The lymphatic map of the lung - Subdivision of N2 non-small cell lung carcinomas-

Authors
[1] Koji Takahashi, M.D., Ph.D., 1) Kaori Nakasjima M.D.
[1]Tomoaki Sasaki, M.D., Ph.D., 1) Masaaki Yamashina M.D.
[1] Eriko Takabayashi, M.D.
[2] Yoshinobu Ohsaki, M.D., Ph.D., 2) Masahiro Kitada, M.D., Ph.D.

Affiliations
[1] Department of Radiology, Asahakiwa Medical University
[2]Respiratory Center, Asahakiwa Medical University

Corresponding author
Koji Takahashi, M.D., Ph. D.,
Department of Radiology
2-1-1-1, Midirigaoka-higashi, Asahakiwa Medical University
Asahikawa, Japan
078-8510
Tel: 81-166-682572,
Fax: 81-166-682579
E-mail:
taka1019@asahikawa-med.ac.jp

Abstract

Background

The prognosis of resected N2 diseases (ipsilateral mediastinu node metastasis) in non-small cell carcinoma of the lung is heterogenous and difficult to predict. To precisely assess the prognosis of N2 diseases, we made a lymphatic map of each pulmonary lobe and subdivided the current N2 diseases.

Methods

We mapped the lymphatic pathways of each pulmonary lobe and classified these lymphatic pathways as follows: Level 1: from the lung to the intrapulmonary or hilar nodes (N1); Level 2: from N1 to the ipsilateral mediastinum nodes (N2); and Level 3: among N2 nodes. We assessed 585 computed tomography (CT) studies of patients with a primary complex of histoplasmosis, which included the association of single, well-defined, calcified lung nodules and hilar and/or mediastinum calcified lymph nodes. And we made the lymphatic map of the each pulmonary lobes.

Results

The lymphatic map disclosed the lymphatic pathways specific for each lobe. The common skip mediastinal station was specific in each lobe: the right lower paratracheal node in the right upper lobe, the sub-aortic node in the left upper lobe, the pulmonary ligament, and paraesophageal node in the bilateral lower lobes. Skip N2 metastases are uncommon in the right middle lobe. The mediastinum stations involved

were as follows: the most commonly involved station was the lower paratracheal node in the right upper lobe, the subcarinal node in the right middle lobe, the subcarinal node in the right lower lobe, the subaortic node in the left upper lobe, and the pulmonary ligament node in the left lower lobe.

Conclusions

We classified the current N2 findings into three stages: minimal, early, and advanced N2 disease progression, depending on which level of the lymphatic system is mainly contributing to nodal involvement.

Key Words: non-small cell carcinoma of the lung, N stage, lymphatics

Introduction

The most important prognostic factor in operable non-small cell lung cancers (NSCLCs) is lymph node metastasis, and the involvement of mediastinal lymph nodes is considered an adverse prognostic factor [1]. However, the prognosis of resected N2 diseases (ipsilateral mediastinum node metastasis) is heterogenous and difficult to predict. Many articles have analyzed prognostic factors in resected N2 disease, with a particular focus on the distribution of mediastinal node metastases [2-17], and several factors, including skip metastasis and single station metastases, have suggested a more favorable prognosis [2-9], whereas multiple stations and extended metastases have lower survival rates.

Currently, the N staging of NSCLCs is determined by the level of metastatic node involvement as follows: within the intrapulmonary or hilar nodes (N1), within the ipsilateral mediastinum nodes (N2), and within the contralateral mediastinum nodes (N3). However, the pulmonary lymphatic drainage patterns are extensive and variable on each pulmonary lobe and still require classification. We think that determing the level of lymphatic pathways contributing to nodal disease more precisely reflects the nodal status. We classified the lymphatic pathways as follows: Level 1: from the lung to the intrapulmonary or hilar nodes; Level 2: from N1 to the ipsilateral mediastinum nodes (N2); and Level 3: among N2 nodes. By considering the lobe with the primary lesion, the status (the site and number) of involved mediastinum nodes, and the lobe specific lymphatic flow, we can determine the level of lymphatic flow, which are the main contributing factors in N2 disease metastases. We developed a lymphatic map to clarify the lobe-specific lymphatic flow based on computed tomography (CT) findings of pulmonary *histoplasmosis* (18).

Histoplasmosis is an endemic fungal disease caused by *Histoplasma capsulatum*, which is particularly prevalent in the central and eastern United States. In primary infection, pulmonary lesions are often solitary and associated with self-limited hilar and/or mediastinal nodal disease. In individuals with normal cellular immunity, pulmonary histoplasmosis spontaneously resolves and results in a calcified primary complex consisting of a calcified pulmonary nodule and calcified hilar and/or mediastinal nodes [Fig. 1][19]. Therefore, these findings on CT disclose pulmonary lymphatic drainage to the mediastinum (see the lymphatic map) [18].

We developed a lymphatic map of each pulmonary lobes to determine the most commonly involved skip N2 disease for Level 1 lymphatics and single station node for Level 2 lymphatics. According to the determined lymphatic level, we subdivided N2 diseases of NSCLCs to predict their prognoses.

