Original Article

Analysis of factors influencing skip lymphatic metastasis in pN_2 non-small cell lung cancer

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Objective: Although many clinical studies on skip lymphatic metastasis in non-small cell lung cancer have been reported, the risk factors for skip lymphatic metastasis are still controversy and debatable. This study investigated, by multivariate logistic regression analysis, the clinical features of skip metastasis to mediastinal lymph nodes (N_2) in non-small cell lung cancer (NSCLC) patients.

Methods: We collected the clinicopathological data of 256 pN_2-NSCLC patients who underwent lobectomy plus systemic lymph node dissection in Fujian Medical University Union Hospital. The cases in the present study were divided into two groups: skip metastasis (N_2 skip+) and non- skip metastasis (N_2 skip-). A retrospective analysis of clinical pathological features of two groups was performed. To determine an independent factor, multivariate logistic regression analysis was used to identify possible risk factors.

Results: A total of 256 pN_2-NSCLC patients were recruited. The analysis results showed that gender, pathologic types, surgery, pleural involvement, smoking history, age, tumor stages, and differentiation were not statistical significant factors impacting on skip metastasis in pN_2-NSCLC ($P>0.05$), whereas tumor size was an independent factor for skip metastasis ($P=0.02$).

Conclusions: The rate of skip lymphatic metastasis increases in pN_2-NSCLC patients, in accompany with an increased tumor size.

Key Words: Lung cancer; lymph node; skip metastasis

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Introduction

Non-small cell lung cancer (NSCLC) constitutes about 85% of all newly diagnosed cases of lung cancer and continues to be the leading cause of cancer-related deaths worldwide (1,2). The majority of patients present with either locally advanced or metastatic disease and only 20-30% of patients have potentially operable, early stage disease at presentation (3,4). It is known as skip mediastinal lymph node metastasis that lung cancer metastasis to mediastinal lymph node (N_2) occurs without involvement of pulmonary or hilar lymph node (5). Mediastinal skip lymphatic metastasis is important for mediastinal lymph node dissection (MLND), because it is an important basis for a reasonable range of MLND (6). N_2 skip metastasis is considered as an independent subtype within the N_2 metastasis (7) and its exact mechanism is currently not clear. The argument regarding risk factors for skip lymphatic metastasis in lung cancer is mainly focused on pathology as well as the localization, stages, and size of tumors. To further explore the factors influencing skip lymphatic metastasis in NSCLC, a retrospective analysis of 256 NSCLC cases were performed in our current study.

Patients and methods

Patients

From January 2001 through January 2012, 256 patients

Table 1 Mediastinal lymph node dissection and lymph node metastasis rate in each group

N_2 lymph node	n=256
Mean number of groups (groups)	4.1±1.3
Mean lymph node	12.3±6.9
Rate of lymph node metastasis	
Group 2	18.18
Group 3	17.79
Group 4	30.83
Group 5	21.74
Group 6	17.79
Group 7	48.62
Group 8	4.74
Group 9	10.67

underwent lobectomy plus systemic lymph node dissection for NSCLC in Fujian Medical University Union Hospital. These patients aged 29-80 years [(58.5±9.6) years]. Tumors were located at the upper lobe(n=138, 53.9%), middle lobe (n=13, 5.1%), lower lobe(n=99, 38.7%) and pulmonary hilum (n=6, 2.3%). The pathological types included adenocarcinoma (n=141, 55.1%), squamous cell carcinoma (n=90, 35.2%), adenosquamous cell carcinoma (n=11, 4.3%), large cell carcinoma of lung (n=9, 3.5%), and other primary lung cancers (n=5, 2%) that included atypical carcinoid (n=3), epidermoid carcinoma (n=1), and sarcomatoid carcinoma (n=1). The size of tumors ranged 10-150mm, with an average size of (47.5±21.6) mm. In 256 cases, the total N_1 lymph nodes for pathological examination was present at least 1 group/case, and up to 4 groups/case, with an average number (2.3±0.8) groups/case. Among the 256 cases, there were 44 cases of skip lymphatic metastasis, which were at least 2 groups/case, and up to 4 groups/case, with an average number (2.4±0.6) groups/case. The other 212 cases non-skip metastasis, which were at least 1 group/case, and up who 4 groups/case, with an average number (2.3±0.8) groups/case. Before surgery, all patients were naive to chemotherapy, without previous cancer history, and with only one localized tumor that had no distant metastasis. In cases that were not suspected of skip metastasis, the number of N_1 lymph nodes for examination was required not less than 2 group/case and the related examinations were carried out to exclude surgery contraindications.

