·Clinical Research·

Clinical analysis of skip N2 metastases in stage ⅢA non-small cell lung cancer

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[Abstract] **Background and Objective:** Clinical characteristics of skip N2 metastasis of stage ⅢA non-small cell lung cancer (NSCLC) are not clear. This study was to investigate the clinicopathologic features and the distribution pattern of N2 lymph nodes, thus to analyze the relationship between the survival rate and skip metastasis of NSCLC patients. **Methods:** Clinical data of 292 patients with stage ⅢA NSCLC undergoing radical surgical resection plus mediastinal nodal dissection in the Affiliated Hospital of Nantong University were retrospectively reviewed. Clinicopathologic features, distribution of skip N2 metastasis and survival were analyzed respectively. **Results:** The incidence rate of skip N2 metastasis in stage ⅢA NSCLC patients was 15.8%, which was correlated to the size of the tumor (P<0.05). Moreover, the relationship between the primary tumor location and N2 positive lymph nodes were described as follows: right upper lobe cancer displayed skip-N2 nodal metastasis mostly in the 3rd and 4th station (85.7%), right middle lobe mostly in the 7th station (75.0%), right lower lobe mostly in the 3rd and 7th station(81.0%), left upper lobe mostly in the 5th and 6th station (80.0%), and left lower lobe mostly in the 7th station (65.0%). The 3-year survival rate of patients with skip N2 metastasis was 45.4%, compared to 29.5% in patients with the involvement of N1 and N2 nodes. Survival analysis showed that skip N2 metastasis was an independent risk factor of stage ⅢA NSCLC in addition to tumor size, histology, type of resection, adjuvant chemotherapy and radiotherapy. **Conclusions:** In stage ⅢA NSCLC, primary tumors in different locations have their own corresponding areas of N2 nodal metastasis. Skip N2 metastasis is an independent prognostic factor for the survival of NSCLC. Patients with skip N2 metastasis have a favorable outcome.

Key words: lung neoplasm, non-small cell, skip metastasis, lymph nodes, prognosis

Mediastinal lymph node (N2) metastasis of stage IIIA non-small cell lung cancer (NSCLC) is critical for the range of resection, the recurrence and the overall survival of patients. The typical lymphatic return of stage IIIA NSCLC is from lymph nodes around the primary tumor to mediastinal lymph nodes through hilar lymph nodes. However, some cases have only N2 metastasis without involving hilar and peripheral (N1) lymph nodes. It is so-called

skip N2 metastasis. Its pathological characteristics, patterns of distribution and impact on prognosis of NSCLC are still controversial. To better define the importance of skip N2 metastasis, we retrospectively analyzed 292 patients with stage IIIA NSCLC.

Data and Methods

Patients. Between January 2002 and December 2006, a total of 756 patients who underwent radical surgical resection plus mediastinal nodal dissection in the Affiliated Hospital of Nantong University were retrospectively reviewed. Of those, 292 were diagnosed as stage IIIA NSCLC. There were 225 males and 67 females, aged from 39 to 78 years (median, 66.5 years). Based on pathological examinations, there were 205 cases of squamous cell carcinoma, 77 adenocarcinoma, five large cell carcinoma, three carcinoid cancer, and two neuroendocrine carcinoma. Ninety-four patients had the central type NSCLC and 198 had the peripheral type. There were 72 patients whose primary tumors were in left upper lobes, 59 in left lower lobes, 69 in right upper lobes, 24 in right middle lobes and 68 in right lower lobes. In total 246 patients had both N1 and N2 metastasis, and 46 patients had skip N2 metastasis. All patients had not been given preoperative chemotherapy or radiotherapy and had routine preoperative examinations to exclude patients with contraindications.

