



# Metabolic phenotypes, serum tumor markers, and histopathological subtypes in predicting bone metastasis: analysis of 695 patients with lung cancer in China

Maoqing Jiang<sup>1,2^</sup>, Ping Chen<sup>3</sup>, Xiaohui Zhang<sup>1</sup>, Xiuyu Guo<sup>1</sup>, Qiaoling Gao<sup>1</sup>, Lijuan Ma<sup>1</sup>, Weiqi Mei<sup>2</sup>, Jingfeng Zhang<sup>1</sup>, Jianjun Zheng<sup>1^</sup>

<sup>1</sup>Department of Radiology and PET/CT Center, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, China; <sup>2</sup>Department of Nuclear Medicine, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, China; <sup>3</sup>Department of Nephrology, Hwa Mei Hospital, University of Chinese Academy of Sciences, Ningbo, China

**Contributions:** (I) Conception and design: M Jiang, P Chen, J Zheng; (II) Administrative support: M Jiang, J Zhang, J Zheng; (III) Provision of study materials or patients: X Zhang, X Guo, Q Gao, L Ma, W Mei; (IV) Collection and assembly of data: X Zhang, X Guo, Q Gao, L Ma; (V) Data analysis and interpretation: M Jiang, P Chen, J Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Jianjun Zheng. Department of Radiology and PET/CT Center, Hwa Mei Hospital, University of Chinese Academy of Sciences, No. 41 Xibei Street, Haishu District, Ningbo 315010, China. Email: zhengjianjun@ucas.ac.cn.

**Background:** Patients with lung cancer who develop bone metastasis (BM) generally have an adverse prognosis. Although several clinical models have been used to predict BM in patients with lung cancer, the results are unsatisfactory. In this retrospective study, we investigated the role of <sup>18</sup>F-2-fluoro-2-deoxyglucose (FDG) metabolic activity, serum tumor markers, and histopathological subtypes in predicting BM in patients with lung cancer.

**Methods:** This study included 695 consecutive patients with lung cancer who underwent <sup>18</sup>F-FDG positron emission tomography/computed tomography (PET/CT) and in whom serum tumor markers were detected prior to treatment. The maximum standardized uptake value of primary tumors (pSUV<sub>max</sub>), metastatic lymph nodes (nSUV<sub>max</sub>) and distant metastases (mSUV<sub>max</sub>), 8 serum tumor markers [carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), squamous cell carcinoma-related antigen (SCCA), cytokeratin 19 fragment (CYFRA21-1), carbohydrate antigen (CA) 125, CA50, CA72-4, and ferritin], and histopathological subtypes were compared between patients with and without BM. Receiver operating characteristic (ROC) curve and multiple logistic regression analyses were performed to identify predictors of BM in patients with lung cancer.

**Results:** BM was identified in 133 (19.1%) patients and not in 562 (80.9%). Patients with BM had significantly higher pSUV<sub>max</sub>, nSUV<sub>max</sub>, and mSUV<sub>max</sub> than did those without BM. High concentrations of 6 serum tumor markers (i.e., CEA, ferritin, NSE, CA50, CA125, and CYFRA21-1) were significantly associated with BM. There were significant differences in the proportion of histopathological subtypes between patients with and without BM ( $\chi^2=32.35$ ;  $P<0.001$ ). The area under ROC-derived curve based on metabolic parameters was 0.737 (95% CI: 0.644–0.829) and 0.884 (95% CI: 0.825–0.943) when combined with the 6 serum tumor markers and histopathological subtypes, respectively.

**Conclusions:** High pSUV<sub>max</sub>, nSUV<sub>max</sub>, and mSUV<sub>max</sub> favor the presence of BM in patients with lung cancer, and serum tumor markers and histopathological subtypes are important factors for predicting BM in these patients.

<sup>^</sup> ORCID: Maoqing Jiang, 0000-0002-8734-2067; Jianjun Zheng, 0000-0002-0591-4528.

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## Introduction

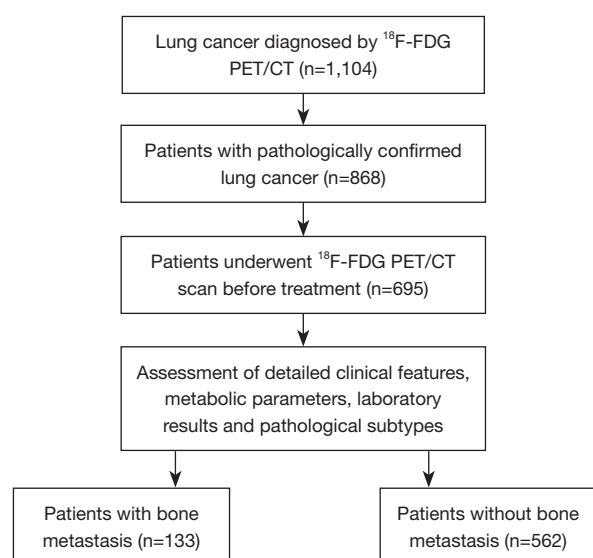
Lung cancer remains one of the most frequent malignancies and the leading cause of cancer-related deaths worldwide despite significant improvements in diagnosis and treatment strategies (1,2). In 2022, there were approximately 236,740 new lung cancer diagnoses and 130,180 lung cancer-related deaths in the United States (1), with corresponding numbers in China of 870,982 and 766,898, respectively (2). The high mortality rate is primarily due to the advanced stage of the lung cancer at the time of diagnosis, including the occurrence of multisite metastasis (e.g., lymph node metastasis, organ metastasis, and, most importantly, bone metastasis [BM]) (3,4). Clinically, approximately 20–30% of patients with non-small cell lung cancer (NSCLC) have BM at diagnosis, and a further 30–40% develop BM during the course of the disease (3,4). Patients with BM often have poor quality of life due to severe bone pain, hypercalcemia, and pathological fractures (5). Therefore, early diagnosis or prediction of the occurrence and development of BM can help clinicians initiate timely and appropriate treatment or preventive measures, thereby improving the quality of life of patients and possibly improving their prognosis.

