Peer Review File
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Reviewer A

I really enjoyed reading the meta-analysis by Woo and colleagues who are attempting to bring to light the challenges that today's thoracic surgeon faces. The findings of GGN in the era of screening guidelines is going to be a major problem that will compound health systems throughout the world. The approaches either watch and wait vs surgically remove is not simple to make. This meta-analysis attempts to shed light on this problem and potentially serve as a nidus for future clinical trials. The statistical analysis is nicely done with tables representing prudent findings that would be of use to every thoracic surgeon. However, as I read the manuscript, I felt that it was incomplete.
The introduction is rather short and I hope the authors will expand on by highlighting importance of the clinical need that this meta-analysis is attempting to answer. The discussion is nicely presented.

Comment 1) The major area of weakness of this article is the lack of association between smoking and sub-types of GGN. The whole reason that we discover GGNs is smoking associated risk factors which makes the patients eligible for screening. If we are not going to include them then we are missing a very large risk factor. Can the authors include smoking associated risk factors, this would strengthen the pape.

Response 1)
Thank you for your acknowledgment of our study. We truly appreciate your thoughts and ideas. As you said, smoking-associated risk factors should be included to have a comprehensive understanding of pure GGN. However, there are several hurdles to including smoking and analyzing it with the features of GGN. First, each included study did not compare the pathologic results according to smoking history. As this is a proportional meta-analysis of pathologic diagnoses, we do not have patients' specific data for their pathology and smoking history. If we get more individualized data, it would be possible to investigate the impacts of smoking on the invasiveness of pure GGN.

Another issue is that there was a significant proportion of patients with no history of smoking. As Table 1 describes, 7 of 22 included studies described the percentage of never-smokers; it ranges from 47.8% to 93.1%. This means that there is a larger portion of patients with pure GGN among non-smokers. Interestingly, the detection of pure GGN among non-smoker female patients has been increasing. Therefore, this study is not suitable to investigate the impact of smoking history on tumor histology. Prospective or retrospective analysis of each patient's data would be needed to reveal the causal relationship between them. We added the comment about this. Thank you for your suggestion and a bright idea for future study.

Changes in the text Line 201-202 :

Especially, the smoking status was found as a contributing factor for the growth of GGN.[47] These factors should be matched to interpret the fate of pure GGNs.

Comment 2. I recommend the authors on the quality of the manuscript but would highly recommend native English speakers to review and improve the grammatical errors.

Response 2. Thank you for your comments. We edited this article with the assistance of Editage company, which specializes in English medical writing. We edited accordingly.

Comment 3. Line 70: suggest changing determining lung cancer prognosis to "assessing lung cancer prognosis"

Response 3. Thank you and we edited accordingly.

Changes in the text Line 63-64 : The advancement of screening programs has led to assessing lung

cancer prognoses according to their radiological characteristics.

Comment 4. Line 123: What do authors mean with favorable outcomes?

Response 4. Thank you so much. The favorable outcome here means a very rare incidence of recurrence or lung cancer-related death. As studies showed, most patients had no recurrence during follow-up. A large-scale prospective study by Kakinuma et al.[1] also described the superior clinical outcome of pure GGNs. To deliver this accurately, we rephrased it as follows.

Changes in the text Line 118-119: 10 studies with clinical outcomes reported nearly no recurrence or death during the follow-up other than one study.

Reviewer B

The authors proposed here a meta-analysis on the histopathologic results from ground-glass nodules (GGN) reported in literature.
Among 24 studies including 3,845 cases of pure GGN undergoing surgery there were 27% of invasive adenocarcinoma, while the pooled proportions of atypical adenomatous hyperplasia (AAH), in situ adenocarcinoma (AIS), and minimally invasive adenocarcinoma (MIA) were 11%, 36%, and 24%, respectively. In any case, about half of these cases (51% with invasive and minimally invasive adenocarcinoma) exhibited an invasive component.
The study is interesting, although contain some critical bias, as expected.

Comment 1. AIS and MIA are recently concept introduced by the fourth(2015) and fifth (2021) edition of the WHO classifications of lung tumors, then one should not consider papers appeared before 2015. Please, discuss this issue.

