

¹⁸F-FDG PET-based radiomics model for predicting occult lymph node metastasis in clinical N0 solid lung adenocarcinoma

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Background: This study aimed to develop a preoperative positron emission tomography (PET)-based radiomics model for predicting occult lymph node metastasis (OLM) in clinical N0 (cN0) solid lung adenocarcinoma.

Methods: The preoperative fluorine-18-fludeoxyglucose (¹⁸F-FDG) PET images of 370 patients with cN0 lung adenocarcinoma confirmed by histopathological examination were retrospectively reviewed. Patients were divided into training and validation sets. Radiomics features and relevant data were extracted from PET images. A nomogram was developed in a training set via univariate and multivariate logistic analyses, and its performance was assessed by concordance-index (C-index), calibration curves, and decision curve analysis (DCA) in the training and validation sets.

Results: The multivariate logistic regression analysis showed that only carcinoembryonic antigen (CEA), metabolic tumor volume (MTV), and the radiomics signature had statistically significant differences between patients with and without OLM (P<0.05). A nomogram was developed based on the logistic analyses, and its C-index was 0.769 in the training set and 0.768 in the validation set. The calibration curve demonstrated good consistency between the nomogram-predicted probability of OLM and the actual rate. The DCA also confirmed the clinical utility of the nomogram.

Conclusions: A PET/computed tomography (CT)-based radiomics model including CEA, MTV, and the radiomics signature was developed and demonstrated adequate predictive accuracy and clinical net benefit in the present study, and was conveniently used to facilitate the individualized preoperative prediction of OLM.

Keywords: Lung adenocarcinoma; positron emission tomography radiomics (PET radiomics); positron emission tomography/computed tomography (PET/CT); lymph node; diagnosis

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Introduction

Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related death worldwide, with an estimated 2.1 million newly diagnosed lung cancer cases and 1.8 million deaths in 2018 (1). Among these, adenocarcinoma is the most prevalent subtype. The routine treatment for early-stage adenocarcinoma patients is anatomical resection and systemic nodal dissection. Recently, several studies have suggested that limited surgery, such as wedge resection or sublobar resection, is a reasonable treatment option for lung cancer patients without lymph node metastasis (LNM) to preserve lung function (2-4). Adjuvant radiotherapy and chemotherapy were recommended for patients with any sign of LNM (5). Also, the International Association for the Study of Lung Cancer (IASLC) suggested that clinical and pathological lymph node status were closely related to the 5-year survival rate (6). Therefore, identification of lymph node status is a crucial step in early-stage lung cancer and is considered a significant prognostic factor that can be used to determine the surgical plan.

Fluorine-18-fludeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/ CT) can noninvasively detect the metabolic activity of the disease. It has become an indispensable methodology for the evaluation of the Tumor Node Metastasis (TNM) staging of lung cancers, especially in higher-risk patients with planned surgical treatment (7). However, studies have reported that the incidence of occult lymph node metastasis (OLM) on PET/CT was up to 12.6–26.7% (8-11). Thus, a novel method is needed to improve the diagnostic accuracy of OLM in clinical N0 (cN0) patients. It has become widely acknowledged that the information obtained from the conventional images with unaided eyes is merely a minor representation, while a large amount of valuable data remains concealed in the images (12-14).

Radiomics provides a vital complementary tool to extract the high-dimensional and valuable data from the images (15,16). With the rapid development of radiomics, many predictive models combining radiomics signatures with clinical and radiologic data have been developed to predict the preoperative stage and prognosis of various malignant tumors (14,17-19). However, to our knowledge, there is currently no PET/CT-based radiomics model for predicting OLM of lung adenocarcinoma. Thus, the purpose of the present study was to develop a preoperative model that incorporates radiomics features, clinical characteristics, and PET parameters to predict the OLM of cN0 solid lung adenocarcinoma.

Methods

Patients

Our Institutional Review Board approved this study, and the requirement for informed consent was waived. The inclusion criteria were as follows: (I) patients underwent surgical resection and lymphadenectomy; (II) patients were confirmed to have lung adenocarcinoma postoperatively via histopathological examination; (III) PET-CT was performed before surgery, with a time interval of less than 1 month; and (IV) the lesion was diagnosed as cN0; all short axis of LN were less than 10 mm and the FDG uptake did not exceed that of normal tissue (20). The exclusion criteria were as follows: (I) the lesion appeared as groundglass opacity (GGO), including pure GGO and GGOpredominant lesion on chest CT scans; (II) FDG uptake of the lesions was lower than or close to the surrounding normal pulmonary parenchyma; (III) patients received chemotherapy or radiotherapy before the PET/CT examination; and (IV) the lesion had distant metastasis.

