

Peer review file

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Reviewer A

Comment 1: Though the focus is the elderly, median age was 73, relatively young given the inclusion criteria of anyone older than 70.

Reply 1: None.

Comment 2: As the authors point out, the predominance of left sided resections in their cohort can skew mortality data.

Reply 2: None.

Comment 3: Stage-specific survivals are not mentioned and would need to be in order to understand what an overall survival of 38% means.

Reply 3: we added the stage specific survivals

Comment 4: The statement in the discussion regarding the role of ERAS is worded too strongly, as this was not evaluated in the context of the manuscript and ERAS and pneumonectomy have not been as extensively studied.

Reply 4: We reformulated the statement about ERAS in the manuscript.

Comment 5: Increasing evidence suggests that it is no longer enough to look at survival and mortality as reasons we should or shouldn't operate on a cohort of patients. Patient recorded outcome measures (PROMS) likely should be paramount in decision making regarding extended procedures in the elderly. Additional measures that would be relevant include discharge disposition, return to function, etc. While it is clear these details could not be retrospectively added, it should be mentioned in the discussion.

Reply: We added a comment regarding the reported outcomes.

Comment 6: Lastly, insight regarding the difference between in house mortality and 30 day mortality, as it represents a substantial number and potentially intervenable or preventable death.

Reply 6: We now additionally commented on that in the section 'Discussion'.

Reviewer B

Comment 1: In general, it is well documented that perioperative risk increases after induction chemoradiotherapy rather than induction chemotherapy. In practice, the choice between chemoradiotherapy and chemotherapy as induction treatment and the method to manage the radiotherapy dose have been controversial. The authors noted that the perioperative risk of radical pneumonectomy for elderly patients did not differ with or without induction therapy; therefore, the author should comment on the indications for induction therapy and why it was chemotherapy or chemoradiotherapy.

Reply 1: As reported in the results, 24 patients had neoadjuvant treatment (15 chemotherapy and 9 chemo-radiotherapy). Regarding the indication for said therapies we added in the comment that indication could differ between all centers due to the heterogeneity of protocols.

Comment 2: It has been reported that the prognosis of patients treated with induction therapy varies greatly depending on the degree of histological effect. Therefore, the histological effect of induction therapy should be shown in patients who underwent induction treatment. This is also associated with perioperative risk.

Reply 2: We reformulated the paragraph according to your suggestion. Patients receiving neo-adjuvant therapy did not experience a higher incidence of postoperative complications ($p=0.633$), did not have a longer postoperative hospital stay ($p=0.588$), nor did they have a higher in-hospital mortality rate ($p=0.863$) (table 2). 14 of 24 patients had downstaging after induction.

Comment 3: In univariate analysis, the number of cases and prognosis for each factor should be presented. In particular, it should be clearly indicated whether the prognosis is the same or different between pN0-1 vs pN2, and p-stage I-II vs III-IV. Previous reports have shown that prognosis is highly dependent on N factors and pathological stage, as shown in the following references below.

Reply 3: We added a comment in the discussion, thanks for this input

Comment 4: I think there is not much references cited focusing on pneumonectomy. I would like the authors to additionally cite the following 4 reports that describe pneumonectomy in detail to more discuss the above points thoroughly.

Alexiou C, Beggs D, Rogers ML, et al. Pneumonectomy for non-small cell lung cancer: predictors of operative mortality and survival. *Eur J Cardiothorac Surg* 2001;20:476-80.

Martin J, Ginsberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. *Ann Thorac Surg* 2001;72:1149-54.

Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1424-30.

Sakakura N, Mizuno T, Kuroda H, et al. Primary pneumonectomy, pneumonectomy after induction therapy, and salvage pneumonectomy: a comparison of surgical and prognostic outcomes. *J Thorac Dis.* 2020;12:2672-82.

Reply 4: We updated the discussion and references with the suggested papers

Comment 5: It should be mentioned whether the TNM classification system used was the 7th or 8th edition.

Information from multicenter databases may be limited. Please consider the above to the extent possible. I hope my comments will be of some help.

Reply 5: We added a clarification in table 2.

Reviewer C

Comment 1: This analysis showed the preoperative cardiac morbidity is a poor prognostic factor. I think preoperative pulmonary morbidity is also an important factor influencing postoperative complications and prognosis. Moreover, the patients' pulmonary function, performance status, and nutrition condition (serum albumin, BMI, etc) are important factors when the pneumonectomy is planned. The authors should evaluate the relations among them.

Reply 1: We analyzed the pulmonary function but we didn't find a correlation with outcomes in the univariate analysis. In our databases, unfortunately there were several missing values regarding performance and nutritional status and therefore we decided to not include them in the analysis.

Comment 2: This study showed high survival rates compared to the past literatures since the proportion of stage I/II patients was high. The authors should show the survival according to the pathological stage

Reply 2: We added stage specific survival rates.

