

Peer Review File

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Round 1:

Reviewer A

Trojnar et al. conducted a comparative study of outcomes between NSCLC aged ≤ 55 and >55 years who underwent surgery. The manuscript is concise, well written, and easy to understand, but there are some points to be addressed.

Comment 1: In this study, the authors chose 55 years as a cut-off point. But the reason is unclear.

Reply 1: We thank the reviewer for the evaluation of our manuscript. We analyzed available studies concerning surgical treatment for NSCLC younger patients. The cut-off point varied from 40 to 66 years. Our study included 11,460 women- we have evaluated statistically different cut-off points for age of younger women. The age of 55 was the youngest age in which the group of young women was large enough to be statistically comparable with the rest of the group. We have expanded the explanation in our text as advised.

Changes in the text: We added new sentence: “The age of 55 was the youngest age in which the group of young women was large enough to be statistically comparable with the rest of the group.” (Methods, Patients, Lines 109-110)

Comment 2: As the authors described in the Introduction, younger patients with lung cancer are the group with an increased likelihood of harboring a targetable genotype. In this study, the data on the genetic alterations is not shown, which was mentioned in the limitations. This is an important point.

Reply 2: We thank the reviewer for pointing this out. The association between young age and specific targetable genomic alterations including EGFR, ALK and ROS1 is important issue and recently molecular diagnosis of adenocarcinoma is recommended also in resectable

NSCLC. However our surgical database has been maintained from 2007 and has not included this information what we highlighted in limitations. Targeted therapy was not accepted as neoadjuvant in these years.

Changes in the text: We added new sentence: “Unfortunately, we do not presented the data on the molecular alterations (EGFR, ALK and ROS1) in tumors that could influence the results because our study includes all years from 2007 when molecular alterations was not yet a standard procedure in resectable NSCLC.” (Methods, Patients, Lines 117-120)

Comment 3: The sample size is relatively large, but the outcomes are so general and this study did not add any additional information on this topic.

Reply 3: Thank you for this suggestion. Surgical treatment is the best standard in NSCLC. The procedures of the treatments are improving and young patients are getting better treatment options. We pay attention to important subject concerning surgical treatment of young women with NSCLC. There are not many studies focusing on this subject. As we showed in discussion the results in survival between younger and older patients are not unequivocal in the literature. Our study brings additional data to the subject. We characterized a group of younger women with NSCLC, proved that despite more advanced stage of the disease in younger group they obtained better survival in selected stages (IA1, IA2, and IIIA). The differences in survival among young women comparing to older females are also seen in histopathology results- adenocarcinoma had better survival, however no differences were found in squamous cell carcinoma. A higher percentage of younger women underwent mediastinoscopy and pneumonectomy what emphasis the seriousness of the issue. In our study the percentage of smokers was similar in both groups -modern smoking cessation programs should be addressed especially to young women.

Changes in the text: We changed a sentence in Conclusions to: “The occurrence of NSCLC among young women and the most effective treatment i.e. tumor resection is noteworthy.” (Conclusions, Lines 414-415)

Reviewer B

The paper like this is important, not only for clinics, but also for public health. Many readers may concentrate to the paper like this. Authors analyzed national data of lung cancer especially for women and did a PSM for fair comparison. However, revisions are inevitable for three reasons.

Comment 1: First, PSM. Authors divided patients into two groups with age, 55. The number of two groups are too different to compare, so PSM is a good choice for comparison. I know that all variables could not be evenly distributed, but important ones should be considered. In your PSM, comorbidities and smoking history is not evenly distributed. These are very important variables that could make different survival. Therefore, repeat PSM is required.

Reply 1: Thank you very much for this comment. As requested, we have decided to rerun the PSM analysis based on additional variables you asked.

Changes in the text: Accordingly to new PSM cohorts, the data post-PSM were changed.

Comment 2: Second, patients and data. Authors included patients of cStage IIIA and IIIB, but those are not usually included in the surgical candidate and for analyzing patients of those stage, neoadjuvant or adjuvant history should be considered. All the above variables are omitted. It will be better to review why authors operated stage III patients and what their adjuvant or neoadjuvant plans are.

Reply 2: Thank you for this question and for pointing out the error to us. In the table, the information does not refer to the clinical stage, but to the pathological stage. Most likely, this is a translator's fault that we did not catch before. We are very sorry. In our work, we do not include cases of neoadjuvant treatment, and the stages IIIA and IIIB shown in the table are due to postoperative upstaging. We would also like to inform you that information about adjuvant treatment is not accurate in our database (not every oncologist cooperate with PLCSG and most of the oncologic units are outside of thoracic centers). We can briefly assume its number based on stage.

Changes in the text: Table 1 was changed, we have corrected word “clinical” to “pathological”.

Comment 3: Third, Statistics. Cox-regression is a good tool to find out prognostic factors for survival, but careful selection of variables is important. Authors presented the table of multivariate analysis, but process of univariate one is omitted. So, we could not find out the condition of variable exclusion and checking of multicollinearity. Please add on the detailed process of Cox-regression including univariate analysis and results of checking multicollinearity.

Reply 3: Statistical methodology for Cox-regression is now provided in statistical section. We chose backward selection as method of choosing variables. We can provide GVIS parameter values but we think these data is too redundant and we have not seen it yet in other works. However, if you would like us to include this data in an additional table, of course we will do so. Results of multivariable analysis are now updated according to new PSM.