Surgery

The metastatic lymph nodes in lung cancer were removed by systemic lymph node dissection, according to Naruke's system, included N_1 and N_2 lymph nodes, the 2nd, 3rd, 4th, 7th, 8th, 9th groups/stations of mediastinal lymph nodes in right lung cancer or the 4th-9th stations of mediastinal lymph nodes in left lung cancer. The detail information on the location, station and number of resected lymph nodes was shown in *Table 1*. TNM classification for NSCLC in this study was based on the revised staging classification for lung cancer issued by UICC/AJCC in 2009, while the pathologic typing of lung cancer was made, according to 2004 WHO classification system for primary lung cancer.

Statistical analysis

Two-sided test was used in all statistical tests and $P<0.05$ was considered statistically significant. Followed by univariate analysis of possible risk factors, multivariate analyses were performed by logistic regression method. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc. Chicago, Illinois, USA).

Results

Univariate analysis of possible risk factors influencing N_2 skip metastasis

In order to determine the possible factors influencing N_2 skip metastasis in NSCLC, univariate analysis with Chi square test were performed in our study, in which there were 6 cases that tumor was found in pulmonary hilum and in more than one lobe of the same lung or in other lung. However, these 6 cases were excluded in Chi square test for the factor regarding tumor location. The analysis showed that there were no statistically significant ($P>0.05$) differences in gender, age, smoking, tumor location, pathology, surgery, pleural involvement, and differentiation between groups of N_2 skip+ and N_2 skip-. The only one significant difference was tumor size (as shown in *Table 2*).

Multivariate analyses using logistic regression method

The major aim of this study is to identify the factors, based on clinical pathological characteristics of NSCLC, which are correlated with skip metastasis of NSCLC. However, the results of univariate analysis revealed that the factors regarding gender, age, smoking history, pathology,

Table 2 Clinopahological data of 256 patients with primary non-small cell lung cancer

Items	Case (n)	N_2 skip-	N_2 skip+	P Value
Gender				0.612
Male	184	151	33	
Female	72	61	11	
History of smoking				0.946
Yes	135	112	23	
No	121	100	21	
Tumor location				0.310
Upper lobe	138	112	26	
Middle lobe	13	10	3	
Lower lobe	99	87	12	
Pathologic type				0.679
Adenocarcinoma	141	119	22	
Squamous cancer	90	72	18	
Others	25	21	4	
Pleura involvement				0.570
Yes	73	62	11	
No	183	150	33	
Mode of surgery				0.469
Open	143	122	21	
Small incision	22	18	4	
Endoscopic	91	72	19	
Age (years)				0.530
<65	182	149	33	
≥65	74	63	11	
T stage				0.122
T_1	41	37	4	
T_2	178	149	29	
T_3	30	21	9	
T_4	7	5	2	
Maximum tumor diameter				0.020
≤3 cm	69	63	6	
>3 cm, ≤5 cm	116	98	18	
>5 cm, ≤7 cm	41	30	11	
>7 cm	30	21	9	
Differentiation				0.898
Poorly	22	19	3	
Moderately	182	150	32	
Highly	52	43	9	

