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Original Article

Prognostic factors predict a poor prognosis of stage III non-small cell lung cancer patients receiving surgical interventions

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Abstract: Aim: This study aimed to investigate prognostic factors of stage III non-small cell lung cancer (NSCLC) patients receiving surgical intervention. Material and Methods: Clinical information of 118 stage III NSCLC patients was retrospectively reviewed, and potential prognostic factors affecting post-operative 5-year survival rate were analyzed. Results: Post-operative chemotherapy (P=0.006), total metastatic lymph nodes (P=0.038), metastatic lymph node ratio (P=0.009), metastatic N1 lymph nodes (P=0.009), metastatic N1 lymph node ratio (P=0.011), metastatic N2 lymph nodes (P=0.011), stations of metastatic N2 lymph nodes (P=0.034), metastatic N2 lymph node ratio (P=0.036) and station 7 lymph node metastasis (P=0.001) were closely related to 5-year survival rate after surgery. Metastatic N2 lymph nodes (P=0.002, RR: 2.588, 95% CI 1.420-4.718) and station 7 lymph node metastasis (P=0.008, RR: 0.467, 95% CI 0.267-0.818) were independent prognostic factors affecting post-operative 5-year survival rate. The risk of death in patients with more than 3 metastatic N2 lymph nodes was 2.588 times higher than that in patients with less metastatic N2 lymph nodes; the risk of death in patients with station 7 lymph node metastasis was 2.141 times higher than patients without. Conclusion: For patients with stage III NSCLC, presence of >4 metastatic lymph nodes, metastatic lymph node ratio of >50%, >2 metastatic N1 lymph nodes, metastatic N1 lymph node ratio of >50%, >3 metastatic N2 lymph nodes, >3 stations of metastatic N1 lymph nodes, metastatic N1 lymph node ratio of >45%, station 7 lymph node metastasis or without post-operative chemotherapy predicts a poor prognosis.

Keywords: Stage III trials, non-small cell lung cancer, lymph nodes, prognosis

Introduction

Lung cancer is the most common solid malignancy [1]. Although therapies of lung cancer have been improved significantly, it is still a leading cause of cancer related death [2-6]. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers [7], 25-30% of patients have developed advanced NSCLC (stage III) at an initial diagnosis [8, 9], and NSCLC is resectable in only no more than 20% of patients with a 5-year survival rate of only 13-36% [10]. In the present study, clinical information of 118 patients with stage III NSCLC who received surgical interventions was collected and analyzed, aiming to investigate prognostic factors of stage III NSCLC after surgeries and to provide evidence for evaluation of surgery and prognosis.

Material and methods

Clinical information

This study has been approved by the Ethics Committee of the Affiliated First Hospital of China Medical University (No. 2009-01-11A). And the consent to publish has been obtained from the participants to report the patients' data. From January 1st, 2009 to December 31th, 2012, there were totally 207 patients with stage III NSCLC in Department of Thoracic Surgery, The First Affiliated Hospital of China Medical University. The inclusion criteria were as follows: 1) Pre-operative cranial MR, abdominal and adrenal ultrasonography, and bone ECT were performed to exclude the metastasis to the brain, liver, adrenal gland and bone; 2) Patients had no history of malignancies, and no

Table 1. Clinical information

Item	Total (n)	Survival	Death
Gender			
Male	66	36	30
Female	52	32	20
Age (median: 57 years)			
28-57	67	41	26
58-77	51	27	24
Surgical method			
Single lobectomy	81	48	33
Multiple lobe resection	25	12	13
Total pneumonectomy	12	8	4
Maximum diameter of NSCLC (median: 3.1 cm)			
1-3.0 cm	59	35	24
3.1-10 cm	59	33	26
Metastatic lymph nodes			
Station 7 lymph node	43	17	26
Station 10 lymph node	47	22	25
T stage			
T1	12	8	4
T2	75	45	30
T3	18	6	12
T4	13	9	4
N stage			
N1	8	6	2
N2	110	62	48
Final stage			
Stage IIIA	110	64	46
Stage IIIB	8	4	4
Pathological type			
Squamous cell carcinoma	34	21	13
Adenocarcinoma	80	44	36
Others	4	2	2
Differentiation			
Well differentiated	21	17	4
Well to moderately differentiated	13	8	5
Moderately differentiated	56	29	27
Moderately to poorly differentiated	20	10	10
Poorly differentiated	8	4	4
Concomitant therapy			
Chemotherapy	77	50	27
Radiotherapy	19	7	12

