

Peer review file

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Comment 1: The title “LDCT lung cancer screening in low-risk Asian patients: Characteristics of malignant subsolid nodules” mentioned a concept of “low-risk Asian patients”. Please clarify the definition.

Reply 1: According to the 2017 Fleischner Guidelines, major high-risk factors used to select candidates for screening include heavy smoking (30 pack-years or more and quitting smoking within the past 15 years), family history of lung cancer, and old age. Many of these “high-risk” factors do not apply to our patient population, and the term “low-risk” was used to illustrate the contrast rather than as a strict exclusion criterion. In order to redirect attention to our observations focusing on imaging and clinical characteristics related to ethnicity, we have changed the title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients” (see Page 1, line 1)

Changes in the text: Page 1, line 1; “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients”

Comment 2: In my opinion, this study focused on the correlation of pathology and radiology. All patients included in this study were prepared for surgical resection, not for lung cancer screening. It means all SSNs in the study is highly suspicious of malignancy. The words, such as “screening” in the title, may not be appropriate.

Reply 2: Though not strictly following any population-wide screening protocols, all of the nodules in our study were detected in asymptomatic patients by LDCT during self-enrolled medical check-ups. We have clarified how patients were enrolled and changed the title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients” to avoid any ambiguity. (see Page 1, line 1; Page 8, line 19)

Changes in the text: “83 ... SSNs detected by LDCT during self-enrolled medical check-ups.”

Comment 3: The eighth edition Lung Cancer Stage Classification recommends solid component size be a new T descriptor instead of total tumor size because solid size predicts the size of invasive component more accurately. Solid size may be a better predictor for IA than total tumor size.

Reply 3: We absolutely agree that solid size may be a better indicator than total tumor size in part-solid nodules. Though our current study puts PSNs alongside pure ground-glass nodules for comparison, we will take this into consideration in future PSN specific studies.

Changes in the text: N/A

Comment 4: A multivariate prediction model is needed for nodule malignancy,

similar as IA prediction.

Reply 4: We have updated a multivariate analysis model in the new Table 4. (see Page 13, Line 12-15; Table 4)

Changes in the text: “Characteristics... These factors besides air bronchograms were further analyzed with multivariate logistic regression (AUC=87.36%) and showed that lesion size and speculation were independent risk factor for malignancy. Air bronchograms were excluded from further analysis due to multi-collinearity (Table 4).”

Comment 5: The reference of this article is too much. 20-30 may be more acceptable.

Reply 5: We have reduced the number of references to 34.

Changes in the text: see References

Comment 6: What's the predictive ability of the multivariate model in the study? A AUC value for the multivariate model may be calculated.

Reply 6: AUC values of multivariate models for malignancy and IA histology were 87.36%, 85.07% respectively. Both results have been added to Tables 4&6 (see Page13, line13; Page14, line 11)

Changes in the text: “These factors besides air bronchograms were further analyzed with multivariate logistic regression (AUC=87.36%)”; “Multivariate logistic regression (AUC=85.07%) showed that PSN presentation was a significant predictor for IA histology...”

Comment 7: First of all, the data of this study is defined based on thin-section CT screening, not on low dose computed tomography as described in Material and Methods section. Thus, this manuscript is out of discussion in the present form.

Reply 7: We have changed “thin-section CT” to “LDCT” in the patients section of Material and Methods to avoid ambiguity. Our CT images were acquired following a low-dose protocol (20 mA, 120 kV) while using 0.6 mm (thin, <1.5mm) section thickness. (see Page9, line1, Page9, line10)

Changes in the text: “... SSNs detected by LDCT during self-enrolled medical check-ups.”

Comment 8: This study includes too small number to conclude about that issue.

Reply 8: We will continue to follow up on this matter and accumulate cases in future studies. In the meantime, a moderate statistical power was achieved with the current sample size in the present study (n= 83). A post hoc power analysis revealed that on the base of a type I error of 0.05, covariate' odds ratios, distributions and effect sizes observed in the present study, approximately 76.5%-96.1% of statistical power was obtained using SAS PROC POWER, which are at the recommended .80 level (Cohen, 1988).

