Systematic Review and Meta-Analysis

Medicine®

OPEN

The value of positron emission tomography computed tomography in predicting invasiveness of ground glass nodules

A protocol for systematic review and meta-analysis

Jitao Xiao, MD, Mengle Li, MD, Qun Du, MD, Hailin Han, MD, Yinglin Ge, MD*

Abstract

Background: The study was conducted to investigate the value of Positron emission tomography computed tomography (PET/CT) in predicting invasiveness of ground glass nodule (GGN) by the method of meta-analysis.

Methods: Two researchers independently searched for published literature on PET/CT diagnosis of GGN as of November 30, 2020. After extracting the data, RevMan5.3 was used to evaluate the quality of the included literature. The Stata14 software was used to test the heterogeneity of the original study that met the inclusion criteria, to calculate the combined sensitivity, specificity, positive likelihood ratio and negative likelihood ratio, the prior probability and posttest probability. The summary receiver operator characteristic curve was drawn and the area under the curve was calculated. Using Deeks funnel plot to evaluate publication bias.

Results: Five studies were finally included, including 298 GGN cases. The included studies had no obvious heterogeneity and publication bias. The combined sensitivity and specificity of PET/CT for predicting invasive adenocarcinoma presenting as GGN were 0.74 (95% confidence interval [CI]: 0.68–0.79), 0.82 (95% CI: 0.71–0.90), positive likelihood ratio and negative likelihood ratio were 4.1 (95% CI: 2.5–6.9), 0.32 (95% CI: 0.25–0.40), and the diagnostic odds ratio was 13 (95% CI: 7–26). The prior probability is 20%, the probability of GGN being invasive adenocarcinoma when PET/CT was negative was reduced to 7%, and the probability of GGN being invasive adenocarcinoma when PET/CT was positive was increased to 51%. The area under the curve of the summary receiver operator characteristic curve was 0.85.

Conclusion: PET/CT has high diagnostic accuracy for invasive adenocarcinoma presenting as GGN.

Abbreviations: AUC = the area under the curve, GGN = ground glass nodule, HRCT = high-resolution computerized tomography, IAC = invasive adenocarcinoma, PET/CT = positron emission tomography computed tomography, SROC = the summary receiver operator characteristic curve.

Keywords: ground glass nodule, invasive adenocarcinoma, meta-analysis, positron emission tomography computed tomography

Editor: Hyunjin Park.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Department of Radiology, the second people's Hospital of Liaocheng City, Shandong Province, China.

** Correspondence: Yinglin Ge, Department of Radiology, the Second People's Hospital of Liaocheng City, NO. 306 Jiankang street, Linqing City, Shandong Province 252600, China (e-mail: 6274941682@qq.com).*

How to cite this article: Xiao J, Li M, Du Q, Han H, Ge Y. The value of positron emission tomography computed tomography in predicting invasiveness of ground glass nodules: A protocol for systematic review and meta-analysis. Medicine 2021;100:41(e27507).

Received: 2 February 2021 / Received in final form: 3 September 2021 / Accepted: 23 September 2021

http://dx.doi.org/10.1097/MD.0000000000027507

Key points

- We evaluated the value of PET/CT in diagnosising invasive adenocarcinoma presenting as GGN by meta-analysis of evidence-based medicine, and drew a reliable conclusion.

1. Introduction

Ground glass nodule (GGN) is a nodule that has ground glass opacity (GGO). It is a characteristic imaging manifestation, which is closely related to lung adenocarcinoma.[1,2] In 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International divided lung adenocarcinoma into atypical adenomatous hyperplasia, adenocarcinoma in situ, microinvasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC), the WHO