severe diseases of the heart, liver, kidney and hematopoietic system; 3) Patients did not receive adjunctive therapies (such as chemotherapy and radiotherapy) before surgery. 4) Patients received surgical intervention with complete resection (negative surgical margin, negative lymph nodes after systemic lymph node resection or sampling, negative highest mediastinal lymph nodes); 5) post-operative pathology conformed NSCLC at stage III; 6) patients well recovered and death was not present; 7) complications and diseases affecting the survival were not observed after discharge. Thus, only a total of 118 patients were enrolled in this study. The clinical information is shown in **Table 1**.

Methods

The potential prognostic factors included age, gender, surgical method, maximum tumor diameter, total metastatic lymph nodes, stations of metastatic lymph nodes, metastatic lymph node ratio, metastatic N1 lymph nodes, stations of metastatic N1 lymph nodes, metastatic N1 lymph node ratio, total resected N2 lymph nodes, stations of resected metastatic N2 lymph nodes, total metastatic N2 lymph nodes, stations of metastatic N2 lymph nodes, metastatic N2 lymph node ratio, station 7 lymph node metastasis, station 10 lymph node metastasis, T stage, N stage, final stage, pathological type, differentiation, post-operative chemotherapy and post-operative radiotherapy. Processing of variables: qualitative variables were categorized into binary or polynary ones; for quantitative variables, the cut-off value of TNM staging system (7^{th} edition) and that used in the ROC analysis of influence on the survival were used, and continuous variables were transformed into binary or polynary ones. The specific cut-off values were as follows: age: 57 years; maximum tumor diameter: 2, 3, 5, and 7 cm; 4 metastatic lymph nodes; 3 stations of metastatic lymph nodes; metastatic lymph node ratio of 50%; 2 meta-

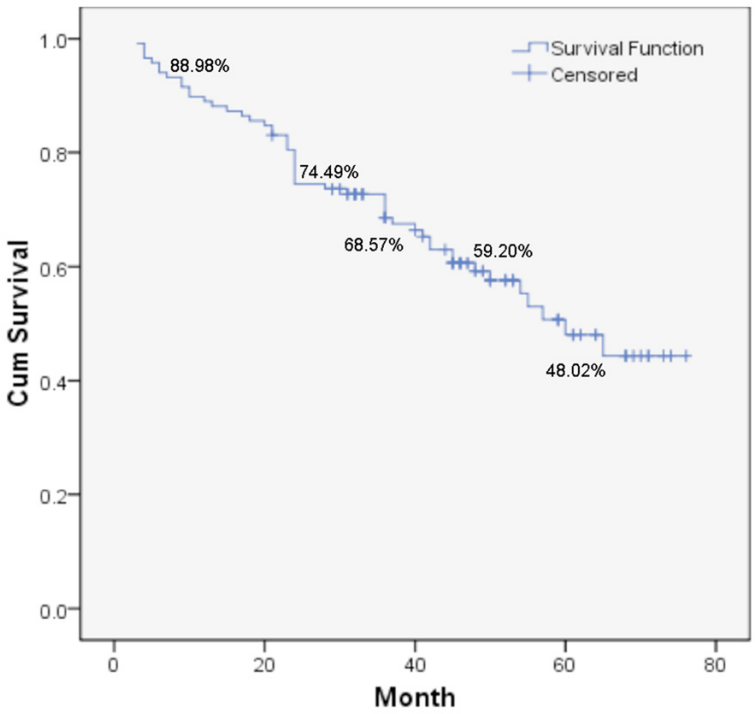

Figure 1. Overall survival curve.

static N1 lymph nodes; 1 station of metastatic N1 lymph nodes; metastatic N1 lymph node ratio of 50%; 6 resected N2 lymph nodes; 4 stations of metastatic N2 lymph nodes; 3 metastatic N2 lymph nodes; 3 stations of metastatic N1 lymph nodes; metastatic N2 lymph node ratio of 45%.

