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OPEN PEER REVIEW

The Effect of PET/CT-Derived Parameters on the Prediction of Survival in Lung Cancer Patients

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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Contents

1 **Original submission** Referee 1, Referee 2, Associate Editor, Editor-in-Chief 2
2 **Revision 1** Abtin Doroudinia, Referee 1, Associate Editor, Editor-in-Chief 5
Authors' reply to reviewers 6
Reviewer and editor comments 13
3 **Revision 2** Referee 2, Referee 1, Associate Editor, Editor-in-Chief 15
Authors' reply to reviewers 16
Reviewer and editor comments 19
4 **Revision 3** Abtin Doroudinia, Associate Editor, Editor-in-Chief 21
Authors' reply to reviewers 22
Reviewer and editor comments 27
5 **Revision 4** Editor-in-Chief 28
Authors' reply to reviewers 29
Reviewer and editor comments 30

1 Original submission

4 comments · 29 Aug 2023 – 15 Oct 2023

Referee 1 Reviewer

MAJOR REVISION 29 Aug 2023

Thanks to the authors for considering IJR as a potential platform for their submission.
The study concluded that the PET variable SUVmax did not demonstrate a significant impact on predicting survival outcomes in patients. However, the analysis revealed that MTV and TLG values, obtained from PET/CT scans, were effective in predicting survival. It is important to note that the study has certain limitations that should be considered during the revision process.

General drawbacks
1. Small Study Population: The small number of patients included in the study may limit the generalizability of the findings and prevent accurate results from being obtained.
2. Limited Outcome Measures: The abstract focuses on the effect of PET/CT variables on survival prediction, but it does not provide information about other important clinical outcomes, such as progression-free survival, treatment response, or overall survival. Including additional outcome measures would provide a more comprehensive understanding of the impact of the variables studied.
3. Potential Confounding Factors: The study focused on evaluating the relationship between tumor SUVmax, MTV, and TLG values from PET/CT scans and survival. It is important to consider that other variables and covariates, such as genetic markers, comorbidities, or treatment regimens, may also influence survival outcomes and were not accounted for in the analysis.
4. Potential Selection Bias: The study selected patients from a specific clinic and included only those who had PET/CT scans taken on the same device in that clinic. This selection criterion may introduce bias and limit the representativeness of the patient population.

Abstract
5. Objectives: It would be helpful to provide a rationale for why this study is important and how it contributes to existing knowledge.
6. Methods: It lacks details about the inclusion and exclusion criteria, data collection procedures, and statistical analysis.
7. Results: It lacks specific numerical values and statistical significance levels. Including these details would make the results more informative and interpretable.
8. Conclusion: It could be expanded to discuss the implications of the findings and potential future research directions.

Methods
9. Sample Selection: The text mentions that the electronic database was searched for patients diagnosed with NSCLC between January 2019 and October 2020. However, it does not provide information on the criteria used for patient inclusion and exclusion. It is important to describe the criteria for selecting patients to ensure the sample represents the target population.
10. Statistical Analysis: The text briefly mentions the statistical tests used, such as Spearman's correlation test and Cox's proportional hazards regression analysis. However, it does not provide information about the rationale, procedure, or other relevant statistical analyses, such as descriptive statistics or potential confounding variables considered in the analysis. Providing more details about the statistical methods used would improve the transparency and reproducibility of the study.

Results
11. Subgroup Analysis: The study performed subgroup analyses based on histopathological type, presence of

lymph node metastasis, presence of distant metastasis, and tumor stage. While these subgroup analyses provide valuable insights, the small sample size within each subgroup may limit the statistical power and reliability of the findings.
12. The content of the results section is not fully aligned with the study's title and objective, and it is much broader. Therefore, instead of conducting subgroup analysis based on different factors, each factor can be considered as an independent variable, and its effect on the survival rate can be measured.
13. The statistical analysis method and the presentation of results should be fully aligned in terms of content and format. Therefore, first, descriptive statistics of demographic and clinical variables of the patients should be provided. Then, the results of the Kaplan-Meier survival analysis along with the log-rank test for significant comparisons should be presented. Finally, the results of the multivariable Cox proportional hazards analysis should be displayed in Table 3.
14. When analyzing categorical variables such as gender or tumor stage, it is important to designate a reference group. The hazard ratio of other groups should be compared to this reference group.
15. Furthermore, in the statistical analysis, it is possible to take a step further and consider two-year survival as a binary outcome (alive-deceased) and evaluate the predictive value of significant PET variables using ROC analysis. This analysis allows for the assessment of sensitivity, specificity, positive and negative predictive values, and accuracy in predicting survival.
Discussion
16. Lack of Subheadings: The discussion section does not have clear subheadings to separate different topics or ideas. This can make it difficult for readers to follow the flow of the discussion and locate specific information.
17. Lack of Integration: The discussion section jumps between different topics without providing a smooth transition or integration of ideas. This can make the discussion feel disjointed and difficult to follow.

