

Stage I synchronous multiple primary non-small cell lung cancer: CT findings and the effect of TNM staging with the 7th and 8th editions on prognosis

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Background: Studies have reported that up to 8% of non-small cell lung cancers (NSCLC) involve multiple lesions; no detailed study has assessed the prognosis of early synchronous multiple primary non-small cell lung cancer (SMPNSCLC) (T1N0M0, T2aN0M0). We aimed to assess the spiral CT manifestations of SMPNSCLC during stage I and evaluate the effect of TNM staging with the 7th and 8th editions on the prognosis.

Methods: We retrospectively analyzed the data of patients who were examined, operated, and pathologically confirmed as having NSCLC from January 1, 2009, to December 31, 2010, and were followed-up for 5 years. The number of cases with stage I SMPNSCLC and solitary primary NSCLC (SPNSCLC) was 36 and 133 as per the 7th edition TNM staging system and 34 and 111 as per the 8th edition TNM staging system, respectively. The relationship between sex, age, smoking history, emphysema, surgical procedure, pathological type, tumor location, and tumor size was evaluated between the two groups, along with the correlation between prognosis and TNM staging with the 7th and 8th editions.

Results: A total of 1,948 cases of NSCLC underwent surgery, including 36 cases of stage I SMPNSCLC (77 lesions; 1.85%) with an age of onset of 44–86 years (median age, 60 years). The tumors primarily included adenocarcinoma (93.5%), with a diameter of 0.4–4.5 cm (median, 2.3 cm). CT indicated round/oval tumors in 81.8% cases, lobulation in 79.2% cases, spiculation sign in 70.1% cases, bronchial truncation sign in 31.2% cases, and pleural indentation in 75.3% cases. Moreover, CT indicated the presence of 36 (46.8%) solid nodules and 41 (53.2%) sub-solid nodules. With the 7th edition TNM staging system, the 5-year overall survival (OS) and disease-free survival (DFS) rates for stage I SMPNSCLC were 86.1% and 72.2%, respectively, which did not significantly differ from the prognosis of 133 cases of stage I SPNSCLC ($P=0.587$, $P=0.273$). With the 8th edition TNM staging system, the 5-year OS and DFS rates for stage I SMPNSCLC were 88.2% and 73.5%, respectively, which also did not significantly differ with the prognosis of 111 cases of stage I SPNSCLC ($P=0.413$, $P=0.235$).

Conclusions: Adenocarcinoma was the main pathological type among the cases with stage I SMPNSCLC. Multiple synchronous lesions almost had the malignant characteristics of primary lung cancer, particularly the presence of single or multiple sub-solid nodules. Moreover, stage I SMPNSCLC has a similar prognosis as stage I SPNSCLC. The postoperative outcomes of stage I SMPNSCLC patients remained consistent regardless of whether the 7th or 8th edition TNM staging system was used for staging.

Keywords: Stage I; multiple primary lung cancer (MPLC); non-small cell lung cancer (NSCLC); X-ray computer; tomography; prognosis

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Introduction

Multiple primary lung cancer (MPLC) is characterized by the simultaneous or successive occurrence of two or more primary lung cancers in the same individual. This condition can be classified as synchronous multiple primary lung cancer (SMPLC) and metachronous multiple primary lung cancer (MMPLC) according to the time of occurrence of foci. The diagnosis interval between 2 malignant lung tumors is often ≤ 6 months for SMPLC, although a different interval may be observed for MMPLC (1).

With the recent improvements in imaging technology, development of screening for high lung cancer risk, use of low-dose chest computed tomography (CT) screening, and physical examination, the detection rate of MPLC has been increasing annually. Studies have reported that up to 8% of non-small cell lung cancer (NSCLC) involve multiple lesions (1), particularly those of multiple primary pulmonary adenocarcinoma (2-5). In 2013, the American College of Chest Physicians (ACCP) issued new diagnostic criteria for MPLC (6), however, early diagnosis still needs to be combined with pathology, molecular biology, and imaging examinations, particularly for the differential diagnosis of metastatic tumors and granulomatous lesions. In recent years, the 5-year overall survival rate of SMPLC ranged from 34.0% to 60.9% (2,5,7-9). Some studies indicated that the prognosis of SMPLC is better than that of single primary lung cancer, except for the III A and IV stages (10). Nevertheless, to our knowledge, no detailed study has assessed the prognosis of early synchronous multiple primary non-small cell lung cancer (SMPNSCLC) ($T_1N_0M_0$, $T_{2a}N_0M_0$), or whether it is consistent with single primary lung cancer. In the present study, we aimed to assess the CT signs of 36 patients with stage I SMPNSCLC and compare the prognoses with those of patients with stage I solitary primary NSCLC (SPNSCLC). The new 8th edition of TNM staging for lung cancer is currently applied in the clinical setting (11,12). We also sought to compare the prognosis of SMPNSCLC with the 7th and 8th edition TNM staging systems (13), and thus determine a basis for the assessment of the early diagnosis

and prognosis of lung cancer.

