echocardiogram | (n=177) | (n=174) |  |
|  LVEF, % | 71 ± 5 | 71±6 | 0.035 |
|  PASP, mmHg | 28 ± 6 | 27±5 | 0.123 |
| Pulmonary function tests | (n=181) | (n=182) |  |
|  FEV1, L | 2.5 ± 0.7 | 2.6 ± 0.6 | 0.202 |
|  FEV1/pred, % | 97.3 ± 19.6 | 98.6 ± 17.6 | 0.007 |
|  FEV1/FRC, % | 74.2 ± 9.6 | 74.7 ± 10.8 | 0.058 |
|  Ventilatory function a, n (%) |  |  | **0.274** |
|  Normal | 73 (40.3) | 74 (40.7) |  |
|  Mild reduction | 83 (46.4) | 96 (52.2) |  |
|  Moderate reduction | 11 (6.0) | 3 (1.6) |  |
|  Moderately severe reduction | 10 (5.5) | 11 (6.0) |  |
|  Severe reduction | 1 (0.6) | 1 (0.5) |  |
|  Diffusion function b, n (%) |  |  | 0.191 |
|  Normal  | 76 (42.0) | 93 (51.1) |  |
|  Mild reduction | 90 (49.7) | 74 (41.2) |  |
|  Significant reduction | 15 (8.3) | 15(8.2) |  |
| Tumor size (CT scan), cm | 2.4 ± 1.6 (n=171) | 2.6 ± 2.0 (n=177) | 0.123 |
| Enlarged neck/axillary lymph nodes c, n (%) | 6 (3.0) | 6 (3.0) | 0.000 |
| Biopsy-confirmed cancer, n (%) | 23 (11.5) | 19 (45.2) | 0.065 |
| Suspected bone metastasis d, n (%)  | 2 (1.0) | 2 (1.0) | 0.000 |
| Tumor biomarkers | (n=178) | (n=192) |  |
|  CEA, ng·ml-1 | 2.4 (1.7, 3.5) | 2.9 (1.8, 5.3) | 0.091 |
|  SCC, ng·ml-1 | 0.8 (0.6, 1.2) | 0.9 (0.6, 1.3) | 0.125 |
|  NSE, ng·ml-1 | 13.0 (11.2, 14.8) | 12.9 (11.5, 15.4) | 0.001 |
|  TPA, U·L-1 | 71.0 (52.1, 96.3) | 72.4 (53.4, 99.0) | 0.086 |
|  ProGRP, pg·ml-1 | 40.7 (31.8, 49.8) | 38.6 (31.0, 50.9) | 0.086 |

Data are mean ± SD, n (%) or median (IQR).

ASD, absolute standardized difference (ASD ≥0.196 was considered unbalanced between the two groups); LVEF, left ventricular ejection fraction (measured by Simpson’s method); PASP, pulmonary artery systolic pressure; FEV1, forced expiratory volume in the first second; FEV1/pre, forced expiratory volume in the first second/predicted value; FEV1/FRC, forced expiratory volume in the first second/functional residual capacity; DLCO/Pre, carbon monoxide diffusing capacity/predicted value; CEA, carcinoembryonic antigen (normal range <5.0 ng·ml-1); SCC, squamous cell carcinoma antigen (normal range <1.5 ng·ml-1); NSE, neuron specific enolase (normal range <16.3 ng·ml-1); CA19-9, cancer antigen 19-9 (normal range <3.3ng·ml-1); TPA, tissue polypeptide antigen (normal range <120 U·L-1); proGRP, pro-gastrin-releasing peptide (normal range <69.2 pg/ml-1).

a Ventilatory dysfunction was classified according to FEV1/pred: mild reduction (>70%), moderate reduction (60-69%), moderately severe reduction (50-59%), severe reduction (35-49%), and very severe reduction (<35%).

b Diffusion dysfunction was classified according to DLCO/pred: mild reduction (60-79%) and significant reduction (<60%).

c Diagnosed by ultrasonography.

d Diagnosed by bone scan.

