

ORIGINAL ARTICLE

A model of malignant risk prediction for solitary pulmonary nodules on ^{18}F -FDG PET/CT: Building and estimating

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Keywords

Deoxyglucose; photon-emission tomography; risk assessment; solitary pulmonary nodule; tomography; x-ray computed.

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Thoracic Cancer **11** (2020) 1211–1215**Abstract**

Background: To develop a model of malignant risk prediction of solitary pulmonary nodules (SPNs) using metabolic characteristics of lesions.

Methods: A total of 362 patients who underwent PET/CT imaging from January 2013 to July 2017 were analyzed. Differences in the clinical and imaging characteristics were analyzed between patients with benign SPNs and those with malignant SPNs. Risk factors were screened by multivariate nonconditional logistic regression analysis. The self-verification of the model was performed by receiver operating characteristic (ROC) curve analysis, and out-of-group verification was performed by k-fold cross-validation.

Results: There were statistically significant differences in age, maximum standardized uptake value (SUV_{max}), size, lobulation, spiculation, pleural traction, vessel connection, calcification, presence of vacuoles, and emphysema between patients with benign nodules and those with malignant nodules (all $P < 0.05$). The risk factors for malignant nodules included age, SUV_{max} , size, lobulation, calcification and vacuoles. The logistic regression model was as follows: $P = 1/(1 + e^{-x})$, $x = -5.583 + 0.039 \times \text{age} + 0.477 \times \text{SUV}_{\text{max}} + 0.139 \times \text{size} + 1.537 \times \text{lobulation} - 1.532 \times \text{calcification} + 1.113 \times \text{vacuole}$. The estimated area under the curve (AUC) for the model was 0.915 (95% CI: 0.883–0.947), the sensitivity was 89.7%, and the specificity was 78.9%. K-fold cross-validation showed that the training accuracy was 0.899 ± 0.011 , and the predictive accuracy was 0.873 ± 0.053 .

Conclusions: The risk factors for malignant nodules included age, SUV_{max} , size, lobulation, calcification and vacuoles. After verification, the model has satisfactory accuracy, and it may assist clinics make appropriate treatment decisions.

Introduction

Solitary pulmonary nodules (SPNs) usually refer to round lesions with a long diameter ≤ 30 mm found in chest imaging, without distal atelectasis, local lymph node enlargement, pleural effusion and surrounding satellite lesions.¹ With the development of modern imaging, the detection of SPNs has increased significantly. How to characterize and treat SPNs is a common concern of imaging diagnosticians, clinicians and patients. PET/CT diagnoses disease using both morphological and functional metabolism, which provides a new path for the diagnosis of SPNs.

Previous models for the identification of benign and malignant SPNs have been reported, such as BIMC, Herder, Mayo, Brock, VA, and PKUPH.^{2,3} There are also documents

that have shown that predictive models have good accuracy in the prediction of malignant SPNs in practice by case verification.² In this study, an SPN malignant risk prediction model was established based on the lesion morphology and functional characteristics obtained in the PET/CT examination to assist clinicians effectively diagnose and treat SPNs.

Methods**Patients**

The study was carried out in accordance with the principles of the Declaration of Helsinki. A retrospective analysis of SPN cases detected by PET/CT from January 2013 to

July 2017 was performed. Patients who had lesions with a long diameter ≥ 5 and ≤ 30 mm were recruited. All patients had intact thin-layer CT scans, PET scans and clinical data. Malignant SPNs had a pathological diagnosis, and benign SPNs were diagnosed according to pathology or follow-up results. The follow-up period was 24 months, and benign lesions were identified when they disappeared, decreased or remained unchanged during the follow-up period.⁴ Excluding patients with a history of malignant tumors and antitumor treatment, 362 patients were eventually recruited, including 194 males and 168 females, with a median age of 61 (22–88) years. There were 291 malignant cases, including 16 cases of small cell carcinoma and 275 cases of non-small cell carcinoma (including 250 cases of adenocarcinoma). There were 71 cases of benign SPNs, including 42 cases confirmed by pathology, and 22 of the remaining 29 cases disappeared (seven cases) or became smaller (15 cases) during follow-up, and the other seven cases did not change significantly. In the benign cases, five cases of ground-glass density nodules were diagnosed by follow-up. One disappeared during the follow-up period, two cases were reduced in size, and the other two cases showed no significant changes. Patient smoking history was evaluated by the smoking index (SI) and was classified into mild smoking and severe smoking according to whether SI was ≥ 20 packs \times year (one pack = 20 cigarettes). PET/CT images are from the MedEx database and picture archiving and communication systems.