Changes in the text: N/A

Comment 9: The authors have mentioned “low-risk” in the title; however, the risk of lung cancer has not been enumerated or reported in this paper. Please consider calculate their predicted risk of lung cancer at 6 years based on available models such as Tammemägi’s model.

Reply 9: The Tammemägi PLCO model would definitely be useful in quantifying cancer risk in ever-smoker patients. However, the PLCOall2014 model or other models based on non-Asian, smoker populations may have limited value since 69 out of 83 of our patients were never-smokers, which will generally yield a 6-year-risk smaller than 1%, and none of our patients fall into the category of heavy smokers with a history of 30 or more pack-years who quit within the past 15 years. We have changed our title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients”, and modified our text to avoid confusion. (see Page1, line 1; Page 20, line 2; Page21, line 4)

Changes in the text: “among East Asian patients, even young individuals with no known risk factor,”; “relatively young females with no known risk factor may be at risk of malignant SSNs in an East Asian population.”

Comment 10: It is unclear whether patients with high-risk were excluded from this study. Please consider stating inclusion and exclusion criteria to select study subjects.

Reply 10: All the included patients were consecutive cases who underwent surgical resection after SSN detection during self-enrolled medical check-ups. Instead of a strict exclusion criterion, the term “low-risk” was used to illustrate the fact that the majority of our patients, despite having malignant lesions, do not qualify as conventional “high-risk” individuals recommended for lung cancer screening according to multiple expert groups (American Cancer Society, Fleischner Guidelines, etc) In order to avoid any ambiguity and redirect attention to our observations focusing on clinical and imaging characteristics related to ethnicity, we have changed the title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients” (see Page1, line1; Page8, line19)

Changes in the text: “We retrospectively reviewed ... and identified a consecutive series of 83 patients who underwent surgical removal”

Comment 11: In page 5, last paragraph, patient characteristics were reported in the material and methods section. This should rather be reported in the results section.

Reply 11: We have moved the characteristics of our patient sample to the result section. (see Page11, line 14).

Changes in the text: see Page11, line14

Comment 12: To understand the value of LDCT screening among low-risk population, it will be important to know how many subjects in total had received LDCT screening in order to yield these 83 patients with SSN nodules. It will also be

important to know how many solid nodules were discovered. Furthermore, since not all subjects with abnormal LDCT screening findings undergo surgery or undergo surgery immediately, it will be necessary to understand how many underwent biopsy before surgery, and how long has it been since the first LDCT screening till the time of surgery, to understand how many repeat screenings needed to be made over time, before surgery was carried out.

Reply 12: We agree that, from a public health standpoint, a more comprehensive analysis is needed to quantify the value of LCDT screening. Our retrospective study focuses more on imaging and clinical characteristics of operated SSN cases; thus we have changed the title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients”

Changes in the text: see Page1, line1

Comment 13: Lung-RADS is a system commonly used to describe finding from LDCT screening. Please report the Lung-RADS finding from T0 (baseline) screening as well as from the last screening conducted immediately before surgery.

Reply 13: The studied nodules include 47 LUNG-RADS 2 (all pGGNs); 22 Lung-RADS 3 (1 pGGN, 21 PSN); 6 Lung-RADS 4a (all PSNs); 8 Lung-RADS 4b (all PSNs). Our management differs from western guidelines, and most of our patients did not have multiple follow-up imaging due to our different pathology and health care system. (see Page12, line8)

Changes in the text: “83 nodules that were analyzed, including 47 LUNG-RADS 2 (all pGGNs); 22 Lung-RADS 3 (1 pGGN, 21 PSN); 6 Lung-RADS 4a (all PSNs); 8 Lung-RADS 4b (all PSNs)”

Comment 14: Is it possible that some patients with SSN did not have surgery? This group of patients may have cancer but since the cancer can be slow growing, they may live for a long time. The conclusion about female having higher risk of malignancy can be misleading because of case selection bias.

