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ヒストプラスマ症における、CT観察に基づく肺葉からの縦隔リンパ排液 非小細胞肺癌の最小N2疾患の示唆(Mediastinal lymphatic drainage from pulmonary lobe based on CT observations of histoplasmosis: implications for minimal N2 disease of non-small-cell lung cancer)

TakahashiKoji, StanfordWilliam, Van BeekEdwin, ThompsonBrad, MullanBrian, SatoYutaka

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ORIGINAL ARTICLE

Mediastinal lymphatic drainage from pulmonary lobe based on CT observations of histoplasmosis: implications for minimal N2 disease of non-small-cell lung cancer

Koji Takahashi · William Stanford · Edwin Van Beek
Brad Thompson · Brian Mullan · Yutaka Sato

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Abstract
Purpose. The aim of this study was to assess mediastinal lymphatic drainage patterns from each pulmonary lobe using computed tomographic (CT) observations of calcified primary complex pulmonary histoplasmosis.
Materials and methods. We assessed 400 CT studies of patients with primary complex histoplasmosis consisting of a single lobe pulmonary lesion and mediastinal nodal disease. We assessed the distribution of mediastinal nodal involvement depending on pulmonary lobes for the total number of involved nodes, the number with single-station involvement (which suggests the initial site of involvement), and the number with skip involvement which suggests direct drainage to the mediastinum.
Results. The most commonly involved mediastinal nodal stations from the right upper lobe, left upper lobe, and left lower lobe were the right lower paratracheal node (97%, 74/76), the subaortic node (72%, 49/68), and the left pulmonary ligament node (61%, 66/108), respectively. These nodes were the most common site of skip involvement in each lobe. In the right lower lobe and middle lobe, the subcarinal node was most commonly involved: 62% (65/105) and 81% (35/43), respectively. By contrast, skip involvement was uncommon in the drainage to this node.
Conclusion. Our data show a predictable pattern of lobar lymphatic drainage to the mediastinum. This may have implications on the minimal N2 disease of non-small-cell lung cancer.

Key words Lung · Mediastinum · Lymphatic drainage · Lymph node · Histoplasmosis

K. Takahashi (✉)
Department of Radiology, Asahikawa Medical College and Hospital, 2-1-1-1 Midorigaoka-higashi, Asahikawa 078-8510, Japan
Tel. +81-166-68-2572; Fax +81-166-68-2579
e-mail: taka1019@asahikawa-med.ac.jp

W. Stanford · E. Van Beek · B. Thompson · B. Mullan · Y. Sato
Department of Radiology, University of Iowa College of Medicine, Iowa, USA

Introduction

The extent of lymphatic involvement is a significant prognostic predictor in non-small-cell lung cancers (NSCLCs), and correct staging is important when determining an optimal treatment plan. Patients without lymph node metastasis (N0) or with intrapulmonary and/or hilar node metastasis (N1) are good candidates for curative surgery, whereas this approach remains controversial in those with ipsilateral mediastinal disease (N2). Currently, there are no generally accepted standards for the extent of lymphadenectomy or indications for systematic mediastinal node dissection versus mediastinal node sampling in N2 lung cancers.[1] Because the prognosis of N2 NSCLCs is varied, many authors have analyzed prognostic factors in resected N2 disease with particular focus on the distribution of mediastinal node metastasis.[2–16] Specific patterns of mediastinal lymph node metastases in relation with the pulmonary lobe of primary cancer have been reported to be associated with a good prognosis, and the concept of "minimal N2 disease" has been advocated.[4,10,13–15]

Anatomically, pulmonary lymphatic drainage to the mediastinum has been assessed using injection techniques.[17,18] However, this technique basically concerns the superficial subpleural lymphatics rather than the

