Pulmonary lymphatic drainage in Non-Small Cell Lung Cancer

Poster No.: C-1869
Congress: ECR 2012
Type: Educational Exhibit
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Keywords: Neoplasia, Metastases, Diagnostic procedure, PET-CT, CT, Lymph nodes, Lung, Anatomy
DOI: 10.1594/ecr2012/C-1869

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Learning objectives

To highlight the anatomic pathways of lung lymphatic drainage, including both pleural and parenchymal network.

To illustrate the new thoracic lymph node (LN) map proposed by the International Association for the Study of Lung Cancer (IALSC) by schemes and axial and multiplanar CT images with attention to the definition of the exact anatomic borders of LN stations and the lymphatic drainage of non-small cell lung cancer (NSCLC).

To discuss how to choose the most adequate diagnostic invasive procedure such as mediastinoscopy, transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided needle aspiration (EBUS-NA), esophageal ultrasound-guided needle aspiration (EUS-NA), according to lymph node involvement assessed by non-invasive imaging modalities such as computed tomography (CT), positron emission tomography (PET) and PET-CT in NSCLC.
**Background**

Lung cancer is lymphophile and its lymphatic drainage crosses through the lymph nodes. In an initial tumoral stage, removing the tumor and the involved LNs may offer a chance of a cure. The extent of LN involvement in patients with NSCLC is the most important prognostic factor and influences therapy.

**PULMONARY LYMPHATIC DRAINAGE**

The lungs have a rich lymphatic supply consisting of a pleural and parenchymal network. Pleural lymphatics course over the parietal and visceral pleural surfaces and drain into the medial aspect of the lung near the hilum, where they anastomose with the parenchymal lymphatics. Parenchymal lymphatics are located in the interlobular septa and bronchovascular bundles. These lymphatic channels anastomose with each other before draining sequentially into the intralobular, interlobular, lobar, hilar and finally the mediastinal nodes (Figure 1) [1]. A study demonstrated the existence of lung lymphatic vessels running directly to the mediastinal nodes bypassing the hilar and interlobar nodes [2]. Lymph is transported by valved and pulsatile lymph vessels from the periphery toward more proximal lymphatics and nodes. LNs are interposed on the way of lymphatic vessels and lymph vessels together with the LNs form anatomical chains. The lymph vessels reach the mediastinum, the thoracic duct and subsequently the blood circulation by a cervical venous confluence. This pathway is responsible for the spread of NSCLC from the lung to the hilum, into the mediastinum and finally into the blood circulation. Anatomy is probably the best way for better understanding of lymphatic spread of lung cancer.

**LN INVOLVEMENT IN NSCLC**

In NSCLC, the nodal status determines surgical resectability. The TNM classification system for lung cancer (table 1) defines N1 disease as involvement of ipsilateral peribronchial, hilar, or intrapulmonary nodes. N1 disease is considered surgically resectable. Ipsilateral mediastinal or subcarinal node involvement is classified as N2 disease. These cases may be amenable to surgery, but treatment also involves chemotherapy and irradiation. Contralateral mediastinal or hilar node involvement and disease in the supraclavicular nodes are classified as N3 disease. This is advanced disease and contra-indicates surgery [1]. Involved LN location is of crucial importance because converts N1 to N2 or N3 disease. Accurate staging of LN involvement is an essential aspect of the management of patients with NSCLC and influences decision about therapy.

Precise and universally accepted nomenclature to describe lymph node involvement is the key to assess treatment outcomes, comparing results across institutions, designing and analyzing clinical trials, and selecting therapy for individual patients [3]. In 2009,
the International Association for the Study of Lung Cancer (IALSC) published the new international LN map that has been adopted in the seventh TNM classification.

Tumor spread is usually sequential, first to the ipsilateral segmental, interlobar, or lobar intrapulmonary nodes (N1), then to ipsilateral hilar node (N1) and thereafter to ipsilateral mediastinal and/or subcarinal LNs (N2) and contralateral mediastinal LNs (N3), but the mediastinal pathways are variable and are related to the lobe of origin of the pulmonary lymphatics. Studies of lung cancer in various lobes confirm that nodal pathways are largely dependent on the lobar origin of the tumor. Various studies indicated that mediastinal LN metastases from right upper lobe tumors occur predominantly in the right paratracheal area, while those from left upper lobe tumors occur most frequently in the peri- and subaortic LNs and those from middle and lower lobe tumors occur in the subcarinal, then in the right paratracheal LNs [3-5].

