Prediction of Occult Lymph Node Metastasis in cN0 Stage Non-Small Cell Lung Cancer Using Contrast-Enhanced CT

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ABSTRACT

Objective: To explore the value of contrast-enhanced CT radiomics in predicting occult lymph node metastasis (OLNM) in patients with clinical N0 (cN0) stage non-small cell lung cancer (NSCLC) prior to surgery.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Radiology, Guangzhou First People's Hospital, Guangzhou, Guangdong, China, from January 2023 to November 2024.

Methodology: A total of 290 NSCLC patients from two hospitals were divided into training and validation sets. Radiomics features were extracted from the tumour volume of interest, and optimal features were selected in the training set to develop a radiomic signature. Univariate and multivariate logistic regression analyses identified clinical characteristics associated with OLNM, leading to the creation of a clinical model. A combined model was developed by integrating the radiomics signature with clinical features. Model performance was assessed using the area under the ROC curve (AUC), with validation conducted in the independent validation set.

Results: Three radiomics features and two clinical characteristics associated with OLNM were identified ($p < 0.05$). The AUCs of the clinical model, radiomic signature, and combined model in the training and validation sets were 0.746, 0.809, 0.838, 0.708, 0.802, and 0.823, respectively, with the combined model showing the highest AUC in both sets.

Conclusion: The combined model, integrating preoperative CT radiomics features and clinical characteristics, effectively predicts OLNM in cN0 stage NSCLC patients, aiding personalised clinical decision-making and improving prognosis.

Key Words: *Non-small cell lung cancer, Occult lymph node metastasis, Radiomics*.

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INTRODUCTION

Lung cancer is one of the most prevalent and deadly malignancies worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of cases and a five-year survival rate of 12-15%.[1,2] Several surgical resection approaches are available for NSCLC, among which lobectomy combined with complete lymph node (LN) resection represents the most common surgery. While complete LN dissection reduces the risk of postoperative LN metastasis (LNM), it also significantly increases physical trauma to the patient.[3] Therefore, accurately assessing the need for complete LN dissection is crucial in the management of NSCLC patients.

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Currently, computed tomography (CT) and positron emission tomography (PET) are frequently used to evaluate LNM. However, even in patients classified as N0 stage on imaging, occult lymph node metastasis (OLNM) is found in 11 to 18% of cases postoperatively.[4] Accurately determining patients' LN status is essential for guiding clinical decisions regarding the need for complete LN dissection.

Radiomics is a high-throughput image analysis method that extracts disease-related information from medical images, aiding in diagnosis, treatment evaluation, and prognosis prediction.[5] The use of radiomics features to assess LN status in cN0 stage NSCLC has also garnered significant attention from researchers.[6] However, some of the models constructed in previous radiomics studies on OLNM have the problem of unstable performance in the training and validation sets.[7] Moreover, some studies are confined to single-centre designs, and their predictive models lack an adequate sample size for independent external validation.[8] In addition, some studies focus only on cN0 stage NSCLC with specific T stages, which also presents certain limitations.[9,10] To date, there remains a critical need for developing a reliable and robust predictive tool for OLNM assess-

ment. This study aims to develop predictive models based on contrast-enhanced CT radiomics features and clinical characteristics to explore their preoperative predictive value for OLNM in cN0 stage NSCLC patients and to validate them in an independent external validation set to improve the generalisability of the models, thereby enhancing clinical decision-making.

METHODOLOGY

This study included 290 NSCLC patients who underwent lobectomy and complete LN dissection from two hospitals, between January 2023 and November 2024. The inclusion and exclusion criteria are shown in Figure 1. Total of 174 patients from one hospital were used as the training set, and 116 patients from another hospital were used as the validation set, and each was grouped according to the presence or absence of OLNM in the pathological results (Figure 1).

All patients were scanned using a GE 64-slice VCT imaging device using the following parameters: Tube voltage 120 kV, tube current 200 mA, slice thickness 0.5–2 mm, collimator width 0.625 mm, field of view 350×350 mm, pitch 0.984, and matrix size 512×512. Iodine contrast medium was injected intravenously at a rate of 2.5 mL/s, with imaging performed at 25 and 60 seconds post-injection.

The tumour was automatically segmented on the enhanced CT images using a tumour segmentation model, with results verified by a physician with 15 years of experience using ITK-SNAP V3.8.0 to obtain a three-dimensional volume of interest (VOI). Radiomics features were then extracted using the Pyradiomics package in Python.

In the training set, Lasso-logistic regression was used to screen out optimal radiomics features and construct a radiomics signature. Univariate and multivariate logistic regression analyses were conducted to screen the clinical features (gender, age, smoking history, family history, tumour location, CT tumour size, and T stage) and build a clinical model. A combined model was then developed by integrating the radiomics signature and clinical model. The performance of each model was assessed using AUC and validated in the independent set.