Therapy. Two hundred and thirteen patients received lobectomy, 23 underwent bilobectomy, 11 received sleeve lobectomy and 45 underwent pneumonectomy. According to Narukes map, all patients underwent systematic N1 and N2 nodal dissection. Lymph nodes at stations 2, 3, 4, 7, 8, 9 were removed for the right-sided cancer and at stations 4 to 9 for the left-sided cancer. Details about the location, the station and the number of lymph nodes were recorded. All lymph nodes were given routine HE pathologic examination by two specialists from the Affiliated Hospital of Nantong University. pTNM was made according to the six edition of the Union Internationale Contre le Cancer (UICC) in 1997, and the histological types of cancers were recorded in accordance with the WHO standard. N2 was divided into three zones according to Mountains[1] map: upper N2 zone (1 to 4 stations), aortic N2 zone (5, 6 stations) and lower N2 zone (7 to 9 stations). The number of N2 in every zone and involved N2 were recorded.

Among 182 patients who received adjuvant chemotherapy, 117 patients received vinorelbine plus cisplatin (NP) (vinorelbine 25 mg/m^2, d1, d8 plus cisplatin 30 mg/m^2 , d1 to d3, 21 days as a cycle); 65 patients received gemcitabine plus cisplatin (GP) (gemcitabine 1000 mg/m^2, d1, d8 plus cisplatin 25 mg/m^2 , d1 to d3, 21 days as a cycle); 36 patients received adjuvant radiotherapy with ^{60}Co using a dose schedule of 40-60 Gy in 20-30 fractions over a period of 4-6 weeks once a day, 2 Gy per time; 42 patients received concurrent chemo-radiotherapy using NP chemotherapy.

Following-up. All patients were followed up once every 1-2 months in the first year and every 3-4 months after the first year. Examinations including chest X-ray, computed tomography (CT) scan, abdominal ultrasound, tumor biomarker or nuclear bone scan were performed. Patients were followed for 8-46 months (median, 28.8 months). Sixteen patients (5.48%) were lost during the follow-up. All data of lost patients during the follow-up and lung cancer-unrelated deaths were taken as censored data for analysis.

Statistical analysis. The statistical analysis was performed using SPSS V17.0 software package (SPSS Inc., Chicago, IL). The Chi-square test was used to compare frequencies. The survival was estimated using the life table and the Kaplan-Meier method. Univariate analysis was performed using the log-rank test and multivariate analysis was performed using the Cox proportional hazards regression model. A p value of less than 0.05 was considered statistically significant.

Results

Lymph node metastasis of 292 patients with stage IIIA NSCLC. A total of 3906 N1 and N2 were removed. The mean (± SD)

number was (13.4± 6.3) per patient. There were 1342 N1 including 1092 metastatic N1 (metastatic rate: 81.37%). A total of 2564 N2 were examined including 2138 N2 from patients with the involvement of N1 and N2 nodes and 426 N2 from patients with skip N2 metastasis. There were 774 metastatic nodes (metastatic rate: 36.20%), (3.55± 4.23) per patient in patients with non-skip N2 nodes and 95 metastatic nodes (metastatic rate: 22.30%), (2.07± 3.17) per patient in patients with skip N2 metastasis, respectively.

There were no statistical significance between patients with skip and non-skip N2 metastasis in terms of sex, age, smoking, tumor location, histology and differentiation ($p < 0.05$) except for the tumor size (Table 1). The frequency of skip N2 metastasis was 20.83%, 19.08% and 2.94% for T1, T2 and T3 NSCLC, respectively. The skip N2 metastatic rate was statistically higher at T1 and T2 stages than at T3 stage ($p < 0.05$).

Table 1 Comparison of clinical data of NSCLC patients with (+) or without (−) skip N2 node metastases

Item	Skip(+) (cases)	Skip(−) (cases)	*P* value
Sex			>0.05
Male	32	193	
Female	14	53	
Age			>0.05
<70 (yrs)	31	177	
⩾70 (yrs)	15	69	
Smoking			>0.05
Yes	29	173	
No	17	73	
Tumor location			>0.05
Right lung	25	136	
Left lung	21	110	
Histology			>0.05
Squamous cell carcinoma	35	170	
Adenocarcinoma	9	68	
Other[a]	2	8	
Differentiation			>0.05
Well	12	75	
Moderate	19	89	
Poor	15	82	
T stage			<0.05
T1	15	57	
T2	29	123	
T3	2	66	

[a]includes five cases of pulmonary large cell carcinoma, three cases of pulmonary carcinoid tumors and two cases of pulmonary neuroendocrine carcinoma.