# Table S2. Pathological results and gene expression

|  |  |  |  |
| --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | **ASD** |
| Pathological cancer stage a | (n=166) | (n=170) |  |
|  Primary tumor (T), n (%) |  |  | **0.386** |
|  Tx  | 1 (0.6) | 5 (2.9) |  |
|  Pre-invasion lesion + MIA | 22 (13.3) | 11 (6.5) |  |
|  T1 (T1a, T1b, T1c) | 108 (65.1) | 109 (64.1) |  |
|  T2 (T2a, T2b) | 21 (12.7) | 35 (20.6) |  |
|  T3 | 7 (4.2) | 8 (4.7) |  |
|  T4 | 7 (4.2) | 2 (1.2) |  |
|  Regional lymph node (N), n (%) |  |  | **0.205** |
|  Nx  | 5 (3.0) | 3 (1.8) |  |
|  N0 | 127 (76.5) | 132 (77.6) |  |
|  N1  | 12 (7.2) | 6 (3.5) |  |
|  N2  | 22 (13.3) | 29 (17.1) |  |
|  N3 | 0 (0.0) | 0 (0.0) |  |
|  Distant metastasis (M), n (%) |  |  | 0.190 |
|  M0 | 166 (100.0) | 167 (98.2) |  |
|  M1 | 0 (0.0) | 3 (1.8) |  |
| TTF1 expression, n (%)  | (n=160) | (n=167) | 0.144 |
|  TTF1- | 38 (23.8) | 36 (21.6) |  |
|  TTF1+ | 13 (8.1) | 14 (8.4) |  |
|  TTF1++ | 38 (23.8) | 50 (29.9) |  |
|  TTF1+++ | 71 (44.4) | 67 (40.1) |  |
| EGFRgene detection (exon21), n (%) | (n=133) | (n=136) | 0.191 |
|  Negative  | 121 (91.0) | 121 (89.0) |  |
|  Mildly positive | 6 (4.5) | 9 (6.6) |  |
|  Mild-moderately positive | 1 (0.8) | 0 (0.0) |  |
|  Moderately positive | 2 (1.5) | 4 (2.9) |  |
|  Positive  | 3 (2.3) | 2 (1.5) |  |
| EGFR gene detection (exon19), n (%) | (n=133) | (n=136) | 0.171 |
|  Negative  | 118 (88.7) | 118 (86.8) |  |
|  Mildly positive | 2 (1.5) | 4 (2.9) |  |
|  Mild- moderately positive | 3 (2.3) | 3 (2.2) |  |
|  Moderately positive | 3 (2.3) | 5 (3.7) |  |
|  Positive  | 4 (3.0) | 2 (1.5) |  |
|  Strongly positive | 3 (2.3) | 4 (2.9) |  |
| ALK gene detection, n (%) | (n=134) | (n=141) | **0.308** |
|  Negative  | 129 (96.3) | 135 (95.1) |  |
|  Moderately positive | 2 (1.5) | 1 (0.7) |  |
|  Positive | 0 (0.0) | 5 (3.5) |  |
|  Strongly positive | 3 (2.2) | 1 (0.7) |  |
| Non-cancer patients | 34 (17.0) | 30 (15.0) | 0.055 |
| Organizing pneumonia | 2 (1.0) | 1 (0.5) |  |
| Cryptococcal infection | 2 (1.0) | 1 (0.5) |  |
| Granulomatous inflammation | 6 (3.0) | 7 (3.5) |  |
| Pulmonary hamartoma | 5 (2.5) | 4 (2.0) |  |
| Sclerosing hemangioma | 4 (2.0) | 2 (1.0) |  |
| Caseous necrosis | 3 (1.5) | 1 (0.5) |  |
| Tuberculosis | 3 (1.5) | 2 (1.0) |  |
| Chronic aspergillus bronchitis | 0 (0.0) | 1 (0.5) |  |
| Interstitial lung disease | 0 (0.0) | 1 (0.5) |  |
| Cystis | 0 (0.0) | 1 (0.5) |  |
| Pulmonary sequestration | 0 (0.0) | 1 (0.5) |  |
| Pulmonary fibrosis | 1 (0.5) | 1 (0.5) |  |
| Sarcoidosis | 1 (0.5) | 1 (0.5) |  |
| Chronic bronchitis | 7 (3.5) | 6 (3.0) |  |

