Peer Review File

Reviewer A

The article entitled "Use Quantitative Parameters in Spectral CT for the Differential Diagnosis of Metastatic Mediastinal Lymph Nodes in Lung Cancer Patients" the authors have explored that, using quantitative parameters in spectral CT for diagnosing mediastinal lymph node metastases in patients with lung cancer.

1. In the introduction section, page number 3, line number 14, the authors stated "PET-CT can also be used to diagnose mediastinal LN metastasis of lung cancer, but it is expensive, and the radiation dose received by patients is high". However, reference should have been given.

Reply: PET/CT is currently considered the most reliable functional imaging technique, but it is more expensive and less available than CT. We added reference as advised.

Changes in the text: We have modified our text as advised (see Page 5, line 14-15).

2. In introduction section, page number 3, line number 16 the authors stated "Studies found that the false positive rate of 30%". However, in reference number 6, the specificity of FDG PET-CT in detecting lymph node was

found to be 96%, the accuracy was 88%, PPV 71%, and NPV 90%. In reference number 7, only PET was evaluated, whereas the authors wrote PET / CT. It should be known that PET and PET / CT are different image modalities. However, they could benefit from more up-to-date studies of FDG PET / CT on mediastinal lymph node assessment in patients with lung cancer.

Reply: We have cited more references, including meta-analysis paper which is more comprehensive.

Changes in the text: We have modified our text as advised (see Page 5, line 15-22).

3. In method section page number 4 line number 5, the authors stated "Our inclusion criteria is that the short diameter of lymph nodes must be larger than 5mm". However, they did not specify how they determined the 5 mm threshold value. No reference is given.

Reply: Because it is technically challenging to position the circular ROI in these small lymph nodes which less than 5 mm. The smaller the lesion, the greater the measurement error. So the short diameter of lymph nodes we have chosen must larger than 5 mm. We also added some references in the text. We have expanded the details in the main text about why we determined 5 mm as threshold value in the selection of lymph nodes.

Changes in the text: We have modified our text as advised.(see Page 7, line 11-13). And we also proofreaded the manuscript and corrected some mistakes.

4. In method section page number five, line number 8, the authors stated that "In this process, we made a one-to-one match between each lymph node on the CT and the pathological confirmation and discarded the LNs that could be matched with pathology". In this retrospective study, how could the authors be sure that the lymph nodes indicated on CT correspond to the lymph node in the pathological specimen? This is an important limitation.

Reply: Mediastinal LNs were divided strictly according to the map of the 2009 International Association for the Study of Lung Cancer (IASLC map). The selection of lymph nodes was according with the surgical record and histological result. Only if those lymph nodes had clear pathological results and accurate location, they can be chosen and recorded.

Changes in the text: We have modified our text as advised (see Page 9, line 13-14).

Reviewer B

In their manuscript, the authors aimed to assess the differences in parameters of spectral CT in metastatic and non-metastatic lymph nodes from lung cancer.

The authors found differences in dimension (short axis) but also in several parameters of material decomposition in dual-energy CT. In particular, the authors found significant differences in iodine density (normalized and not), water density, and spectral curves in metastatic and non-metastatic lymph nodes.

Some issues need to be addressed:

1. The authors use a two-material decomposition algorithm to analyze the dual-energy datasets of a rapid switching scanner (GE) using the couple iodine/water as basis-materials. The authors found some differences in water concentration. Even if intriguing, this result may not be reproducible since other platforms do no use the water as basis-material.

Reply: Iodine/water is the most common material decomposition algorithm in spectral CT in the assessment of lung cancer patients. Actually, we focus more on iodine content rather than water because iodine content can reflect micro-vessels and perfusion of the lesion.

2. The authors found differences in slopes of spectral curves. These slopes were calculated with an equation provided by the authors, without any reference. Please explain, clarify, and add a reference.

Reply: The slope of spectral curve was calculated, with 40 and 100 keV serving as the reference points, by dividing the difference in CT value by the difference in energy between the two points. These slopes were calculated by referring to references and we have added reference in the text.

Changes in the text: We have modified our text as advised (see Page 8, line 21-22 and Page 9, line 1-3).

3. The authors found significant differences among the spectral parameters and lymph node dimensions, with relevant results in the AUC parameters. However, the statistical analysis is poor since a multivariate analysis is not performed.

Reply: All the parameters that had significant differences, including spectral and traditional CT parameters, were combined analyzed statistically. And we found that the diagnosis value of spectral parameters combined with traditional CT parameters improved, better than any of them.

Changes in the text: We have modified our text as advised in methods (see Page 10, line 3-4) and results(see Page 12 , line 5-7).

4. Terminology. The overall quality of the manuscript is acceptable. However, there are some conceptual issues. The dual-energy CT does not analyze a chemical concentration of a basis-material but its relative density, thus the term "density" should be preferred over "concentration".

Reply: Dual-energy CT applications are based on two distinct capabilities: material differentiation and material identification and quantification. Material identification and quantification mean accurate assessment of the presence and amount of, for example, iodine in a target lesion. The iodine content, is calculated by detection of the presence of iodine itself and quantification of iodine in each voxel, is not the accurate chemical concentration. The word "concentration" we used is cited from references.

5. Please, double-check also written English.

Reply: We wrote English in double-check.

6. References. Some references are not up-to-date, in particular on the Dual-Energy technique.

Reply: We added some references.

Changes in the text: We have modified our text as advised (see Page 6, line 6).

7. Tables and figures. Some of the tables are cut. For an adequate evaluation, they must be complete.

Reply: Tables were complete in the original .docx paper, some of them were cut probably due to format. We have adjusted the tables.

