PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Wu, Hsiang-Ling; Tai, Ying-Hsuan; Chan, Min-Ya; Tsou, Mei-Yung; Chen, Tony Hsiu-Hsi; Chang, Kuang-Yi

VERSION 1 – REVIEW

REVIEWER	Vijaya Gottumukkala, M.B;B.S, M.D (Anes), F.R.C.A The University of Texas MD Anderson Cancer Center, USA
REVIEW RETURNED	05-Dec-2018

GENERAL COMMENTS	Congratulations. Very well written. Minor suggestions: Page 12, line 19: Change replacement with placement Page 17, line 46: Change replacement with placement

REVIEWER	Anders Bugge Dep. o. Cardiothoracic Surgery, Oslo University Hospital, Norway
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	To the Authors, Congratulations on a well-written MS. The research question is in my opinion of interest. The MS enlightens the concerns of postoperative analgesia influencing long-term outcome after lung cancer resection. However, to clarify the MS further, I have some questions and comments: 1. From a clinical aspect, I am used to supply the patients with orally administrated opioids when gradually reducing the epidural anesthesia. What is common in your institution? In that case, did you record the consumption of oral narcotics? May a higher dose or continued oral administration of opioids have an impact on recurrence and overall survival? 2. In the Results you refer to p-values concerning FEV1 and VATS-procedures in Table 1. However, in the referred table, I cannot find any of the p-values? 3. You only list the FEV1 and FVC in liters, and do not link them to any predicted value? The liters do not make much sense to me, knowing that an Asian population have smaller predicted lung volumes compared to Caucasians. Further, you list in Table 1 the number of patients with COPD to approximately one fourth of your population. How was COPD diagnosed? Did you measure the FEV1/FVC ratio from the registered FEV1 and FVC results? If so, why not categorize the lung function variables according to the GOLD-grading guidelines?

	4. A proposal, but not decisive to follow: Comorbidities may also be grouped according to the charlson comorbidity index. The number of variables reduces, but the effect of comorbidity on the outcome is still accounted for. 5. In my opinion you list in the supplementary tables to many variables, not found anywhere in your analysis. Examples here of is; Surgeons and Anesthesiologists experience. Does it bring any clarification? All in all, the study enlightens in a thorough and trustworthy manor the question concerning the influence of epidural anesthesia on cancer recurrence and OS in a lung cancer population.

REVIEWER	Zimmitti Giuseppe Istituto Ospedaliero Fondazione Poliambulanza
REVIEW RETURNED	12-Mar-2019

GENERAL COMMENTS	This manuscript aims at retrospectively assessing eventual association between type of perioperative analgesia (epidural analgesia (EA) or intravenous analgesia (IA)) and survival following lung resection for Nonsmall cell lung cancer at a single high volume center. A significant impact of type of analgesia on overall and recurrence free survival was not found, both for the overall study group and after a propensity score matched analysis was performed. The manuscript is well written, the statistical analysis is correctly performed, but some comments are due: it is important to note that, along the study period, the use of EA gradually decreased, concomitant to the increasing use of thoracoscopic surgery. However, discussion is not well focused and shoud be improved: impact of an increased use of thoracoscopic surgery with concomitant decreased use of EA on surviviale should be highlighted and better discussed.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Vijaya Gottumukkala, M.B;B.S, M.D (Anes), F.R.C.A,
The University of Texas MD Anderson Cancer Center, USA
Minor suggestions:
Page 12, line 19: Change replacement with placement
Page 17, line 46: Change replacement with placement
Response: Thank you for the suggestion. We have corrected them in the manuscript.

Reviewer: 2
Anders Bugge
Dep. o. Cardiothoracic Surgery, Oslo University Hospital, Norway
The research question is in my opinion of interest. The MS enlightens the concerns of postoperative analgesia influencing long-term outcome after lung cancer resection.
However, to clarify the MS further, I have some questions and comments:

1. From a clinical aspect, I am used to supply the patients with orally administrated opioids when gradually reducing the epidural anesthesia. What is common in your institution? In that case, did you record the consumption of oral narcotics? May a higher dose or continued oral administration of opioids have an impact on recurrence and overall survival?
Response: In our hospital, epidural analgesia for lung resection surgery was typically continued postoperatively for 48 to 72 hours and switched to oral acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) thereafter. Oral or intravenous opioids were seldom administered for patients using epidurals postoperatively. Contrarily, patients without epidurals were offered an intravenous patient-controlled analgesia delivering morphine-based analgesics. We apologized for lack of information about narcotics consumption for each patient due to data unavailability in our electronic database. However, presumably patients using epidurals received lower dose of opioids compared with their counterparts, so the putative tumor-promoting effect of opioids should not affect our study results. We have added relevant description in the method section. (P7L17-P8L2) (P18L5-L6)

2. In the Results you refer to p-values concerning FEV1 and VATS-procedures in Table 1. However, in the referred table, I cannot find any of the p-values?
Response: Standardized differences is the difference in mean, proportion or rank divided by the pooled standard error, expressed as percentage and in general, imbalance should be considered as absolute value greater than 20. This index is commonly used in a propensity score matching study because it is more convenient for a reader to assess the quality of bias adjustment by comparing the standardized differences of collected variables before and after matching. We have replaced the p values concerning VATS-procedures and follow up time with standardized difference in the section of results. (P12L4-L5)
Reference:
Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083-107.

