Application of dual-stream 3D convolutional neural network based on 18F-FDG PET/CT in distinguishing benign and invasive adenocarcinoma in ground-glass lung nodules

Xiaonan Shao
Third Affiliated Hospital of Soochow University

Rong Niu
Third Affiliated Hospital of Soochow University

Xiaoliang Shao
Third Affiliated Hospital of Soochow University

Jianxiong Gao
Third Affiliated Hospital of Soochow University

Yunmei Shi
Third Affiliated Hospital of Soochow University

Zhenxing Jiang
Third Affiliated Hospital of Soochow University

Yuetao Wang (✉ yuetao-w@163.com)
the Third Affiliated Hospital of Soochow University  https://orcid.org/0000-0003-2859-8625

Research Article

Keywords: Lung adenocarcinoma, differential diagnosis, deep learning, fluorodeoxyglucose F18, positron emission tomography-computed tomography

Posted Date: June 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-636120/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Purpose:** This work aims to train, validate and test a dual-stream three-dimensional convolutional neural network (3D-CNN) based on Fluorine 18 ($^{18}$F)-fluorodeoxyglucose (FDG) PET/CT to distinguish benign lesions and invasive adenocarcinoma (IAC) in ground-glass nodules (GGNs).

**Methods:** We retrospectively analyzed patients with suspicious GGNs who underwent $^{18}$F-FDG PET/CT in our hospital from November 2011 to November 2020. The patients with benign lesions or IAC were selected for this study. According to the ratio of 7:3, the data was randomly divided into training data and testing data. Partial image feature extraction software was used to segment PET and CT images, and the training data after using the data augmentation was used for the training and validation (5-fold cross-validation) of the three CNNs (PET, CT, and PET/CT networks).

**Results:** A total of 23 benign nodules and 92 IAC nodules from 106 patients were included in this study. In the validation set, the performance of PET network (accuracy of 0.92 ± 0.02; sensitivity and specificity of 0.97 ± 0.03 and 0.94 ± 0.04) were better than CT network (accuracy of 0.84 ± 0.03; sensitivity and specificity of 0.90 ± 0.07 and 0.90 ± 0.04); in the testing set, the performance of both networks declined. However, when the specificity was close, the accuracy and sensitivity of PET network (0.79 ± 0.05 and 0.90 ± 0.05) were still higher than CT network (0.72 ± 0.05 and 0.79 ± 0.08). For the dual-stream PET/CT network, its performance was almost the same as PET network in the validation set; while in testing set, although its performance decreased (accuracy was 0.81 ± 0.03; sensitivity and specificity were 0.92 ± 0.03 and 0.86 ± 0.00), it was still higher than CT or PET networks. Moreover, the accuracy of PET/CT network was higher than two nuclear medicine physicians [Physician 1 (3-year experience): 0.70 and Physician 2 (10-year experience): 0.73].

**Conclusion:** The 3D-CNN based on $^{18}$F-FDG PET/CT can be used to distinguish benign lesions and IAC in GGNs, and the performance is better when both CT and PET images are used together.

Introduction

With the application of low-dose CT (LDCT) and the screening of COVID-19, the incidence of early lung adenocarcinoma manifested as ground-glass opacity nodule (GGN) has increased rapidly [1, 2]. To treat lung GGN, an important early step is to estimate the probability of malignancy. If the predicted probability of malignancy is high, more aggressive treatment methods should be considered [3]. GGNs are associated with various lung diseases, such as inflammatory pseudotumor, tuberculoma, sclerosing hemangioma, lymphoepithelioma, and non-small cell lung cancer (NSCLC), etc. [4]. The imaging features used to determine lesion malignancy include size, density, follow-up stability, edge appearance, wall thickness, and the presence of cavitation and calcification [5-7]. The clinical management of GGN is determined based on the assessed risk, which may involve routine CT follow-up, functional imaging, and/or tissue biopsy [5, 8, 9].
Several studies [10, 11] found that a single CT morphological feature and quantitative parameter did not have a good diagnostic value for GGN. In recent years, the extraction of quantitative imaging features from medical scans (“Radiomics” [12-14]) has attracted broad research interest, and it has been considered as a possible method for distinguishing benign and malignant lung nodules [15]. The basic principle of Radiomics is to use the image information that may be clinically relevant but not noticed by human eyes [16]. Radiomics can perform a comprehensive analysis of the region of interest, while the biopsy can only capture a small part of the lesion [17]. Radiomics has been extensively studied in PET/CT imaging [18]. The latest study from Palumbo et al. [19] found that the shape and texture features of $^{18}$F-FDG PET/CT could provide more information for distinguishing benign and malignant lung nodules than conventional imaging functions alone.