Reviewer C

General comments

This study aims to determine the effectiveness of quantitative parameters in spectral CT for assessing mediastinal lymph node metastases in lung cancer patients.

1. The analysis based on spectral parameters is no better than the decision based on the short diameter of the lymph nodes, which indicates that the spectral CT does not offer any additional benefit that conventional CT equipment can provide.

Reply: We aim not to compare the quality of spectral CT and traditional CT in evaluating lymph node metastasis of lung cancer, but to explore using quantitative parameters in spectral CT for diagnosing mediastinal lymph node metastases. The analysis based on spectral parameters is no better than the decision based on the short diameter of the lymph nodes,

but combined diagnosis value improved, with combined AUC 0.877(95%

CI: 0.829-0.952).

Changes in the text: We have modified our text as advised in methods (see

Page 10, line 3-4) and results (see Page 12, line 5-7).

2. There were statistically significant differences in some spectral CT

parameters between metastatic and non-metastatic lymph nodes.

The sensitivity and specificity of the spectral CT parameters are not

overwhelming. The role of the spectral CT parameters in the decision-

making is expected to be small.

Reply: The role of the spectral CT parameters in the decision-making is no

better than traditional CT, but, combining morphology, the diagnostic

value improved. So far, spectral CT parameters play a supporting role in

the decision-making of lymph node metastasis. But this work had its

limitations and we considered that with more and more in-depth research

on spectral CT, its will play a more important role.

3. The difference in the spectral parameters on non-contrast scans is

intriguing. However, this observation does not lead to improved

discrimination between metastatic and non-metastatic lymph nodes.

Reply: In our research, there was also significant difference on non-

contrast scan. For CT value on non-contrast scans, non-metastatic lymph

nodes tend to have higher density than metastatic lymph nodes (P < 0.001), with the critical value of 48.95Hu. For those lymph nodes with no obvious necrosis, high density suggests the possibility of non-metastatic lymph nodes. Also, we found that λHU of non-metastatic LNs was larger than that of metastatic lymph nodes in non-contrast scan, which is not reported in references.

4. FDG-PET is currently thought to be a more readily accessible and arguably more established non-invasive method for lung cancer staging than dual-energy CT equipment that makes spectral analysis possible. Comparison of diagnostic performance with FDG-PET would be desirable.
Reply: We have added diagnostic performance of FDG-PET or FDG-PET/CT in the text.
Changes in the text: We have modified our text as advised (see Page 5, line 15-22).

5. Although this paper includes some potentially intriguing pieces of observation about the metastatic lymph nodes, overall results do not add any new knowledge about the mediastinal lymph node assessment in lung cancer.
Reply: The purpose of this paper was to explore using quantitative parameters in spectral CT for diagnosing mediastinal lymph node

metastases. Different from previous paper, which focus on analyzing enhanced images, we found differences in CT value and IC on non-contrast scan.

Changes in the text: We have modified our text as advised (see Page 15, line 11-14).

Specific comments

Materials and methods

6. For the title of the second paragraph, "Image acquisition" instead of "Imaging acquisition" seems to be more appropriate.

Reply: We have change "Imaging acquisition" to "Image acquisition".

Changes in the text: We have modified our text as advised (see Page 7, line 21).

7. Please replace the "Wilconxon" test with the "Wilcoxon" test in the statistical analysis subsection.

Reply: We have change "Wilconxon" to "Wilcoxon" in the text.

Changes in the text: We have modified our text as advised (see Page 9, line 22).

Results

8. Page 6, line 22-23. The sentence, "All the curves were above the reference line.", seems to be self-evident and needs not explicitly stated in the result section.

Reply: We have deleted this sentence.

Changes in the text: We have modified our text as advised and deleted this sentence.

Discussions

9. The difference in the spectral parameters on unenhanced CT would be the most outstanding result in this study that needs some remarks in the discussion section. I would be happy if the authors could provide a plausible explanation for this observation.

Reply: We considered that the slope of spectral curve of unenhanced scan simply reflects the heterogeneity of the tissue composition originally. In enhanced scan, the enhancement of each lymph nodes varies. We considered that different concentration of iodine will affect the ability on identifying substances of spectral curve, so, as the result indicated, λHU on unenhanced scan was more meaningful than enhanced scan. We added discussion in the text.

Changes in the text: We have modified our text as advised (see Page 13, line 6-15).

10. The comments in the third paragraph on the contrast enhancement and vascular structures are not very relevant considering the result of the current study.

Reply: Pathophysiological changes that affect tissue microvascularity, for example due to increased neoangiogenesis, which lead to increased blood volume and capillary hyperpermeability, will result in a higher degree of enhancement. According to the results, the IC and NIC of metastatic LNs are lower than those of non-metastatic LNs. We consider contrast enhancement is closely related to vascular structures, so we made the discussion about enhancement and vascularity. And we have delete some content about lymph node structures appropriately.

Changes in the text: We have modified our text as advised (see Page 14).

Tables

11. Table 1. Special characters such as ① should be avoided if you can.

Reply: We have changed "①" to "(I)" in the text.

Changes in the text: We have modified our text as advised (see Page table).

12. I wonder if the term "lymphoepithelioma-like carcinoma" would be more appropriate than "lymphoepitheliomatoid carcinoma."

Reply: We have changed "lymphoepitheliomatoid carcinoma" to "lymphoepithelioma-like carcinoma" in the text.

Changes in the text: We have modified our text as advised (see table 1 and figure 4 legend).

13. The right end of table 4 is not presented.

Reply: We have adjusted table 4 appropriately.

Changes in the text: We have modified our text as advised (see table 4).