Differentiation of Primary Lung Cancer from Solitary Lung Metastasis in Patients with Colorectal Cancer Using Computed Tomography Features and Clinical Characteristics : A Retrospective Cohort Study

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Research

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Abstract

Purpose: To evaluate the features of solitary pulmonary nodule (SPN) that can be used to differentiate between primary lung cancer (LC) and solitary lung metastasis (LM) in patients with colorectal cancer (CRC).

Materials and Methods: This retrospective study included SPNs resected in CRC patients between 2011 and 2019. The diagnosis of primary LC or solitary LM was based on histopathologic report by thoracoscopic wedge resection. Chest computed tomography (CT) images were assessed by two thoracic radiologists, and features were identified by consensus. Predictive parameters for the discrimination of primary LC from solitary LM were evaluated using multivariate logistic regression analysis.

Results: We analyzed 199 patients (mean age, 65.95 years; 131 men). The clinical characteristics suggestive of primary LC rather than solitary LM was clinical stage I-II CRC ($P < 0.001$, odds ratio (OR): 21.70). The CT features of SPNs indicative of primary LC rather than solitary LM were a spiculated margin ($P = 0.020$, OR: 8.34), a sub-solid density ($P < 0.001$, OR: 115.56), and presence of an air-bronchogram (OR: 5.32; $P = 0.032$).

Conclusions: CT features and clinical characteristics of SPNs in patients with CRC could help differentiate between primary LC and solitary LM.

Introduction

Chest computed tomography (CT) is an important surveillance tool for pulmonary metastases. As the lung is a common site of metastasis in colorectal cancer (CRC) and chest CT supports improved identification of pulmonary nodules, many current guidelines recommend chest CT in pre-operative evaluation and post-operative surveillance of patients with CRC [1]. Detection of multiple pulmonary nodules supports a diagnosis of metastasis [2]. However, diagnosis is more difficult when a solitary pulmonary nodule (SPN) is detected because primary lung cancer (LC) can mimic a solitary lung metastasis (LM) in patients with CRC. Furthermore, 10% of pulmonary metastases are present as SPNs in patients with CRC. This rate is higher than that in patients with other extra-thoracic malignancies [3, 4]. Therefore, it is sometimes difficult to determine whether a SPN is a primary LC or a solitary LM.

Surgical strategies for treating primary LC and solitary LM are quite different. The treatment of choice for LM is minimally invasive surgical resection in order to preserve as much healthy lung parenchyma as possible in case repeat operations are needed. However, complete surgical resection with lobectomy and mediastinal lymph node dissection is the gold standard for LC [5].

Image-guided needle biopsies may be useful for distinguishing between primary LC and solitary LM before surgical planning. However, it is difficult and risky to perform needle biopsies in some cases, especially for those with small lesions. Additionally, the small volume of biopsy specimen obtained can sometimes impede histological differentiation between primary LC and solitary LM.

Imaging characteristics of SPN can be used for non-invasive alternatives to determine whether a SPN is a primary LC or a solitary LM. However, compared to the generally accepted imaging findings of metastatic nodules including multiple peripherally located round variable sized nodules [4], the comparison of imaging findings between primary LC and solitary LM are not well established. Therefore, the aim of this study was to determine clinical characteristics and CT features that could be used to differentiate between primary LC and solitary LM in patients with CRC.

Materials And Methods

Patients

We retrospectively reviewed CRC patients by searching electronic medical records from January 2011 to December 2019 at a single tertiary referral center. Patients with the following criteria were included: presence of a SPN which measured less than 30 mm on pre-diagnostic chest CT image, evidence of malignant potential such as size growth of a SPN that has increased in diameter of at least 2 mm, and availability of histopathologic report by thoracoscopic wedge resection. To this initial inclusion of 224 patients, we applied the exclusion criteria of patients whose SPN was not diagnosed as either primary LC or solitary LM (n = 13) and patients whose SPN deemed too small to characterize at pre-diagnostic chest CT image (less than 8 mm) (n = 12). Finally, 199 CRC patients were enrolled in this study (Table 1).