Direct drainage to the mediastinal lymph nodes bypassing the hilar and interlobar nodes explain the so-called skip metastases that can be seen in up to 25% of lung segments injected experimentally. Clinically, skip metastases have been reported in 7 to 26% of resected lung cancer specimens and appear to be most frequent in upper lobe tumors. Possible mechanism of skip metastases is the anatomic lung lymph drainage pattern [6].

**STAGING DIAGNOSTIC PROCEDURES**

The aim of staging procedures, both non-invasive and invasive, in patients with NSCLC is guiding the multidisciplinary decision on whether the patient is candidate to resection and non-invasive techniques (chest CT scan, PET scan and PET-CT scan) represent the first step for staging. These imaging modalities may guide the choice of the most adequate diagnostic invasive techniques including surgical (mediastinoscopy) and non-surgical methods (TBNA, EBUS-NA, EUS-NA) [7].
Fig. 1: PULMONARY LYMPHATIC DRAINAGE

Lymph is transported from the periphery toward more proximal lymphatics and nodes. Lymphatic usually drain sequentially into the intralobular, interlobular, lobar, hilar and mediastinal nodes.

Fig. 1

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TABLE 1: NODAL STAGING IN LUNG CANCER ACCORDING TO AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM CLASSIFICATION

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to ipsilateral peribronchial, hilar, or intrapulmonary nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal and/or subcarinal nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to contralateral mediastinal or hilar nodes or to ipsilateral or contralateral supraclavicular nodes</td>
</tr>
</tbody>
</table>

Sharma A RadioGraphics 2004

Table 1

THE IALSC LYMPH NODE MAP

The IALS lymph node map and the anatomic definitions for each of the LN stations are shown in Figures 2-11.

LYMPHATIC PATHWAYS OF LUNG CANCER

We show schemes and cases from our archive, with the aim to localize lymphatic metastatic pathways of NSCLC including the most frequently involved lymphatic stations according to the tumor origin (Figures 12-19) and skip metastases (Figure 20).

N STAGING NON-INVASIVE TECHNIQUES

Chest CT

CT still plays a central role in NSCLC imaging. For the N factor, contrast CT is accurate in detecting enlarged LN, but the clinical relevance of LN enlargement is poor because small nodes may contain metastases in up to 20% and large nodes may be benign. A diameter larger than 1 cm in the short axis is generally considered as the standard criterion for suspecting malignant LN. In a review [8], CT shows a sensitivity of 57%, a specificity of 82%, a positive predictive value (PPV) of 56% and a negative predictive value (NPV) of 83% (Table 2). This performance is insufficient for clinical decision making but it can be of help in selecting the most appropriate procedure for tissue sampling of suspected LNs [7].

PET and PET-CT

Non-invasive NSCLC staging was substantially improved by the use of PET with 18F-fluoro-2-deoxy-D-glucose (FDG-PET). A large number of accuracy studies and meta-analyses have demonstrated that PET is superior to CT for mediastinal LN staging, as shown in table 2. An increased diagnostic accuracy is guaranteed by integrated PET-CT scanners (sensitivity 86%; specificity 85%; NPV 95%; PPV 64%) [9] with respect to PET scan alone (Figure 21). The great advantage of PET-CT consists of the precise anatomical correlation of FDG-uptake [7, 8]. Due to the high NPV of PET-CT scan, invasive staging procedures can generally be omitted in patients with clinical stage I NSCLC with negative mediastinal PET-CT images. However, caution should be used in case of patients with central tumors, central hilar N1 disease, in all situations with low FDG uptake in the primary tumor and mediastinal PET-CT negative LNs measuring #16 mm on CT scan [10]. Nevertheless the implementation of PET-CT reduced the number of mediastinoscopies by 65% [7]. On the other hand PPV of PET-CT scan is only 64%
[9] and in case of positive mediastinal PET, tissue confirmation is still needed to confirm LN metastasis.

N STAGING INVASIVE TECHNIQUES

Mediastinoscopy

Mediastinoscopy remains the gold standard for invasive N-staging of patients with potentially operable lung cancer. Cervical mediastinoscopy is the most commonly used surgical open biopsy technique under general anesthesia. Stations 1, 2R, 2L, 4R, 4L and 7 can be evaluated by cervical mediastinoscopy. Mediastinoscopy show a sensitivity of 81% with a NPV of 91% (Table 2). More recently, mediastinoscopy is performed by the use of a videomediastinoscope. This definitely improves visualisation of the operative field and may lead to a higher accuracy in staging. Left parasternal mediastinotomy, extended cervical mediastinoscopy, and left thoracoscopy allow exploration and biopsy of stations that cannot be reached by cervical mediastinoscopy (stations 5, 6, 8 and 9) and should be used in combination with cervical mediastinoscopy to stage these LN stations [7].

