Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-457

Response to Reviewer A

I read with interest this paper and I would congratulate the authors for the quality and the amount of the harvested radiological and pathological data. The major conclusions of the paper were: upstaging was extremely rare in GGO patients and lepidic predominant adenocarcinoma (LPA); some GGO patients have also invasive pathological pattern; strong correlation between pathological invasive size and radiological solid size; recurrence-free survival was better in pure GGO patients and i LPA; GGO pattern at CT-scan is a favorable factor. These are remarkable findings but are not completely new and I think that similar results have been just reported in literature. Moreover, I suggest some modification to improve the overall paper quality:

Comment 1: the conclusions are not completely clear and I suggest re-thinking and re-write them focusing on the major findings of the study such as the better recurrence free survival for GGO patients and for lepidic predominant adenocarcinoma;

Response 1: Thanks for your kind suggestion. We have modified the text as "*Among T1 invasive lung adenocarcinoma, GGO ratio showed independent prognostic value for RFS, regardless of RRS. Meanwhile, lepidic ratio was not an independent RFS factor. GGO component rather than lepidic component should be considered as an additional T descriptor.* "
Changes in the text: Marked version, Page 3, Line 57-60; Page 14, Line 335-338

Comment 2: I suggest clarifying the study objective focusing on the recurrence-free survival and not on "generic" survival;

Response 2: Thanks for your kind suggestion. In **Abstract-Method**, we mentioned "*Impacts of these pathological and radiological T descriptors on recurrence-free survival (RFS) were comparatively analyzed.*"
Following your suggestion, we modified the last sentence in **Introduction** as "*To adequately address these concerns and controversies, we comprehensively evaluated the correlations between pathological and radiological T descriptors in invasive lung adenocarcinoma and analyzed the prognostic significance of these T descriptors (lepidic component, GGO component, PIS and RSS) on recurrence-free survival (RFS).*"
Changes in the text: Marked version, Page 6, Line 106-110

Comment 3: I suggest including a more concise inclusion and exclusion criteria to improve the readability of the paragraph methods;

Response 3: Thanks for your kind suggestion. We apologize for inconvenience in

reading. We have revised this part as "*Patients who received neoadjuvant chemotherapy, patients with pathologically diagnosed adenocarcinoma in situ, minimally invasive adenocarcinoma or adenocarcinoma with mucinous component, patients with previous cancer history or multiple synchronous lung nodules were excluded.*"
Changes in the text: Marked version, Page 7, Line 116-120

Comment 4: how was cancer recurrence demonstrated? only imaging or cite-histologically. It should be defined into methods
Response 4: Thanks for your great comment. We have added the details about recurrence detection in **Follow-up Strategy** as "*At each follow-up, we routinely conducted chest CT, brain CT or magnetic resonance imaging, bone scanning, and ultrasonography of the abdominal and supraclavicular regions to detect any evidence of local or distant recurrence.*"
Changes in the text: Marked version, Page 8, Line 165-168

Comment 5: what was the role of FGD-PET-CT scan in this study? I think PET-CT scan is a very important and essential tool in clinical staging, but in your paper there is no mention of PET-CT. If PET-CT was not used in the study, it is a strong limitation and should be discussed in the discussion paragraph
Response 5: Thanks for your great comment. We agree that this is an important issue. However, PET-CT is rarely performed because the expensive cost is not covered by fundamental medical insurance in China. It is a limitation that we lack the data of PET-CT. We have added discussion about this condition as "*Besides, PET-CT is rarely performed because the expensive cost is not covered by fundamental medical insurance in China. Another limitation is the lack of data of PET-CT.*"
Changes in the text: Marked version, Page 14, Line 326-328

Comment 6: log rank test is used to compare the survival curves and should clearly defined in methods
Response 6: Thanks for your great comment. We have modified the text in **Statistical Analysis** as "*RFS was estimated by Kaplan–Meier method and log-rank test is used to compare the survival curves.*"
Changes in the text: Marked version, Page 9, Line 178-180

Comment 7: the word varied is not good. I suggest using different (P5L174)
Response 7: Thanks for your great comment. We have revised "varied" into "different" and also modified the legend of **Supplementary Table 1**.
Changes in the text: Marked version, Page 10, Line 206

Comment 8: the subgroup division between lepidic+GGO+, lepidic+GGO- and so on should be defined in the paragraph methods
Response 8: Thanks for your great suggestion. We clarified the definition in the first paragraph **Results-Comparative Analysis on the Prognostic Significance of Pathological and Radiological Features** as "*Patients were divided into "lepidic+*

