

Lobe-Specific Skip Nodal Metastasis in Non-Small Cell Lung Cancer Patients

Ryoji Kawano, MD, PhD, Enjo Hata, MD, PhD, Shingo Ikeda, MD, and Toshiya Yokota, MD

Purpose: The purpose of this study is to clarify the lobe-specific nodal metastasis and optimal range of mediastinal nodal dissection in lung cancer patients with skip metastasis.

Materials and Methods: A total of 136 patients with pN2/3 disease were treated between 1988 and 2002, and these patients were divided into two groups according to whether skip metastasis was identified or not. We drew a comparison of the lobe specificity of mediastinal nodal involvement between skip positive and negative groups.

Results: Skip metastasis was identified in 48 (35.3%) of 136 pN2/3 patients. The lymph nodal regions most frequently found (target nodes) were as follows: right upper-#3 and right #4, middle & lower-#3, right #4 and #7, left upper-left #4, #5, and #6, and left lower-#7, #8, and #9. Skip metastasis can be detected at a rate of 82.6% to 91.7% by means of a histological examination of these target nodes. However, the frequency of skip metastasis in other mediastinal nodal regions excluding the target nodes was found to progress to a level of 33.3% to 57.1% insofar as tumor metastasis to these target nodes was identified.

Conclusions: The examination of lobe-specific nodal regions may be helpful for determining patients with skip metastasis. If metastasis is found somewhere in these target nodes, then a systematic nodal dissection may be acceptable for a complete resection even if N1 metastasis is not identified. (*Ann Thorac Cardiovasc Surg* 2008; 14: 9-14)

Key words: non-small cell lung cancer, skip metastasis, lymph node metastasis, nodal dissection

Introduction

When we determine the need to perform a dissection of mediastinal lymph nodes in non-small cell lung cancer (NSCLC) patients, an examination of metastasis in the N1 nodes is often performed. However, some patients demonstrate tumor involvement only in the N2/3 nodes, and none in the N1 nodes, and this phenomenon is called "skip metastasis."¹⁻⁵ As a result, an examination of metastasis of the N1 nodes alone may thus often result in an

inappropriate therapeutic approach. A detailed clinico-pathological analysis of patients with skip metastasis thus provides a useful information regarding the surgical treatment of such patients.

The purpose of this study is to elucidate whether any differences in the distribution of nodal metastasis exist between the pN2/3 patients with and without skip metastasis. Furthermore, we also attempted to consider an appropriate management of nodal dissection in patients with skip metastasis.

Materials and Methods

The subjects were collected from 136 primary lung cancer patients with mediastinal nodal metastasis (pN2 to pN3) treated from March 1988 to April 2002 at the Surgical Department of Respiratory Center of Mitsui Memorial Hospital. Of the 136 patients investigated, 75 pa-

From Surgical Department of Respiratory Center, Mitsui Memorial Hospital, Tokyo, Japan

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Address reprint requests to Ryoji Kawano, MD, PhD: Surgical Department of Respiratory Center, Mitsui Memorial Hospital, Kandaizumicho-1, Chiyoda-ku, Tokyo 101-8643, Japan