Several clinical modalities have been used to evaluate BM in patients with lung cancer. Positron emission tomography/computed tomography (PET/CT), a molecular imaging technique with  $^{18}\text{F}$ -2-fluoro-2-deoxyglucose (FDG), has been widely used in the diagnosis and pretreatment staging of lung cancer (6–8). In terms of BM detection, the sensitivity of  $^{18}\text{F}$ -FDG PET/CT is higher than that of conventional CT and  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) bone scans in both NSCLC (9) and small cell lung cancer (SCLC) (10). The maximum standard uptake value ( $\text{SUV}_{\text{max}}$ ), a semiquantitative parameter on PET/CT, has been proven to be a promising metabolic indicator for predicting the risk of FDG-avid BM in various tumors (11,12). However, although the detection of BM by  $^{18}\text{F}$ -FDG PET/CT has high sensitivity, the development of BM is an ongoing process, and there is still no effective way to predict which patients with lung cancer are likely to

develop BM based on imaging.

Carcinoembryonic antigen (CEA), an oncofetal protein, is often overexpressed in different types of carcinomas (e.g., lung cancer, colorectal cancer, gastric cancer, pancreatic cancer) (13–15). Serum CEA concentrations have been shown to be associated with the development of brain metastasis in patients with advanced NSCLC (16). In addition, studies assessing the use of the serum tumor markers carbohydrate antigen (CA) 50, CA125, squamous cell carcinoma-related antigen (SCCA), cytokeratin 19 fragment (CYFRA21-1), neuron-specific enolase (NSE), and ferritin to predict the prognosis of patients with lung cancer showed that high concentrations of these serum tumor markers at baseline were associated with poor prognosis (17,18). Moreover, other studies investigated correlations between serum tumor markers (CEA, CA125, CYFRA21-1, SCCA, and NSE) and histopathological subtypes of lung cancer and showed that tumor markers play an auxiliary role in the histological diagnosis of patients with NSCLC (19). The poor prognosis of patients with lung cancer has been shown to be associated with BM and the high concentrations of these serum tumor markers. However, whether the concentrations of serum tumor markers contribute to the occurrence of BM and how they are correlated remain poorly understood.

In the present study, we speculated that high concentrations of serum tumor markers and high metabolic activity of primary and/or metastatic lesions may be risk factors for BM in patients with lung cancer and that combining these factors would achieve a higher efficiency in predicting BM than would each factor alone. Thus, we investigated the associations between metabolic phenotypes, serum tumor markers, and histopathological subtypes in patients with and without BM, and established corresponding models to predict the possibility of BM in patients with lung cancer. We present the following article in accordance with the STARD reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-741/rc>).



**Figure 1** Flowchart showing patient disposition. FDG, 2-fluoro-2-deoxyglucose; PET, positron emission tomography; CT, computed tomography.

## Methods

### Patients

The study was performed in accordance with the International Guidelines for Human Research Protection of the Declaration of Helsinki (as revised in 2013) and the International Conference on Harmonization in Good Clinical Practical (ICH-GCP). This study was approved by the Institutional Review Board of Hwa Mei Hospital, University of Chinese Academy of Sciences (protocol No. YJ-NBEY-KY202108401). Because this study was a retrospective study, the need for written informed consent was waived.

In this study, we analyzed 1,104 consecutive patients who had been initially diagnosed as having lung cancer with <sup>18</sup>F-FDG PET/CT at Hwa Mei Hospital, University of Chinese Academy of Sciences (Ningbo, China) between September 2019 and March 2022. To be eligible for inclusion in this study, patients had to meet the following 3 criteria: (I) histopathology confirmed lung cancer [e.g., SCLC, squamous cell carcinoma (SCC), adenocarcinoma (ADC), and not otherwise specified (NOS)]; (II) no treatment before <sup>18</sup>F-FDG PET/CT scans; and (III) pretreatment detection of at least 1 of serum tumor markers CEA (normal  $\leq 5.00$  ng/mL), CA50 (normal  $< 25.00$  U/mL), CA125 (normal  $\leq 16.00$  U/mL), CA72-4 (normal  $< 10.00$  U/mL),

**Table 1** Characteristics of the 695 patients with lung cancer

Characteristics	Number
Age (years)	
Mean $\pm$ SD	66.39 $\pm$ 9.11
Range	29–86
Sex, n (%)	
Male	478 (68.8)
Female	217 (31.2)
Smoking status, n (%)	
Never smokers	378 (54.4)
Smokers	317 (45.6)
Clinical TNM stage, n (%)	
I	238 (34.24)
II	82 (11.80)
III	150 (21.58)
IV	225 (32.37)
Histopathological subtype, n (%)	
ADC	416 (59.86)
SCC	188 (27.05)
SCLC	61 (8.78)
NOS	30 (4.32)
Distant metastasis, n (%)	
Bone	133 (19.14)
Lung	54 (7.77)
Liver	45 (6.47)
Brain	26 (3.74)
Adrenal	39 (5.61)
Others	37 (5.32)

SD, standard deviation; TNM, tumor-node-metastasis; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NOS, not otherwise specified.

