·Original Article·

Survival analysis of 220 patients with completely resected stage-II non-small cell lung cancer

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[Abstract] Background and Objective: Surgery is the main therapy for patients with stage-II non-small cell lung cancer (NSCLC), but patients still have an unsatisfactory prognosis even though complete resection is usually possible. Adjuvant chemotherapy provides low rates of clinical benefit as well. We retrospectively analyzed prognostic factors of patients with completely resected stage-II NSCLC to find patients with unfavorable factors for proper management. **Methods:** Clinical data of 220 patients with complete resections of stage-II NSCLC at the Sun Yat-sen University Cancer Center between January 1998 and December 2004 were retrospectively analyzed. Cumulative survival was analyzed by the Kaplan-Meier method and compared by log-rank test. Prognosis was analyzed by the Cox proportional hazards model. **Results:** The overall 3- and 5-year survival rates were 58.8% and 47.9%, respectively. The 3- and 5-year disease-free survival rates were 45.8% and 37.0%, respectively. Of the 220 patients, 86 (39.1%) had recurrence or metastasis. A univariate analysis demonstrated that age (> 55 years), blood type, the presence of symptoms, chest pain, tumor volume (> 20 cm^3), total number of removed lymph nodes (≥ 10), number of involved N1 lymph nodes (≥3), total number of removed N2 lymph nodes (> 6), and the ratio of involved N1 lymph nodes (≥ 35%) were significant prognostic factors for 5-year survival. In the multivariate analysis, age (> 55 years), chest pain, tumor volume (> 20 cm^3), total number of removed lymph nodes (≥ 10), and number of involved N1 lymph nodes (≥ 3) were independent prognostic factors for 5-year survival. **Conclusions:** For patients with completely resectable stage-II NSCLC, having > 55 years, presenting chest pain, tumor volumes > 20 cm^3, and ≥ 3 involved N1 lymph nodes were adverse prognostic factors, and ≥ 10 removed lymph nodes was a favorable one. Patients with poor prognoses might be treated by individual adjuvant therapy for better survival.

Key words: Lung neoplasm, non-small cell, surgery, multivariate analysis, overall survival, prognostic factors

The Third National Retrospective Sample Investigation on the Cause of Death (2004–2005) points out that lung cancer has become the leading cause of death in China, accounting for 22.7% of malignant tumors, with the mortality increasing by 465% in the past 30 years. At present, surgery is the standard treatment for stage-II non-small cell lung cancer (NSCLC), but little research has been done on the prognosis of these patients since they account for a such small part of the patients treated with surgery. The benefit of postoperative adjuvant chemotherapy in patients with NSCLC is only about 4%–15%[1]. It is particularly important to identify patients with adverse factors and at high risk of recurrence, metastasis, and death, and give them individualized adjuvant therapy. Therefore, it is of great significance to study the prognostic factors in patients with stage-II NSCLC. This study retrospectively analyzed the clinical data of 220 patients with completely resected stage-II NSCLC at the Sun Yat-sen University Cancer Center between January 1998 and December 2004, and explored the clinical factors affecting postoperative prognosis.

Patients and Methods

Clinical information

Between January 1998 and December 2004, 1548 NSCLC patients received surgery at the Sun Yat-sen University Cancer Center, in which 220 patients with completely resected stage-II NSCLC were selected. There were 176 men and 44 women, with a median age of 60 years (30–82 years). According to the sixth edition of the International Union Against Cancer (UICC) Tumor

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Node Metastasis (TNM) classification, there were 16 patients with stage-IIA (T1N1M0) disease, 204 patients with stage-IIB (105 T2N1M0 and 99 T3N0M0) disease, and 96 patients with squamous cell carcinoma, 95 patients with adenocarcinoma, and 29 patients with other types (adenosquamous carcinoma, large cell carcinoma, and mucoepidermoid carcinoma). A total of 46 patients received postoperative adjuvant chemotherapy and 21 patients received adjuvant thoracic radiotherapy. All patients had no other malignant tumors. Relevant preoperative examinations were performed to exclude distant metastasis, and no patients received preoperative chemotherapy or radiotherapy.