Image acquisition

The PET/CT used was Discovery VCT type produced by GE Company, USA. ¹⁸F-deoxyglucose (FDG) is produced by the cyclotron and automatic synthesis module of Sumitomo Company, Japan. Its radiochemical purity is more than 95%, and the half-life of the drug is approximately 110 minutes. Patients were required to fast for more than six hours before the examination, so their blood glucose level was lower than 11.1 mmol/L (mostly less than 8.3 mmol/L). ¹⁸F-FDG 5.5–6.6 MBq/kg was intravenously injected, patients were instructed to urinate after 60 minutes, and then images were collected. The scanning range was from the cranium to the upper thigh, and the CT scan was acquired first with the following acquisition conditions: voltage 120 kV, current 110 mA, bed speed 29.46 cm/second, matrix 512 \times 512, layer thickness 5 mm. A PET scan was then performed: matrix 128 \times 128, 1.5–3.0 minutes/bed, collect 8–9 beds. After the PET data were attenuation corrected and reconstructed by iterative reconstruction, the image was merged with the CT image on the Xeleris workstation. For the routine chest CT scans, the acquisition conditions were as follows: voltage 120 kV, current 200 mA, bed speed 29.46 mm/second, matrix

512 \times 512, layer thickness 5 mm; in addition, 1.25 mm thin layer reconstruction was performed by a standard algorithm.

Image analysis

All PET/CT images were independently evaluated by two experienced PET/CT diagnosticians, and the third diagnosticians was consulted for any disagreements. The window width of the lung window was 1000 HU, the window position was -700 HU; the window width of the mediastinal window was 300 HU, and the window position was 45 HU. The CT features of the lesions were analyzed and included size, marginal signs (lobulation, spiculation, vessel connection, pleural traction), internal features (calcification, vacuoles, air bronchogram), and whether the patient also had emphysema or pulmonary fibrosis. Metabolic characteristics of the lesion were evaluated on multiple elliptical regions of interest (ROIs), on which the maximum standard uptake value (SUVmax) was measured, and the maximum value was used for semiquantitative analysis.

Statistical analysis

SPSS 22.0 and R3.4.2 statistical software was used. Some characteristics of the measurement data (patient's age, lesion size, SI, SUVmax, etc) did not meet the normal distribution, as expressed by $M (P_{25}, P_{75})$. The differences between the benign and malignant nodules were compared using the Mann-Whitney U test. When performing logistic analysis, the benign and malignancy of nodules were used as dependent variables (benign = 0, malignant = 1), and numerical variables, such as age (years), size (mm), and SI (packs \times year), and binary variables (without = 0, with = 1), such as lobulation, spiculation, pleural traction, vessel connection, calcification, vacuoles, air bronchogram, emphysema, and pulmonary fibrosis, were used as independent variables. Univariate logistic regression analysis was performed first, and regression equations were established by multivariate unconditional logistic regression analysis (backward method). Model self-verification was evaluated by area under the curve (AUC) of the receiver operating characteristic (ROC) curve, and out-of-group verification was performed by k-fold cross-validation ($k = 10$).

Results

Case records

There were 34, 26, 19, 59, 17, 11, 15, 13 and two cases showing lobulation, spiculation, pleural traction, vessel connection, calcification, vacuoles, air bronchogram, emphysema, and pulmonary fibrosis, respectively, among

the 71 benign cases. There were 260, 187, 186, 277, 40, 95, 96, 97 and 22 cases showing lobulation, spiculation, pleural traction, vessel connection, calcification, vacuoles, air bronchogram, emphysema, and pulmonary fibrosis, respectively, among the 291 malignant cases. Among the patients with benign nodules, 48 were nonsmokers, six were mild smokers, 17 were heavy smokers, and among the patients with malignant nodules, 174 were nonsmokers, 25 were mild smokers, and 92 were heavy smokers.