GGO+", "lepidic- GGO+", "lepidic+ GGO-" and "lepidic- GGO-" subcategories (+: presence, -: absence)." We believe it is clearer for reading when the results is showing right behind the definition. It is our pleasure to further modify if needed.
Changes in the text: Marked version, Page 10, Line 219-221
Besides,We have added all the sub-groups definition in **Supplementary Table 4. The scheme of all the sub-groups**
"Lepidic-present ADC: Invasive adenocarcinomas with lepidic component
Lepidic-absent ADC: Invasive adenocarcinomas without lepidic component
Lepidic+ GGO+: Invasive adenocarcinomas with both lepidic and ground-glass opacity component
Lepidic- GGO+: Invasive adenocarcinomas with ground-glass opacity component and without lepidic component
Lepidic+ GGO-: Invasive adenocarcinomas with lepidic component and without ground-glass opacity component
Lepidic- GGO-: Invasive adenocarcinomas without neither lepidic and ground-glass opacity component
pT1(a,b,c)+: Pathological T-stage1(a,b,c) invasive adenocarcinomas with lepidic component
pT1(a,b,c)-: Pathological T-stage1(a,b,c) invasive adenocarcinomas without lepidic component
cT1(a,b,c)+: Clinical T-stage1(a,b,c) invasive adenocarcinomas with ground-glass opacity component
cT1(a,b,c)+: Clinical T-stage1(a,b,c) invasive adenocarcinomas without ground-glass opacity component"

Comment 9: I suggest dividing the clinical and pathological stage I into its subdivision IA and IB due to their survival differences.
Response 9: Thanks for your great suggestion. In our article, we mentioned this part in **Discussion** as "*We found that RFS of cT1b GGO-present nodule was comparable to cT1a solid nodule and better than cT1b solid nodule, meanwhile, cT1c GGO-present nodule had similar survival to cT1b solid nodule and favorable prognosis than cT1c solid nodule. Hence, we recommend that cT1b and cT1c adenocarcinoma with GGO component should be classified into cT1a and cT1b, respectively.*"
Based on the results showing in **Figure 4**, we have added the discussion about subdivision of pathological stage I following your suggestion as "*Similarly, pT1b and pT1c adenocarcinoma with lepidic component could be considered to be classified into pT1a and pT1b, respectively.*"
Changes in the text: Marked version, Page 13, Line 312-318

Comment 10: i think that too many variables are present in the multivariable model. Please revise this with the help of a statistician
Response 10: Thanks for your kind advice. We have re-checked the multivariate survival analysis model with an experienced statistician of Department of Statistic from Fudan University Shanghai Cancer Center (Zezhou Wang). Dr wang and authors

believed all variables included in univariate and multivariate survival analysis had potential impacts on RFS.
Besides, we separately tested pathological factors and radiological factors in the multivariate analysis. That maybe the reason there were many variables presented in **Table 2&3**. It is hard for us to balance conciseness and comprehensive presentation. We hope you can understand we choose to provide a comprehensive presentation as this is the main result of our study.

Comment 11: I do not understand the table 3 because the authors included lymphvascular invasion (LVI) and N1-N2 clinical stage as variables that have an association with survival in stage I ADC. How did the authors assess the LVI in the clinical setting? How did the authors assess N1 or N2 metastatis if they did not do PET-CT-scan or EBUS? Please clarify this issue.
Response 11: Thanks for your kind comment. In this study, LVI and lymph node metastasis were confirmed by postoperative pathological slides. N-stage is pathological stage.
We have added explanation in **Methods-Histopathological Assessment** as "LVI and lymph node metastasis were confirmed by postoperative pathological slides."
Changes in the text: Marked version, Page 8, Line 159-160

Thank you again for your careful review, constructive comments, and valuable suggestions. We hope the answers above address your concerns and it is our pleasure to answer further questions if needed.

Reviewer B

This paper investigates the relationship between pathological and radiological features in T1 invasive lung adenocarcinoma, focusing on the lepidic component for pathological assessment and the ground-glass opacity (GGO) component for radiological assessment. The authors observe that the clinical T-stage is often downstaged compared to the pathological T-stage and identify a weak correlation between pathological invasive size (PIS) and radiological solid size (RSS). Importantly, the study suggests that GGO is a more effective predictor of recurrence-free survival (RFS) than the lepidic component.

