Original Study

Role of Skip Mediastinal Lymph Node Metastasis for Patients With Resectable Non—small-cell Lung Cancer: A Propensity Score Matching Analysis

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Abstract

Stage N2 non—small-cell lung cancer shows prognostic heterogeneity. We investigated the prognostic relevance of skip N2 in patients with N2 non—small-cell lung cancer using propensity score matching. Skip N2 was significantly associated with the better survival outcomes in patients with a tumor size ≤ 3 cm or with single N2 station involvement. Subgroups of patients with stage N2 disease may improve the accuracy of prognostic prediction.

Background: N2 disease represents a heterogeneous group of non—small-cell lung cancer (NSCLC) with varying 5-year overall survival (OS) rates. The skip N2 phenomenon is quite frequent, and its prognostic impact remains a matter of debate. The aim of this study is to further assess the clinical significance and prognostic value of skip N2 disease using propensity score matching. **Patients and Methods:** The study cohort included 437 patients with stage pN2 NSCLC who underwent resection from 2005 to 2011. Differences in clinicopathologic characteristics were identified in the overall cohort. The effect of skip N2 on OS was assessed, stratified by histology, tumor size, N2 involved stations, and T stage after propensity score matching. **Results:** A total of 130 patients had skip N2 diseases in our study. Skip N2 metastasis was associated with age, tumor size, histology, and number of involved N2 stations. Matching of 130 pairs of patients showed that skip N2 was associated with a significantly better 5-year OS rate when compared with non-skip N2 disease (42.7% vs. 25.3%; $P = .004$), and OS is significantly better in the patients with tumor size of ≤ 3 cm ($P = .014$) or patients with single N2 station involvement ($P = .002$). Skip N2 conferred a significantly better OS in stage IIIA ($P = .026$) and IIIB ($P = .029$) disease. **Conclusion:** The presence of skip N2 metastasis was a good prognostic factor of resectable N2 disease. N2 disease may be classified into more subgroups in the revision of the current tumor-lymph node-metastasis (TNM) system.

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Introduction

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer-related death.[1] The 5-year overall survival (OS) rates of patients with lung cancer remain low because most cases are diagnosed at an advanced stage. The TNM stage is closely associated with the treatment outcome and prognosis of

non—small-cell lung cancer (NSCLC). Mediastinal nodal involvement is one of the most important factors for staging according to the TNM staging system. Patients with positive mediastinal lymph nodes (N2) found in approximately 20% to 40% of patients with NSCLC are classified as stage IIIA or an even later stage regardless of N1 lymph node involvement or not.[2] Some researchers suggested that pN2-NSCLC may include various subgroups of different prognoses.[3,4] And several factors have been proposed for the prognosis of resected pN2-NSCLC.[5-7] Many studies indicated that prognosis was better in skip N2 metastasis (pN1−/pN2+) than in non-skip N2 metastasis (pN1+/pN2+) patients, suggesting that the current TNM classification regarding N status is challenging. It is quite important to identify homogeneous subgroups of N2 patients according to prognosis to clarify N2 patients who can benefit

from radical resection. However, it is difficult to clarify the role of skip N2 in patients with NSCLC, because the distribution of clinical characteristics was significantly different between the skip N2 and non-skip N2 groups in previous studies. The aim of the present study was to elucidate the clinical significance and prognostic value of skip N2 metastasis using propensity score matching (PSM).

Patients and Methods

Approval

The study protocol was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Shanghai, China), and written informed consent was obtained from every study participant.

Patient Selection

The medical records of patients with primary lung cancer who were treated in the Department of Thoracic Surgery of Zhongshan Hospital, Fudan University, from January 2005 to March 2011 were retrospectively reviewed. Patients with NSCLC who underwent pulmonary surgical resection with systemic lymphadenectomy and were staged as pN2 were included in this study. Patients with preoperative neoadjuvant chemotherapy or radiation therapy, incomplete resection, and no systematic mediastinal lymphadenectomy were excluded. The pathologic stage of these patients were reevaluated according to the eighth edition of the American Joint Committee on Cancer TNM staging.