Data are n (%).

ASD, absolute standardized difference (ASD ≥0.196 was considered unbalanced between the two groups); MIA, micro-infiltrating carcinoma; TTF1, thyroid transcription factor 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

a According to the 8th edition International Association for the Study of Lung Cancer (IASLC) and the American Joint Committee on Cancer (AJCC) TNM classification.

# Table S3. Intraoperative data

|  |  |  |  |
| --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | ***P* value** |
| First ABG during OLV | (n=127) | (n=126) |  |
|  pH | 7.38 (7.32, 7.42) | 7.36 (7.32, 7.39) | 0.158 |
|  PCO2, mmHg | 45 (40, 52) | 48 (42, 48) | 0.154 |
|  PO2, mmHg | 116 (88, 269) | 127 (94, 297) | 0.633 |
|  Hemoglobin, g·dL-1 | 12.9 ± 1.9 | 12.8 ± 1.7 | 0.900 |
| Second ABG during OLV | (n=48) | (n=35) |  |
|  pH | 7.31 (7.28, 7.34) | 7.32 (7.27, 7.38) | 0.887 |
|  PCO2, mmHg | 53 (48, 58) | 53 (47, 59) | 0.788 |
|  PO2, mmHg | 124 (80, 213) | 148 (88, 236) | 0.239 |
|  Hemoglobin, g·dL-1 | 12.8 ± 2.3 | 12.3 ± 2.0 | 0.250 |
| Lowest hemoglobin, g·dL-1 | 12.5 ± 1.7 (n=124) | 12.6 ± 1.8 (n=92) | 0.673 |

Data are median (IQR) or mean ± SD.

ABG, arterial blood gas; OLV, one-lung ventilation.

# Table S4. Cancer recurrence/metastasis during long-term follow-up

|  |  |  |  |
| --- | --- | --- | --- |
|  | **General anesthesia alone****(n=200)** | **Combined epidural-general anesthesia (n=200)** | ***P* value** |
| Recurrence, n (%) | 5 (2.5) | 5 (2.5) | >0.999 |
| Metastasis, n (%) | 50 (25.0) | 42 (21.0) | 0.342 |
|  Intracranial | 6 (3.0) | 11 (5.5) | 0.215 |
|  Bone | 8 (4.0) | 7 (3.5) | 0.792 |
|  Lymph nodes (mediastinal/supraclavicular) | 17 (8.5) | 8 (4.0) | 0.063 |
|  Liver  | 1 (0.5) | 1 (0.5) | >0.999 |
|  Gastrointestinal/pancreas  | 2 (1.0) | 2 (1.0) | >0.999 |
|  Kidney  | 2 (1.0) | 2 (1.0) | >0.999 |
|  Adrenal gland | 2 (1.0) | 0 (0.0) | 0.499 |
|  Pleura  | 3 (1.5) | 5 (2.5) | 0.724 |
|  Bronchus | 0 (0.0) | 1 (0.5) | >0.999 |
|  Lung (contralateral/bilateral) | 20 (10.0) | 11 (5.5) | 0.092 |
|  Multiple sites | 14 (7.0) | 11 (5.5) | 0.535 |
|  Unknown  | 2 (1.0) | 4 (2.0) | 0.685 |
| **Total**  | 53 (26.5) | 45 (22.5) | 0.352 |

Data are n (%).

