Ann Thorac Cardiovasc Surg 2021; 27: 304–310
Online March 31, 2021
doi: 10.5761/atcs.oa.20-00289

Original Article

The Significance of Skip Mediastinal Lymph Node Metastasis in the Prognosis of Patients with Resected Non-Small-Cell Lung Carcinoma: Is It Really a Better N2 Disease Subtype?

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Objective: In this study, we aimed to reveal the prognostic differences between skip and non-skip metastasis mediastinal lymph node (MLN) metastasis.
Methods: A total of 202 patients (179 males and 23 females; mean age, 59.66 ± 9.89 years; range: 29–84 years) who had ipsilateral single-station MLN metastasis were analyzed in two groups retrospectively between January 2009 and December 2017: "skip ipsilateral MLN metastasis" group (sN2) (n = 55,27.3%) [N1(–), N2(+)], "non-skip ipsilateral MLN metastasis" group (nsN2) (n = 147,72.7%) [N1(+), N2(+)].
Results: The mean follow-up was 42.63 ± 34.91 months (range: 2–117 months). Among all patients, and in the sN2 and nsN2 groups, the median overall survival times were 63.5 ± 4.56, 68.8 ± 7, and 59.3 ± 5.35 months, respectively, and the 5-year overall survival rates were 38.2%, 46.3%, and 36.4%.
Conclusion: Skip metastasis did not take its rightful place in TNM classification; thus, further studies will be performed. To detect micrometastasis, future studies on skip metastasis should examine non-metastatic hilar lymph nodes (LNs) through staining methods so that heterogeneity in patient groups can be avoided, that is, to ensure that only true skip metastasis cases are included. Afterwards, more accurate and elucidative studies on skip metastasis can be achieved to propound its prognostic importance in the group of N2 disease.

Keywords: single-station N2 disease, skip metastasis, micrometastasis, lung cancer

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Received: September 10, 2020; Accepted: November 18, 2020
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Introduction

Pulmonary resection can be performed in 10–20% of patients who are diagnosed with lung cancer, for which it is the most effective treatment.[1)] The histopathological status of the mediastinal lymph nodes (MLNs) is one of the most important factors for estimating the prognosis of non-small-cell lung cancer (NSCLC). MLN metastasis (N2) is an adverse prognostic factor.[2)] N2 disease without involvement of the pulmonary or hilar lymph nodes (LNs; N1) is known as skip metastasis.[3)] N2 skip metastasis is considered a subtype of N2 disease with a better prognosis. In this study, we analyzed patients with single-station N2 who underwent resection due to NSCLC and aimed to reveal the prognostic differences between skip and non-skip metastasis.

Materials and Methods

After obtaining the local ethics committee approval (2017.8/4-72), we gathered the data of 2582 patients who underwent pulmonary resection for NSCLC at our institution between January 2009 and December 2017. The surgical procedure was complete curative resection combined with hilar and mediastinal lymphadenectomy. Patients with carcinoid tumors, as well as those who had undergone preoperative neoadjuvant chemotherapy or radiotherapy and those with extrapulmonary metastasis, multiple tumors, a history of previous cancer, metastatic bulky LNs, or multiple metastatic N2 LN stations were excluded from this study. A total of 202 patients (179 males and 23 females; mean age, 59.66 ± 9.89 years; range: 29–84 years) who had ipsilateral single-station N2 were analyzed retrospectively.

Patients were evaluated preoperatively using X-ray, thoracic computed tomography (CT) and whole-body positron emission tomography/computed tomography (PET/CT). Preoperative invasive mediastinal staging procedures included endobronchial ultrasound (EBUS) and cervical mediastinoscopy (CM) for patients who had LNs with a shortest diameter exceeding 1 cm, suspected hilar, or MLN metastases on PET/CT or CT, in addition to central tumors that necessitated pneumonectomy. All patients were former smokers and stopped smoking at least 2 weeks prior to surgery.

The patients were divided into two groups: a "skip ipsilateral MLN metastasis" group (sN2) (n = 55, 27.3%) [N1(–), N2(+)] and a "non-skip ipsilateral MLN metastasis" group (nsN2) (n = 147,72.7%) [N1(+), N2(+)]. In patients with skip metastasis, the effect of skip metastasis on prognosis, and the factors underlying this phenomenon were investigated. Tumors were staged according to the 8th edition of the TNM classification, and the pathological examination was based on the 2004 World Health Organization (WHO) classification.[4] The criterion for LN positivity was the shortest nodal diameter of ≥10 mm on CT[5] or metabolic activity of nodes higher than that of adjacent normal mediastinal and soft tissue on PET.[6] Patients with clinical N1 and N2 disease were diagnosed according to institutional clinical conference or cancer board.