Classification of Lymph Nodes

Standard lobectomy or pneumonectomy with systemic lymphadenectomy was performed for all patients. The criteria for systemic lymphadenectomy were in accordance with the European Society of Thoracic Surgeons guidelines, which recommend that at least 3 mediastinal nodal stations (always including the subcarinal nodes) should be excised and beside the mediastinal nodes, the hilar and intrapulmonary lymph nodes should also be dissected. The skip N2 group included patients with metastasized pN2 nodes without positive pN1 nodes. The non-skip N2 group included those patients with both pN1 and pN2 metastasis. N2 patients were also divided into 2 groups according to the number of positive pN2 stations: single positive station group and multiple positive stations group.

Follow-up and Data Collection

Preoperative, perioperative, and postoperative details were recorded for all cases. Follow-up evaluations were performed every 3 months for the first 2 years after surgical intervention and every 6 months thereafter. OS data were updated based on information obtained from telephone interviews, mail, or direct outpatient clinical visits. The follow-up endpoint was the date of death or March 30, 2016.

Statistical Analysis

All analyses were performed with SPSS 22.0 statistical software (IBM Corporation, Armonk, NY) and R software version 3.0.0 (R Foundation for Statistical Computing, Vienna, Austria). PSM was conducted with R software using the "MatchIt" package to reduce differences among baseline variables between groups. Age, gender, smoking status, surgical type, surgical procedure, tumor size,

histology, pleural involvement, tumor location, number of positive N2 stations, T stage, and use of adjuvant therapy were included in PSM. Patients were matched on the basis of PSM via the greedy nearest-neighbor method. The matching ratio was 1:1. The caliper used for matching was set at 0.1. Categorical variables were compared using the Fisher exact test and Pearson χ^2 test. Binary logistic regression analysis was performed to identify predictors for skip metastasis. The Kaplan-Meier method with the log-rank test was used to compare OS curves. The Cox proportional hazards regression model was applied to perform univariate and multivariate analyses, and those variables that achieved statistical significance in univariate analysis were entered into the multivariable analysis. All statistical tests were 2-sided, and a probability (P) value of < .05 was considered statistically significant.

Results

As shown in Figure 1, a total of 437 patients were enrolled in this study, which included 130 (29.7%) with skip N2 diseases and 307 (70.3%) with non-skip N2 diseases. There were no differences in surgical type, surgical procedure, pleural involvement, tumor location, T stage, or use of adjuvant therapy between the 2 groups. Patients in the skip N2 group were older ($P = .036$) and more likely to be male ($P = .030$) with a smaller tumor size ($P = .029$). The number of positive pN2 stations was significantly higher in the non-skip N2 group ($P < .001$), and there were more smokers ($P = .007$) and patients with squamous cell carcinoma (SCC) ($P = .020$) in the skip N2 group. The baseline clinical characteristics before PSM are shown in Table 1. Multivariate logistic analysis was performed to identify potential predictors of skip N2 lymph node metastasis. As shown in Table 2, older age ($P = .036$), smaller tumor size ($P = .001$), and SCC ($P = .016$) were independent predictors for skip N2 lymph node metastasis. The presence of skip N2 was significantly associated with a better survival ($P = .001$) compared with the non-skip N2 group in the overall cohort before matching, as shown in Supplemental Figure 1 (in the online version).

After PSM, 130 matched patients from the non-skip N2 group and 130 from the skip N2 group were included in the final analysis.

Figure 1 — The Study Flow Diagram of the Selection Process
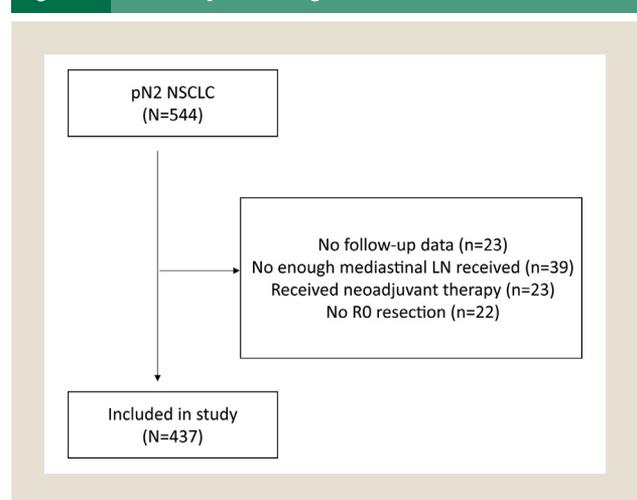
Abbreviations: LN = lymph node; NSCLC = non—small-cell lung cancer.