Distribution of skip N2 metastasis in lymph node stations. Distribution of skip N2 metastasis in mediastinal lymph node stations was related to tumor locations. When the primary tumors were in right upper lobes, 85.7% of N2 metastasis belonged to No. 3 and No. 4 stations; for right middle lobe-tumors, 75.0% of N2 metastasis belonged to the No.7 station; for right lower-tumors, 81.0% of N2 metastasis was in No. 3 and No. 7 stations; 80.0% of N2 metastasis was located in No. 5 and No. 6 stations for left upper lobe-tumors; and 65.0% of N2 metastasis was in the No. 7 station when primary tumors were in left lower lobes. Distribution of skip N2 metastasis was statistically different among primary tumors located at different lobes ($p < 0.05$, Table 2).

In patients with skip N2 metastasis, 84.8% of N2 metastasis was limited in only one station. In patients with non-skip N2 metastasis, 20.7% of N2 metastasis involved three or more stations (Table 3). The difference between the two groups was statistically significant ($p < 0.05$).

Table 2 Distribution of skip N2 metastasis in the lymph node stations according to the location of the primary tumor

Lymph node site	Right upper (cases)	Right Middle (cases)	Right lower (cases)	Left upper (cases)	Left lower (cases)
Highest mediastinal	–	–	–	–	–
Upper paratracheal	2	–	–	–	–
Pre-vascular and retrotracheal	12	2	4	–	–
Lower paratracheal	6	–	2	3	3
Subaortic	–	–	–	8	2
Para-aortic	–	–	–	12	–
Subcarinal	1	6	13	2	13
Paraesophageal	–	–	2	–	1
Pulmonary ligament	–	–	–	–	1
Total	21	8	21	25	20

Table 3 Relationship between positive N2 lymph nodes and lymph node involvement in NSCLC patients

Item	Cases	N2(+) status		
		One station	Two stations	⩾3 stations
Skip(+)	46	39	7	0
Skip(−)	246	121	74	51
Total	292	160	81	51

$\chi^2=21.579$, $P<0.05$

Distribution of skip N2 metastasis in N2 zones. Forty-one patients (89.1%) had skip N2 metastasis in only one N2 zone, most of which were in the upper N2 zone from the right upper lobe tumors. Five patients had skip N2 metastasis in two N2 zones. Two of them, whose tumors were in the right lower lobes, had skip N2 metastasis in both upper and lower zones (Table 4). The difference in the distribution of skip N2 metastasis in N2 zones was not statistically significant ($p > 0.05$).

Survival analysis of stage IIIA NSCLC. Univariate analysis. The Log-rank test was used to determine potentially prognostic factors of IIIA NSCLC. The one- and three-year overall survival (OS) rates for patients with skip N2 metastasis and non-skip N2 metastasis were 67.1%, 45.4% and 51.2%, 29.5%, respectively ($\chi^2 = 5.921$, $p = 0.023$. Figure 1). Eight statistically significant factors were determined: smoking ($\chi^2 = 4.561$, $p = 0.042$), pulmonary function ($\chi^2 = 5.614$, $p = 0.025$), tumor size ($\chi^2 = 6.004$, $p = 0.021$), histology ($\chi^2 = 8.751$, $p = 0.008$), differentiation ($\chi^2 = 7.324$, $p = 0.012$), surgical procedure ($\chi^2 = 5.214$, $p = 0.034$), adjuvant chemotherapy ($\chi^2 = 5.671$, $p = 0.028$) and adjuvant radiotherapy ($\chi^2 = 4.579$, $p = 0.044$). Four factors were disclosed as statistically non-significant ones: age ($\chi^2 = 1.345$, $p = 0.234$), sex ($\chi^2 = 0.994$, $p = 0.561$), tumor location ($\chi^2 = 2.3479$, $p = 0.115$) and surgery ($\chi^2 = 1.024$, $p = 0.453$).

