Peer Review File

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Review Comments to Reviewer A

Comment 1: First, the title needs to indicate the comparison of diagnostic accuracy of the volumetric quantitative analysis of spectral CT vs. conventional spectral analyses.

Reply 1: Thanks for this comment. Accordingly, we revised the title into "Differentiating between pulmonary adenocarcinoma and squamous cell carcinoma by spectral CT volumetric quantitative analysis: a comparative study with conventional spectral analysis". As suggested by the results in this article that the volumetric quantitative analysis of spectral CT owns significant advantages over the conventional spectral analysis.

Changes in the text: We have revised the title as advised (see page 1, line4-5).

Comment 2: Second, the abstract needs further revisions. The background did not explain why the volumetric quantitative analysis of spectral CT is potentially accurate for the differential diagnosis between ADC and SQCC, the limitations of conventional spectral analyses, and what the knowledge gap is on the diagnostic accuracy of spectral CT. The methods need to describe the inclusion of subjects and the calculation of sensitivity and specificity, as necessary diagnostic accuracy parameters. The results need to quantify the findings by reporting the accurate mean and SD and accurate P values of different groups. The AUC and other diagnostic accuracy parameters of the two diagnostic methods should be reported. The conclusion needs more detailed comments for the clinical implications of the findings.

Reply 2: Thanks a lot for pointing these out. In the Background part, we have detailed the advances of volumetric quantitative analysis vs. conventional spectral analyses. Also, the results and conclusion parts have been revised according to these comments.

Changes in the text: The text has been revised accordingly as advised (see page 1-2, line33-34, 1-4, 14-38, 1).

Comment 3: Third, the introduction of the main text, the authors need to have comments on the clinical importance of the differential diagnosis between ADC and SQCC, the limitations of conventional and available methods, and explanations on the potential strengths and accuracy of spectral CT.

Reply 3: Thanks a lot for pointing these out. In the Introduction part, we have detailed the clinical importance of the differential diagnosis between ADC and SQCC, the limitations of conventional and available methods, and explanations on the potential strengths and accuracy of spectral CT.

Changes in the text: The text has been revised accordingly as advised (see page 3,4, line18-23, 13-18,26).

Comment 4: Fourth, in the methodology of the main text, please clearly describe the clinical research design, sample size estimation, and ethics approval of this study. In statistics, AUC alone is not adequate for assessing the diagnostic accuracy. Please describe the calculation of sensitivity and specificity, as well as their threshold values for a good diagnostic test. Please describe the statistical methods for comparing the AUC between two diagnostic tests.

Reply 4: Thanks a lot for pointing these out. In the Clinical Data part, we have detailed the ethics of this study. The sensitivity and specificity were determinate in our revised manuscript. We also introduced the DeLong test to compare the differences in AUC.

Changes in the text: We have modified our text as advised (see page 4,6,7, line 35-39, 17-18, 16-20).

Review Comments to Reviewer B

1. There's no such information in your paper. Please confirm if you have registered your trial and if a study protocol is prepared to be shared; if both are not, please just fill "N/A" in **Item 28 and Item 29** in STARD checklist.

OTHER INFORMATION			
	28	Registration number and name of registry	page 1/11me10-15
	29	Where the full study protocol can be accessed	The author can provi de

Reply: Thanks. We have corrected the checklist.

Changes in the text: We have revised the checklist as advised (see checklist, Item 28 and 29).

2. Abstract should be within 200-350 words. Please shorten your Abstract.

Reply: Thanks for this comment. We revised the abstract accordingly.

3. What's meaning of those data? Please either define the data inside Table 1 or in table footnote.

Table 1 Comparison of the spectral CT analysis results for 2 types of lung cancer

Pathological type	PS		AP	
	Concentrations of calcium (mg/cm³)	Eff-Z	Concentrations of iodine (mg/cm³)	Concentration of water (mg/cm³)
Volumetric spectral analysis				
ADC (n=35)	6.97±2.83	7.90±0.14	1.42(0.84)	995.00(38.70)
SQCC (n=22)	5.14±2.39	7.80±0.10	1.16(0.65)	1007.00(14.38)
t or Z	2.513*	2.860*	−2.246**	−2.082**
P	0.015	0.006	0.025	0.037
Conventional spectral analysis				
ADC (n=35)	8.51±4.28	7.97±0.20	1.33(0.80)	1026.15(14.00)
SQCC (n=22)	5.96±2.50	7.86±0.13	0.94(0.63)	1029.28(10.49)
t or Z	2.534*	2.475*	−2.524**	−1.885**
P	0.014	0.016	0.012	0.059

Reply: Sorry for the confusion caused. We have defined the data inside Table 1.

Changes in the text: We have revised the define of the data as advised (see Table 1, page 14).

4. Please also either define these data inside Table 2 or in table footnote.

Table 2 Comparisons of the 2 spectral CT analysis methods for lung cancer

Spectral parameters	PS		AP	
	Concentrations of calcium (mg/cm^3)	Eff-Z	Concentrations of iodine (mg/cm^3)	Concentration of water (mg/cm^3)
ADC (n=35)				
Volumetric spectral analysis	6.97±2.83	7.90±0.14	1.42(0.84)	995.00(38.70)
Conventional spectral analysis	8.51±4.28	7.97±0.20	1.33(0.80)	1026.13(14.00)
t or Z	−4.357*	−4.340*	−1.900**	−5.159**
P	0.000	0.000	0.057	0.000
SQCC (n=22)				
Volumetric spectral analysis	5.14±2.39	7.80±0.10	1.16(0.65)	1007.00(14.38)
Conventional spectral analysis	5.96±2.50	7.86±0.13	0.94(0.63)	1029.20(10.49)
t or Z	−2.328*	−3.796*	−3.036**	−4.107**
P	0.030	0.001	0.002	0.000

* Student *t* test; ** ... test; CT ... data ... PS ... AP ... ADC ... SQCC ...

Reply: We defined the data inside Table 2.

Changes in the text: We have revised the define of the data as advised (see Table 2, page 14).