**Reviewer’s report**

**Title:** Trimodally treatment for stage IIIa NSCLC patients increases survival while not effecting surgical mortality or complexity

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**Reviewer:** Emmanouil Ioannis Kapetanakis

**Reviewer's report:**

It was my pleasure to review the work submitted by Dr. Aravot and colleagues from the Rabin Medical Center and from the University of Tel Aviv in Israel. I find the concept of their work and their premise quite interesting and I was looking forward to sitting down and reading their study's findings. Having finished assisting a senior colleague this morning in the performance of a right sided pneumonectomy in a patient with IIIa disease who received neoadjuvant chemotherapy subsequently downstaged for surgery I can tell you things are not as easy as the authors describe!

The manuscript and the methodology of the study suffers from a number of deficiencies. Although the English language used is understandable to an extent the authors are too verbose and floral with their descriptions. For example: "attempts to perform pneumonectomy proved to be deadly due to hemorrhage, sepsis..." or "...surgery is only one player in the fight against cancer..." all sound exaggerated!!! This language pattern is diffuse throughout the manuscript! In addition in certain areas I am not sure I understand what the authors are trying to propose - support. Therefore, the manuscript needs rewriting to make it more succinct, specific and understandable.

To this effect I am also confused as to what the primary aim - purpose and conclusion(s) of the study is(are). As I understood it and what I really wanted to know as a practicing surgeon is if patients with IIIa disease (which is the gray area group of patients) undergoing first neoadjuvant chemo-radiation therapy and subsequently surgery were technically easier or as easy to operate as patients with IIIa disease which underwent surgery first and subsequently adjuvant chemotherapy!! As a secondary endpoint I would like to know which approach had better survival benefit (which is a bit problematic I know as I will explain later on). From reading the abstract and the introduction this is what peaked my interest. In contrast the authors presented a hodge podge of patients ranging from stages Ib to IIIa in the adjuvant group and an array of different analysis which made no sense!! As a result their primary analysis is biased as lower stages of patients were mixed with more advanced ones.

The authors claim that when a sub-analysis was performed in the IIIa stage patients the 8-year survival was better in the neoadjuvant group. This is what I feel is the "meat and potatoes" of the study and the authors should focus their survival analysis on this groups. Naturally there is an inherent bias in this approach, which is that the group that received neoadjuvant chemo-radiation therapy and downstaged has already proven that its cancer is susceptible to treatment and therefore may have a better survival benefit due to other (i.e. genetic - histopathology - grade ect) factors!
In addition another interesting subject the authors have tried to address but I feel their work has deficiencies, is the surgical complexity present in the neoadjuvant group. As previously mentioned, personal experience notwithstanding, patients which had neoadjuvant chemo-radiation treatment often present with extensive fibrosis and difficult dissection, i.e. of mediastinal lymph nodes, especially if the 3-4 week window prior to radiation induced inflammation and fibrosis is missed. The authors report that all cases were performed by one senior surgeon using the same technique but was this done exclusively? In training centers, often an easy case is performed by trainees with the assistance of a senior trainer while more complex cases are usually performed either by more experienced trainees or consultants! Therefore, length of operation time might not be the best way to delineate surgical complexity because a training case performed by a trainee in a Ib or Iib patient may take as long as a senior surgeon performing surgery on a IIIa neoadjuvant case. The best way to delineate complexity of case is by multivariable analysis of the factors mentioned above (length of case, training or non training, intra-operative events - bleeding) and by a review of the op. notes of all cases by the surgeons and the grading of complexity in a scale. This naturally is subjective and biased but this reviewer knows of no other way to rate case difficulty.

In addition to these main general points, the study suffers from a number of other minor deficiencies that need to be addressed if possible:

1. It has a small sample size (169 patients) and I know I propose it is reduced even further to only patients with advanced disease!

2. It is a single institution, single center, single surgeon study.

3. The aims of the study as described in lines 45-51 of the introduction make no sense and do not correspond with the title! If this is a study on morbidity and mortality of pneumonectomy patients ect then due to reasons 1 & 2 it is too weak an analysis and it represent things already known and presented in the literature!

4. Why was not EBUS used to stage the mediastinum and mediastinoscopy was utilized instead. Modern guidelines recommend EBUS first and re-staging preferably with VAMS following recurrence!

5. Why was the 2009 revision of the International System for the Staging of Lung Cancer used and not the more recent one.

6. Comments 4 & 5 and considering the retrospective nature of the work (10 years span) make me question the applicability of the findings of the analysis as staging and management guidelines have evolved and changed.

7. Why did only patients which downstaged by clearing of the mediastinum undergo surgery (line 10-14, neoadjuvant protocol)? What about patients which went from N2 to N1 disease or their tumor size was significantly reduced or they had a reduction on the number of positive nodes? What if patients had a partial response according to RECIST?

8. I was totally lost reading the Re-admission and transfer between departments section of the manuscript! What is the point the authors are trying to make looking at this?

9. Similarly I was lost when reading the prognosis part and the similar section in the discussion!
What is the point comparing left and right pneumonectomies and survival in this study? It make no sense considering its small numbers and it is something already reported in the literature.

In conclusion; this is a study with a lot of potential and an interesting concept which has unfortunately been weighted down by extensive, extraneous and unrelated analyses and thought tangents! I suggest to the authors a more succinct, brief and specific analysis looking only on stage IIIa patients undergoing pneumonectomy either with neoadjuvant chemo-radiation therapy or adjuvant treatment looking only at surgical complexity (with the adjustments suggested above) and long term survival. Therefore an extensive re-write is needed into a more focused and specific paper. I comment the authors for their effort and idea and prompt them to follow my suggestions. I also thank the editor for allowing me to review this very interesting work.

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