Fig 1

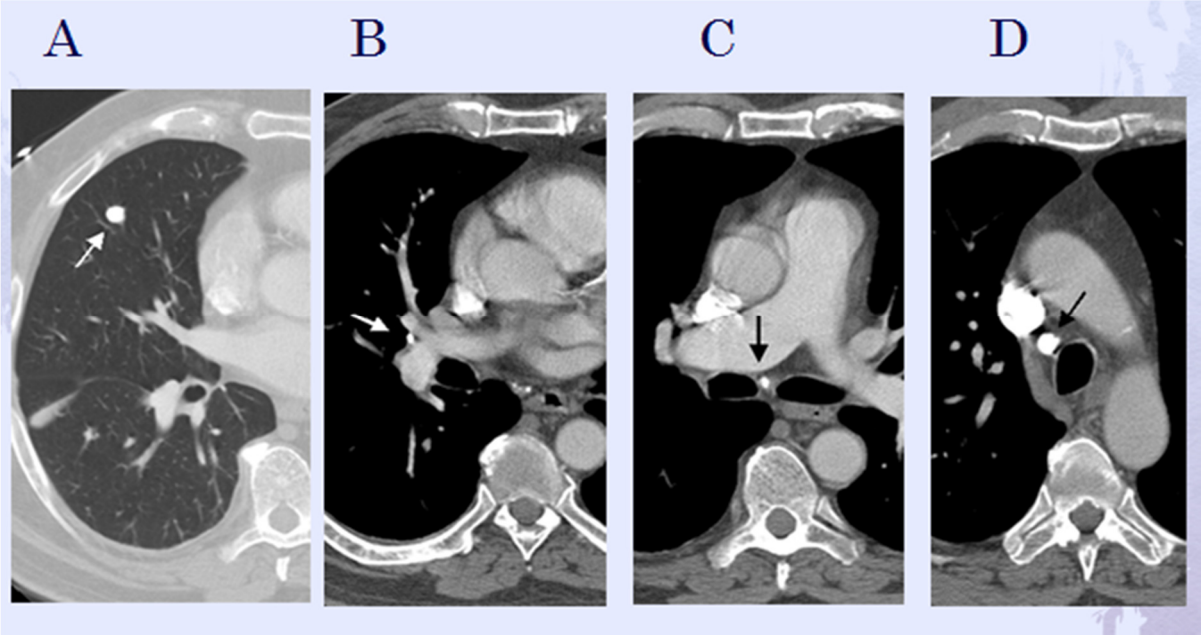


Fig. 1: *A 45-year old man with primary complex histoplasmosis in the right middle lobe. CT with lung window settings shows a calcified nodule in the right middle lobe (arrow). CT with mediastinum window settings at the level of the hilum (B), carina (C), and mid trachea (D) shows a hilar (arrow on (B)), subcarinal (arrow on (C)), and lower paratracheal (arrow on (D)) calcified lymph node, respectively*

Materials and methods

Study Subjects

We examined all subjects with a clinical diagnosis of primary complex of pulmonary histoplasmosis. Diagnoses were determined with CT findings between January 2004 to January 2005. These findings included the association of single, well-defined, calcified lung nodules and hilar and/or mediastinal calcified lymph node. These findings were generally considered to be diagnostic of complex of pulmonary histoplasmosis in a geographical area with endemic histoplasmosis occurrence. Patients with a

clinical history of tuberculosis, sarcoidosis, or pneumoconiosis were excluded to avoid intrathoracic calcifications of other etiologies. In 585 patients with primary complex pulmonary histoplasmosis, especially those with solitary pulmonary lesions, 191 showed only hilar node calcifications (N1), 320 showed both hilar and mediastinal node calcifications (N1, N2), and 74 showed only mediastinal node calcifications (skip N2) [Fig,2].

The institutional review board approved this retrospective study without a requirement of informed consent.