Changes in the text: We described the methodology in more detail, the data in the main text and table have changed.

Comment 4: Finally, English is good, but it will be better with professional editing service because some sentences have complex structures and are redundant. One more thing, the message in conclusion is vague. According to the conclusion, surgery is more recommended to younger patients, but current paradigm about indication looks different. Not a age, but a comorbidity is thought to be a decisive factor for surgery. Above revisions may make conclusion be clear and strong.

Reply 4: As we are not native speakers, so our work was sent to native English-speaking editors. They edited our study for proper language, grammar, spelling etc. After editing, we did not make any changes (except for statistical purposes or required for the journal, eg. word limit). We attached the Editing Certificate in the process of submitting.

In conclusion we presented our findings and we didn't suggest that comorbidities decide on treatment. The decision about treatment should be in line with the recommendations.

Changes in the text: none.

Round 2:

Reviewer B

Authors could improve the paper because their raw material is exquisite and important. Some revisions could improve the paper.

Comment 1: Data

A. The histologic data is comprised of just adenocarcinoma and squamous cell carcinoma in the paper, but in real word, there are adenosquamous, large cell, or other mixed one. Where are they? Authors re-defined them into one of both type?

B. Clinical stage is important because readers could evaluate the work-up ability comparing clinical and pathologic stage. In the first paper, they stated only clinical stage and then in the revised one, only pathologic one. Please state both.

C. Record of adjuvant treatment. There are advanced stages over stage I in the paper and they usually are required adjuvant treatment. Adjuvant treatment can make different survival, so collecting and analyzing the history of adjuvant treatment is very important. Please consider adjuvant treatment.

Reply 1:

A: Due to the fact that this is a large material, and the other cancers are a definite minority, they were therefore omitted from the statistical calculations in order to make the results clearer. Many articles on thoracic surgery did not raise this issue, so we also did not include it in our study.

Changes in the text: none.

B: Thank you for this comment. We have decided to add the required information to the table.

Changes in the text: Table 1 has been revised.

C: You have raised an important point here. However, in our study we focused on surgical treatment. Unfortunately, we do not have such information. In Poland after surgical treatment patients are referred to different oncology centers with their own databases. Reaching full data about such treatment would be very difficult.

Changes in the text: none.

Comment 2: Statistics

A. When we analyze the patients with different age group, the AGE should be adjusted, because age, itself is a strong prognostic factor. It seemed that the authors did not consider age when they analyzed their survival. Please consider age.

B. When we do a multivariate analysis, selecting variables is very important. We usually do a univariate analysis for each variable, then select them for multivariate analysis. The inclusion criteria could be a certain p value, clinical implications, or others. After we select the variables for the multivariate analysis, the violation of multicollinearity should be checked. In this paper, authors did not present how to select variables for multivariate analysis.

Moreover, there may be violation of multicollinearity among VATS, stage, and pN. Please state the detailed process of uni- and multivariate analysis and check the multicollinearity.

Reply 2:

A: Thank you for your comment, however, we do not know how to address it because we include a marker of whether the patient's age is above or below 55. Of course, you can include age in addition to this, but then the marker whether the patient's age is above or below 55 is statistically insignificant. This is because then we are entering similar information into the model twice, and more information is given by the untransformed age. This alone undermines the whole approach to the analysis.

Changes in the text: none.

B: During the last review, we changed the description of statistical research according to the recommendations, and we don't know how else we could still complete this section. Please take another careful look at the changes we made last time, but nevertheless we also decided to add a new Supplementary Table with the values we describe. We chose backward selection as method of choosing variables.

Changes in the text: Statistical section was changed, we have added a new Supplementary Table 1a and 1b.

Comment 3: Conclusion

Authors started with a valuable material for the paper, but the conclusion was weak and short of something new. "Young people live longer than the old one" is a fact and there is no

something new. This was what the authors presented. What we should focus is why the survival between young and the old is similar in specific stages. Is the opportunity of treatment equal to everyone? Are the young people limited to the medical resource? How to improve the survival of them? Answering these questions could improve the conclusions. Please improve the conclusion with the right question.

Authors did their best for revising the paper, but it is not enough to accept for the journal. The raw data of the paper is a good one and valuable to be analyzed. However, authors are not good at analyzing the BIG data like this, so more logical revision is required, and the conclusion is weak and vague. Nevertheless, I believe that more revision could upgrade the paper, so I want to give them second chance of revision for data, statistics, and conclusion. And one more, I want to check the certificate of English editing.

Reply 3: We thank reviewer for your suggest. We corrected the conclusions as suggested.

Changes in the text: We have changed and added new sentences in the Conclusion section: “However mortality in both groups was comparable (0.4% vs. 0.7%, $p=0.24$) what prompts us to the same careful care for young women as for older. Despite the more advanced stage of the disease, basing on PSM analysis survival was much better in younger than in older women only in selected stages of NSCLC (IA2, IIB, IIIA) whereas no significant differences were found in other stages of advancement. In Poland the opportunity of treatment is equal despite age. Our results do not show significant differences in terms of access to academic centers in both groups. To improve the survival of young women with NSCLC we should take into account lung cancer in differential diagnosis in early stages, enable faster diagnostic path for young patients and be aware of the need for aggressive diagnostics in younger women knowing that they have more often advanced disease at the time of diagnosis and modernize anti-smoking programs.”

We attached the necessary language certificate already twice during the submitting, we do not know what the problem is that you did not get it. We are also posting a copy of the certificate here:

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