Table 1 Patient Characteristics According to the Status of Skip N2 Before and After PSM

Variable	Before Matching			After Matching		
	Skip N2, n (%)	Non-skip N2, n (%)	P	Skip N2, n (%)	Non-skip N2, n (%)	P
Age, y			.036			.263
≤60	66 (50.8)	189 (61.6)		66 (50.8)	75 (57.7)	
>60	64 (49.2)	118 (38.4)		64 (49.2)	55 (42.3)	
Gender			.030			.884
Male	100 (76.9)	204 (66.4)		100 (76.9)	99 (76.2)	
Female	30 (23.1)	103 (33.6)		30 (23.1)	31 (23.8)	
Smoking status			.007			.619
Never	68 (52.3)	203 (66.1)		68 (52.3)	72 (55.4)	
Ever	62 (47.7)	104 (33.9)		62 (47.7)	58 (44.6)	
Surgical procedure			.929			.966
Lobectomy	102 (78.5)	242 (78.8)		102 (78.5)	99 (76.2)	
Pneumonectomy	12 (9.2)	25 (8.2)		12 (9.2)	13 (10.0)	
Bilobectomy	10 (7.7)	28 (9.1)		10 (7.7)	12 (9.2)	
Sleeve lobectomy	6 (4.6)	12 (3.9)		6 (4.6)	6 (4.6)	
Surgical type			.766			.424
VATS	16 (12.3)	41 (13.4)		16 (12.3)	12 (9.2)	
Open	114 (87.7)	266 (86.6)		114 (87.7)	118 (90.8)	
Tumor size, cm			.029			.304
≤3	52 (40.0)	90 (29.3)		52 (40.0)	44 (33.8)	
>3	78 (60.0)	217 (70.7)		78 (60.0)	86 (66.2)	
Number of N1 lymph nodes	7.35 ± 3.79	7.82 ± 3.83	.238	7.35 ± 3.79	7.56 ± 3.80	.648
Histology			.020			.410
Squamous cell carcinoma	59 (45.4)	97 (31.6)		59 (45.4)	55 (42.3)	
Adenocarcinoma	62 (47.7)	189 (61.6)		62 (47.7)	70 (53.8)	
Others	9 (6.9)	21 (6.8)		9 (6.9)	5 (3.9)	
Pleural involvement			.506			.796
No	84 (64.6)	188 (61.2)		84 (64.6)	82 (63.1)	
Yes	46 (35.4)	119 (38.8)		46 (35.4)	48 (36.9)	
Tumor location			.446			.500
Central	19 (14.6)	54 (17.6)		19 (14.6)	23 (17.7)	
Peripheral	111 (85.4)	253 (82.4)		111 (85.4)	107 (82.3)	
Involved N2 stations			<.001			.202
1	85 (65.4)	156 (50.8)		85 (65.4)	92 (70.8)	
2	40 (30.8)	81 (26.4)		40 (30.8)	29 (22.3)	
3 or more	5 (3.8)	70 (22.8)		5 (3.8)	9 (6.9)	
T stage			.615			.358
1	28 (21.5)	50 (16.3)		28 (21.5)	24 (18.5)	
2	59 (45.4)	150 (48.8)		59 (45.4)	67 (51.5)	
3	29 (22.3)	69 (22.5)		29 (22.3)	20 (15.4)	
4	14 (10.8)	38 (12.4)		14 (10.8)	19 (14.6)	
Adjuvant treatment			.158			.352
No	14 (10.8)	49 (16.0)		14 (10.8)	19 (14.6)	
Yes	116 (89.2)	258 (84.0)		116 (89.2)	111 (85.4)	

Abbreviations: PSM = propensity score matching; VATS = video-assisted thoracoscopic surgery.

The distribution of clinical parameters included in PSM is shown in Table 1. The distribution of baseline patient characteristics was well-balanced between the 2 groups after PSM.

The OS curves of patients after matching the skip N2 and non-skip N2 groups are shown in Figure 2. The presence of skip N2 was significantly associated with a better 5-year OS rate (42.7% vs.