Table 1
Clinical Characteristics of Patients

	LC (n = 70)	LM (n = 129)	P value
Age (years)	68.53 ± 8.15	64.55 ± 1.72	**0.004**
Sex (M/F)	44/26	87/42	0.515
History of smoking	37 (52.9)	49 (38)	**0.043**
Index tumor location	41 (58.6)	47 (36.4)	**0.003**
Colon	29 (41.4)	82 (63.6)	
Rectum			
Index tumor stage			**< 0.001**
Stage I-II	53 (75.7)	29 (22.5)	
Stage III-IV	17 (24.3)	100 (77.5)	
Histopathology of the pulmonary nodule	55 (78.6)	129 (100)	N/A[++]
Metastatic	14 (20)		
Adenocarcinoma	1 (1.4)		
Squamous cell carcinoma			
Small cell carcinoma			

Values in parentheses are percentages. Values are presented as mean ± standard deviation where applicable.

Note: significant P values are shown in bold

LC, lung cancer; LM, lung metastases

[++]N/A, not applicable

Histopathological diagnosis

Patients were divided into two groups based on histopathology: those with primary LC and those with solitary LM. Histopathological differentiation between primary LC and solitary LM was achieved by performing a comprehensive histological assessment and immunohistochemistry staining. Nodules of different histological types including squamous cell carcinoma and small cell carcinoma were considered to be primary LC. Nodules with morphological features of pulmonary adenocarcinoma and positive staining for CK7 and TTF-1 were also considered to be primary LC. Nodules with morphological features of enteric adenocarcinoma, positive staining for CK20, and negative staining for TTF-1 were considered to be solitary LM [6].

Imaging protocols

Chest CT scans including high resolution CT were obtained using a Lightspeed 16 (n = 87; GE Medical Systems, Milwaukee, Wisconsin, USA), a Lightspeed VCT (n = 68; GE Medical Systems, Milwaukee, Wisconsin, USA), a Somatom Definition Flash multi-detector CT system (n = 32; Siemens Medical Systems, Erlangen, Germany), or a Revolution (n = 11; GE Medical Systems, Milwaukee, Wisconsin, USA). For Lightspeed VCT, Lightspeed 16, and Revolution, the following parameters were used: reconstruction thickness of the enhanced CT scan, 2.5 mm; rotation time, 0.5 to 0.8 sec; peak kilovoltage, 120 kVp; and tube current, 220 mAs. For Somatom Definition Flash, the following parameters were used: reconstruction thickness, 2.5 or 3.0 mm; rotation time, 0.5 sec; peak kilovoltage, 120 kVp; and tube current, 110 mAs. Contrast-enhanced chest CT images were obtained after an intravenous injection of 120 to 130 mL nonionic contrast medium (either iohexol [Omnipaque®, GE Healthcare, Amersham, UK] or iopromide [Ultravist 300®, Bayer Schering Pharma, Berlin, Germany]) at an average injection rate of 2 mL/sec.

Analysis of CT features

Chest CT images were interpreted independently by two thoracic radiologists with 20 and 8 years of experience, respectively. They were blinded to clinical and histopathologic information of patients. If interpretations differed, the decision was made based on consensus reading of two designated thoracic radiologists.

Qualitative CT features such as location (upper or non-upper, central or peripheral), margin (smooth, lobulated, or spiculated), and density (solid or sub-solid) of pulmonary nodules and the presence of an air-bronchogram, cavitation, pleural tags, pleural abutment, or background emphysema were assessed. A central location was defined as the area within 2 cm of the pulmonary hilum [7]. Nodules were classified as smooth, lobulated, or spiculated based on margin characteristics (Fig. 1). Nodules were classified as having a sub-solid density if they contained a portion of ground-glass opacity (GGO) without completely obscuring bronchial or vascular margins of the lung parenchyma (Fig. 1) [8]. An air-bronchogram was defined as a gas-filled bronchus surrounded by abnormal lung parenchyma (Fig. 1) [8]. Pleural tags were defined as linear strands that extended between nodule surface and adjacent pleural surface [9].

Quantitative CT features such as sizes of lung nodules were also assessed. The size of a nodule was measured using the longest diameter, including any portion of GGO seen on axial CT images obtained with lung window settings.

Statistical analysis

All statistical analyses were performed using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA). CT features of primary LC and solitary LM were compared using Pearson Chi-square test for categorical variables and independent t-test for continuous variables.

Inter-reader agreement for CT features was assessed by percent of concordant cases and Kappa of agreement with 95% confidence intervals [10]. Univariate and multivariate logistic regression analyses

were used to evaluate which factors were predictive of differentiation between the two groups. In initial univariate analysis, a *P* value of < 0.25 was used as the threshold for retaining factors in multivariate analysis [11]. A receiver operating characteristic (ROC) curve was drawn to discriminate LC from LM according to each significant clinical characteristic and CT feature. Corresponding area under the curve (AUC) was calculated. Statistical significance was considered when p-value was less than 0.05.