NSE (normal  $< 20.00$  ng/mL), SCCA (normal  $< 1.50$  ng/mL), CYFRA21-1 (normal  $< 3.30$  ng/mL), or ferritin (normal 10.0–291.0 ng/mL). After application of the inclusion criteria, 695 patients were enrolled in this study (*Figure 1*). The clinical characteristics of the patients in the study are summarized in *Table 1* and included age, sex, smoking status, clinical tumor-node-metastasis (TNM) stage, histopathological subtypes, and distant metastatic area.

Never-smokers were strictly defined as patients who had smoked <100 cigarettes in their lifetime (20).

### *PET/CT scan technique*

PET/CT scans were performed on a GE Discovery 710 PET scanner (GE Healthcare, Chicago, IL, USA). All patients fasted for  $\geq 6$  h before PET/CT examination. Blood glucose concentrations were tested and confirmed to be <7.0 mmol/L before intravenous injection of 5.2–7.4 MBq/kg of  $^{18}\text{F}$ -FDG, with the PET/CT scan performed 45–60 min after  $^{18}\text{F}$ -FDG administration. A low-dose CT scan was performed using the following parameters: 140 kV, 10 mA, 0.5 s rotation time, and 40 mm collimation. Then, a PET scan was conducted in 3-dimensional mode from the skull base to the upper thigh at 2.5 min per bed position, and the CT data of the iterative algorithm were used for reconstruction. PET, CT, and fusion PET/CT images in the transverse, sagittal, and coronal planes were obtained on the Xeleris Workstation (GE Healthcare) for evaluation.

### *Analysis of PET/CT imaging*

All PET and CT images were evaluated consistently by 2 senior nuclear physicians (MJ and QG; both with >10 years experience) who were familiar with the clinical data. Abnormal  $^{18}\text{F}$ -FDG uptake within the lesion was defined as metabolic activity that was greater than that of the surrounding background; the uptake intensity of  $^{18}\text{F}$ -FDG was quantified by calculating the  $\text{SUV}_{\text{max}}$ . Two-dimensional regions of interest (ROIs) were manually drawn at the edges of the tumor lesions and placed in the region of the tumor with the highest  $^{18}\text{F}$ -FDG uptake.  $\text{SUV}_{\text{max}}$  is defined as the peak SUV on the pixel with the highest count in the ROI and can be calculated as follows:

$$\text{SUV} = \frac{\text{RC}_{\text{ROI}}}{\text{Dose}/\text{BW}} \quad [1]$$

Where  $\text{RC}_{\text{ROI}}$  is the concentration of radioactivity in the ROI (MBq/g), dose is the dose of  $^{18}\text{F}$ -FDG injected (MBq), and the BW is the patient's total body weight (g). According to visual qualitative analysis, when the metabolic activity of the lymph nodes was higher than that of the background mediastinal blood pool, metastatic lymph nodes were considered to be present (21).

### *Evaluation of lung cancer with BM*

All patients underwent baseline  $^{18}\text{F}$ -FDG PET/CT scans,

and BMs were assessed. Bone lesions were classified into 3 groups: (I) obvious normal or benign; (II) obvious BM on PET and CT images; and (III) equivocal (i.e., PET and CT images could not be categorized definitively into the first 2 categories, requiring additional imaging procedures). In case of differences between the 2 nuclear physicians (MJ and QG), the following criteria were used to enable a consensus to be reached: (I) confirmation by histopathology; (II) confirmation by conventional anatomic imaging during follow-up (e.g., X-ray, CT, and magnetic resonance); (III) confirmation by follow-up PET/CT scans or whole-body bone scan on  $^{99\text{mTc}}$ -MDP single photon emission CT/CT; and (IV) classification of no BM for patients without evidence of BM during clinical or imaging feature-based follow-up.

### *Statistical analysis*

Demographic patient data are presented using descriptive statistics. Clinical characteristics, including sex (male *vs.* female), smoking status (never-smokers *vs.* smokers), and histopathological subtypes (ADC, SCC, SCLC, and NOS), were compared between patients with and without BM using Fisher exact test and the chi-squared test. Quantitative data are presented as the mean  $\pm$  SD. Serum concentrations of tumor markers are presented as the median with interquartile range (IQR). The significance of differences in continuous variables [e.g.,  $\text{SUV}_{\text{max}}$  of the primary tumor ( $\text{pSUV}_{\text{max}}$ ), lymph node ( $\text{nSUV}_{\text{max}}$ ), and distant metastasis ( $\text{mSUV}_{\text{max}}$ )] and serum tumor marker concentration were compared between patients with and without BM using Mann-Whitney tests.

Receiver operating characteristic (ROC) curves were constructed using parameters or factors that were significantly different between patients with and without BM. The area under the ROC curve (AUC) was calculated to evaluate the predicted value for an established criterion. Multiple logistic regression analysis was used to establish a model to predict the risk of BM in patients with lung cancer. The Hosmer-Lemeshow test was used to evaluate the fitting effect of the model.

In all analyses, a 2-sided P value <0.05 was considered statistically significant. GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses and to draw graphs.

## **Results**

### *Patient characteristics*

Patient characteristics stratified according to the presence

of BM are summarized in *Table 2*. All patients underwent baseline  $^{18}\text{F}$ -FDG PET/CT scans. Of the 695 patients in this study, 359 (51.65%) had lymph node metastasis and 218 (31.37%) had distant metastasis; 133 (19.14%) patients had BM and 562 (80.86%) did not. Of the 695 patients, 672 (96.69%) were tested for serum CEA, 668 (96.12%) were tested for ferritin and CA125, 607 (87.34%) were tested for CA50 and CA72-4, and 615 (88.49%) were tested for NSE, CYFRA21-1, and SCCA.