Table 2 Multivariable Analysis of Predictors of Skip N2 in the Unmatched Overall Cohort

Variable	HR	95% CI	P
Age, y			
≤60	Reference		
>60	1.583	1.030-2.413	.036
Gender			
Male	1.190		
Female	Reference	0.668-2.120	.555
Smoking status			
Never	Reference		
Ever	1.505	0.916-2.473	.107
Tumor size, cm			
≤3	Reference		
>3	0.457	0.285-0.731	.001
Histology			
Squamous cell carcinoma	1.842		.055
Adenocarcinoma	Reference	1.120-3.031	.016
Others	1.431	0.607-3.375	.413

Abbreviations: CI = confidence interval; HR = hazard ratio.

Figure 2 Kaplan-Meier Curves Comparing Overall Survival Stratified by Skip N2 Status for the Propensity Score Matching Cohort

25.3%; *P* = .004). Furthermore, subgroup analysis was conducted to better characterize the relationship between pN2 status and its affecting factors. Comparisons of OS curves are shown in Figure 3. Skip N2 with a tumor size ≤ 3 cm (60.7% vs. 36.5%; *P* = .014) or single pN2 station involvement (47.8% vs. 25.6%; *P* = .002) was associated with significantly better OS. However, there was no significant difference between the 2 groups in the incidence of multiple pN2 stations involvement (*P* = .527) or tumor size of > 3 cm (*P* = .193). The 5-year OS rate was significantly better in the skip N2 group regardless of a diagnosis of SCC (38.5% vs. 18.6%; *P* = .032) or adenocarcinoma (48.3% vs. 31.3%; *P* = .032) (see Supplemental Figure 2 in the online version). As compared with the non-skip N2 group, the OS rate of skip N2 patients was significantly better in the stage IIIA (T1/T2) group (48.0% vs. 31.0%; *P* = .026) and stage IIIB (T3/T4) group (31.9% vs. 12.4%; *P* = .029) (see Supplemental Figure 3 in the online version).

Univariate analysis of predictors of OS showed that male gender (*P* = .003), smoking history (*P* = .001), bilobectomy (*P* = .009), larger tumor size (*P* < .001), SCC (*P* = .033), non-skip N2 metastasis (*P* = .005), and later T stage (*P* < .001) were associated with poorer prognosis. In multivariable analysis, smoking history (*P* = .002), presence of skip N2 (*P* = .006), and later T stage (*P* = .026) remained independent prognostic factors (Table 3).

Discussion

Pathologic N2 involvement is a wide range of disease that is important in the management of NSCLC. Skip N2 accounts for about 30% of patients with pN2 diseases.[3] Several previous studies showed better prognosis in skip N2 patients than non-skip N2 patients.[3,8] However, how to classify pN2 disease has been a topic of investigation for decades. Recently, the International Association for the Study of Lung Cancer proposed that skip N2 should be considered as a new pN subclassification because of its better
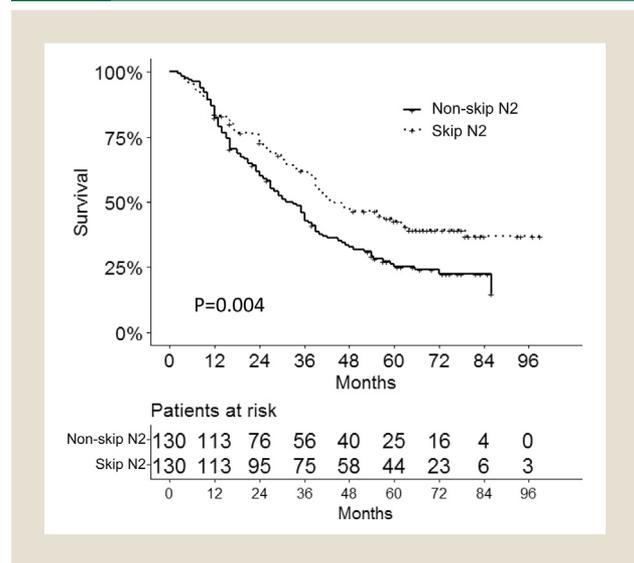
survival in pN2 patients.[9,10] However, obvious baseline differences usually exist between the skip N2 group and non-skip N2 group in previous studies. It is hard for the researchers to conclude that the better survival of skip N2 patients than non-skip N2 patients is related to the biological feature.