Results

Clinical characteristics of patients enrolled in this study are summarized in Table 1. The mean age of patients was 65.95 ± 1.5 years. There were 131 men and 68 women. In CRC patients, preoperative and surveillance chest CTs revealed 78 and 121 SPNs, respectively. The proportion of patients in which the index tumor was located in the rectum was significantly higher in the solitary LM group than that in the primary LC group (63.6% vs. 41.4%, *P* = 0.003). According to the American Joint Committee on Cancer tumor-node-metastasis staging system [12], the proportion of patients with clinical stage I-II index tumor was significantly higher in the primary LC group than that in the solitary LM group (77.5% vs. 24.3%, *P* < 0.001).

CT features of SPNs were compared between primary LC and solitary LM groups (Table 2). The mean size of nodules was significantly greater in the primary LC group (1.91 cm; IQR: 1.50–2.25 cm) than the solitary LM group (1.49 cm; IQR: 1.00 – 1.70 cm) (*P* < 0.001).

Table 2
Comparison of CT Features of SPNs

	LC (n = 70)	LM (n = 129)	P value
Size	1.91 ± 0.55	1.49 ± 0.62	**< 0.001**
Cranial-caudal location			0.188
Upper	35 (50.0)	52 (40.3)	
Non-upper	35 (50.0)	77 (59.7)	
Axial location			0.105
Central	12 (17.1)	12 (9.3)	
Peripheral	58 (82.9)	117 (90.7)	
Margin			**< 0.001**
Smooth	7 (10)	54 (41.9)	
Lobulated	30 (42.9)	68 (52.7)	
Spiculated	33 (47.1)	7 (5.4)	
Density			**< 0.001**
Solid	47 (67.1)	128 (99.2)	
Sub-solid	23 (32.9)	1 (0.8)	
Air-bronchogram	30 (42.9)	7 (5.4)	**< 0.001**
Cavitation	13 (18.6)	19 (14.7)	0.296
Pleural tags	41 (58.6)	25 (19.4)	**< 0.001**
Pleural abutment	32 (45.7)	53 (41.1)	0.528
Background emphysema	18 (25.7)	13 (10.2)	**0.004**

Values in parentheses are percentages. Values are presented as mean ± standard deviation where applicable.

Note: significant P values are shown in bold

CT, computed tomography; LC, lung cancer; LM, lung metastases; SPNs, solitary pulmonary nodules

The proportion of nodules with spiculated margins was significantly higher in the primary LC group than in the solitary LM group (47.1% vs. 5.4%, $P < 0.001$). The proportion of nodules with a sub-solid density was significantly higher in the primary LC group than in the solitary LM group (32.9% vs. 0.8%, $P < 0.001$). Air-bronchograms were significantly more frequent in the primary LC group than in the solitary LM group

(42.9% vs. 5.4%, $P < 0.001$). Pleural tags were significantly more frequent in the primary LC group than in the solitary LM group (58.6% vs. 19.4%, $P < 0.001$). There were no statistically significant differences in the location of nodules or the presence of cavitation between the two groups (Table 2).

Inter-observer agreement for studied CT features was substantial (kappa > 0.60, ≤ 0.8) for central-peripheral location (kappa = 0.66), margin (kappa = 0.80), air-bronchogram (kappa = 0.71), cavitation (kappa = 0.80), pleural tags (kappa = 0.80), and pleural abutment (kappa = 0.66). It was almost perfect (kappa > 0.80) for all remaining CT features (Table 3).

Table 3
Analysis of inter-reader agreement showing the percent of concordance and kappa of agreement

CT features	Number (% of concordance)[+]	kappa (95% CIs)[++]
Cranial-caudal location	199/199 (100)	1 (1, 1)
Central-peripheral location	136/199 (68.3)	0.66 (0.50, 0.80)
Margin	174/199 (87.4)	0.80 (0.72, 0.87)
Density	192/199 (96.5)	0.83 (0.72, 0.95)
Air-bronchogram	182/199 (91.5)	0.71 (0.58, 0.84)
Cavitation	188/199 (94.5)	0.80 (0.69, 0.91)
Pleural tags	180/199 (90.5)	0.80 (0.71, 0.88)
Pleural abutment	166/199 (83.4)	0.66 (0.55, 0.77)
Background emphysema	198/199 (99.5)	0.98 (0.94, 1.00)

Note: [+]Values in parentheses are percentages

[++]Values in parentheses are 95% CIs

CI, confidence interval.