Multivariate analysis. Independent prognostic factors of OS were tumor size, histology, surgical procedure, skip N2 metastasis, adjuvant chemotherapy and adjuvant radiotherapy (Table 5).

Table 4 Relationship between mediastinal lymph nodes compartment involved in skip (+) group and location of primary non-small cell lung cancer

Item	Skip (+) (cases)						
	Superior mediastinal nodes	Inferior mediastinal nodes	Aortic nodes	Superior + Inferior	Superior + Aortic	Inferior + Aortic	Superior, Inferior + Aortic
Right upper	11	0	–	1	–	–	–
Right middle	1	3	–	0	–	–	–
Right lower	1	6	–	2	–	–	–
Left upper	2	1	9	0	0	1	0
Left lower	1	5	1	0	0	1	0

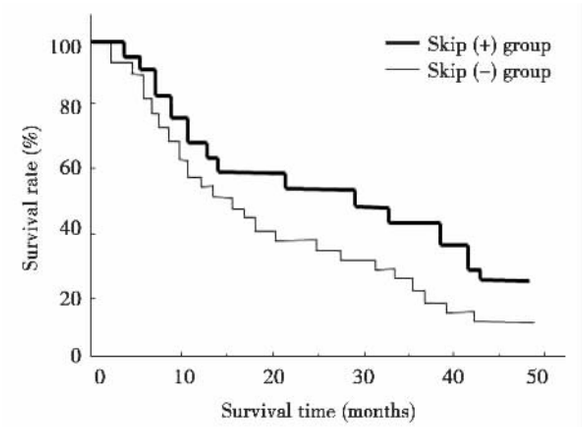

Figure 1 Survival curves of patients with non-small cell lung cancer with or without skip N2 metastasis after operation

Discussion

Our results indicated that skip N2 metastasis in NSCLC is one of the most important prognostic factors to determine the surgical procedure. In some reports, the skip N2 metastasis rates were 13%-42%,[2,3] similar to the results of our study (15.8%). Kotoulas et al.[4] reported that lung adenocarcinomas tend to have skip N2 metastasis. However, we found that in the skip N2 metastasis group, the proportion of adenocarcinoma was lower than that in the non-skip N2 metastasis group. There was no significant difference in the proportion between

Table 5 Cox regression analysis for the prognosis of 292 non-small cell lung cancer patients

Variant	B	SE	Wald	df	*P*	RR
Smoking	0.284	0.157	3.841	1	0.372	1.328
Pulmonary function	0.324	0.231	4.012	1	0.273	1.382
Histology	0.516	0.146	7.564	2	0.036	1.675
T stage	1.342	0.561	12.102	2	0.001	3.824
Differentiation	0.716	0.114	9.356	2	0.010	2.046
Type of resection	0.545	0.226	7.495	1	0.032	1.724
Skip metastasis	0.472	0.188	6.534	1	0.042	1.603
Postoperative chemotherapy	0.733	0.152	9.873	1	0.009	2.081
Postoperative radiotherapy	0.701	0.142	8.832	1	0.013	2.015
Postoperative radiochemotherapy	0.721	0.149	9.772	1	0.010	2.056

adenocarcinoma and squamous cell carcinoma in the skip N2 metastasis group. We found that skip N2 metastasis was closely related to tumor size, and the skip N2 metastasis rate in T1, T2 was much higher than that in T3, consistent with Misthos et al.s study.[5] Therefore, we recommend systematic mediastinal nodal dissection for the peripheral type of T1 NSCLC.