Statistical analysis

Statistical analysis was performed with SPSS version 18.0. Survival analysis was conducted with Kaplan-Meier method. Log-rank test was employed for the univariate analysis of prognostic factors. Cox proportional hazards model was used for the multivariate analysis of prognostic factors with significant difference from univariate analysis as well as T-stage, which has significance in clinical practices. A value of $P<0.05$ was considered statistically significant.

Results

Overall survival

All patients were followed up by telephone until death or before May 1, 2015. The survival time was presented as months. Of these patients, seven were lost in follow-ups and a follow up rate was 94.07%. Data of patients lost in follow-ups were regarded censored ones. Remaining patients were followed up for a median of 40.5 months (range: 3-76 months). Among them, 61 patients were still alive, and 50 died during the study.

The median overall survival time was 60 months (SEM: 6.08 months). The cumulative 1, 2, 3, 4, and 5-year survival rate was 88.98%, 74.49%, 68.57%, 59.20% and 48.02%, respectively. The overall survival curve is displayed in **Figure 1**.

Survival analysis

Univariate analysis showed post-operative chemotherapy, total metastatic lymph nodes, metastatic lymph node ratio, metastatic N1 lymph nodes, metastatic N1 lymph node ratio, metastatic N2 lymph nodes, stations of metastatic N1 lymph nodes, metastatic N2 lymph node ratio and station 7 lymph node metastasis was closely related to 5-year survival rate (**Table 2**). Gender, age, surgical method, maximum tumor diameter, stations of metastatic lymph nodes, stations of metastatic N1 lymph nodes, resected N2 lymph nodes, stations of resected N2 lymph nodes, station 10 lymph node metastasis, T stage, N stage, final stage, pathological type, differentiation, and post-operative radiotherapy had no relationship with post-operative 5-year survival rate (**Table 2**).

The prognostic factors with statistical significance from univariate analysis as well as T-stage were recruited for multivariate analysis with Cox proportional hazards model. Results showed metastatic N2 lymph nodes and station 7 lymph node metastasis were independent risk factors affecting 5-year survival rate (**Table 3**; **Figures 2** and **3**).

Discussion

Patients with stage IIIB NSCLC usually have a poor prognosis, even after surgeries. Currently,

Table 2. Univariate survival analysis

Prognostic factor		n	5-year survival rate (%)	P	Prognostic factor		n	5-year survival rate (%)	P
Gender	Male	66	41.82	0.400	Station of metastatic N2 lymph nodes	≤3	102	50.52	0.034*
	Female	52	44.53			>3	16	41.02	
Age (years)	≤57	67	52.75	0.459	Metastatic N2 lymph node ratio (%)	≤45	67	58.43	0.036*
	>57	51	41.25			>45	51	35.22	
Surgical method	Single lobe resection	81	49.40	0.218	Station 7 lymph node metastasis	Yes	43	21.48	0.001*
	Multiple lobe resection	25	27.86			No	75	56.51	
	Total pneumonectomy	12	48.89		Station 10 lymph node metastasis	Yes	47	34.00	0.110
Maximum tumor diameter (cm)	≤2	21	61.26	0.689		No	71	52.07	
	>2 and ≤3	38	43.74		T stage	T1	12	64.81	0.105
	>3 and ≤5	40	44.82			T2	75	43.26	
	>5 and ≤7	12	42.86			T3	18	25.78	
	>7	7	42.86			T4	13	37.02	
Total metastatic lymph nodes (n)	≤4	72	52.81	0.038*	N stage	N1	8	70.00	0.431
	>4	46	39.37			N2	110	47.26	
Stations of metastatic lymph nodes	≤3	71	46.84	0.298	Final stage	IIIA	110	46.05	0.951
	>3	47	46.29			IIIB	8	28.13	
Metastatic lymph node ratio (%)	≤50	80	56.29	0.009*	Pathological type	Squamous cell carcinoma	34	48.91	0.403
	>50	38	30.42			Adenocarcinoma	80	42.19	
Metastatic N1 lymph nodes (n)	≤2	81	53.51	0.009*		Others	4	50.00	
	>2	37	35.81		Differentiation	Well differentiated	21	77.92	0.362
Station of metastatic N1 lymph nodes	≤1	65	48.56	0.365		Well to moderately differentiated	13	56.98	
	>1	53	47.69			Moderately differentiated	56	44.16	
Metastatic N1 lymph node ratio (%)	≤50	76	53.14	0.011*		Moderately to poorly differentiated	20	33.32	
	>50	42	27.01			Poorly differentiated	8	50.00	
Resected N2 lymph nodes (n)	≤6	65	34.35	0.208	Post-operative chemotherapy	Yes	77	55.98	0.006*
	>6	53	58.13			No	41	20.02	
Stations of Resected N2 lymph nodes	≤4	69	44.23	0.930	Post-operative radiotherapy	Yes	19	30.61	0.066
	>4	49	54.71			No	99	50.65	
Metastatic N2 lymph nodes (n)	≤3	88	52.82	0.011*					
	>3	30	37.70						