Difference analysis of benign and malignant nodules

- 1 Univariate logistic analysis showed that lobulation, spiculation, pleural traction, vessel connection, calcification, vacuoles and emphysema had significantly different presentations in benign and malignant pulmonary nodules, while there was no significant difference in gender, air bronchogram or pulmonary fibrosis between benign and malignant pulmonary nodules (Table 1).
- 2 Nonparametric rank sum test results. The age, SUVmax, and size of SPNs in the malignant pulmonary nodules group were 62 (55, 67) years, 3.6 (1.5, 6.5), and 20.6 (16.8, 24.4) mm, respectively. The age, SUVmax, and size of SPNs of the benign pulmonary nodules group were 55 (49, 65) years old, 1.0 (0.4, 1.8), and 11.7 (9.2, 15.5) mm, respectively. The results of the rank sum test showed that there were significant differences in age, SUVmax and nodule size between the benign and malignant groups ($z = -3.192, -8.123, -8.364$, both $P < 0.01$), while the SI difference was not statistically significant ($z = -1.279, P > 0.05$).
- 3 Multivariate logistic regression analysis and model establishment. Multivariate logistic analysis of the above factors showed that the differences in age, SUVmax, size, lobulation, calcification, and vacuoles were statistically significant (Table 2), while gender, SI, spiculation,

pleural traction, vessel connection, air bronchogram, emphysema and pulmonary fibrosis were not associated with the prediction of benign and malignant pulmonary nodules. A regression model was established: $P = 1/(1 + e^{-x})$, where P represented the probability that SPN was malignant, and the closer the value was to one, the greater the malignancy; $x = -5.583 + 0.039 \times \text{age} + 0.477 \times \text{SUVmax} + 0.139 \times \text{size} + 1.537 \times \text{lobulation} - 1.532 \times \text{calcification} + 1.113 \times \text{vacuole}$.

- 4 Validation of the risk prediction model. Model self-verification was used to verify the test efficiency of the model. The malignant probability of different pulmonary nodules was obtained by multivariate logistic regression. The AUC (95% CI) of the regression model was 0.915 (0.883–0.947), with a sensitivity of 89.7% and a specificity of 78.9%. Out-of-group verification of the model was performed by k-fold cross-validation to test the stability of the model. The results showed that the training accuracy of the 10 groups was 0.899 ± 0.011 , and the prediction accuracy was 0.873 ± 0.053 (Table 3).

Discussion

How to identify malignant pulmonary nodules from SPNs and treat them early is the key to improving the prognosis of patients with pulmonary nodules. Early diagnosis of pulmonary nodules by PET/CT can improve the diagnostic efficiency of early lung cancer. In this study, the risk prediction model based on logistic regression analysis took into account the morphological characteristics of the lesion, such as density, internal characteristics and peritumoral boundary, as well as the ^{18}F -FDG metabolic characteristics of pulmonary nodules.

This study identified age, SUVmax, size, lobulation, vacuoles and calcification as risk factors for malignant pulmonary nodules by multivariate logistic regression analysis. Based on this, the SPN risk prediction model was established: $P = 1/(1 + e^{-x})$, $x = -5.583 + 0.039 \times \text{age}$

Table 1 Univariate logistic analysis of benign and malignant pulmonary nodules

Variable	Partial regression coefficient	Standard error	P-value	Odds ratio	95% CI	
					Lower limit	Upper limit
Gender	-0.074	0.265	0.781	0.929	0.552	1.562
Lobulation	2.211	0.304	0.000	9.127	5.028	16.568
Spiculation	1.135	0.275	0.000	3.112	1.815	5.335
Pleural traction	1.579	0.295	0.000	4.848	2.722	8.636
Vessel connection	1.392	0.419	0.001	4.024	1.771	9.143
Calcification	-0.681	0.326	0.037	0.506	0.267	0.959
Vacuoles	0.972	0.351	0.006	2.644	1.329	5.260
Air bronchogram	0.609	0.316	0.054	1.838	0.989	3.417
Emphysema	0.802	0.331	0.015	2.231	1.166	4.269
Pulmonary fibrosis	1.037	0.751	0.167	2.822	0.648	12.290

Table 2 Significant variables revealed by multivariate logistic analysis of benign and malignant nodules

Variable	Partial regression coefficient	Standard error	P-value	Odds ratio	95% CI	
					Lower limit	Upper limit
Age	0.039	0.017	0.019	1.040	1.007	1.075
SUVmax	0.477	0.115	0.000	1.612	1.287	2.017
Size	0.139	0.034	0.000	1.149	1.074	1.230
Lobulation	1.537	0.396	0.000	4.650	2.138	10.115
Calcification	-1.532	0.475	0.001	0.216	0.085	0.548
Vacuoles	1.113	0.433	0.010	3.043	1.302	7.111
Constant	-5.583	1.138	0.000	-	-	-

SUVmax, maximum standard uptake value; ‘-’ indicates no data.