Fig 2

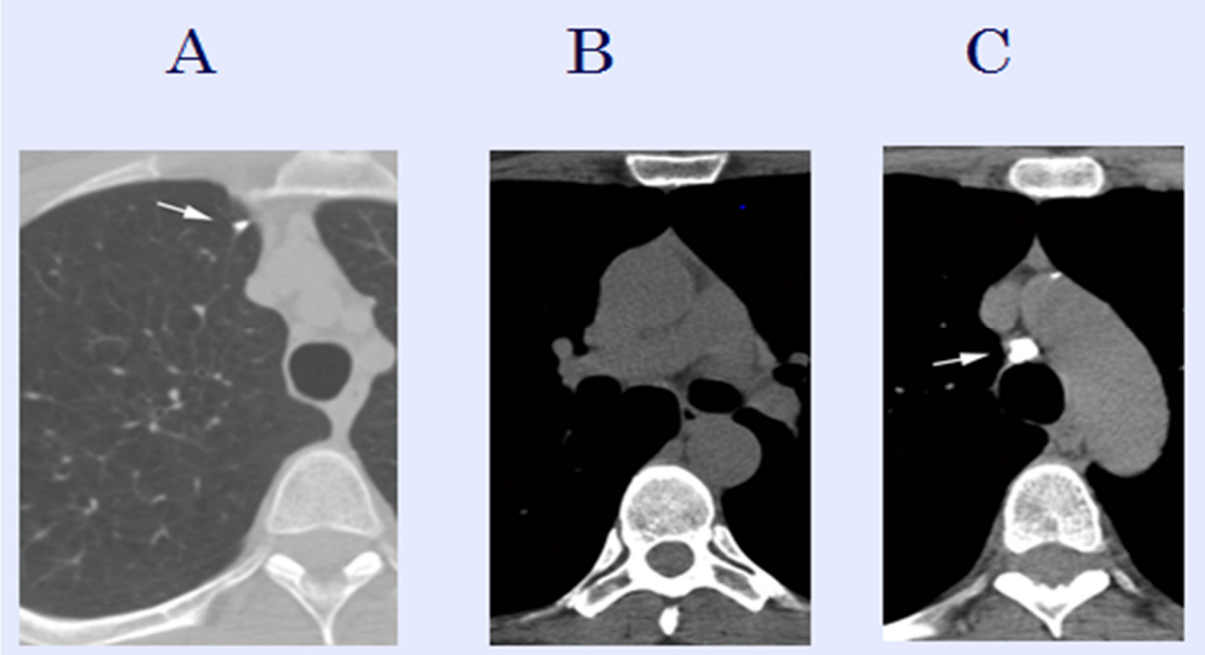


Fig. 2: *A 56-year-old woman with skip involvement from a right upper lobe histoplasmosis. (A)CT with the lung window settings showed a calcified nodule in the upper lobe (arrow in(A)) CT with the mediastinum window settings at the level of the hilum(B) and mid-trachea(C) showed a calcified right lower paratracheal node (arrow in(C) but no calcified node in the hilum.*

CT Examination and Interpretation

All CT studies were performed with four or six-detector row CT scanners (Aquillion, Toshiba Medical Systems or Emotion 6, Siemens Medical Solutions) with the following scan parameters: 135kV, 130mAs, gantry rotation time of 0.5 second, 3-mm collimation, and a pitch of 1. All CT images

were reconstructed with contiguous 3-mm thick slices and displayed on a workstation monitor (AR28, System 5 workstation, Kodak). The images were assessed with both lung (window level of –500 HU and window width of 2000 HU) and soft tissue (window level of 40 HU and window width of 400 HU) window settings, which were voluntarily adjusted as, necessary. The patients received 80 to 150 ml of nonionic IV contrast material (Omnipaque [240 mg I/ml], Amersham Health) at an injection rate of 2 ml/s, depending on the clinical indications of the CT studies.

A single experienced pulmonary radiologist (KT, 30 year's experience) subsequently assessed all CT data. In patients with a calcified primary complex of histoplasmosis, we determined the pulmonary lesion segment within a lobe and the nodal disease extent by using the N-staging method of NSCLCs: hilar (N1), ipsilateral mediastinal (N2), and contralateral mediastinal (N3). Skip involvement was defined as mediastinal node involvement without intrapulmonary or hilar node involvement [20,21]. In patients with mediastinal nodal disease, the site of nodal involvement was determined according to the classification advocated by the American Thoracic Society, American Joint Committee on Cancer and the Union Internationale Contre le Cancer (AJCC-UICC). This classification was designed primarily for the staging of bronchogenic carcinomas [20]: #1 the highest mediastinal, # 2 upper paratracheal, #3 prevascular and retrotracheal, #4 lower paratracheal, #5 subaortic, # 6 paraaortic, #7 subcarinal, #8 paraesophageal, and #9 pulmonary ligament node.

We further assessed the distribution of the involved mediastinum node station depending on whether the primary tumor was in the upper or lower lobe. We divided the mediastinum nodal stations into two groups: the upper mediastinum N2, including # 1-6 and the lower mediastinum N2, including #7-9. We graded some mediastinum node disease cases as limited; in cases with an upper lobe tumor with N2 in the upper group or a lower lobe tumor with N2 in the lower group. We cases as extensive that had an upper lobe tumor with N2 in the lower group or the lower lobe tumor with N2 in the upper group.

The lymphatic map of the lung

Based on CT observations of 394 findings of N2 involvement with solitary pulmonary lesions (Table 1), we made the lymphatic map, which showed the most commonly

involved mediastinum and skip N2 stations in each lobe. The mean number of the involved mediastinum station in all subjects was 1.4. The map nearly corresponded with the initial phase of N2 disease and mainly showed single station mediastinum node involvement through the Level 2 lymphatic pathway.

We found that, in addition to the single station node in Level 2 lymphatics, the map also included some nodes involved by Level 3 lymphatics among N2. The actual occurrence of the second most commonly involved mediastinum node was less. We deleted mediastinum stations with the incidence of less than 10% from the map.

Table 1A Rt lung: preferentially involved mediastinal nodes in early N2

	#2	#3	#4	#5	#6	#7	#8	#9
RULN=76	2	2	75 (17)	1		7		
RMLN=42	1		24 (1)			34 (1)		
RLLN=94	3		23 (1)			63 (5)	25 (10)	35 (11)
N=212								

The number in parenthsis is skip N2.

Table 1B Lt lung preferenctally involved mediastinal nodes in early N2

33	#2	#3	#4	#5	#6	#7	#8	#9
LUL N=63			8 (1)	48 (9)	9	7 (3)	2 (1)	1
LLL N=102			11	5	1	34 (3)	36 (9)	67 (21)
N=165								

The number in parenthsis is skip N2.

Results

The lymphatic map in each pulmonary lobe.