The regional LN classification of Mountain and Dressler was used.[7] All patients received platinum-based adjuvant chemotherapy following surgery. This study was conducted in accordance with the ethical standards of relevant committees on Human Experimentation (institutional and national), and with the Declaration of Helsinki.

Statistical Analysis

Means, standard deviations, medians, minimums, maximums, frequencies, and percentages were used for descriptive statistics. Mann–Whitney U tests were used to compare quantitative data. Chi-square tests were used to compare qualitative and categorical data. IBM SPSS Statistics for Windows, version 22.0 was used for statistical analyses. Factors for skip metastasis formation in univariate analyses were estimated using Pearson's Chi square test or Fisher's exact test. Survival analysis was performed using Kaplan–Meier plots and the log-rank test. A p value <0.05 was considered significant.

Results

The average hospitalization duration was 6.4 ± 2.1 days (range: 2–45 days). Mean age was 61.2 ± 8.6 years in sN2 group, whereas it was 59±10.3 years in nsN2 group (p = 0.27). Of the 202 patients, 158 underwent CM and 90 underwent both EBUS and CM before pulmonary resection. Clinical N1 diseases were diagnosed in 3 sN2 patients (5.4%) and 143 nsN2 patients (97.2%). Clinical N2 diseases were diagnosed in 40 sN2 patients (72.3%) and 118 nsN2 patients (80.3%). Cardiac, respiratory, endocrinological, and nephrological comorbidities were observed in the study and comorbidity rate was 33% in sN2 group (n = 18) and 31% in nsN2 group (n = 46) (p = 0.493). In total, 77 patients had a right lung tumor (38%) and 125 had a left lung tumor (62%). In our study, 78 patients underwent pneumonectomy (39%) and 134 patients underwent lobectomy (61%). The pneumonectomy rate tended to be lower in the sN2 group (29%, n = 16) than in the nsN2 group (42.1%, n = 62; p = 0.089). N2 skip metastasis was more frequent when the tumor was located in the upper lobes (49%, n = 27; p = 0.093). About 42% of the nsN2 group had central tumors (n = 62s), and 70% of the sN2 group had peripheral tumors (n = 39). The most common T stage was T2 in both groups (**Table 1**). In nsN2 group, 72.1% of the cases (n = 106) had single N1 metastasis and 27.8% of the cases (n = 41) had multiple N1 metastasis.

Squamous cell carcinoma was the most common histological type of tumor (n = 109, 54%). The histological assessment revealed squamous cell carcinoma in 25 patients (45.5%), adenocarcinoma in 26 patients (47.3%), and large-cell carcinoma in 4 patients (7.3%) in

Table 1 A comparison on characteristics of sN2 and nsN2 groups

Quantity/Frequency	sN2 (n = 55)	nsN2 (n = 147)	p*
Gender			0.53
Male	50 (91%)	129 (88%)	
Female	5 (9%)	18 (12%)	
Comorbidities	18 (33%)	46 (31%)	0.49
N2 disease (LN)			
2R	–	1 (0.7%)	0.54
3	2 (4%)	1 (1%)	0.12
4R	10 (18%)	22 (15%)	0.34
4L	–	4 (3%)	0.22
5	17 (31%)	45 (31%)	0.61
6	3 (5%)	11 (8%)	0.51
7	13 (22%)	40 (27%)	0.25
8	5 (9%)	12 (8%)	0.71
9	5 (9%)	11 (8%)	0.7
Tumor histology			0.23
Adenocarcinoma	26 (47%)	58 (39%)	
Squamous cell carcinoma	25 (46%)	84 (57%)	
Large-cell carcinoma	4 (7%)	5 (3%)	
Pulmonary resection type			
RUL	11 (20%)	21 (14%)	0.32
RML	1 (2%)	2 (1%)	0.56
RLL	6 (11%)	18 (12%)	0.83
RP	4 (7%)	14 (10%)	0.52
LUL	16 (29%)	29 (19%)	0.15
LLL	5 (9%)	15 (10%)	0.81
LP	12 (22%)	48 (33%)	0.13
T status			0.68
T1	15 (27%)	34 (23%)	
T2	22 (40%)	54 (37%)	
T3	9 (16%)	34 (23%)	
T4	9 (16%)	25 (17%)	
Stages			0.22
Stage IIIA	37 (67%)	88 (60%)	
Stage IIIB	18 (33%)	59 (40%)	
Complications	4 (7%)	18 (12%)	0.39