The histologic classification of the tumor was defined according to the 2015 World Health Organization classification (21). The clinical and pathological staging of the tumor was based on the TNM Classification of Malignant Tumors, the eighth edition (22). Ultimately, a total of 370 patients were enrolled in our study between January 2012 and May 2019. The patients were divided into two groups according to the date they underwent PET/CT imaging. Specifically, patients examined before January 2018 were assigned to the training set, and patients examined after January 2018 was assigned to the validation set (18,23). Their clinical data, including age, gender, surgical procedure, and serum carcinoembryonic antigen (CEA) level, were recorded.

PET/CT image acquisition and analysis

All PET/CT examinations were performed using a hybrid PET/CT system (Gemini 64 TF, Philips Medical Systems, Best, The Netherlands). An intravenous injection of approximately 3.7 MBq/kg of ¹⁸F-FDG was administered after fasting for at least 6 hours (blood glucose levels below 110 mL/dL). After resting for 60 minutes, the PET/CT scan was performed with patients in the supine position. For precise anatomical localization and attenuation correction, a low dose unenhanced CT was performed from the skull base to the mid-thigh with the following parameters: tube voltage of 120 kV, tube current of 249 mA, detector collimation of 64 mm × 0.625 mm, the pitch of 0.829, a tube rotation speed of 0.5 seconds, and reconstruction thickness and interval of 5.0 mm. Subsequently, PET images were obtained by using the three-dimensional model, and the

parameters were set as follows: field of view of 576 mm, a matrix of 144×144, slice thickness and interval of 5 mm, and an emission scan time of each bed position of 1.5 minutes. PET images with CT attenuation correction were reconstructed using the time of the fight algorithm.

Data measurement and collection were performed on the Philips EBW 3.0 by two radiologists. The tumor size was measured at the longest diameter of the lesion on transverse lung window settings of the CT images (window width, 1,500 HU; window level, -750 HU). Volume viewer software was used to calculate PET parameters, and the tumor volumes of interest (VOIs) were automatically generated using the threshold standardized uptake value (SUV). The maximum standardized uptake value (SUVmax) was defined as the highest SUV voxel in the volume of interest (VOI). Metabolic tumor volume (MTV) was defined as the sum of voxels with SUV \geq 40% of the SUVmax (24). Total lesion glycolysis (TLG) was calculated by using the result of MTV multiplied by the mean SUV of the tumor. SURmax represents the ratio of SUVmax to the mean SUV of descending aorta (blood SUVmean). TLGsur represents the ratio of TLG to blood SUVmean.

Tumor segmentation and feature extraction

Commercial software (Region Studio, Regiontec Ltd., Shanghai, China) was used to extract radiomics features. FDG-PET images were imported into the software using the Digital Imaging and Communications in Medicine (DICOM) protocol. Regions of interest (ROIs) were manually delineated around the tumor outline slice-byslice on the PET images by one radiologist (reader 1) who was blinded to the clinical information and pathological results, and segmentation of the tumor was then performed semi-automatically by the software. The image analysis pipeline was built to extract radiomics features from PET imaging. After 1 week, 60 cases were randomly selected for repeat delineation of the ROIs by reader 1 and another radiologist (reader 2). Both readers had 5 years of clinical experience in CT diagnosis. The inter- and intra-class correlation coefficients (ICCs) were used to assess interand intra-observer agreement of the radiomics feature. The intra-observer ICCs were calculated based on the two-time feature extraction of reader 1, and the interobserver ICCs were calculated based on the first-extracted features drawn by both readers, with ICCs greater than 0.75 denoting a favorable agreement. The radiomics features included first-order features, shape features, gray level cooccurrence matrix (GLCM) features, gray level size zone matrix (GLSZM) features, gray level run length matrix (GLRLM) features, neighbouring gray tone difference matrix (NGTDM) features, and gray level dependence matrix (GLDM) features. The specific radiomics features are provided in Table S1.

Radiomics feature selection and development of a radiomics signature

The 10-fold cross-validated least absolute shrinkage and selection operator (LASSO) method, which is suitable for the regression analysis of high-dimensional data, was used to select valuable radiomics features from the training set (18). Multivariate logistic regression analysis was subsequently applied to the selected radiomics features. A radiomics signature was calculated via a linear combination of finally selected features weighted by their respective coefficient.