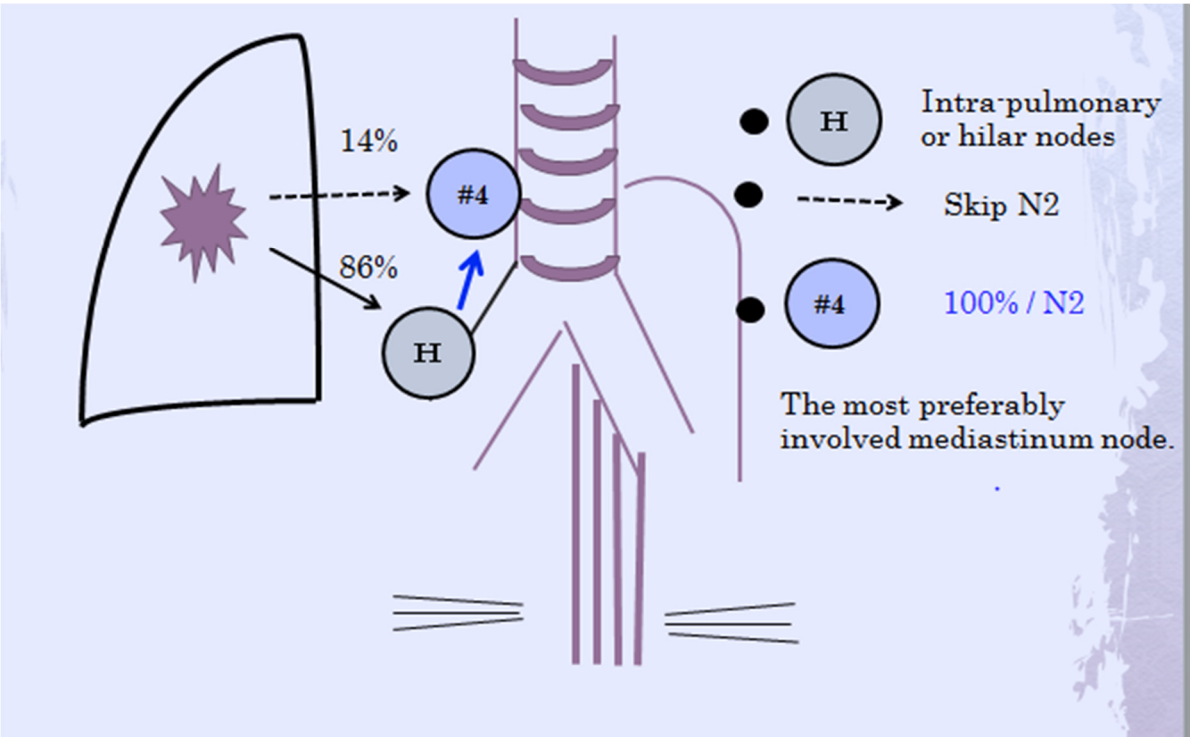
The most common skip mediastinal station was specific in each lobe (Figs. 3A-E): the right lower paratracheal node in the right upper lobe, the subaortic node in the left upper lobe, the pulmonary ligament and paraesophageal node in the bilateral lower lobes. A skip N2 is uncommon in the right middle lobe.

Fig. 3 The lymphatic map of each pulmonary lobe

We classified the lymphatics from the lung to the mediastinum into three levels: dotted black arrow: skip N2 (from lung to N2); black arrow: Level 1 (from the lung to N1); blue arrow: Level 2 (from N1 to N2); and red line: Level 3 (among N3) .H: the hilar node, # 2 upper paratracheal, #3 prevascular and retrotracheal, #4 lower paratracheal, #5 subaortic, # 6 paraaortic, #7 subcarinal, #8 paraesophageal, and #9 pulmonary ligament node.

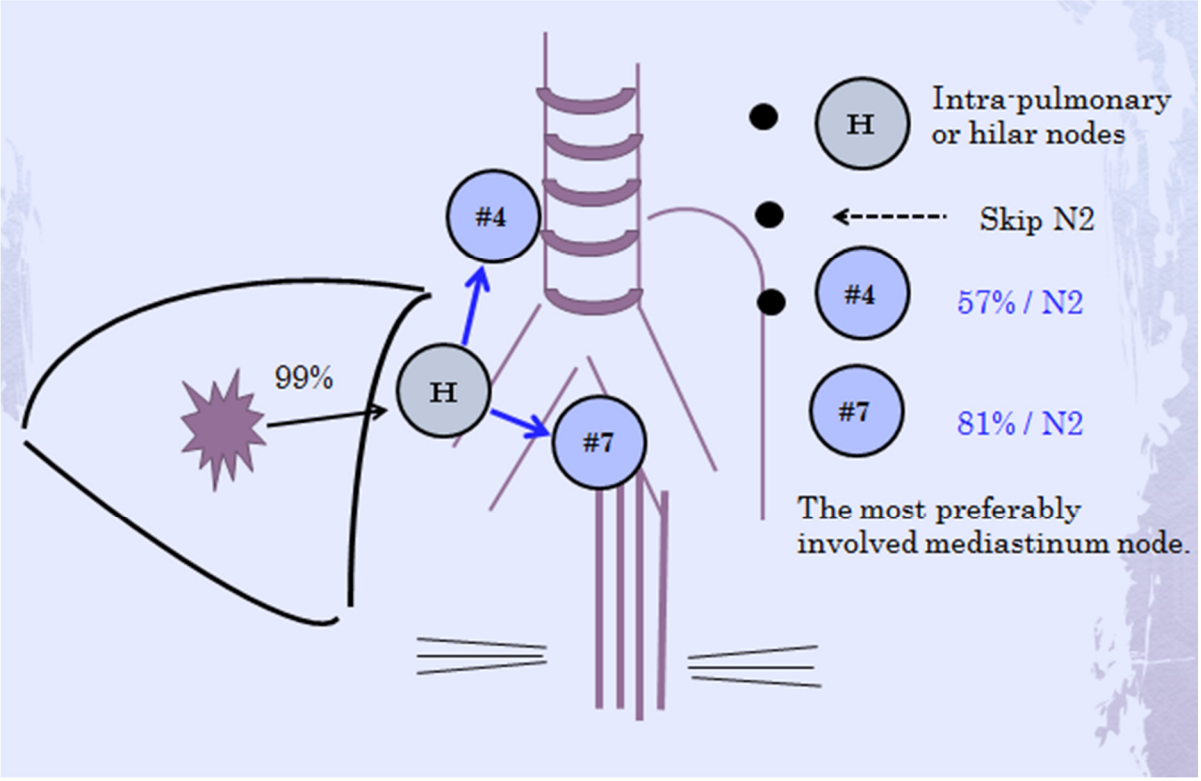
Right upper lobe: The most common skip N2 station was the right lower paratracheal node.