#

# Table S5. Exploratory analysis of long-term survival

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | **Rate difference (95% CI) a** | ***P* value** |
| Recurrence-free survival rate, % |  |  |  |  |
|  12 months after surgery | 91.5 (87.6 to 95.4) | 91.0 (87.1 to 94.9) | -0.5 (-6.0 to 5.0) | 0.859 |
|  24 months after surgery | 80.4 (74.9 to 85.9) |  79.3 (73.6 to 84.0) | -1.1 (-8.3 to 6.1) | 0.766 |
|  36 months after surgery | 75.8 (69.5 to 82.1) | 75.1 (68.8 to 81.4) | -0.7 (-9.6 to 8.2) | 0.878 |
| Overall survival rate, % |  |  |  |  |
|  12 months after surgery | 97.0 (94.6 to 99.4) | 97.0 (94.6 to 99.4) | 0 (-3.4 to 3.4) | >0.999 |
|  24 months after surgery | 90.9 (87.0 to 94.8) | 91.4 (87.5 to 95.3) | 0.5 (-5.0 to 6.0) | 0.859 |
|  36 months after surgery | 88.0 (83.1 to 92.9) | 84.0 (74.9 to 87.1) | -4.0 (-9.8 to 1.8) | 0.176 |
| Cancer-specific survival rate, % |  |  |  |  |
|  12 months after surgery | 97.0 (94.6 to 99.4) | 97.5 (95.3 to 99.7) | 0.5 (-2.8 to 3.8) | 0.763 |
|  24 months after surgery | 90.9 (87.0 to 94.8) | 92.4 (88.7 to 96.1) | 1.5 (-3.9 to 6.9) | 0.584 |
|  36 months after surgery | 88.0 (83.1 to 92.9) | 84.9 (79.0 to 90.8) | -3.1 (-10.8 to 4.6) | 0.428 |

Data are rate (95% CI).

a Calculated as combined epidural-general anesthesia *minus* general anesthesia alone.

# Table S6. Prespecified long-term survival analyses in cancer patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Events, n (%)** | **Unadjusted HR (95% CI) a** | ***P* value** | **Adjusted HR (95% CI) b** | ***P* value** |
| Recurrence-free survival c |  |  |  |  |  |
| General anesthesia alone, n=166 | 54 (32.5) | Ref |  | Ref |  |
| Combined epidural-general anesthesia, n=170 | 48 (28.2) | 0.90 (0.61 to 1.32) | 0.577 | 0.90 (0.60 to 1.36) | 0.619 |
| Overall survival d |  |  |  |  |  |
| General anesthesia alone, n=166 | 25 (15.1) | Ref |  | Ref |  |
| Combined epidural-general anesthesia, n=170 | 31 (18.2) | 1.26 (0.75 to 2.14) | 0.384 | 1.12 (0.64 to 2.00) | 0.697 |
| Cancer-specific survival d |  |  |  |  |  |
| General anesthesia alone, n=166 | 24 (14.5) | Ref |  | Ref |  |
| Combined epidural-general anesthesia, n=170 | 29 (17.1) | 1.23 (0.72 to 2.11) | 0.452 | 1.08 (0.61 to 1.91) | 0.802 |

HR, hazard ratio; CI, confidence interval.

a Survival analysis and log-rank test.

bMultivariable Cox proportional hazards model adjusted for age (< 65 years *vs*. ≥ 65 years), 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 anti-cancer therapy (no *vs*. yes).

c Endpoint events include death, recurrence or metastasis, whichever came first.

d Endpoint event is all-cause death.

e Endpoint event is cancer-specific death.