followed this classification in 2015.[3,4] The 5-year survival rate after resection of atypical adenomatous hyperplasia, adenocarcinoma in situ, and microinvasive adenocarcinoma was almost 100%, whereas IAC was only 60% to 80%.[5,6] Inflammation, infection, and tumor can all be shown as GGN, and high-resolution computerized tomography (HRCT) can distinguish by its shape, density, and other signs or reexamination. However, GGN in cancer of different pathological stages can have the same HRCT findings. The diagnosis and differential diagnosis of invasive adenocarcinoma presenting as GGN is a difficult point in imaging diagnosis, which is of great significance to the selection of surgical methods, postoperative treatment and prognosis.[7] As an advanced examination method with both anatomical and metabolic functions, PET/CT has high sensitivity and specificity in the diagnosis of benign and malignant tumors with solid nodules in the lung. At present, there are few studies on the diagnosis of GGN by PET/CT, and the conclusion is controversial. Based on the PRISMA statement, we performed meta-analysis to evaluate the diagnostic efficacy of PET/CT for invasive adenocarcinoma presenting as GGN, so as to provide an evidence-based basis for clinical decision making.

2. Methods

2.1. Literature search strategies

Two researchers independently searched Pubmed, Embase, Cochrane Library, CNKI, Wanfang Data, and CBM for related literature published as of November 30, 2020. The search strategy was: (PET/CT [the medical subject headings OR free terms]) and (ground glass nodule OR ground glass opacity OR GGN OR GGO). The language was not limited, and the problems encountered were solved through discussion.

2.2. Inclusion and exclusion criteria

Inclusion criteria: in the studies, ground glass nodule were diagnosed by PET/ CT, and the lesions were divided into invasive adenocarcinoma group and noninvasive adenocarcinoma group; the ground glass nodule had definite pathological diagnosis; the number of true positive, false positive, false negative and true negative could be extracted from the literature; the literature was the original research; the full text of the literature was available.

Exclusion criteria were: irrelevant literature, duplicate literature; review, conference abstract, case, other nonoriginal research; the pathologic classification of ground glass nodule did not conform to the 2011 IASIA/ATS/ERS classification of lung adenocarcinoma.

2.3. Literature quality evaluation and data extraction

Two researchers independently conducted quality evaluation and data extraction of the included studies according to QuadAS-2. In case of disagreement, the 2 researchers discussed to solve the problem or added 1 researcher to solve the problem. The information extracted for each study included the first author, publication year, number of true positives, false positives, false negatives, and true negatives.

2.4. Statistical methods

RveMan5.3 software was used to evaluate the quality of the included studies. The Stata14 software was used to evaluate the heterogeneity, to calculate the combined sensitivity, specificity, positive likelihood ratio and negative likelihood ratio, the previous probability, and posttest probability. The summary receiver operator characteristic curve (SROC) was drawn and the AUC was calculated. At last, Deeks funnel plot was used to evaluate the publication bias.

2.5. Ethical statement

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

3. Results

3.1. Features of the included studies

Initially, a total of 191 relevant studies were retrieved. According to the inclusion and exclusion criteria, 67 duplicate studies, 109 irrelevant studies, 3 reviews, and 4 cases were excluded. After reading the full text of the study, 3 studies were excluded because they did not meet the third requirement in the inclusion criteria. Finally, 5 studies, 298 cases of GGN were included.[8–12] The characteristics and data of the included studies are shown in Table 1.

3.2. Sensitivity and specificity analysis

The sensitivity and specificity of PET/CT for the diagnosis of invasive adenocarcinoma presenting as GGN were 0.74 (95% confidence interval [CI]: 0.68–0.79) and 0.82 (95% CI: 0.71–0.90). The results of heterogeneity test were $Q=1.05$, $P=.9$, $I^2=0$ for sensitivity and $Q=2.56$, $P=.63$, $I^2=0$ for specificity. The forest graph is shown in Figure 1.

Table 1

Main characteristics of the included studies.