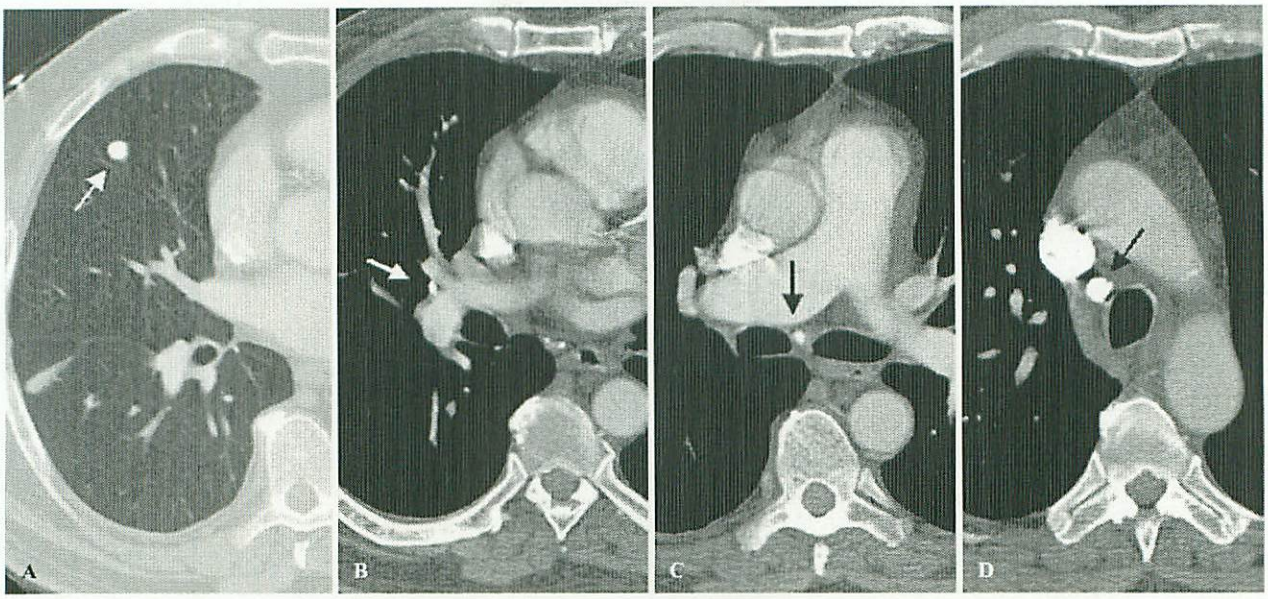

Fig. 1. A 45-year-old man with a primary complex histoplasmosis in the right middle lobe. **A** Computed tomography (CT) with lung window settings shows a calcified nodule in the right middle lobe (*arrow*). **B–D** CT with mediastinum window settings at the level of the hilum (**B**), the carina (**C**),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

deep intrapulmonary lymphatics, and the rate of injection may affect the drainage patterns. Recently, intraoperative radioisotope sentinel lymph node mapping has been applied to NSCLCs. Although this technique may improve the precision of pathological staging, its accuracy and role in NSCLCs remains to be clarified.[19–21] Thus, physiological lymphatic drainage patterns to the mediastinum from each pulmonary lobe should be elucidated in detail.

Histoplasmosis is an endemic fungal disease caused by *Histoplasma capsulatum*, and its infection is particularly prevalent in the central and eastern United States, notably in the Ohio, Mississippi, and St. Lawrence river valleys. The infection results from inhalation of airborne spores, and usually the lung is the primary site of involvement. With the primary infection, pulmonary lesions are solitary in about 90% and commonly associated with hilar and/or mediastinal nodal disease.[22] In individuals with normal cellular immunity, pulmonary histoplasmosis spontaneously resolves and results in a calcified primary complex similar to primary tuberculosis.[22] Therefore, a calcified primary complex is a common finding on chest CT studies in patients from areas endemic for histoplasmosis (Fig. 1).

We hypothesized that physiological lymphatic drainage to the mediastinum from each lung lobe could be studied by reviewing the patterns of primary complex of histoplasmosis using chest CT.

Materials and methods

Study subjects

The institutional review board approved this study without requirement of informed consent. From October 2003 to January 2005, we collected all subjects for whom a clinical diagnosis of pulmonary histoplasmosis was made using CT findings: single or multiple well-defined lung nodules with central or dense calcification. In this area of endemic histoplasmosis (state of Iowa in the United States), the presence of central or diffuse calcification in a pulmonary nodule ≤3 cm in diameter is invariably diagnostic of a granuloma most likely due to histoplasmosis.[22] Patients with a clinical history of tuberculosis, sarcoidosis, or pneumoconiosis according to their medical records were excluded to avoid intrathoracic calcifications due to other etiologies. Patients with mediastinal and/or hilar lymphadenopathies were also excluded irrespective of the presence of calcification in the nodes.

Pulmonary lesions were seen in a single lobe in 666 patients and in multiple lobes in 175 patients (total 841 patients). In the 666 patients with pulmonary histoplasmosis in a single lobe, 184 showed only hilar node calcifications, 319 showed both hilar and mediastinal node calcifications, 81 showed only mediastinal node calcifications, and 82 did not show any nodal calcifica-

tions. The 400 patients (234 males and 166 females with a mean age of 60 years) with primary complex histoplasmosis consisting of single-lobe pulmonary lesions and calcified mediastinal nodal disease were enrolled in this study.