Surgery

All patients underwent complete resection, including the lung lobe (bilateral lobes) or total lung resection plus mediastinal hilar lymph node dissection, in which 154 patients received single lobe resection, 58 patients received bilateral lobe resection, and 8 patients received pneumonectomy. In addition to the lung lobes, and interlobar and hilar lymph nodes, at least the left mediastinal lymph nodes at levels 5/6 and 7 and right mediastinal lymph nodes at levels 2, 4, and 7 were dissected. The bronchial stump was required to be pathologically negative.

Observation indicators

The observation indicators included age, sex, symptoms (the presence of symptoms, chest pain, cough), disease duration, blood type, smoking index, surgical method (whole lung, single lung lobe, bilateral lobes), TNM stage, pathologic type, degree of differentiation, tumor diameter, tumor size (pathologic specimen volume = (length × width × height)/2)^2, the total number of lymph nodes dissected, and the total number of N2 lymph nodes dissected, the number of positive N1 lymph nodes, the degree of N1 lymph node metastasis, the lobe location of the tumor, postoperative adjuvant chemotherapy, and adjuvant radiotherapy.

Selected cut-off

The best cut-off points were selected referring to the mean values of continuous variables and their receiver operating characteristic (ROC) curves impacting the survival rate, and continuous variables were divided into 2 categories. Specific cut-off points were as follows: an age of 55 years, smoking index of 400, tumor diameter of 3 cm, tumor volume of 20 cm^3, a total of 10 dissected lymph nodes, a total of 6 dissected N2 lymph nodes, a total of 3 positive N1 lymph nodes, and a ratio of N1 lymph node metastasis of 35%.

Follow-up

All patients were followed by telephone, outpatient interviews, and letters. Follow-up mainly included whether the patient died, with or without recurrence and metastasis, and what the postoperative treatment was. Follow-up ended on June 1, 2008.

Statistical methods

SPSS version 16.0 was used. A χ^2 test was used for comparing count data. Survival and disease-free survival rates were calculated by the Kaplan-Meier method, and a log-rank test was used for univariate survival analysis. The Cox proportional hazards model was used for analyzing statistically significant factors found in the univariate analysis. A P value of < 0.05 has considered statistically significant.

Results

The 3- and 5-year overall survival and disease-free survival rates

Up to June 1, 2008, the median follow-up time was 50 months (2–137 months), and the 5-year follow-up rate was 94.55%. In the 220 patients with completely resected stage-II NSCLC, 127 patients died, of whom 121 died of lung cancer and 6 died of other causes. A total of 86 (39.1%) patients had recurrence or metastasis, of whom 62 died of lung cancer, 2 died of other causes, and 22 were still alive. In the 86 patients with metastasis, 27 had simple recurrence at the ipsilateral chest and 59 had metastases outside the ipsilateral chest, including the lung (35 patients), bone (19), brain (8), liver (6), and adrenal glands (5). The 3-year overall survival rate was 58.8% and the 5-year survival rate was 47.9%, with an average survival time of (72.2 ± 3.9) months, (95% CI, 64.510–79.790), and a median overall survival time of (50.0 ± 9.4) months (95% CI, 31.482–68.518). The 3-year disease-free survival rate was 45.8% and the 5-year disease-free survival rate was 37.0%, with an average disease-free survival time of (57.8 ± 3.8) months (95% CI, 50.291–65.241) and a median disease-free survival time of (27.0 ± 3.9) months (95% CI, 19.286–34.714).

Univariate analysis

The univariate analysis showed that age, blood type, the presence of symptoms, the presence of chest pain, tumor size, the total number of dissected lymph nodes, the number of dissected N2 lymph nodes, the number of positive N1 lymph nodes, and the ratio of N1 lymph node metastasis had a relationship with prognosis ($P < 0.05$) (Table 1). Sex, disease duration, the presence of cough, TNM stage (IIA and IIB), pathologic type, degree of differentiation, tumor diameter, the number of dissected N2 lymph nodes, the lobe where the tumor was located, surgical method (whole lung, single lung lobe, or bilateral lobes), postoperative adjuvant chemotherapy, and adjuvant radiotherapy had no relationship with prognosis ($P > 0.05$) (Table 1).