Author	Year	Tp	Fp	Fn	tn	SUVmax
Jie Chen	2019	26	2	12	12	1.04
Xiaonan Shao	2019	37	1	11	7	1.3
Rong Niu	2019	55	5	18	11	1.3
Jun Zhou	2019	31	2	12	13	0.95
Xiaohong Lv	2020	22	2	7	12	1.55

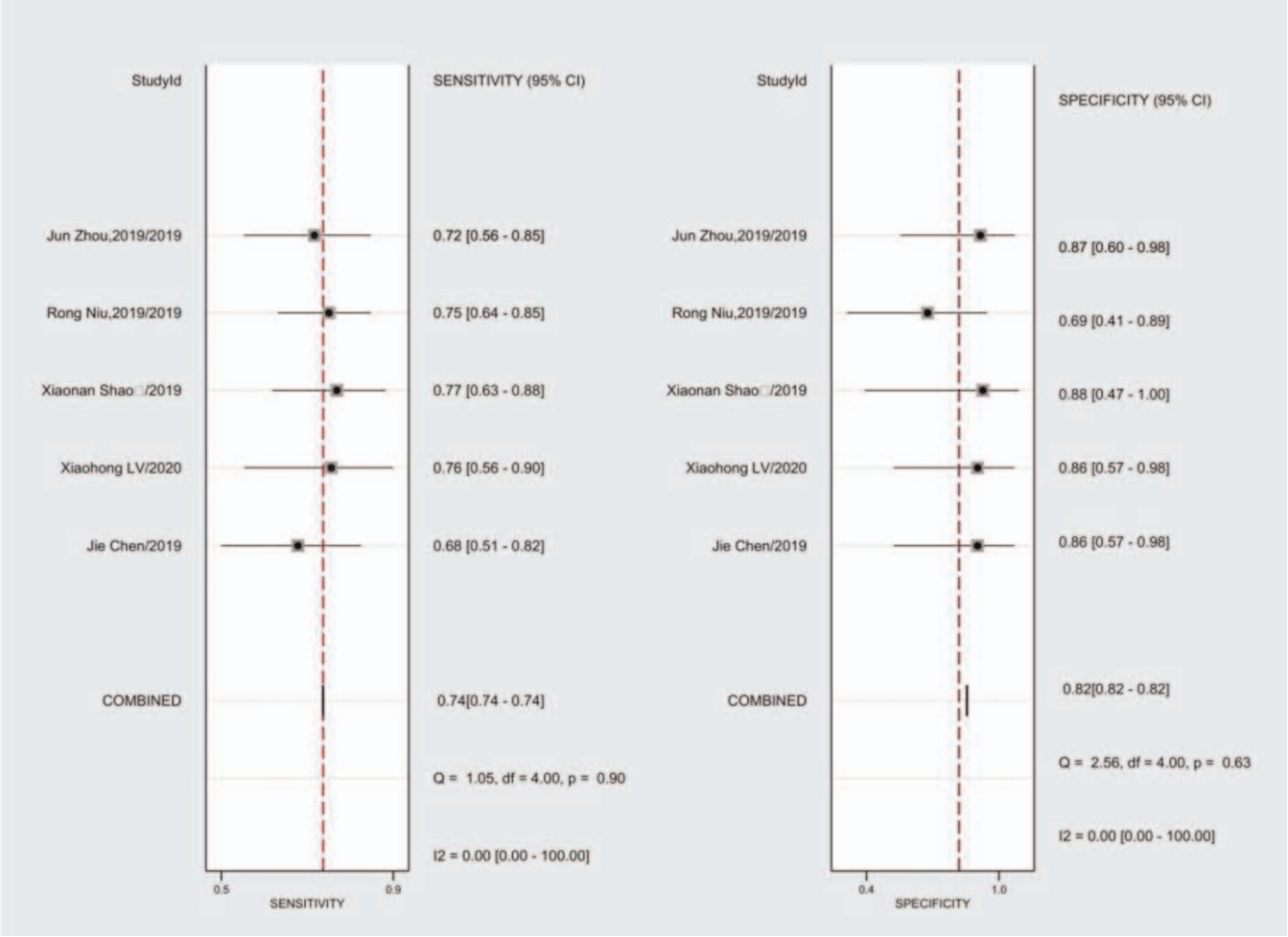

Figure 1. Combined sensitivity and specificity of the forest plots.