Referee 2 Reviewer

MAJOR REVISION 3 Sep 2023

I think this manuscript has unprofessional language that is not clearly understandable. Overall, the language quality is not good, and the manuscript is not recommended for publication at this time:

Here are some comments:

1- Incorrect wording such as: "Maximum tracer uptake (SUVmax) values". SUVmax stands for: Standard uptake value. (Abstract line 5)
2- Poor English language: “were found” should be “were calculated” (Abstract line 6)
3- Unclear sentence: increasing what risk? “In multivariate analysis, it was observed that MTV value was significantly effective in increasing risk in patients with adenocarcinoma (ACA), patients with lymph node involvement, or patients with distant metastasis” (Abstract findings)
4- Unclear: “MTV may be effective in increasing risk and TLG in decreasing risk.” (Abstract conclusion). Again, what risk?
5- Redundant wording: we are not supposed to teach what SUV is! “A standardized version of this value according to the weight of the patient is called the "standardized uptake value (SUV), the highest SUV value detected in the tumor tissue "maximum SUV" (SUVmax), and the average value in all areas of the tumor tissue is called the "mean SUV" (SUVmean).” (background).
6- In the first paragraph of the results, under general variables, it is not clear what size and lymph node involvement are based on. Are they based on imaging, CT, PET, or pathology results?
7- What do you mean by “Mass PET variables”? Do you mean “primary tumor”?
8- How is “survival” defined in your study? This is probably the most important issue with this manuscript.
9- How are patients staged? How many patients are in each stage?
10- What do you mean by “increasing risk” in this sentence: “It was observed that the MTV value, one of the PET

variables, continued to significantly affect survival in increasing risk"? Do you mean decreasing survival?
11- What do you mean by "decreasing risk" in this sentence: "TLG level was non-significant but tended to affect survival in decreasing risk"? Do you mean improving survival?
12- Overall, the language in this manuscript is unclear and not clearly understandable. You have repeated multiple times: "increase in MTV value increases the risk on survival". I guess you mean " increase MTV values is associated with decreased survival". Am I correct?

And many other unclear phrases and sentences...

Associate Editor MAJOR REVISION 15 Oct 2023

Major Revision.

Editor-in-Chief MAJOR REVISION 15 Oct 2023

Dear authors,
Your article needs Major Revision.
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

Thank you for your prompt review of our work, entitled ‘ The effect of PET/CT variables on the prediction of survival in lung cancer’ ; Manuscript ID: 139822. We also thank you for allowing us to revise and resubmit this manuscript. We changed the title as “The effect of PET/CT derived parameters on the prediction of survival in lung cancer”. We also revised the text in the light of the valuable suggestions and contributions of the reviewers. All the changes have been highlighted in the revised manuscript. Our responses to the comments are below.

I hope that this version of the manuscript is acceptable for publication in “Iranian Journal of Radiology”.

Thank you in advance for your efforts on this revised manuscript.

Sincerely,

Nurdan Şimşek Veske

Corresponding Author

Response Letter

Reviewer 1

1- Incorrect wordings such as: "Maximum tracer uptake (SUVmax) values". SUVmax stands for: Standard uptake value. (Abstract line 5)

Response

The incorrect statements have been corrected.

2- Poor English language: “were found” should be “were calculated” (Abstract line 6)

Response

The English was revised throughout the text

3- Not clear sentence: increasing what risk? “In multivariate analysis, it was observed that MTV value was significantly effective in increasing risk in patients with adenocarcinoma (ACA), patients with lymph node involvement, or patients with distant metastasis” (Abstract findings)

Response

To clarify, we changed the sentences and defined the risk as “risk of death”

4- Not clear: “MTV may be effective in increasing risk and TLG in decreasing risk.” (Abstract conclusion). Again what risk?

Response

To clarify, we changed the sentences and defined the risk as “risk of death”

5- Redundant wording: we are not supposed to teach what is SUV! “A standardized version of this value according to the weight of the patient is called the "standardized uptake value (SUV), the highest SUV value detected in the tumor tissue "maximum SUV" (SUVmax), and the average value in all areas of the tumor tissue is called the "mean SUV" (SUVmean).” (background).

Response

The unnecessary expressions mentioned in the article have been deleted.

6- In first paragraph of results, under general variables, it is not clear size and lymph node involvement is based on what? It is based on imaging, CT, PET? Or pathology results?

Response

Tumor size and lymph node involvement was determined according to CT and PET/CT. This information was added to the methods section.

7- What do you mean by “Mass PET variables”? do you mean “primary tumor”?