Fig 3A: Rt upper lobe



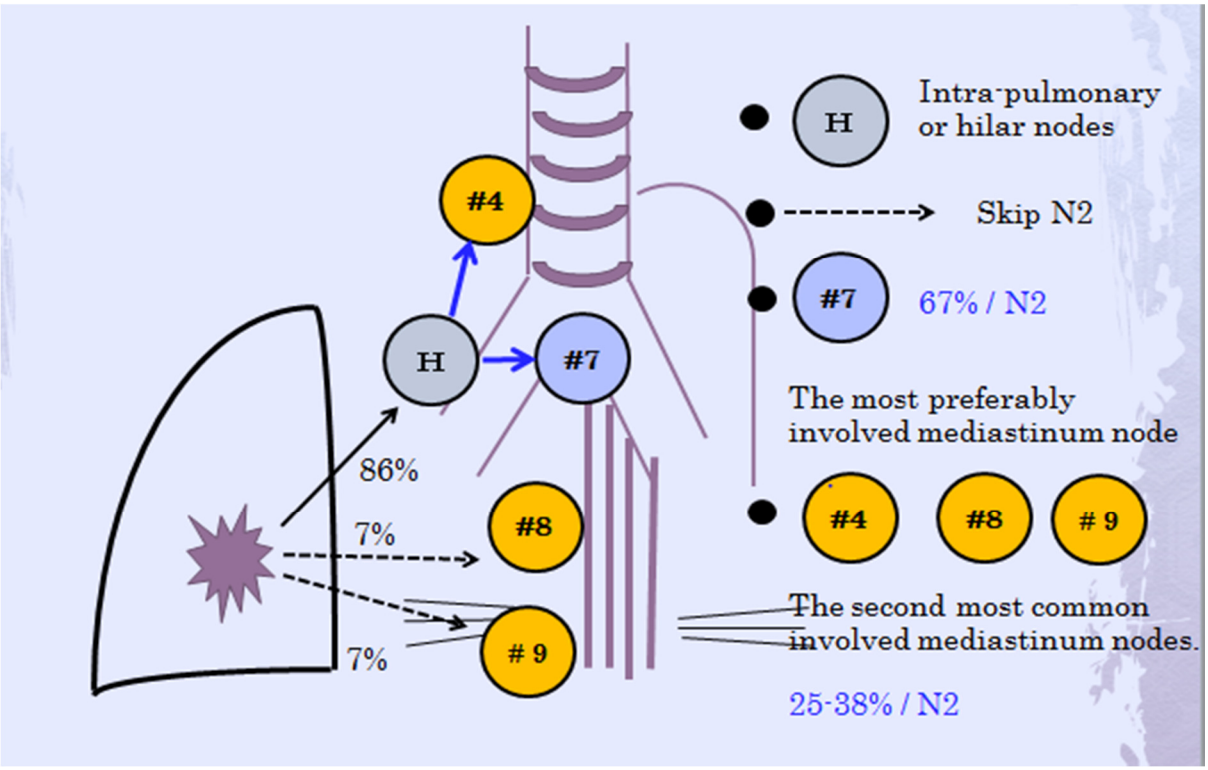
***(A)** The most commonly involved station was the lower paratracheal node in the right upper lobe.*