Machine learning methods have been introduced into medical image analysis and evolved into deep learning methods (especially the use of multilayer convolutional neural networks (CNN)) [20-24]. Tau et al. [25] showed that using CNN to analyze the primary tumors of newly diagnosed NSCLC patients with segmented PET images could make reasonable predictions for N category. Another study found that it was feasible to use CNN to automatically locate and classify the $^{18}$F-FDG PET uptake patterns in foci suspicious and nonsuspicious for cancer in patients with lung cancer and lymphoma; moreover, it could achieve higher diagnostic performance when using CT and PET images at the same time [26]. As far as we know, three-dimensional convolutional neural networks (3D-CNN) have not been used to analyze PET/CT images, and the dual-stream CNN (data obtained from PET and CT as inputs) [24] has not been tested to distinguish benign and malignant GGN.

Since the clinical management strategies for treating benign lesions and invasive adenocarcinoma (IAC) are completely different [9], the accurate identification of benign and malignant GGN is of great importance. Therefore, this study aims to train, validate, and test the 3D-CNN based on $^{18}$F-FDG PET/CT images and evaluate CT, PET, and PET/CT 3D-CNN performance in distinguishing benign lesions and IAC.

**Materials And Methods**

**Participants**

In this single-center study, we reviewed 228 GGN patients who underwent $^{18}$F-FDG PET/CT examinations in our hospital from November 2011 to November 2020. The Institutional Ethics Committee reviewed the retrospective analysis (No. [2020] KD 075) and agreed that the written informed consent was not required. The inclusion criteria for patients were as follows: (1) Patients received a clear diagnosis by surgery within one month after PET/CT examination, or the benign GGN volume decreased during CT follow-up; (2) Maximum GGN diameter $\leq$30mm. The exclusion criteria were as follows: (1) Lung adenocarcinoma stage >IA; (2) Poor image quality or low FDG uptake, and the lesion was difficult to measure; (3) History of malignant tumors in the past 5 years; (4) Severe liver disease or diabetes; (5) Other pathological subtypes: atypical adenoma hyperplasia (AAH), adenocarcinoma in situ (AIS) or microinvasive
adenocarcinoma (MIA). The data of included patients were collected by reviewing the cases or follow-up by telephone. The patient selection process was shown in Figure 1.

**FDG PET/CT image acquisition**

The image acquisition protocol was based on the Imaging Biomarker Standardization Initiative (IBSI) Reporting Guide [27]. The details of all procedures are described in the supplementary material. Within one month before surgery, the patient received $^{18}$F-FDG PET/CT examination (Biograph mCT 64, Siemens, Erlangen, Germany). According to the European Association for Nuclear Medicine (EANM) guideline 1.0 (version 2.0 was released in February 2015) [28], $^{18}$F-FDG PET/CT images were acquired at 60 ± 5 minutes after $^{18}$F-FDG injection. All PET/CT images were reconstructed on the processing workstation (TrueD software, Siemens Healthcare). CT data were used to perform attenuation correction on PET images, and the corrected PET image was combined with CT image.

**Image preprocessing**

Figure 2 summarized the overall approach to developing a deep learning model. All images were segmented using 3D-Slicer (version 4.11.20200930, www.slicer.com). For PET images, we used a semi-automatic segmentation method developed by Beichel et al. [29]. In order to consider the pattern of tumor edge, the generated boundary was dilated by 1 pixel. To eliminate the influence of lung background noise, we set the outside area of lesion boundary as a value 0. Since the sample size was small, to ensure the learning effect, simplify the task, and reduce the memory requirements and processing time, we segmented a 3D volume that occupied a small part of the entire image. This 3D volume was used as the input for PET model. Because the matrix size of FDG PET varied according to the reconstruction algorithm, the Nearest Neighbor interpolation method was used to resliced the segmented cube-shaped volume into isotropic spacing (for example, 4.07mm$^3$).