Note: *P<0.05.

Table 3. Multivariate survival analysis with Cox proportional hazards model

Prognostic factors	β	β SEM	Wald value	P	RR	95% CI
Total metastatic lymph nodes	-	-	0.019	0.891	-	-
Metastatic lymph node ratio	-	-	0.414	0.520	-	-
Metastatic N1 lymph nodes	-	-	1.137	0.286	-	-
Metastatic N1 lymph node ratio	-	-	0.916	0.339	-	-
Metastatic N2 lymph nodes#	0.951	0.306	9.632	0.002*	2.588	1.420-4.718
Stations of metastatic N2 lymph nodes	-	-	0.044	0.833	-	-
Metastatic N2 lymph node ratio	-	-	0.113	0.737	-	-
Station 7 lymph node metastasis#	-0.761	0.286	7.076	0.008*	0.467	0.267-0.818
Post-operative chemotherapy	-	-	3.378	0.053	-	-
T stage	-	-	0.006	0.941	-	-

Note: *P<0.05, #dependent variable.

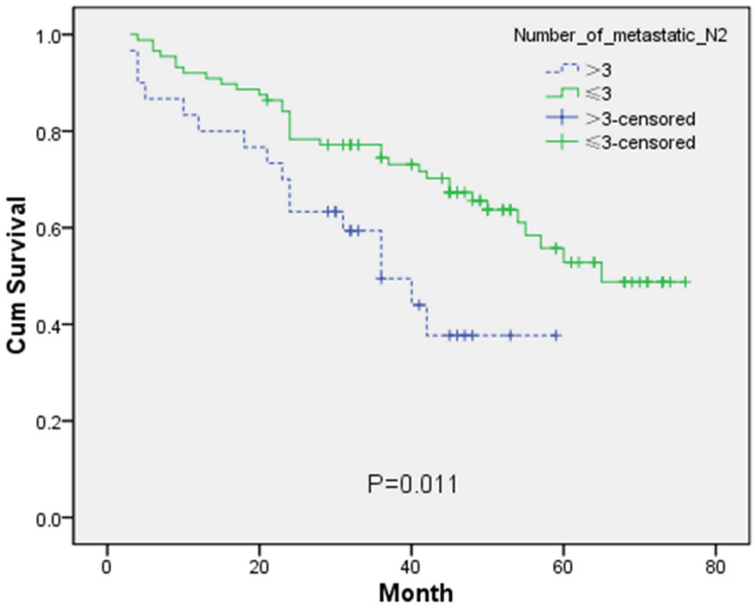

Figure 2. Survival curve of patients with N2 lymph node metastasis.

most studies focused on stage IIIA or IIIA-N2 NSCLC patients, and few studies have been conducted to investigate prognosis of entire stage III NSCLC patients after surgeries. In the NCCN guideline, surgery is not a treatment choice for stage IIIB NSCLC patients who are often treated with non-surgical interventions such as chemotherapy and radiotherapy as stage IV NSCLC patients. In addition, a surgery is also not recommended when stage N2 or N3 NSCLC is suspected before the surgery. In the present study, 8 patients with stage IIIB NSCLC had no definite evidence supporting a diagnosis of stage IIIB NSCLC, but post-operative pathology confirmed stage N2 NSCLC. In this study, all patients with stage IIIB NSCLC were diagnosed with stage T4N2M0 NSCLC according to TNM staging system and 1-5 year survival rate of stage III NSCLC patients was higher than previously reported, which might be ascribed to that more patients had stage IIIA NSCLC and few were diagnosed with IIIB NSCLC. Only a few patients were diagnosed with stage IIIB NSCLC, and thus clinical information of these patients was valuable.