CT examination and interpretation

All CT studies were performed with 4- or 6-detector row CT scanners (Aquillion, Toshiba Medical Systems, Tokyo, Japan or Emotion 6, Siemens Medical Solutions, Erlangen, Germany) with the following scan parameters: 135 kV, 130 mA, gantry rotation time of 0.5 s, 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, Tokyo, Japan). The images were assessed with both lung (window level −500 HU, window width 2000 HU) and soft tissue (window level 40 HU, window width 400 HU) window settings; these were voluntarily adjusted, if necessary. Patients received 80–150 ml of nonionic intravenous 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.

Calcifications in the lesion were initially evaluated by qualitative assessment, and region of interest (ROI) measurement was used in equivocal cases. An attenuation value greater than +200 HU was considered to reflect calcifications. For nodal disease, we considered both partial and total calcifications to be significant.

In patients with a primary complex of histoplasmosis, we determined the lobe with the pulmonary lesion and the site of nodal disease: hilar, mediastinal, or both. In patients with mediastinal nodal disease, the site of nodal involvement was assessed according to the classification advocated by the American Thoracic Society, American Joint Committee on Cancer, and the Union Internationale Contre le Cancer (AJCC-UICC), which was designed primarily for staging bronchogenic carcinoma[23]: #1, highest mediastinal; #2, upper paratracheal; #3, prevascular and retrotracheal; #4, lower paratracheal; #5, subaortic; #6, paraaortic; #7, subcarinal; #8, paraesophageal; #9, pulmonary ligament node (Fig. 2). We assessed the distribution of the involvement of each mediastinal nodal station according to the involved pulmonary lobe. We further assessed the incidence and site of single-station involvement and those of skip involvement in relation to the pulmonary lobes. Skip involvement was defined as mediastinal node involvement without intrapulmonary or hilar node involvement.[24,25] Subjects were retrospectively identified based on the diagnosis; and a single experienced pulmonary radiologist subsequently reassessed all CT studies with an emphasis on lymph node localization in relation to the primary histoplasmosis lesion.

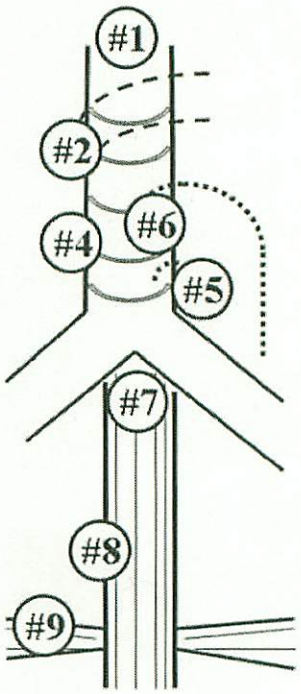

Fig. 2. Classification of mediastinal nodal station. #1, highest mediastinal; #2, upper paratracheal; #3, prevascular and retrotracheal (not shown); #4, lower paratracheal; #5, subaortic; #6, paraaortic; #7, subcarinal; #8, paraesophageal; #9, pulmonary ligament node

Statistical analysis

For statistical comparative analysis, the mean values and proportions between two groups were assessed using the two-sample *t*-test and chi-squared test (Fisher's exact probability test of data including the subset <5). $P < 0.05$ was considered to indicate statistically significant difference.

Results

Mediastinal node involvement in relation to pulmonary lobes

The mean number of involved mediastinal nodal stations in this population was 1.1 in the right upper lobe (RUL), 1.5 in the right middle lobe (RML), 1.5 in the right lower lobe (RLL), 1.3 in the left upper lobe (LUL), and 1.6 in the left lower lobe (LLL). For the right lung, the number of involved mediastinal node stations in the middle and lower lobes was significantly larger than that in the upper lobe, with $P < 0.001$ and $P < 0.001$, respectively. For the left lung, the number of involved mediastinal nodal stations in the lower lobe was significantly larger than that for the upper lobe. with $P < 0.05$.

