

Peer Review File

Article information: <https://dx.doi.org/10.21037/asj-21-52>

Reviewer A:

Indeed the topic is of great interest and the review is well done. It reviews aspects such as size, volume doubling time shape and location, margins, attenuation and internal characteristics.

Answer: We want to thank the reviewer A very much for the kind comments and for the contribution to ameliorate our manuscript.

1. A major review on artificial intelligence (AI) programs, Computer-Aided Detection/Diagnosis (CADe/CADx) in terms of lesion's characterization and volumetry is missing. The review does not answer some questions, there may be no data on this and it is aimed at follow-up. But it would be interesting to know in what tumor percentage solid/non-solid we should consider resection of the nodule or the size in volume that artificial intelligence programs could allow us to measure, which could be more reliable than the linear measurement of diameters.

Answer: Thank you for pointing out this issue. A major review on artificial intelligence (AI) programs, including CAD systems, deserves a separate chapter. We just wanted to cite and highlight the growing potentiality of AI in this context. However, we are aware that this paragraph is too summarized and incomplete, and we decided to not include it into the manuscript by itself. As recommended also by the reviewer B, we mentioned AI relevant papers directly in the previous sessions.

2. The bibliography should be homogeneous. Most of them have three authors except for citations 17 and 31.

Answer: Thank you for the observation. We corrected reference 17 (now reference 21, page 11 line 501). On the other hand, reference 31 (now reference 37, page 13 line 542) lists the first three authors, homogeneously with the bibliography.

Reviewer B:

We want to thank the reviewer B very much for the crucial comments and great contribution to improving our manuscript.

We have made an extensive work of revision in order to solve the critical points highlighted by the reviewer B. Here are our detailed answers to the reviewer B.

1. Introduction:

Rather than specifically mentioning the NLST and NELSON, perhaps a review article of lung cancer screening trials should be referenced instead to avoid overlooking the various other studies?

Answer: Thank you for the clever advice. We did not find a comprehensive review on this topic however, in keeping with your observation, we added the other randomized controlled trials for which results have been published (LUSI, ITALUNG, DANTE MILD) with their respective references (page 2 lines 68-71).

2. Methods:

Very brief; perhaps a bit more detail would be adequate.

For example, did the authors search for the given terms specifically or did they also consider variations of the key words (e.g., "part-solid" or "subsolid")? How were the search results filtered (e.g., based on title and abstract)? Were the reference lists from relevant papers also used to find other potentially relevant papers?

Answer: We really appreciate the suggestion. The methods section has been reformulated as requested. We added data to detail our search (pages 3-4 lines 105-129).

3. Discussion:

Line 159: please specify as "MAXIMUM diameter up to 12 mm".

Answer: Thank you very much. We added the term "maximum" according to your suggestion (page 6 line 219).

Lines 160-161: I would replace the mention of extending linear densities (for which there is still insufficient evidence) with "a lack of arterial attachment" (as recommended in Figure 7 of Schreuder et al [2020]).

Answer: Thank you for the suggestion. We modified the sentence in order to highlight the typical "lack of arterial attachment" of an intrapulmonary lymph node pointing out the frequent connection to an interlobular septum, location of the lymphatics (page 6 lines 220-221).

Nodules with a high probability of being lymph nodes are discussed; perhaps the term "perifissural nodules" should be mentioned? This is becoming an increasingly familiar term, though it should also be mentioned that there is no strong consensus on the definition (ref: Schreuder et al., 2020).

Answer: We really appreciate the advice. We mentioned the term "perifissural nodule" into our text, with the relative reference (Schreuder et al., 2020) in which the topic is discussed (page 6 lines 223-225).

Some statements should be accompanied by some additional context to avoid misinterpretation; some examples are given below:

- Please consider specifying that the proportion of PSNs found to be malignant from studies older than 10 years ago are likely to be overestimations (i.e., 63% [line 77] or even 22.2% [line 79] would now be considered as unlikely estimates). This is also reflected in the fact that a disproportionate number (up to half) of the PSNs found in these studies were larger than 10 mm compared to <10% in "positive" solid nodules.

Answer: We really appreciate the clarification and the clever advice. In fact, we added the clarification into the text, immediately after the reported percentages based on the relative references (Henschke CI et al. 2002, McWilliams A et al. 2013) (page 3 lines 95-97).

