Lung adenocarcinoma: Are skip N2 metastases different from non-skip?

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ABSTRACT

Objective: This study investigated the association between clinical pathologic features, especially adenocarcinoma subtypes and prognosis, and skip N2 metastasis in patients with lung adenocarcinoma.

Methods: In this study, 177 patients with lung adenocarcinoma and N2 metastasis were enrolled. Patients who had N2 lymph node metastases without N1 lymph node involvement were defined as skip N2 and otherwise as non-skip N2. We investigated the difference of clinicopathologic characteristics, recurrence-free survival, overall survival, and spectrum of well-identified molecular alterations in *EGFR*, *KRAS*, *HER2*, *BRAF*, *ALK*, *ROS1*, and *RET* genes in the 2 groups.

Results: Skip N2 metastasis was found in 45 patients, in whom a remarkably lower incidence of lymphovascular invasion was revealed ($P = .01$). Skip N2 metastasis was also associated with acinar subtype, good differentiation, and right lung cancer. The recurrence-free survival and overall survival were significantly better in the skip N2 group (5-year recurrence-free survival 37.4% vs 5.7%; log-rank $P = .005$; 5-year overall survival 60.7% vs 32.1%; log-rank $P = .024$). The predictive value of skip N2 was more significant in patients with lesions in the right lung (5-year recurrence-free survival 36.6% vs 0.0%; log-rank $P = .002$; 5-year overall survival 57.2% vs 27.9%; log-rank $P = .016$) and in patients whose tumor diameter was no more than 3 cm (5-year recurrence-free survival 43.1% vs 6.7%; log-rank $P = .01$; 5-year overall survival 74.6 vs 27.6%; log-rank $P = .04$).

Conclusions: There are distinct differences in clinicopathologic features and prognosis in patients with or without skip N2 metastasis. Considering the results of our study, subclassifications of mediastinal lymph node metastases could have clinical significance for patients with lung adenocarcinoma. (*J Thorac Cardiovasc Surg* 2015;150:790-5)

RFS and OS of patients with lung adenocarcinoma with or without skip N2 status.

Central Message

Patients with skip N2 metastases have more acinar adenocarcinoma subtypes, well-differentiated metastases, and metastases located in the right lung than patients with non-skip N2. In view of the results of our study, subclassifications of mediastinal lymph node metastases could have clinical significance for patients with lung adenocarcinoma.

Perspective

Skip N2 is not a rare phenomenon in lung adenocarcinoma cases. Patients with skip N2 metastasis have better survival according to former studies and the current work. However, its predictive value for better clinical outcome is stronger in patients with lesions in the right lung and patients whose tumor diameter is no more than 3 cm. In view of our results, skip N2 should not be recognized as a predictor for better survival in all lung adenocarcinoma cases, but in a more specific group of patients.

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the whole world.¹ Pathologic N2 metastasis is defined in NSCLC as metastases to the ipsilateral mediastinal lymph nodes (LNs), and it significantly worsens the prognosis. If a patient is diagnosed with pathologic N2, adjuvant chemotherapy and radiotherapy are recommended by the National Comprehensive Cancer Network guidelines. However, in clinical practice, some patients with NSCLC present mediastinal LN metastases without corresponding peribronchial or ipsilateral hilar region LN involvement, which is called skip N2 metastasis.^{2,3} Skip N2 metastasis occurs in approximately 20% to 30% of patients with NSCLC N2, and it is associated with a favorable prognosis.³⁻⁶ Because mediastinal LN involvement of patients with NSCLC

Abbreviations and Acronyms

ATS	= American Thoracic Society
CI	= confidence interval
ERS	= European Respiratory Society
IASLC	= International Association for the Study of Lung Cancer
LN	= lymph node
NSCLC	= non-small cell lung cancer
OR	= odds ratio
OS	= overall survival
PCR	= polymerase chain reaction
RFS	= recurrence-free survival

influences the multidisciplinary treatment and patients with skip N2 have a remarkably better clinical outcome, it is crucial to distinguish patients with skip N2 from patients with NSCLC with N2 status.