tients had right lung cancer and 61 patients had left lung cancer. A “skip metastasis” of the lymph nodes was defined as a condition of pN2 and/or pN3 disease without any pN1 nodal involvement. The histologic diagnosis of the tumors and the tumor staging were made based on the criteria of the International Union Against Cancer staging system.⁶⁾ The lymph nodes were numbered according to the lymph node mapping criteria⁷⁾ as follows: #1, superior mediastinal or highest mediastinal; #2, paratracheal; #3, pretracheal; #3a, anterior mediastinal; #3p, retrotracheal or posterior mediastinal; #4, tracheobronchial; #5, subaortic; #6, paraaortic; #7, subcarinal; #8, paraesophageal; and #9, pulmonary ligamentum lymph nodes. The lymph node regions in the mediastinum, which was the area in which skip metastasis were most frequently found, were regarded as the key stations of skip metastasis, and they are thus called “target nodes.” In contrast, the patients with metastasis of the lymph nodes in pN1 to pN2/3, are hereinafter referred to as non-skip pN2/3 patients. The patient’s profiles are shown in Table 1. The operative procedures for primary lesions of the lung consisted of 102 patients with a lobectomy, 11 with a bilobectomy, and 23 with a pneumonectomy. The extent of lymph node dissection in all patients was classified into 12 of ND2a, 38 of ND2b, 76 of ND3 α , and 10 of ND3 γ based on the General Rules of the Japan Lung Cancer Society.⁸⁾ The detailed circumstances concerning the operative methods and indications of so called “extended nodal dissection, such as ND3 α and ND3 γ ” for primary lung cancer patients have previously been described.^{9,10)} The patients were compared regarding several variables, and the differences between them were evaluated using the χ^2 test. The mean follow-up period, which ranged from 0.1 to 149.7 months, was 36.5 months. The survival rate was calculated by the Kaplan-Meier method. A comparison among survival rates was examined by the logrank test. The data were considered to be significant when the p value did not exceed 0.05.

Results

1. Skip metastasis in primary lung cancer patients based on various clinicopathological factors

Skip metastasis was identified in 48 (35.3%) of 136 lung cancer patients. Of the 48 patients with skip metastasis, 19 (25.3%) were right lung cancer patients (out of a total 75 right lung cancer patients), and 29 (47.5%) were left lung cancer patients (out of a total of 61 left lung cancer patients). The frequency of skip metastasis based on the

various clinicopathological factors is shown in Table 1. Skip metastasis in left lung cancer patients was more frequently detected than that in right lung cancer patients. Furthermore, there were statistically significant differences in the gender and pN status between the two groups.

2. The frequency and distribution of skip metastasis based on the location of the primary lesion

1) Right lung cancer (Figs. 1 and 2)

a) Upper lobe (RUL) tumors: Skip metastasis was found in 12 (30.8%) of the 39 patients with RUL tumors. The lymph node region with skip metastasis which was most frequently found were the #3 and right #4 nodes; the number of patients with metastasis in either region accounted for 11 (91.7%) of the 12 patients. These nodes were regarded as the target nodes in RUL tumors. Some patients with nodal involvement to the contralateral mediastinum and #7 were also observed. The distribution of mediastinal nodal metastasis in non-skip pN2/3 patients was similar to that in skip pN2/3 metastasis.

b) Middle lobe (RML) tumors: Only two patients with RML tumors showed involvement of the #3 node while demonstrating single station metastasis. The distribution of nodal metastasis in non-skip pN2/3 patients showed both characteristics in the upper and lower lobe cases. Nodal involvement in the regions from ipsilateral superior mediastinum to subcarina was also observed.

c) Lower lobe (RLL) tumors: A low frequency of skip metastasis was observed in comparison to that of the patients with upper lobe tumors. Skip metastasis was mainly detected in the right #4 and #7 nodes, whereas non-skip pN2/3 patients showed more extensive metastasis in the ipsilateral mediastinal area. In particular, non-skip pN2/3 patients tended to show lymph node spreading in the superior mediastinal area.

2) Left lung cancer (Figs. 3 and 4)

a) Upper lobe (LUL) tumors: Skip metastasis was found in 23 (51.1%) of the 45 patients, which was the highest frequency of skip metastasis among all the lobes demonstrating primary lesions. The most frequent region of skip metastasis was the #5 node, while the second and third most frequent regions were the left #4 and the #6 nodes, respectively. The number of patients with skip metastasis in any of these three regions accounted for 19 (82.6%) of 23 patients. Thereafter, these regions were regarded as target nodes of LUL tumors. Because the frequency of single station metastasis to the left #4 node was limited, this region may be linked to a skip metastasis in collaboration with the nodal metastasis of the #5 or #6. When

Table 1. Clinicopathological characteristics of pN2/3 lung cancer patients with and without skip metastasis

