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Original Article

Prognostic factors for surgically managed patients with stage II non-small cell lung cancer

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Abstract: Background: To investigate the prognostic factors in surgically managed patients with stage II non-small cell lung cancer. Material and methods: A retrospective analysis of clinical data of surgically managed 93 patients with stage II non-small cell lung cancer in our hospital between May 2005 and November 2009 was conducted, and prognostic factors that may impact the postoperative 5-year survival rate were statistically analyzed. Results: Univariable survival analysis showed that new TNM staging, total number of dissected lymph nodes, number of dissected N1 and N2 lymph nodes and N1 lymph groups, metastasis rate of N1 lymph nodes, and 10th group of lymph nodes metastatic or not, were related to the postoperative 5-year survival rate in the patients. Multivariable survival analysis showed that the metastasis rate of N1 lymph nodes and 10th group of lymph nodes metastatic or not were independent prognostic factors for the postoperative 5-year survival rate in the patients. Conclusion: When patients with stage II non-small cell lung cancer are treated with surgery, the total number of dissected lymph nodes greater than 6, the number of dissected N1 lymph nodes over 5, N2 over 2, and the number of dissected N1 groups over 3, may improve their postoperative 5-year survival rate. The metastasis rate of N1 lymph nodes over 50%, and the metastasis of the 10th group of lymph nodes imply poor prognosis of the patients.

Keywords: Carcinoma, non-small-cell lung, lymph nodes, prognosis

Introduction

Since 70%~80% of lung cancer patients are diagnosed at the advanced stage [1], its mortality rate ranks first of the cancers in many countries and regions around the world. With the development of diagnostic and therapeutic techniques, the prognosis of lung cancer has been improved. However, its five-year survival rate can only reach 16%. Non-small cell lung cancer (NSCLC) patients account for about 80% to 85% [2, 3] of all lung cancer patients, whose treatment is determined according to the TNM staging system. For early (Stage I and Stage II) and locally advanced (Stage III) NSCLC patients, radical surgery is the most appropriate treatment [4]. In this study, we summarized and made statistical analysis of clinical data of surgically managed 93 cases of stage II non-small cell lung cancer, aiming to explore the prognostic factors of stage II non-small cell lung cancer and provide the basis for assessment of surgical treatment and its prognosis.

Material and methods

Clinical data

From May 2005 to November 2009 in the First Affiliated Hospital of China Medical University, a total of 93 cases of stage II NSCLC patients received surgery, including 65 male cases and 28 female cases aged 33~77 with a median age of 59 years. The 93 patients received surgery in accordance with the NCCN "complete resection" standard [5], including 70 cases of single lobectomy, 14 cases of double lobectomy and 9 cases of pneumonectomy, with 0.5-10 cm maximum tumor diameter and 4cm median maximum diameter. The results of lymphadenectomy were: 93 patients were dissected of 855 lymph nodes in total, of which there were 423 NI lymph nodes and 432 N2 lymph nodes; 263 groups of N1 lymph nodes and 298 groups of N2 lymph nodes; 87 metastatic NI lymph nodes and 78 groups of meta-

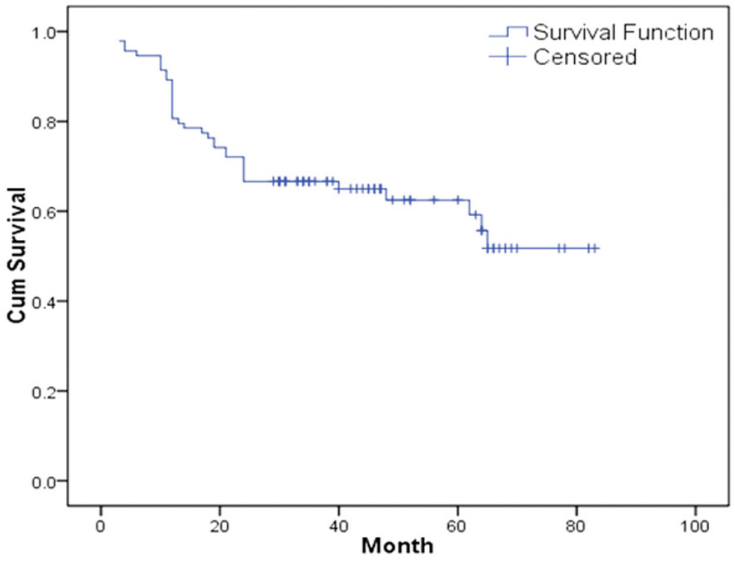

Figure 1. Total survival curve. Cum Survival: cumulative survival.

