Endoscopic and Endobronchial Ultrasonography According to the Proposed Lymph Node Map Definition in the Seventh Edition of the Tumor, Node, Metastasis Classification for Lung Cancer

Kurt G. Tournoy, MD, PhD, Jouke T. Annema, MD, PhD,† Mark Krasnik, MD, PhD,‡ Felix J. F. Herth, MD, PhD,§ and Jan P. van Meerbeeck, MD, PhD**

Abstact: Accurate assessment of lymph node involvement is a critical step in patients with non-small cell lung cancer in the absence of distant metastases. The International Association for the Study of Lung Cancer has proposed a new lymph node map, which provides precise anatomic definitions for all intrathoracic lymph nodes. Transoesophageal endoscopic ultrasound with fine-needle aspiration and endobronchial ultrasound with transbronchial needle aspiration are two minimally invasive techniques that are increasingly implemented in the staging of non-small cell lung cancer. Therefore, recognition of the proposed anatomic borders by these techniques is very relevant for an accurate clinical staging. We here discuss the reach and limits of endoscopic ultrasound in the precise delineation and approach of the intrathoracic lymph nodes according to the new lymph node map for the seventh edition of the tumor, node, metastasis classification for lung cancer.

Key Words: Endoscopic ultrasound, EUS-FNA, EBUS-TBNA, Lymph node map, Lung cancer, TNM classification.

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Both transoesophageal endoscopic curved-linear ultrasound with fine-needle aspiration (EUS-FNA) and endobronchial curved-linear ultrasound with transbronchial needle aspiration (EBUS-TBNA) are minimally invasive techniques that are increasingly implemented in the diagnosis and staging of non-small cell lung cancer. Current lung cancer staging guidelines advocate EUS-FNA and EBUS-TBNA, hereafter referred to as "endoscopic ultrasound," as an alternative for surgical staging.[1,2] When performed in an outpatient setting under local anesthesia with or without mild sedation, EUS-FNA and EBUS-TBNA allow the identification and real-time-guided sampling of intrathoracic lymph nodes.[3–5] Endoscopic ultrasound has a high accuracy for demonstrating malignant lymph node metastasis.[3–11] By consequence, EUS-FNA or EBUS-TBNA can avoid surgical staging procedures in a considerable proportion of patients.[12–14] The negative predictive value remains a matter of concern. The cytoaspirations can be false negative due to a detection, a sampling, or an interpretation error. Because patients are selected on the clinical suspicion of lymph node metastasis based on computed tomography (CT) or F-18 fluorodeoxyglucose-positron emission tomography/CT imaging, negative EUS-FNA or EBUS-TBNA findings should be confirmed by other methods. In general, a cervical mediastinoscopy is advised in these conditions.[1]

The possibility of real-time tissue sampling is the reason why curved linear rather than radial endoscopic ultrasound represents an opportunity in the nodal staging of lung cancer. The reach of EUS-FNA and EBUS-TBNA is partly overlapping and partly complementary. EBUS-TBNA follows the large airways, whereas EUS-FNA is excellent for the left and lower mediastinal and paraoesophageal stations. When both techniques are available, many of the mediastinal and hilar lymph nodes can be reached for fine-needle aspiration (Figure 1). In addition, with EUS-FNA, the left liver lobe, celiac trunc nodes, and the left adrenal gland can be assessed.

In the new International Association for the Study of Lung Cancer (IASLC) staging map,[15] the anatomic borders of the lymph node stations have been redefined. The precise endoscopic delineation and sampling of these lymph nodes is important to obtain an accurate clinical stage and for differentiation between single and multiple level metastasis of the lymph node stations. This article describes the new anatomic landmarks and borders of the intrathoracic lymph node stations when visualized by either EUS-FNA or EBUS-TBNA.

BORDERS OF RELEVANCE AND ENDOSCOPIC ULTRASOUND

The new IASLC lymph node map with its new anatomic definitions contains notable changes relative to the

*Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; †Department of Respiratory Medicine, Leiden University Medical Center, Leiden, The Netherlands; ‡Department of Thoracic Surgery, Gentofte University Hospital, Copenhagen, Denmark; and §Department of Respiratory Diseases, University of Heidelberg, Thoraxklinik, Heidelberg, Germany.