Methods

Subject

To perform this retrospective study, we obtained exemption and waivers from obtaining written informed consent from the institutional review board. We retrospectively examined the data of 1,948 patients with NSCLC who underwent surgery and pathological confirmation between January 1, 2009, and December 31, 2010, and underwent 5 years of follow-up (with complete data).

Diagnostic and staging criteria

Using the 2013 ACCP criteria and the 8th edition lung cancer stage classification (6,12), SMPLC was diagnosed as follows: the histological types are different, molecular genetic characteristics are different, or SMPLC originates from different *in situ* carcinoma; and the histology type is the same, but each lesion shows *in situ* carcinoma, tumors are present on different sides (leaves or segments of the lungs), no N1-N3 transfer is noted, and no systemic body transfer is observed.

In this study, 169 patients were enrolled based on the 7th edition of the lung cancer TNM staging system (13), and were then finally staged based on the maximum lesion diameter and the highest pathological stage. According to the 8th edition of the TNM staging system, if the maximum lesion diameter is >4 cm, it is classified as T2b, which represents non-early stage lung cancer (11,12). Thus, a total of 34 cases of stage I SMPNSCLC (excluding two cases), were detected and 111 cases of stage I SPNSCLC were detected (excluding 22 cases).

Research methods

All the cases were diagnosed by 2 senior radiologists and two senior pathologists. Stage I SMPNSCLC was confirmed by combining the clinical and imaging data,

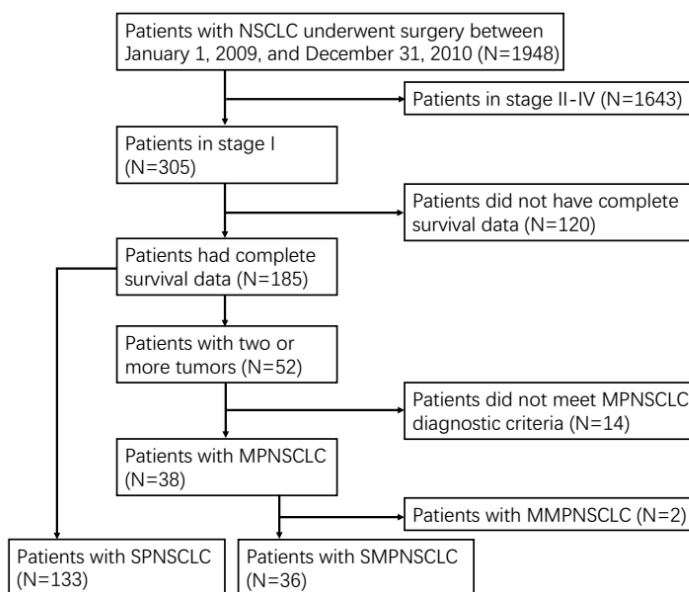


Figure 1 Flow diagram for the selection of patients having synchronous multiple primary non-small cell lung cancer (SMPNSCLC) and the control group with solitary primary non-small cell lung cancer (SPNSCLC). NSCLC, non-small cell lung cancer; MPNSCLC, multiple primary non-small cell lung cancer; MMPNSCLC, metachronous multiple primary non-small cell lung cancer.

as well as the surgical histology, while excluding the lung metastases. The location (same lobes, different ipsilateral lobes, bilateral lobes), size, pathological type (adenocarcinoma, SCC, other), staging (Ia, Ib) and CT morphological features, including the following: lesion density [pure ground glass nodules (pGGNs), part-solid nodules (pSNs), solid nodules], shape (round/oval, irregular shape), edge (lobulation, spiculation), internal findings (bubble lucency, cavitation), and peripheral manifestations (bronchial truncation, pleural indentation) of each tumor were analyzed.

Follow-up was performed via telephone. The overall survival (OS) was estimated from the date of surgery to the day of death, whereas disease-free survival (DFS) was estimated from the date of surgery to the day of disease recurrence or death due to disease progression. The patients were followed up until December 31, 2015.

Kaplan-Meier single factor survival analysis was performed to assess the age, sex, smoking history, emphysema, and pathological type, as well as the tumor number, location, and size in the patients. Moreover, the survival prognosis of SPNSCLC was simultaneously examined. To control the factors of age, gender, smoking history, emphysema, pathological type, TNM stage, which might confound the interpretation of prognosis between SMPNSCLC and SPNSCLC, Cox regression analysis was

performed. SPSS 22.0 was used for data processing. A P value of <0.05 indicates that the difference is statistically significant.