Multivariate analysis by the Cox model

The statistically significant indicators in univariate analysis were introduced into the Cox proportional hazards model (the forward stepwise method) to perform multivariate analysis. In the final model, the independent factor for a favorable prognosis was the total number of dissected lymph nodes greater than or equal to 10, and the independent factors for poor prognosis were being older than 55 years, having chest pain before surgery, having a tumor volume larger than 20 cm^3, and having more than 3 dissected N1 positive lymph nodes (Table 2 and Figures 1–5).

The comparison between the sixth and seventh edition of TNM classification

In the seventh edition of the TNM classification released in 2009, T stage was modified as follows: (1) T1 was divided into

Table 1 Univariate survival analysis of 220 patients with stage-II non-small cell lung cancer (NSCLC)

Clinical factor	Patient No.	Survival rate (%)		*P*
		3-year	5-year	
Age (years)				0.021
⩽ 55	76	68.4	59.6	
> 55	144	53.8	41.8	
Sex				0.298
Men	176	56.3	46.2	
Women	44	68.2	54.2	
Blood type				0.026
AB	13	84.6	69.2	
O	99	63.5	53.2	
A	62	54.8	47.9	
B	46	46.2	30.1	
Time of symptom (days)				0.184
⩽ 14	53	66.4	54.1	
> 14	167	56.4	45.9	
Symptoms				0.030
No	40	68.1	59.9	
Yes	180	56.8	45.3	
Chest pain				<0.001
No	173	64.0	54.1	
Yes	47	38.1	22.9	
Cough				0.280
No	84	62.3	49.0	
Yes	136	56.6	47.2	
Tumor location				0.842
Left upper lobe	73	53.7	44.7	
Left lower lobe	38	55.0	48.9	
Right upper lobe	60	59.0	49.8	
Right median lobe	11	80.0	60.0	
Right lower lobe	38	65.8	47.4	
Smoking index				0.096
⩽ 400	107	53.6	42.6	
> 400	113	63.8	53.1	
Type of resection				0.399
Pneumonectomy	8	87.5	62.5	
Double lobectomy	58	53.5	43.6	
Lobectomy	154	59.0	48.5	
Histology				0.472
Squamous	96	59.2	51.1	
Adenocarcinoma	95	63.7	46.5	
Other	29	41.4	41.4	
Differentiation				0.815
Well	26	65.4	49.0	
Moderate	105	56.9	45.2	
Poor	59	60.1	49.2	
Not specified	30	56.7	53.1	
Tumor size				0.056
⩽ 3 cm	54	68.5	55.7	
> 3 cm	166	55.6	45.3	
Tumor volume				0.005
⩽ 20 cm^3	84	69.1	57.2	
> 20 cm^3	136	52.3	41.3	
Total number of removed lymph nodes (N1 + N2)				0.002
< 10	99	48.3	42.9	
⩾ 10	121	67.4	54.7	
Number of removed N2 lymph nodes				0.002
⩽ 6	143	53.3	41.2	
> 6	77	69.0	60.6	
Number of involved N1 lymph nodes				0.019
< 3	196	61.0	51.0	
⩾ 3	24	41.7	23.3	
Frequency of involved N1 lymph nodes				0.011
< 35%	167	61.9	52.7	
⩾ 35%	53	49.0	33.1	
Pathologic stage				0.269
IIA	16	75.0	61.9	
IIB	204	57.5	46.8	
Adjuvant chemotherapy				0.589
Yes	46	65.2	53.5	
No	174	57.0	46.4	
Adjuvant radiotherapy				0.077
Yes	21	33.3	33.3	
No	199	61.6	49.6	