Some studies had focused on the clinical characteristics associated with skip N2 metastasis.[11,12] The results of the present study showed that skip N2 was more frequent in older, male, smoking patients, and was also significantly associated with SCC. The further study of logistic regression analysis showed that age > 60 years and SCC were independent predictors of skip N2. However, the correlation between histology and skip N2 remains controversial. Most studies showed there was no difference in the incidence of skip N2 metastasis according to NSCLC histology.[13] Few authors have suggested that SCC was more likely to be associated with skip N2 metastasis.[8,14] Although the cause remains a matter of debate, there are various hypotheses about the mechanism on skip N2 metastasis. Previous studies concluded that skip N2 was a biological feature of tumor cells or lymph nodes.[8] And anatomical studies showed direct lymphatic drainage from the lung segments to the mediastinal lymph nodes,[15] and mediastinal lymph nodes directly metastasized through lymphatic vessels of the parietal pleura.[16] There are several studies that tried to explain the mechanism about the relationship between skip N2 metastasis and adenocarcinoma. A recent report suggested that epidermal growth factor receptor mutations were significantly more frequent in skip N2 adenocarcinoma,[17] whereas a previous study of an Asiatic cohort found no correlation between hot-spot mutations (epidermal growth factor receptor and KRAS) and the skip N2.[18] In our study, we found that SCC is more associated with skip N2 disease. We hypothesize that SCC often originates from the larger airway than the alveolar, and its lymphatic return pathway may not be completely similar to other lung cancer types, leading to SCC that may directly transfer to the N2 lymph nodes without passing

Figure 3 Kaplan-Meier Curves Comparing Overall Survival Stratified by Skip N2 Status for Patients With a Tumor Size of ≤ 3 cm (A) or > 3 cm (B) After Matching. Kaplan-Meier Curves Comparing Overall Survival Stratified by Skip N2 Status for Patients With Single N2 Station (C) or Multiple N2 Stations Involvement (D) After Matching
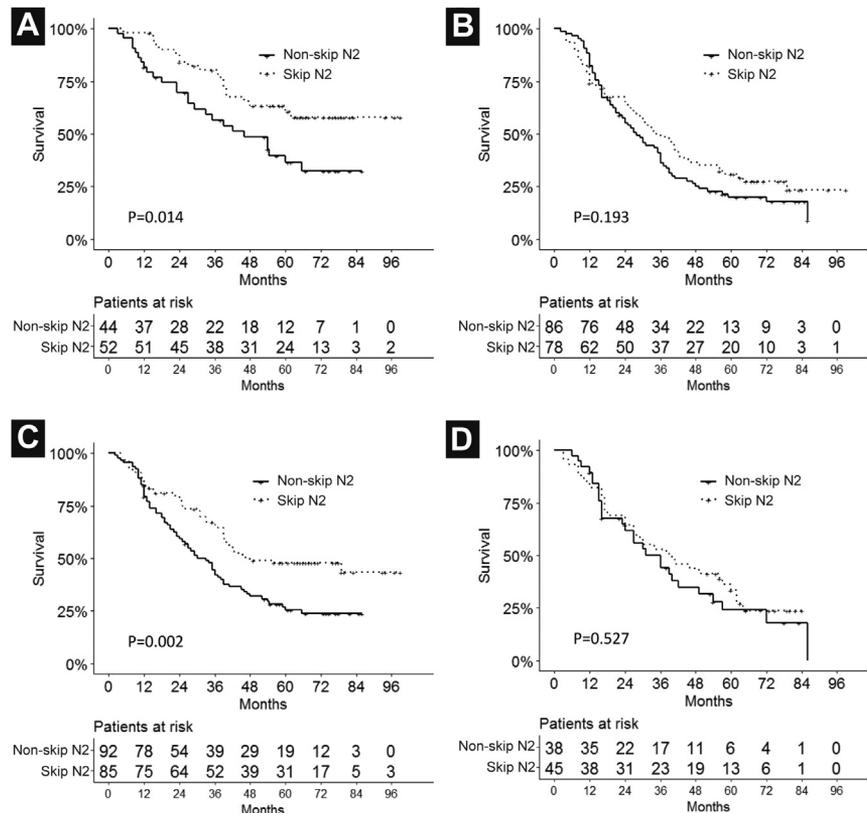
through the hilum area. It might be concluded that skip N2 was a biological feature of squamous lung carcinoma cells. However, no study has focused on the cause of skip N2 metastasis and the underlying molecular mechanism in SCC. Hence, further investigations are warranted to investigate the cause of the higher incidence of skip N2 in SCC. Another variable found to be significantly associated with skip N2 metastasis in this study was tumor size. Few studies have addressed the correlation between tumor size and skip N2. Riquet et al[11] reported that skip N2 was more frequent in tumors larger than 5 cm in diameter. However, there were more tumors with a diameter less than 3 cm found in the skip N2 group in our study, and the logistic regression analysis results showed that increasing tumor size was associated with a decreased risk of skip N2. These findings suggested that skip N2 may be in the early stages of metastasis. We hypothesized that increased tumor size significantly enhanced tumor burden in the original site as well as lymphatic flow. Because the incidence of hilar lymph nodes metastasis was increased in cases with a larger tumor size, the occurrence of skip N2 metastasis decreased as well. Mediastinal lymph node dissection cannot be ignored even if the tumor is small, because skip N2 was more common in small size tumors. Our previous study addressed the incidence of skip metastasis in clinical stage IA lung cancer.[19] All the findings