Table 3 K-fold cross-validation results

Group number	Predictive accuracy	Training accuracy
1	0.917	0.899
2	0.946	0.892
3	0.889	0.905
4	0.919	0.905
5	0.778	0.905
6	0.861	0.887
7	0.917	0.890
8	0.833	0.920
9	0.833	0.905
10	0.833	0.887
$\bar{x} \pm s$	0.873 ± 0.053	0.899 ± 0.011

+ 0.477 × SUVmax + 0.139 × size + 1.537 × lobulation - 1.532 × calcification + 1.113 × vacuole. The model's self-validation and out-of-group validation results showed that the model had good accuracy and stability in predicting malignancy risk of SPNs. Further case validation work is also under way.

In the existing research on SPNs, many mathematical models have been established, but only the Herder model and BIMC model contain ¹⁸F-FDG metabolic factors. The Herder model was established on the basis of the Mayo model, and its incorporation of morphological features is consistent with the Mayo model. The weight of morphological features in the Mayo model comes from chest X-ray or thick-slice CT. Modern imaging techniques have been improved, and thin-slice CT provides more details of the lesion than earlier examinations. Changes in these details may lead to changes in the accuracy of the model. The BIMC model contains factors such as tumor doubling time and enhancement degree, which can undoubtedly improve the accuracy of model prediction. However, the greater data demand is, the more examinations patients have to undergo. Additionally, in the clinical setting in our country, a large number of patients do not have comprehensive examination conditions, which makes the model less accurate when used in the clinical population of patients.

Moreover, from the perspective of health economics, the BIMC model is not conducive to reduce costs for patients.

Previous models include factors such as smoking history and spiculation, but this model does not. Nejentsev *et al.*⁵ showed that the incidence of lung squamous cell carcinoma was more closely related to smoking than that of lung adenocarcinoma. The proportion of patients with lung adenocarcinoma in China was higher than that reported elsewhere, and its proportion and incidence have increased year by year. In the present study, patients with lung adenocarcinoma were the main selected cases, which may be the main reason why there is no significant difference in SI between benign and malignant patients. Spiculation is the marginal sign of malignant tumors, but some studies have shown that only short spiculation is a sign of malignant tumors, while long spiculation is often found in benign lesions.⁶ The existing models define spiculation in an “all or none” manner when spiculation is included as a predictor, and false positivity occurs easily. In SPNs with different densities, the frequency of spiculation is also different; spiculation mainly occurs in solid nodules and is relatively rare in ground glass and mixed density nodules.⁷ In this study, cases with ground-glass and mixed density nodules were not removed from the analysis, which is one of the reasons why spiculation was not included in this model.

In the current model, calcification as a negative correlative factor of malignant nodules was included in the model, which is uncommon in previous reports. Because of the abundant blood supply of malignant lesions, necrosis and calcification are not easy to detect when the lesions are small. Fleischner Society guidelines for the management of incidental pulmonary nodules in 2017 also note that calcified nodules are mostly benign.⁸ Therefore, the author believes that calcification as a negative correlation predictor is reasonable and can improve the test efficiency of the model.

In Table 3, the accuracy of this model does not appear to be as good compared with that of previous studies. This could be due to the following reasons: (i) The difference in sample population between this study and other studies. Most of the population in this study were Han nationality,

and other studies focus on people from western countries. The living conditions and population distributions are different. (ii) Compared with developed countries, the air pollution in China improves the incidence of lung cancer among non-smokers, which makes the high risk factors of lung cancer more complicated. This is a preliminary study and the lack of external validation is one of the main limitations in this study. External validation will be carried out in further research.

In conclusion, a logistic regression-based malignant risk prediction model for SPN was established based on the data of 362 patients in our hospital's PET/CT center and it showed the risk factors for malignant nodules included age, SUVmax, size, lobulation, calcification and vacuoles. The model incorporated both anatomical and metabolic features. It is helpful to control false positivity while preserving the high sensitivity of PET and combining CT features of malignant nodules. The model can be conveniently used in the clinical setting and help to make a definite diagnosis as soon as possible to improve the long-term prognosis.

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Not applicable.

Disclosure

No authors report any conflict of interest.

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