Response 1. Thank you for your thoughtful response. As you described, the concepts of AIS/MIA were recently introduced and there could be some variability in pathologic diagnosis. To deliver more accurate information, we additionally added the pathologic diagnostic criteria that each study introduced in Table 1. As you can see, almost all studies introduced the concepts from IASLC/ATS/ERS 2011. This has been correlated with WHO 2015 and WHO 2021 classifications. A study from Sawada et al. is the only one that used the WHO 2004 classification in which most MIA and AIS were described as bronchoalveolar carcinoma. Other than this study, all had common pathologic diagnostic criteria. We described the shift in the concepts of MIA and AIS in the discussion and explained this problem. We truly appreciate your comments.

Changes in the text Line 185-193:
First, there has been a shift in determining pathologic diagnosis of early-stage lung cancer. Bronchoalveolar carcinoma, which was defined in the WHO 2004 classification, was later further differentiated into AIS, MIA, and IA based on the 2011 IASLC/ATS/ERS guideline. Though most studies other than one introduced the concepts of new classification, there could be some variations. Another factor is interobserver variability in the pathologic diagnosis of GGN. Depending on patients' population and the number of experienced pathologists, final diagnosis could vary from institutions[44–46]. Though several studies evaluated good correlation between pulmonary pathologists, the discrepancy exists due to complicated lung pathology such as emphysema, fibrosis, or inflammatory tissue.

Comment 2. Have the authors checked if histologic criteria based on WHO have been considered in the 24 analyzed papers?

Response 2. As we responded in the previous comment, we added information related to pathologic diagnostic criteria. Thank you for your comment.

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[1] Kakinuma R, Noguchi M, Ashizawa K, et al. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. J Thorac Oncol. 2016;11(7):1012-1028. doi:10.1016/j.jtho.2016.04.006

Comment 3. AAH, AIS and MIA are relatively subjective concept on histology with some inter-variability. So, results from literature should be taken with caution. Please, discuss this point if you agree.

Response 3. We appreciate your comments. AAH, AIS and MIA are difficult to diagnose and it requires certain level of experience and knowledge. Depending on patients' population and number of experienced pathologist, the results could be different. We further added several articles related to inter-observer variability regarding this and discussed it further as you recommended.

Boland et al. examined the interobserver variability among 296 slides in academic center.[2] It had good correlation between pulmonary pathologists, but there were 2% disagreements between AIS and MIA. Thunnissen et al. also evaluated this and they assessed 94 typical and 21 difficult cases among 26 pathologists.[3] The mean kappa value went down to 0.08 for difficult cases compared to 0.55 for typical cases. This discrepancy is related to superimposition of neoplastic growth on the underlying lung structure and it further complicated with pre-existing emphysema or interstitial fibrosis. Other than this, there could be variability interpreting stromal components, elastin wall, and inflammatory tissue.

Changes in the text Line 190-193:

Depending on patients' population and the number of experienced pathologists, final diagnosis could vary from institutions[44–46]. Though several studies evaluated good correlation between pulmonary pathologists, the discrepancy exists due to complicated lung pathology such as emphysema, fibrosis, or inflammatory tissue.

Comment 4. international recommendation consider a major criteria the size of GGN (up to 8 mm merit follow up without surgery). Have the authors considered the dimension of GGN ? Again, according to the WHO classification, <3 cm is invasive per se.

Response 4. Thank you for your comments. We did not consider the size of GGN when it comes to the eligibility criteria. However, we added information regarding size on CT scan and Hounsfield unit if they are available. It was only available from 8 studies and the range was somewhat different according to each study. Therefore, we could not analyze the impact of size on the invasiveness of tumors. However, several studies that analyzed risk factors for invasive adenocarcinoma revealed that size is one of important factors that we need to consider. Two studies suggested 10mm or 13mm cut-off value to determine the invasiveness of tumors.

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[2] Boland JM, Froemming AT, Wampfler JA, et al. Adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive pulmonary adenocarcinoma--analysis of interobserver agreement, survival, radiographic characteristics, and gross pathology in 296 nodules. *Hum Pathol*. 2016;51:41-50. doi:10.1016/j.humpath.2015.12.010

[3] Thunnissen E, Beasley MB, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. *Mod Pathol*. 2012;25(12):1574-1583. doi:10.1038/modpathol.2012.106