Table 3 Results of logistic regression analysis

Items	B	S.E.	wald	df	P	OR	95% C.I for Exp (B)	
							lower	upper
Tumor locations			4.567	2	0.102			
Upper lobe	0[a]							
Middle lobe	0.895	0.759	1.393	1	0.238	2.448	0.553	10.829
Lower lobe	–0.588	0.373	2.482	1	0.115	0.555	0.267	1.154
Maximum tumor diameter			10.834	3	0.013			
≤3 cm	0[a]							
>3 cm but ≤5 cm	0.75	0.508	2.179	1	0.140	2.117	0.782	5.729
>5 cm but ≤7 cm	1.559	0.573	7.398	1	0.007	4.754	1.546	14.622
>7 cm	1.648	0.600	7.558	1	0.006	5.198	1.605	16.832

[a]This parameter is set to zero because it is redundant

differentiation, tumor stage, surgery, tumor location and pleural involvement were not significantly correlated with skip metastasis in NSCLC. Only the factor regarding tumor size was found statistically significant in the test. In the multivariate analysis, there were two candidates for our consideration, i.e. two highly relevant factors: tumor size and tumor stage. The former, tumor size was finally chosen for multivariate analysis, because only one potential factor can be included in the analysis. Precluding the confound of independent variables, multivariate analysis was performed, using logistic regression model, by taking tumor location and tumor size as covariant and skip metastasis as a dependent variable. The results in *Table 3* show that in patients with clinical N_2 NSCLC, tumor size was an dependent factor influencing N_2 skip metastasis, but tumor location was not statistically significantly associated with N_2 skip metastasis (P>0.05).

Discussion

Misthos *et al*. considered that squamous cell carcinomas are most prone to skip metastasis (8). Gunluoglu *et al*. reported that patients with adenocarcinoma were easier to have skip lymphatic metastasis (9). In our current study, we found that the difference of pathological classification between the two groups was not statistically significant, and perhaps pathological type was not an independent factor influencing skip metastasis.

Whether the location of the primary tumor is associated with N_2 skip metastasis is currently still disputed. Melfi *et al*. argued that the incidence of N_2 skip metastasis was highest in right lower lobe of lung cancer (10). Our study found that the incidence of N_2 skip metastasis was higher in tumors that occurred in either upper lobe or middle lobe on both sides of the lung. This finding is consistent with Riquet's report (11). However, the difference is not statistically significant, due to limited case number and larger variations of tumor volume between the tumors in different locations as well as other involved mechanisms such as a larger variation in the channel and modes of lymphatic return between pulmonary lobes and mediastinal lymph nodes.

Riquet *et al*. found that there was subpleural lymphatic channel that was directly linked to mediastinal lymph nodes (11). They think it is a reason why skip mediastinal lymphatic metastasis occurred in the patients with NSCLC. Furthermore, the pulmonary lymphatic channels also directly connect the bottom of lower lobes to upper lobes of the lung. The lymphatic drainage from interlobular lymph nodes to hilar lymph nodes, also directly to mediastinal lymph nodes, is mainly through the widespread subpleural lymphatic network, suggesting the anatomic basis for N_2 skip metastasis. Accordingly, if there is pleura involvement in these NSCLC patients, will the incidence of skip mediastinal lymphatic metastasis be even higher? It is unclear whether those patients with pleura involvement have a greater chance of shedding of tumor cells into the pleural cavity, thereby leading to an increase in skip mediastinal lymphatic metastasis. Since there are no statistically significant (P>0.05) differences between pleura involvement and skip lymphatic metastasis in our study, we consider that the pleura involvement is not an independent factor influencing skip metastasis.

Whether the tumor size is correlated with skip mediastinal lymphatic metastasis is currently still disputed.