Yes. We changed the Word as “primary tumor” throughout the text

8- How is “survival” defined in your study? This is probably most important issue whit this manuscript.

Response

Survival was defined as “to be alive”, and survival time was defined as the time between diagnosis and death or, if the patient was alive, between diagnosis and the last day the patient was heard from. We included this information to the text

9- How patients are staged? how many patients are in each stage?

Response

Using PET/CT data and additional brain magnetic resonance imaging, tumor stage was determined according to the 8th edition of the TNM staging system. This information was added to the text

10- What do you mean by “increasing risk” in this sentence “It was observed that the MTV value, one of the PET variables, continued to significantly affect survival in increasing risk” Do you mean decreasing survival?

Response

Yes. We used clearer sentences to define the effect of the parameters.

11- What do you mean “decreasing risk” in this sentence “TLG level was non-significant but tended to affect survival in decreasing risk”. Do you mean improving survival?

Response

Yes. We used clearer sentences to define the effect of the parameters.

12- Overall the language in this manuscript is unclear and not clearly understandable. You have repeated multiple times: “increase in MTV value increases the risk on survival”. I guess you mean “ increase MTV values is associated with decreased survival”. Am I correct?

Response

You are correct. We used clearer sentences to maket he manuscript more easily understandable.

Reviewer 2

General drawbacks

1. Small Study Population: The small number of patients included in the study may limit the generalizability of the findings and prevent accurate results from being obtained.

Response

As you mentioned, further studies with larger sample size is needed to generalize the findings. However this study is a pivot study to show the effect of PET-CT parameters.

2. Limited Outcome Measures: The abstract focuses on the effect of PET/CT variables on survival prediction, but it does not provide information about other important clinical outcomes, such as progression-free survival, treatment response, or overall survival. Including additional outcome measures would provide a more comprehensive understanding of the impact of the variables studied.

Response

This study was designed to evaluate the overall survival. Our sample size is not enough to analyze the impacts of other outcome measures.

3. Potential Confounding Factors: The study focused on evaluating the relationship between tumor SUVmax, MTV, and TLG values from PET/CT scans and survival. It is important to consider that other variables and covariates, such as genetic markers, comorbidities, or treatment regimens, may also influence survival outcomes and were not accounted for in the analysis.

Response

During the statistical analysis, all of the major variables that could affect survival were analyzed. However there may be many minor covariates. We did not add these covariates to the analyes and limited the analysis to make the study understandable.

4. Potential Selection Bias: The study selected patients from a specific clinic and included only those who had PET/CT scans taken on the same device in that clinic. This selection criterion may introduce bias and limit the representativeness of the patient population.

Response

It was planned to minimize the differences that may arise from both the device and the interpreters by evaluating PET-CT images taken in a single center, with the same device, under the same technical conditions, by the same nuclear medicine specialists.

Abstract

5. Objectives: It would be helpful to provide a rationale for why this study is important and how it contributes to existing knowledge.

Response

We added a rationale to the Abstract

6. Methods: It lacks details about the inclusion and exclusion criteria, data collection procedures, and statistical analysis.

Response

Since the Abstract section is limited to 250 words, we could not include detailed information but we did include details of the selection criteria and statistical analysis in the text.

7. Results: It lacks specific numerical values and statistical significance levels. Including these details would make the results more informative and interpretable.

Response:

Specific values and significance levels were added to Results section in the Abstract.

8. Conclusion: It could be expanded to discuss the implications of the findings and potential future research directions.

Response

We added a sentence indicating necessity of new studies.

Methods

9. Sample Selection: The text mentions that patients diagnosed with NSCLC between January 2019 and October 2020 were searched through the electronic database. However, it does not provide information on the criteria used for patient inclusion and exclusion. It is important to describe the criteria for selecting patients to ensure the sample represents the target population.

Response

We clarified selection criteria in the text.

10. Statistical Analysis: The text briefly mentions the statistical tests used, such as Spearman's correlation test and Cox's Proportional Hazards Regression analysis. However, it does not provide information about the ration, procedure, and on other relevant statistical analyses, such as descriptive statistics or potential confounding variables considered in the analysis. Providing more details about the statistical methods used would improve the transparency and reproducibility of the study.

Response

We changed the “Statistics” section to describe the analyzes more clearly.

Results

11. Subgroup Analysis: The study performed subgroup analyses based on histopathological type, presence of lymph node metastasis, presence of distant metastasis, and tumor stage. While these subgroup analyses provide valuable insights, the small sample size within each subgroup may limit the statistical power and reliability of the findings.

Response

You are correct. We pointed out this in the Limitations section

12. The content of the results section is not fully aligned with the study's title and objective, and it is much broader. Therefore, instead of conducting subgroup analysis based on different factors each of them can be considered as an independent variable and their effects on the survival rate can be measured.