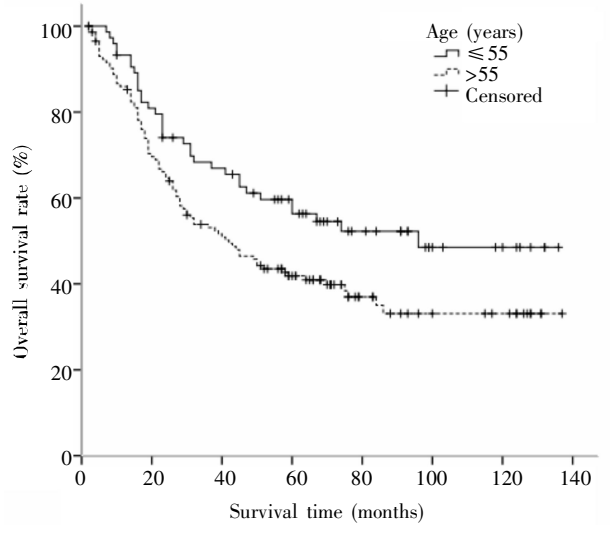

Figure 1 Overall survival curves of patients aged ⩽ 55 years and > 55 years

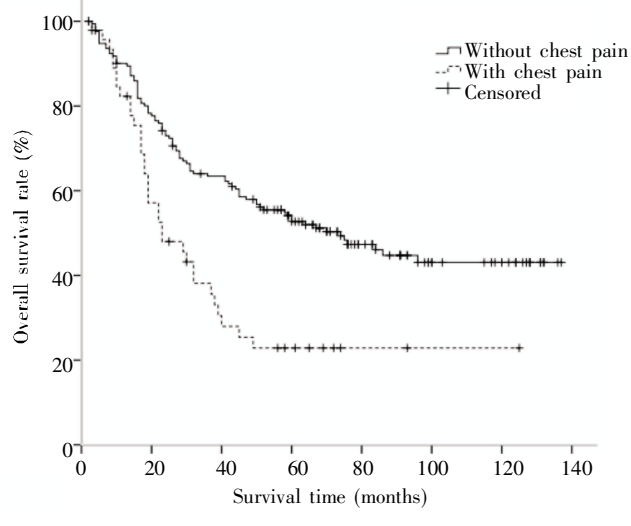

Figure 2 Overall survival curves of patients with and without chest pain

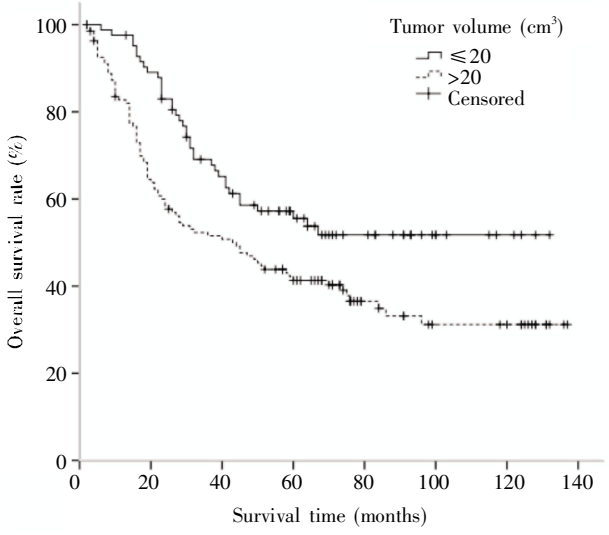

Figure 3 Overall survival curves of patients with tumor volumes ≤ 20 cm^3 and > 20 cm^3

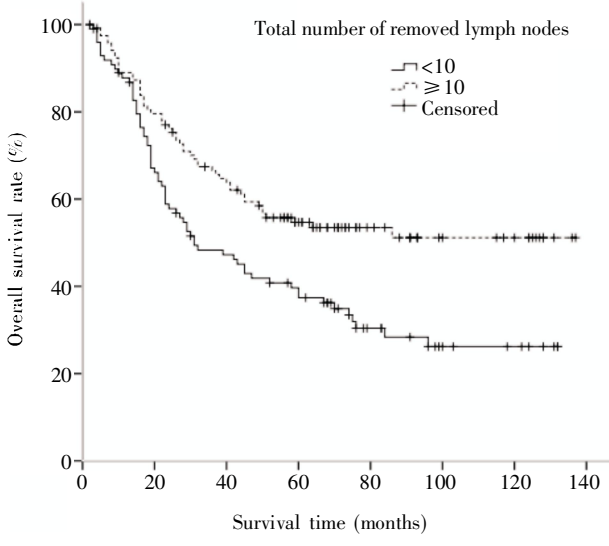

Figure 4 Overall survival curves of patients with the total number of removed lymph nodes < 10 and ≥ 10