3.3. Positive and negative likelihood, diagnostic odds ratios, prior probability and post-test probability

The positive likelihood ratio and negative likelihood ratio were 4.1 (95% CI: 2.5–6.9), 0.32 (95% CI: 0.25–0.40), and the diagnostic odds ratio was 13 (95% CI: 7–26). According to Fagan normogram, the previous probability was 20%, when PET/CT indicated positive, the probability of GGN being invasive adenocarcinoma increased to 51%, and when PET/CT indicated negative, the probability of GGN being invasive adenocarcinoma decreased to 7%. The details were shown in the Figure 2.

3.4. The SROC and the AUC

The SROC was calculated by sensitivity against 1-specificity using Stata14 software., and the AUC was 0.85 (Fig. 3).

3.5. Evaluation of studies quality and publication bias

The quality evaluation graph was made by RveMan5.3. The Risk of bias graph and Risk of bias summary were shown in Figures 4 and 5. Both sides of the Deeks funnel plot are basically symmetric, and $P = .09$ (Fig. 6). The results showed that there was no significant publication bias. In short, the quality of the studies could well meet the requirements of our meta-analysis.

4. Discussion

At present, the main diagnostic method of GGN is HRCT, but HRCT manifestations of lung adenocarcinoma at different pathological stages still have certain imaging overlap.[13] More and more postoperative pathology confirmed the existence of over diagnosis and treatment in the resection of GGN.[14,15] Therefore, accurate diagnosis of GGN is the key point. PET/CT provides a possibility for imaging pathology diagnosis of GGN due to its special anatomical and functional metabolic characteristics. Recently, the studies on PET/CT diagnosis of lung adenocarcinoma presenting as GGN has been published gradually, but no meta-analysis or systematic evaluation has been published.

We searched the relevant studies as of November 30, 2020, and included 5 high-quality studies with 298 GGN. The overall quality of the included studies was good, without obvious

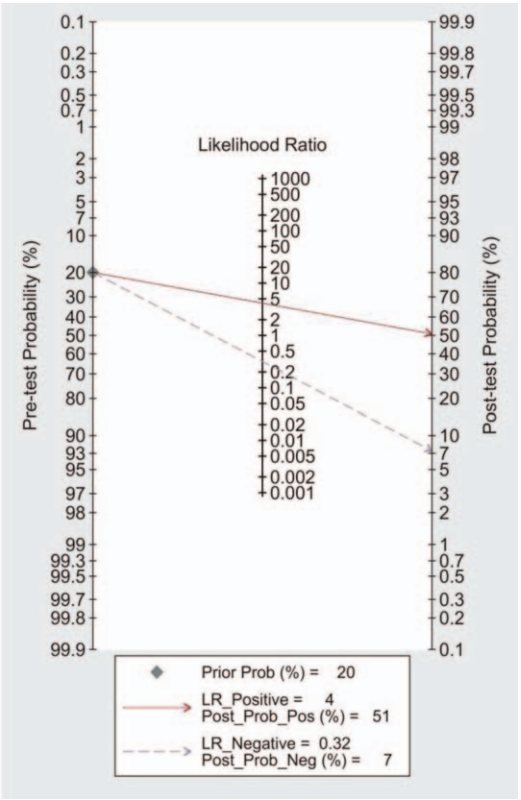

Figure 2. Fagan normogram, the prior probability was 20%, when PET/CT indicated positive, the probability of GGN being invasive adenocarcinoma increased to 51%, and when PET/CT indicated negative, the probability of GGN being invasive adenocarcinoma decreased to 7%. GGN = ground glass nodule, PET/CT = Positron emission tomography computed tomography.

heterogeneity and publication bias. The results of meta-analysis showed that PET/CT had high sensitivity, specificity and accuracy for invasive adenocarcinoma with GGN in the lung. For the diagnosis of GGN, PET/CT results were reliable, which could provide image basis for the diagnosis of GGN difficult on HRCT.