*Pearson's chi-square test. LLL: left lower lobectomy; LN: lymph node; LP: left pneumonectomy; LUL: left upper lobectomy; RLL: right lower lobectomy; RML: right middle lobectomy; RP: right pneumonectomy; RUL: right upper lobectomy

the sN2 group (p >0.05). In sN2 group, there was visceral pleura invasion (VPI) in 23 patients (42%) (p = 0.42), lymphatic invasion in 30 patients (55%) (p = 0.34), and vascular invasion in 14 patients (25%) (p = 0.67). Subaortic MLN was the most frequent metastatic LN in both groups (sN2: 31%, nsN2: 33%). The multiple N2 ratio was 3.5% in the sN2 group (n = 2) and 32.3% in the nsN2 group (n = 70) (p = 0.01). The complication rate was 7.2% in the sn2 group (n = 4) and 12.2% in the nsN2 group (n = 18) (p = 0.395). Complications were bronchopleural fistula (n = 2), postoperative hemorrhage (n = 2), pneumonia (n = 4), atrial fibrillation (n = 8), wound infection (n = 5), and chylothorax (n = 1). No significant differences in age, gender, comorbidities, incidence of LN metastasis, pulmonary resection type, complication, localization/size/stage/histological type of tumor were observed between the groups; thus, no significant factor causing skip metastasis formation was found in our study (**Table 1**).

The mean follow-up was 42.63 ± 34.91 months (range: 2–117 months). Among all patients, and in the sN2 and nsN2 groups, the median overall survival times were 63.5 ± 4.56, 68.8 ± 7, and 59.3 ± 5.35 months, respectively, and the 5-year overall survival rates were 38.2%, 46.3%, and 36.4%. The 5-year overall survival rate tended to be higher in the sN2 group (p = 0.06) (**Fig. 1**). When survival rates were comparatively analyzed according to parameters presented in **Table 2**, sN2 group

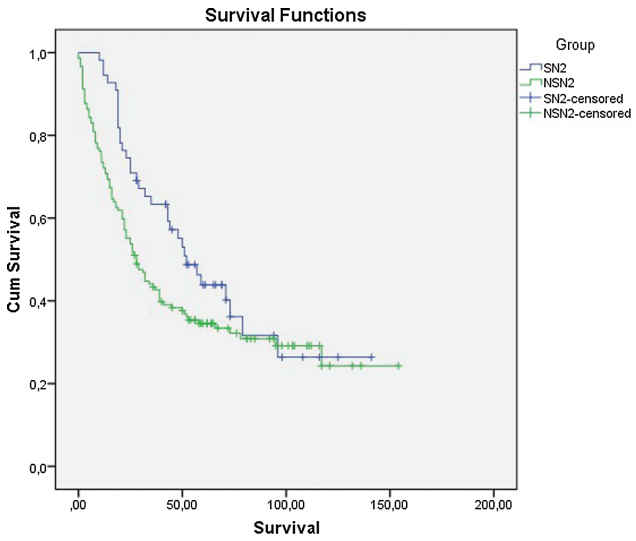

Fig. 1 Overall survivals of sN2 and nsN2 patients.

showed better survival in almost all parameters compared to nsN2 group. Patients with upper lobe tumors in the sN2 group had a significantly better 5-year overall survival rate and time than those in the nsN2 group (45% and 64 ± 11.85 months vs. 28% and 25.6 ± 6.2 months, respectively; p = 0.032). Patients with skip metastasis in the 4R station had a higher 5-year overall survival rate and time (44% and 64 ± 10.6 months, respectively) than patients in the nsN2 group (20% and 23 ± 5.76 months) (p = 0.03). The 5-year overall survival rate and time of patients with squamous cell carcinoma were significantly better in the sN2 group than in the nsN2 group (61% and 84.3 ± 12.52 months vs. 32% and 51.75 ± 6 months, respectively; p = 0.014). No significant survival differences in gender, size/stage/location of tumor was observed between the groups (**Table 2**).