Results

Clinical, surgical, and pathological manifestations

The patients' selection process is shown in *Figure 1*. Of these, 36 cases exhibited stage I SMPNSCLC (77 lesions; 1.85%), including 22 men and 14 women aged 44–86 years (median age, 60 years). Moreover, a total of 133 patients with stage I SPNSCLC were enrolled in this study, including 78 men and 55 women aged 19–85 years (median age, 61 years). Of 169 cases, 66 exhibited pulmonary lesions on physical examination, without any clinical symptoms. In the remaining 103 cases, clinical manifestations, including cough, chest pain, hemoptysis or sputum bloody, and shortness of breath, were first detected, followed by the observation of lung cancer on CT examination. All the patients underwent examination with brain magnetic resonance imaging, abdominal CT, and whole body bone scan (ECT). Eighteen patients underwent systemic PET/CT examination, excluding the hilar lymph nodes, mediastinal lymph node metastasis, and extrapulmonary metastasis. Surgical methods included standard lobectomy,

Table 1 Comparison of clinical, surgical, and pathological findings between stage I SMPNSCLC (36 cases, 77 lesions) and SPNSCLC (133 cases)

Variables	SMPNSCLC (n=36), n (%)	SPNSCLC (n=133), n (%)	P value
Gender (male/female)	22/14	78/55	0.7
Age (years; mean ± SD)	59.7±9.6	61±10	0.008
>60 years	30 (83.3)	71 (53.4)	
≤60 years	6 (16.7)	62 (46.6)	
Smoking history (Y/N)	15/21	37/96	0.21
Emphysema (Y/N)	14/22	32/101	0.17
Surgical procedure			0.011
Lobectomy	48 (62.3)	121 (91)	
Localized resection	25 (32.5)	9 (6.8)	
Sleeve resection	4 (5.2)	3 (2.2)	
Diameter (cm; mean ± SD)	2.3±1.0	2.7±1.0	–
Tumor location			–
Same lobes	5 (13.9)		
Different ipsilateral lobes	8 (22.2)		
Bilateral lobes	23 (63.9)		
Pathological type			0.003
Adenocarcinoma	72 (93.5)	94 (70.7)	
SCC	4 (5.2)	29 (21.8)	
Other	1 (1.3)	10 (7.5)	
TNM stage			<0.001
Stage Ia	27 (75)	28 (21.1)	
Stage Ib	9 (25)	105 (78.9)	

SMPNSCLC, synchronous multiple primary non-small cell lung cancer; SPNSCLC, solitary primary non-small cell lung cancer; SCC, squamous cell carcinoma.

localized resection, or sleeve resection, along with cleaning of the hilar and mediastinal lymph nodes.

Based on the 7th edition, the comparison of the gender, age, smoking history, emphysema, surgical procedure, tumor size, location, type, and staging between stage I SMPNSCLC (36 cases) and stage I SPNSCLC (133 cases) is shown in *Table 1*.

Of the 36 cases of stage I SMPNSCLC, 33 (91.7%) had the same pathological type i.e., adenocarcinoma. In

Table 2 Pathological type and tumor location in 36 cases with stage I SMPNSCLC

Pathological type	Same lobes	Different lobes		Total (%)
		Ipsilateral	Bilateral	
Same				
IAC + IAC	3	5	10	18 (50.0)
IAC + AIS/MIA	1	3	8	12 (33.3)
AIS/MIA + AIS/MIA	1	0	1	2 (5.56)
SCC + SCC	0	0	1	1 (2.78)
Different				
IAC + SCC	0	0	2	2 (5.56)
IAC + adenosquamous carcinoma	0	0	1	1 (2.78)
Total (%)	5 (13.9)	8 (22.2)	23 (63.9)	–

SMPNSCLC, synchronous multiple primary non-small cell lung cancer; IAC, invasive adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; SCC, squamous cell carcinoma.

particular, 32 cases (88.9%) exhibited an adenocarcinoma–adenocarcinoma combination, including 14 cases with adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA). The combination of the specific pathological type and tumor location are detailed in *Table 2*.

CT findings

Based on the difference in lesion densities on CT, pulmonary nodules could be classified as solid and sub-solid nodules (including pGGNs and pSNs). The CT findings of all the lesions were analyzed, including the shape, edge, density, and internal and peripheral findings (*Table 3,4*). 7 cases with more separate solid lung cancers have different histologic type. CT primarily indicated a round/oval appearance, lobulation, and the spiculation sign, adjacent to the pleural indentation (*Figure 2,3*).