For CT images (3mm), we used NVIDIA AI-Assisted Annotation (3D-Slicer built-in) and the boundary-based CT segmentation models to process lung nodule images. In order to consider the pattern of tumor edge, the generated boundary was dilated by 3.00mm. To eliminate the influence of lung background noise, we filled the outside area of lesion boundary with a value -2000 (all values were 0 after normalization). Similarly, we segmented a 3D volume that occupied a small part of the entire image. This 3D volume was used as the input for CT model. Since the size of CT matrix varied, the Nearest Neighbor interpolation method was used to resliced the segmented cube-shaped volume into isotropic spacing (for example, 0.73mm$^3$).

**The training of deep learning model**

Due to the limited size of training data, we used a rotation method for data augmentation. More specifically, image augmentation aimed to develop a robust deep learning model against the rotation of tumors, which can be affected by position and location of tumors. For each image in the training data, we
rotated the segmented tumor by 90°, 180°, and 270°. This type of image augmentation is usually used in deep learning training for natural images and medical images [30, 31].

The segmented tumor was the deep learning model's input whose architecture was based on 3D-CNN [32]. FDG-PET was converted to SUVbw (bodyweight units), and the SUV values ranging from [0-15] were linearly mapped to a [0-1] range. Similarly, CT images were expressed in Hounsfield units (HU), and HU values ranging from [-1000-400] were linearly mapped to a [0-1] range. Since the sizes of input images were different, CNN was designed to generate output regardless of the input matrix size.

Due to the lack of available data, we adopted a cross-validation method to reliably evaluate the model [33]. The 5-fold cross-validation was applied for the training data, and the testing data was used until the model was optimized by the training set/internal validation set of the cross-validation. To train the model, the Adam optimizer (initial learning rate 0.0001) was used. The number of epochs for iterative training was set as 50. For comparison, we constructed three 3D-CNNs: CT, PET, and PET/CT. The supplementary material provides more detailed 18F-FDG PET/CT image acquisition methods, tumor segmentation, and deep learning model generation.

**Statistical Analysis**

Propensity score matching (PSM) was used to identify a group of GGNs with similar baseline characteristics. The propensity score was the conditional probability of a specific exposure given a set of covariates measured at baseline. The non-parsimonious multivariate logistic regression model was used to estimate the propensity score, with benign and malignant as grouping variables, and all the baseline characteristics listed in Table 1 were covariates. The greedy-matching algorithm was used to generate 1:4 matching pairs with replacement. Since the sample size was small, the difference in propensity score between the two groups was set within 0.6 [34]. The specific parameters were listed in the supplementary material.

The continuous variables were expressed as mean (standard deviation) (Gaussian distribution) or median (range) (Skewed distribution), and categorical variables were expressed as number or proportion. \( \chi^2 \) (categorical variables), student T test (normal distribution), or Man Whitney U test (skewed distribution) were used to detect the differences between benign and malignant groups (binary variable). All the analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). \( P \) values less than 0.05 (two-sided) was considered statistically significant.

We used different CNNs to analyze the data, and the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, and F1-score (a score that measures the accuracy of CNN, ranging from 0 to 1 (perfect test accuracy)) was calculated to evaluate the performance of different CNNs on the validation set and testing set.

**Results**
The characteristics of patient nodule

A total of 157 GGNs were included in the final data analysis. Among them, 23 were benign (including 4 fungal infections, 1 tuberculosis, 4 granulomatous inflammation, 2 organizing pneumonia, 1 alveolar epithelial bronchiolar metaplasia, and 11 with other inflammatory lesions), and 134 were IAC. The comparison of baseline characteristics between the two GGN groups after PSM was shown in Table 1.

23 benign nodules (maximum diameter 16.4 ± 6.6mm; range 4.5-28.5 mm) and 92 IAC nodules (maximum diameter 19.4 ± 6.5mm; range 5.5-30.0 mm) were included in the study. These 115 nodules were from 106 patients, including 46 males and 60 females. The average age was 59.2 ± 9.1 years old (range: 31-78 years old), and the fasting blood glucose was 6.8 ± 1.7 mmol/L (range: 4.1-11.0 mmol/L). There were 29 smokers (27.4%), and 22 cases (20.8%) had multifocal GGNs. We randomly divided the data set (n = 115) into training data (n = 82; IAC = 65, benign = 17) and testing data (n = 33; IAC = 27, benign = 6) according to a 7:3 ratio. There was no overlap between the two sets.