Our study revealed that an increased tumor size increased the incidence of skip lymphatic metastasis in NSCLC patients, which is consistent with Riquet's results (12). In their study, the analysis of the correlation of tumor stage or size respectively with skip metastasis indicated that in the test, tumor stage had a P value of 0.1, while tumor size had a P value of 0.0079. However, in the report of Misthos *et al.* (8), the incidences of skip lymphatic metastasis in T_1 and T_2 were significantly higher than that in T_3. Benoit *et al.* also found that the case with higher tumor stage had a higher rate of skip lymphatic metastasis (13). However many reports showed that the correlation of tumor stage and N_2 skip metastasis is not statistically significant. As we know, tumor staging actually includes several factors regarding tumor size, plural involvement, and involvement of important structures. Therefore, tumor size is not equal to tumor stage. We think that only tumor size that is also a parameter for tumor staging contributes to skip metastasis. If the analyses of skip metastasis are based on the data of tumor stage, the results are less reliable. Tumor size or tumor stage, which one is actually main factor influencing skip metastasis? What is the cause of the larger tumor with a higher risk for N_2 skip metastasis? The following factors should be considered: the larger tumor size or volume, the more interlobular lymphatic channels around the tumor, as well as higher risk for the metastasis of tumor cells into subpleural lymphatic channel through interlobular lymphatic channel. Previous studies found that the presence of subpleural lymphatic channels that are directly linked to mediastinal lymph nodes, increased the risk of N_2 skip metastasis in larger tumor, although the tumor metastasis through the lymphatic channels that are accompanied by bronchus, artery, and vein is not increased.

In the literatures (14,15), the percentage of patients with skip metastasis is about 13% to 42% of total N_2 patients; similarly, it was 17.2% in our study. The rates of N_2 skip lymphatic metastasis varied in the different reports, possibly due to the missed diagnosis of hilar lymph node micrometastasis. However, N_1 lymph node micrometastasis might be not detected by conventional pathological examination. It is reported that the rates of missed diagnosis for pulmonary or hilar lymph node micrometastasis were around 20% (16). Passlik *et al.* reported approximately 20% N_1 lymph node micrometastasis detected by immunohistochemical methods (17). Using RT-PCR assay, Wu *et al.* investigated the expression of LUNX, a specific gene related to lung cancer, in mediastinal lymph nodes (18). They found that the percentage of the lymph nodes that are LUNX-mRNA positive, were up to 62.5% in the patients with stage III of lung cancer, suggesting very high rate of mediastinal lymph node micrometastasis in the patients with NSCLC that underwent surgery. Meanwhile, this phenomenon may also be caused by the absence of intrapulmonary lymph nodes (12-14 groups/stations) in the specimens for pathological examination. The specimen of N_1 lymph nodes of the case with skip metastasis for pathological examination had at least 2 groups/case in our study, thus it would be better to reduce such effect. Moreover, studies also found that pN_0 lymph node micrometastases might be associated with the stage, size, and location of tumors, in which there were a part of cases with skip metastasis (19), indicating the similarity in clinical pathological features between pN_0 lymph node micrometastases and N_2 skip metastasis. Therefore, we think that N_2 skip metastasis research will be benefited from the studies on pN_0 lymph node micrometastases.

Current studies suggest that the patient with skip metastasis has a better survival rate, but the underlying mechanism is not clear. Benoit *et al.* believed that less group number of the positive mediastinal lymph nodes is a reasonable explain for better prognosis of skip metastasis (13); in other words, the duration of survival for the patients with skip metastasis depends on the group number of the positive N2 lymph nodes. N_2 skip lymphatic metastasis may be an earlier stage of lymphatic metastasis in NSCLC and its significance is similar to N_1 lymph node metastasis. In addition, some scholars proposed that dysregulation of gene expression associated with primary tumor is one of the most important factors influencing lymph node metastasis (20). Prenzel *et al.* found that decreased expression of Bcl-2 and elevated expression of P21 were associated with N_2 skip metastasis in lung cancer (21). Whether there are more aberrant biological changes in the cases with N_2 skip metastasis positive than that in N_2 skip metastasis negative cases is still unclear.

In conclusion, the rate of skip lymphatic metastasis increases in pN_2-NSCLC patients, in accompany with an increased tumor size.

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