### BM risk factors in patients with lung cancer

In terms of  $^{18}\text{F}$ -FDG metabolic activity,  $\text{pSUV}_{\max}$ ,  $\text{nSUV}_{\max}$ , and  $\text{mSUV}_{\max}$  were higher in patients with BM ( $12.63 \pm 5.28$ ,  $11.01 \pm 4.92$ , and  $12.30 \pm 5.90$ , respectively) than in those without ( $11.13 \pm 6.52$ ,  $9.62 \pm 5.46$  and  $8.09 \pm 5.71$ , respectively; *Figure 2*). Moreover, the incidence rates of lymph node metastasis, lung metastasis, liver metastasis, brain metastasis, and adrenal metastasis were all significantly higher in patients with than without BM (*Table 2*).

The median (IQR) concentrations of the 8 serum tumor markers (CEA, ferritin, CA50, CA125, CA72-4, NSE, SCCA, and CYFRA21-1) are presented in *Table 2*. Concentrations of CEA, ferritin, CA50, CA125, NSE, and CYFRA21-1 were significantly higher in patients with BM than without BM (all  $P$  values  $< 0.001$ ; *Figure 3*). There were no significant differences in serum CA72-4 and SCCA concentrations between patients with and without BM ( $P = 0.547$  and  $P = 0.151$ , respectively).

With regard to histopathological subtypes (*Table 2*), the incidence of ADC and SCLC was significantly higher among patients with BM (69.62% and 16.54%, respectively) than among those without BM (57.47% and 6.94%, respectively). However, the incidence of SCC was significantly lower among patients with than without BM (9.77% vs. 31.14%, respectively).

### Prediction of BM in patients with lung cancer

Values of  $\text{pSUV}_{\max}$ ,  $\text{nSUV}_{\max}$ , and  $\text{mSUV}_{\max}$  were significantly correlated with BM in patients with lung cancer, with corresponding AUCs of 0.586, 0.603, and 0.741, respectively. In addition, the AUC of the combination of  $\text{pSUV}_{\max}$ ,  $\text{nSUV}_{\max}$ , and  $\text{mSUV}_{\max}$  was 0.737 (95% CI: 0.644–0.829), with a sensitivity of 76.77% and a specificity of 83.33% (*Figure 4A*).

Of the serum tumor markers, high serum CEA, CA50, CA125, NSE, ferritin, and CYFRA21-1 concentrations

were significantly correlated with BM in patients with lung cancer, with corresponding AUCs of 0.670, 0.623, 0.748, 0.700, 0.619, and 0.697, respectively. The combination of these 6 serum tumor markers resulted in a higher AUC (0.784; 95% CI: 0.738–0.829), with a sensitivity of 70.00% and a specificity of 82.81% (*Figure 4B*).

Histopathologically, a high incidence of ADC and SCLC and a low incidence of SCC were significantly correlated with BM in patients with lung cancer, with corresponding AUCs of 0.562, 0.548, and 0.607, respectively. The combination of these 3 factors resulted in an AUC of 0.722 (95% CI: 0.675–0.768) for predicting BM in patients with lung cancer (*Figure 4C*).

When all these factors (i.e., metabolic parameters, significant serum tumor markers, and histopathological subtypes) were combined, the AUC was significantly higher (0.884; 95% CI: 0.825–0.943; *Figure 4D*). Moreover, we established a model using multiple logistic regression to predict the risk of BM in patients with lung cancer as follows:

$$\begin{aligned} \text{Logit}(P) = & 0.023 + 1.004\text{CEA} + 1.000\text{ferritin} + 1.004\text{CA50} + \\ & 1.011\text{CA125} + 1.012\text{NSE} + 1.059\text{CYFRA21-1} + \\ & 1.121\text{pSUV}_{\max} + 0.945\text{nSUV}_{\max} + 1.135\text{mSUV}_{\max} + \\ & 15.450\text{ADC} + 0.132\text{SCC} + 2.946\text{SCLC} \end{aligned} \quad [2]$$

The sensitivity and specificity of this model were 87.72% and 72.97%, respectively. The Hosmer-Lemeshow  $P = 0.239$ , indicating that the model fit well.

Representative images from patients with and without BM showing the association between  $^{18}\text{F}$ -FDG uptake and serum tumor markers are presented in *Figure 5*.

## Discussion

We performed a retrospective analysis using  $^{18}\text{F}$ -FDG PET/CT, serum tumor markers, and histopathological subtypes to evaluate the risk factors for BM and predict BM in patients with lung cancer. Our results demonstrated that high  $\text{pSUV}_{\max}$ ,  $\text{nSUV}_{\max}$ , and  $\text{mSUV}_{\max}$  favor the presence of BM in patients with lung cancer and that serum tumor markers (CEA, CA50, CA125, NSE, ferritin, and CYFRA21-1) and histopathological subtypes (ADC, SCC, and SCLC) are important factors for predicting BM in these patients.