After the three 3D-CNNs were cross-validated (5-fold cross-validation) on augmented training data, they were used to predict GGN malignancy (IAC vs. benign) on the validation set. The average accuracy of the CT network in validation set was 0.84 ± 0.03, with the average sensitivity of 0.90 ± 0.07, specificity of 0.90 ± 0.04, F1-score of 0.89 ± 0.02, and average AUC of 0.87 ± 0.04. The average accuracy of CT network in the testing set was 0.72 ± 0.05, with the average sensitivity of 0.79 ± 0.08, specificity of 0.86 ± 0.04, and F1-score of 0.82 ± 0.04 (Figure 3 and Table 2).

The average accuracy of PET network in the validation set was 0.92 ± 0.02, with the average sensitivity of 0.97 ± 0.03, specificity of 0.94 ± 0.04, F1-score of 0.95 ± 0.01, and average AUC of 0.97 ± 0.02. The average accuracy of PET network on the testing set was 0.79 ± 0.05, with the average sensitivity of 0.85 ± 0.02, and F1-score of 0.87 ± 0.03 (Figure 3 and Table 2). These results showed that, in the validation set, the performance and average AUC of PET network were better than CT network, while in the testing set, the performance of both CT and PET networks declined; however, when the specificity was similar, the accuracy, sensitivity, and F1-score of PET network were still higher than CT network.

The average accuracy of the dual-stream PET/CT network in the validation set was 0.92 ± 0.02, with the average sensitivity of 0.98 ± 0.01, specificity of 0.94 ± 0.02, F1-score of 0.96 ± 0.01, and average AUC of 0.97 ± 0.02. The average accuracy of PET/CT network in the testing set was 0.81 ± 0.03, with the average sensitivity of 0.92 ± 0.03, specificity of 0.86 ± 0.00, and F1-score of 0.89 ± 0.02 (Figure 3 and Table 2). Thus, the performance and average AUC of PET/CT network were almost the same as PET network in the validation set; but in the testing set, the performance indicators of PET/CT network were better than CT and PET networks, even though they all declined.

To further test and evaluate the performance of dual-stream PET/CT network, we used the testing set to compare the accuracy of two nuclear medicine physicians with the PET/CT network. The results showed
that the accuracy of PET/CT network was higher than the two nuclear medicine physicians [0.81 vs. Physician 1 (3-year experience): 0.70 vs. Physician 2 (10-year experience): 0.73].

**Discussion**

In this study, we developed a dual-stream 3D-CNN that can distinguish between benign lesions and IAC based on clinical 18F-FDG PET/CT GGN images. In the testing set (n = 33), the sensitivity, specificity, and accuracy of PET/CT network were 0.92 ± 0.03, 0.86 ± 0.00 and 0.81 ± 0.03, respectively, which were comparable to or higher than those of the CT and PET networks. Moreover, compared with the diagnosis results of two nuclear medicine physicians, PET/CT network also showed better performance.

The 2017 Fleischner Association Guidelines [9] recommend that the planned CT follow-ups be carried out for GGNs, and persisted GGNs can be determined according to the dynamic changes of the nodules; for example, the infectious or inflammatory lesions may shrink or disappear during follow-up. However, long-term CT follow-up brings severe anxiety and repeated radiation exposure to patients, not applicable to some patients. Therefore, more effective imaging techniques or the construction of multi-factor predictive models are needed to distinguish between benign and malignant GGNs. Among the many models, only the Brock model [35] considers the characteristics of GGNs and adjusts the correlation coefficient according to the nodule type. However, this model's application is complicated, and its modeling data came from the initially screened patients whose malignancy rate was low (5.5%). Although in recent years, the focus of CT radiomics has turned to the field of GGN invasiveness [36], the problem of distinguishing benign and malignant GGNs is still unsolved. Gong et al. [37] developed a radiomics feature analysis method based on CT images to distinguish benign and malignant GGNs and confirmed its feasibility. The AUC of identifying benign and IAC nodules in the training set was 0.93, and the accuracy in the testing set was 0.61, which was higher than the two radiologists (0.53 and 0.56, respectively) [37]. In this study, the average AUC of CT network also reached 0.87, and the accuracy was higher than CT radiomics method as mentioned above (0.72 vs. 0.61), suggesting that CNN had better classification performance.