Fig. 3B: Rt middle lobe



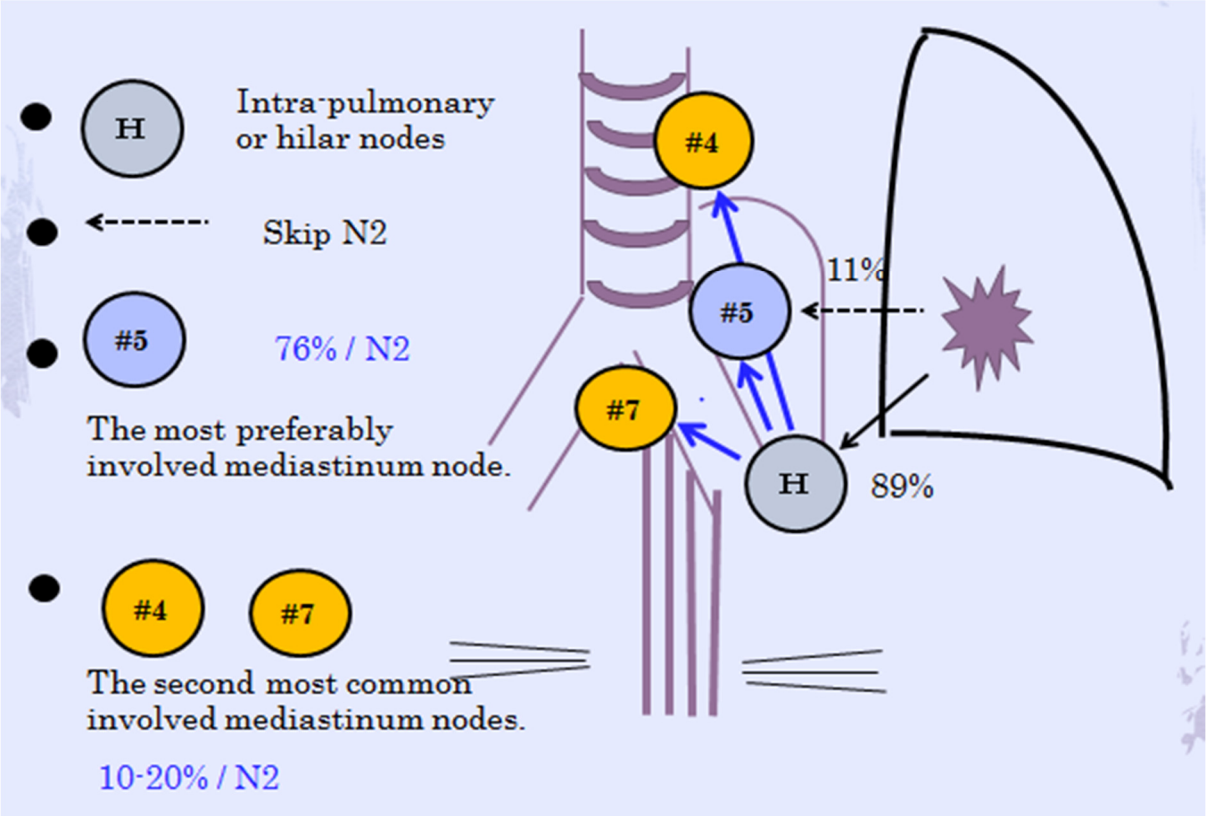
(B) *The right middle lobe: The skip N2 was uncommon in the right middle lobe. The subcarinal node was the most common, and the lower paratracheal node was the next most commonly involved station in the right middle lobe.*

Fig. 3C: Rt lower lobe



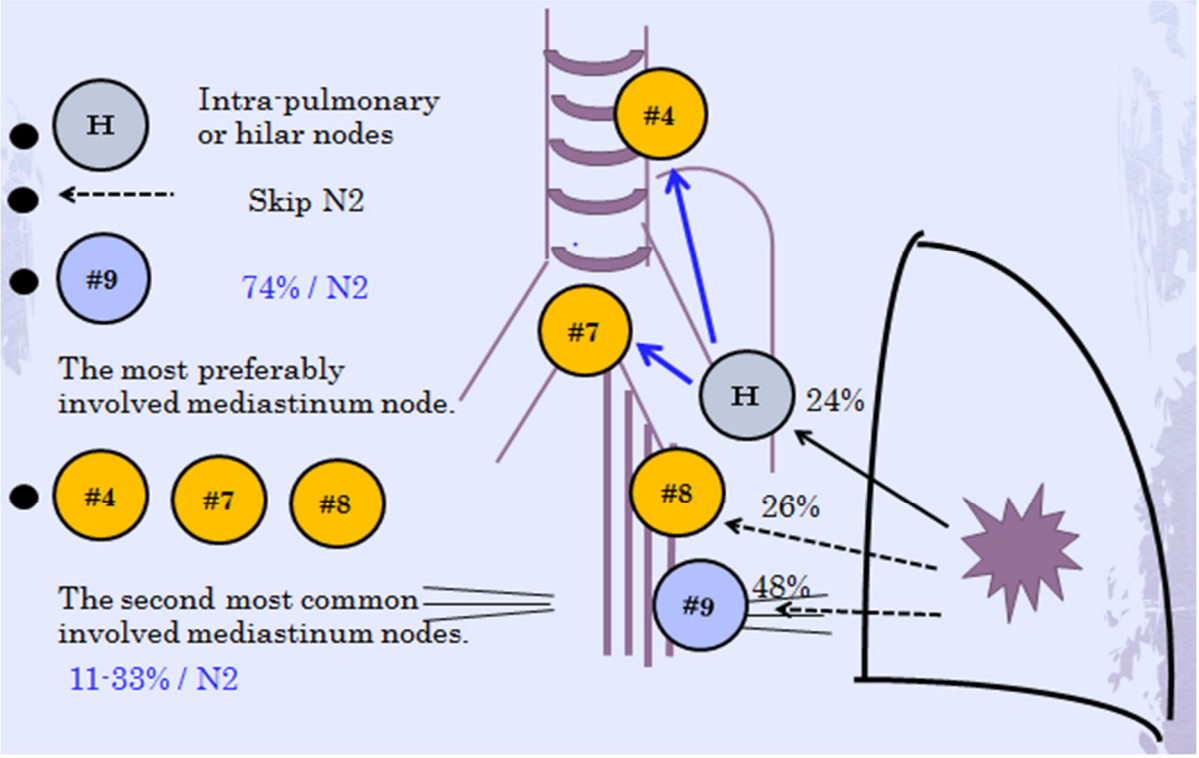
(C) *The right lower lobe: The most common skip N2 stations were the pulmonary ligament and paraesophageal node. In the right lower lobe, the most commonly involved station was the subcarinal node and pulmonary ligament; paraesophageal, and lower paratracheal node were the second most comnonly involved nodes.*

Fig. 3D: Lt upper lobe



(D)*The left upper lobe: The most common skip N2 station was the subaortic node. The most commonly involved station was the subaortic node. The lower paratracheal and subcarina nodes were the second most commonly involved nodes.*

Fig. 3E: Lt lower lobe



(E) *The left lower lobe: The most and second most common skip N2 stations were the pulmonary ligament and paraesophageal nodes, respectively. The most commonly involved station was the pulmonary ligament node. The lower paratracheal, subcarinal, and paraesophageal nodes were the second most commonly involved nodes.*

The percent occurrence of extended N2 in the right upper lobe, the left upper lobe, the right lower lobe and left lower lobe was 8.0%, 11.8%, 16.3%, and 11.6%, respectively.