Adenocarcinoma, which has been considered to be associated with skip N2 metastasis,⁷ is the most prevalent pathologic subtype of diagnosed NSCLC. The new classification for lung adenocarcinoma, which was proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS), has been proved to be related to several clinical features,^{8,9} but its effect on skip metastasis has not been discussed. Therefore, we performed this retrospective study on patients with lung adenocarcinoma with or without pathologic skip N2 metastasis, aiming to further elucidate the clinical significance and prognostic value of skip N2.

MATERIAL AND METHODS

Patients

Patients with primary diagnosed NSCLC were consecutively enrolled from September 2009 to September 2011. Inclusion criteria for this study were the following: (1) Patients underwent R0 resection and systematic ipsilateral mediastinal lymphadenectomy; (2) a re-review of the pathologic diagnosis of adenocarcinoma was confirmed by 2 pathologists; (3) each LN was examined with consecutive sections; and (4) patients were proved to have N2 status and received 4-cycle cisplatin-based adjuvant chemotherapy. The stations of N1 and N2 were determined according to the description proposed by the IASLC.¹⁰ Skip N2 was defined as patients with N2 LN metastases without N1 LN involvement. Single N2 was defined as patients who had only 1 station mediastinal LN involvement, and otherwise as multiple N2. Patients who received any neoadjuvant chemotherapy or radiotherapy were excluded (Figure 1). Written informed consent was received from all enrolled patients. This study was approved by the ethics committee in Fudan University Shanghai Cancer Center.

Clinical and Pathologic Features

Clinical and pathologic characteristics, which were collected from the medical history system at the Fudan University Shanghai Cancer Center, included sex, smoking history, age at diagnosis, tumor size and differentiation, lymphovascular and pleura invasion, tumor location, and adenocarcinoma subtypes according to the IASLC/ATS/ERS multidisciplinary

classification.¹¹ Contrast chest computed tomography, brain magnetic resonance imaging, bone emission computed tomography, and abdominal ultrasound were performed for preoperative staging. These examinations were also performed postoperatively to detect local recurrence or metastases in other organs. Patients were contacted every 3 months after the date of diagnosis in clinic or by telephone about disease recurrence and survival information. The median follow-up phase was 48.5 months for the skip N2 group and 52.8 months for the non-skip N2 group. Recurrence-free survival (RFS) was calculated from the date of diagnosis and date of recurrence or last follow-up. Overall survival (OS) was defined as the time elapsed between the date of diagnosis and the date of death or last follow-up.

Mutation and Gene Fusion Analysis

EGFR (exons 18 to 21), *KRAS* (exons 2 to 3), *HER2* (exons 18 to 21), *BRAF* (exons 11 to 15), and *PIK3CA* (exon 9 and exon 20) were amplified by polymerase chain reaction (PCR) using complementary DNA as previously described.⁸ A combined strategy of quantitative real-time PCR and reverse transcriptase PCR was performed to assess *ALK*, *ROS1*, and *RET* fusion, with validation using fluorescence in situ hybridization as previously described.¹²

Statistical Analyses

We adopted Pearson chi-square test or Fisher exact tests to assess the correlations between clinicopathologic variables and patterns of LN metastases. For the characteristics, which were proved to be significantly associated with skip N2 in univariate analysis, binary logistic regression model was used to test their odds ratios (ORs). Survival curves were made using the Kaplan–Meier method. RFS and OS were compared using log-rank test. Cox proportional hazards regression was applied to analyze the ORs of these risk factors including the skip N2 phenomenon (present vs absent), LN metastasis (single station vs multiple stations), tumor size (≤ 3 vs > 3 cm), and lesion location (right vs left), using a likelihood forward stepwise selection model. The statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, Ill). All the tests were 2 tailed.