Predictive parameters for differentiation between primary LC and solitary LM were analyzed using univariate and multivariate logistic regression models (Table 4). Age ($P = 0.009$), a history of smoking ($P = 0.044$), a colon location of the index tumor ($P = 0.009$), a clinical stage I-II CRC ($P < 0.001$), size of SPN ($P < 0.001$), a spiculated margin ($P < 0.001$), a lobulated margin ($P = 0.007$), sub-solid density ($P \leq 0.001$), presence of an air-bronchogram ($P < 0.001$), presence of pleural tags ($P < 0.001$), and background emphysema ($P = 0.005$) were significant on univariate analysis. On multivariate analysis including these 13 factors as variables of interest, clinical stage I-II CRC ($P < 0.001$, odds ratio (OR) : 21.70), a spiculated margin ($P = 0.020$, OR: 8.34), a sub-solid density ($P < 0.001$, OR: 115.56), and presence of an air-bronchogram ($P = 0.032$, OR: 5.32) were significant predictive parameters for discriminating primary LC from LM.

Table 4
Multivariate Analysis of Clinical Characteristics and CT features for Discriminating LC from LM

	Univariate		**Multivariate**	
	OR	P value	OR	P value
Age	1.04 (1.01–1.08)	**0.009**	1.05 (0.99–1.11)	0.102
Smoking	1.83 (1.02–3.30)	**0.044**	2.81 (0.91–8.64)	0.072
Index tumor (colon cancer)[+]	2.47 (1.36–4.48)	**0.009**	1.41 (0.52–3.85)	0.503
Stage I-II CRC	10.75 (5.42–21.33)	**< 0.001**	21.70 (6.56–71.73)	**< 0.001**
Size of SPN	3.34 (1.92–5.83)	**< 0.001**	2.01 (0.70–4.80)	0.197
Upper lobe location	1.48 (0.82–2.66)	0.189	1.33 (0.46–3.79)	0.600
Central location	0.50 (0.21–1.17)	0.110	2.11 (0.55–8.14)	0.280
Spiculated margin	36.37 (11.71–112.99)	**< 0.001**	8.34 (1.39–50.08)	**0.020**
Lobulated margin	3.40 (1.39–8.35)	**0.007**	2.41 (0.66–8.89)	0.186
Sub-solid density	62.64 (8.23–476.85)	**< 0.001**	115.56 (9.96–1341.06)	**< 0.001**
Air-bronchogram	13.07 (5.33–32.05)	**< 0.001**	5.32 (1.15–24.51)	**0.032**
Cavitation	1.32 (0.61–2.87)	0.482		
Pleural tags	5.88 (3.08–11.22)	**< 0.001**	2.41 (0.77–7.53)	0.131
Pleural abutment	1.21 (0.67–2.17)	0.529		
Background emphysema	3.06 (1.40–6.71)	**0.005**	1.83 (0.55–6.06)	0.322

Data in parentheses are 95% confidence intervals. Each variable with a P value ≤ 0.25 in univariate analysis was analyzed in the multivariate model. All statistical analyses were performed using the logistic regression model.

Note: significant ORs and P values are shown in bold

CT, computed tomography; LC, lung cancer; LM, lung metastases; OR, odds ratio

[+]Reference value is the rectal location of index tumor

ROC curves were used to assess the discrimination of primary LC from LM using clinical characteristics (clinical stage I-II CRC) and CT features (independent predicted factors: spiculated margin, sub-solid density, and air-bronchogram) both alone and in combination. Areas under ROC curve values of clinical stage I-II CRC, spiculated margin, subsolid density, and airbronchogram were 0.766, 0.772, 0.660, and 0.687, respectively. The area under the ROC curve value was 0.926 when both clinical and CT features were used (Fig. 2).

Discussion

CT features can be used to differentiate between primary LC and solitary LM. In our multivariate analysis, three CT features of nodules were found to be useful for differentiating primary LC and solitary LM. These were nodules with spiculated margins, sub-solid density, and a presence of air-bronchogram.

