Peer Review File

**Reviewer A:**

Comment 1: This review is entitled "Functional imaging for screening detected lung nodule management with CT - which techniques and what is the current evidence".

If you read the publication now, you will find nothing at all on the topic of "Functional Imaging"!

Reply 1: Thank you for the useful suggestion. The Title has been changed to "Early-stage Lung Cancer Detection from Radiomics to Deep Learning in Thoracic CT Images: A Narrative Review with Contemporary Clinical Recommendations".

Change 1: We have changed the title of the track changes version.


Comment 2: The introduction lacks a clear distinction between lung tumors and round lung foci. This is a common theme throughout the paper.

Reply 2: Thank you for the useful suggestion. We have revised the introduction thoroughly.


Comment 3: Further weaknesses are that e.g. ground glass nodules are mentioned, but the actual nodules are subsolid. In all sections there is no structure whatsoever. It is rather a sequence of cited publications.

In general, tables and figures are missing. This is indispensable for this kind of topic.

Reply 3: Thank you for the useful suggestion. Our review was focus on the detailed text explains.


Comment 4: Screening and techniques are hardly mentioned. Current screening studies and their follow-up work are not included. Information on current guidelines is also missing.

Reply 4: Thank you for the useful suggestion. Current screening studies and their follow-up work was added in chapter 1.2.1.

Comment 5: Chapter 1.4. on early stage lung cancer is out of place.
Reply 5: Thank you for the useful suggestion. Chapter 1.4 was used to connect with the foregoing radiomics study and carry forward deep learning study.

Comment 6: The topics on AI are treated only generally and with little reference to the topic of pulmonary nodules.
Reply 6: Thank you for the useful suggestion. We have added the reference.
Change 6: We have changed in the reference of the track changes version.

**Reviewer B:**
Comment 1: I read with great interest the manuscript entitled 'Functional imaging for screening detected lung nodule management with CT – which techniques and what is the current evidence'.

My remarks:
Overall remark:
The authors describe a lot of aspects regarding pulmonary nodules. They should focus on the topic of this manuscript: the challenges and importance of correct characterization of screen-detected nodules (characterization) and the possible role of innovative imaging techniques.

Writing/language
There are a number of points missing, number of spelling mistakes. Minor language editing is needed. It is confusing to see a point after the references (for example 'Revel et al(36). demonstrated') or is this according to the journals guidelines?
Reply 1: Thank you for the useful suggestion. Two native-English speakers have revised the article.

Comment 2:

Title:

The title is confusing and the word order is not logical. It would seem better 'Functional imaging for the management of screen-detected lung nodules on low-dose CT. Which techniques and what is the current evidence'. Consider adjusting the title.

Reply 2: Thank you for the useful suggestion. The Title has been changed to "Early-stage Lung Cancer Detection from Radiomics to Deep Learning in Thoracic CT Images: A Narrative Review with Contemporary Clinical Recommendations".

Change 2: We have changed the title of the track changes version.

Comment 3:

Keywords:

Consider adding the keywords 'LDCT' and 'lung cancer screening'

Reply 3: Thank you for the useful suggestion. The keywords 'LDCT' and 'lung cancer screening' have been added.

Change 3: We have changed the keywords of the track changes version.

Comment 4:

Introduction:

- The most powerful to reduce lung cancer mortality in the world definitely is not screening, but is smoking cessation

Reply 4: Thank you for the useful suggestion. We have changed the sentence as "Computed tomography (CT) screening, diagnosis and treatment in the early stage of lung cancer are one of the important means to reduce its mortality".

Change 4: We have changed the line 93 of the track changes version.

Comment 5: Page 4 – line 57: rephrase – Lung cancer screening with low-dose CT (LDCT) allows diagnosis and treatment …

Reply 5: Thank you for the useful suggestion. We have changed the sentence as "Lung cancer screening with low-dose CT (LDCT) allows diagnosis and treatment of early stage lung cancer".

Change 5: We have changed the line 94 -100 of the track changes version.

Comment 6: Page 4 – lines 61-63: this sentence is difficult to understand. I suppose what the authors mean is that the morphology of the lesion (and categorization into subsolid) defines the choice of nodule management protocol

Reply 6: Thank you for the useful suggestion. We have deleted the sentence.

Change 6: We have changed the line 94-100 of the track changes version.

Comment 7: Page 4 – line 70: CT-images may contain quantitative data that may have a complementary role in assessment of diagnosis, treatment and prognosis.