Table 1. Distribution of mediastinal lymph node involvement in relation to pulmonary lobes

	Lymph node station													
	Ipsilateral									Contralateral				
Site	#1	#2	#3	#4	#5	#6	#7	#8	#9	#1	#2	#3	#4	#5
RUL (n = 76)		2	2	74			6						1	1
RML (n = 43)		1		25			35		2				1	1
RLL (n = 105)	1	3		24			65	26	37					
LUL (n = 68)				10	49	3	11	3	3		2		6	
LLL (n = 108)		1	2	16	7	1	37	35	66	1	2	1	4	

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; #1, highest mediastinal; #2, upper paratracheal; #3, prevascular and retrotracheal; #4, lower paratracheal; #5, subaortic; #6, paraaortic; #7, subcarinal; #8, paraesophageal; #9, pulmonary ligament

Table 2. Distribution of single station mediastinal lymph node involvement in relation to pulmonary lobes

	Lymph node station													
	Ipsilateral									Contralateral				
Site	#1	#2	#3	#4	#5	#6	#7	#8	#9	#1	#2	#3	#4	#5
RUL (n = 67)				65 (17)			2 (0)							
RML (n = 24)				7 (1)			17 (1)							
RLL (n = 65)				5 (0)			36 (1)	9 (5)	15 (7)					
LUL (n = 55)				4 (0)	40 (8)	1 (0)	5 (3)	2 (1)	1 (0)				2 (0)	
LLL (n = 64)				7 (0)	2 (0)		13 (0)	8 (4)	33 (15)				1 (0)	

Data in parentheses are number of single station skip involvement

Distribution of mediastinal node involvement in relation to pulmonary lobes

The distribution of involved mediastinal nodes, both as total number involved and the number of single stations involved are shown in Tables 1 and 2. The most commonly involved nodal stations in each lobe were the lower paratracheal node in the RUL (74/76), the subcarinal node in the RML (35/43) and in the RLL (65/105), the subaortic node in the LUL (49/68) and the pulmonary ligament node in the LLL (66/108). These nodes also most commonly had single-station involvement from corresponding pulmonary lobes.

The incidences of skip involvement in each pulmonary lobe were 22.4% (17/76) in the RUL, 4.7% (2/43) in the RML, 20.0% (21/105) in the RLL, 23.5% (16/68) in the LUL, and 23.1% (25/108) in the LLL. Skip involvement was significantly less frequent in the RML than in other lobes (vs. RUL, $P < 0.05$; vs. RLL, $P < 0.05$; vs. LUL, $P < 0.05$; vs. LLL, $P < 0.01$).

The most common station of skip involvement in each lobe was as follows: lower paratracheal node in the RUL (17/17) (Fig. 3); pulmonary ligament node in the RLL (12/21); subaortic node in the LUL (11/16) (Fig. 4); and pulmonary ligament node in the LLL (21/25) (Fig. 5). These skip involvements also were most commonly single-station involvement.

Discussion

In our observations, calcified pulmonary nodules suspicious for histoplasmoma were localized in a single lobe in 79% (666/841) of cases, and 88% (584/666) of them showed regional calcified lymph nodes in the hilum and/or mediastinum: 86% (503/584) in the hilum and 68% (400/584) in the mediastinum. During the observation period, we found a total of 877 cases with calcified nodal disease in the hilum and/or mediastinum, and 744 (85%) of the cases showed calcified pulmonary lesions. Based on these data, we think that the calcified primary complex of pulmonary histoplasmosis is an appropriate model for assessing lymphatic drainage to the mediastinum from each pulmonary lobe due to its high incidence of single-lobe lesions and frequent association between lung and nodal disease. Furthermore, it seems appropriate to use 3-mm contiguous CT slices and evaluate them on a workstation to detect calcifications in both pulmonary and nodal lesions.