Data analysis was performed using Python 3.7, R 4.0.5, and SPSS version 26.0 software. All continuous variables were tested for normality. The t-test was applied for comparison between the two groups of normally distributed measures. The Mann-Whitney U test was applied for comparison between the two groups of non-normally distributed measures. The Chi-square test was applied for comparison between the two groups of count data. A p-value of <0.05 was considered statistically significant.

RESULTS

Table I presents a comparison of clinical features between the two groups. Significant differences were found in smoking history and CT tumour size in both sets. T stage differed significantly in the training set but not in the validation set. No other clinical characteristics showed significant differences. Figure 2 (A-D) shows CT images of tumour lesions and mediastinal and hilar LNs from two patients.

A total of 944 radiomics features were extracted from the contrast-enhanced CT images. After the screening, three features related to OLNM were identified (Figure 3A, B) and used to create a radiomics signature, which showed an AUC of 0.809 (0.730-0.887) in the training set and 0.802 (0.723-0.880) in the validation set (Figure 3C, D).

In the training set, two significant clinical features were screened out: Smoking history and CT tumour size (Table II), and these features were used to construct a clinical model, which achieved AUCs of 0.746 (0.652-0.840) in the training set and 0.708 (0.613-0.803) in the validation set. The combined model, integrating the selected clinical features and radiomics signature, had AUCs of 0.838 (0.764-0.911) in the training set and 0.823 (0.751-0.895) in the validation set, demonstrating the highest performance in both sets (Figure 3C, D).

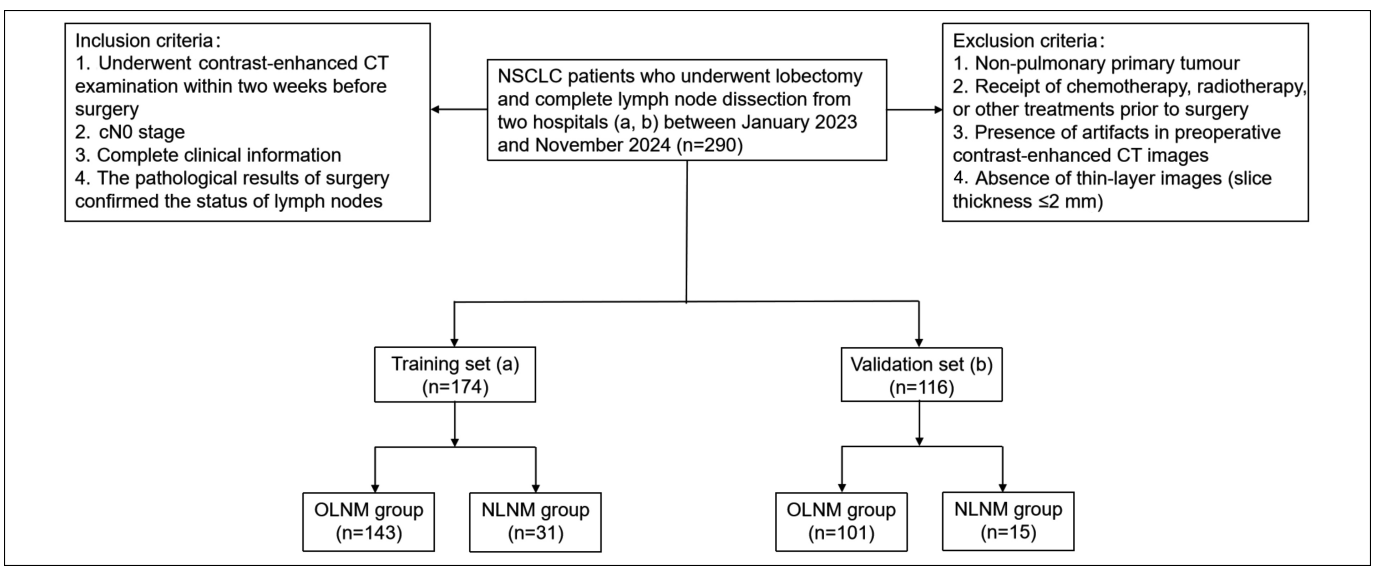

Figure 1: Diagram of patient recruitment and allocation.

Table I: Comparison of clinical characteristics between the two groups in the training and validation sets.