showed the necessity of complete mediastinal lymph node dissection in small-cell lung cancer for precise staging.

The role of skip N2 metastasis remains controversial. A number of studies suggested better OS of skip N2 disease than non-skip N2 disease,[8,20] whereas others found no significant difference in 5-year OS rates between the 2 groups.[21,22] And a recent study reported that skip N2 disease may increase the risk of distant or disseminated metastasis.[23] However, the conclusions of all these reports should be accepted with caution because the distribution of some clinical characteristics was significantly different between the skip N2 and non-skip N2 groups. The distribution of gender, age, smoking status, tumor size, and histology was also significantly different between the 2 groups in the present study. In particular, the number of involved N2 stations was significantly higher in the non-skip N2 group. The better OS of skip N2 patients is usually attributed to the lower frequency of multiple N2 station involvement.[8] The improved prognosis of a single positive N2 station compared with involvement of multiple N2 stations has been reported by previous studies.[3] Therefore, we cannot exclude the effect of good skip N2 prognosis as a different distribution of variables, because it is difficult to conduct randomized controlled trials to verify the role of skip N2. Thus, we adjusted multiple sources of bias, including the number of N2 station involvement, by PSM. To

Table 3 Univariate and Multivariate Analyses of OS in the Cohort After PSM

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y						
≤60	Reference					
>60	1.249	0.924-1.688	.148			
Gender						
Male	1.770			1.215		
Female	Reference	1.209-2.592	.003	Reference	0.769-1.920	.403
Smoking status						
Never	Reference			Reference		
Ever	1.685	1.245-2.281	.001	1.643	1.197-2.255	.002
Surgical procedure			.051			.235
Lobectomy	Reference			Reference		
Pneumonectomy	1.320	0.805-2.167	.272	0.779	0.431-1.409	.540
Bilobectomy	1.915	1.180-3.109	.009	1.492	0.875-2.543	.142
Sleeve lobectomy	0.913	0.426-1.955	.814	0.757	0.339-1.689	.496
Surgical type						
VATS	Reference					
Open	1.575	0.927-2.678	.093			
Tumor size, cm						
≤3	Reference			Reference		
>3	2.071	1.475-2.909	<.001	1.449	0.926-2.268	.105
Histology						.663
Squamous cell carcinoma	1.405		.056	0.839	0.556-1.266	.403
Adenocarcinoma	Reference	1.029-1.918	.033	Reference		
Others	1.669	0.887-3.139	.112	1.028	0.523-2.019	.936
Pleural involvement						
No	Reference					
Yes	1.072	0.784-1.466	.663			
Tumor location						
Central	Reference			Reference		
Peripheral	0.640	0.439-0.933	.020	0.890	0.555-1.428	.630
Involved N2 stations			.322			
1	Reference					
2	1.284	0.923-1.787	.138			
3 or more	0.991	0.483-2.032	.981			
Skip N2						
No	Reference			Reference		
Yes	0.646	0.477-0.876	.005	0.645	0.473-0.881	.006
T stage			<.001			.026
1	Reference			Reference		
2	1.821	1.139-2.913	.012	1.432	0.792-2.588	.235
3	2.180	1.270-3.742	.005	1.556	0.798-3.034	.195
4	3.971	2.268-6.956	<.001	2.584	1.287-5.190	.008
Adjuvant treatment						
No	Reference					
Yes	0.676	0.448-1.020	.062			

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PSM = propensity score matching; VATS = video-assisted thoracoscopic surgery.

the best of our knowledge, this study is the first PSM analysis in effect of skip N2 on OS in patients with resectable NSCLC.