Prognosis

Based on 7th edition of the TNM staging system, the 5-year postoperative OS and DFS rates of stage I SMPNSCLC were 86.1% and 72.2%, respectively. Kaplan-Meier single-factor survival analysis was used to assess the age, sex, smoking history, emphysema, pathological type, and tumor number, location, and size among the patients. The

Table 3 CT findings in the 36 cases with stage I SMPNSCLC (77 lesions)

CT signs	Cases (%)
Shape	
Round/oval	63 (81.8)
Irregular shape	14 (18.2)
Edge	
Lobulation	61 (79.2)
Spiculation	54 (70.1)
Lesion density	
Pure ground glass nodules	12 (15.6)
Part solid nodules	29 (37.7)
Solid nodules	36 (46.8)
Internal findings	
Bubble lucency	20 (26)
Cavitation	4 (5.2)
Bronchial truncation	24 (31.2)
Pleural indentation	58 (75.3)

SMPNSCLC, synchronous multiple primary non-small cell lung cancer.

Table 4 Different types of CT findings in 36 cases with stage I SMPNSCLC

Types	Cases	Percent
Sub-SN	11	30.56
pGGN + pGGN	1	2.78
pGGN + pSN	4	11.11
pGGN + pSN + pSN	2	5.56
pSN + pSN	4	11.11
SN + Sub-SN	18	50.00
pGGN + SN	3	8.33
pGGN + pGGN + SN	1	2.78
pGGN + pSN + SN + SN + SN	1	2.78
pSN + SN	13	36.11
SN + SN	7	19.44

SMPNSCLC, synchronous multiple primary non-small cell lung cancer; Sub-SN, sub-solid nodule; pGGN, pure ground glass nodule; pSN, part solid nodule; SN, solid nodule.

findings showed that only the T stage was related to DFS; in particular, the proportion of patients with T_{1a}, T_{1b}, and T_{2a} significantly differed according to the DFS (P=0.015; *Figure 4A*). However, when cases with stage I SPNSCLC were compared (5-year OS and DFS of 83.5% and 64.7%, respectively), the difference was not significant (P=0.587, P=0.273; *Figure 4B,C*).

Based on 8th edition of the TNM staging system, a total of 34 cases exhibited stage I SMPNSCLC in this group, and the 5-year OS and DFS rates were 88.2% and 73.5%, respectively. Kaplan-Meier single-factor survival analysis was used to assess the age, sex, smoking history, emphysema condition, T stage, operation pattern, pathological type, tumor number, and tumor location. The results indicated that the OS and DFS rates from stage Ia and stage Ib were significantly different (P=0.044, P=0.008; *Figure 5A,B*). However, when the 5-year OS and DFS rates of stage I SMPNSCLC were compared with those of stage I SPNSCLC (85.6% and 66.7%, respectively), the difference was not significant (P=0.413, P=0.235; *Figure 5C,D*).

The Cox regression analysis showed that, based on 7th edition of the TNM staging system, the 5-year OS and DFS of stage I SMPNSCLC compared with those of stage I SPNSCLC, the difference was not significant (P=0.978, P=0.496, respectively; *Figure 6A,B*); base on 8th edition of the TNM staging system, the difference was not also significant (P=0.799, P=0.468, respectively; *Figure 6C,D*).

Discussion

The incidence of MPLC differs in various reports and ranges from 0.2% to 20%, most of which include cases of NSCLC. The detection rate of NSCLC has recently been increasing, and in the present study, we identified 36 cases of stage I SMPNSCLC, which accounted for 1.85% of the cases of NSCLC. Thus, the overall incidence of stage I SMPNSCLC is low, consistent with that reported in the literature (14).

Previous studies (2-5) showed that SMPNSCLC more commonly involves adenocarcinoma. The main SMPNSCLC pathological type in the present study was adenocarcinoma-adenocarcinoma (88.9%), consistent with the literature. The reason for this phenomenon may include the high current incidence of adenocarcinoma in NSCLC patients and the wide application of spiral CT examination, which markedly increased the detection rate of sub-solid nodules. In cases with solid tumor lesions, SMPNSCLC exhibited the characteristics of primary lung cancer; in