Skip metastasis	Negative group, n=88	Positive group, n=48 (%)
Mean age	60.2	60.7
Gender		<i>p</i> =0.03
male	63	42 (40.0)
female	25	6 (19.4)
Location of tumor		<i>p</i> =0.007
Right lung	56	19 (25.3)
upper	27	12 (30.8)
middle	11	2 (15.4)
lower	18	5 (21.7)
Left lung	32	29 (47.5)
upper	22	23 (51.1)
lower	10	6 (37.5)
pT-factor		n.s.
T1	16	9 (36.0)
T2	43	20 (31.7)
T3	15	13 (46.4)
T4	14	6 (30.0)
pN-factor		<i>p</i> =0.04
N2	64	42 (39.6)
N3	24	6 (20.0)
Histology		n.s.
adenoca.	59	35 (37.2)
squamous cell ca.	28	12 (30.0)
adenosquamous ca.	1	1 (50.0)
Differentiation of tumor		n.s.
well	30	12 (28.6)
moderate	35	15 (30.0)
poor	23	21 (48.8)
p-factor		n.s.
0	40	17 (29.8)
1	12	9 (42.9)
2	12	5 (29.4)
3	24	17 (41.5)

n.s., not significant.

either #5 or #6 node is positive for malignancy, the frequency of left #4 nodal metastasis was 5 (31.2%) of 16 patients with skip metastasis. The distribution of nodal metastasis of non-skip pN2/3 patients tended to extend to the mediastinum in comparison to that of patients with skip metastasis. On the other hand, the frequency of patients with LUL tumors demonstrating skip metastasis in other regions except for target nodes was comparatively high in comparison to those of other lobes. This frequency accounted for 4 (17.4%) out of 23 patients, as shown in Table 2.

b) Lower lobe (LLL) tumors: Skip metastasis was identified in 6 (37.5%) of 16 patients. The frequency of skip

metastasis of LLL tumors was low in comparison to that in the upper lobe. The prevailing skip sites were the lower mediastinal regions of #7, #8, and #9. Nodal metastasis in non-skip pN2/3 patients had a tendency to be distributed over a wide area, such as in the #3, left #4, #5, #6 nodes.

3) Lobe-specific target nodal regions in patients with skip metastasis and frequency of patients demonstrating skip metastasis to other nodal regions (except for the target nodes) in the presence of metastasis to the target nodes (Table 2)

The determination of the target nodes of skip metastasis in each lobe was based on its frequency.

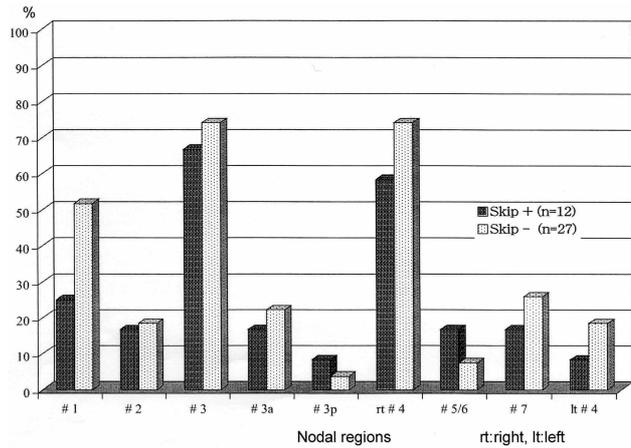


Fig. 1. Frequency and distribution of skip metastasis based on the location of the primary lesion: patients with right upper lobe tumor.

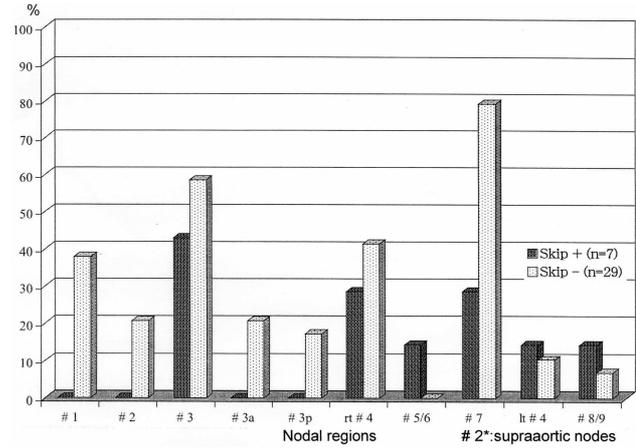


Fig. 2. Frequency and distribution of skip metastasis based on the location of the primary lesion: patients with right middle and lower lobe tumors.