Table 1. Accumulated survival

Survival time	Case (n)	Survival rate (%) (Mean ± SE)
1 year	75	80.65 ± 0.04
2 years	62	66.67 ± 0.05
3 years	39	65.00 ± 0.05
4 years	25	62.50 ± 0.05
5 years	18	59.21 ± 0.06

static N1 lymph nodes; overall metastatic rate of N1 were 20.57%. According to the latest 7th edition of TNM staging in 2009, there were 66 cases of stage II A patients (of which 15 cases of T2bN0M0 patients, 9 cases of T1aN1M0 patients, 9 cases of T1bN1M0 patients and 33 cases of T2aN1M0 patients) and 27 cases of stage II B patients (of which 5 cases of T2bN1M0 patients and 22 cases of T3N0M0 patients). Postoperative pathology: 44 cases of squamous cell carcinoma, 40 cases of adenocarcinoma and 9 cases of other types (including 2 cases of adeno-squamous carcinoma, 5 cases of large cell carcinoma and 2 cases of giant cell carcinoma). Follow-up visits were ended on May 1, 2012 and the survival time of patients was 3-83 months. 8 cases were lost and the follow-up rate was 91.40%. In the 85 patients that were visited, 49 cases were still alive (including 2 cases of recurrence and 1 case of brain metastases) and 36 cases were dead. There were 25 cases treated with chemotherapy after surgery and 14 cases treated with radiotherapy.

Methods

Possible prognostic factors include: gender, age, surgical approach, maximum tumor diameter, the total number of dissected lymph nodes, the number of dissected N1, N2 lymph nodes, N1 groups and N2 groups, the metastasis number of N1 and N1 group, the metastatic rate of N1 lymph nodes, 10th group of lymph nodes metastatic or not, new TNM staging, pathological type, degree of differentiation and whether the patient receives postoperative chemotherapy and radiotherapy. For measurement data, continuous variable was converted into binary variable and polytomous variable by setting boundary point according to 7th edition TNM staging and ROC curve that affects survival rate. Specific boundary points are as follows: age 60; four border points including 2 cm, 3 cm, 5 cm, 7 cm of maximum tumor diameter; total number of dissected lymph nodes was 6; 5 N1 lymph nodes; 2 N2 lymph nodes; 3 groups of N1 lymph nodes; 2 groups of N2 lymph nodes; 1 N1 metastasis; 1 group of N1 metastasis; metastatic rate of N1 was 50%.

Statistical analysis

SPSS18.0 statistical software was used for data processing and calculate survival rate using the Kaplan-Meier method; the log-rank test was used for univariate survival analysis of possible prognostic factors; Cox proportional hazards model was used for multivariate survival analysis of prognostic factors which were statistically significant in univariate survival analysis. Test level $\alpha = 0.05$.

Results

Total survival situation

The total mean survival time of this group of patients was 56.3 months, and the cumulative survival rates of 1-5 years were as follows (**Figure 1**; **Table 1**).

Survival analysis

Univariate survival analysis showed that: new TNM staging, the total number of dissected

Table 2. Univariable analysis of general characteristics

Prognostic factors	Cases	5-year survival rate (%)	*P* value
Sex			
Male	65	56.33	0.475
Female	28	66.33	
Age			
≤ 60 y	51	57.58	0.417
> 60 y	42	52.91	
Surgery			
Single lobe	70	60.27	0.097
Two-lobe	14	64.29	
All lung	9	0.00	
Diameter			
(0, 2]	18	40.74	0.307
(2, 3]	17	82.35	
(3, 5]	23	46.82	
(5, 7]	26	65.38	
> 7	9	33.33	
Staging			
II A	66	61.35	0.049*
II B	27	43.21	
Pathologic type			
Squamous	44	64.05	0.637
Adenocarcinoma	40	56.27	
Other	9	55.56	
Differentiation			
Highly	15	80.00	0.154
High-moderately	8	62.50	
Moderately	45	58.90	
Moderately-low	14	42.86	
Low	11	63.64	
Radiotherapy			
Yes	25	60.00	0.699
No	68	59.72	
Chemotherapy			
Yes	14	35.71	0.816
No	79	57.10	