Controversies still exist regarding the correlation between the location of the primary tumor and the frequency of skip N2 metastasis. In our study, the frequency of skip N2 metastasis was higher in patients with primary tumors in both upper lobes than that in others locations, but the difference was not significant. Melfi et al. 7 regard that the frequency of skip N2 metastasis in patients with tumors in right lower lobes is the highest, which may be explained by the variation in the pathway and pattern of lymphatic return between lobes and mediastinal lymph nodes. Riquet et al.[8] reported that 22.5% of lymph nodes in patients with primary tumors in left lobes and 25% of lymph nodes in right lobes had a direct way to mediastinal lymph nodes through lymph vessels under pleura, and this was mostly seen in patients with primary tumors in both upper lobes. Therefore, they suppose that the frequency of skip N2 metastasis in patients with primary tumors in upper lobes might be higher than that in other lobes. Misthos et al. [5] proposed that there are considerable extents of variations and different pathways of lymphatic return between lobes and mediastinal lymph nodes, which could explain the result discrepancy between their and or studies.

Our study showed that skip N2 metastasis happened in the corresponding stations according to the tumor location. For tumors in the right upper lobes, skip N2 metastasis was mostly seen in No. 3 and No. 4 stations; for tumors in both lower lobes, skip N2 metastasis was involved in No. 7, No. 3 and No. 4 stations. This finding was consistent with Prenzel et als report.[9] They suggest that the chance of harvesting involved mediastinal lymph nodes is improved to 82.6% to 91.7% by checking the corresponding stations of skip N2 metastasis. We also found that though most of skip N2 metastasis were in the corresponding N2 zones according to the tumor location, there were still 10.9% patients whose skip N2 metastasis were in different zones, especially those whose tumors were in the right lower lobes. Their skip N2 metastasis were usually in both upper and lower N2 zones, which was in line with the study of Benoit et al.[6] Thus, we recommend systematic mediastinal nodal dissection to avoid missing skip N2 metastasis.

In our study, the survival rate of patients with skip N2 metastasis was much better compared to those with the involvement of N1 and N2 nodes. Prenzel et al.[9] reported that the OS of IIIA NSCLC patients was correlated to the number of N2 metastasis. We found the mean number of involved N2 nodes in patients with skip N2 metastasis was 2.07 compared to 3.55 in patients with involvement of N1 and N2 nodes. Zhang et al.[10] demonstrated that the relative risk for survival in patients with multistations lymph node metastasis was 2.207 times higher than that in those with single-station lymph nodes metastasis, and the five-year survival rate was lower in patients with multistations lymph node metastasis than in those with single N2 station metastasis. In our study, 84.8% of patients with skip N2 metastasis had single station metastasis and 72.7% of patients with the involvement of N1 and N2 nodes had more than one station metastasis. The better OS in patients with skip N2 metastasis meant that they had less number and stations of lymph node metastasis than those with involved N1 and N2 nodes. We suppose that skip N2 metastasis should belong to early stage of lymph nodes metastasis, perhaps as the same as the status of N1. Zhang et al.[10] confirmed that mediastinal nodal dissection is the prognostic factor of IIIA NSCLC, and the relative risk for survival was 1.36 time higher in patients receiving sampling mediastinal nodal dissection than that in those undergoing systematic mediastinal nodal dissection. Many factors of surgery can impact prognosis of patients with involved N1 and N2 nodes, such as the range of mediastinal nodal dissection, surgical technique, standard procedure, especially unfinished

mediastinal nodal dissection and residual metastatic nodes, which would lead to poor survival. Additionally, micrometastasis is found in lymph nodes, blood and bone marrow at the early stage of lung cancer. [11] Meanwhile, low expression of Bcl-2 and overexpressed of P21 are closely related to the stage and the invasion of lung cancer. [12] Further studies are needed to determine whether micrometastasis and molecular biological status in patients with skip N2 metastasis are dramatically different from those with involved N1 and N2 nodes.

In summary, our results suggest that skip N2 metastasis has high frequency in NSCLC and the corresponding stations according to the tumor location. Removing N2 metastasis with systematic mediastinal nodal dissection would increase the staging accuracy and decrease recurrence. Additionally, skip N2 metastasis is an independent favorable prognostic factor for the survival of NSCLC patients, and thus should be included in the staging strategy.

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