18F-FDG PET has been clinically recognized as a method to identify malignant solitary pulmonary nodules (SPN). Under the diagnostic criteria of maximum standard uptake value (SUV_{max}) > 2.5, the sensitivity and specificity of 18F-FDG PET are 79%-100% and 60%-100%, respectively [38]. However, the diagnostic value of PET for GGN is still controversial. Many literatures reported that GGNs were different from solid nodules, and PET imaging had a higher false-negative rate and false-positive rate for GGNs [39]. In this study, the classification performance of PET network was better than CT network, which seems to contradict the higher spatial resolution of CT. The latest study on identifying benign and malignant SPNs also found that the models based on PET radiomics features were generally better than the models based on CT characteristics [19], consistent with previously published results [40-42]. These findings are interesting because they demonstrate that using PET texture features to assess radiotracer uptake's heterogeneity (discussed in [43, 44]) is as important as using CT texture features to analyze tissue density, although most literature is focused on CT.
Another possible factor that limits the accuracy of CNN is the use of data from only one imaging modality (PET or CT), which is an attempt to simplify and standardize data extraction [25]. The various machine learning techniques that have been studied (including CNN) have not yet produced predictions that can change the clinical practice. In this study, we combined the data from PET and CT images, used these data to train a dual-stream CNN, and evaluated and analyzed the model performance [24]. Although PET/CT’s performance was almost the same as PET network in the validation set, its performance indicators were still higher than both CT and PET networks in the testing set. From the perspective of multi-modal deep learning, we confirmed PET/CT dual-mode imaging’s advantages compared to conventional single-mode imaging. Besides, in this study, we only used limited testing set to compare and evaluate the performance of PET/CT network and two nuclear medicine physicians. If our PET/CT network is robust in future tests with larger and more diverse data sets, this study may have a major clinical impact on assisting nuclear medicine physicians in making decisions about GGN detection and diagnosis.

Our study still had some limitations: (1) Although we used a data augmentation strategy in the training data, single-center research and small sample size still affected CNN’s performance. Specifically, three networks’ performance all declined in the testing set compared to in the validation set, indicating that there was overfitting. The solution is to continue to collect samples to increase the size of training data or to adopt multicenter research to improve the robustness of the network. (2) To ensure the sample size of CT data, we used 3mm conventional CT instead of 1mm HRCT (better detail performance), which may affect the performance of CT network. (3) During the screening of PET data, we removed a small number of IAC nodules that could not be segmented due to low PET uptake. For these GGNs, $^{18}$F-FDG is not applicable, and we look forward to developing a new PET imaging agent. (4) Also, our network was not "smart" enough. Although both CT and PET images use semi-automatic segmentation methods, there were still too many manual manipulations during the image preprocessing process. In the future, CNN should be used for image segmentation to achieve an "end-to-end" workflow truly.

**Conclusions**

In this study, we successfully constructed, trained, validated, and tested a dual-stream 3D-CNN based on $^{18}$F-FDG PET/CT and used it to classify benign lesions and IAC in GGNs. The dual-stream network was better than the CNN based on CT or PET alone. Therefore, in the absence of well-trained and experienced physicians, this CNN may help the differentiation and clinical management of benign and malignant GGNs. Besides, we also expect clinicians to use this CNN for other tumor research suitable for PET/CT imaging.

**List Of Abbreviations**

- low-dose CT (LDCT)
- ground-glass opacity nodule (GGN)
- non-small cell lung cancer (NSCLC)
- convolutional neural networks (CNN)
- three-dimensional convolutional neural networks (3D-CNN)
- invasive adenocarcinoma (IAC)
- atypical adenoma hyperplasia (AAH)
- adenocarcinoma in situ (AIS)
Declarations

Ethical approval

Our study was approved by the ethics committee of the Third Affiliated Hospital of Soochow University for retrospective analysis and did not require informed consent.

Consent for publication

Written informed consent was obtained from all the patients.

Availability of data and materials

The data supporting our findings are available upon request.

Competing Interests

The authors of this manuscript declare to have no conflict of interest related to this study.

Funding

This study was supported by Key Laboratory of Changzhou High-tech Research Project (Grant No. CM20193010) and Young Talent Development Plan of Changzhou Health Commission (Grant No. CZQM2020012).

Authors’ contributions

XS and YW contributed to the study concepts and the study design. RN, JG, YS, and ZJ contributed to data acquisition and reconstructions. XS, RN, XS, and ZJ contributed to data analyses and interpretation. XS contributed to the statistical analysis. XS, RN, and YW contributed to the manuscript preparation and manuscript editing and reviewing. All authors read and approved the final manuscript.