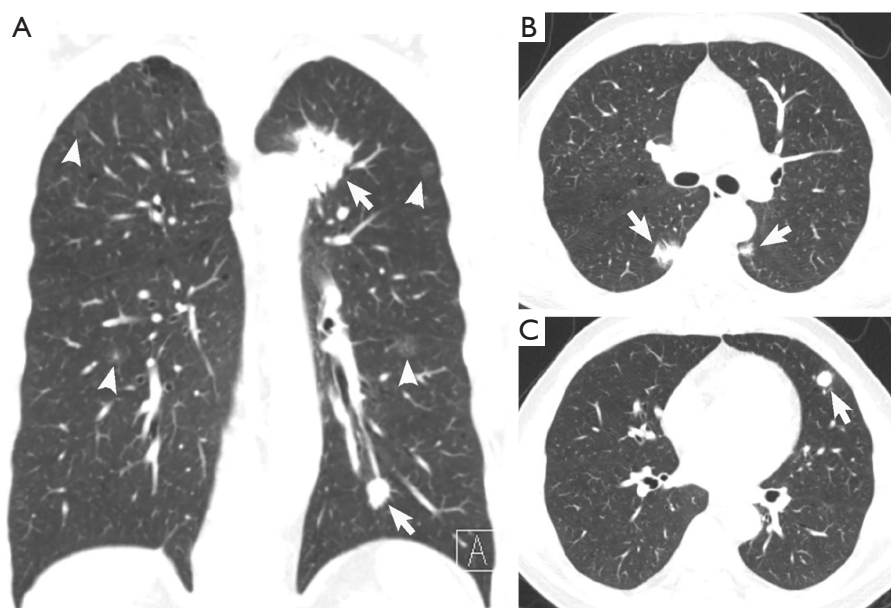


Figure 2 Chest CT indicates multiple lung nodules/masses (≥ 9) located in the lungs bilaterally. (A) Coronal CT showing a solid mass (4.0 cm \times 2.5 cm) with lobulation and spiculation sign in the left upper lobe (S1+2) (short arrow), a solid nodule (1.5 cm \times 1.0 cm) in the left lower lobe (S7) (short arrow), and some pure GGNs in the bilateral lung fields (arrowheads); (B) chest CT showing a part solid GGN in the bilateral lower lobe (S6) (short arrow); (C) a solid nodule (1.5 cm \times 2.0 cm) with lobulation sign is noted in the left upper lobe (S4) (short arrow). Except for the pure GGNs, the five lung nodules/masses were confirmed as invasive adenocarcinoma by operation and pathology. GGNs, ground-glass nodules.

particular, most were isolated or had an isolated round or oval nodular opacity, and exhibited lobulation or spiculation signs, as well as pleural indentation sign. Among the stage I SMPNSCLC cases, the spiculation sign was observed in 70.1% of patients, lobulation was noted in 79.2% of patients, and pleural indentation sign was observed in 75.3% of patients, consistent with that noted in the literature.

Previous studies suggested that the proportion of AIS and MIA in SMPNSCLC is high, which supports the trend of multiple centers of lung adenocarcinoma (15). Suzuki *et al.* found that up to 52% of cases of SMPLCs are associated with atypical adenomatous hyperplasia (16). In the present study, 41 (53.2%) lesions showed sub-nodules that included AIS or MIA, as confirmed by surgery and pathology examination, thus strongly suggesting that lung adenocarcinoma tends to occur in multiple centers. Hence, if lung cancer (mostly solid mass) is detected on CT, and if the other lobes or segments have ≥ 1 sub-solid nodules, SMPNSCLC should be considered, and if the side of the lungs or both lungs simultaneously exhibit multiple sub-solid nodules, SMPNSCLC should be initially considered.

Some patients with a solid primary lung cancer have

one or more separate solid tumor nodule(s) of the same histologic type, whose staging is currently controversial. The three major lung cancer research institutions—the American Cancer Joint Commission (AJCC), International Union Against Cancer (UICC), and International Lung Cancer Research Association (IASLC)—have yet to reach a consensus regarding the staging of SMPLC.

As per the 8th edition of the lung cancer staging system, these tumors should be classified according to the location of the separate nodule relative to the index tumor—T3 for a same-lobe, T4 for a same-side (different lobe), and M1a for an other-side location—with a single N and M category (11,12). Previous studies indicated that, for patients without lymph node metastasis for SMPLC, treatment and prognosis should be performed according to the maximum diameter of the lesion or the highest stage (10). The prognosis is similar to that of single primary lung cancer at the same stage (17,18). Thus, the highest stage is an independent prognostic factor for SMPLC. Hence, each lesion should be assessed with TNM staging, and the largest lesion or the highest pathological stage should be considered as the final TNM stage, based on which the