Comment 3: After pneumonectomy, it was known that patients died except for lung cancer such as respiratory or cardiac failure. So please show the causes of death in detail.

Reply 3: Unfortunately, in our database due to the retrospective and multicentric nature we don't have the cause of death in detail.

Comment 4: In this paper, the authors describe line 156 - 157 "survival rates at 1-, 3-, and 5-years were 93.3%, 80.3%, and 65.6%, respectively". But Kaplan-Meier curve in Figure 3 is different from that.

Reply 4: We apologize for it, it was a typo.

Comment 5: In this manuscript, Kaplan-Meier curves according to the cardiac complications was not showed.

Reply 3: We added an additional figure to cover this.

Reviewer D

Comment: This report is a multicentric retrospective study, analyzing 136 patients older than 70 years who underwent pneumonectomy for lung malignancy between 2009 and 2019 in 7 departments.

It is valuable information because it has a large number of cases and has been analyzed in detail. However, additional information is needed.

Please list the number of all lung cancer surgeries and pneumonectomy in 7 institutions from 2009 to 2019.

In Japan, the number of operations and the mortality rate are reported every year, so please refer to it. (Thoracic and cardiovascular surgeries in Japan during 2017, Annual report by the Japanese Association for Thoracic Surgery, Gen Thorac Cardiovasc Surg. 2020.) According to the report, 44,140 cases of lung cancer were operated on annually, of which 403 were pneumonectomy. The 30-day mortality rate for Pneumonectomy was 2.0% and the hospital mortality rate was 3.7%.

Minor comment,

Please describe the figure legend.

Figure 2. shows the same figure. Please correct it.

Reply: We reviewed the manuscript according to your suggestions and included the requested numbers. Furthermore, we took care of Figure 2 and its legend - thanks.

Reviewer E

The stated study outcomes of the paper are to assess the in hospital mortality and morbidity, the re-admission rate, the need for re-intervention, the 30 and 90 day mortality and the survival at 1, 3 and 5 years following pneumonectomy.

The in hospital mortality is 1.5%. This is impressive considering the patient cohort. So also are the 30 and 90 day mortalities. The longer term survival data needs some clarification as it appears to represent cancer free survival rather than overall survival.

The readmission rate is higher than expected, as also is the re-operation rate. There is no explanation for this observation.

The abstract results section does not align well with the stated primary and secondary aims of the overall study. For example, the hospital mortality is not mentioned at all and neither are the stated secondary outcomes of re-admission and need for re-intervention.

The conclusions in both the abstract and the discussion state that older age is not an absolute contraindication for pneumonectomy and that careful selection of patients is important. Whilst the good outcomes being due to careful patient selection is implied, it is not specifically addressed as such it is a general statement about pneumonectomy in the elderly rather than a conclusion from this study.

Comment 1: The authors need to be more specific about the study aims and to align both the results and conclusions to these.

Reply 1: We reformulated the aims, also in the abstract, to make clear that main aims were to investigate the weight of the factors age and neoadjuvant treatment in the pneumonectomy patients.

Comment 2: I would also like to know more about the significant re-operation rate in this cohort as it seems higher than expected.

Reply 2: 16 patients were readmitted and of those 14 required surgery (12 due to BPF)

Comment 3: General statements about pneumonectomy in the elderly should only inform the conclusion section if they are supported by the results or the study design. Perhaps amending the paragraph about the confounding patient selection aspects of retrospective studies would suffice.

Reply 3: Agreed, the selection bias problem of any retrospective study is now mentioned under 'limitations'.

Reviewer F

In your manuscript, patients at the age of 70 or older who underwent pneumonectomy were analyzed with regard to postoperative morbidity / mortality and survival. The enrolled number of patients (136) was large at the era of contemporary minimally invasive trend. Therefore, your data seem to be precious.

However, I would like to recommend several modifications.

Comment 1: Age of 70-74 yr is not so old in these days. I think that this age group will be regarded as reference group and comparisons between 70-74 yr group and 75 or older group should be done in order to clarify the significance of "age factor".

Reply 1: We understand your point, nevertheless we had to convene on a cut-off value, which in the end was decided to be 70. After all pneumonectomy in octogenarians is rarely done, so if we would follow your suggestions we would be merely looking at a population of patients between 75 and 80 who underwent this kind of procedure, which would hardly provide any useful data.

Comment 2: In your study, primary outcomes were short-term morbidity and mortality. However, detailed analyses on them were not fully performed, compared to prognostic analyses. Factors affecting short-term morbidity and mortality should be scrutinized.

Reply 2: Short-term morbidity and mortality were of course analyzed, but besides that mainly their impact on long term outcome – as shown in the Kaplan-Meier curves, was analyzed

Comment 3: The causes of 30- / 90- mortality should be described because they are of great concern for most of thoracic surgeons.