Response

Initially, we analyzed all factors together as independent variables. And then repeated the analysis in subgroups for more detailed analysis.

13. The statistical analysis method and the presentation of results should be fully aligned in terms of content and format. Therefore, first, descriptive statistics of demographic and clinical variables of the patients should be provided. Then, the results of the Kaplan-Meier survival analysis along with the log-rank test for significant comparisons should be presented. Finally, the results of the multivariable Cox proportional hazards analysis should be displayed in Table 3.

Response

At the beginning of the Results section, we presented descriptive statistics, demographic and clinical variables under the title of general variables. Then we gave the results of survival analysis, first univariate and then multivariate analysis results. .

14.When analyzing categorical variables such as gender or tumor stage, and etc. it is important to designate a reference group. The hazard ratio of other groups should be compared to this reference group.

Response:

We had already designated a category as a reference category when making the analysis. To clarify, we added a statement in the “Statistical Analyses” sections, indicating this issue (Categorical confounding variables [sex, tumor histologic type (squamous cell carcinoma vs adenocarcinoma), disease stage] were analyzed by considering the category with the lowest risk as the reference group). We also re-design the table 2 to show the reference categories.

15. Furthermore, in the statistical analysis, it is possible to take a step further and consider the two-year survival as a binary outcome (alive-deceased) and evaluate the predictive value of significant PET variables using ROC analysis.

This analysis allows for the assessment of sensitivity, specificity, positive and negative predictive values, and accuracy in predicting survival.

Response

As the survival is depend on many factors, mainly the stage of the disease, and as the survival is a result about time, we think that it is not appropriate just to compare dead and alive patients

Discussion

16. Lack of Subheadings: The discussion section does not have clear subheadings to separate different topics or ideas. This can make it difficult for readers to follow the flow of the discussion and locate specific information.

Response

We added subheadings to the discussion section.

17. Lack of Integration: The discussion section jumps between different topics without providing a smooth transition or integration of ideas. This can make the discussion feel disjointed and difficult to follow.

Response

We have rewritten the discussion section to make it more understandable.

2 Revision 1

4 comments · 21 Feb 2024 – 9 Mar 2024

Abtin Doroudinia Reviewer

MAJOR REVISION 21 Feb 2024

Thank you for providing the revisions.
Unfortunately, the language of your manuscript is still unclear and difficult to understand.
1- The main part of your article is the calculation of MTV and TLG. I do not see any details about how the MTV and TLG values are being calculated.
The task of calculating MTV and TLG could be very complicated. It could be either manual or automatic. You should explain in detail how the ROIs were drawn and what cutoff value was used to calculate MTV. Which software was used for your MTV and TLG calculations?
2- Another point is that, as you have stated, the calculation of TLG is based on MTV according to this equation:
TLG= MTV x SUVmean
Since SUVmean is an important player here, it should be included in your data analysis.
It is very difficult to accept your conclusion: "Higher MTV values are associated with worse survival, but higher TLG values are associated with better survival!"
One possibility would be an error in the calculations, as these 2 variables almost always move in one direction, not in opposite directions.
You have suggested in the discussion that the reason might be the SUVmean values. The values of SUVmean are easily available, and they should be provided to support your conclusion.

Referee 1 Reviewer

MINOR REVISION 24 Feb 2024

Thank you for addressing some of the previous comments appropriately in your revised manuscript. However, there are a few points that should be considered in the next round of revisions:

Abstract:
1. It is important to provide sufficient background information on the current understanding of survival prediction in lung cancer and the relevance of PET/CT-derived parameters.
2. In observational studies like yours, it is preferable to use the term 'association' instead of 'effect' since the latter implies a causal relationship typically seen in randomized controlled trials. Please revise the terminology accordingly to accurately represent the nature of your study.
3. The abstract should include more details regarding the study design, including the retrospective cohort design. Additionally, provide information on the sample size, inclusion/exclusion criteria, data collection tools, and specific statistical analyses used.
4. Methods:
a. Specify the exact version of the IBM SPSS Statistics software used for data analysis. Reporting the precise software version is necessary for
transparency and reproducibility.
b. Justify the selection of the statistical tests used, including Spearman's correlation test, the Kaplan-Meier method, and Cox's Proportional Hazards
Regression analysis. Explain how these specific tests align with the study objectives and the characteristics of the data. Providing this rationale will
enhance the validity of your statistical analysis.

I believe that addressing these points will significantly improve the clarity and quality of your manuscript. I look forward to reviewing the revised version.