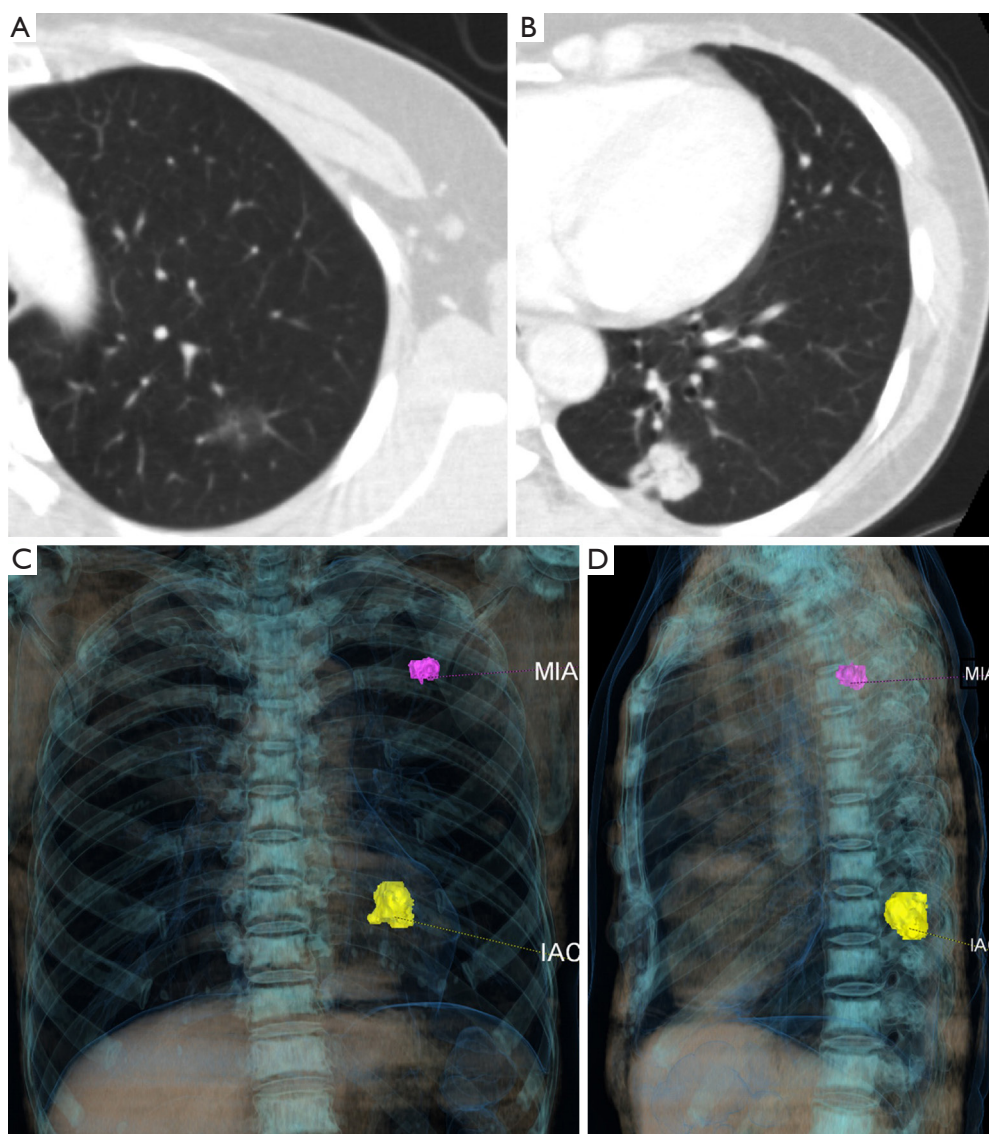


Figure 3 A 52-year-old woman with double primary lung cancer. (A) There was a part solid GGN in the left upper lung (1.6 cm × 1.0 cm) (S1+2), with lobulation signs. Pathology examination indicated minimally invasive adenocarcinoma (MIA); (B) there was also a solid nodule in the left lower lung (2.3 cm × 1.7 cm) (S7), which was lobulated and had a pleural indentation sign at the edge. The pathology result was invasive adenocarcinoma (IAC); (C,D) double primary lung cancers in the left lung are observed via three-dimensional reconstruction. GGN, ground-glass nodule.

treatment can be designed.

According to the 7th and 8th edition of the TNM staging system for lung cancer, the prognosis of stage I SMPNSCLC in the present study did not significantly differ from that of stage I SPNSCLC. The reasons for this finding include: (I) the stage I SPNSCLC we screened had no lymph nodes and distant metastasis, and the prognosis was relatively good; and (II) adenocarcinoma was the main pathological type in stage I SMPNSCLC

and had better prognosis, particularly AIS/MIA which exhibited lazy growth and had the best prognosis. A total of 72 patients (93.5%) with stage I SMPNSCLC exhibited adenocarcinoma in this group, including 14 cases (38.9%) with AIS/MIA. Due to the higher survival rate of patients, we believe that for stage I NSCLC (regardless of whether single or multiple primary cancer), radical surgery should be considered first when there is no mediastinal lymph node metastasis or systemic metastasis, and if heart and lung