RESULTS

Patient Characteristics

A total of 177 patients, with tumors ranging from 0.6 to 9 cm, were included. Some 48% of patients had a tumor in the left lung, and 52% of patients had a tumor in the right lung. Lobectomy was performed in 152 patients, wedge resection was performed in 17 patients, sleeve lobectomy was performed in 2 patients, and pneumonectomy was performed in 6 patients. The other characteristics, including sex, age, smoking history, lymphovascular or pleura invasion, lesion location, differentiation, and adenocarcinoma subtypes, are listed in Table 1.

Correlation Between Skip N2 and Clinicopathologic Features

In the 177 patients, skip N2 occurred in 45 (25.4%). Through further comparison of the clinical pathologic variables between skip N2 and non-skip N2 cases, we found a remarkably lower incidence of lymphovascular invasion in those with skip N2 lung adenocarcinoma ($P = .01$). Meanwhile, a lower incidence of pleura invasion was also found in these patients, but it did not reach statistical significance ($P = .07$). We also investigated the association

FIGURE 1. Process of patient enrollment.

between tumor location and LN status. Skip N2 occurred more frequently in patients with a lesion in the right lung ($P = .02$). No remarkable difference was found in age at diagnosis and gender between the 2 categories, or in smoking history and tumor size (Table 2).

According to the IASLC/ATS/ERS multidisciplinary classification of lung adenocarcinoma, we recorded the predominant subtypes of these 177 N2 adenocarcinoma cases. Skip N2 metastasis occurred more frequently in patients with acinar-predominant subtype ($P = .004$), whereas the incidence of non-skip N2 was significantly higher in those with papillary-predominant subtype ($P = .015$). The frequency of skip N2 did not remarkably vary from other adenocarcinoma subtypes (Table 2).

In the 177 patients, 94 (53.1%) *EGFR* mutations and 11 (6.2%) *KRAS* mutations were found. Information on the mutational status of other genes is listed in Table 2. Considering the common driver genes involved in our study, the incidence of molecular alterations did not significantly vary with LN metastases pattern (Table 2).

Correlations between the skip N2 metastasis and the clinicopathologic features were further evaluated by logistic regression analysis, including lymphovascular invasion, differentiation, adenocarcinoma subtype, and lesion location. Absence of lymphovascular invasion (OR, 1.67, 95% confidence interval [CI], 1.04-2.72; $P = .02$), acinar subtype (OR, 2.53, 95% CI, 1.39-4.37; $P = .01$), and right lung cancer (OR, 1.78, 95% CI, 1.16-3.25; $P = .02$) were independently associated with skip N2 metastasis.

Skip N2 and Clinical Prognosis

We further investigated the difference of clinical outcome between patients with skip N2 and non-skip N2.

TABLE 1. Clinicopathologic and molecular features of patients

Variables	No	%
Sex		
Male	96	54.2
Female	81	45.8
Age		
≥60 y	117	66.1
<59 y	60	33.9
Smoking history		
Smoker	75	42.4
Never	102	57.6
Tumor size		
≤3 cm	92	52.0
>3 cm	85	48.0
Lymphovascular invasion		
+	59	33.3
–	118	66.7
Pleura invasion		
+	114	64.4
–	63	35.6
Differentiation		
Well	10	5.6
Moderate	122	68.9
Poor	45	25.4
Adenocarcinoma subtype		
Acinar	74	41.8
Papillary	34	19.2
Solid	50	28.2
IMA	12	6.8
MP	7	4.0
Lesion location		
Left	85	48.0
Right	92	52.0
Left lung		
Upper lobe	53	29.9
Lower lobe	32	18.1
Right lung		
Upper lobe	40	22.6
Middle lobe	16	9.0
Lower lobe	36	20.3

IMA, Invasive mucinous adenocarcinoma; MP, micropapillary.