In surgical interventions of lung cancer, besides resection of primary cancer, lymph node resection is also important for pathological staging and helpful to improve therapeutic efficacy [11, 12]. N1 lymph nodes are usually removed during lobectomy, and thus theoretically the resected N lymph nodes, stations of resected N1 lymph nodes, total resected lymph nodes, and total stations of resected lymph nodes have no influence on prognosis. Thus, these parameters were not employed as potential prognostic factors in the present study. Theoretically, the more the lymph nodes resected, the lower the possibility of lymphatic metastasis is. However, excessive lymph node resection may also expand wound, increase operation time and duration of anesthesia, delay post-operative recoveries and increase post-operative complications. In real surgeries,

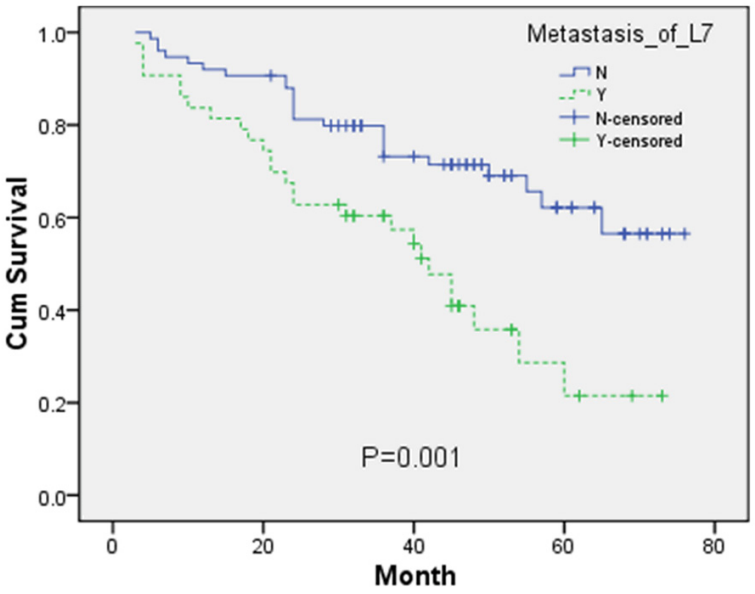

Figure 3. Survival curve of patients with or without stage 7 lymph node metastasis.

it is not always a fact that the more the lymph nodes resected, the better the prognosis is. Thus, some investigators proposed the concept of "lymph node sampling" [13]. In the present study, total resected N2 lymph nodes and stations of resected N2 lymph nodes were used to reflect an extent of lymph node resection. Statistical analysis showed both were not prognostic factors of patients with stage III NSCLC, which confirmed the above findings.

For stage III NSCLC patients, following parameters are used for the evaluation of lymph node metastasis: total metastatic lymph node, stations of metastatic lymph nodes, metastatic N1 lymph nodes, stations of metastatic N1 lymph nodes, metastatic N2 lymph nodes and stations of metastatic N2 lymph nodes. Theoretically, the larger these parameters, the poorer the prognosis is. Univariate analysis showed total metastatic lymph nodes, metastatic N1 lymph nodes, metastatic N2 lymph nodes, and stations of metastatic N2 lymph nodes were factors affecting prognosis of stage III NSCLC patients (P=0.038, 0.009, 0.011 and 0.034, respectively). Thus, presence of total metastatic lymph nodes of >4, metastatic N1 lymph nodes of >2, metastatic N2 lymph nodes of >3 or >3 stations of metastatic N2 lymph nodes predicted a poor prognosis. Multivariate analysis showed metastatic N2 lymph nodes was an independent prognostic factor affecting 5-year survival rate of stage III NSCLC patients (P=0.002). This implied that N2 lymph node metastasis was more accurate to reflect prognosis when compared with N1 lymph node metastasis and total metastatic lymph nodes. Analysis with Cox proportional hazards model indicated that the risk for death in patients with more than 3 metastatic N2 lymph nodes was 2.588 times higher than that in those with no more than 3 metastatic N2 lymph nodes.