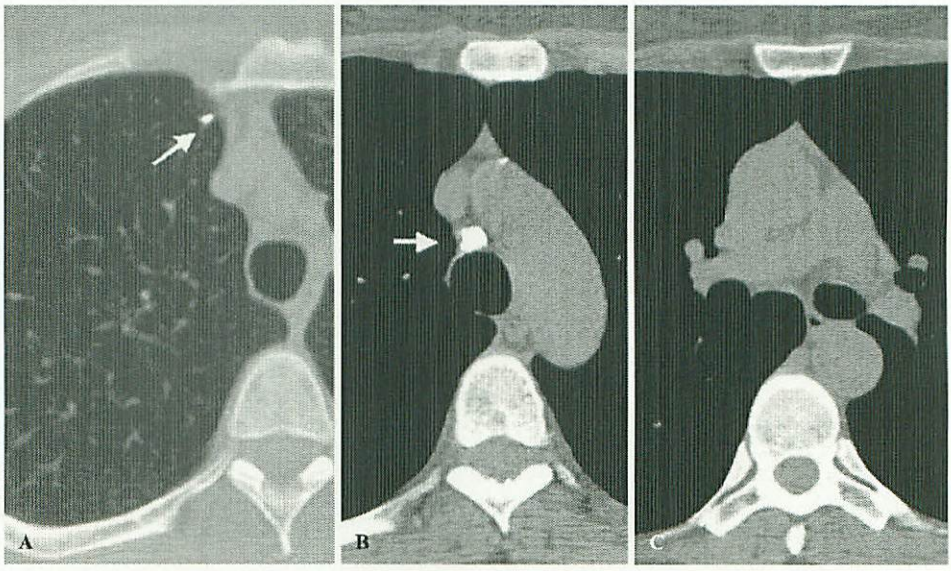

Fig. 3. A 56-year-old woman with a skip involvement due to right upper lobe histoplasmosis. **A** CT with lung window settings shows a calcified nodule in the right upper lobe (*arrow*). **B, C** CT with mediastinum window settings at the level of the mid-trachea (**B**) and hilum (**C**) show a calcified right lower paratracheal node (*arrow* in **B**) but no calcified node in the hilum (**C**)

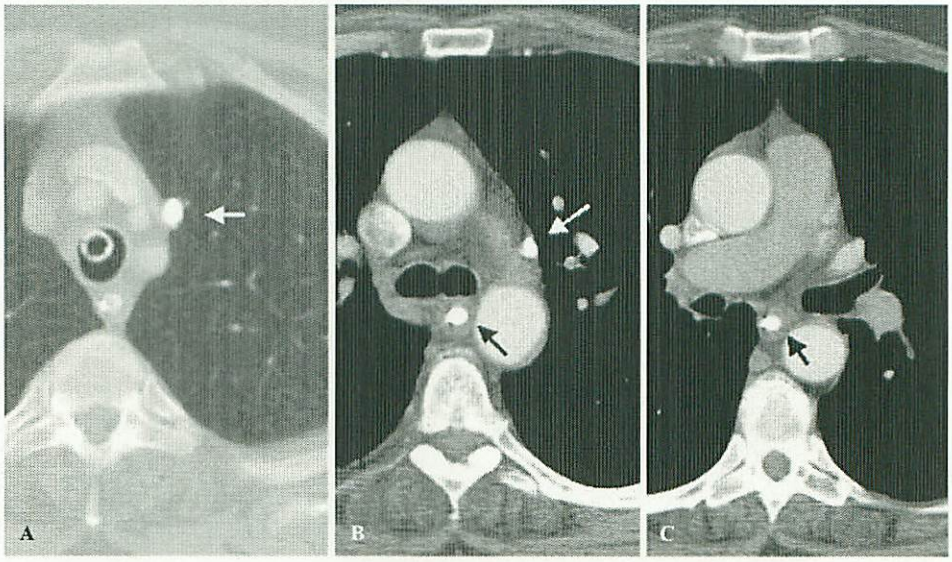

Fig. 4. A 63-year-old woman with a skip involvement due to left upper lobe histoplasmosis. **A** CT with lung window settings shows a calcified nodule in the left upper lobe (*arrow*). **B, C** CT with mediastinum window settings at the level of the carina (**B**) and the hilum (**C**) show a calcified subaortic node (*white arrow* in **B**) but no calcified node in the hilum (**C**). *Black arrows* in **B** and **C** indicate a nasogastric tube in the esophagus