Acknowledgments

None.

References

1. Tsutsui S, Ashizawa K, Minami K, Tagawa T, Nagayasu T, Hayashi T, et al. Multiple focal pure ground-glass opacities on high-resolution CT images: Clinical significance in patients with lung cancer.
2. Miller A, Markowitz S, Manowitz A, Miller JA. Lung cancer screening using low-dose high-resolution CT scanning in a high-risk workforce: 3500 nuclear fuel workers in three US states. Chest. 2004;125:152s-3s.

3. Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. Radiology. 2009;253:606-22. doi:10.1148/radiol.2533090179.

4. Jiang L, Situ D, Lin Y, Su X, Zheng Y, Zhang Y, et al. Clinical model to estimate the pretest probability of malignancy in patients with pulmonary focal Ground-glass Opacity. Thoracic cancer. 2013;4:380-4. doi:10.1111/1759-7714.12032.

5. Chan EY, Gaur P, Ge Y, Kopas L, Santacruz JF, Gupta N, et al. Management of the Solitary Pulmonary Nodule. Archives of pathology & laboratory medicine. 2017;141:927-31. doi:10.5858/arpa.2016-0307-RA.

6. Edey AJ, Hansell DM. Incidentally detected small pulmonary nodules on CT. Clinical radiology. 2009;64:872-84. doi:10.1016/j.crad.2009.03.006.

7. Truong MT, Ko JP, Rossi SE, Rossi I, Viswanathan C, Bruzzi JF, et al. Update in the evaluation of the solitary pulmonary nodule. Radiographics : a review publication of the Radiological Society of North America, Inc. 2014;34:1658-79. doi:10.1148/rg.346130092.

8. Nasim F, Ost DE. Management of the solitary pulmonary nodule. Current opinion in pulmonary medicine. 2019;25:344-53. doi:10.1097/mcp.0000000000000586.

9. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284:228-43. doi:10.1148/radiol.2017161659.

10. Dai J, Yu G, Yu J. Can CT imaging features of ground-glass opacity predict invasiveness? A meta-analysis. Thoracic cancer. 2018;9:452-8. doi:10.1111/1759-7714.12604.

11. Yang W, Sun Y, Fang W, Qian F, Ye J, Chen Q, et al. High-resolution Computed Tomography Features Distinguishing Benign and Malignant Lesions Manifesting as Persistent Solitary Subsolid Nodules. Clin Lung Cancer. 2018;19:e75-e83. doi:10.1016/j.cllc.2017.05.023.

12. Bianconi F, Palumbo I, Spanu A, Nuvoli S, Fravolini ML, Palumbo B. PET/CT Radiomics in Lung Cancer: An Overview. Applied Sciences. 2020;10:1718.

13. Kaseda K. Recent and Current Advances in FDG-PET Imaging within the Field of Clinical Oncology in NSCLC: A Review of the Literature. Diagnostics (Basel, Switzerland). 2020;10.
doi:10.3390/diagnostics10080561.

14. Vallières M, Zwanenburg A, Badic B, Cheze Le Rest C, Visvikis D, Hatt M. Responsible Radiomics Research for Faster Clinical Translation. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;59:189-93. doi:10.2967/jnumed.117.200501.

15. Wilson R, Devaraj A. Radiomics of pulmonary nodules and lung cancer. Translational lung cancer research. 2017;6:86-91. doi:10.21037/tlcr.2017.01.04.

16. Cook GJR, Goh V. A Role for FDG PET Radiomics in Personalized Medicine? Seminars in nuclear medicine. 2020;50:532-40. doi:10.1053/j.semnuclmed.2020.05.002.

17. Mayerhoefer ME, Materka A, Langs G, Häggström I, Szczypiński P, Gibbs P, et al. Introduction to Radiomics. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020;61:488-95. doi:10.2967/jnumed.118.222893.

18. Hatt M, Le Rest CC, Antonorsi N, Tixier F, Tankyevych O, Jaouen V, et al. Radiomics in PET/CT: Current Status and Future AI-Based Evolutions. Seminars in nuclear medicine: Elsevier; 2020.