PET/CT for the diagnosis of lung benign and malignant tumors began around 2000, with Standardized Uptake Value Maximum (SUVmax) >2.5 as the standard for the diagnosis of malignant tumors. Since 2010, a large number of adenocarcinoma with GGN has been found in lung low-dose screening, which has revolutionary significance for the diagnosis and prognosis of early lung cancer. At the same time, whether SUVmax >2.5 is also suitable for the evaluation of GGNs is also under test. In the included studies, the SUVmax ranged from 0.95 to 1.55, with a median of 1.3, which was significantly different from the traditional criteria.[16,17] Therefore, SUVmax >2.5 is not suitable for the evaluation of benign and malignant GGN. When SUVmax of ground glass nodules is >0.95, especially >1.55, the possibility of invasive adenocarcinoma should be considered. This is because the density and metabolic activity of proliferative tumor cells in GGN are lower than those in solid tumors, which also confirms that the prognosis of lung adenocarcinoma shown as GGN is better. Our meta-analysis results also show that the cutoff values of the included studies are reliable.

The limitation of our study is that there are few published studies, so the potential publication bias may exist. Therefore, we need to constantly include new studies to make our meta-analysis conclusions more reliable

In conclusion, our meta-analysis showed that PET/CT has a high diagnostic accuracy for invasive adenocarcinoma presenting as GGN. PET/CT is an effective supplement to HRCT in the diagnosis of GGN.

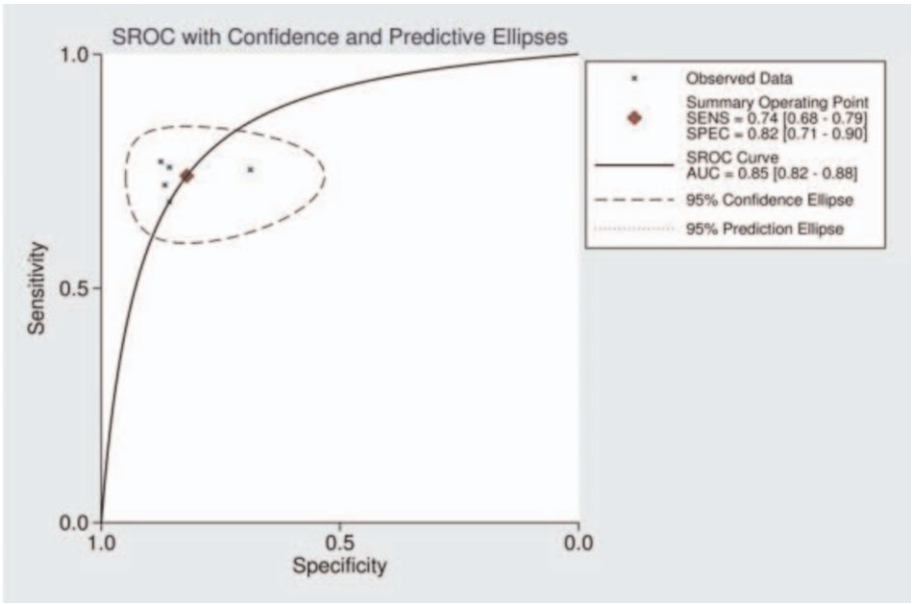

Figure 3. ROC for PET/CT diagnosis of invasive adenocarcinoma presenting as GGN. The was 0.85. AUC = area under the curve, GGN = ground glass nodule, PET/CT = Positron emission tomography computed tomography; ROC = receiver-operating characteristic.