The TNM staging system plays a critical role in the choice of treatment strategy and prognosis evaluation for patients with lung cancer (22). BM indicates an advanced stage of the disease, and the quality of life and outcomes



**Table 2** Comparison of clinical, laboratory, and imaging features between patients with and without bone metastasis

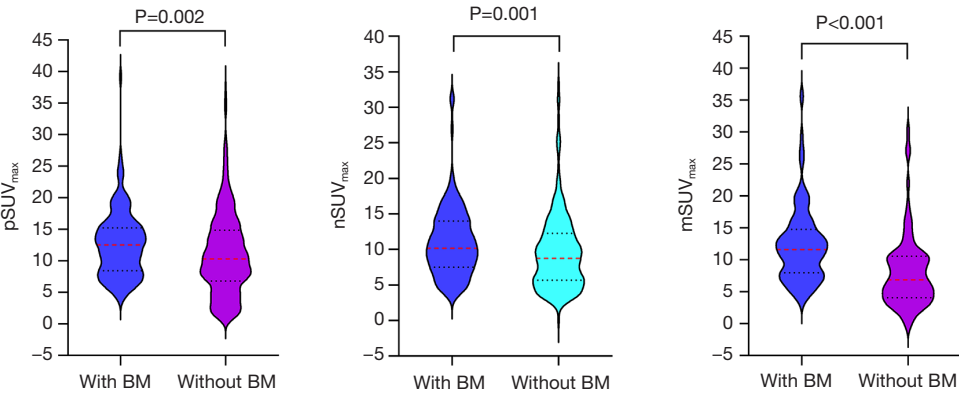
Characteristics	With BM (n=133)	Without BM (n=562)	P value
Age (years)			0.760
Mean $\pm$ SD	66.17 $\pm$ 9.57	66.44 $\pm$ 9.01	
Range	29–86	29–86	
Sex, n (%)			0.999
Male	92 (69.2)	386 (68.7)	
Female	41 (30.8)	176 (31.3)	
Smoking status, n (%)			0.772
Never smokers	74 (55.6)	304 (54.1)	
Smokers	59 (44.4)	258 (45.9)	
Serum tumor markers			
CEA (ng/mL)	7.54 [2.05–56.72]	2.60 [1.44–5.14]	<0.001
Ferritin (ng/mL)	256.2 [170.7–456.4]	199.6 [108.4–347.7]	<0.001
CA50 (U/mL)	12.69 [6.82–30.04]	9.22 [5.53–14.66]	<0.001
CA125 (U/mL)	34.55 [12.70–108.9]	10.70 [6.53–20.48]	<0.001
CA72-4 (U/mL)	1.93 [1.00–4.57]	1.86 [1.00–4.22]	0.547
NSE (ng/mL)	11.60 [8.69–21.94]	8.27 [5.88–11.64]	<0.001
SCCA (ng/mL)	0.62 [0.48–1.04]	0.73 [0.47–1.34]	0.151
CYFRA21-1 (ng/mL)	5.23 [3.00–14.38]	3.03 [1.87–5.12]	<0.001
Histopathological subtype, n (%)			<0.001
ADC	93 (69.92)	323 (57.47)	
SCC	13 (9.77)	175 (31.14)	
SCLC	22 (16.54)	39 (6.94)	
NOS	5 (3.76)	25 (4.45)	
Metabolic phenotype			
pSUV <sub>max</sub>	12.53 [8.42–15.23]	10.30 [6.81–14.86]	0.002
nSUV <sub>max</sub>	10.17 [7.51–13.98]	8.74 [5.68–12.28]	0.001
mSUV <sub>max</sub>	11.60 [8.00–14.77]	6.86 [4.08–10.56]	<0.001
Lymph node metastasis, n (%)			<0.001
Yes	121 (90.98)	237 (42.17)	
No	12 (9.02)	325 (57.83)	
Lung metastasis, n (%)			<0.001
Yes	34 (25.56)	20 (3.56)	
No	99 (74.44)	542 (96.44)	
Liver metastasis, n (%)			<0.001
Yes	35 (26.31)	10 (17.80)	
No	98 (73.69)	552 (82.20)	

**Table 2** (continued)

Table 2 (continued)

Characteristics	With BM (n=133)	Without BM (n=562)	P value
Brain metastasis, n (%)			<0.001
Yes	17 (12.78)	9 (1.60)	
No	116 (87.22)	553 (98.40)	
Adrenal metastasis, n (%)			<0.001
Yes	27 (20.30)	12 (2.14)	
No	106 (79.70)	550 (97.86)	

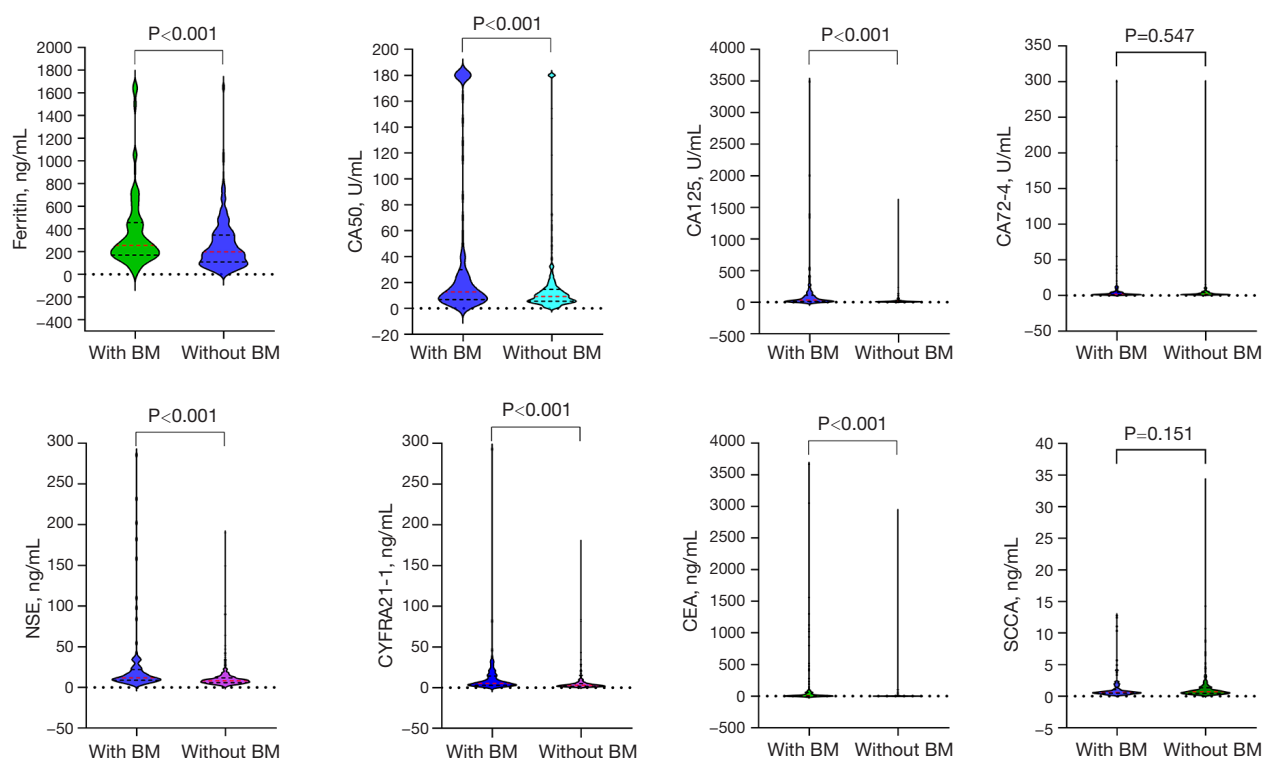
Unless indicated otherwise, data are given as the median [interquartile range] or n (%). BM, bone metastasis; SD, standard deviation; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; NSE, neuron-specific enolase; SCCA, squamous cell carcinoma-related antigen; CYFRA21-1, cytokeratin 19 fragment; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NOS, not otherwise specified; pSUV<sub>max</sub>, maximum standardized uptake value of primary tumor; nSUV<sub>max</sub>, maximum standardized uptake value of metastatic lymph node; mSUV<sub>max</sub>, maximum standardized uptake value of distant metastasis.