19. Palumbo B, Bianconi F. Value of Shape and Texture Features from (18)F-FDG PET/CT to Discriminate between Benign and Malignant Solitary Pulmonary Nodules: An Experimental Evaluation. 2020;10. doi:10.3390/diagnostics10090696.

20. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521:436-44. doi:10.1038/nature14539.

21. Yamashita R, Nishio M, Do RKG, Togashi K. Convolutional neural networks: an overview and application in radiology. Insights into imaging. 2018;9:611-29. doi:10.1007/s13244-018-0639-9.

22. Fazal MI, Patel ME, Tye J, Gupta Y. The past, present and future role of artificial intelligence in imaging. European journal of radiology. 2018;105:246-50. doi:10.1016/j.ejrad.2018.06.020.

23. Suzuki K. Overview of deep learning in medical imaging. Radiological physics and technology. 2017;10:257-73. doi:10.1007/s12194-017-0406-5.

24. Sollini M, Antunovic L. Towards clinical application of image mining: a systematic review on artificial intelligence and radiomics. 2019;46:2656-72. doi:10.1007/s00259-019-04372-x.

25. Tau N, Stundzia A, Yasufuku K, Hussey D, Metser U. Convolutional Neural Networks in Predicting Nodal and Distant Metastatic Potential of Newly Diagnosed Non-Small Cell Lung Cancer on FDG PET Images. AJR American journal of roentgenology. 2020;215:192-7. doi:10.2214/ajr.19.22346.

26. Sibille L, Seifert R. (18)F-FDG PET/CT Uptake Classification in Lymphoma and Lung Cancer by Using Deep Convolutional Neural Networks. 2020;294:445-52. doi:10.1148/radiol.2019191114.
27. Zwanenburg A, Leger S, Vallières M, Löck S. Image biomarker standardisation initiative. arXiv preprint arXiv:161207003. 2016.

28. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. European journal of nuclear medicine and molecular imaging. 2015;42:328-54.

29. Beichel RR, Van Tol M, Ulrich EJ, Bauer C, Chang T, Plichta KA, et al. Semiautomated segmentation of head and neck cancers in 18F-FDG PET scans: A just-enough-interaction approach. Medical physics. 2016;43:2948-64. doi:10.1118/1.4948679.

30. Uzunova H, Wilms M, Handels H, Ehrhardt J. Training CNNs for image registration from few samples with model-based data augmentation. International Conference on Medical Image Computing and Computer-Assisted Intervention: Springer; 2017. p. 223-31.

31. Perez L, Wang J. The effectiveness of data augmentation in image classification using deep learning. arXiv preprint arXiv:171204621. 2017.

32. Zhou B, Khosla A, Lapedriza A, Oliva A, Torralba A. Learning deep features for discriminative localization. Proceedings of the IEEE conference on computer vision and pattern recognition; 2016. p. 2921-9.

33. Ling CX, Huang J, Zhang H. AUC: a better measure than accuracy in comparing learning algorithms. Conference of the canadian society for computational studies of intelligence: Springer; 2003. p. 329-41.

34. Patino CM, Ferreira JC. Propensity scores: a tool to help quantify treatment effects in observational studies. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2017;43:86. doi:10.1590/s1806-37562017000000099.

35. Baldwin DR. Management of pulmonary nodules according to the 2015 British Thoracic Society guidelines. Key messages for clinical practice. Pol Arch Med Wewn. 2016;126:262-74. doi:10.20452/pamw.3379.

36. Wu G, Woodruff HC. Diagnosis of Invasive Lung Adenocarcinoma Based on Chest CT Radiomic Features of Part-Solid Pulmonary Nodules: A Multicenter Study. 2020;297:451-8. doi:10.1148/radiol.2020192431.

37. Gong J, Liu J, Hao W, Nie S, Wang S, Peng W. Computer-aided diagnosis of ground-glass opacity pulmonary nodules using radiomic features analysis. Physics in medicine and biology. 2019;64:135015. doi:10.1088/1361-6560/ab2757.

38. Hubner KF, Buonocore E, Singh SK, Gould HR, Cotten DW. Characterization of chest masses by FDG positron emission tomography. Clinical nuclear medicine. 1995;20:293-8. doi:10.1097/00003072-
199504000-00001.

39. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung cancer (Amsterdam, Netherlands). 2004;45:19-27. doi:10.1016/j.lungcan.2004.01.009.