Issues to Address Before Publication:
Comment 1: The paper concludes that the radiological GGO component is a superior prognostic indicator compared to the pathological lepidic component. However, the scientific rationale for this conclusion appears insufficient. The authors should elaborate on the methodologies used for radiological evaluation, including the type of CT scan and the thickness of the images evaluated.
Response 1: Thanks for your kind comment. We have added the information of radiological evaluation in **Methods-Radiological Evaluation** as "*All CT scans were*

conducted with a 64- or 40-slice multidetector scanner (Siemens Somatom Sensation, Berlin, Germany). The scanning parameters were as follows: pitch, 1.2; section thickness and interval, 5.0 and 5.0 mm, respectively; reconstruction section width and interval, 1.0 and 1.0 mm, respectively; field of view, 375 mm; voltage, 120 kV; and electric charge, 270 mAs."
Changes in the text: Marked version, Page 7, Line 131-135

Comment 2: The Discussion section should include a detailed explanation of the potential mechanisms underlying why the radiological assessment of the GGO component is more prognostic than the pathological assessment of the lepidic component. Clinical implications of these findings should also be discussed.
Response 2: Thanks for your kind comment. We believe it is an important point of this study. We have modified paragraphs about this point in **Discussion** to clarified the potential mechanisms and clinical implications of these findings:
"*Nearly half APA and PPA presenting GGO component indicated that GGO component does not entirely correspond to lepidic component, the superior survival of lepidic-absent invasive adenocarcinoma with GGO component probably blunts the favorable prognostic value of lepidic component. These facts indicate a possibility that the malignancy of invasive histological subtypes featured as GGO is not as severe as those featured as solid. And it might be the reason why the radiological assessment of the GGO component was more valuable for RFS than the pathological assessment of the lepidic component. Extensive resection and timely postoperative follow-up are more needed for adenocarcinoma without GGO component.*"
Changes in the text: Marked version, Page 13, Line 302-310

Comment 3: Table 1 presents a comparison between three groups based on the pathological assessment of the lepidic component. Given the emphasis on the GGO component in this study, an additional table comparing three groups based on the radiological assessment of the GGO component would be beneficial.
Response 3: Thanks for your kind comment. As we mentioned in **Introduction** "*Studies have indicated lepidic component tended to be corresponded with GGO component. However, the latest study demonstrated lepidic ratio was weakly correlated with GGO ratio.....Recently, studies have demonstrated that the presence of GGO component was an independent prognostic factor, regardless of RSS.*" The main unrevealed issues are: A. Is lepidic component corresponded with GGO component? B. Is the presence of lepedic component was an independent prognostic factor, regardless of PIS?
With these issues, we preferred to pay more attention to lepidic component and divided patients into three groups based on the pathological assessment of the lepidic component. On the other hand, we hope you can understand that there were so many variables, tables and supplementary tables, we found it was difficult to add another baseline table. It is our pleasure to further modify if needed.

Thank you again for your careful review, constructive comments, and valuable suggestions. We hope the answers above address your concerns and it is our pleasure

to answer further questions if needed.

Reviewer C

I read with interest the manuscript by Zelin Ma and colleagues on the role of lepidic component and GGO component in radical resected lung adenocarcinoma.
This article is very innovative and interesting, and it could be part of a very interesting discussion on the main clinical, radiological and pathological features of the adenocarcinoma besides the genetic mutations
(see PMID: 35988096, PMID: 33169397).
There are just some minor issues and concerns.

Comment 1: Introduction has too many single sentences that are poorly linked together. Please provide a more harmonic introduction on the role of RSS and PIS. Moreover, introduction is set as a discussion by reporting the opinion of different authors.
Response 1: Thanks for your kind comment. We apologized for causing inconvenience in reading. We have modified the text of **Introduction** to make it clear and harmonic. It is our pleasure to further modify if needed.
Changes in the text: Marked version, Page 6, Line 83-110

Comment 2: In Histopathological assessment author should define predominant pattern (more than 50% or other definition), moreover how did they evaluate lesions with predominant high-grade pattern (solid or micropapillary) with just a smaller part of lepidic pattern. Since High pattern (primary or secondary as reported by several authors: PMID: 35988096, PMID: 33169397) may affect prognosis despite the lepidic part, have the author evaluated the opportunity of diving the entire cohort according to the main pattern or by excluding patients with high-grade pattern?
Response 2: Thanks for your kind comments. Here are our answers:
A. In Histopathological assessment author should define predominant pattern (more than 50% or other definition).
Answer: We added the definition in **Methods-Histopathological Assessment** as "*Predominant pattern was defined when a type of histological component was over 50%.*"
B. how did they evaluate lesions with predominant high-grade pattern (solid or micropapillary) with just a smaller part of lepidic pattern.
Answer: Pathological invasive size (PIS) was defined as the maximum diameter of invasive component.
C. Since High pattern may affect prognosis despite the lepidic part, have the author evaluated the opportunity of diving the entire cohort according to the main pattern or by excluding patients with high-grade pattern?
Answer: In **Table 1**, the results showed only 3(0.6%) MPA had lepidic component and no SPA had lepidic component. These findings indicated lepidic rarely presented in high-grade pattern, so we believe the rare lepidic component will not significantly affect

the prognosis of high-grade adenocarcinoma.
Changes in the text: Marked version, Page 8, Line 148-149