**Figure 2** Metabolic activity of lung cancer on <sup>18</sup>F-2-fluoro-2-deoxyglucose positron emission tomography/computed tomography. pSUV<sub>max</sub>, nSUV<sub>max</sub>, and mSUV<sub>max</sub> were compared between patients with and without BM. Red dotted line represents the median, and black dotted line represents the 1st and 3rd quartiles value. pSUV<sub>max</sub>, maximum standardized uptake value of primary tumor; nSUV<sub>max</sub>, maximum standardized uptake value of metastatic lymph node; mSUV<sub>max</sub>, maximum standardized uptake value of distant metastasis; BM, bone metastasis.

of these patients are significantly worse than for patients without BM (3,5,23,24). To date, the detection of BM in patients with lung cancer using anatomical and functional imaging modalities (e.g., <sup>18</sup>F-FDG PET/CT) has been highly accurate (9,10). Studies have shown that BM can be identified at the time of initial diagnosis in 20–30% of patients, but up to 30–40% of patients develop BM in the subsequent disease course (3-5). Thus, it is of considerable importance to identify patients who are likely to develop BM so that clinicians can initiate timely, preventive measures. Lung cancer patients with high metabolic activity on PET/CT tend to have poor survival (25-28). Therefore, in this study, we compared differences in metabolic parameters (e.g., pSUV<sub>max</sub>, nSUV<sub>max</sub>, and

mSUV<sub>max</sub>) between patients with and without BM. These comparisons revealed that pSUV<sub>max</sub>, nSUV<sub>max</sub>, and mSUV<sub>max</sub> are significantly higher in patients with than without BM, suggesting that patients with high metabolic activity are prone to developing BM. We further conducted multiple logistic regression analysis to evaluate the ability of PET/CT based on these 3 parameters to predict the probability of BM in patients with lung cancer. The AUC for this analysis was 0.737, indicating moderate predictive power. In clinical practice, the serum tumor markers CEA, CA50, CA125, CA72-4, ferritin, NSE, SCCA, and CYFRA21-1 are routinely measured in patients with lung cancer or suspected lung cancer before and/or after treatment. Several studies have demonstrated the significant



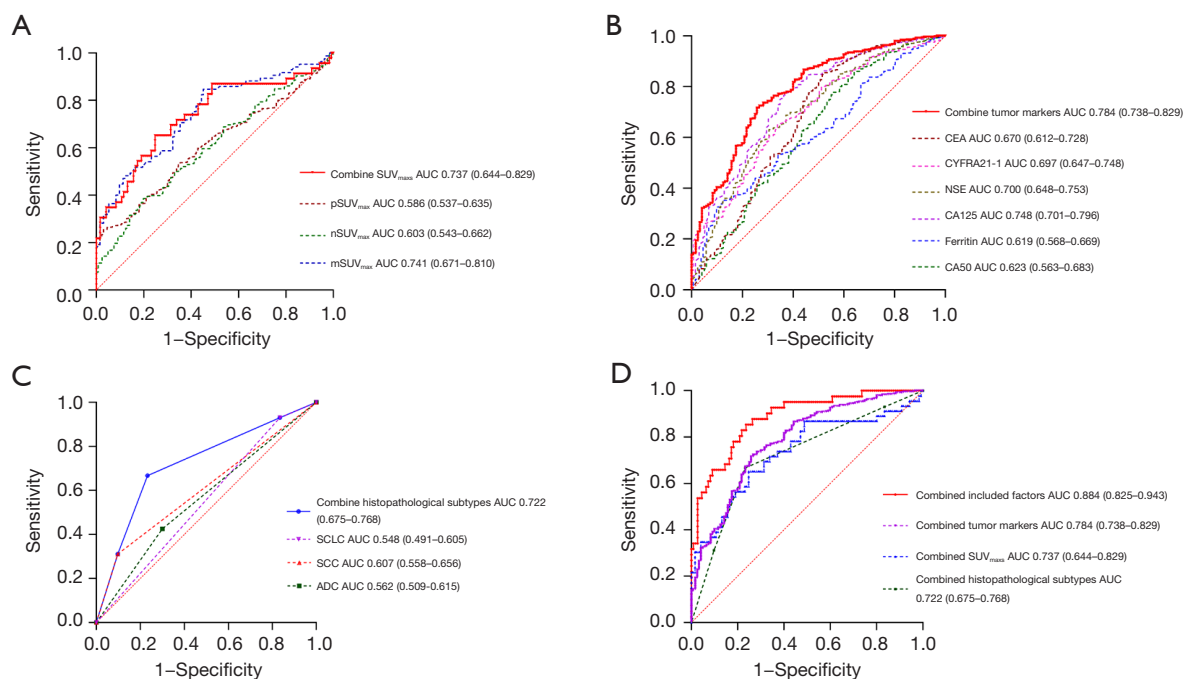
**Figure 3** Serum tumor marker concentrations in patients with and without BM. Red dotted line represents the median, black dotted line represents the 1st and 3rd quartiles value. CA, carbohydrate antigen; NSE, neuron-specific enolase; CYFRA21-1, cytokeratin 19 fragment; CEA, carcinoembryonic antigen; SCCA, squamous cell carcinoma-related antigen; BM, bone metastasis.