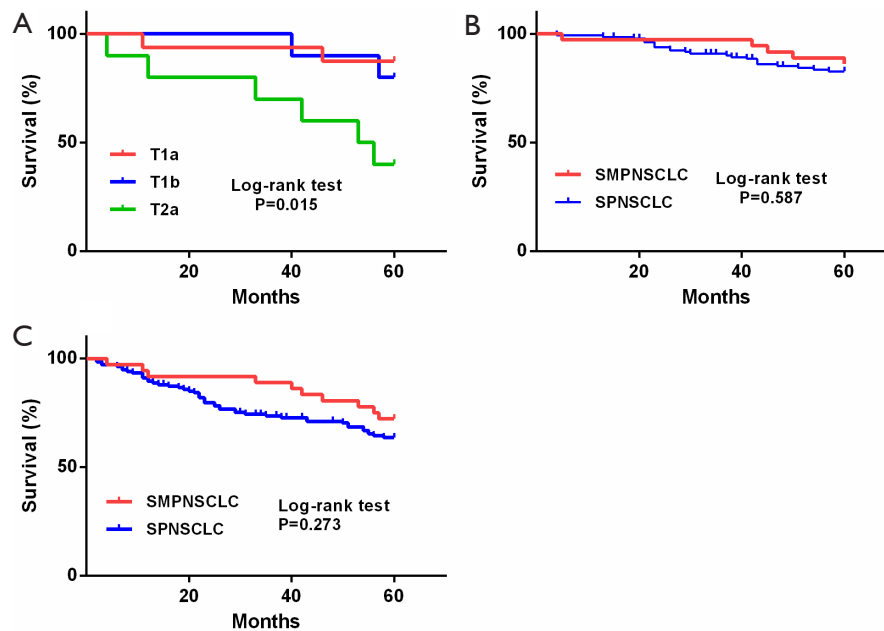


Figure 4 Classification based on the 7th edition of the TNM staging system. (A) Relationship between the T stage and DFS in stage I SMPNSCLC; (B) relationship between the 5-year OS in stage I SMPNSCLC and stage I SPNSCLC; (C) relationship between the 5-year DFS in stage I SMPNSCLC and stage I SPNSCLC. OS, overall survival; DFS, disease-free survival; SMPNSCLC, synchronous multiple primary non-small cell lung cancer; SPNSCLC, solitary primary non-small cell lung cancer.

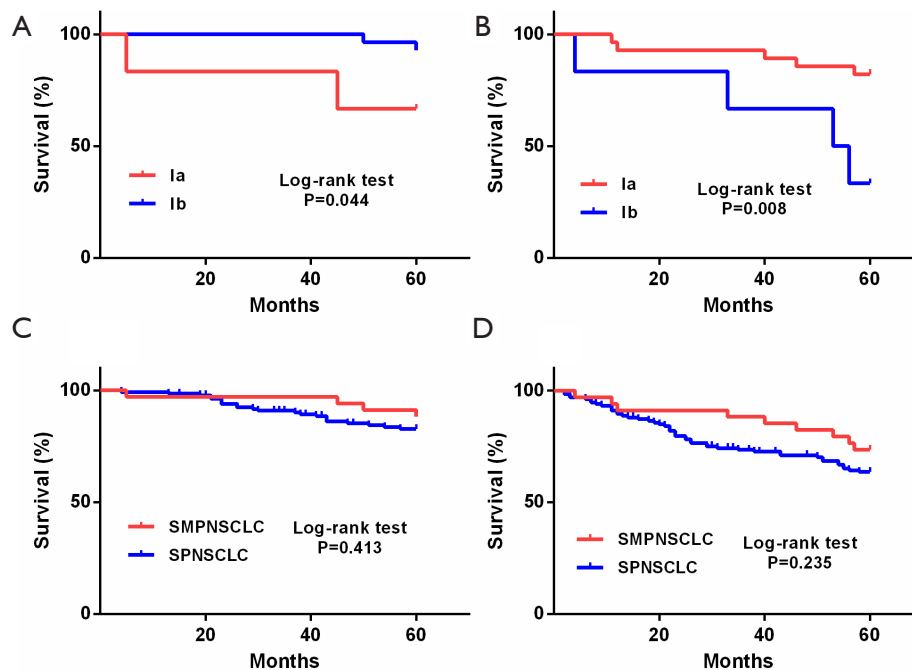


Figure 5 Classification based on the 8th edition of the TNM staging system. (A) Relationship between the 5-year OS in stage Ia and Ib SMPNSCLC; (B) relationship between the 5-year DFS in stage Ia and Ib SMPNSCLC; (C) relationship between the 5-year OS in stage I SMPNSCLC and stage I SPNSCLC; (D) relationship between the 5-year DFS in stage I SMPNSCLC and stage I SPNSCLC. OS, overall survival; DFS, disease-free survival; SMPNSCLC, synchronous multiple primary non-small cell lung cancer; SPNSCLC, solitary primary non-small cell lung cancer.

