

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-583>

Reviewer A

Comment 1: Is there a difference between malignant and benign tumor depending on the ration of GGO component?

RESPONSE: We appreciate the reviewer's insight into the important topic of the presence and amount of a solid component to a GGO. In response to this comment, we have compared to the part-solid component between the benign and malignant groups for all of the patients in the study. There was no statistically significant difference between the percent solid component of the lung nodule between the adenocarcinoma and the benign patients ($59.6\pm 32.8\%$ versus $65.7\pm 36.1\%$, $p=0.32$). The manuscript has been revised to show this data in table A, and in the results section (2nd paragraph, last sentence). In addition, we have revised the methods section to more explicitly state how percent solid was calculated (materials and methods section, paragraph 1, 7th sentence).

Comment 2: Authors should evaluate between adenocarcinoma and radiologic features including the ratio of GGO and solid component, PET findings.

RESPONSE: We appreciate the reviewer's comment. In response, we have provided this additional radiologic data and compared them between the two groups. The data related to ratio of GGO and solid component has been added and compared, as detailed above in the response to Reviewer A comment 1. We have also added data related to PET scans for the patients in table A, the Materials and Methods section (paragraph 2, 4th sentence), and the Results section (2nd paragraph, last 2 sentences).

Comment 3: In addition to race and sex information, I want to know how to clinically decide whether GGO dominant tumor is lung adenocarcinoma or benign tumor.

RESPONSE: We appreciate the reviewer's comment regarding this very important clinical topic. We feel that our response to their comments 1 and 2 above that added more radiographic detail to the study provides some additional data that can be used to assess whether a nodule is benign or cancer. However, we feel that in these details alone are limited in addressing this critical clinical element, as we saw no differences in PET findings or percent solid component in our benign and malignant groups. In addition, the appearance on CT scan often cannot adequately delineate the two possibilities, as illustrated in our new figure 2 that was suggested to be added

by Reviewer C. We feel that our discussion does touch on points that can be used to determine the likelihood of cancer, where gender and race can be factored into the decision process. In addition, we have revised the methods section (paragraph 1, 3rd paragraph) of the manuscript to also list our own institution's general criteria used to define a nodule as suspicious for lung adenocarcinoma.

Comment 4: The histological subtypes of adenocarcinoma should be added to evaluate oncological features in this study.

RESPONSE: We appreciate the reviewer's comment regarding this very important topic, and have revised the manuscript to include this data in Table B of the revised manuscript.

Reviewer B

Comment 1. GGO appearance on CT images is greatly affected by imaging parameters. Currently, high-resolution CT is recommended for the nodules with GGO features, but this study did not state the imaging parameters. The patients were selected according to the GGO appearance, so it should be noted in detail.

RESPONSE: We appreciate the reviewer's comment, and have revised the Materials and Method section of the revised manuscript to explicitly state that high resolution CT scans with 1mm thick slices were used to calculate the GGO component when available (paragraph 1, 7th sentence). We do note that the type of CT scans used throughout the study were somewhat heterogeneous due to the relatively long time period included in the study, as well as that the practice pattern in our institution is to generally not repeat CT scans unless absolutely clinically necessary if patients have had a lower resolution scan done at an outside facility. We recognize that this reduces the specific accuracy of the percent solid measurements for the patients in the study, but feel the impact on our study's findings is likely minimal given that our goal was to assess patients with ANY GGO component, and did not rely on a specific cut-off for the inclusion or exclusion of patients.

Comment 2. As many studies indicated, the size of the solid part in part-solid nodules was tightly associated with the diagnosis of adenocarcinoma. These data should be included and discussed.

RESPONSE: We appreciate the reviewer's comment, which is similar to reviewer A comment 1. As discussed in the response to that comment, the manuscript has been revised to compare the part-solid component between the benign and malignant groups for all of the patients in the study. There was no statistically significant difference between the percent solid component of the lung nodule between the adenocarcinoma and the benign patients ($59.6 \pm 32.8\%$ versus $65.7 \pm 36.1\%$, $p=0.32$). The manuscript has been revised to show this data in table A, and in the

results section (2nd paragraph, last sentence). In addition, we have revised the methods section to more explicitly state how percent solid was calculated (materials and methods section, paragraph 1, 7th sentence).

Comment 3. Despite CT diagnosis with suspicious GGO, most tumors in the patients with lobectomy resulted in adenocarcinoma. Although the authors discussed this in the text, it would be likely that the other features on CT images might prevent selecting a wedge resection. Therefore, this reviewer has an interest in the nine patients with benign tumors who underwent surgery. The authors should provide more data on these patients with full discussion in the text.

RESPONSE: We appreciate the reviewer's comment, and their interesting query regarding the use of a lobectomy for a benign process. A presentation of this topic of a "diagnostic lobectomy" was recently presented at the 2022 American Association for Thoracic Surgery by Onwugbufor and colleagues from the Massachusetts General Hospital (Lobectomy For Suspected Lung Cancer Without Prior Diagnosis, <https://www.aats.org/resources/1645>), where 70 patients with a suspicious lung nodule had a lobectomy for what ultimately was proven to be a benign process. Considering that presentation and our own experience, we suspect that other centers also sometimes have to consider lobectomy for a suspicious nodule where a diagnosis has not been established. In response to the reviewer's comment, we have revised the results section of the manuscript (3rd paragraph, 4th sentence) to explicitly state that, for the nine patients in the benign group who had a lobectomy, the reasons a sublobar resection was not performed were: multiple abnormalities in one lobe (1 patient); nodule location in the central aspect of the middle lobe (3 patients); nodule presence location in the central aspect of the right or left upper lobe with suspicious appearance but previous non-diagnostic biopsy (4 patients); and nodule presence in a lobe that had previously been partially resected (1 patient).