Associate Editor MAJOR REVISION 9 Mar 2024

Dear EIC,
According to the reviewers, the article needs Major Revision.
Regards

Editor-in-Chief MAJOR REVISION 9 Mar 2024

Dear authors,
Your article needs Major Revision.
Regards

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Responses to the Reviewers

Reviewer 1:

Comment 1. Unfortunately, the language of your manuscript is still unclear and difficult to understand.

Response 1: The English in this document has been re-checked by at least two professional editors, both native speakers of English. For a certificate, please see:

http://www.textcheck.com/certificate/KlBcgT

Comment 2: The main part of your article is calculation of MTV and TLG. I do not see any detail about how the MTV and TLG values are being calculated.
The task of calculation of MTV and TLG could be very complicated. It could be either manual or automatic. You should explain in detail how the ROIs were drawn and what cut off value was used to calculate MTV? Which software was used for your MTV and TLG calculations?

Response 2: Information about the MTV calculation has been added. Since TLG is calculated based on MTV and SUVmean, no additional explanation about the calculation was provided.

Comment 3: The calculation of TLG is based on MTV according to this equation: TLG= MTV x SUVmean. Since SUVmean is an important player here, it should be included in your data analysis.

Response 3: We added the analyzes about the SUVmean.

Comment 4: It is very difficult to accept your conclusion claiming that: Higher MTV values are associated with worse survival, but higher TLG values are associated with better survival! One possibility would be any error in calculations, as these 2 variables almost always move in one direction, not in opposite directions.
You have discussed that the reason might be the values of SUVmean. The values of SUVmean are easily available and they should be provided to support your conclusion.

Response 4: We checked the TLG calculation procedures. We re-analyzed the effect of TLG on survival. There was no calculation error. We also added the analysis of SUVmean to the text. In the Discussion section, we have added the following section on the effect of TLG on survival, which we hope will be more descriptive:

“One of the variables affecting the TLG value is the MTV value, and there is a good correlation between them. The opposite effects of MTV and TLG on

patient survival in this study are therefore difficult to interpret. Survival was found to worsen as MTV levels increased and TLG levels decreased. The inverse relationship between these two parameters suggests a role for SUVmean, the other variable in the TLG calculation. Thus, a decrease in the TLG level with an increasing MTV implies a lower SUVmean. However, the association between the SUVmean value alone and survival was not significant. This suggests that SUVmean is heterogeneously associated with survival. According to our study, if there is no increase in the SUVmean as the MTV increases, survival will be worse. It may therefore be the case that the systemic effects of tumour cells are more important than their local activity, with negative consequences for survival. For patients with a primary tumour characterised by a high SUVmean and a small MTV, the higher local activity and fewer systemic effects of the tumour may improve survival".

Reviewer 2:

Abstract:
Comment 1. It is important to provide sufficient background information on the current understanding of survival prediction in lung cancer and the relevance of PET/CT-derived parameters.

Response 1: We added some background information.

Comment 2. In observational studies like yours, it is preferable to use the term 'association' instead of 'effect' since the latter implies a causal relationship typically seen in randomized controlled trials. Please revise the terminology accordingly to accurately represent the nature of your study.

Response 2: We revised the terminology. Thank you very much for this valuable knowledge.

Comment 3. The abstract should include more details regarding the study design, including the retrospective cohort design. Additionally, provide information on the sample size, inclusion/exclusion criteria, data collection tools, and specific statistical analyses used.

Response 3: We added information to the Abstract section.

Methods:

Comment 4a.
a. Specify the exact version of the IBM SPSS Statistics software used for data

analysis. Reporting the precise software version is necessary for transparency and reproducibility.

Response 4a: The version of the software is Version 22. It has been included.

Comment 4b. Justify the selection of the statistical tests used, including Spearman's correlation test, Kaplan-Meier method, and Cox's Proportional Hazards Regression analysis. Explain how these specific tests align with the study objectives and the characteristics of the data. Providing this rationale will enhance the validity of your statistical analysis.

Response 4b: We added information about the rationale why these methods were selected.

3 Revision 2

4 comments · 6 May 2024 – 13 May 2024

Referee 2 Reviewer

MAJOR REVISION 6 May 2024

Thank you for providing answers.
I personally need more detailed information about your raw data and statistical analysis.
I have not seen a single article consistent with your conclusion about the completely opposite effects of MTV and TLG on survival.
I have mentioned a few for your review:

1- Jin A, Lin X, Yin X, Cui Y, Ma L. Prognostic value of MTV and TLG of 18 F-FDG PET in patients with head and neck squamous cell carcinoma: A meta-analysis. Medicine (Baltimore). 2022 Sep 30;101(39):e30798. doi: 10.1097/MD.0000000000030798. PMID: 36181127; PMCID: PMC9524907.
2- Wen W, Piao Y, Xu D, Li X. Prognostic Value of MTV and TLG of 18F-FDG PET in Patients with Stage I and II Non-Small-Cell Lung Cancer: a Meta-Analysis. Contrast Media Mol Imaging. 2021 Nov 22;2021:7528971. doi: 10.1155/2021/7528971. PMID: 34887713; PMCID: PMC8629622.
3- James E. McDonald, Marcus M. Kessler, Michael W. Gardner, Amy F. Buros, James A. Ntambi, Sarah Waheed, Frits van Rhee, Maurizio Zangari, Christoph J. Heuck, Nathan Petty, Carolina Schinke, Sharmilan Thanendrarajan, Alan Mitchell, Antje Hoering, Bart Barlogie, Gareth J. Morgan, Faith E. Davies; Assessment of Total Lesion Glycolysis by 18F FDG PET/CT Significantly Improves Prognostic Value of GEP and ISS in Myeloma. Clin Cancer Res 15 April 2017; 23 (8): 1981–1987. https://doi.org/10.1158/1078-0432.CCR-16-0235

Please send some sample raw data for at least 5 patients in whom MTV and TLG have opposite effects in predicting survival, including MTV, SUVmean, and calculated TLG.
This is just for confirmation, since your conclusion in this article is unique and differs from the literature.

Good Luck.

Referee 1 Reviewer

ACCEPT 7 May 2024

I have carefully reviewed the revisions you made in response to my previous comments, and I am pleased to see that you have applied the appropriate edits to address the concerns raised. From a methodological viewpoint, I believe the manuscript now deserves publication in IJ Radiology.

Associate Editor

MAJOR REVISION 13 May 2024

Dear EIC,
According to the reviewer comments, the article needs Major Revision.
Best Regards

Editor-in-Chief MAJOR REVISION 13 May 2024

Dear authors,
Your article needs Major Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Responses to the Reviewers

Reviewer 1:

Comment 1: I have carefully reviewed the revisions you made in response to my previous comments, and I am pleased to see that you have applied the appropriate edits to address the concerns raised. From a methodology viewpoint, I believe the manuscript now deserves publication in the IJ Radiology.

Response 1: Thank you very much.

Reviewer 2:

Comment 1: Please send some sample raw data for at least 5 patients in whom effects of MTV and TLG are opposite in prediction of survival; Including MTV, SUVmean and calculated TLG.

Response 1: Below you can find a table of our database including MTV, TLG, SUVmean values and other prognostic variables. You can check the survival analysis. Mean value for MTV is 59, for TLG is 523. If you search the patients have MTV value higher than the mean but TLG value lower than the mean, you can find 6 one. Five of those patients are dead and average survival time of those patients is 10 months. Whereas, there are 30 patients have MTV values higher than the mean and TLG values also higher than the mean. The mean survival time of those patients is longer (11.3 months) and 9 of the patients are alive.

AGE	TYPE	DIAMETER	DISTANT METASTASIS	LYMPH METASTASIS	STAGE	MTV	TLG	SUVMEAN	EVENT	TIME
70		3,7	0	0	1	17,1	57,6	3,37	0	17
68		3,5	0	1	3	8,8	45,9	5,22	0	17
61	1	6,3	0	0	1	30,68	772,3	25,17	0	33
62	1	4,2	0	0	1	33,9	148,7	4,39	0	22
65	1	7	0	0	1	34,5	435	12,61	0	14
57	1	1,6	0	0	1	4	17	4,25	0	17
74	1	7,8	0	0	3	97,37	1604,6	16,48	1	16
64	1	6	0	0	3	45,4	726,3	16	1	6
79	1	6,8	0	0	3	48,3	516,2	10,69	1	4
74	1	4,2	0	0	3	12,4	103,1	8,31	1	12
60	1	4,4	0	0	3	29,6	226,8	7,66	1	11
69	1	7,1	0	0	3	87,5	800,4	9,15	1	2
58	1	4,5	0	0	3	15,2	126,1	8,3	1	2