Construction of the model and clinical utility

Clinical features, PET parameters, and radiomics signatures with statistical significance (P<0.05) in the univariate analysis of the training set were selected into a multivariable binary logistic regression analysis using backward stepwise selection. Next, a nomogram was constructed based on the multivariable binary logistic regression analysis with P<0.05. The model was applied to the validation dataset to assess accuracy. The performance of the nomogram was assessed in the training and validation sets by concordanceindex (C-index), and calibration curves. Analysis decision curve analysis (DCA) was performed by calculating the net benefits of joint training and validation sets under different threshold probabilities to evaluate the clinical effectiveness of the nomogram.

Statistical analysis

The analyses were performed using IBM SPSS (version 23.0) and R software (version 3.6.1). Continuous variables were described as mean \pm standard deviations and analyzed by the Mann-Whitney U test. Categorical variables, including sex and tumor location, were expressed as frequency and analyzed using the Chi-square test. The "glmnet" package administered LASSO binary logistic

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regression analysis. Multivariate binary logistic regression analysis, nomograms, and calibration plots were performed with the "rms" package. The C-index calculation was conducted using the "Hmisc" package. DCA was performed using the "rmda" package. A two-sided P value <0.05 was considered statistically significant.

Results

Baseline characteristics

The characteristics of 370 patients (165 men, 205 women; mean age, 62.95±9.40 years) are shown in *Table 1*. A total of 236 patients were assigned to the training set, and 134 patients were assigned to the validation set. There were no statistically significant differences in age, gender, and tumor location between patients with and without OLM in both the training and validation sets, while CEA, tumor size, SUVmax, MTV, TLG, SURmax, and TLGsur were significantly different between the two sets.

Radiomics feature selection and development of the radiomics signature

One hundred seven robust radiomics features were extracted in the present study. After removing the features with an ICC ≤ 0.75 , a total of 62 stable radiomics features were retained for subsequent analysis. After LASSO logistic regression analysis (*Figure 1A,B*), only skewness, total energy, small dependence low gray-level emphasis (SDLGLE) and gray level non-uniformity normalized (GLNN) of the gray level run length matrix (GLRLM) features were incorporated into the radiomics signature: Radiomics signature =-0.995-0.398 skewness + 1.416 total energy + 1.119 SDLGLE - 1.519 GLNN.

The radiomics signature in patients with OLM was significantly higher than those without OLM in the training set (-1.43 ± 0.87 vs. 0.14 ± 2.75 , P<0.0001). These findings were confirmed in the validation set (-1.42 ± 1.06 vs. -0.35 ± 2.74 , P<0.0001).

Construction of the model and clinical utility

The results of the univariate and multivariate binary logistic regression analysis in the training set are shown in *Table 2*. The univariate analysis showed significant differences between patients with and without OLM in eight parameters, including CEA, tumor size, SUVmax, MTV, TLG, SURmax,

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TLGsur, and the radiomics signature. The multivariate logistic regression analysis showed that CEA, MTV, and the radiomics signature were significant independent risk factors in the prediction of OLM. Subsequently, CEA, MTV, and the radiomics signature were incorporated to construct the nomogram (*Figure 2*). The prediction nomogram showed a C-index of 0.769 in the training set and 0.768 in the validation set. The calibration curve demonstrated good agreement between the nomogram-predicted probability of OLM and the actual OLM rate in the training and validation sets (*Figure 3A,B*). The decision curve showed that if the threshold probability of a patient was >10%, using this nomogram to predict OLM would provide greater benefit than the treat-all-patients strategy or the treat-none strategy (*Figure 4*).

Discussion

In recent years, radiomics have been widely studied as a noninvasive and reproducible method to extract highdimensional features from radiological images. Radiomics features can objectively describe tumor characteristics in terms of border, shape, texture, and spatial structure, which could reflect intra-tumor heterogeneity and gene-expression patterns (25-27). They can also help to discriminate different types of cancer, differentiate LNM from benign LN, and determine tumor treatment plans (28,29). Furthermore, it was reported that the predictive accuracy of the radiomics signature based on CT scans was favorable for predicting OLM in patients with lung adenocarcinoma (17). However, the radiomics model based on PET/CT for predicting OLM of lung adenocarcinoma is rarely reported. Thus, this study aimed to develop a PET-based radiomics model to predict OLM.