Comment 3: A scheme of all the sub-groups created for the "Comparative Analysis on the Prognostic Significance of Pathological and Radiological Features" could improve the readability of the text.
Response 3: Thanks for your kind comment. We agree that the numbers of sub-groups may affect the readability. We have added all the sub-groups definition in **Supplementary Table 4. The scheme of all the sub-groups**
"Lepidic-present ADC: Invasive adenocarcinomas with lepidic component
Lepidic-absent ADC: Invasive adenocarcinomas without lepidic component
Lepidic+ GGO+: Invasive adenocarcinomas with both lepidic and ground-glass opacity component
Lepidic- GGO+: Invasive adenocarcinomas with ground-glass opacity component and without lepidic component
Lepidic+ GGO-: Invasive adenocarcinomas with lepidic component and without ground-glass opacity component
Lepidic- GGO-: Invasive adenocarcinomas without neither lepidic and ground-glass opacity component
pT1(a,b,c)+: Pathological T-stage1(a,b,c) invasive adenocarcinomas with lepidic component
pT1(a,b,c)-: Pathological T-stage1(a,b,c) invasive adenocarcinomas without lepidic component
cT1(a,b,c)+: Clinical T-stage1(a,b,c) invasive adenocarcinomas with ground-glass opacity component
cT1(a,b,c)+: Clinical T-stage1(a,b,c) invasive adenocarcinomas without ground-glass opacity component"

Comment 4: Conclusion should include limitation and strengths of the manuscript.
Response 4: Thanks for your kind comment. We have modified the text about the study limitations as "*The limitations are that this is a single-center retrospective research and 41.9 months is a relatively short mean follow-up time. Besides, PET-CT is rarely performed because the expensive cost is not covered by fundamental medical insurance in China. Another limitation is the lack of data of PET-CT. Studies on pathological and radiological T descriptors are warranted to offer more evidence for future T classification.*"
Changes in the text: Marked version, Page 14, Line 325-330

Thank you again for your careful review, constructive comments, and valuable suggestions. We hope the answers above address your concerns and it is our pleasure to answer further questions if needed.

Reviewer D

I can find some interesting data that can be used as a reference in clinical practice in their results.
To improve persuasiveness and clarity of the data, I have made some suggestions and modifications.

Major comment:

Comment 1: Most of the data highlighted by the authors were about T1 disease. There were few important findings about T2-4 disease. So, I propose that the author should restrict the study patients to T1 disease only. It will make their results more clear, simple and easier to understand, especially for Figure 1 and Table 1.
Response 1: Thanks for your kind comment. We agree that our main result is about T1 lung adenocarcinoma. However, at the beginning of the study design, we focused T descriptors among all T-stages. In this study, we tried figure out the correlations of four T descriptors (lepidic component, ground-glass opacity component, pathological invasive size and radiological solid size) and challenged the eighth classification excluding lepidic and ground-glass opacity component from T classification. Some important results are appropriate for all T-stages (such as *The correlation between pathological invasive size (PIS) and radiological solid size in solid nodule was stronger than that in part-solid nodule* and *Some pathological invasive component except solid component featured as GGO*). We hope you can understand we prefer to provide a comprehensive presentation of our results.

Comment 2: The authors concluded GGO component rather than lepidic component should be considered as T descriptor.
However, the evidence for this conclusions is difficult to understand.
As shown in Figure 3A, the presence of lepidic component would also have an impact on prognosis in the same T descriptor, as would the GGO component.
Response 2: Thanks for your kind comment. Indeed, the presence of lepidic component would also have an impact on prognosis in the same T descriptor. Based on these findings, we decided to perform multivariate Cox Regression analysis, aiming to figure out the independent prognostic value of lepidic component, ground-glass opacity component, pathological invasive size and radiological solid size for RFS. As results, GGO ratio was an independent prognostic factor for RFS in T1 invasive lung adenocarcinoma, whereas lepidic ratio was not. Thus, we recommended GGO component rather than lepidic component should be considered as T descriptor.

Minor comment:
Comment 3: What is a definition of lepidic ratio? Does it mean the percentage area of lepidic component to the total area (i.e. two dimension)?

However, GGO ratio was measured in one dimension on CT findings. Why was their correlation linear?