The RFS and OS were significantly better in the skip N2 group (5-year RFS; 37.4% vs 5.7%; log-rank $P = .005$; 5-year OS; 60.7% vs 32.1%; log-rank $P = .024$) (Figure 2). Skip N2 was found to be a better prognosis predictor in patients with tumor diameter no more than 3 cm (5-year RFS; 43.1% vs 6.7%; log-rank $P = .01$; 5-year OS; 74.6 vs 27.6%; log-rank $P = .04$) (Figure 3, A and B), but it had no predictive significance in patients whose tumor diameter was more than 3 cm. The predictive value of skip N2 was more significant in patients with a lesion in the right lung (5-year RFS; 36.6% vs 0.0%; log-rank $P = .002$; 5-year OS; 57.2% vs 27.9%; log-rank $P = .016$) (Figure 3, C and D). In further comparison, we divided patients into the single station N2 group and

TABLE 2. Clinicopathologic and molecular features of patients with or without skip N2

Variables	Skip N2 (n = 45)	Non-skip N2 (n = 132)	P value
Mean No. of dissected LNs	22.3 ± 3.2	20.7 ± 2.8	.83
Sex			
Male	20 (44.44%)	76 (57.58%)	.127
Female	25 (55.56%)	56 (42.42%)	
Age			
Mean	56.9 ± 1.6	56.1 ± 1.4	.675
≥60 y	32 (71.11%)	85 (64.39%)	.09
<59 y	13 (28.89%)	47 (35.61%)	
Smoking history			
Smoker	17 (37.78%)	58 (43.94%)	.47
Never	28 (62.22%)	74 (56.06%)	
Tumor size			
Mean	3.56 ± 0.25	3.57 ± 0.15	.96
≤3 cm	25 (55.56%)	67 (50.76%)	.578
>3 cm	20 (44.44%)	65 (49.24%)	
Lymphovascular invasion			
+	8 (17.78%)	51 (38.64%)	.01*
−	37 (82.22%)	81 (61.36%)	
Pleura invasion			
+	24 (53.33%)	90 (68.18%)	.078
−	21 (46.67%)	42 (31.82%)	
Mutational status			
<i>EGFR</i>	25 (55.56%)	69 (52.27%)	.703
<i>KRAS</i>	3 (6.67%)	8 (6.06%)	.884
<i>HER2</i>	3 (6.67%)	5 (3.79%)	.421
<i>BRAF</i>	1 (2.22%)	3 (2.27%)	1
<i>ALK</i>	0 (0%)	5 (3.79%)	.331
<i>ROS1</i>	0 (0%)	3 (2.27%)	.572
<i>RET</i>	0 (0%)	5 (3.79%)	.331
Pan-negative	13 (28.89%)	34 (25.76%)	.699
Differentiation			
Well	7 (15.56%)	3 (2.27%)	.003*
Moderate	27 (60.00%)	95 (71.97%)	.134
Poor	11 (24.44%)	34 (25.76%)	.861
Adenocarcinoma subtype			
Acinar	27 (60.00%)	47 (35.61%)	.004*
Papillary	3 (6.67%)	31 (23.48%)	.015
Solid	11 (24.44%)	39 (29.55%)	.512
IMA	4 (8.89%)	8 (6.06%)	.504
MP	0 (0%)	7 (5.30%)	.194
Lesion location			
Left	15 (33.33%)	70 (53.03%)	.022*
Right	30 (66.67%)	62 (46.97%)	
Left lung			
Upper lobe	12 (80%)	41 (58.57%)	.15
Lower lobe	3 (20%)	29 (41.43%)	
Right lung			
Upper lobe	14 (46.67%)	26 (41.94%)	.668
Middle lobe	7 (23.33%)	9 (14.52%)	.296
Lower lobe	9 (30%)	27 (43.54%)	.212

LN, Lymph node; IMA, invasive mucinous adenocarcinoma; MP, micropapillary.

*Compared with all the other cases.

multiple stations N2 group. Patients who had skip single N2 metastasis had the best clinical outcome in the 4 groups (5-year RFS; 34.4%; log-rank $P = .001$; 5-year OS; 64.3%; log-rank $P = .006$) (Figure 3, E and F). We also investigated the predictive significance of lung adenocarcinoma subtype in the N2 group. No remarkable difference was found between patients with different subtypes (log-rank $P = .179$). In multivariate analysis, skip N2 retained its predictive significance for better RFS (OR, 0.493; 95% CI, 0.314-0.773, $P = .002$), but had no significance for predicting OS. Single N2 metastasis also was an independent predictor for better RFS (OR, 0.346; 95% CI, 0.128-0.633, $P = .001$) and OS (OR, 0.429; 95% CI, 0.237-0.751, $P = .004$).