In the data after PSM, the distribution of characteristics was well-balanced between the 2 groups. We found that the presence of skip N2 had a positive impact on OS. Thus, we conclude that the better survival of skip N2 disease was owing to the pathologic or biological features other than fewer N2 stations involvement than non-skip N2 disease. We then conducted further subgroup analysis to get more data about the role of skip N2. The prognosis of a single positive N2 station between the skip N2 and non-skip N2 groups remains contradictory; some studies reported that there was no significant difference in the 5-year OS rates between the 2 groups,[8] whereas Riquet et al reported a significant difference in OS in their study.[11] The results of the present study demonstrated that the prognosis of patients with a single positive N2 station was better in the skip N2 group, whereas there was no significant difference in the 5-year OS rates in multiple N2 station-involved diseases between the skip N2 and non-skip N2 groups. The current results again supported the eighth edition of the American Joint Committee on Cancer TNM staging system, which includes the breakdown of N2 into N2a1 (skip single station involved), N2a2 (non-skip single station involved), and N2b (multiple stations involved). The new subclassification is the first landmark proposal that specified the significance of multiplicity of involved N2 stations and the presence of skip metastasis after surgery. The skip single station involved patients showed significantly better survival among N2 patients. Our finding suggested that these patients should be carefully selected and that surgery might be an optimal treatment for these patients. Although multiple station-involved patients did not show significant difference according to the presence of skip N2 metastasis, this may be owing to the small number of patients with multiple N2 stations metastases in our study, and the prognosis of these patients is extremely poor, resulting in no significant difference between the 2 groups. We should include more patients to make sure the influence of skip N2 in multiple N2 stations involved diseases. Other subgroups were also analyzed in our study. The prognosis of the skip N2 group was significantly better in patients with a tumor size $\leq$ 3 cm, but not significantly different with a tumor size > 3 cm. Li et al[18] found skip N2 was associated with better survival than non-skip N2 in adenocarcinoma less than 3 cm. We supposed that N2 disease with multiple stations involvement or tumor size > 3 cm is associated with heavy tumor burden and poor prognosis. Thus, the positive influence of skip N2 on the OS of these patients would be relatively mild. Further research with a larger scale of cases are needed to verify this issue.

Limitations of the present study should be noted, including the retrospective nature of the analysis and the limited number of cases from a single center. Another limitation should also be addressed that no clear boundary of the nodes was indicated around the main bronchus. Although PSM was used to reduce potential bias, these limitations might have influenced the results of this study, in spite of the skip N2 and OS rates in this study being consistent with those in previous reports. Also, the data collection period (2005 to 2011) was relatively short. Nonetheless, the consistency of preoperative assessment, surgical technique, and homogeneous postoperative treatment was adequate. Further multi-center, prospective studies are warranted to clarify the influence of skip N2 on the prognosis of N2 disease.

Conclusions

In conclusion, the presence of skip N2 metastasis was a good prognostic factor of resected N2-involved patients, and the survival is significantly better in the subgroup with a tumor size of $\leq$ 3 cm or single N2 station involvement. N2 disease may be classified into more subgroups in the revision of the current TNM system similar to the new pN subclassifications proposed in the eighth edition of the TNM classification.

Clinical Practice Points

- N2 disease represents a heterogeneous group with varying 5-year OS rates in NSCLC. Although skip N2 has to be considered as a new pN-sub-classification, the prognostic impact of skip N2 phenomenon remains a matter of debate.
- The aim of this study was to further assess the clinical significance and prognostic value of skip N2 disease using PSM.
- The findings indicated that skip N2 metastasis was associated with age, tumor size, histology, and number of involved N2 stations. Matching of 130 pairs of patients showed that skip N2 was associated with a significantly better 5-year OS rate (42.7% vs. 25.3%; $P = .004$), and the survival is significantly better in the subgroup with a tumor size of $\leq$ 3 cm ($P = .014$) or with single N2 station involvement ($P = .002$).
- According to our research, N2 disease may be classified into more subgroups in the revision of the current TNM system. Skip N2 was related to prognosis and is valuable to subdivide N2 patients, similar to new pN subclassifications proposed in the eighth edition of the TNM classification.

