

## Peer Review File

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### Reviewer A

This is a single center retrospective study to evaluate the features of nodular lung adenocarcinoma by comparing those of benign lung nodules. The preoperative prediction of solitary pulmonary nodules is important for clinicians. My comments are as follows.

1. So far, numerous larger reports on the clinicoradiological features of solitary pulmonary nodules including adenocarcinomas have been published. Why did the authors conduct this study? What is new?

Reply 1: Although numerous larger reports on the clinicoradiological features of solitary pulmonary nodules including adenocarcinomas have been published, it is basically related to the pathological types of lung adenocarcinoma, that is, AAH/AIS, MIA, ADC.

In this study, nodular lung adenocarcinoma was taken as the research object. According to the current clinical classification of nodular lung adenocarcinoma, the clinical, CT imaging and postoperative pathological features of nodular lung adenocarcinoma in each group were comprehensively analyzed.

According to the 2021 WHO classification of lung tumors, we refer to the pulmonary gland precursor lesions or microinvasive adenocarcinoma or invasive adenocarcinoma that appear as ground glass nodules or solid nodules on chest CT images as nodular lung adenocarcinoma. According to the density of pulmonary nodules, nodular lung adenocarcinoma can be divided into ground glass nodular lung adenocarcinoma and solid nodular lung adenocarcinoma.

According to different postoperative histopathological types, nodular lung adenocarcinoma is divided into glandular precursor lesions, MIA and IAC. The glandular precursor lesions include AAH and AIS.

According to the histopathological grading of IAC, invasive nodular lung adenocarcinoma can be divided into LPA), APA/PPA and MPA/SPA. Because invasive mucinous adenocarcinoma (IMA) is easy to spread in the lungs, and it has been reported that there was no significant difference in the overall survival rate between patients with IMA and high-grade histopathological types, so we classified IMA and MPA/SPA as a group.

2. Abstract is too long. The upper limit in the abstract is 450 words. In addition, Discussion is also too long. Please shorten.

Reply: Thank you for your suggestions! We have shortened the Abstract and Discussion sections.

Changes in text: Abstract, page 2-4; Discussion, page 14-21.

3. Please describe information on the patient number in the Abstract (e.g. total, patients with adenocarcinoma, patients with benign).

Reply: We have added the information on the patient number in the Results part of abstract.

Changes in text: Line 44.

4. Please describe the details of benign diseases (pathological diagnosis and number of patients).

Reply: we have added the details of benign diseases.

Changes in text: see Line 281-286.

5. How many patients had preoperative diagnosis?

Reply: Benign or malignancy pulmonary nodules confirmed via postoperative pathological examination, so there were no cases of pulmonary nodules before operation. see Line 158-159.

6. Please describe the exact P-values. The description, “ $P < 0.05$ ” and “ $P > 0.05$ ,” seems to be unclear for readers.

Reply: The exact P-values were shown in Table 1-12.

7. This is merely a small single-center retrospective study. “Real-world data,” in which the data is usually collected from a large population, in the title seems not to be appropriate.

Reply: In our study, “Real-world data” are more reflected in different classifications data of nodular lung adenocarcinoma based on current clinical practice.

8. Which method did you use for NGS analysis?

Reply: Thank you for your timely reminder! We have added the method for NGS analysis NGS based on Illumina sequencing platform

Changes in text: see page 8, Line 229-230.

### **Reviewer B**

My congratulations to the authors for a study with excellent design and development. The characteristics of the nodules studied are perfectly defined, however, I would like to ask some practical questions:

- In the sample we found a significant percentage of resected benign nodules (approximately 28%). One of the main criticisms of lung screening studies is the overdiagnosis of benign nodules and the consequences that this has, such as an increase in invasive and non-invasive diagnostic tests and unnecessary surgical procedures. I understand that in the design of your study, ignorance of the radiological evolution of suspicious lesions is precisely to avoid a confounding factor when studying the characteristics of the nodules. In your usual practice, is radiological follow-up carried out prior to a surgical decision or do you proceed to resection any potentially suspicious nodule directly?

Reply: Thank you for your congratulations! According to the Chinese expert consensus on the diagnosis and treatment of pulmonary nodules, we routinely performed chest CT follow-up for the first discovered pulmonary nodules, with the follow-up frequency 3 to 12 months. The longest follow-up period of this study was more than 3 years, and of course, there were some patients who directly chose surgical resection due to excessive anxiety.