role of these tumor markers in the diagnosis, evaluation of treatment response, and assessment of prognosis for patients with lung cancer (14,17-19,29,30). Molina *et al.* showed that after combining the serum tumor markers CEA, CYFRA21-1, NSE, SCCA, CA153, and gastrin-releasing peptide precursor, the diagnostic sensitivity and specificity for lung cancer rose to 88.5% and 82%, respectively (29). High serum concentrations of CYFRA21-1 have been shown to be associated with poor prognosis in patients with NSCLC (31). Ayan *et al.* assessed the correlations between serum CEA and osteopontin (OPN) concentrations and  $^{18}\text{F}$ -FDG uptake in patients with lung cancer and BM and did not find any significant correlations; however, the increase in CEA and OPN concentrations may be a risk factor in patients with lung cancer and BM (32). Thus, differences in concentrations of serum tumor markers between lung cancer patients with and without BM needs to be clarified to identify more closely related risk factors. In this present study, we found that serum CEA, CA50, CA125, ferritin, NSE, and CYFRA21-1 concentrations were higher in patients with than without BM, but there was no

significant difference between the 2 groups in serum CA72-4 and SCCA concentrations. Therefore, we also performed multiple logistic regression analysis to evaluate the role of these 6 serum tumor markers in predicting the probability of BM in patients with lung cancer. Our results yielded an AUC of 0.784, showing moderate predictive power.

The prognosis of different histopathological subtypes varies greatly, and patients with SCLC usually have a poor prognosis (33). Moreover, the clinical TNM stage is another important prognostic factor for patients with lung cancer. Patients with BM, regardless of histopathological subtype, often have adverse outcomes (34,35). Thus, early diagnosis and/or prediction of BM can play a central role in the management of patients with lung cancer. In the present study, the proportion of ADC and SCLC was significantly higher among patients with than without BM, but the opposite was true for SCC. Subsequently, we performed multiple logistic regression analysis to evaluate the role of histopathological subtype in predicting the probability of BM. This analysis yielded an AUC of 0.722, which was higher than the predictive power of individual





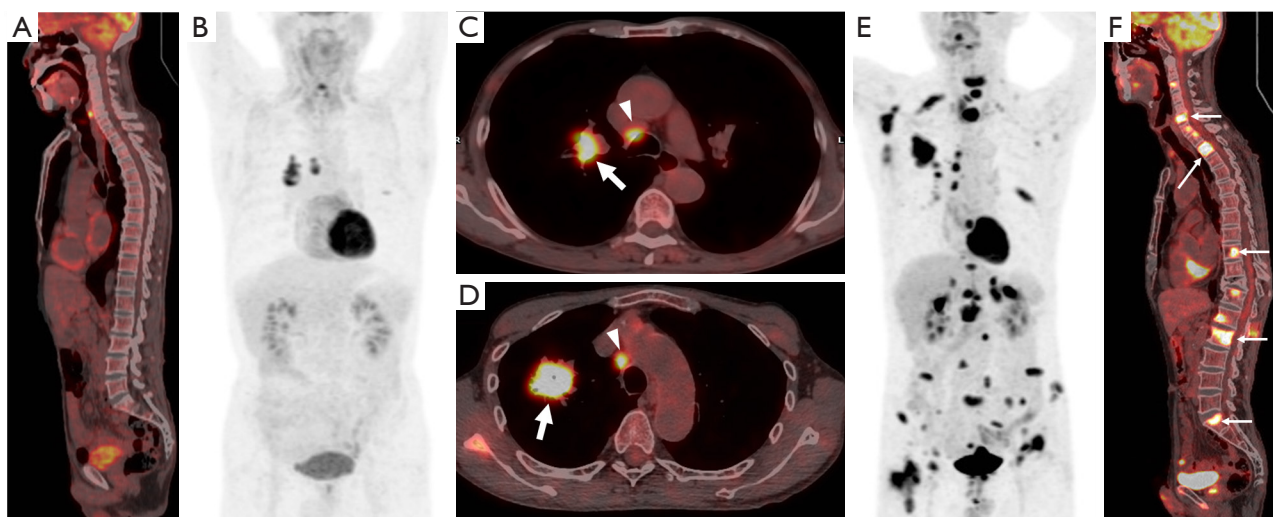
**Figure 4** AUC for individual factors (A–C) and all factors within a group combined (D) for predicting bone metastasis in patients with lung cancer. (A) Metabolic parameters; (B) serum tumor markers; (C) histopathological subtypes. SUV, standardized uptake value; pSUV<sub>max</sub>, maximum standardized uptake value of primary tumor; nSUV<sub>max</sub>, maximum standardized uptake value of metastatic lymph node; mSUV<sub>max</sub>, maximum standardized uptake value of distant metastasis; AUC, area under the ROC curve; ROC, receiver operating characteristic; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment; NSE, neuron-specific enolase; CA, carbohydrate antigen; SCLC, small cell lung cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

histopathological subtypes.