Reply 3: Unfortunately, we don't have in the examined database this data but it's the topic of a new paper from our group.

Reviewer G

This paper reports on the tolerability of pneumonectomy as a surgical treatment for lung cancer in the elderly.

In an aging society, the number of lung cancer patients is increasing, as pointed out in the text.

On the other hand, pneumonectomy is risky in itself, and the risks and benefits of this procedure for the elderly are still debatable.

This paper concludes that we should refrain from deciding the indication for surgery based on age alone. This is very useful information.

However, there are some serious problems with this paper.

Comment 1: The analysis was done on patients over 65 years old. Is it possible to compare the results with those of patients under 65 years old, or to compare the difference in complications between pneumonectomy cases and non- pneumonectomy cases even in patients over 65 years old?

Reply 1: Unfortunately, it's not possible in our cohort since we used 70 years all cutoff- Table 1 shows preoperative variables. Tumor stages – and what is important here is the pathological stage after surgery - are given in Table

Comment 2: In Table 1, the clinical stage is not given. In Table 1, the cardiovascular history is given, but no other history is given. For example, whether the patient has diabetes mellitus or is currently taking steroids should be indicated in the table, as they have a significant impact on wound healing.

Reply 2: Other variables were not available in our database

Comment 3: In Table 2, the reason for redo surgery is not written. Were there any complications such as bronchial fistula? What kind of treatment was used in those cases?

Reply 3: 16 patients were readmitted and of those 14 required surgery (12 due to BPF). 1 BPF was treated with decortication and shortening of the bronchus stump, 11 were treated with repeated surgical deb-ridement combined with closure of bronchopleural fistula with omentum patch.

Comment 4: In Table 2, 20.6% of patients had pathological stage I. In addition, the guideline states that postoperative adjuvant chemotherapy should be given to patients with stage II or higher pathology, but in this paper, 80% of patients had stage II or higher pathology, but only 28% received adjuvant treatment. The absence of adjuvant treatment may have an impact on the prognosis.

Reply 4: The suggestion is true and that patients were either not willing or not able to tolerate chemo.

Reviewer H

This was a multicentric retrospective cohort study analyzing the outcomes of pneumonectomy in lung cancer patients aged 70 years and older. The study demonstrated that the outcome of pneumonectomy in the elderly was comparable to that in ordinary cases. The outcomes could be predicted owing to the progress of medical technology and equipment and the improvement of the physical strength of elderly patients. The results of pneumonectomy for elderly with lung cancer compared in this study are citations from past literature with a limited number of cases. This study presented recent trends based on international data and deserves recognition. However, despite surviving the initial surgery, elderly patients may have a reduced ability to cope with other diseases due to activities of daily living deterioration and cardiopulmonary function. In this study, the predicted peak age of patients was in the early 70s, but these trends were remarkable after the age of 75. We are interested in the effect of poor tolerance to other diseases on the survival rates obtained in this study.

Please consider adding the following points.

Comment 1: Please clarify the exclusion criteria.

Reply 1: We excluded patients who underwent pneumonectomy in emergency setting or due to benign disease in order to focus our attention on morbidity and mortality in NSCLC elderly patients who need a pneumonectomy.

Comment 2: The coexistence of heart disease affected the overall survival. It is necessary to present how to evaluate preoperative cardiac function.

Reply 2: We added an explanation in the main text.

Comment 3: Fourteen out of 16 readmission patients needed re-surgery. What was the reason for the re-surgery?

Reply 3: 12 patients needed surgery after re-admission due to bronchopleural fistula and 2 due to hemothorax.

Reviewer I

Thank you very much for the opportunity to review the paper titled "Pneumonectomy for lung cancer in the elderly: lessons learned from a multicenter study".

In summary, the authors focused on short-term and long-term outcomes in patients undergoing pneumonectomy on the basis of their multi-institutional database.

I have several major and minor comments.

Major comments

Comment 1: The sample size is too small to draw a reasonable conclusion. At least, they should have a control group consisting of younger patients.

Reply 1: Thank you, but we think that our sample size is substantial considering the evidence that is so far available on the topic.

Comment 2: Postoperative complications should be reported along with CTCAE grading.

Reply 2: Thanks for your comment. We reported now the postoperative complications according to the NCI classification

Comment 3: 30-day and 90-day mortality are too high. What complications were responsible for those mortalities? This should be described and discussed in the main text.

Minor comments

Comment 4: It is not common or reasonable to report continuous variables as mean and range.

Reply 4: Unfortunately, in our database we don't have the cause of death in detail.

Comment 5: They should change from univariate and multivariate to univariable and multivariable, to be precise.

Reply 5: We changed them accordingly.