# Table S7. Pain intensity during the first 3 postoperative days

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | **Median difference (95% CI) a** | ***P* value** |
| NRS of pain, at rest, score b |  |  |  |  |
|  Postoperative day 1  | 3 (2, 4) | 2 (1, 3) | -1 (-1 to -1) | **<0.001** |
|  Postoperative day 2 | 2 (1, 3) | 1 (0, 3) | -1 (-1 to 0) | **<0.001** |
|  Postoperative day 3 | 2 (0, 3) | 1 (0, 2) | 0 (-1 to 0) | **<0.001** |
| NRS of pain, with cough, score b |  |  |  |  |
|  Postoperative day 1 | 6 (4, 7) | 4 (3, 6) | -1 (-2 to -1) | **<0.001** |
|  Postoperative day 2 | 5 (3, 6) | 3 (2, 5) | -1 (-2 to -1) | **<0.001** |
|  Postoperative day 3 | 3 (2, 4) | 2 (1, 3) | -1 (-1 to -1) | **<0.001** |

Data are median (IQR).

NRS, numeric rating scale (an 11-point scale where 0=no pain and 10=the worst pain).

a Calculated as combined epidural-general anesthesia *vs.* or *minus* general anesthesia alone.

b Assessed between 8:00-10:00 am during the first 3 postoperative days.

# Table S8. Individual complications during hospital stay after surgery

|  |  |  |  |
| --- | --- | --- | --- |
|  | **General anesthesia alone (n=200)** | **Combined epidural-general anesthesia (n=200)** | ***P* value** |
| Severe ischemic-hypoxic brain injury a, n (%) | 0 (0.0) | 1 (0.5) | >0.999 |
| Pulmonary complication, n (%) | 27 (13.5) | 25 (12.5) | 0.766 |
|  Pulmonary infection b | 13 (6.5) | 15 (7.5) | 0.154 |
|  Respiratory failure c | 3 (1.5) | 1 (0.5) | 0.623 |
|  Atelectasis d | 8 (4.0) | 5 (2.5) | 0.398 |
| Cardiovascular complication, n (%) | 16 (8.0) | 8 (4.0) | 0.092 |
|  New-onset atrial fibrillation | 15 (7.5) | 6 (3.0) | **0.044** |
|  Ventricular fibrillation e | 1 (0.5) | 0 (0.0) | >0.999 |
|  Deep venous thrombosis/pulmonary embolism f | 2 (1.0) | 1 (0.5) | >0.999 |
|  Congestive heart failure g | 9 (4.5) | 3 (1.5) | 0.079 |
| Surgical complication, n (%) | 29 (14.5) | 19 (9.5) | 0.124 |
|  Secondary insertion of chest tube  | 4 (2.0) | 1 (0.5) | 0.372 |
|  Massive drainage (>3000 ml)  | 5 (2.5) | 3 (1.5) | 0.724 |
|  Emphysema (mediastinal/subcutaneous) h | 4 (2.0) | 9 (4.5) | 0.159 |
|  Hoarseness i | 4 (2.0) | 1 (0.5) | 0.372 |
|  Chylothorax  | 7 (3.5) | 1 (0.5) | 0.068 |
|  Bronchopleural fistula j  | 0 (0.0) | 1 (0.5) | >0.999 |

Data are n (%).

a Resulted from persistent hypotension due to intraoperative pulmonary artery rupture and massive bleeding.

b Receiving antibiotics for a suspected respiratory infection and met at least one of the following: new or changed sputum, new or changed pulmonary shadows, fever, leucocyte count >14×109·L-1 or <3×109·L-1.

c Requirement of mechanical ventilation for >48 hours.

d Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung.

e Due to an acute pulmonary embolism on the 9th day after surgery.

f Confirmed by venous ultrasonography and CT pulmonary angiography.

g Diagnosed by the presence of symptoms (i.e. shortness of breathing) and signs (i.e. chest X-rays findings) suggesting heart failure, a serum B-type natriuretic peptide >400 pg·ml-1, and a typical clinical response to diuretic therapy.

h Suction or incision drainage is required.

i Due to surgical injury of the recurrent laryngeal nerve.

j Confirmed by bronchoscopy.