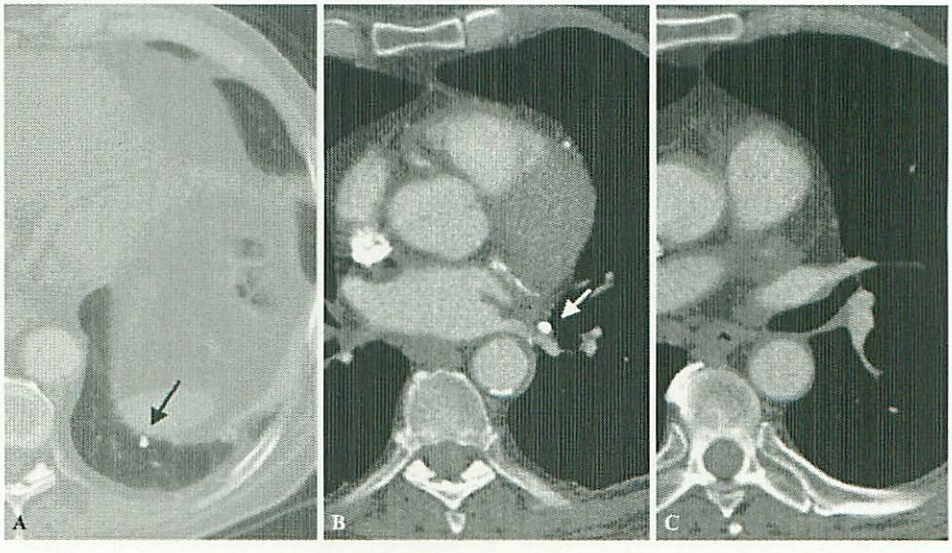

Fig. 5. A 65-year-old man with a skip involvement due to left lower lobe histoplasmosis. **A** CT with lung window settings shows a calcified nodule in the left lower lobe (*arrow*). **B, C** CT with mediastinum window settings at the level of the pulmonary ligament (**B**) and the hilum (**C**) show a calcified pulmonary ligament node (*arrow* in **B**) but no calcified node in the hilum (**C**)

We assessed the distribution of involvement in each mediastinal nodal station for the total number of involved stations, the number of single-station involvements, and the number of skip involvements. Because the mean total number of involved stations in each pulmonary lobe was limited (1.1–1.6 stations), we think this distribution is likely to reflect early-phase involvement of the mediastinal node. Although we cannot determine the actual incidence of initial involvement in each mediastinal node station, the distribution of single-station involvement was believed to reflect the preferred initial mediastinal node involvement from the particular lobe. Skip metastases in lung cancers have been suspected to occur owing to a direct lymphatic pathway to the mediastinum, overlooked small metastatic foci in the hilar and/or intrapulmonary node, or some factors involving tumor biology, such as the proliferative potential of metastatic tumor cells.[24] Our data showed that skip involvement also occurs with fungal infections. In a study of 360 cadavers by Riquet, direct passage to the mediastinal nodes from segmental lymph channels were observed in 20%–40%,[18] which is similar to the incidence of skip metastases from lung cancers.[9,11,12,14,16,24,25] Although we cannot exclude overlooked minimal hilar disease, we argue that skip involvement, especially seen as a single-station disease, mainly reflects a direct lymphatic pathway to the specific mediastinal node—based on the similarity of the incidence in our data to that in an anatomical study.[25]

The lymphatic drainage of the right lung can thus be summarized as follows: The upper lobe drains into the right lower paratracheal node (Fig. 6A) partly through the direct lymphatic pathway. The middle lobe drains bidirectionally into the subcarinal and right lower paratracheal node mainly via the hilar node (Fig. 6B). The lower lobe has a more complex pattern, involving the subcarinal node, the pulmonary ligament, the paraesophageal node, and the right lower paratracheal node. Subcarinal node involvement usually occurs through the hilar node, and a direct connection could only be suggested through skip involvement of the pulmonary ligament and paraesophageal nodes (Fig. 6C).

Left lung drainage is marginally different. The upper lobe tends to drain to the subaortic node and less frequently to the subcarinal node. The presence of a direct pathway to the subaortic node was suspected. Subcarinal node involvement was more common from lingular segments than from upper segments (Fig. 6D). Finally, the lower lobe most commonly drains into the pulmonary ligament node, with the subcarinal and paraesophageal nodes as the next common sites. There seemed to be direct drainage into the pulmonary ligament node (Fig. 6E).

The anatomical pathways of lymphatic drainage from each pulmonary lobe to the mediastinal lymph node have been described in several articles.[17,18,26,27] The distribution of the predominantly involved mediastinal nodes from each pulmonary lobe in our results agrees with previous descriptions except for the left lower lobe, in which the subcarinal node has been reported to be the most frequent site. However, in the anatomical studies, the presence of drainage to the ipsilateral pulmonary ligament node and subsequently to the inferior paraesophageal node from the lower lobe is more common on the left side because these nodes are more abundant on the left.[26,27]

With localized NSCLCs, intrathoracic lymph node metastases are the most important predictor of survival and curability. With resected N2 NSCLCs, it has been generally accepted that patients with single-station mediastinal node metastasis have a better prognosis (5-year survival 35%–48%) than those with involvement of multiple mediastinal node stations (5-year survival 11%–18%).[3,7,8,11–15] Some authors have reported that patients with LUL tumors and a single metastasis to the subaortic lymph node had a good prognosis after complete resection, with a 5-year survival of 42%–63%, and suggested that the subaortic nodes constitute an important pathway of lymph drainage for the left upper lobe and may be equivalent to the hilar lymph nodes.[4,13,14] Similarly, the right paratracheal or tracheobronchial node metastases from RUL tumors are also associated with a good prognosis (5-year survival 48%–60%) compared with other N2 diseases.[14,15] These mediastinal nodes were the most common single-station node metastasis from the corresponding lobe[8,9,12,15] and also common sites of skip metastasis.[9,24] In a few articles, a good prognosis of single-station metastasis to the pulmonary ligament or paraesophageal node was suggested for left lower lobe cancers.[10,14] These specific patterns of mediastinal spread of lung cancers with a favorable prognosis agree with the initial site of mediastinal node involvement and the contribution of a direct pathway in our results, and we think that they could reflect minimal N2 disease.

