

Peer Review File

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Reviewer A

I have thoroughly read the manuscript and acknowledge the potential significance of the research topic. However, to maximize the impact and quality of the publication, there are several areas that require attention and improvement. While the manuscript shows promise, I suggest focusing on enhancing the clarity and depth of the methodology section to ensure a more comprehensive understanding of the study's design and execution. Additionally, providing a more robust literature review to establish the context and significance of the research would be beneficial. Further, I recommend strengthening the discussion section to offer a more in-depth analysis of the results and their implications. In summary, the research topic is promising, and addressing these areas of improvement would contribute to a more impactful and well-rounded publication.

1. In the method section, the inclusion criteria to include only stage 4 NSCLC patients. However, the data studied includes some patients with stage 3B. Please explain or amend to align with the inclusion criteria.

Response: We apologize for the oversight in the inclusion criteria mentioned in the method section of our manuscript. We appreciate your attention and would like to clarify and amend the inclusion criteria to align with the intended study population. To ensure consistency and accuracy, we have carefully reviewed the patient data and re-evaluated the staging information. The revised statement in the method section should read as follows:

Inclusion criteria included Saudi patients with stage IV NSCLC or stage III, aged between 40 to 85 years, with primary lung cancer and one-year follow-up. Exclusion criteria included non-Saudi patients, SCLC, stages I and II of NSCLC, and metastatic lung cancer from other primary origins.

2. In Table 3, please provide clear definitions for the terms "stable," "regression," and "progression." Additionally, on lines 140-141 in the text, the term "relapsed" is used, which appears to have the same meaning as "regression." Please add definitions for clarity.

Response: Thank you for bringing these concerns to our attention. We apologize for any confusion caused by the terminology used in Table 3 and the text. We agree that providing clear definitions for the terms "stable" "regression" "progression," and "relapsed" is essential to ensure clarity and accuracy in our manuscript.

We have addressed these issues as follows:

Definitions in Table 3: We have revised Table 3 to include clear definitions for the terms "stable" "regression" and "progression".

"progression" was identified as follows: progression (metastasis) in the primary site (lung) alone, or beyond the lungs to other parts of the body).

"regression" is the partial or complete disappearance of a tumor with/without cancer therapy.

"stable" is defined as fitting the criteria neither for progressive nor regressive disease.

The revised table provided concise explanations of these terms. This will help readers better understand the interpretation of the data presented in the table.

In the text (lines 140-141): the "relapsed" has been changed to "regressed".

3. In the third paragraph of the discussion section, the author mentions data related to the treatment by surgery or radiation in stage 3, which may not be directly relevant since this study focuses on stage 4 NSCLC. Therefore, it is suggested to rewrite the discussion section to better align with the study's focus.

Response: Thank you for your suggestion regarding the alignment of the discussion section with the focus of our study on stage 4 NSCLC (Non-Small Cell Lung Cancer). To address this concern, we have carefully revised the discussion section to ensure that the content is directly relevant to the stage 4 NSCLC and III patients studied in our research.

4. In line 178, the author writes "(surgery + definitive chemoradiation)," it is recommended to revise it to "Combination of surgery with definitive chemoradiation."

Response: Thank you for your suggestion. To ensure accuracy and improve readability, we have revised the sentence to state "combination of surgery with definitive chemoradiation" instead of using "(surgery + definitive chemoradiation)."

5. The lines from 184-187, which discuss the multivariate Cox regression model and median survival, should be relocated to the Results section. Currently, the Results section does not include the mentioned analysis data, such as tables and Kaplan-Meier curves. It is recommended to present this information in the Results section for a more comprehensive presentation.

Response: Thank you for this comment. We agree that including the details of the multivariate Cox regression model and median survival analysis in the results section would provide a more coherent and complete presentation of our findings. We have made the necessary modifications and transferred the relevant information to the results section.

6. In summary, the writing in the discussion section should be improved to be more appropriate and aligned with the objectives of this study.

Response: Thank you for this comment. We have carefully reviewed the discussion section and made necessary revisions to ensure that the discussion is more suitable and aligned with the study's objectives.

Addressing the points mentioned above will enhance the clarity, depth, and

overall quality of the manuscript, making it a valuable contribution to the field.

Reviewer B

While this is an interesting and important manuscript addressing disease prognosis and treatment options in advanced stage NSCLC, the manuscript lacks methodologic detail. For example, there is a sparsity of information regarding how the Cox regression models were constructed (e.g., systematic versus stepwise variable selection), goodness of fits statistics, and details regarding how missing values were handled (e.g., piecewise vs listwise deletion, imputation, EM algorithm). Noticeably absent are important statistical values like hazard ratios and 95% confidence intervals and test results of the proportional hazards assumption. Oddly, Cox regression is not mentioned in the methods section but is only referred to in the Abstract and Discussion sections. Further concerning is that “cox regression” is not appropriately capitalized, as this method is named after a somewhat famous statistician. This would suggest that a formally trained statistician did not perform the analysis for the manuscript. Before revising their paper, I would suggest that the authors consult with a PhD statistician and also include this person as a coauthor on the manuscript to safeguard the methodologic integrity of the statistical analyses.

Response: Thank you for this comment. We completely agree with you that providing comprehensive methodological information is essential for transparency and reproducibility. We apologize for any omissions and lack of clarity in the manuscript. In the revised version, we have addressed these concerns. Besides, we did not encounter any major missing data. However, our data has variables with a small number of missing values and the data distribution was approximately normal. Therefore, imputation was minimally used to fill in the missing values with the mean, median, or mode value of the non-missing values for that variable. We have also included the hazard ratios and 95% confidence intervals to tables 2 and 3.