68	1	2,7	0	1	1	3,9	43,3	11,1	0	18
77	1	2,5	0	1	1	10,7	78,4	7,33	1	8
57	1	2,5	0	1	2	8,8	44,7	5,08	0	32
70	1	4,7	0	1	2	17,68	149,3	8,44	0	11
71	1	4,5	0	1	2	32	209,8	6,56	1	14
73	1	4,5	0	1	3	35,9	314,7	8,77	1	16
64	1	6,3	0	1	3	90,6	1162,8	12,83	1	10
63	1	0	0	1	3	38,1	653,6	17,15	0	21
69	1	4,6	0	1	3	36,3	316,3	8,71	1	5
73	1	5,8	0	1	3	67,1	1047,9	15,62	1	2
68	1	4,8	0	1	3	44,6	572	12,83	1	12
77	1	7	0	1	3	103	915,9	8,89	0	13
52	1	0	0	1	3	13	132,9	10,22	0	12
54	1	4,5	0	1	3	153	1350,8	8,83	0	12
55	1	3,9	0	1	3	25,6	251,5	9,82	0	24
53	1	4,4	0	1	3	32,4	304,8	9,41	0	22
77	1	3,2	0	1	3	13,7	72,7	5,31	0	19
63	1	6,5	0	1	3	42,4	184,7	4,36	0	27
69	1	5,6	0	1	3	154	2274,5	14,77	1	1
79	1	3,6	0	1	3	34,5	138	4	0	29
67	1	8,4	0	1	3	37,4	641,2	17,14	0	10
80	1	6,1	0	1	3	30,1	707,7	23,51	0	22
60	1	9	0	1	3	80	552	6,9	1	17
54	1	3,6	0	1	3	12,7	86,7	6,83	1	0,5
50	1	6,6	0	1	3	60,1	487,8	8,12	0	18
59	1	6,4	0	1	3	58,5	710	12,14	1	10
60	1	4,3	0	1	3	21	415,7	19,8	0	21
76	1	7,3	0	1	3	32,2	295,7	9,18	1	4
57	1	4	0	1	3	19,7	173,7	8,82	1	6
71	1	4,4	1	1	4	19,7	304	15,43	1	13
49	1	10,3	1	1	4	117	1559	13,33	1	8

							,8			
63	1	6,1	1	1	4	19,8	271,2	13,7	0	20
50	1	8,08	1	1	4	1,5	5,6	3,73	1	1
62	1	0	1		4	99,4	1594,5	16,04	1	7
44	1	4,8	1	0	4	30,5	560,7	18,38	0	18
68	1	6,4	1	0	4	52,87	565,6	10,7	1	3
55	1	5,1	1	0	4	15,9	119,8	7,53	1	4
63	1	8,6	1	1	4	91,3	1228,9	13,46	1	0,5
7	1	6,6	1	1	4	49,7	359,3	7,23	0	12
62	1	0	1	1	4	11,9	21,6	1,82	1	5
71	1	7	1	1	4	207	1552	7,5	1	1,5
61	1	11,2	1	1	4	240	2117	8,82	0	23
55	1	5	1	1	4	25,4	180,2	7,09	1	12
57	1	8,5	1	1	4	319	2276	7,13	1	13
85	1	0	1	1	4	63	984,2	15,62	1	5
70	1	4,3	1	1	4	16,3	124,3	7,63	1	14
62	1	8	1	1	4	111	1055	9,5	1	1
68	1	8,8	1	1	4	118	1113	9,43	1	9
68	2	2,4	0	0	1	1,69	15	8,88	1	34
48	2	1	0	0	1	2,5	3,9	1,56	0	29
59	2	3,8	0	0	1	17,4	37,1	2,13	0	13
63	2	1,6	0	0	1	2,5	4,3	1,72	0	18
65	2	1,6	0	0	1	3,3	11,8	3,58	0	19
51	2	3	0	0	3	6,6	45,6	6,91	0	11
69	2	8,1	0	0	3	120	1165,2	9,71	0	13
55	2	2,7	0	0	3	26,9	150,6	5,6	0	13
54	2	6,7	0	0	3	60,7	648,6	10,69	0	26
55	2	9,1	0	0	3	163	1283	7,87	0	11
52	2	0	1	0	4	33,2	264	7,95	0	17
49	2	3,6	0	1	1	11,5	71,8	6,24	0	14
60	2	5	0	1	2	37,1	406,1	10,95	0	12
72	2	6	0	1	3	31,3	234,8	7,5	1	7
67	2	6,5	0	1	3	51,7	443,7	8,58	0	11
70	2	6,8	0	1	3	27,7	728,	26,29	0	20