There has been controversy as to the significance of subcarinal node involvement as a prognostic predictor. Initially, poor survival of patients with a subcarinal metastasis has been suggested,[2,3] but neither the site of primary tumors nor the presence of associated other nodal metastases were considered in these analyses. More recent studies have reported that subcarinal node involvement predicts a poor prognosis only when it is a metastasis from an upper lobe tumor or when there are other station nodal metastases associated.[5,9,13,15] In our observations, the subcarinal node was considered the

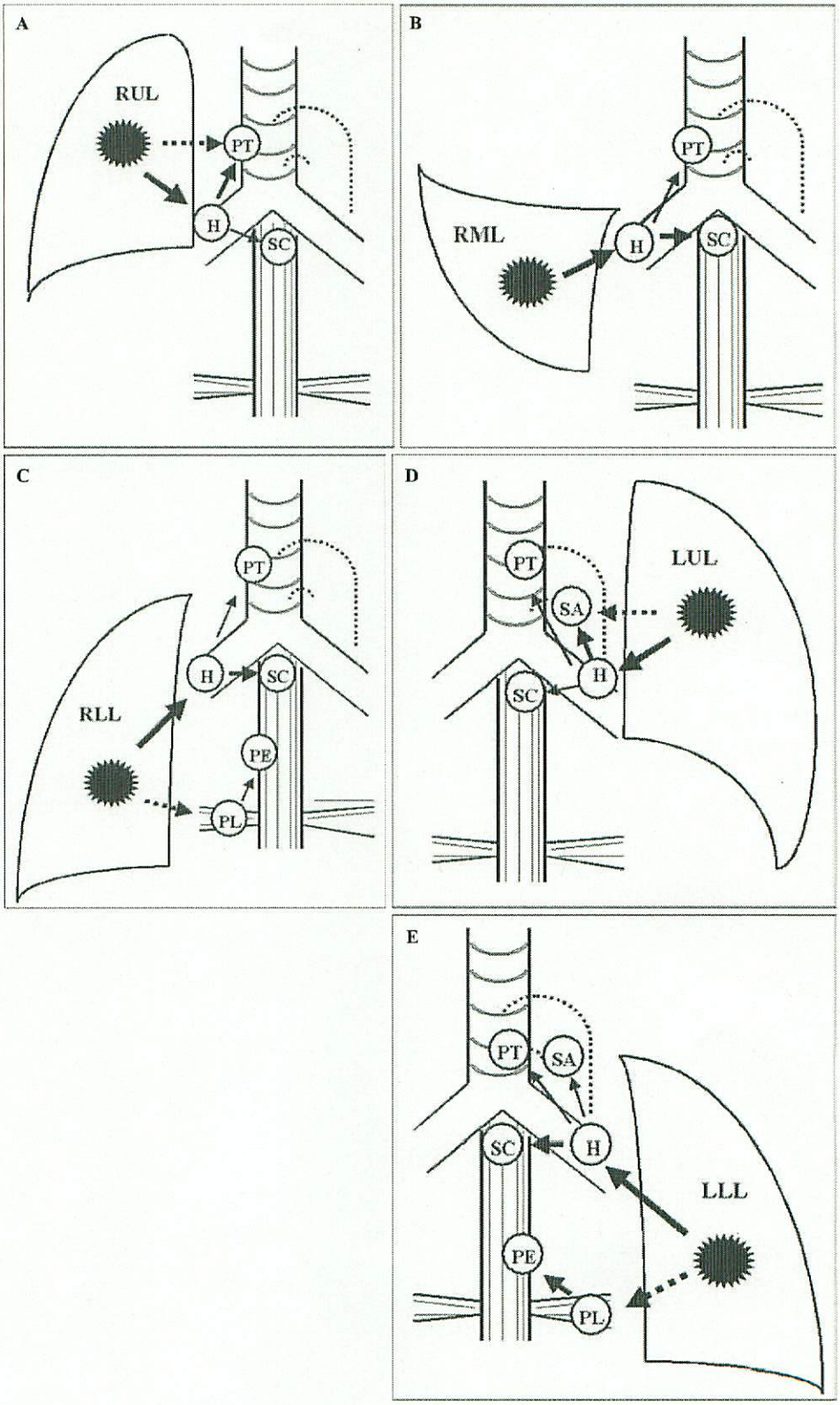

Fig. 6. Main lymphatic drainage pattern to the mediastinum depending on each pulmonary lobe. **A** Right upper lobe (*RUL*). The right lower paratracheal node is considered to be the initial mediastinal site of lymphatic drainage partly through the direct lymphatic pathway (*dotted arrow*). **B** Right middle lobe (*RML*). Lymphatic drainage to the mediastinum is usually via the hilar node and bidirectional to the subcarinal node and the right lower paratracheal node. **C** Right lower lobe (*RLL*). Main lymphatic drainage to the mediastinum is to the subcarinal node commonly via the hilar node and pulmonary ligament node through a direct pathway (*dotted arrow*). *PE*, paraesophageal node. **D** Left upper lobe (*LUL*). The subaortic node was initially involved via the hilar node and a direct pathway (*dotted line*). **E** Left lower lobe (*LLL*). Pulmonary ligament node was most commonly involved probably through a direct pathway (*dotted line*). Subcarinal node was the next most common site of involvement usually via the hilar node. *H*, hilar node; *PE*, paraesophageal node; *PL*, pulmonary ligament node; *PT*, paratracheal node; *SA*, subaortic node; *SC*, subcarinal node

primary station for both the RLL and RML. Thus, tumors located in these lobes with isolated subcarinal nodal metastasis could be classified as surgically resectable. Naruke et al., who assessed 35 patients with N2 NSCLCs and who survived 5 years or more, noted that 8 patients following surgical resection had subcarinal node metastasis as a single-station involvement: right lower lobectomy in 4, right middle and lower lobectomy in 1, left lower lobectomy in 1, right pneumonectomy in 1, and left pneumonectomy in 1.[28]