Characteristics	Training set (n = 174)		p-value	Validation set (n = 116)		p-value
	NLNM (n = 143)	OLNM (n = 31)		NLNM (n = 101)	OLNM (n = 15)	
Gender, n (%)			0.570*			0.406*
Female	68 (47.6)	13 (41.9)		49 (48.5)	9 (60.0)	
Male	75 (52.4)	18 (58.1)		52 (51.5)	6 (40.0)	
Age (year)	60.3 ± 11.3	58.3 ± 12.2	0.373†	63.7 ± 10.0	59.6 ± 7.7	0.136†
Smoking history, n (%)			<0.001*			<0.001*
No	111 (77.6)	13 (41.9)		74 (73.3)	3 (20.0)	
Yes	32 (22.4)	18 (58.1)		27 (26.7)	12 (80.0)	
Family history, n (%)			0.258*			0.729*
No	132 (92.3)	26 (83.9)		88 (87.1)	12 (80.0)	
Yes	11 (7.7)	5 (16.1)		13 (12.9)	3 (20.0)	
Tumour location, n (%)			0.352*			0.826*
Left upper lobe (LUL)	38 (26.6)	10 (32.3)		17 (16.8)	4 (26.7)	
Left lower lobe (LLL)	14 (9.8)	5 (16.1)		19 (18.8)	2 (13.3)	
Right upper lobe (RUL)	44 (30.8)	11 (35.5)		41 (40.6)	5 (33.3)	
Right middle lobe (RML)	13 (9.0)	1 (3.2)		10 (9.9)	1 (6.7)	
Right lower lobe (RLL)	34 (23.8)	4 (12.9)		14 (13.9)	3 (20.0)	
CT tumour size (cm)	2.0 (1.6, 3.0)	2.8 (1.9,4.5)	0.009‡	2.1 (1.6, 3.0)	3.2 ± 1.3	0.026‡
T stage						
T1	112 (78.3)	17 (54.9)	0.018*	81 (80.2)	8 (53.3)	0.065*
T2	23 (16.1)	9 (29.0)		16 (15.8)	6 (40.0)	
T3-4	8 (5.6)	5 (16.1)		4 (4.0)	1 (6.7)	

**Chi-square test; †Independent samples t-test; ‡Mann-Whitney U tests.*

Table II: Univariate and multivariate logistic regression analyses of clinical characteristics in the training set.

Characteristics	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Gender				
Female	Ref			
Male	1.26 (0.58-2.80)	0.570		
Age	0.98 (0.95-1.02)	0.371		
Smoking history				
No	Ref		Ref	
Yes	4.80 (2.15-11.06)	<0.001	4.36 (1.90-10.22)	<0.001
Family history				
No	Ref			
Yes	2.31 (0.68-6.93)	0.150		
Tumour location				
LUL	Ref			
LLL	1.36 (0.37-4.57)	0.628		
RUL	0.95 (0.36-2.52)	0.917		
RML	0.29 (0.02-1.76)	0.262		
RLL	0.45 (0.11-1.47)	0.206		
CT tumour size	1.40 (1.12-1.78)	0.004	1.34 (1.06-1.72)	0.017
T stage				
T1	Ref			
T2	2.58 (0.99-6.42)	0.045		
T3-4	4.12 (1.13-13.89)	0.024		

†Stepwise logistic regression.

DISCUSSION

This study developed a combined model integrating three radiomics features and two clinical characteristics to preoperatively predict OLNM in cN0 NSCLC patients. The model demonstrated the highest predictive performance in both the training and validation sets, providing valuable guidance for treatment decision-making.

In this study, CT tumour size was an independent predictor of OLNM ($p < 0.05$), consistent with the findings of Mitsui *et al*.[11] Larger tumour size may indicate more invasive components and a higher risk of LN metastasis.[12] However, the clinical T stage, which is based on tumour size, was not an independent predictor in this study. This study also found a significant association between smoking history and OLNM ($p < 0.001$), with a higher proportion of smokers in the OLNM group, supporting previous studies suggesting that smoking increases cancer aggressiveness and metastasis.[13,14] While Moon *et al*. reported a correlation between tumour location and OLNM,[15] this correlation was not observed in this study. This study also indicated that gender and age were not associated with OLNM, which aligns with past studies.[16]

Recent advancements in radiomics have enabled rapid and efficient quantification of tumour characteristics, offering new methods for diagnosis, prognosis evaluation, and a more comprehensive, objective approach to guiding clinical treatment.[17-19]