*P < 0.05, 5-year survival rate (%) of staging II A vs II B.

lymph nodes, the number of dissected N1 and N2 lymph nodes and N1 groups, the metastatic rate of N1 lymph nodes, and the 10th group of lymph nodes metastatic or not, are related to the postoperative 5-year survival rate of the patients (**Tables 2** and **3**). Gender, age, overall surgical approach, overall maximum tumor diameter, the total number of dissected N2 lymph nodes, the metastasis number of N1 and N1 group, overall pathological type, degree of differentiation and whether the patient receives postoperative chemotherapy and radiotherapy were not related to postoperative 5-year survival rate (**Tables 2** and **3**). In the prognostic factors of polytomous variable, comparisons of the results of each group showed that: for the surgical approach, there was statistically significant difference of 5-year survival rate between single lobectomy group and pneumonectomy group (P = 0.036); for the maximum tumor diameter, there was statistically significant difference of postoperative 5-year survival rate between "> 2 cm and ≤ 3 cm" group and the "> 7 cm" group (P = 0.049); for the degree of differentiation, there was statistically significant difference of postoperative 5-year survival rate between well-differentiated group and poorly differentiated group (P = 0.042). Put prognostic factors which were statistically significant in univariate survival analysis in the Cox proportional hazards model for multivariate survival analysis and the result showed that: the metastatic rate of N1 lymph nodes and if the 10th group of lymph nodes were metastatic or not are independent prognostic factors for the postoperative 5-year survival rate of the patients (**Table 4**; **Figures 2** and **3**).

Discussion

In 2009, Union for International Cancer Control (UICC), American Joint Committee on Cancer (AJCC) and the International Association for the Study of Lung Cancer (IASLC) jointly issued the 7th edition TNM staging of lung cancer. It is the latest version for now and it's more scientific and authoritative due to its sample size that far exceeds the previous versions and its improved research methods. However, now it seems that there are still some limitations in the 7th edition staging. First, the representation is poor. Before the promulgation of the 7th edition staging, the cases included in the study were unevenly distributed. For example, for the Asia with huge population, its number of cases accounted for only 14%. Second, the uniformity is poor. The localization of treatment modalities in research institutes of different nations and regions had inevitably affected the statistics of the patient survival rate. Third, the real-time performance is poor. In recent years, molecular biology technique, especially gene expression microarray, proteomics, and next-generation sequencing have been more widely used in clin-

Table 3. Univariable survival analysis of lymph node related factors

Prognostic factors	Cases	5-year survival (%)	*P* value
Number of lymph nodes			
≤ 6	36	43.75	0.047*
> 6	57	63.77	
Number of N1 nodes			
≤ 5	65	50.13	0.038*
> 5	28	78.57	
Number of N2 nodes			
≤ 2	28	37.50	0.040*
> 2	65	63.11	
Number of N1 groups			
≤ 3	65	49.58	0.015*
> 3	28	82.14	
Number of N2 groups			
≤ 2	35	42.86	0.050
> 2	58	63.41	
Number of metastatic N1 nodes			
≤ 1	70	61.04	0.586
> 1	23	46.91	
Number of metastatic N1 groups			
≤ 1	75	60.31	0.925
> 1	18	48.63	
Metastatic rate of N1			
≤ 50%	78	64.62	0.044*
> 50%	15	28.57	
L10 metastasis			
Yes	36	37.56	0.002*
No	57	73.68	

*P < 0.05, Metastatic rate of N1: ≤ 50% vs > 50%; L10 metastasis: Yes vs No.

ical diagnosis and treatment [6], while the 7th edition staging did not include the techniques as a staging basis. So can our population could be phased in accordance with the 7th edition TNM staging criteria? The 93 patients in this study were all patients of stage II non-small cell lung cancer in particular areas of our country under the new staging criteria and the univariate survival analysis showed that there existed a difference in postoperative 5-year survival rate of II A and II B patients, and the difference was statistically significance (P = 0.049). Thus it could be considered that patients of stage II non-small cell lung cancer in particular areas of our country can be phased in accordance with the criteria of 7th edition of TNM staging of lung cancer. As the number of cases in this study was limited, and they were limited to particular areas and patients of stage II non-small cell lung cancer, if we are to determine whether the 7th edition of TNM staging criteria is applicable to our population, we should take national and multicentered research results with large sample that cover all the stages as a basis.