Metastatic lymph node ratio refers to the ratio of metastatic lymph nodes to total resected lymph nodes and reflects both metastatic lymph nodes and resected lymph nodes, which also implies that metastatic lymph nodes or resected lymph nodes alone fail to reflect the severity of lymph node metastasis [14]. In this study, univariate analysis showed total metastatic lymph node ratio, metastatic N1 lymph node ratio and metastatic N2 lymph node ratio were prognostic factors affecting the 5-year survival rate (P=0.009, 0.011 and 0.036, respectively). Thus, for patients receiving surgeries due to stage III NSCLC, presence of total metastatic lymph node ratio of >50%, metastatic N1 lymph node ratio of >50% or metastatic N1 lymph node ratio of >45% predicted a poor prognosis.

Lymphatic metastasis is the most common route of metastasis in lung cancer, and lymph nodes serve as a relay station during the lymphatic metastasis. Except for the skip lymph node metastasis, the intrathoracic lymph drainage functions according to a certain regulation: from proximal to distal region and from intrathoracic to mediastinal region via the hilus of the lung. Generally, the cancer cells first invade the lymph nodes of adjacent lung segments or lobe bronchus via the lymphatic channels around the bronchus and pulmonary blood vessels (L11-14), then the lymph nodes of the hilus of the lung (L10), the subcarinal lymph nodes (L7) and the mediastinal lymph nodes (L1~L9) sequentially. Thus, L10 and L7 lymph node

metastasis may affect the prognosis of lung cancer patients to a great degree. In this study, univariate and multivariate analysis showed L7 lymph node metastasis was an independent prognostic factor affecting the survival of NSCLC patients (univariate analysis: P=0.001; multivariate analysis: P=0.008). Analysis with Cox proportional hazards model showed the risk for death in patients with L7 lymph node metastasis was 2.141 times higher than that in patients without it (1/0.467). However, the L10 lymph node metastasis had no influence on the survival of NSCLC patients (P=0.110). This might explained as that patients with L10 lymph node metastasis might not necessarily develop L7 lymph node metastasis, which further confirms the lymph drainage in the lung and suggests that L7 lymph node metastasis is a better parameter used to evaluate the prognosis of stage III NSCLC as compared to L10 lymph node metastasis.

Surgeries, chemotherapies, and radiotherapies are three major strategies for the therapy of NSCLC [15]. Some investigators have proposed that stage N2 NSCLC was a contradiction to surgeries, and only a few patients with stage N2 NSCLC may achieve a favorable efficacy after surgery. With a development of surgical technologies and wide applications of multidisciplinary treatment in lung cancer patients, stage N2 NSCLC is no longer a contradiction to surgeries. In recent years, multidisciplinary treatment has been a dominant strategy in the therapy of focally advanced NSCLC [16, 17]. Surgery is the unique method to cure NSCLC [18, 19] and able to not only remove the cancer completely or most of cancer tissues and but also create conditions for the post-operative comprehensive therapy (such as radiotherapy, chemotherapy and immune therapy). In the present study, post-operative radiotherapy tended to affect prognosis of stage III NSCLC patients although significant difference was not indicated (P=0.066), which might be ascribed to indications of post-operative radiotherapies (not all patients were suitable for radiotherapies after surgeries). Univariate analysis showed post-operative chemotherapy was a prognostic factor affecting prognosis (P=0.006), suggesting that post-operative chemotherapy was effective to improve survival rate of stage III NSCLC patients. Some patients with stage IIIB NSCLC were still alive after this study, indicating that a surgery dominant multidisciplinary therapy is feasible to stage III NSCLC, even in some cases of stage IIIB NSCLC.

Conclusions

For patients with stage III NSCLC, a presence metastatic lymph nodes >4, metastatic lymph node ratio >50%, metastatic N1 lymph nodes >2, metastatic N1 lymph node ratio >50%, metastatic N2 lymph nodes >3, stations of metastatic N1 lymph nodes >3, metastatic N1 lymph node ratio >45%, station 7 lymph node metastasis or without post-operative chemotherapy predicts a poor prognosis.

Disclosure of conflict of interest

None.

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