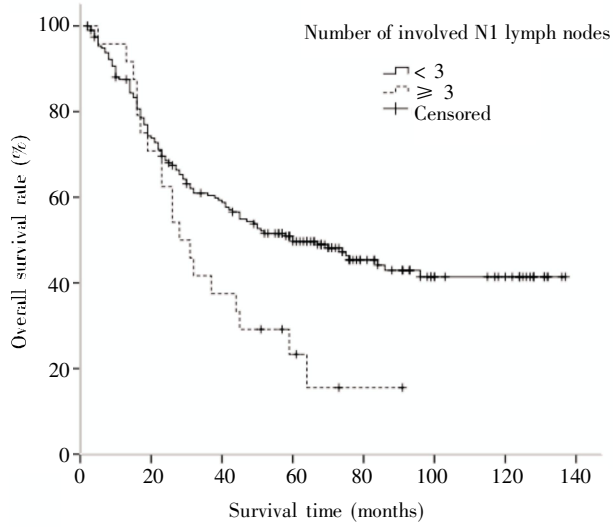

Figure 5 Overall survival curves of patients with the number of involved N1 lymph nodes < 3 and ≥ 3

T1a (≤ 2 cm) and T1b (> 2 cm and ≤ 3 cm); (2) T2 was divided into T2a (> 3 cm and ≤ 5 cm) and T2b (> 5 cm and ≤7 cm); (3) tumors larger than 7 cm were classified as T3 instead of the original T2; (4) separate tumor nodules in the same lobe were classified as T3 instead of the original T4; and (5) separate tumor nodules in different ipsilateral lobes were classified as T4 instead of the original M1. Changes related to stage II included T2bN0M0 being classified as IIA instead of IB and T2aN1M0 being classified as IIA instead of IIB. Tumors with a diameter greater than 7 cm were classified as T3 instead of the original T2, the original T2N0M0 IB was restaged as T3N0M0 IIB, and the original T2N1M0 IIB was restaged as T3N1M0 IIIA (Table 3).

Discussion

The natural survival rate of patients with stage-II NSCLC has been reported in few research studies. It was reported[3] that 31 patients without surgery, radiotherapy, or chemotherapy had a median survival time of 11 months and a 2-year survival rate of only 6%. The 5-year survival rate of patients with stage-II NSCLC after surgery was 32%–50%[4-8]. In this study, the 5-year survival

Table 2 Cox regression analysis for the prognosis of 220 patients with stage-II NSCLC

Variable	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI
Age	0.510	0.206	6.115	1	0.013	1.665	1.112–2.494
Chest pain	0.999	0.217	21.090	1	0.000	2.715	1.773–4.158
Tumor volume	0.586	0.201	8.475	1	0.004	1.798	1.211–2.668
Total number of removed lymph nodes	–0.759	0.190	15.977	1	0.000	0.468	0.323–0.679
Number of involved N1 lymph nodes	1.006	0.265	14.421	1	0.000	2.735	1.627–4.597

rate was 47.9%, which was in line with the reported literature. TNM stage was an important prognostic indicator. In this study, the 5-year survival rates of IIA (pT1N1M0) and IIB (pT2N1M0, pT3N0M0) were 61.9% and 46.8%, respectively, without statistical significance. A number of previous studies[6,9], have found that the difference between the survival curves of patients with stage-IIA and -IIB disease had no statistical significance.