Marginal characteristics of nodules can be used to determine whether these nodules are primary or metastatic and whether they are benign or malignant. Previous studies have reported that a smooth or well-defined margin is more common in metastatic nodules than an irregular margin [4, 13]. In contrast, up to 80% of primary lung cancer can present with non-smooth margin, especially a spiculated margin which is already well known to be associated with primary lung cancer [14, 15]. The proportion of nodules with spiculated margins was significantly higher in patients with primary LC than in patients with solitary LM in both univariate and multivariate analyses of our study. The margin of a nodule appeared more irregular even in solitary LM as the size increased. But a solitary LM tended to show a lobulated margin rather than a spiculated margin in our study.

Nodules with a sub-solid density contain a GGO component commonly seen in lepidic growth of primary lung adenocarcinomas [16, 17]. Lepidic growth is defined as tumor progression along the alveolar wall. It is typically observed in primary lung adenocarcinomas. Only a few reports have described cases of lepidic growth of pulmonary metastases [18, 19]. Typically, pulmonary metastases present as solid, round nodules that are peripherally located [4]. In our study, sub-solid density of nodules was mostly observed in primary LC. It was rarely observed in solitary LM. Thus, sub-solid density of SPNs can be used to support a diagnosis of a primary LC rather than a solitary LM.

An air-bronchogram is defined as an air-containing bronchus or bronchioles within an area of opacification of the surrounding alveoli. The presence of an air-bronchogram within a nodule raises a high suspicion of a primary lung malignancy [20]. Air-bronchograms have been reported to occur in primary LC of all histological types [21]. Only a few reports have described cases of pulmonary metastases showing air-bronchograms [18]. The rate of air-bronchograms within nodules was significantly higher in primary LC than in solitary LM in both univariate and multivariate analysis of our study.

Pleural tags are known as interlobular septal thickening of the lung between the nodule and visceral pleura. They may result from localized edema, tumor extension within or outside lymphatic vessels, inflammatory cells, or fibrosis [9]. A previous study has reported that pleural tags are commonly seen in primary LC and in up to 80% of surgically resected primary LC without abutting the pleura [22]. In the present study, pleural tags were found in 56.4% of primary LC. They were also significantly more frequent in primary LC than in solitary LM in univariate analysis of our study.

Besides CT features, clinical characteristics can also aid the differentiation between primary LC and solitary LM. Several studies have previously characterized indeterminate pulmonary nodules in patients with CRC [23–26]. Among factors predicting pulmonary metastasis, presence of lymph node metastasis

in patients with CRC has been identified as a significant risk factor [23–26]. Kim et al. [27] have reported that the probability of pulmonary metastasis is low in patients with CRC without hepatic or lymph node metastasis, that is, in clinical stage I-II CRC patients. Similarly, the present study showed that solitary LM was associated with higher clinical stage (III-IV) CRC patients than lower clinical stage CRC patients (I-II) in both univariate and multivariate analyses.

Previous studies have reported that the location of the index tumor in the rectum rather than the colon is a risk factor of pulmonary metastasis in patients with CRC [23, 25]. The venous bloodstream of the rectum bypasses the liver, meaning that the first organ encountered is the lung [28]. Similarly, the proportion of index tumors located in the rectum was significantly higher in the solitary LM group than in the primary LC group in univariate analysis of the present study.

This study has several limitations. Firstly, only nodules confirmed as either primary LC or solitary LM on histopathological analysis after surgical resection were included. There was an inherent selection bias towards patients who underwent surgery. Prospective studies (particularly randomized, controlled trials) is needed to confirm our results. Secondly, as this was a single-center and retrospective study, the sample size was relatively small. A study with a larger sample size is needed to validate our results. Thirdly, visual analysis of CT features raises the possibility of inter-observer and intra-observer variability regarding categorization despite the use of consensus reading. For a more accurate interpretation, more quantitative analysis tool such as radiomics would be more helpful.

Conclusion

Understanding of the CT features of primary LC versus solitary LM allows better discrimination of SPNs in patient with CRC. Furthermore, both CT features of SPNs and clinical characteristics are needed to aid the differentiation between primary LC and solitary LM in CRC patients.