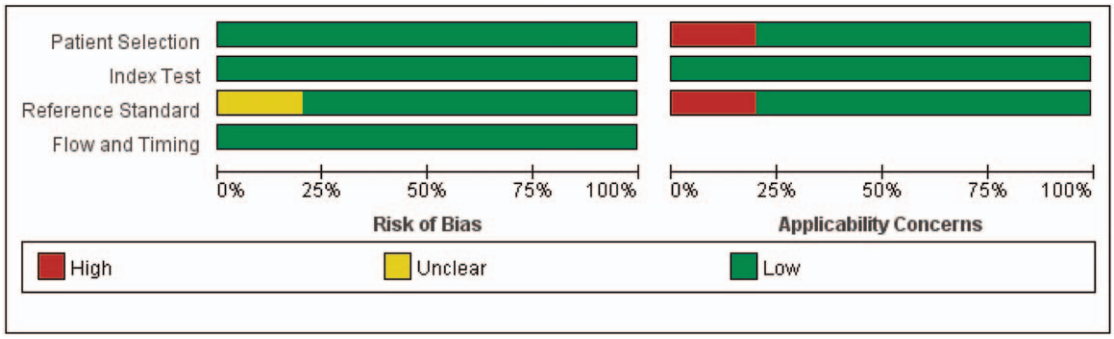

Figure 4. Methodological quality graph.

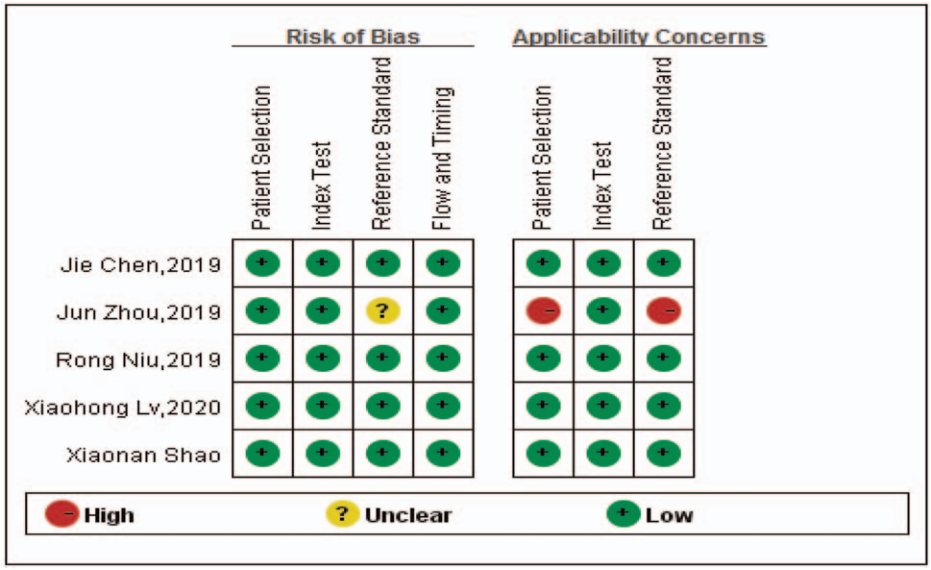

Figure 5. Methodological quality summary.

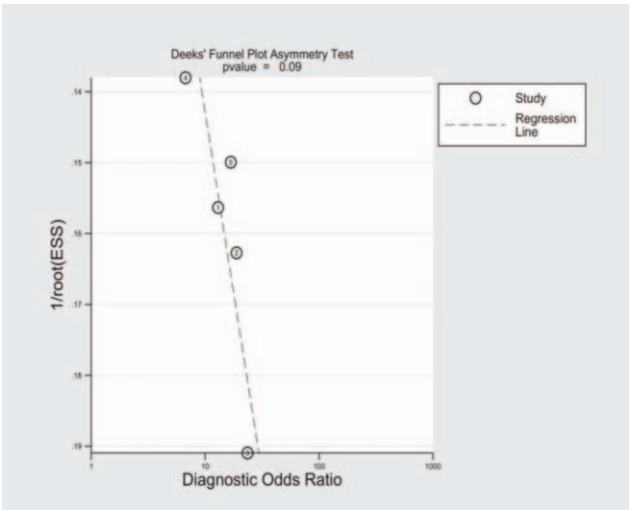

Figure 6. Deeks funnel plot, $P = .09$.