Based on the results of the LASSO binary logistic regression analysis, skewness, total energy, SDLGLE, and GLNN were considered the four most valuable features in our study. Among these, skewness and total energy belonged to the first-order features. The skewness measured the asymmetry of the distribution of values about the mean value. The total energy was defined as the value of energy feature (a measure of the magnitude of voxel values in the image) scaled by the volume of the voxel (in cubic mm). This ensured that voxels with the lowest gray values contributed least to energy, instead of voxels with gray level intensity closest to zero. SDLGLE belonged to the gray level dependence matrix (GLDM) features and measured the joint distribution of small dependence with lower gray-

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Characteristics -	Training set (n=236)			Validation set (n=134)		
	OLM- (n=170)	OLM+ (n=66)	Р	OLM- (n=102)	OLM+ (n=32)	Р
Gender			0.521			0.007
Male	80	28		50	7	
Female	90	38		52	25	
Age, year	63.36±9.38	61.89±9.43	0.342	63.63±9.03	61.25±8.89	0.220
Location			0.561			0.645
RUL	51	22		27	6	
RML	12	5		9	1	
RLL	33	17		25	10	
LUL	48	12		25	10	
LLL	26	10		16	5	
Surgical procedure						
Approach			0.331			0.422
VATS	152	56		101	31	
Thoracotomy	18	10		1	1	
Procedure			0.555			1
Lobectomy	163	65		100	32	
Sublobar resection	7	1		2	0	
Pathological N stage			<0.001			<0.001
NO	170	0		102	0	
N1	0	34		0	12	
N2	0	32		0	20	
CEA, ng/mL	4.55±4.53	13.17±29.96	0.001	3.70±3.76	8.44±12.31	0.002
Tumor size, mm	21.6±7.30	28.23±10.26	<0.001	21.16±10.33	25.19±12.83	0.066
SUVmax	5.24±2.60	7.07±3.59	<0.001	4.29±2.11	7.07±3.51	<0.001
MTV	4.40±3.14	9.13±8.70	<0.001	5.54±5.86	8.17±8.97	0.037
TLG	13.52±10.84	44.10±65.79	<0.001	13.15±14.33	28.00±26.48	<0.001
SURmax	3.39±1.71	4.52±2.61	0.003	2.39±1.13	3.91±1.99	<0.001
TLGsur	8.76±7.35	30.40±53.10	<0.001	7.08±6.68	16.25±15.51	<0.001

Table 1 Baseline characteristics of cN0 patients

The Mann-Whitney U test analyzed continuous variables. The Chi-square test analyzed qualitative variables. OLM+, occult lymph node metastasis positive; OLM–, occult lymph node metastasis negative; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; VATS, video-assisted thoracoscopic surgery.



Figure 1 Radiomics feature selection using the least absolute shrinkage and selection operator (LASSO) model. (A) The LASSO model selected the tuning parameter (λ) using 10-fold cross-validation based on minimum criteria. During the LASSO regression cross-validation procedure, binomial deviances were plotted as a function of log (λ). The y-axis was defined as binomial deviances. The lower x-axis indicated the log (λ), and numbers along the upper x-axis represented the average number of predictors. Red dots indicated average deviance values for each model with a given λ , and vertical bars showed the upper and lower values of the deviances. The vertical black dotted lines defined the optimal values of λ . The optimal λ value of 0.009 with log (λ) =-4.746 was chosen. (B) LASSO coefficient profiles (y-axis) of the 62 radiomics features. The picture clearly showed the LASSO selection of variables by reducing the coefficient weights of non-related features to zero.

Variables	Univariate an	alysis	Multivariate analysis		
variables –	OR (95% CI)	Р	OR (95% CI)	Р	
CEA	1.075 (1.026–1.127)	0.002	1.046 (1.000–1.109)	0.048	
Size	1.097 (1.057–1.139)	<0.001	NA	NA	
SUVmax	1.465 (1.231–1.743)	<0.001	NA	NA	
MTV	1.184 (1.102–1.271)	<0.001	1.093 (1.001–1.193)	0.048	
TLG	1.052 (1.029–1.075)	<0.001	NA	NA	
SURmax	1.297 (1.124–1.496)	<0.001	NA	NA	
TLGsur	1.066 (1.034–1.099)	<0.001	NA	NA	
Radiomics signature	2.718 (1.865–3.963)	<0.001	2.026 (1.326–3.096)	0.001	

Table 2 Results of univariate and multivariate logistic regression analysis

CEA, carcinoembryonic antigen; MTV, metabolic tumor volume; TLG, total lesion glycolysis; OR, odds ratio; CI, confidence interval.

level values. GLNN of GLRLM features measured the similarity of gray-level intensity values in the image, where a lower GLNN value correlated with a greater similarity in intensity values. The features reflected the heterogeneity of the various aspects of the ROIs in the images. The radiomics signature constructed by these radiomics features was superior to a single variable and was similar to the multi-dimensional panels method (17,18). As an important radiomics predictive index, the radiomics signature in this study resulted in a more accurate diagnosis and helped to predict OLM before surgery, with a greater value indicating a higher likelihood of OLM.