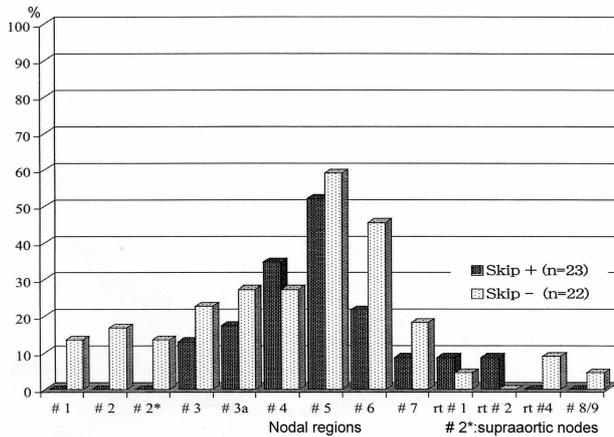


Fig. 3. Frequency and distribution of skip metastasis based on the location of the primary lesion: patients with left upper lobe tumor.

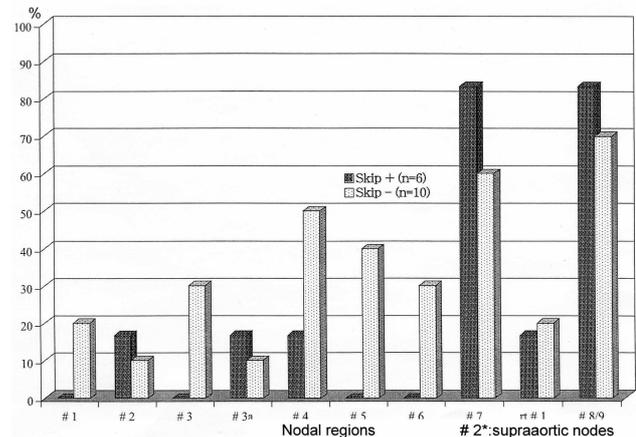


Fig. 4. Frequency and distribution of skip metastasis based on the location of the primary lesion: patients with left lower lobe tumor.

However, when tumor metastasis to the target nodes was identified, relatively high frequency of metastasis to other nodal regions (except for the target nodes) was revealed.

3. Skip metastasis to a single station

The frequency of skip metastasis to a single station was 11 (57.9%) of 19 patients with right lung cancer and 16 (55.2%) of 29 patients with left lung cancer. There was no particular difference between the skip patients with and without single station metastasis, and we could not identify any distinctive factors for skip patients with single station metastasis (data not shown).

4. Prognosis

The 5-year survival rate and the median survival time of all the patients with 48 skip metastases was 42.4% and 38.7 months, respectively, whereas the same values for 92 pN2/3 patients without skip metastasis were 38.7% and 37.7 months, respectively. No statistically significant difference was recognized in the survivals between the two groups ($p=0.50$). The 5-year survival rate of skip patients with single-station metastasis was 43.8%, and multi-station metastasis was 35.6%. No significant difference between the two groups was identified ($p=0.46$).

Table 2. Lobe-specific target nodal regions and frequency demonstrating skip metastasis in other nodal regions (except for the target nodes) in the presence of tumor involvement of the target nodes according to primary lobes

Primary lobe	Target nodes	Frequency of other nodal metastasis except for the target nodes with metastasis
RUL	#3, rt #4	6/12 (50.0%)
RML & RLL	#3, rt #4, #7	4/7 (57.1%)
LUL	lt #4, #5, #6	9/23 (39.1%)
LLL	#7, #8, #9	2/6 (33.3%)

RUL, right upper lobe; RML & RLL, right middle and lower lobes; LUL, left upper lobe; LLL, left lower lobe; rt, right, lt, left.