The most commonly involved mediastinum stations identified within each lobe Level 2 lymphatic flow were as follows (Figs. 3A-E). In the right upper lobe, the most commonly involved station was the lower paratracheal node. In the right middle lobe, the subcarinal node was the most common, and the lower paratracheal node was the next most commonly involved station. In the right lower lobe, the most commonly involved station was the subcarinal node and the pulmonary ligament, paraesophageal, and the right lower paratracheal node were the second most commonly involved stations. In the left upper lobe, the subaortic node was the most commonly involved; the right lower paratracheal node and, the subaortic

node were the second most commonly involved stations. In the left lower lobe, the pulmonary ligament node was the most commonly involved, the paraesophageal, the subcarinal, and lower paratracheal nodes were the second most commonly involved nodes.

Subdivision of current N2 diseases

We classified the currently known N2 metastases into three stages: minimal, early, and advanced N2 (Fig. 4). When the most commonly involved nodes, which are shown on the map of each lobe, are involved in skip N2 or single station N2, the main lymphatic level contributing the nodal involvement are Level 1 and Level 2 lymphatics, respectively. They are considered localized N2 disease. When N2 metastases include multiple or extended mediastinum stations, there is involvement of Level 3 lymphatics, this is an advanced N2 stage reflecting widespread nodal metastases. In the case, that show other uncommon nodal station metastasis in skip N2 and single station N2, we classified the cases as advanced disease, since we could not exclude Level 3 lymphatics.

Discussion

The lymphatic map of the lung based on CT observations of primary complex of histoplasmosis

Our observations of pulmonary histoplasmosis CT images have several unique advantages in assessing pulmonary lymphatic drainage to the mediastinum. First, this generally self-limited infectious disease is considered to be suitable for assessing which mediastinal node is involved from each pulmonary lobe. Second, using dissection to assess the distribution of mediastinal node metastases in NSCLCs may be limited depending on the extent of nodal dissection in a thoracotomy. In contrast, in our histoplasmosis study, we evaluated the entire distribution of involved mediastinal nodes within the whole thorax in all cases.

Third, since the pulmonary lesion of the primary complex was self-limited and finally calcified into a few mm in size, we could assess the N status while avoiding the effect of T factor classification.

There are some map limitations. First, although the involved lymph nodes usually reveal calcification in patients with resolved pulmonary histoplasmosis, and we assessed the presence of calcifications on thin-slice 3-mm CT images, we may have missed

insufficient calcification of some healed nodes. Second, in cases of skipN2 or single station N2 in an atypical mediastinum node station, including extensive disease, we cannot determine if the atypical location it is due to the anatomical variation of lymphatic drainage or involvement of Level 3 lymphaics. Since there is a curious about involvement of Level 3 lymphatics, this must be judged as advanced disease. We need further analyses of NSCLCS to provide a prognosis of such groups.

Skip N2 metastases

Several studies suggest a more favorable prognosis for skip-N2 metastases than for non-skip N2 metastases [5-10]. Skip metastases in lung cancers are suspected to occur due to overlooked small metastatic foci in the N1 nodes, a direct lymphatic pathway to the mediastinum, or some biological factors involving the tumor cells, such as their proliferative potential [21,22], previous reports suggest that skip metastases are also found in micrometastatic disease [23], and that overlooked micro-metastasis in the N1 node is not the main mechanism of skip N2 disease.

The lobe specific skip involvement was similar in both tumors and histoplasmosis infection. In the study by Takahashi [18], the incidence of skip involvement differed depending on the lobe segment affected, and showed an inverse correlation of N1 involvement in the same segments, suggesting that an anatomical direct lymphatic drainage to the mediastinum contributes to skip metastases from the lung. Sasaki et al. suggested that septal structures between the pulmonary veins and mediastinum, which are occasionally seen on high-resolution CT images of normal subjects and of pneumothorax patients, might be a direct communication between the upper lobe and the mediastinum, and may provide a pathway for skip involvement [24]. Similar patterns of skip metastases of NSCLCs in our infection study results also exclude biological factors as the cause of cancers.

Although its endpoint is N2 node involvement, skip N2 occurs the Level 1 lymphatics and is considered to be an extremely limited N2. Our lymphatic map might show the difference of infection from lung cancers. Since the involvement of pulmonary ligament node is uncommon in lung cancers, more peripherally involved sites in histoplasmosis would account for these findings.