Many studies have shown that radiomics signatures combined with clinical and radiological data have a better

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Figure 2 The nomogram incorporated with CEA, MTV, and radiomics signature (Radscore) was developed in the training set for the prediction of OLM. CEA, carcinoembryonic antigen; MTV, metabolic tumor volume; OLM, occult lymph node metastasis.



Figure 3 Calibration curves of the nomogram in the training set (A) and the validation set (B), respectively. The diagonal dotted line represents a perfect prediction of OLM, and the solid line represents the predictive performance of the nomogram. OLM, occult lymph node metastasis.

predictive value (30-34). Thus, we also studied PET/CT parameters and clinical data. We identified that the CEA, tumor size, and ¹⁸F-FDG PET/CT parameters, including SUVmax, MTV, TLG, SURmax, and TLGsur, were risk factors for OLM, which is consistent with reports from previous studies (9,10,20,35). Also, multivariate logistic regression analysis found that CEA, MTV, and the

radiomics signature were independent risk predictors for OLM. Numerous studies had reported that serum CEA level was associated with the pathological stage, rate of LNM, and prognosis of cancer (8,31,36,37). Also, Miao *et al.* found that CEA was an independent risk factor for LNM in adenocarcinoma (8). Our study also demonstrated that CEA was an independent risk predictor for OLM,





Figure 4 Decision curve analysis of the nomogram in the combined training and validation sets. The y-axis represents the net benefit, and the x-axis represents the threshold probability. The red line represents the nomogram. The grey line represents the net benefit of assuming all patients with OLM, and the black line represents the net benefit of assuming all patients without OLM. OLM, occult lymph node metastasis.

which was consistent with the findings of Miao et al. MTV was a composite parameter reflecting both tumor metabolic activity and tumor volume, and was significantly associated with OLM in patients. Previous studies reported that MTV had a better predictive performance than other PET parameters and might be a possible indicator for sublobar resection in clinically node-negative lung cancer (9,24). However, it is always difficult to identify OLM from benign LN by conventional methods, and using a sole parameter to differentiate malignant from benign LN remains challenging. Thus, the present study developed a PET/CTbased nomogram model incorporating CEA, MTV, and the radiomics signature to predict OLM in patients of cN0 solid lung adenocarcinoma, and demonstrated adequate discrimination in the training set (C-index, 0.769) and the validation set (C-index, 0.768).

A nomogram is a statistical model that can calculate the numerical probability of a patient by integrating multiple variables and provides an intuitive and convenient method for doctors to clinically diagnose OLM as well as fulfilling the drive towards personalized medicine (38). Moreover, it is more concise and effective than other methods in the prediction of the LN metastasis

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in lung adenocarcinomas (39,40). Another advantage of the nomogram is its noninvasiveness and repeatability, thereby allowing for routine application. In this study, a PET/CTbased nomogram model was developed and demonstrated high diagnostic accuracy. The C-index, calibration curve, and DCA indicated that the nomogram shows good clinical utility. Given that our nomogram has favorable discrimination and clinical utility, it might facilitate the individualized prediction of OLM and precise individualized medical treatment.

A further advantage of this study is that only solid lung adenocarcinoma patients were enrolled. This is because patients with different histological types would influence the size, metabolic parameters of the primary tumor, among many others (24). For example, SUVmax of squamous cell carcinoma is higher than adenocarcinoma in general (41). Therefore, a combined analysis of these histological types is not logical, especially in a PET study. The ground glass nodules of lung adenocarcinoma manifested most frequently as lepidic predominant growth patterns microscopically and generally considered as without LNM (8,42), which can affect the incidence of OLM. Therefore, only solid lung adenocarcinoma patients were enrolled in the present study, thus allowing us to avoid such problems.

However, although the results were encouraging, our study still had several limitations. Firstly, this was a singlecenter retrospective study, which means that it has potential data selection bias. Secondly, the number of patients with OLM was much lower than the number of patients with negative LNM, which may affect the P value in comparative analysis. Consequently, more prospective and large-samples studies are needed to determine these predictive factors and confirm the accuracy of the nomogram for predicting OLM. Finally, the pathological stage and CT features of the tumor were not included in the present study, which may have affected the results.

Conclusions

In our study, the diagnostic PET/CT-based radiomics nomogram, including CEA, MTV, and the radiomics signature, was developed to predict the OLM in cN0 solid lung adenocarcinoma. The nomogram demonstrated adequate predictive accuracy and clinical net benefit and was conveniently used to facilitate the individualized preoperative prediction of OLM in cN0 solid lung adenocarcinoma.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/qims-20-337). The authors have no conflicts of interest to declare.

Ethical Statement: The local institutional review board approved this retrospective study and waived the requirement for informed consent.

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