Discussion

The frequency of skip metastasis in primary lung cancer patients with mediastinal nodal involvement has been reported to range approximately from 20–40%.^{1–5)} Although we herein further analyzed skip metastasis in lymph nodes obtained by a more extensive nodal dissection than that described in previous reports, the frequency was almost the same as that for the previously reported results. Riquet and co-workers described the causative mechanism of skip metastasis to be direct lymphatic channels to the mediastinum through the subpleural lymph ducts. The lymphatic flows, which directly reached the mediastinum, were present in 22.2% with right lung involvement, and 25.0% with left lung involvement. It appears that direct passages existed more often from the RUL and LUL, and less often from the RML, RLL and LLL.¹¹⁾ The findings of the present study were also consistent with their results, since our findings suggested that the direct route to mediastinum from the LUL is the most highly developed among all lobes. Based on our findings regarding the frequency of skip metastasis, on histological findings of the N1 nodes are thus considered to be an unreliable indicator of patients with mediastinal nodal involvement. The locations of these target nodes presented in this study were similar to the mediastinal prevailing ones of non-skip pN2/3 patients.¹²⁾ Accordingly, the target nodes are the most important key stations in the mediastinum along the lymph route regardless of presence or absence of skip metastasis.

The nodal involvement of many patients with skip metastasis tended to be confined to a localized region in the mediastinum, in comparison to those with non-skip

pN2/3. The difference in nodal distribution between patients with and without skip metastasis may be speculated as described below. Since several lymph routes arising from N1 node toward the proximal sites along the bronchial tree exist, N1 metastasis may lead to an increased chance of tumor spread in the mediastinal nodes. Furthermore, patients with skip metastasis tended to often have single station metastasis, which has a possibility of including the concept of a “sentinel lymph node” in the mediastinal area.¹³⁾ Even though these skip patients are diagnosed with advanced IIIA and/or IIIB stages, certain number of early stage-patients might be involved in them. Therefore, it follows that nodal spread of skip metastasis converges on a narrow range of the mediastinal area.

There was no particular difference in the distribution of nodal metastasis in RUL tumors between patients with and without skip metastases. Since RUL tumors are occasionally predisposed to metastasize to the neck nodes, nodal spread in non-skip pN2/3 patients is thus suggested to occur in a wider area such as the neck region.⁹⁾ A detailed study must be made on a large number of patients concerning the wider distribution of such lymph node metastasis.

When lung cancer patients show no metastasis in regional N1 nodes originating from a primary lesion, a histological examination of the lobe-specific target regions provides the most useful information as to whether the patient has a skip metastasis or not. As a result, the presence of skip metastasis can be detected at a range of 82.6 to 91.7%. Furthermore, we herein showed that, if nodal metastasis to the target nodes cannot be detected, then the number of skip metastases to other nodal regions in the mediastinum was limited to some degree. It follows that an absence of tumor involvement in these target nodes might be helpful in limiting mediastinal dissections in patients without N1 metastasis.

In other words, when tumor metastasis to these target nodes is found, skip metastasis to other nodal regions was simultaneously identified in 33.3 to 57.1%. Furthermore, unfortunately no clinicopathological evidence regarding the occurrence of single station metastasis, which converged on the target nodes, was disclosed.¹⁴⁾ Accordingly, it is reasonable to suppose under any circumstances that a systematic nodal dissection is essential for a complete elimination of tumor cells.

In conclusion, the prevailing skip sites of nodal metastasis were specifically disclosed according to the tumor lobes. The distribution of nodal metastasis in patients

with skip metastasis tends to be localized in comparison to that of patients with non-skip pN2/3. Further studies are called for, however, to elucidate the nodal involvement to the N1 region of pN2/3 patients in order to clarify the impact on an extensive spread of tumor cells in the mediastinum.

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