According to the new edition of the TNM classification released in 2009[10,11], although the proportion of patients with stage-IIA disease has increased, the survival curves of IIA and

Table 3 Comparison of the 6th edition and the 7th edition of the TNM staging system for 220 patients with stage-II NSCLC

	6th edition					7th edition				
				Survival rate(%)					Survival rate(%)	
Stage	TNM	*n*	*N*	3-year	5-year	TNM	*n*[a]	*N*	3-year	5-year
						T1aN1M0	9			
IIA	T1N1M0	16	16	75.0	61.9	T1bN1M0	7	88	63.4	49.5
						T2aN1M0	72			
IIB	T2N1M0	105	204	57.5	46.8	T2bN1M0	17	116	56.5	48.2
	T3N0M0	99				T3N0M0	99			

n, subsets of patients; *N*, total patients. [a] Sixteen cases which tumor size is > 7 cm were excluded. They were T2N1M0, stage IIB according to the 6th edition. However, in the 7th edition, they were T3N1M0, stage IIIA.

IIB still cross at the fifth year, indicating that the distinction between stage-IIA and IIB disease is still inadequate. In this study, restaging according to the seventh edition, patients with stage-IIA disease increased from 16 patients to 88 patients, but the 5-year survival rate decreased from 61.9% to 49.5%, while the patients with stage-IIB disease decreased from 204 patients to 116 patients with no significant change in the 5-year survival rate. This may be relevant to the change from stage IIB to stage IIA. However, the data cannot fully reflect the real status of the new stage IIB, because T2bN0M0 IIA and T3N0M0 IIB from the original IB were not included in this study, separate tumor nodules in the same lobe were classified as T3 instead of the original T4, and this kind of T3N0M0 IIB was not included too. According to the new stages, 16 patients with tumor diameters more than 7 cm, which were restaged as T3N1M0 III, were excluded. According to the seventh edition, the number and proportion of patients with stage-IIA disease were more than in the sixth edition, and changes in disease stage would lead to changes in treatment. The N0 patients with tumor diameters of 5–7 cm and more than 7 cm had changed stages from IB to IIA and IIB, and adjuvant chemotherapy is worthy of further study in these patients.

At present, most research proposes that age is a prognostic factor of NSCLC. Two large retrospective analyses (13 010 patients and 6644 patients) from Japan [5,7] showed that the patients younger than 50 years had significantly better prognosis than those older than 70 years. Chansky *et al.*[10] reported that age was an independent prognostic factor of patients with NSCLC after surgery and patients younger than 70 years had a better prognosis than those older than 70 years. Kuo *et al.*[12] reported that in patients with NSCLC, compared with the old group (older than 80 years), women and patients with adenocarcinoma accounted for the majority of the youth group (younger than 40 years) with more treatment and better prognosis. In this study, age was an independent prognostic factor, both the 3- and 5-year survival rates of patients younger than or equal to 55 years were higher than for those older than 55 years, which might be because the general condition and immune status of younger patients was better than older patients, and at the same time, these two groups had different compositions by sex, pathologic type, stage, and other indicators. Further analysis showed that in patients younger than or equal to 55 years, there were more women than in those older than 55 years, with a different sex ratio between the 2 groups (28.9% vs. 15.3%, $\chi^2 = 5.810$, $P = 0.016$). Although our data did not show sex as a prognosis-related factor, many studies[5-7,10,13,14] found that being a woman was an independent factor for favorable prognosis. Therefore, sex and age are likely to produce a common effect on prognosis.

Many studies[6,14] have proposed that symptoms or performance status were prognostic factors. Our data showed that both symptoms and chest pain had an impact on prognosis. The 5-year survival rate of asymptomatic patients (discovered by physical examination) was significantly higher than that of those with symptoms, while the 5-year survival rate of patients with chest pain was significantly lower than that of those without chest pain. Further analysis found that in the chest pain group, the proportion of patients with stage T3N0M0 disease was significantly higher than in the non-chest pain group (68.1% vs. 38.7%, $\chi^2 = 14.556$, $P < 0.001$). No patient with chest pain was found with T1N1M0 disease, and patients with chest pain all had stage-IIB disease. It could be seen that chest pain in patients with stage-IIB disease was mostly associated with the violation of the parietal pleura, and these patients mostly had stage-T3 disease and worse prognosis than those without chest pain.