Fig. 4

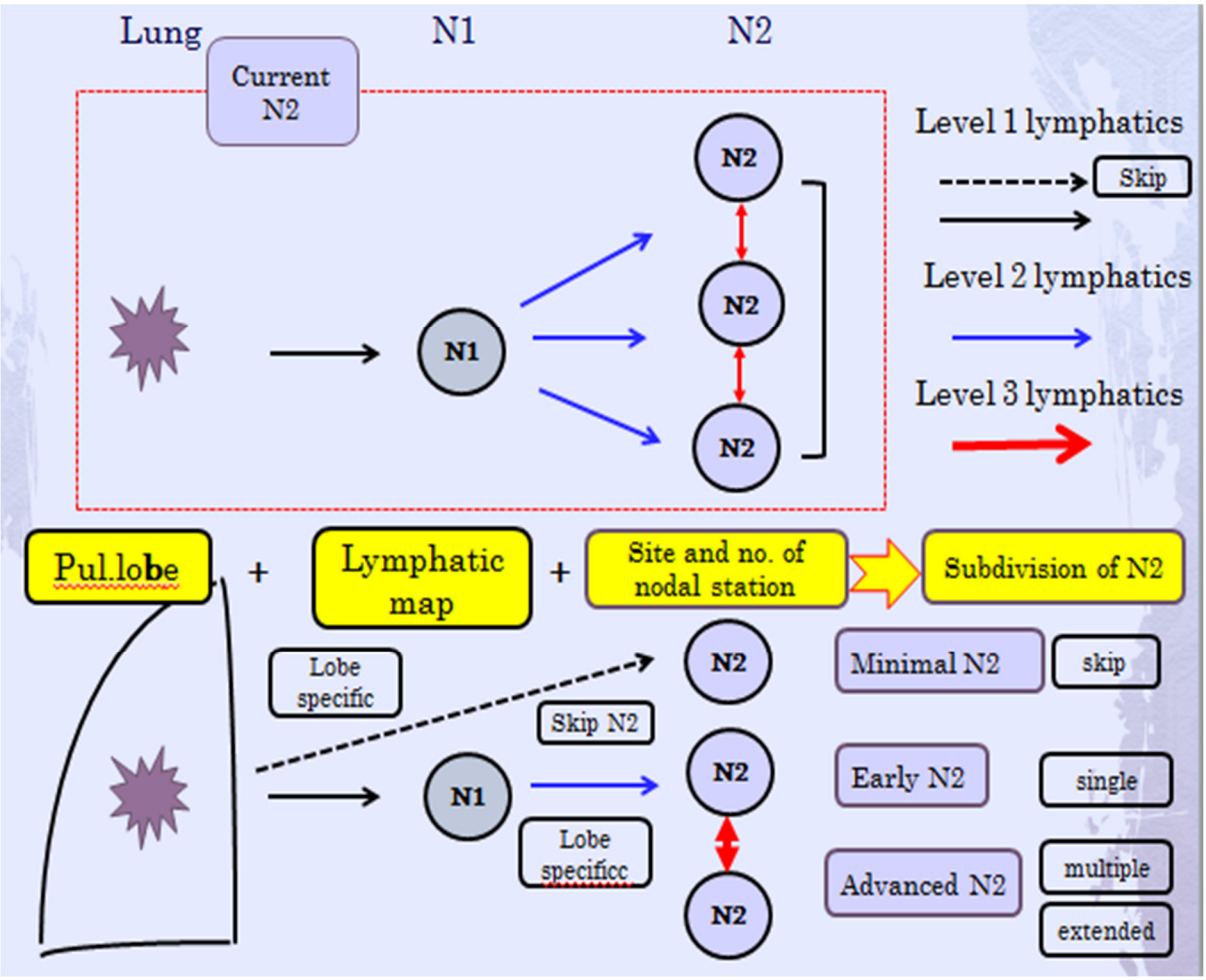


Fig. 4: *Comparison of the current N stages and our proposal of subdivision of N2 stages*

In the current N staging of NSCLCs (the encircled area by dotted line), the nodal metastatic pattern is considered similar in all pulmonary lobes and to progress from N1 to N3 subsequently in order and in the radial fashion.

The lower half of the figure shows subdivision of N2 diseases. Our lymphatic map shows the lobe specific direct lymphatic pathway from the lung to N2 and that from N1to N2 metastasis. Considering of the primary lobe, the site and number of N2 station, and the lymphatic map of each lobes, we can determine the main level of lymphatics and subdivide the current N2 into minimum, early, and advanced N2

Subdivision of N2diseases in NSCLCs

In the current N staging of NSCLCs, neither the pulmonary lobe of primary lesion nor the status of mediastinum station of nodal metastases is needed. The nodal metastasis patterns are considered similar in all pulmonary lobes and progress from N1 to N3 subsequently in order and in radial fashion.

However, our lymphatic map showed lobe-specific direct lymphatic pathways from the lung to N2 and that from N1 to N2 metastasis-. These are considered limited N2 (skip N2 and single station N2). The advanced disease stage (multiple and extended stations) results from Level 3 lymphatics. By considering the primary lobe, the status of N2 station, and the lymphatic map of each lobes, we can determine the main level of lymphatics and subdivide the current N2 into minimal, early, and advanced N2, with significant correlation with prognosis. As previously mentioned, a limitation of our staging is that in cases, that show other uncommon nodal station metastasis in skip N2 and single station N2, we cannot differentiate the anatomical variation of lymphatics and joined N3 lymphatic involvement. Therefore, these cases should be classified as advanced disease.

In conclusion, our results showed that the physiological lymphatic drainage of the lung is specific for each lobe. We subdivided current N2 diseases into, minimal, early, and advanced N2. We need to make the lymphatic map based on collected cases of single station N2 and skip N2 of resected NSCLCs from multiple institutes.

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