Acknowledgments

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures and accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.12.007.

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Supplemental Figure 1	Kaplan-Meier Curves Comparing Overall Survival Stratified by Skip N2 Status for the Unmatched Cohort
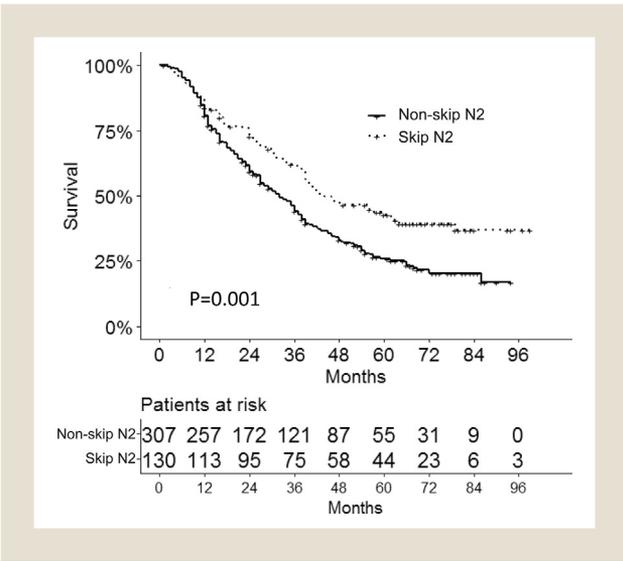
Supplemental Figure 2	Kaplan-Meier Curves Comparing Overall Survival Stratified by Skip N2 Status for Patients With Squamous Cell Carcinoma (A) or Adenocarcinoma (B) After Matching
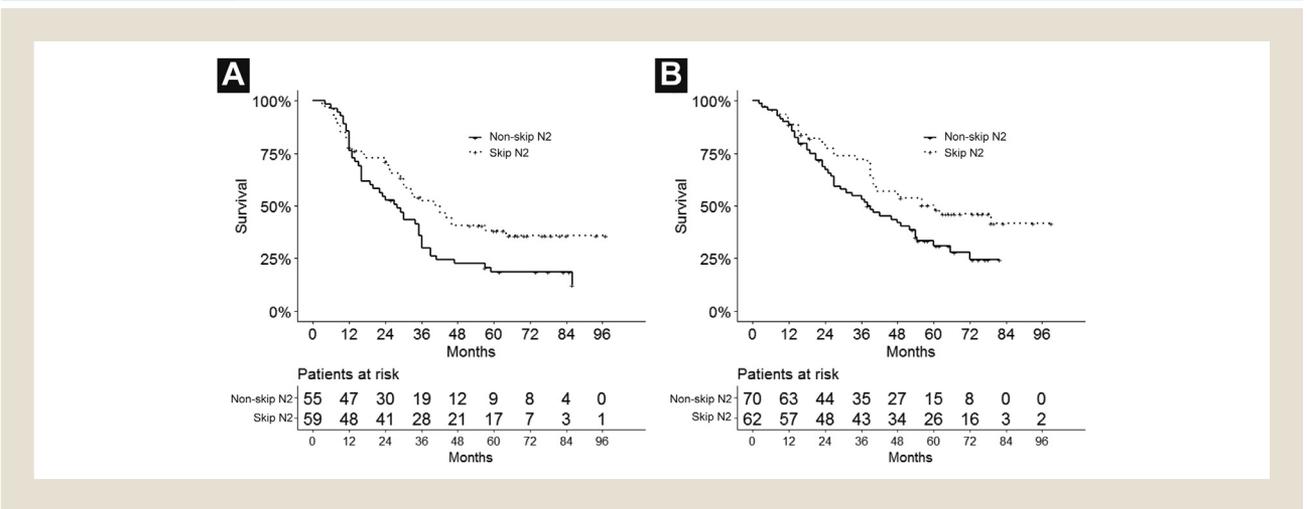
| Supplemental Figure 3 | Kaplan-Meier Curves Comparing OS Stratified by Skip N2 Status for Patients With Stage IIIA (A) or IIIB (B) Disease After Matching |