The maximum tumor diameter is an important basis for T staging, but lung cancer mostly has irregularly shaped tumors, and diameter alone does not provide enough accuracy. Iwasaki *et al.*[15] reported in 385 patients with completely resected NSCLC, univariate analysis showed that tumor diameter and volume were both prognostic factors, while in multivariate analysis neither had significance, but the author still recommended that tumor volume should be calculated preoperatively by computed tomography to estimate prognosis. Tsai *et al.*[2] reported a retrospective study of 236 patients with stage-IA NSCLC, and found that the tumor volume of postoperative specimens could be a better representation of tumor size and was an independent prognostic factor. Our data found that tumor specimen volume was an independent prognostic factor for patients with stage-II NSCLC, while tumor diameter had no significance in either univariate or multivariate analysis. Therefore, tumor specimen volume was a better prognostic indicator than tumor diameter, and the 5-year survival rate of patients with tumor specimen volumes more than 20 cm^3

was significantly lower than that of those with tumor volumes less than or equal to 20 cm^3.

In this study it was found that the total number of dissected lymph nodes more than or equal to 10 was a favorable prognostic factor, and the 5-year survival rate of patients with the total number of dissected lymph nodes more than or equal to 10 was significantly higher than those with less than 10. Similar studies[16-18] have similar results that the total number of dissected lymph nodes is a prognostic factor, the specific number ranging from 6 to 15. The adequate number of dissected lymph nodes may have 3 roles: (1) with more dissected lymph nodes at each level and more dissected levels, the probability of finding lymph node metastasis will increase, which leads to more accurate pathologic N stage, and downgrades and excludes patients that do not have stage-I disease; (2) dissection of positive lymph nodes can play a therapeutic effect in early NSCLC; and (3) lymph node dissection can reduce local recurrence and distant metastasis and improve overall survival rates. Gajra *et al.* [16] found that patients with stage-I NSCLC with more than 6 lymph nodes dissected had higher overall survival rates and lower risks of recurrence, and the number was an independent prognostic factor. Wu *et al.* [17] found that the total number of dissected lymph nodes affected overall survival in patients with stage-I NSCLC and adequate lymph node dissection should remove at least 15 lymph nodes. Recently, Varlotto *et al.* [18] reported that patients with stage-I NSCLC with lymph node dissection had a better prognosis than those without lymph node dissection, and at least 11 lymph nodes should be dissected.

Lymph node metastasis is one of the significant ways NSCLC metastasizes. In this study it was found that having more than 3 positive N1 lymph nodes was an independent poor prognostic factor in patients with stage-II NSCLC. With the increase of tumor burden in the lymph nodes, this might indicate a risk of recurrence and an increase in metastasis. Similarly, Marra *et al.*[19] analyzed patients with stage-N1 NSCLC and found in univariate analysis the number of positive N1 lymph nodes was related to the 5-year overall survival rate, but in multivariate analysis it was not. Cerfolio *et al.* [13] found that in patients with stage-N1 NSCLC, those with multiple N1 lymph node metastases had a worse overall survival than those with single positive N1 lymph node, and the number of positive N1 lymph nodes was an independent prognostic factor. However, recently, Gonfiotti *et al.*[20] did not find a relationship between the number of positive N1 lymph nodes and prognosis in patients with N1-positive NSCLC.

In conclusion, in patients with completely resected stage-II NSCLC, the independent factor for favorable prognosis was having at least 10 dissected lymph nodes, and the independent factors for poor prognosis were being older than 55 years, having chest pain before surgery, having tumor volumes larger than 20 cm^3, and having more than 3 dissected positive N1 lymph nodes. Patients with adverse prognostic factors should receive stronger postoperative follow-up and active individualized adjuvant therapy to reduce the risk of recurrence, metastasis, and death. Although there are many prognostic factors in NSCLC, including continuously discovered new molecular indicators, a practical prediction system has not been formed. The independent predictors for patients with completely resected stage-II NSCLC found in this study cannot accurately predict the prognosis of patients, but can provide a reference to further prospective clinical research on prognosis.

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