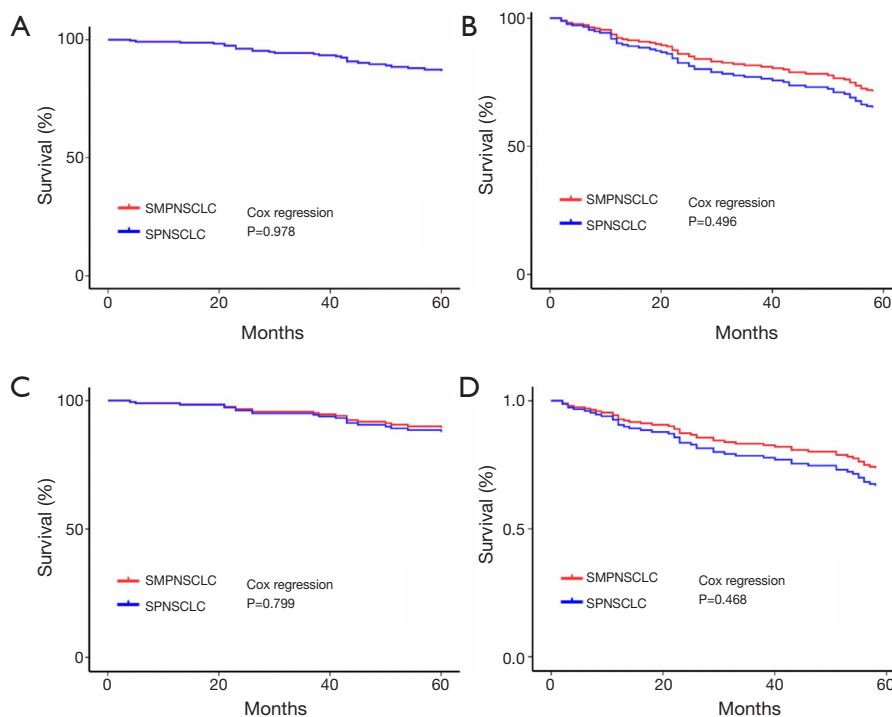


Figure 6 Relationship between stage I SMPNSCLC and stage I SPNSCLC. (A,B) Based on the 7th edition of the TNM staging system, the 5-year OS and the 5-year DFS between stage I SMPNSCLC and stage I SPNSCLC; (C,D) based on the 8th edition of the TNM staging system, the 5-year OS and the 5-year DFS between stage I SMPNSCLC and stage I SPNSCLC. OS, overall survival; DFS, disease-free survival; SMPNSCLC, synchronous multiple primary non-small cell lung cancer; SPNSCLC, solitary primary non-small cell lung cancer.

function and the general condition permits. The currently performed video-assisted thoracic surgery ensures minimal trauma and rapid postoperative recovery, and yields the same prognosis as traditional thoracotomy. For non-surgical resection of the lesions, the surgery can be integrated with chemotherapy, radiotherapy, stereotactic ablative body radiotherapy (SABR), radiofrequency ablation (RFA), and molecular targeted therapy. If this is not adopted, then the illness may be delayed, which could affect the prognosis of the patient.

The 8th edition of the TNM staging system for lung cancer was introduced in the clinical settings in January 2017 (11,12). The guideline subdivides T1 into T1a, T1b, and T1c, and T2 into T2a and T2b; hence, T2bN0M0 belongs to stage II, which belongs to stage I as per the 7th edition. Some studies have indicated that, when comparing the survival of cases of pT1-T4N0M0, the 8th edition of the TNM staging survival curve is better than that of the 7th edition (11). In the present study, 36 patients with stage I SMPNSCLC were examined via survival analysis with the 7th and 8th editions of the TNM staging system; the results

indicated that there was no significant difference in the OS and DFS rates in the two staging systems.

There are some limitations of this study. First, patients with multiple pulmonary tumors who did not receive surgical intervention were not included in this retrospective study, which caused selection and information biases inherent. Additionally, the number of this study is small and included only stage I SMPNSCLC, we intend to study more cases, including stage II–IV patients in the future.

Conclusions

Adenocarcinoma was the main pathological type in stage I SMPNSCLC. Multiple synchronous lesions exhibited the malignant characteristics of primary lung cancer, particularly the presence of single or multiple sub-solid nodules. The prognosis of stage I SMPNSCLC was good, and did not show any significant difference with that of stage I SPNSCLC. The 7th and 8th edition of the TNM staging system for lung cancer yield consistent results during the postoperative evaluation of stage I SMPNSCLC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This retrospective study was approved by our institutional review board, which waived informed consent.

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