- Lines 202-204 & 213-215: Cohen et al (2015) only included PSNs which had been pathologically confirmed to be adenocarcinomas, which is a strong selection bias against PSNs which were not adenocarcinomas and which were not of sufficiently high risk to undergo invasive testing. The sensitivity and specificity reported therefore only apply to a small subgroup of PSNs.

Answer: Thank you again for the smart observation, that we added into the manuscript to better contextualize the assertion (page 7 lines 276-280).

- Lines 2013-2015: Lee et al (2016) only had the pathological outcome of 58 of 213 SSNs. It would be sufficient to specify in this review that these statements only apply to a minority of nodules which had been resected based on subjective factors in the medical decision-making process.

Answer: Thank you very much for pointing out this issue. We modified the sentence according to your suggestion (page 8 lines 300-302).

- Lines 239-241: VDT estimates from Hasegawa et al (2000) are based exclusively on confirmed cancers (of which 19 were PSNs). Please specify this.

Answer: Thank you. We specified this point. (page 8 lines 326-327).

- Lines 262-265: please provide references for recent CAD systems with "excellent results" and CAD systems for "stratifying lesions according to degree of malignancy".

Answer: according to your recommendation, we decided to not use the term "CAD" into the text.

4. References:

#22 is missing the paper title.

Answer: Thank you for the observation, we corrected reference 22 (now reference 26).

5. Please consider adding the following relevant papers where applicable (doi):

- 10.1016/j.jtho.2018.10.006 -> on mean diameter VS. volume measurements.
- 10.1007/s00330-017-5055-x -> on incidental perifissural nodules in routine care.
- 10.21037/tlcr-2020-lcs-06 -> a review of the role of AI in lung cancer screening

Answer: Thank you very much for the input. We used these interesting papers on the new version of the manuscript:

- Page 6 lines 205-208 (reference 27)
- Page 6 lines 222-225 (reference 34)
- Page 9 lines 364-365 (reference 51)

6. Figures:

Would it be possible to obtain better quality images of Figures 1b, 1c, and 2?

Answer: Thank you. We modified Figures 1 and 2, as requested.

7. Overall comments:

Well written overall; some easily corrigible grammar mistakes.

It seems to me a strange decision to focus on solid and partsolid nodules in one article while leaving the discussion of ground glass nodules for another article (instead of grouping PSNs and GGNs together), but this is not an important issue.

Answer: We agree with your observation, however we were invited to write a review on solid and part-solid nodules, holding out pure ground glass nodules that will be discussed elsewhere.

This may be a personal preference, but I thought that the term "CAD" is not commonly accepted anymore due to its vague meaning (it remains unclear from this term what exactly the task of the algorithm is). The distinction into CADe and CADx is insufficient (see 10.21037/tlcr-2020-lcs-06).

I would therefore recommend simply using the term "AI algorithm" and specifying the task when applicable.

Answer: Thank you very much for your recommendation. We modified the text accordingly.

The section "Computer-Aided Detection/Diagnosis (CADe/CADx) systems" is perhaps too brief and lacking of various important references to be considered part of a narrative review. There is a relatively large proportion dedicated to praising Ciompi et al (2017), but completely overlooks the 2017 Kaggle Challenge (www.kaggle.com/c/data-science-bowl-2017/), the algorithm from the challenge winners (10.1109/TNNLS.2019.2892409), the AI algorithm from Google (10.1038/s41591-019-0447-x), and dozens of other articles from before 2017. Due to the fact that there are already more comprehensive reviews of AI algorithms for nodule detection, I argue that this section should not be included in this manuscript. AI papers which would be directly relevant to one of the previous sections (on solid and partsolid nodules) should simply be discussed there. An alternative would be to at least ensure that various review articles on AI algorithms are included in this final section.

Answer: Thank you. We really appreciate the suggestion, and we agree that this paragraph is too brief and incomplete. A comprehensive review on AI in the context of pulmonary nodules would deserve a dedicated chapter. Based on your recommendation, we decided just to mention the potential power of AI algorithm in a small paragraph addressed to "present and future perspective", which does not claim to provide an overview of AI but only to give an input to the reader, citing only the most relevant papers on this topic and the review advised (10.21037/tlcr-2020-lcs-06). For completeness we have chosen to write something about AI even though we are aware that it is a subject that is still evolving and not used in daily clinical practice. Our review is intended to provide practical information on the pulmonary nodule management and the inclusion of AI studies in the context of the main paragraphs would have been confusing as AI algorithms are not yet routinely used tools.

Please check page 9 lines 353-367 if it can be a potential solution.