- When discussing role of LDCT in screening and lung cancer specific survival: use the most relevant data from large trials, such as NLST, NELSON, large Asian trials? The reference number 4 is wrong, data is missing. When referring to NLST data on survival, use the NEJM publication as reference. Same for referencing NELSON trial. Final data have been published in NEJM

Reply 7: Thank you for the useful suggestion. We have changed the sentence as "For example, the National Lung Screening Trial (NLST) found that Screening with the use of low-dose CT reduces mortality from lung cancer; The Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) reported that lung-cancer mortality was significantly lower among those who underwent volume CT screening than among those who underwent no screening".

Change 7: We have changed the line 110-118 of the track changes version.

Comment 8: Research in determining the nature of pulmonary nodules: The authors should keep the focus on screen detected nodules and should not mix this up with incidental nodules.

Patients with incidentally detected nodules and those with screening-detected nodules have different risk profiles. According to most guidelines, they have different nodule management systems.

The Fleischner criteria from 2005 were not used for screening purposes. The same remark for the different models. Some models are developed for lung cancer screening purposes, other for incidental nodules. The one the authors refer to, from the title I might expect that this is not for screen-detected nodules?

Reply 8: Thank you for the useful suggestion. We have changed the subtitle as "Research in determining the nature of incidental pulmonary nodules". We believe that the Fleischner criteria from 2005 were correlated with the subtopic in the review.

Change 8: We have changed the line 127 of the track changes version.

Comment 9: Paragraphs 1.2.1 and 1.2.2 are confusing and too extended as introduction for 1.2.3.

What is the reason that there is only focus on characterization of ground glass nodules (1.2.3)?

Reply 9: Thank you for the useful suggestion. We have deleted the chapters 1.2.2 and 1.2.3.

Comment 10: The authors state that after nearly 30 years of the development of decision models, the role of CT images is still irreplaceable. Why would it not be irreplaceable? These algorithms are based on the imaging findings.

Reply 10: Thank you for the useful suggestion. We have deleted the sentence.

Change 10: We have changed the line 165-166 of the track changes version.

Comment 11: Line 145: to what degree does the infiltration also affects the clinical decision? Precise what you mean with infiltration. Or doe you mean invasion/invasive tumor part?

Reply 11: Thank you for the useful suggestion. We have changed the subtitle as "In addition, with changes in the pulmonary nodule disease spectrum, the simple differentiation of benign and malignant has been unable to meet the needs of clinical work, including resection extension, Lymph node dissection range and adjuvant treatment modality".

Change 11: We have changed the line 168-169 of the track changes version.

Comment 12: Why does the manuscript only focuses on pulmonary ground glass nodules and not on solid nodules? Since both have a different malignant potential and different management guidelines, they should both be discussed.

Reply 12: Thank you for the useful suggestion. We have deleted the chapters 1.2.2 and 1.2.3.

Comment 13: The features that might add value to the diagnosis are morphological features typical of pulmonary nodules.

Reply 13: Thank you for the useful suggestion. We have deleted the chapters 1.2.2 and 1.2.3.

Comment 14: The classification of SSNs and determination of the solid component is not controversial in clinical practice. It is agreed upon that they require different nodule management. What the problem is, is that there is a variability in defining on imaging which nodule is part-solid and which is solid, and there is also variability in defining and measuring the size of the solid component. These aspects will impact the possible histopathological classification.

Reply 14: Thank you for the useful suggestion. We have deleted the chapters 1.2.2 and 1.2.3.

Comment 15: 1.2.4 The continuous development of CAD technology is not really related to the evolution of radiomics

Reply 15: Thank you for the useful suggestion. We have changed the subtitle as "Over the past 10 years, scholars have proposed that a large number of high-dimensional quantitative features can be mined and combined with statistical models to comprehensively classify medical tumor images, namely, radiomics".

Change 15: We have changed the line 284-285 of the track changes version.

Comment 16: 1.4. Challenges of CT radiomics

New deep-learning radiomics algorithms don't require manual acquisition, but they have DL-driven segmentation methods.

I think there are much more challenges than the ones mentioned.

A lot of research and validation still needs to be performed.

Reply 16: Thank you for the useful suggestion. We have changed the subtitle as "After all, there are much more challenges than the ones mentioned. A lot of research and validation still needs to be performed".

Change: We have changed the line 461-463 of the track changes version.

Comment 17: The limitations should not be separately discussed in the conclusion, but in the rest of the manuscript.

A critical note on the value of Radiomics in lung cancer patient care should be added. It has potential, but still a lot of research is needed.

Reply 17: Thank you for the useful suggestion. We have changed the subtitle as "the value of radiomics in lung cancer patient care was still at research stage". We have moved the limitation to Paragraphs 1.4.

Change 17: We have changed the line 456-460 of the track changes version.

Comment 18:

References:

Should be double checked. Some data is missing.

Reply 18: Thank you for the useful suggestion. We have changed the references according to the journal guidance.

Change 18: We have changed the references of the track changes version.