TBNA/EBUS-NA

Endoscopic techniques are minimally invasive approaches under conscious sedation and local anesthesia that provide histological or cytological confirmation of LN tumor involvement (Figure 21). TBNA has been shown to be safe and useful in patients with enlarged mediastinal LNs. However this technique is a "blind" technique, operator dependent, and the results depend on the LN size. A sensitivity of 76% and a false negative rate of 29% were reported for conventional TBNA in clinical N2 disease (Table 2). The accuracy can be improved by guidance with endoscopic ultrasonography (EBUS-NA). Stations 1, 2R, 2L, 4R, 4L, 7, 10 and 11 can be biopsied with TBNA or EBUS-NA [7].

EUS-NA

EUS-NA is mainly suitable for the assessment of LNs in the posterior and inferior mediastinum (stations 3P, posterior 4L, 5, 7, 8 and 9). It shows a sensitivity of 88%, a specificity of 91%, a PPV of 98% and a NPV of 77% (Table 2) [7,8].

It is generally accepted that endoscopic techniques (both EBUS-NA and EUS-NA) are suitable to provide proof of tumoral LN involvement but cannot be used to exclude mediastinal LN disease because of the low NPV (Figure 22). Guidelines for pre-treatment mediastinal N staging are summarized in the algorithm proposed by Council of the European Society of Thoracic Surgeons (ESTS) (Table 3).
Fig. 2: THE IALSC LYMPH NODE MAP

Rusch VW JThorac Oncol 2009

Fig. 2

Fig. 3: LOW CERVICAL, SUPRACLAVICULAR, STERNAL NOTCH NODES

STATION 1

Upper border: lower margin of cricoid cartilage

Lower border: clavicles bilaterally and, in the midline, the upper border of the manubrium

The midline of the trachea serves as the border between 1R and 1L
Fig. 4: UPPER PARATRACHEAL NODES

**STATION 2**

**2R** Upper border: apex of the right lung and pleural space, and in the midline, the upper border of the manubrium

Lower border: intersection of caudal margin of innominate vein with the trachea

Left lateral border: left lateral wall of the trachea

**2L** Upper border: apex of the left lung and pleural space, and in the midline, the upper border of the manubrium

Lower border: superior border of the aortic arch

Right lateral border: left lateral wall of the trachea

Fig. 4

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Fig. 5: PREVASCULAR AND RETROTRACHEAL NODES

**STATION 3**

*3a Prevascular* Upper border: apex of chest

Lower border: level of carina

Anterior border: posterior aspect of sternum

Posterior border: anterior border of superior vena cava on the right; left carotid artery on the left

*3p Retrotracheal* Upper border: apex of the chest

Lower border: carina

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Fig. 5

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Fig. 6: LOWER PARATRACHEAL NODES

**STATION 4**

4R Upper border: intersection of caudal margin of innominate vein with the trachea

Lower border: lower border of azygos vein

Left lateral border: left lateral wall of the trachea

4L Upper border: upper margin of the aortic arch

Lower border: upper rim of the left main pulmonary artery

Right lateral border: left lateral wall of the trachea

Fig. 6

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Fig. 7: SUBAORTIC NODES (AORTOPULMONARY WINDOW)

**STATION 5**

Upper border: the lower border of the aortic arch

Lower border: upper rim of the left main pulmonary artery

Right lateral border: ligamentum arteriosum

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Fig. 8: PARAAORTIC NODES

**STATION 6**

Upper border: a line tangential to the upper border of the aortic arch

Lower border: the lower border of the aortic arch
Fig. 9: SUBCARINAL NODES

**STATION 7**

Upper border: the carina of the trachea

Lower border: the upper border of the lower lobe broncus on the left; the lower border of the bronchus intermedius on the right
Fig. 10: PARAESOPHAGEAL and PULMONARY LIGAMENT NODES

**STATION 8** Paraesophageal nodes
Nodes lying adjacent to the wall of the esophagus

Upper border: the upper border of the lower lobe broncus on the left; the lower border of the bronchus intermedius on the right

Lower border: the diaphragm

**STATION 9** Pulmonary ligament nodes
Nodes lying within the pulmonary ligament

Upper border: the inferior pulmonary vein

Lower border: the diaphragm

Fig. 10

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Fig. 11: HILAR, INTERLOBAR, LOBAR, SEGMENTAL, SUBSEGMENTAL NODES

**STATION 10 Hilar nodes**

Upper border: the lower rim of the azygos vein on the right; upper rim of the pulmonary artery on the left