Various models have been proposed to predict BM in patients with lung cancer using serological molecular bone markers (36,37). Zhou *et al.* established a model combining the biomarkers chemokine receptor type 4, bone sialoprotein, OPN, and bone morphogenetic protein-4 to predict BM in resected patients with stage III NSCLC, achieving a sensitivity and specificity of 71% and 70%, respectively (36). In addition, a serological molecular model based on parathyroid hormone-related peptide, osteoprotegerin, and the bone resorptive markers carboxyterminal telopeptide of type I collagen ( $\beta$ -CTX) and procollagen type I N-terminal propeptide (tP1NP) was established for early diagnosis and to monitor the progress of BM in patients with lung cancer, achieving a sensitivity and specificity of 85.8% and 89.7%, respectively (37). However, these above molecular bone markers are not routinely checked in patients with lung cancer. With the development of molecular imaging,  $^{18}\text{F}$ -FDG PET/CT is often used for diagnosis, staging or

restaging, and monitoring the treatment response of lung cancer (38,39). The significance of PET/CT metabolic parameters, concentrations of serum tumor markers, and histopathological subtypes in the diagnosis and/or prediction of BM in patients with lung cancer has been studied. However, to our knowledge, the risk stratification of patients with or without BM based on metabolic parameters, serum tumor markers, and histopathological subtypes has not been reported. The results of the present study demonstrate a significant role for these factors in distinguishing between patients with and without BM, with an AUC 0.884 for predicting BM in patients with lung cancer; thus, this model could be used in clinical practice for the early identification of and intervention in patients at high risk of BM.

Although the results of this study are interesting, there are some limitations that need to be acknowledged. First, this was a retrospective study, and the number of patients enrolled, especially those with BM, was relatively low. Second, the 8 serum tumor markers were not tested in all patients. Third, due to the small number of patients, this



**Figure 5** Representative PET/CT images in patients with and without BM. (A-C) A 67-year-old male with lung ADC and normal serum tumor markers. The sagittal PET/CT image showed no BM in the body (A). A 3-D MIP PET image showed lung ADC with mediastinal lymph node metastasis (B). An axial PET/CT image (C) showed increased uptake of  $^{18}\text{F}$ -FDG with a  $\text{pSUV}_{\text{max}}$  of 9.02 (arrow) and a  $\text{nSUV}_{\text{max}}$  of 8.87 (arrowhead). (D-F) A 61-year-old male with lung ADC and increased serum tumor markers [carcinoembryonic antigen 33.74 ng/mL (increased), ferritin 1,520.20 ng/mL (increased), CA125 282.10 U/mL (increased), CA50 10.05 U/mL (normal), neuron-specific enolase 26.60 ng/mL (increased), and cytokeratin 19 fragment 18.12 ng/mL (increased)]. The axial PET/CT image (D) showed increased uptake of  $^{18}\text{F}$ -FDG with a  $\text{pSUV}_{\text{max}}$  of 20.26 (arrow) and an  $\text{nSUV}_{\text{max}}$  of 16.13 (arrowhead). The 3-D MIP PET image showed lung ADC with multiple metastases (E). The sagittal PET/CT image showed multiple BM (arrows) in the spine (F). PET, positron emission tomography; CT, computed tomography; BM, bone metastasis; ADC, adenocarcinoma; 3-D MIP, 3-dimensional maximum intensity projection; FDG, 2-fluoro-2-deoxyglucose;  $\text{pSUV}_{\text{max}}$ , maximum standardized uptake value of primary tumor;  $\text{nSUV}_{\text{max}}$ , maximum standardized uptake value of metastatic lymph node; CA, carbohydrate antigen.

study did not evaluate the correlation between BM and other distant metastatic organs, including the lung, liver, brain, and adrenal gland. Finally, there was no validation model in our study, and further research is needed to confirm our results.

## Conclusions

In summary, this study investigated whether PET/CT parameters, 8 conventional serum tumor markers, and histopathological subtypes can be used to predict BM in patients with lung cancer. We identified significant associations between metabolic phenotypes (i.e.,  $\text{pSUV}_{\text{max}}$ ,  $\text{nSUV}_{\text{max}}$ , and  $\text{mSUV}_{\text{max}}$ ), serum tumor markers (i.e., CEA, CA50, CA125, NSE, ferritin, and CYFRA21-1), and histopathological subtype (i.e., ADC, SCC, and SCLC) in patients with and without BM. Our combined model had an AUC of 0.884, which was significantly higher than that of each of the individual prediction models. However, further prospective studies are needed to verify our results.

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## Footnote

**Reporting Checklist:** The authors have completed the STARD reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-22-741/rc>

**Conflicts of Interest:** All authors have completed the ICMJE

uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-741/coif>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of Hwa Mei Hospital, University of Chinese Academy of Sciences (No. YJ-NBEY-KY202108401). Because of the retrospective nature of this study, the need for written informed consent was waived.

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