In the surgical treatment of lung cancer, in addition to removal of the primary lesion of the lungs, lymph node dissection is also an important means to get accurate pathologic staging [7] as well as the premise to ensure the efficacy. Theoretically, the more lymph nodes are dissected, the smaller the possibility of postoperative lymphatic metastasis, but it also causes greater trauma for the patients. Therefore, to determine the safety limit of the number of dissected lymph nodes is particularly important, as it can ensure the efficacy of surgery, but also avoid unnecessary vice injury. Currently, studies of relations between the number of dissected lymph nodes and prognosis of patients have mostly concentrated on stage I and stage III A/N2 non-small cell lung cancer [8-13], and there are relatively few studies related to stage II. Although the present study two independent prognostic factors obtained by multivariate survival analysis do not include the indicator number of dissected lymph nodes, in the univariate survival analysis, the patients with the total number of dissected lymph nodes greater than 6, the number of dissected N1 lymph nodes greater than 5 and N2 the 2, the number of dissected N1 groups greater than 3 had a clear survival advantage (P < 0.05), and this point shouldn't be ignored. Therefore, we recommend when doing the lymph node dissection, the total number of dissected lymph nodes should be more than 6, number of N1 lymph nodes over 5 and N2 over 2 and the number of dissected N1 groups greater than 3.

In the surgery, number of dissected N1 lymph nodes of each patient couldn't be the same, so simple comparison of "metastasis number of N1 lymph nodes" has no practical significance, and this set of data has proved the point (P = 0.586). Metastatic rate of N1 lymph nodes is the ratio of metastatic N1 lymph nodes account-

Table 4. Cox proportional hazard model

Prognostic factors	β	SE of β	Wald value	*P* value	RR	95% CI of RR
Metastatic rate of N1	0.785	0.365	4.624	0.032	2.191	1.072-4.480
Whether L10 metastasized	-0.815	0.339	5.778	0.016	0.443	0.228-0.860

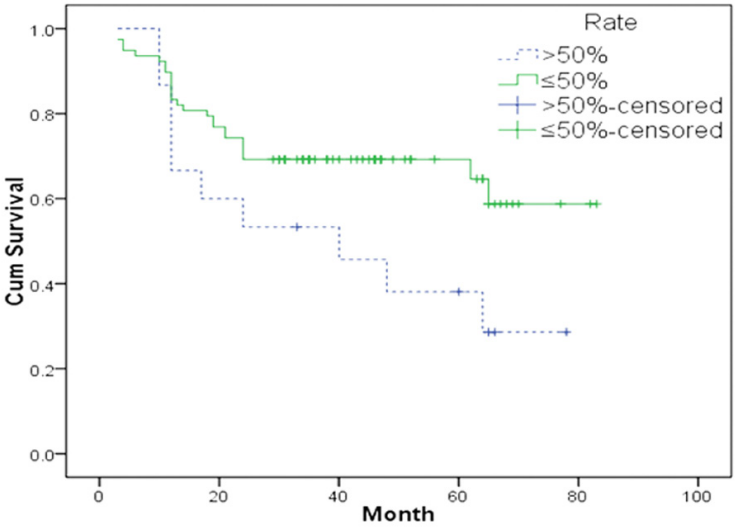

Figure 2. Survival curve of patients with metastatic N1 lymph nodes. Cum Survival: cumulative survival.

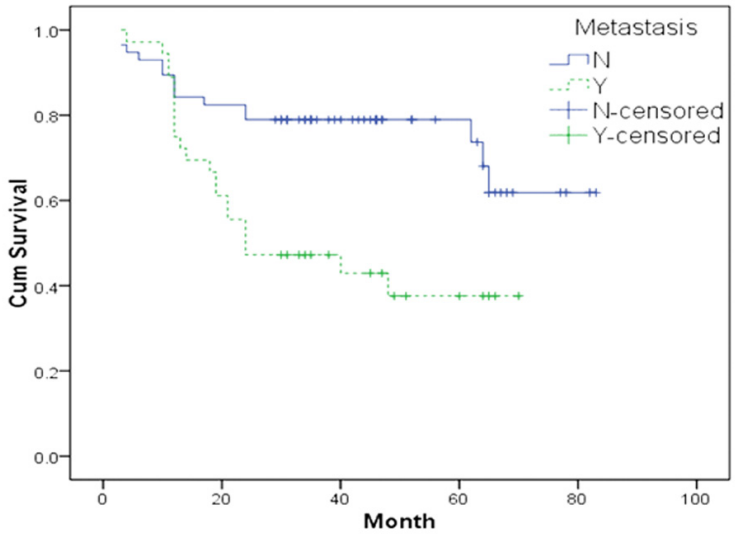

Figure 3. Survival curve of patients with L10 metastasis. Cum Survival: cumulative survival.