							2			
62	2	4,3	0	1	3	29,3	206,3	7,04	0	12
64	2	5,4	0	1	3	46	301,9	6,56	0	27
67	2	6,1	0	1	3	36,5	510	13,97	1	18
56	2	3,7	0	1	3	17,8	209,4	11,76	0	18
71	2	16,8	0	1	3	23,3	260,2	11,17	0	12
74	2	9,8	0	1	3	196	2621,3	13,37	0	12
73	2	2,4	0	1	3	7,28	13,8	1,9	0	20
73	2	4,4	0	1	3	15	202	13,47	1	5
57	2	4,5	0	1	3	35,2	202,3	5,75	1	17
74	2	6,6	0	1	3	139	1015,3	7,3	1	5
60	2	6,6	0	1	3	49,5	501,9	10,14	0	10
66	2	7,2	0	1	3	25,1	314,9	12,55	1	7
58	2	6,5	0	1	3	64,9	948,8	14,62	0	11
68	2	3	0	1	3	14	97,7	6,98	0	13
74	2	6,9	0	1	3	63,4	709	11,18	1	9
45	2	4,8	1	1	4	29,3	143	4,88	1	11
75	2	1,7	1	1	4	6,76	51,4	7,6	1	7
59	2	7,1	1	0	4	111	853,6	7,69	1	6
36	2	8	1	1	4	117	464,9	3,97	1	6
76	2	3,9	1	1	4	41,2	243,1	5,9	1	1
31	2	7	1	1	4	78	584,2	7,49	0	24
77	2	3,6	1	1	4	8,5	46,5	5,47	1	2
58	2	6,5	1	1	4	148	1341,2	9,06	1	11
63	2	1,6	1	1	4	4	26,3	6,58	1	6
62	2	1,8	1	1	4	86,4	459,6	5,32	1	4
50	2	4,8	1	1	4	24,2	273	11,28	0	19
59	2	6,6	1	1	4	110	604	5,49	1	1
57	2	6,9	1	1	4	59,7	714	11,96	1	5
59	3	3,61	0	0	2	14,5	87,4	6,03	0	14
64	3	5	0	1	1	15,3	135,5	8,86	0	26
82	3	4,4	0	1	3	32,4	268,8	8,3	1	4

52	3	7,7	0	1	3	31,4	192	6,11	1	15
67	3	6,8	0	1	3	56,9	789,1	13,87	1	12
73	3	4,95	0	1	3	40,3	325,3	8,07	1	2
60	3	5,5	1	1	4	46,6	339	7,27	0	13
32	3	4,3	1		4	18,1	95	5,25	0	17
63	3	10	1	1	4	258	2405	9,32	1	1
77	3	7,8	1	1	4	26,1	324,6	12,44	1	1
49	3	3,3	1	1	4	9,3	69,9	7,52	1	4
54	3	7,5	1	1	4	73,8	391,6	5,31	1	1
53	3	11,3	1	1	4	560	3593,6	6,42	1	6
72	3	7	1	1	4	40,3	412,7	10,24	1	9
62	3	7,8	1	1	4	30,3	114,4	3,78	1	0,5
85	3	8,2	1	1	4	62	792	12,77	1	2
57	3	5,7	1	1	4	17,5	32,6	1,86	1	0,5
67	3	6,2	1	1	4	10,5	101,9	9,7	1	1
70	3	9,3	1	1	4	40,2	654,5	16,28	1	1
49	3	9,9	1	1	4	161	1121	6,96	1	15
51	3	6,7	1	1	4	49,7	379,1	7,63	1	4
48	3	3,6	1	1	4	15,6	157,5	10,1	1	4
57	3	3,1	1	1	4	6,1	23,9	3,92	1	8
60	3	3,5	1	1	4	15	218,2	14,55	1	21
69	3	6,3	1	1	4	554	446	0,81	1	0,5
58	3	8,1	1	1	4	78,9	325,4	4,12	1	0,5
45	3	4	1	1	4	4,1	15,7	3,83	1	13

4 Revision 3

3 comments · 19 May 2024 – 27 May 2024

Abtin Doroudinia Reviewer

ACCEPT 19 May 2024

Thank you for providing revisions and complementary raw data for my review.
Although it is still unusual to accept the inverse correlation of MTV and TLG with survival in some lung cancer patients, I think this article in its current form can at least introduce a topic for discussion in the literature and receive comments from researchers who work in this area.

Good Luck

Associate Editor

ACCEPT 25 May 2024

Dear EIC,
According to the reviewers, the article is acceptable for publication.
Best Regards

Editor-in-Chief

MINOR REVISION 27 May 2024

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

Thank you for your prompt review of our work, entitled ‘ The effect of PET/CT variables on the prediction of survival in lung cancer’ ; Manuscript ID: 139822. We also revised the text in the light of your valuable suggestions and contributions. All changes are highlighted in the revised manuscript.

Thank you in advance for your efforts on this revised manuscript.

Sincerely,

Nurdan Şimşek Veske

Corresponding Author

Responses to the Reviewers

Reviewer1:

Thank you for providing revisions and complementary raw data for my review. Although it is still unusual to accept the inverse correlation of MTV and TLG with survival in some lung cancer patients, I think this article in current shape can add at least an area of discussion in the literature and receive comments from related research persons who work in this area.

Good luck

Response 1: Thank you very much.

Reviewer 2:

This paper is suitable for publication in IJR.

Response 1: Thank you very much.

5 Revision 4

1 comment · 1 Jun 2024

Editor-in-Chief

ACCEPT 1 Jun 2024

Dear authors,
Your article is acceptable for publication in IJR.
Regards