DISCUSSION

In the last decade, a number of studies have reported that the incidence of skip N2 in patients with NSCLC N2 ranges from 19.5% to 36%.¹³⁻¹⁵ Skip N2 seems to be an important subgroup of N2 cases, because it is not a rare phenomenon in NSCLC and patients with skip N2 were proved to have different clinical features and outcome.^{16,17} In this series, we investigate the clinical variables associated with patients with lung adenocarcinoma having skip N2. To the best of our knowledge, there is no similar study that has revealed the association between adenocarcinoma subtypes and skip N2 metastasis.

In our study, we found that the frequency of skip N2 in patients with acinar- predominant adenocarcinoma was remarkably high, and in those with papillary- predominant subtype it was significantly low. In previous work,¹⁸ we demonstrated the association between papillary subtype and lymphovascular invasion. Hilar LNs may be involved first through lymphovascular invasion, and this finding may explain the higher incidence of continuous N2 metastasis in the papillary predominant subtype. Warth and colleagues¹⁹ revealed that pathologic N2 status correlated with the acinar subtype of lung adenocarcinoma. In our series, 36.5% of acinar cases were skip N2 status, which is significantly higher than the overall incidence of skip N2 in other adenocarcinoma subtypes. No previous study has focused on the correlation between acinar subtype and skip N2 metastasis.

We further investigated the relationship between lesion location and skip N2 phenomenon. In this series, we found a higher incidence of skip N2 in right lung cancer, but there was no association between upper, middle, and lower right lobe cancer and skip N2. Riquet and colleagues²⁰ investigated the lymphatic drainage of different sides of lung to the mediastinal LNs in cadavers. Similar percentages of direct drainage occurrence to the mediastinal nodes were found in the right and left lungs. Some investigations

FIGURE 2. RFS and OS of patients with lung adenocarcinoma with or without skip N2 status.

performed in patients showed a higher occurrence rate of direct drainage in the right lung.^{21,22} Our current results also verified this difference of lymphatic drainage between right and left lung cancers. This result

emphasized the need for complete dissection of the mediastinal LNs in right lung adenocarcinoma, and no enlarged hilar LNs were found in the preoperative imaging examinations.

FIGURE 3. RFS (A) and OS (B) of patients with tumor diameter no more than 3 cm with or without skip N2 status. RFS (C) and OS (D) of patients with right lung cancer with or without skip N2 metastasis. RFS (E) and OS (F) of patients with single or multiple N2 metastasis. *mN2*, Multiple stations N2 metastasis; *sN2*, single station N2 metastasis.

Many previous studies have demonstrated a favorable prognosis of patients with skip N2.^{3,23,24} The results of our series also confirmed these findings, especially in patients whose tumor diameter was no more than 3 cm. When classifying the patients by lesion location, the predictive value of skip N2 is more significant in right lung adenocarcinoma. Considering these results, skip N2 should be taken as a predictor for a better prognosis in particular subgroups of patients. However, further perspective investigations could be performed to demonstrate the prognostic significance of skip N2 phenomenon in patients with lung adenocarcinoma.

Study Limitations

Our work is a retrospective study, and the number of patients with skip N2 is relatively small. With continuous collection of patients and clinical data, more detailed and precise results may be revealed in the future. A randomized trial should be designed to validate the findings of our work.

CONCLUSIONS

We found that the incidence of skip N2 was significantly associated with acinar subtype, lesion location in the right lung, and good differentiation in patients with lung adenocarcinoma. There was also a distinct clinical prognosis between patients with or without skip N2 metastasis. In view of the results of our study and previous investigations, subclassifications of mediastinal LN metastases could have clinical significance for patients with lung adenocarcinoma.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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