Changes in the text: Page 6, Line 149-153.

- The results of the different types and characteristics of the resulting nodules are perfectly defined, however, we do not know the type of lung resection performed, as well as the definitive pathological staging. Did the surgical technique performed vary depending on the characteristics of the suspicious lung nodule? Was any type of lung marking used prior to surgery? Did the result of intraoperative pathology vary the type of lung resection performed?

- Following this line of doubts. We do not know the pathological lymph node involvement and its relationship with the definitive histological type or with the degree of infiltration according to the type of Adenocarcinoma. This information is important to decide the appropriate type of lung resection according to current standards for

performing anatomical, non-anatomical segmentectomies or lobectomies. Do the authors know these data that they can exploit in another publication or minimally describe in this study?

Reply: Thank you for your questions! The pathological staging can be reflected in pT and pN data, see Table 8; the relationship between the pathological lymph node involvement and the histopathological grade of IAC has been shown in Table 8.

Thank you for your suggestions! As for these data on the surgical technique including CT-guided percutaneous lung marking prior to surgery, the type of surgical resection for lung nodules (wedge resection or Segmentectomy or Lobectomy) and so on, will be exploited in another publication.

I reiterate my congratulations for the work done by the authors.

Thank you very much!

### **Reviewer C**

The authors report data on a large series of lung nodular adenocarcinomas. As far as understood, CT-scan criteria were evaluated with the aim to detect those useful in a presurgical diagnosis of lung malignant nodule. The topic is of interest, the manuscript is difficult to read. The authors could revise and reorganize the manuscript in order to simplify the manuscript (include data as supplementary material) and in order to facilitate the reading/transmission of knowledge.

Reply: We apologize for the poor readability of our manuscript. We worked on the manuscript for a long time and the repeated addition and removal of sentences and sections obviously led to this problem. We now have modified our text as advised and really hope that the new version of the manuscript has been substantially improved.

Methods: The authors should clearly note the selection criteria: lung primary adenocarcinomas (TTF1+) confirmed on microscopy of resected nodules (without presurgical treatments)? Were these cases evaluated for microscopy tumor features? genetic tumor features? preoperative CT-scan features? The CT-scan features evaluated should be precisely noted. The authors could add data on the CT-scan material: number of images/case/tumor, number of images used for reconstruction, criteria evaluated on standard images and on reconstruction images, similar. Once the Methods section is revised, the authors could organize the data in main tables (and several as supplementary material), and then note the Results, Introduction and Discussion sections. The Abstract and the Key findings, in the present format are difficult to read.

Reply: Thank you for your suggestions! We have added “lung primary adenocarcinomas was confirmed on microscopy and tumor features were further evaluated”, see Line 159-161;

The genetic tumor features have been highlighted in the IAC section, see page 8 Line 227-251.

We have added the CT-scan features, see page 6, Line 178-181.

Due to the different length of the thorax in each patient, the number of images in CT scan varies from person to person.

We apologize for the poor readability of the previous version of the manuscript and sincerely hope that the new version is now easier to read and understand.

#### **Reviewer D**

The authors' aim in this paper is to discriminate nodular lung adenocarcinoma from benign pulmonary nodules, which is investigated using a multivariate analysis approach using extensive clinicopathologic data. Figures 1 to 3 do not need to be displayed as they are known general medical information. To identify whether a nodule is benign or malignant, it is necessary to compare the data for benign and malignant nodules, and Tables 3 to 12 deviate from the purpose of this paper because they only compare within the lung adenocarcinoma series.

Reply: Although they are known general medical information, figures 1 to 3 displayed in the paper is to highlight the common chest CT signs of pulmonary nodules, the measurement of  $CT_m$  values of pulmonary nodules with different densities and the pathological morphology of the histopathological grades of IAC, closely follow the theme, combine pictures and texts, and facilitate understanding.

Thank you for your suggestions! This study aimed to explore differential diagnosis of nodular lung adenocarcinoma by comprehensively analyzing its clinical, computed tomography (CT) imaging, and postoperative pathological and genetic features. So we believe that Tables 3 to 12 don't deviate from the purpose of this paper.

Changes in the text: Line 33-38.