Author contributions

Conceptualization: Yinglin Ge.
Data curation: Yinglin Ge, Qun Du, Hailin Han.
Formal analysis: Yinglin Ge.
Investigation: Menglei Li.
Methodology: Yinglin Ge.
Project administration: Yinglin Ge.
Software: Jitao Xiao, Menglei Li.
Writing – original draft: Jitao Xiao.
Writing – review & editing: Jitao Xiao.

References

[1] Lee SM, Park CM, Goo JM, et al. Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: differentiation by using CT features[J]. Radiology 2013;268:265–73.
[2] Heidinger BH, Anderson KR, Nemec U, et al. Lung adenocarcinoma manifesting as pure ground-glass nodules: correlating CT size, volume, density, and roundness with histopathologic invasion and size[j]. J Thorac Oncol 2017;12:1288–98.
[3] Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European

Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma- ScienceDirect[J]. J Thorac Oncol 2011;6: 244–85.
[4] William D, Travis , et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification-ScienceDirect[J]. J Thorac Oncol 2015;10:1243–60.
[5] Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011;24:653–64.
[6] Dembitzer FR, Flores RM, Parides MK, et al. Impact of histologic subtyping on outcome in lobar vs sublobar resections for lung cancer: a pilot study. Chest 2014;146:175–81.
[7] Escriu C, Oudkerk , et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:1–21.
[8] Shao X, Shao X, Niu R, et al. A simple prediction model using fluorodeoxyglucose-PET and high-resolution computed tomography for discrimination of invasive adenocarcinomas among solitary pulmonary ground-glass opacity nodules. Nucl Medicine Commun 2019;40:1256–62.
[9] Niu Rong, Shao X, Jiang Z, et al. Lung adenocarcinoma manifesting as ground-glass opacity nodules 3 cm or smaller: Evaluation with combined high-resolution CT and PET/CT modality. Am J Roentgenol 2019;213: W236–45.
[10] Zhou J, Li Y, Zhang Y, et al. Solitary ground-glass opacity nodules of stage IA pulmonary adenocarcinoma: combination of 18F-FDG PET/CT and high-resolution computed tomography features to predict invasive adenocarcinoma. Oncotarget 2017;8:23312–21.
[11] Jie Chen, Qingjie Ma. Solitary ground-grass opacity nodules of Pulmonaryadeno carconoma:combination of 18F-FDG PET/CT and high-resolution computerd tomography features to predict incasive adenocarcinama[D]. Jilin University of China 2019;1–49.
[12] Xiaohong Lv, Xiang Yang, Ning LIU, et al. The diagnostic value of PET/CT combined with HRCT in the aggressiveness of pulmonary solitary ground glass nodules. J Pract Radiol 2020;36:722–6.
[13] Lee JH, Park CM, Lee SM, et al. Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: their natural course and predictors of interval growth. Eur Radiol 2016;26: 1529–37.
[14] Aberle DR, Adams AM, Berg CD, et al. National Lung Screening Trial Research TeamReducedlungcancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.
[15] Brodersen J, Voss T, Martiny F, et al. Overdiagnosis of lung cancer with low-dose computed tomography screening: meta-analysis of the randomised clinical trials. Breathe 2020;16:200013–23.
[16] Iwano S, Kishimoto M, Ito S, et al. Prediction of pathologic prognostic factors in patients with lung adenocarcinomas: comparison of thin-section computed tomography and positron emission tomography/computed tomography. Cancer Imaging 2014;14:1–8.
[17] Hiromitsu D, Yasuhiro H, Shozo O, et al. Histopathologic characterization of lung adenocarcinoma in relation to fluorine-18-fluorodeoxyglucose uptake on positron emission tomography. Jpn J Clin Oncol 2013;43:874–82.