Discussion

N2 disease was detected in 10% of patients who underwent pulmonary resection due to lung cancer, and the 5-year overall survival rates were 20–25%.[8] MLN metastasis is the most significant prognostic factor in lung cancer. Skip metastasis is detected in 13–42% of patients with N2 disease who undergo pulmonary resection due to NSCLC.[9] In our study, the incidence of N2 disease was 10.6% and the incidence of skip N2 metastasis was 2.9%. The incidence of sN2 in the N2 group was 27.2%. The multiple N2 disease rates were 3.5% and 32.3% in the sN2 and nsN2 groups, respectively. The incidence of multiple N2 disease was significantly lower in the sN2 group than the nsN2 group (p = 0.01). It is possible that metastatic hilar LNs promoted multiple N2 LN metastasis. The N2 group of diseases is extensive and heterogeneous, and multiple N2 metastasis is the most important factor affecting overall survival in patients with N2 disease.[10] Thus, patients with multiple N2 metastasis were excluded from this study to better analyze the effect of skip metastasis on the overall survival of patients with N2 disease.

There are several putative factors involved in skip metastasis formation, including the histopathological tumor type, size, anatomical location, and thoracic lymphatic flow variation. In our study, no significant association was observed between skip metastasis and tumor histopathology or size. As expected, skip metastasis was mostly observed in upper lobe tumors in our study because subpleural aberrant lymphatic channels that drain directly into the mediastinum are more frequently localized in the upper lobes.[11,12] Riquet et al. reported VPI as a factor for skip metastasis.[11] On the other hand, absence of VPI and lymphatic invasion were reported to be associated with skip metastasis in some studies.[13,14] In our study, VPI was detected in 42% of patients in the sN2 group, whereas 55% of the sN2 group had lymphatic invasion. Skip metastasis occurred more frequently in patients with lymphatic invasion (p >0.05). Although both were not significant factors in our study, we can speculate that tumors with lymphatic invasion may also cause skip metastasis.

Skip metastasis is a subtype of N2 disease with a better prognosis than other N2 subtypes.[11,14] In our study, the 5-year overall survival rate of the sN2 group (46.3%) was better than that of the nsN2 group (36.4%), but the difference was not significant (p = 0.06). Skip metastasis phenomenon presented itself as a good prognostic factor as it is mentioned in literature. SN2 patients who had squamous cell carcinoma, 4R LN metastasis, and right upper lobectomy presented significantly better survival compared to nsN2 group. There was no literature on survival advantage of sN2 patients with squamous cell carcinoma compared to non-skip metastatic patients. On the other hand, related studies have stated that patients with skip metastasis who underwent right upper lobectomy have better survival rates compared to patients with non-skip metastasis.[12,14] The 4R metastasis is often spotted in patients with right upper lobe tumors; so, it occurred naturally to have correlated results. Out of 32 patients with 4R LN metastasis, 23 had upper lobe tumors in the cohort. In our opinion, the significant difference in survival

Table 2 A comparison of 5-year overall survival rates of sN2 and nsN2 groups

5-Year overall survival (%)	sN2 (n = 55)	nsN2 (n = 147)	p*
Overall	46%	36%	0.06
Gender			
Male	48%	38%	0.14
Female	44%	40%	0.62
N2 disease (LN)			
4R	44%	20%	0.004
5	50%	37%	0.43
6	64%	49%	0.38
7	33%	38%	0.92
8	31%	23%	0.9
9	59%	53%	0.88
Tumor histology			
Adenocarcinoma	37%	37%	0.7
Squamous cell carcinoma	61%	32%	0.01
Large-cell carcinoma	22%	39%	0.87
Pulmonary resection type			
RUL	45%	28%	0.03
RLL	50%	32%	0.07
RP	34%	28%	0.7
LUL	51%	47%	0.46
LLL	45%	48%	0.37
LP	42%	38%	0.31
T status			
T1	38%	36%	0.89
T2	50%	33%	0.15
T3	33%	29%	0.66
T4	37%	38%	0.11
Stages			
Stage IIIA	40%	33%	0.27
Stage IIIB	52%	31%	0.14

*Kaplan–Meier Method. LLL: left lower lobectomy; LN: lymph node; LP: left pneumonectomy; LUL: left upper lobectomy; RLL: right lower lobectomy; RP: right pneumonectomy; RUL: right upper lobectomy

was also due to unexpected low survivals of nsN2 patients with 4R metastasis (5-year overall survival of 20% and mean survival of 23 ± 5.76 months) in addition to skip metastasis' prognostic precedence.

