

Analysis of factors influencing skip lymphatic metastasis in pN₂ 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 (N₂) in non-small cell lung cancer (NSCLC) patients.

Methods: We collected the clinicopathological data of 256 pN₂-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 (N₂ skip+) and non- skip metastasis (N₂ 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 pN₂-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 pN₂-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 pN₂-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 (N₂) 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).

N₂ skip metastasis is considered as an independent subtype within the N₂ 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 N₁ 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 to 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 N₁ 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 N₁ and N₂ 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 N₂ skip metastasis

In order to determine the possible factors influencing N₂ 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 N₂ skip+ and N₂ 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,