Response 3: Thanks for your great comments. We have added the definition of lepidic ratio in **Methods-Histopathological Assessment** as "*Lepidic ratio was defined as the percentage area of lepidic component to the total area.*" Indeed, the best way to define lepidic and GGO ratio is measuring in three dimensions. But advanced techniques are demanded. In this study, we chose the acknowledged methods measuring lepidic and GGO ratio referring to latest study (J Thorac Oncol. 2022 Jan;17(1):67-75; PMID: 34634451). We agreed with you that using linear correlation analysis on lepidic and GGO ratio is not appropriate. We have deleted Supplementary Figure 2A and related sentences in **Results**.
Changes in the text: Marked version, Page 8, Line 153-154

Comment 4: Figure 1B can be replaced with Supple Figure 2A.
Response 4: Thanks for your great comment. As our answer of **Comment 3**, We agreed with you that using linear correlation analysis on lepidic and GGO ratio is not appropriate and we have deleted Supplementary Figure 2A.

Comment 5: Supple Figure 2 is important data and should be shown in main figures. The author should add the case numbers in each figures. Because they are different from figure to figure.
Response 5: Thanks for your great comment. We have revised Supple Figure 2 into Figure 2 and added the case numbers in each figures.

Comment 6: All the tables are really hard to read with small letters and breaks.
Response 6: Thanks for your great comment. We apologize for inconvenience in reading. We have modified the letters and breaks to make it clear.

Comment 7: Line 46 and 292, RRS should be RSS.
Response 7: Thanks for your great comment. We apologize for this mistake. We have modified as you advised.

Comment 8: Line 171, the author should present specific ratios and statistical comparisons about downstaging and upstaging.
Response 7: Thanks for your great comment. We have presented the numbers and ratios in **Introduction, Results** and **Figure 1**.
Changes in the text: Marked version, Page 3, Line 46-47; Page 10, Line 203

Comment 9: Line 176-178, interpretations from the results should be described in discussion.
Response 9: Thanks for your great comment. We have delete the sentence in **Results**. We have modified paragraphs about this point in **Discussion** as you advised:
"*Nearly half APA and PPA presenting GGO component indicated that GGO component does not entirely correspond to lepidic component, the superior survival of lepidic-absent invasive adenocarcinoma with GGO component probably blunts the favorable prognostic value of lepidic component. These facts indicate a possibility that the*

malignancy of invasive histological subtypes featured as GGO is not as severe as those featured as solid. And it might be the reason why the radiological assessment of the GGO component was more valuable for RFS than the pathological assessment of the lepidic component."
Changes in the text: Marked version, Page 3, Line 302-309

Comment 10: Line 285-288, poor description about the study limitations.
Response 10: Thanks for your great comment. We have modified the text about the study limitations as "*The limitations are that this is a single-center retrospective research and 41.9 months is a relatively short mean follow-up time. Besides, PET-CT is rarely performed because the expensive cost is not covered by fundamental medical insurance in China. Another limitation is the lack of data of PET-CT. Studies on pathological and radiological T descriptors are warranted to offer more evidence for future T classification.*"
Changes in the text: Marked version, Page 14, Line 325-330

Comment 11: The author should describe that more carefully. For example, the difficulty in measurement of GGO rate and RFS evaluation, instead of OS.
Response 11: Thanks for your great comments.
We have added the information of radiological evaluation in **Methods-Radiological Evaluation** as "*All CT scans were conducted with a 64- or 40-slice multidetector scanner (Siemens Somatom Sensation, Berlin, Germany). The scanning parameters were as follows: pitch, 1.2; section thickness and interval, 5.0 and 5.0 mm, respectively; reconstruction section width and interval, 1.0 and 1.0 mm, respectively; field of view, 375 mm; voltage, 120 kV; and electric charge, 270 mAs.*"
We have added the details about in **Follow-up Strategy** as "*Patients were followed up every 6 months for the first 3 years after the operation, every 8 months for the next 2 years, and every 12 months thereafter. At each follow-up, we routinely conducted chest CT, brain CT or magnetic resonance imaging, bone scanning, and ultrasonography of the abdominal and supraclavicular regions to detect any evidence of local or distant recurrence. Survival information were recorded from the follow-up visits and supplemented by telephone. The last telephone follow-up for all patients in this cohort was performed at August 2022. RFS was defined as the time from the date of surgery to the date of first recurrence and death or last negative follow-up.*"
Changes in the text: Marked version, Page 7, Line 131-135; Page 8, Line 164-172

Thank you again for your careful review, constructive comments, and valuable suggestions. We hope the answers above address your concerns and it is our pleasure to answer further questions if needed.