ing for in the total number of dissected N1 lymph nodes, so it can take into account both the two indicators "metastasis number of N1 lymph nodes" and "number of dissected N1 lymph nodes", reflecting the situations that cannot be reflected by any one of the two indicators alone. In this study, univariate survival analysis showed that "number of dissected N1 lymph nodes" and "metastatic rate of N1" were prognostic factors for postoperative 5-year survival rate of patients ($P < 0.05$). However, in multivariate survival analysis, only the "metastatic rate of N1" is the independent prognostic factor of postoperative 5-year survival rate of patients ($P = 0.032$). So "metastatic rate of N1" can better reflect the patient's prognosis than the "N1 number of dissected lymph nodes" [14]. Cox proportional hazards model showed that death risk of patients with metastatic rate of N1 > 50% is 2.19 times that of patients with metastatic rate of N1 ≤ 50%. The study showed that the metastatic rate of N1 lymph nodes greater than 50% revealed poor prognosis of the patients.

Lymph node metastasis is an important prognostic factor in patients with NSCLC. Some studies have showed [15] that 5-year survival rate of patients without lymph node metastasis (N0) is about 56%, while that of patients with pulmonary lymph node metastasis (N1) is only 38%. Lymph node is equivalent to a relay station in metastasis. Except for jumping metastasis, the cancer cells usually pass through bronchus and lung perivascular lymphatic channels in accordance with the direction of lymph drainage, first invade into adjacent lung segment of cancer or lymph nodes around lobe bronchus (Group 11-14), and then invade into hilar lymph nodes (Group 10), and then go up or down to invade into mediastinal lymph nodes (groups 1-9). It can be seen that hilar lymph nodes are the demarcation point between pul-

monary lymph nodes (N1) and mediastinal lymph nodes (N2) and hilar lymph node metastasis directly determines mediastinal lymph node metastasis and is the key prognostic factor. Univariate survival analysis and multivariate survival analysis all showed that hilar lymph node were metastatic or not indeed had an impact on postoperative 5-year survival rate of patients with statistical significance ($P < 0.05$). Cox proportional hazards models suggested that the death risk of patients with hilar lymph node metastasis is 2.26 times that of patients without hilar lymph node metastasis. The study showed that hilar lymph node metastasis revealed poor prognosis of the patients.

In this study, although there was no significant difference in general of surgical approach, maximum tumor diameter and degree of differentiation, comparison between groups found that there was significant difference of the postoperative 5-year survival rate between some groups. For surgical approach, the postoperative 5-year survival rate of pneumonectomy group was significantly lower than that of double lobectomy group ($P = 0.036$), which may be associated with complications after pneumonectomy and reduced quality of life. For the maximum tumor diameter, postoperative 5-year survival rate of "> 7 cm" group was significantly lower than that of "> 2 cm and ≤ 3 cm" group ($P = 0.049$). In stage II non-small cell lung cancer, T > 7 cm could only be T3N0M0 and stage II B, while T > 2 cm and ≤ 3 cm could be T1bN1M0 or T2aN1M0 (involving the visceral pleura) and were both stage II A, so this difference can be interpreted. It is worth noting that not the greater maximum tumor diameter, the worse the prognosis, but it should be comprehensively assessed according to other factors such as tumor location, the invasion situation around and metastasis circumstances of lymph nodes, and this set of data has proved this point. For the degree of tumor differentiation, the postoperative 5-year survival rate of moderately differentiated group and poorly differentiated group was significantly lower than that of the well-differentiated group ($P = 0.042$). Theoretically, the degree of differentiation should be positively correlated with the prognosis. Although this study showed this trend, but the postoperative 5-year survival rate of poorly differentiated group was not the lowest, which may be related to the small sample size and relatively large bias in the study. Meanwhile, in this study, whether the patient receives postoperative chemotherapy and radiotherapy were found unrelated to the postoperative 5-year survival of patients, which may be related to small sample size and nonstandard postoperative chemotherapy and radiotherapy programs of the study.

Disclosure of conflict of interest

None.

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