40. Taralli S, Scolozzi V, Foti M, Ricciardi S, Forcione AR, Cardillo G, et al. (18)F-FDG PET/CT diagnostic performance in solitary and multiple pulmonary nodules detected in patients with previous cancer history: reports of 182 nodules. European journal of nuclear medicine and molecular imaging. 2019;46:429-36. doi:10.1007/s00259-018-4226-6.

41. Miwa K, Inubushi M, Wagatsuma K, Nagao M, Murata T, Koyama M, et al. FDG uptake heterogeneity evaluated by fractal analysis improves the differential diagnosis of pulmonary nodules. European journal of radiology. 2014;83:715-9. doi:10.1016/j.ejrad.2013.12.020.

42. Christensen JA, Nathan MA, Mullan BP, Hartman TE, Swensen SJ, Lowe VJ. Characterization of the solitary pulmonary nodule: 18F-FDG PET versus nodule-enhancement CT. AJR American journal of roentgenology. 2006;187:1361-7. doi:10.2214/ajr.05.1166.

43. Vicente AMG, Pérez-García VM, Castrejón ÁS. 18F-fluorodeoxyglucose positron emission tomography/computed tomography characterization of solitary pulmonary nodules: can we do better? Journal of thoracic disease. 2015;7:E215.

44. Schillaci O, Calabria FF. Comments on characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative activity distribution analysis. Journal of thoracic disease. 2015;7:1708-12. doi:10.3978/j.issn.2072-1439.2015.10.61.

Tables

Table 1 Comparison of baseline characteristics of the two GGN groups after PSM
| Variables                  | Benign | IAC  | Standardized diff. | P-value |
|---------------------------|--------|------|--------------------|---------|
| N                         | 23     | 92   |                    |         |
| Age (years)               | 57.83 ± 10.90 | 59.16 ± 8.62 | 0.1361 | 0.530 |
| Fasting blood glucose     | 6.93 ± 1.87 | 6.73 ± 1.71 | 0.1124 | 0.621 |
| Gender                    | 0.3991 | 0.147|
| female                    | 9 (39.1)| 54 (58.7)|         |         |
| male                      | 14 (60.9)| 38 (41.3)|         |         |
| Smoking history           | 0.3714 | 0.168|
| no                        | 13 (56.5)| 68 (73.9)|         |         |
| yes                       | 10 (43.5)| 24 (26.1)|         |         |
| GGN number grouping       | 0.0967 | 0.875|
| solitary                  | 16 (69.6)| 68 (73.9)|         |         |
| multifocal                | 7 (30.4)| 24 (26.1)|         |         |

The results in the table are expressed as Mean ± SD / N (%). GGN, ground-glass nodule; PSM, propensity score matching; IAC, invasive adenocarcinoma.

**Table 2** The performance indicators of three 3D-CNNs

| Model                  | Accuracy  | Sensitivity | Specificity | F1-score |
|------------------------|-----------|-------------|-------------|----------|
| **Validation set**     |           |             |             |          |
| CT 3D-CNN              | 0.84 ± 0.03 | 0.90 ± 0.07 | 0.90 ± 0.04 | 0.89 ± 0.02 |
| PET 3D-CNN             | 0.92 ± 0.02 | 0.97 ± 0.03 | 0.94 ± 0.04 | 0.95 ± 0.01 |
| PET/CT 3D-CNN          | 0.92 ± 0.02 | 0.98 ± 0.01 | 0.94 ± 0.02 | 0.96 ± 0.01 |
| **Testing set**        |           |             |             |          |
| CT 3D-CNN              | 0.72 ± 0.05 | 0.79 ± 0.08 | 0.86 ± 0.04 | 0.82 ± 0.04 |
| PET 3D-CNN             | 0.79 ± 0.05 | 0.90 ± 0.05 | 0.85 ± 0.02 | 0.87 ± 0.03 |
| PET/CT 3D-CNN          | 0.81 ± 0.03 | 0.92 ± 0.03 | 0.86 ± 0.00 | 0.89 ± 0.02 |

The results in the table are expressed as Mean ± SD. 3D-CNN, three-dimensional convolutional neural network.

**Figures**
Figure 1

Study flowchart. GGN, ground-glass nodule; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.
Figure 2

The overview of the process of generating deep learning algorithms to predict benign and malignant GGNs.
Figure 3

The ROC of three 3D-CNNs after 5-fold cross-validation

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• Supplementarymaterials.docx