Abbreviations

SPN: Solitary pulmonary nodule

CT: Computed tomography

CRC: Colorectal cancer

LC: Lung cancer

LM: Lung metastasis

GGO: Ground-glass opacity

Declarations

Availability of data and materials

The study data is not available

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Author Contributions

Jong Eun Lee and Yun-Hyeon Kim designed the research; Jong Eun Lee and Won Gi Jeong analyzed data; Jong Eun Lee and Yun-Hyeon Kim wrote the paper. The authors read and approved the final manuscript.

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Ethics approval and consent to participate

This study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the Institutional Review Board of Chonnam Hwasun National University Hospital (Approval number : IRB.CNUHH-2020-077). Informed consent from patients to be included in this study was omitted according to the policy of our Institutional Review Board.

Consent for publication

Informed consent from patients to be included in this study was omitted according to the policy of our IRB.

Competing interests

The authors declare that they have no competing interests

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Figures

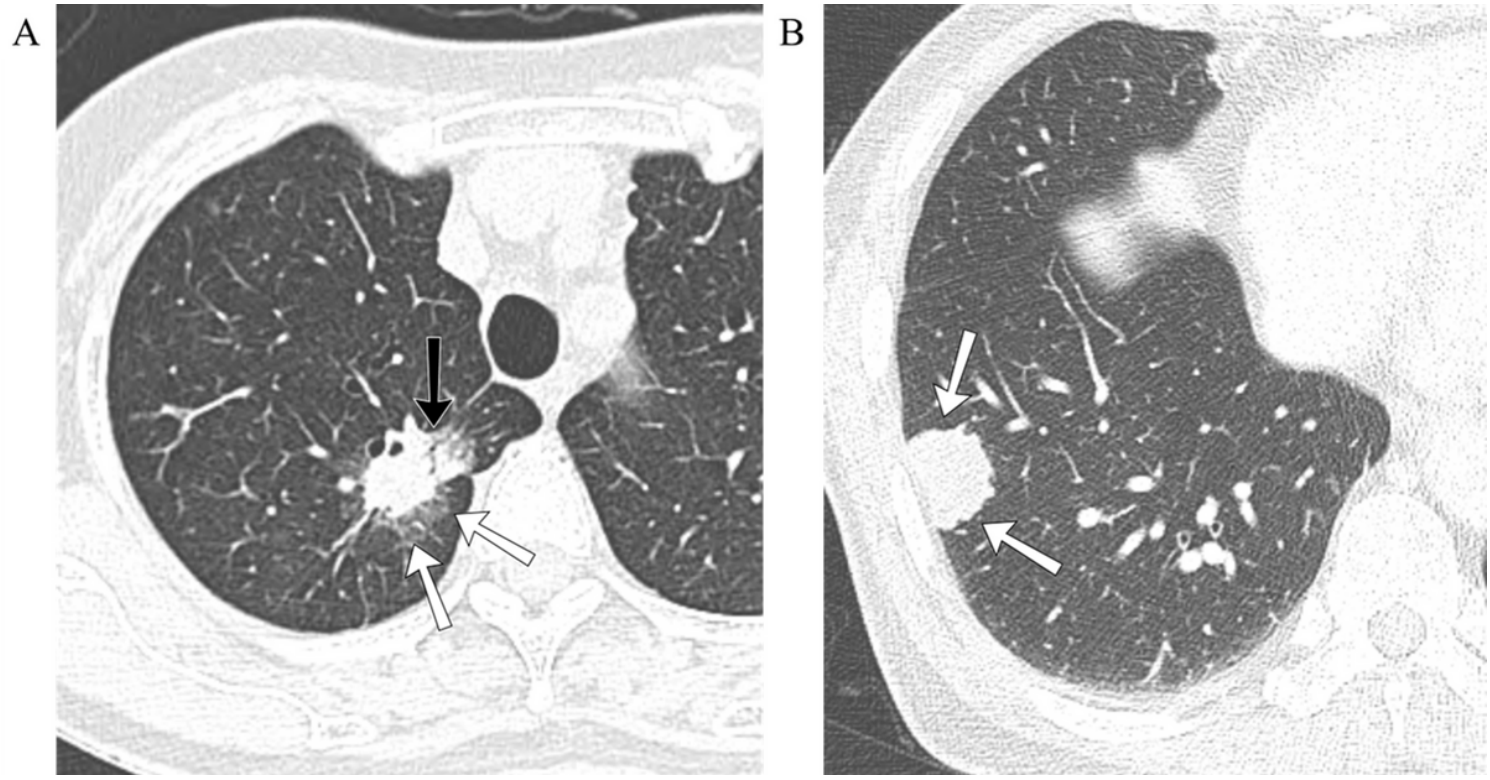

Figure 1

CT findings of primary lung cancer (LC) and solitary lung metastasis (LM). A. Lung window image of contrast-enhanced chest CT scan showing a solitary nodule (white arrows) with sub-solid density, spiculated smooth margin, and presence of an air-bronchogram (black arrow) in the right upper lobe. The nodule was histopathologically confirmed to be LC. B. Lung window image of contrast-enhanced chest CT scan showing a solitary nodule (white arrows) with solid density and lobulated margin in the right lower lobe. The nodule was histopathologically confirmed to be LM.

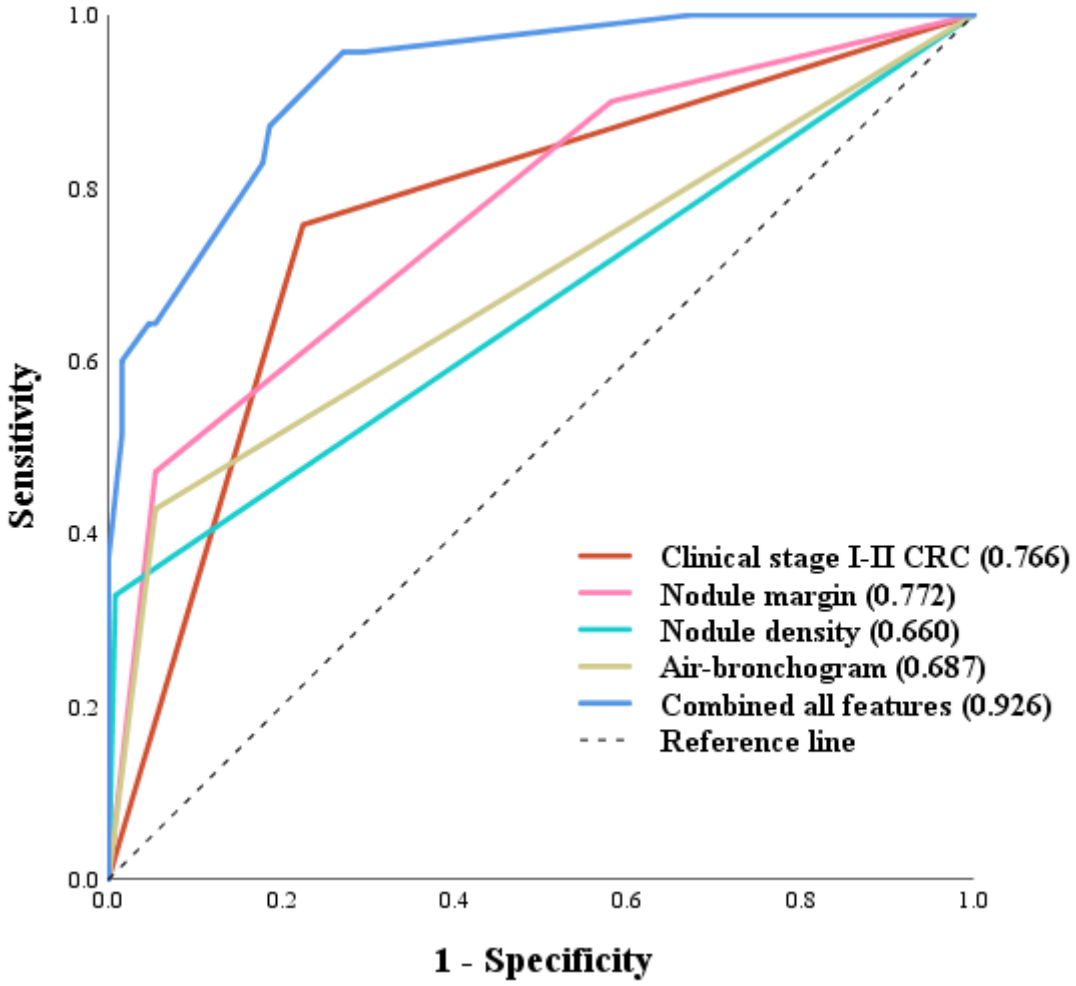

Figure 2

Receiver operating characteristic curves for assessing the ability of CT features, both alone and in combination with clinical characteristics, to discriminate primary lung cancer from solitary lung metastases.