Reply 14: All operated patients were consecutive cases selected based on lesion imaging features, but, due to variable patient preferences, not every patient with suspicious SSNs had surgery. However, there is no reason to suggest there is a significant difference between male and female preferences regarding surgery. Lung cancer in never-smokers is a well-documented phenomenon in female Asian patients. We believe the effect of selection bias on sex ratio, if present, is negligible. (see Page 9, line2-5).

Changes in the text: “The indication for invasive interventions was determined by a combination of imaging features and patient characteristics such as lesion size, lesion morphology, and patient history. All patients who chose invasive intervention underwent surgical resection”

Comment 15: Did any patients had a biopsy proven malignant and decide to undergo

radiotherapy or observation alone? How many? The study only included patients who had surgery and the observations may be problematic as it does not offer the whole picture of all patients who had LDCT screening.

Reply 15: There were no biopsy confirmed malignancies. All patients who opted for invasive interventions preferred surgical resection. We agree that a more comprehensive analysis is needed to quantify the value of LDCT screening, and have changed our title to “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients” which better represents the results of our study. (see Page1, line1; Page 9, line2-5)

Changes in the text: “Predicting malignancy: Subsolid nodules detected on LDCT in a surgical cohort of East Asian patients” “The indication for invasive interventions was determined by a combination of imaging features and patient characteristics such as lesion size, lesion morphology, and patient history. All patients who chose invasive intervention underwent surgical resection”

Comment 16: What are the criteria used in this study to select patients for surgery? Some patients with smaller solid component in their GGO should not have been selected for surgery.

Reply 16: As we believe that our patients with SSNs may differ from those in western countries, we do not strictly follow western guidelines in the management of SSNs. There is currently no consensus regarding the optimal timing for surveillance or surgical intervention in many Asian countries. In Taiwan, we might even have a lower threshold for surgery due to national health insurance coverage and easy accessibility to minimal invasive surgery. General considerations for surgery include: Suspicious lesion morphology, pGGOs > 7 mm, PSNs > 5 mm, increasing size or change to part-solid type, past history or family history of lung cancer, patient anxiety. We added clarification in the methods section. (see Page9, line2-5)

Changes in the text: “The indication for invasive interventions was determined by a combination of imaging features and patient characteristics such as lesion size, lesion morphology, and patient history. All patients who chose invasive intervention underwent surgical resection”

Comment 17: The authors mentioned VDT. Is VDT predictive of malignancy in this study?

Reply 17: Unfortunately, VDT was not assessed in the current study. Literature on VDT was mentioned in the introduction to illustrate the slow growing yet unpredictable nature of SSNs.

Changes in the text: N/A

Comment 18: In Table 5, only PSN remains the independent predictor of invasive adenocarcinoma. The authors should mention this in their abstract. It appears that most of the significant observations reported in the abstract became insignificant in

the multivariable analysis.

Reply 18: We have added the new results of a multivariate analysis for malignancy (not just for IA histology) to complement our reported findings in the abstract. The new multivariate results (new Table 4) showed that size and spiculation were independent risk factors for malignancy, while air bronchograms were excluded due to strong multi-collinearity. Though not self-conflicting, we speculate that the variation in significance between univariate and multivariate results stems from the limitation of our sample size. For example, if we only assessed female sex, pleural tail, and spiculation, then female sex would become significant in the multivariate analysis (results not included). However, with the inclusion of more and more parameters, we would require a larger sample size to maintain statistical power. (see Page4, line19; Page5, line1-2; Page13, line12-15, Page20, line 14)

Changes in the text: “Abstract...Further multivariate analysis found that lesion size and spiculation were independent factors for malignancy while part-solid nodules were associated with IA histology.” “These factors besides air bronchograms were further analyzed with multivariate logistic regression (AUC=87.36%) and showed that lesion size and speculation were independent risk factor for malignancy. Air bronchograms were excluded from further analysis due to multi-collinearity (Table 4).” “... relatively small sample size; thus perhaps resulting in the variation of significant factors in univariate and multivariate analysis.”

Comment 19: The discussion is somewhat lengthy.

Reply 19: We have reworded the discussion and reduced the word count by approximately 100 words (see Pages 14-21).

Changes in the text: see Pages 14-21