Lower border: interlobar region

**STATION 11 Interlobar nodes**

Between the origin of the lobar bronchi

**STATION 12 Lobar nodes**

Adjacent to the lobar bronchi

**STATIONS 13 and 14 Segmental and subsegmental nodes**

Adjacent to the segmental and subsegmental bronchi respectively

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Fig. 11

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RIGHT UPPER LOBE (RUL) TUMOR: Following the departure from the RUL through the hilar LNs, the right paratracheal LNs are the most common site of LN metastasis in the mediastinum without significant differences in patterns of lymphatic pathway between segments.
Fig. 13: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

Mediastinal LN metastasis in RUL tumor

✓ right paratracheal LNs (2R and 4R)

Kim AW Semin Thorac Cardiovasc Surg 2009
Watanabe S Interactive Cardiovasc Thoracic Surg 2004

Fig. 13

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**Fig. 15: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN**

*Mediastinal LN metastasis in ML tumor*

- right paratracheal LNs (2R and 4R)
- subcarinal LNs (7)

Kim AW Semin Thorac Cardiovasc Surg 2009
Watanabe S Interactive Cardiovasc Thoracic Surg 2004

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Fig. 14: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

MIDDLE LOBE (ML) TUMOR: ML tumors can metastatize to both right paratracheal and subcarinal LNs without significant differences in patterns of lymphatic pathway between lateral and medial segments.

Fig. 14

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Fig. 16: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

LEFT UPPER LOBE (LUL) TUMOR: LUL malignancies tend to drain towards the aortopulmonary zone but have high incidence of subcarinal involvement, maybe because of the different drainage pattern of the lingula (that metastatizes to subcarinal LNs)
Fig. 17: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

*Mediastinal LN metastasis in LUL tumor*

✓ subaortic and paraaortic LNs (5 and 6)
✓ subcarinal LNs (7)

Kim AW Semin Thorac Cardiovasc Surg 2009
Watanabe S Interactive Cardiovasc Thoracic Surg 2004

Fig. 17

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Fig. 18: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

RIGHT and LEFT LOWER LOBE
The lower lobe can be divided into two main segments, the superior and the basal. Tumors of the superior segment shows higher incidence of upper mediastinal metastasis than the basal. Tumors of the basal segment shows significantly higher incidence of subcarinal metastasis than the superior segment.

(A) Basal segment tumor metastatizes to the superior mediastinum mostly through the subcarinal LNs
(B) Superior segment tumor often metastatizes directly to the superior mediastinum, without concomitant metastasis to the subcarinal LNs

Watanabe S Ann Thorac Surg 2008

Fig. 18
Fig. 19: LYMPH NODE METASTASIS ACCORDING TO THE TUMOR ORIGIN

Mediastinal LN metastasis in lower lobe tumor

✓ basal segments to the upper zone LNs mostly through subcarinal LNs

✓ superior segment directly to the upper zone LNs w/out subcarinal involvement

Watanabe S Ann Thorac Surg 2008
Fig. 20: SKIP METASTASES

*Involvement of N2/3 nodes in the absence of N1 (direct connection of intraparenchimal lymphatic vessels to mediastinal LNs)*

✓ *ipsilateral mediastinal LNs (N2)* in 7-26%
✓ *contralateral mediastinal LNs (N3)* not infrequent

Rusch VW – J Thorac Oncol

© - Rome/IT
PET-CT is superior to CT for mediastinal LN staging: a case of 2R CT negative (LN short axis <1cm) and PET-CT positive LN in RUL adenocarcinoma:

**Cytology:** metastatic node from pulmonary adenocarcinoma

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Fig. 22: LN STAGING INVASIVE TECHNIQUES

TBNA/EBUS-NA  
✓ for anterior and superior mediastinal LNs:
1, 2R/L, 4R/L
7, 10, 11

EUS-NA  
✓ for posterior and inferior mediastinal LNs:
3P, posterior 4L, 5
7, 8, 9

If EBUS-EUS are negative  ➔  Mediastinoscopy

EBUS + EUS-FNA  ➔  SENS 96%
NPV 96%

Heth FJF CHEST 2010

Fig. 22

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<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
<th>Prevalence (%)</th>
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Table 2

Table 3

Conclusion

The knowledge of pulmonary lymphatic drainage is pivotal to understand the NSCLC spread. Non-invasive imaging procedures may identify the precise location of suspected tumor involved LNs and help selection of the most appropriate biopsy techniques. The correct use of different diagnostic modalities allow an accurate pre-treatment staging of NSCLC, therefore a tailored management of the patient.
References