MLN dissection, rather than MLN sampling, is essential to accurately determine the lung cancer stage. MLN dissection increases the possibility of detecting micrometastasis.[15] Micrometastasis is defined as a 0.2–2-mm residual tumor, which may not be detected by hematoxylin–eosin staining. Unidentified micrometastasis might be the cause of unexpected lung cancer recurrence, particularly in patients who undergo pulmonary resection due to early stage lung cancer. Immunohistochemical (IHC) staining, flow cytometry, and reverse transcription-polymerase chain reaction can be used to detect micrometastasis.[16] Gu et al.[17] reported a 45% tumor recurrence rate in operated patients who had micrometastasis due to lung cancer. Undetected micrometastasis occurs due to either human error or an inadequate histopathological technique. N2 metastases with undetected micrometastatic N1 LNs appear as N2 skip metastases.

Some limitations to our retrospective study should be mentioned. Biogenetic markers which may be involved in skip metastasis were not analyzed. The examination of biogenetic markers, such as epidermal growth factor and sialyl lewis x which are presumably linked with skip metastases,[18,19] may be convenient in further studies on skip metastasis. The 5-year overall survival rate of patients with squamous cell carcinoma were significantly better in the sN2 group; but, we could not reveal the pathogenesis behind this difference due to lack of histological marker analysis. Only analyzed specific marker was "p63" in squamous cell carcinomas which was ineffective in clarifying survival difference solely, p40 and cytokeratin 5/6 were necessary for further evaluation.[20] Ultimately, the N1 LNs in the sN2 group were not

Table 3 Literature overview on articles about single-station skip N2 metastasis

	Number of patients with single-station skip N2 metastasis / frequency of skip metastasis in N2 diseases (%)	5-year overall survival rate (%) / p
Fukuse 2000[21]	30 / 34	51 / 0.12
Prenzel 2003[22]	17 / 38	41 / 0.019
Tanaka 2004[23]	49 / 13	30 / 0.950
Riquet 2007[10]	161 / 28.6	34.4 / 0.0051
Li 2015[14]	45 / 25.4	37.4 / 0.005
Akçay 2017[24]	55 / 49.5	20 / 0.084
Yazgan 2018[25]	59 / 45	51.2 / 0.01

routinely examined by IHC or other techniques to detect micrometastasis. The unexpectedly poor survival time of some patients with N2 skip metastases may have been due to the presence of undetected N1 micrometastasis.

Similar results have been seen in studies conducted for nearly 20 years, and skip metastasis has been reported to have better survival. A literature review of 5-year overall survival rates for single-station N2 skip metastasis and N2 non-skip metastasis patients was performed; the data are presented in **Table 3**.[11,14,21–25] We observed that patients with single-station N2 skip metastasis had better overall survival in literature, but statistical significance was only seen in some of the studies. These equivocal heterogenic results in literature may have been due to undetected micrometastatic N1 LNs in the skip metastatic group, since none of the studies have used examination techniques for N1 LNs in search for micrometastasis.

Skip metastasis was planned for inclusion within "N2a1" in the proposed "N" classification of the 8th TNM staging system, but "N2a1" was in fact not within the classification due to an inadequate number of reported patients with skip metastasis and multicenter studies with larger skip metastasis patient groups were reported to be necessary.[26]

Conclusion

Skip metastasis is an N2 disease subtype resulting from an anatomical variation and can be considered as the N2 subgroup with the best prognosis in the N2 disease group; but still, skip metastasis did not take its rightful place in TNM classification, thus further studies will be performed. To detect micrometastasis, future studies on skip metastasis should examine non-metastatic N1 LNs through staining methods, such as IHC staining so that heterogeneity in patient groups can be avoided, that is, to ensure that only true skip metastasis cases are included. Biogenetic and pathological markers of tumors should be further investigated to elucidate the mechanism underlying skip metastasis formation. Afterwards, more accurate and elucidative studies on skip metastasis can be achieved to propound its prognostic importance in the group of N2 disease.

Disclosure Statement

The authors have no conflict of interest.

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