3. You only list the FEV1 and FVC in liters, and do not link them to any predicted value? The liters do not make much sense to me, knowing that an Asian population have smaller predicted lung volumes compared to Caucasians. Further, you list in Table 1 the number of patients with COPD to approximately one fourth of your population. How was COPD diagnosed? Did you measure the FEV1/FVC ratio from the registered FEV1 and FVC results? If so, why not categorize the lung function variables according to the GOLD-grading guidelines?
Response: Thank you for the valuable comment. We have added the percentages of predicted FEV1 and FVC. Note that these values are derived from the actual FEV1 and FVC measurements divided by their predicted values determined by patient characteristics and the nominators are more important determinant of pulmonary function rather than the denominators. Accordingly, we keep the original FEV1 and FVC measurements and use them to generate propensity score as we did in the previous analysis. Further analysis also demonstrated that after matching, the percentages of predicted FEV1 and FVC were balanced between the EA and non-EA groups. (Table 1)
With respect to the COPD diagnosis, we obtained its information from our electronic medical system. Although the prevalence of COPD looks relatively high in our study population, it should not cause a serious analytic problem since both the EA and non-EA groups had similar COPD rates before and after matching.

4. A proposal, but not decisive to follow: Comorbidities may also be grouped according to the Charlson comorbidity index. The number of variables reduces, but the effect of comorbidity on the outcome is still accounted for.
Response: Thank you for the suggestion. We have calculated the Charlson comorbidity index and found no significant difference in the mean value of this comorbidity index was noted between the EA

and non-EA groups before and after matching. The analytical results are presented as follows and we hope to keep original comorbidity variables instead of using Charlson scores.

Before matching After matching
EA (N=1799) Non-EA (N=392) SD EA (N=372) Non-EA (N=372) SD
Charlson comorbidity index 4.72 ± 1.88 4.77 ± 1.95 2.5 4.80 ± 1.86 4.74 ± 1.92 3.0

5. In my opinion you list in the supplementary tables to many variables, not found anywhere in your analysis. Examples here of is; Surgeons and Anesthesiologists experience. Does it bring any clarification?
Response: One of the strengths of our study is including a comprehensive collection of clinical and pathologic variables in the analysis to generate more reliable estimation of the EA effects on lung cancer outcomes. Supplementary table 2 is the result of logistic regression analysis for propensity score generation, and distributions of clinicopathologic factors of the EA and non-EA groups before and after propensity score matching is shown in table 1 and 2 (including all the variables). For sensitivity tests, table 3 shows the results of multivariable Cox regression analysis for cancer recurrence and all-cause mortality “after model selection”, and therefore only significant outcome predictors obtained after the model selection processes and adjusted EA effects are presented in this table. We have mentioned how to perform model selection in Method section of the original manuscript. (P10L12-L17)

Reviewer: 3
Giuseppe Zimmitti
Istituto Ospedaliero Fondazione Poliambulanza
The manuscript is well written, the statistical analysis is correctly performed, but some comments are due: it is important to note that, along the study period, the use of EA gradually decreased, concomitant to the increasing use of thoracoscopic surgery. However, discussion is not well focused and should be improved: impact of an increased use of thoracoscopic surgery with concomitant decreased use of EA on survival should be highlighted and better discussed.
Response: Thank you for the suggestions. We have added a paragraph describing how the thoracoscopic surgery affects lung cancer outcomes in the section of Discussion. (P17L11-L17)
Reference:
1. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 2016;17:836-44.
2. Yamamoto K, Ohsumi A, Kojima F, et al. Long-term survival after video-assisted thoracic surgery lobectomy for primary lung cancer. Ann Thorac Surg. 2010;89:353-9.

VERSION 2 – REVIEW

REVIEWER	Anders Bugge Dep. of Cardiothoracic Surgery, Oslo University Hospital - Rikshospitalet, Norway
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	The revised ms is in my opinion of high quality. All my questions and comments have been sufficient answered and commented upon. Hence, I raise no further questions. The ms is recommended for publication.

REVIEWER	Giuseppe Zimmitti Fondazione Poliambulanza, Italy
REVIEW RETURNED	07-Apr-2019

GENERAL COMMENTS	I'm satisfied with the corrections made by the authors.