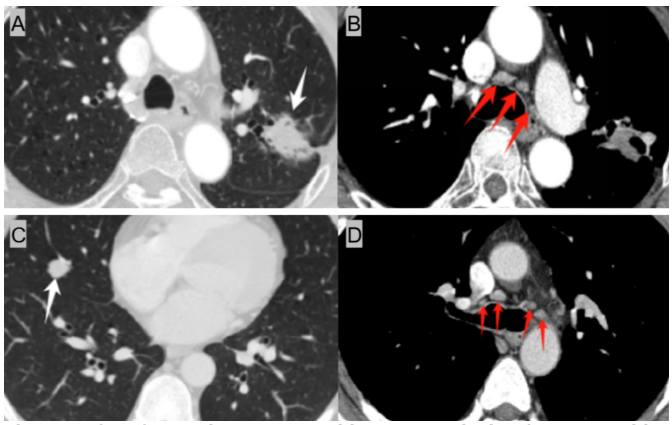

Figure 2: (A, B) Female, 83 years old, a tumour lesion (3.6 mm, white arrow) and mediastinal and hilar lymph nodes (largest short diameter <10 mm, red arrow). Postoperative pathology confirmed metastasis in the left hilar lymph nodes. (C, D) Male, 44 years old, a tumour lesion (1.5 mm, white arrow) and mediastinal and hilar lymph nodes (largest short diameter <10 mm, red arrow). Postoperative pathology showed no lymph node metastasis.

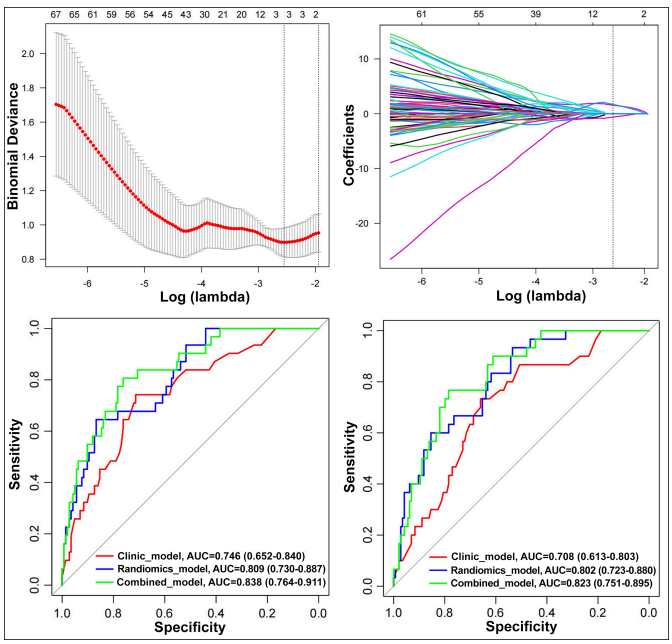

Figure 3: (A) Cross-validation plot for Lasso-logistic regression. (B) Distribution of Lasso-logistic regression coefficients. ROC curves for the clinical model, radiomics signature, and combined model in the training (C) and validation sets (D).

Liu *et al*. developed a model for predicting OLNM in NSCLC using first-order statistical features and clinical characteristics, achieving an AUC of 0.758.[8] However, the combined model developed in this study demonstrated superior predictive performance. Das *et al*. predicted OLNM in NSCLC using radiomics features from intratumoural, peritumoural, and LN regions, achieving AUCs of 0.90 and 0.79 in the training and internal validation sets.[7] Although their models demonstrated marginally superior performance in the training set compared to this study, their performance in the validation sets was lower. Additionally, peritumoural and LN features were not included in this study, yet the combined model still outperformed that developed by Das *et al*. in the validation set (0.823 *vs*. 0.79). Gu *et al*. developed a model for predicting OLNM in cT1N0M0 stage NSCLC, achieving an AUC of 0.883.[9] However, its applicability is limited to cT1N0M0 stage NSCLC. Jiang *et al*. and Zhang *et al*. used radiomics and clinical features to predict OLNM in cT1-2N0 stage NSCLC,[10,20] but the combined model in this study outperformed their overall.

This study has several limitations: Firstly, it is a retrospective analysis. Secondly, only the global radiomics features of the tumour were extracted, and the radiomics features of different subregions of the tumour were not studied. Thirdly, other medical image data, such as histopathological images, were not included in this study. Future research should collect prospective data, explore subregional radiomics for OLNM prediction, and integrate multidimensional medical data to improve model accuracy.

CONCLUSION

The combined radiomics-based prediction model developed in this study can preoperatively predict OLNM in cN0 stage NSCLC patients, supporting clinical decision-making.

ETHICAL APPROVAL:

This study was approved by the Institutional Review Board of the Guangzhou First People's Hospital, Guangzhou, Guangdong, China.

PATIENTS' CONSENT:

Informed consent was taken from the patients to publish the data of this study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

JL, HZ, YL: Study design, conception, data analysis, and manuscript writing.

LL, XY, HD: Patient selection and providing clinical expertise.

All authors approved the final version of the manuscript to be published.

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