During ROC analysis, there was imbalance data for malignant nodule ( $n = 137$ ) and benign nodule ( $n = 53$ ) because of resected cases due to selection bias (Table 1), and the results of ROC analysis indicated that the performance was inappropriate. This is likely to lead to undesirable evaluation results (overestimation of AUC and underestimation of false positive rate), and care must be taken when interpreting the results. If possible, we would like to collect additional data on benign nodules (for example, cases of long-term follow-up of unresected nodules, cases of nodules that have shrunk or disappeared, etc.) and conduct a comparative review.

Reply: I appreciate your profession and gladly accept your suggestions. However, the cases enrolled were surgically resected and confirmed by pathology from February 2022 to April 2023, and the number of patients admitted during the study period determined the sample size (see Line 146-147). We have noticed some limitations such

as selection bias just as you mention here. Therefore, our findings need to be further verified in a multicenter, prospective, randomized, large-sample study (Line 639-645).

Minor points:

# Line 16: Please change “Background” of Abstract to “Purpose” or “Objective”.

Reply: Good suggestion!

Changes in the text: Line 33.

# Line 34: Please be specific about what you mean by “these four factors”.

Reply: these four factors are gender, age, lobulation, and speculation, and we have revised the sentence.

Changes in the text: Line 50-53.

## **Reviewer E**

This study aims to correlate clinical, CT, pathological and genetic features of lung adenocarcinoma in a single-center case series. This paper statistics are very well presented and performed. On the other hand, it has to be better clarified in the text that the CT findings can be only predictive of malignancy, but they are not sufficient for a preoperative differential diagnosis.

Reply: Thank you for your suggestion! We have modified it.

Changes in the text: see “key findings” box.

English grammar and synthax need revision.

Text revision:

“Key findings” box: “can be informed by”. Typing error? (formed by) Please rephrase the sentence

Reply: Thank you for your suggestion! We have modified our text as advised.

What is known and what is new box:the CT signs can be only suggestive of, but cannot discriminate between malignant and benign nodules. The differential diagnosis has to be done only on histology

Reply: Thank you for your suggestion! We have modified our text as advised.

Line 26: Firstly, ....

Reply: Thank you for your suggestion! We have revised it, see Line 44.

Line 42: ....Secondly, ....

Reply: Thank you for your suggestion! We have revised it, see Line 57.

Line 77-81“With the spread”, better rephrase as “Thanks to the spread of [...] the detection rate of asymptomatic pulmonary nodules [...] is increasing

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 103-107.

Line 107: please declare the type of the study: i.e. prospective, retrospective etc...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 126.

Line 115: “the total number of patients admitted during...”

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 143-146.

Line 155: ...bronchi, vacuoles and other structures, with....

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 197.

Line 160: were referred? will be referred? Please choose the form and correct

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 201-203.

Line 189-194, Sample preparation: is this paragraph necessary? The Authors clarified the NGS use in the previous paragraph.

Reply: Thank you for your question! This paragraph is to introduce the specific processing of NGS samples before delivery, so I retain the paragraph.

Line 204-205: ”...detected. We stratified the clinical, CT imaging and pathological features according to each gene mutation”

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 249-250.

Line 226: “There was no missing outcome...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 272.

Line 227: In the exclusion criteria, the Authors have already clarified that if some features was missing, the patient were not included in the study.

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 272.

Line 402: Smoking is a widely recognized risk factor for lung cancer.

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 460.

Line 411: ...with the EGFR mutation being the most common genetic aberration that is present in nonsmoking females....

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 469-470.

Line 475: ...owing to the lack of an unified....

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 539.

Line 479: ...some authors....

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 542.

Line 483: ...of patients with GGNs have multiple GGNs.

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 547.

Line 490: ..., which has....

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 558.

Line 495: prognosis, followed by those with...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 563.

Line 501-502: “increased incrementally”? Please consider rephrasing

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 570-572.

Line 518: “continuous modification”?

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 595.

Line 543: “the current molecular targeted therapy for lung adenocarcinoma is mainly...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 617-620.

Line 550: “were the most...”

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 627.

Line 559: ...Firstly, ...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 637.

Line 562: ...Secondly, ...

Reply: Thank you for your suggestion! We have modified our text as advised, see Line 640.

Line 565: ...In conclusion, there might have been...

Reply: Thank you for your suggestion! For the connection of the third limitation, 'Besides ' may be more appropriate than 'In conclusion ' , , see Line 643.

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