In the LLL, the subcarinal node was the second most common site of involvement in our results, whereas it was the most common metastatic site in most studies of lung cancers.[8,9,12,15] We speculate that this disagreement could be due to differences in location within a lobe for lung cancers with a more central distribution and histoplasmosis with a more peripheral distribution. Kayser et al. indicated that centrally localized tumors are more predisposed to involve the main bronchus and subcarinal lymph nodes than are peripherally located tumors.[6] Nohl observed that lower lobe cancers tend to involve the pulmonary ligament nodes, especially on the left side.[29]

Our results and these assessments of N2 NSCLCs suggest the following conditions for minimal N2 NSCLC disease: single-station involvement in the right lower paratracheal node from lung cancer in the RUL, subaortic node from the LUL, and pulmonary ligament node from RLL and LLL.

Recently, a few authors[19–21] have utilized the sentinel mapping technique for NSCLCs. Among NSCLCs, a mediastinal sentinel node was identified in 22%–48% with the following common patterns: right superior mediastinal nodes from the RUL, aortic or superior mediastinal nodes from the LUL, subcarinal or other inferior mediastinal nodes from the RLL, and aortic, superior mediastinal, or inferior mediastinal nodes from the LLL. Because the accumulated data of sentinel nodal mapping for lung cancers are still limited, we think that correlation with our lymphatic drainage mapping contributes to the assessment of its significance as a predictor of distal nodal metastases.

Our study is limited owing to a lack of a definitive diagnosis of histoplasmosis based on culture or histological studies. Although in patients with resolved pulmonary histoplasmosis involved lymph nodes usually reveal calcification, we cannot deduce that only those lymph nodes that are calcified are those that drained the specific region of the lung. However, our analysis of a large amount of data from 400 patients revealed specific patterns of mediastinal lymphatic drainage from each pulmonary lobe; and the data were well correlated with the described patterns of mediastinal lymph node metastases in NSCLCs and anatomical descriptions of a mediastinal lymphatic pathway from each pulmonary lobe. We believe that our data reflect the main features of a lymphatic drainage pattern from each pulmonary lobe.

Conclusion

Our results demonstrate a clear lymphatic drainage pattern that is lobe-specific and involves primary stations in the mediastinum. Although additional variation undoubtedly occurs, these drainage patterns facilitate recognition of minimal N2 NSCLC disease. Further studies using a correlation with surgical findings and pathological specimens may be useful.

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