Reviewer C

Major Comment 1. In the inclusion criteria, the author stated that a lung nodule that was "clinically suspicious for lung cancer" was included in the study. This is too ambiguous. Did the authors repeated scans every year and confirmed the growth on CT images? Conducted FDG-PET? Needle biopsy? Without this point, it is extremely hard to utilize their conclusion. For instance, If I find a 2cm subsolid nodule on CT images of a 70-year old Asian female, should I immediately recommend surgery based on the author's result? The answer would be No. We have more detailed guidelines (such as Lung-RADS) how to follow-up or further investigate these subsolid nodules.

RESPONSE: We appreciate the reviewer's comment, and their clinical acumen. We certainly agree that management strategy must depend on many factors other than simple radiologic appearance. We also agree that very good guidelines to steer clinical management exist, and the goal of our study was not to evaluate how change in nodule character over time, which has been characterized well by previous studies. In response to the comment, we have revised the

manuscript to describe our institution's general approach to evaluation and management (Materials and Methods section, paragraph 1, 3rd paragraph) when a patient is found to have a part solid lung nodule.

Major Comment 2. Basically, resected benign subsolid nodules are false positives of preoperative imaging. The authors included cases from 20 years ago to 5 years ago. Since 2001, a lot of new evidence and guidelines based on larger cohorts and prospective studies have been released. Therefore, false positive cases in 2001 and 2017 would be completely different in nature, and unfortunately, the authors mixed up these cases in this analysis.

RESPONSE: We appreciate the reviewer's comment and this very important point. In response, we have examined the time distribution of the cases in the study, and found that the majority of cases were in the years 2010 or later (n=202, 83.1%) while only 41 cases were in earlier years (16.9%). Thus, we feel that the impact of changes in patient management is somewhat limited given that most patients had care in a more modern time period. We do feel including the patients in the earlier time period is important to investigating the main topic, specifically the use of race and gender when considering whether a part solid lung nodule could be lung cancer. In response to this comment, we have revised the manuscript to explicitly state the distribution of cases in the study throughout the study period so readers can be aware of this possible limitation (results section, 1st paragraph, 2nd sentence).

Minor Comment 1: Adding example images of adenocarcinoma and benign cases are desirable.

RESPONSE: We appreciate the reviewer's comment, and as suggested have revised the manuscript to include images of both benign and malignant part-solid nodules (new Figure 2 in the revised manuscript). We feel that these examples illustrate well the limitations of using CT scan appearance alone in distinguishing a benign and malignant process, and feel the reviewer's suggestion really improved the manuscript.

Reviewer D

Comment 1: Research similar to this paper has already been published by Lee et al. in Radiology 2004.

RESPONSE: We appreciate the reviewer's comment and their knowledge of the literature regarding this topic. We agree that the topic of risk of lung adenocarcinoma in a part-solid nodule has been broadly studied, including by our group, and recognize the many studies that have contributed greatly to this topic. However, we do feel that our study has value in specifically looking at the impact of race and gender on the likelihood of cancer in this clinical situation, particularly given that we have a diverse cohort in a somewhat more modern time period. Specifically, we think that our study can be particularly useful to clinicians who practice in a setting where they may not have as much experience and exposure to patients with part-solid

lung nodules, and we hope that our data will allow them to use both race and gender in their decision process on their next steps in management. The discussion section of the manuscript has been revised to explicitly state this possible use of our data (6th paragraph, 1st sentence).

Comment 2. Has high-resolution computed tomography (HRCT) been performed on all patients? HRCT is necessary for evaluating GGO.

RESPONSE: We appreciate the reviewer's comment, and agree with them. This comment is very similar to Reviewer B comment 1. As detailed above in our response to that comment, we have revised the Materials and Method section of the revised manuscript to explicitly state that high resolution CT scans with 1mm thick slices were used to calculate the GGO component when available (paragraph 1, 7th sentence). We do note that the type of CT scans used throughout the study were somewhat heterogeneous due to the relatively long time period included in the study, as well as that the practice pattern in our institution is to generally not repeat CT scans unless absolutely clinically necessary if patients have had a lower resolution scan done at an outside facility. We recognize that this reduces the specific accuracy of the percent solid measurements for the patients in the study, but feel the impact on our study's findings is likely minimal given that our goal was to assess patients with ANY GGO component, and did not rely on a specific cut-off for the inclusion or exclusion of patients.

Comment 3: The characteristics of GGO should be described and evaluated in more detail. The nodules should be divided into two groups according to consolidation tumor ratio (CTR) > 0.5 and ≤ 0.5 .

RESPONSE: We appreciate the reviewer's comment, which is similar to comments from Reviewer A Comment 1 and Reviewer B comment 2. As detailed above in the responses to those comments, we have revised the manuscript to explicitly provide data related to the percent solid component of the suspicious lung nodule for all of the patients in the study. There was no statistically significant difference between the percent solid component of the lung nodule between the adenocarcinoma and the benign patients ($59.6 \pm 32.8\%$ versus $65.7 \pm 36.1\%$, $p=0.32$). The manuscript has been revised to show this data in table A, and in the results section (2nd paragraph, last sentence). In addition, we have revised the methods section to more explicitly state how percent solid was calculated (materials and methods section, paragraph 1, 7th sentence).