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Address for correspondence: Kurt G. Tournoy, MD, PhD, Department of Respiratory Medicine, Ghent University Hospital De Pintelaan 185, Ghent 9000, Belgium. E-mail: kurt.tournoy@Ugent.Be

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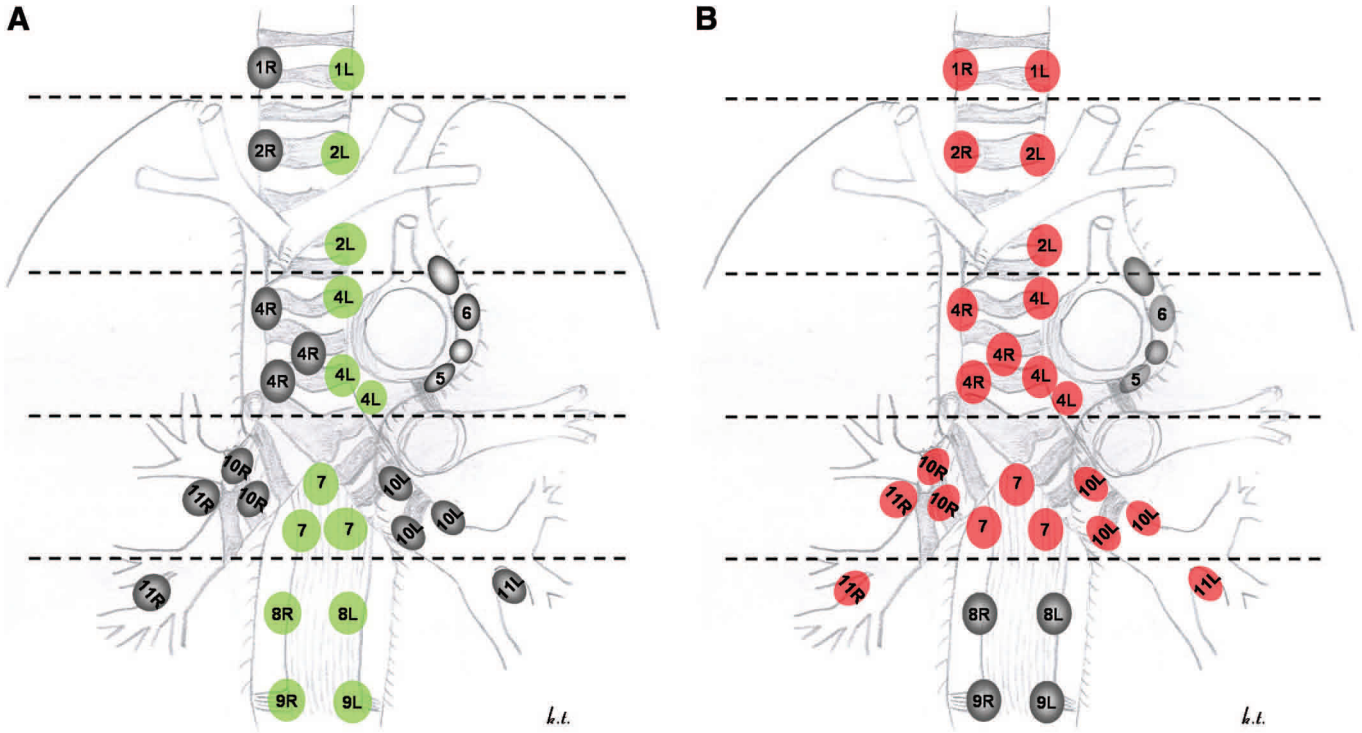

FIGURE 1. The different thoracic lymph node stations according to the newly proposed definition and the complementary reach to take biopsies with endoscopic curved-linear ultrasound with fine-needle aspiration (EUS-FNA) (A; green nodes) or endobronchial curved-linear ultrasound with transbronchial needle aspiration (EBUS-TBNA) (B; red nodes). Nodes that generally cannot be sampled with endoscopic ultrasound are dark gray. The dot lines indicate anatomic borders that are important for identification of the different lymph node stations by means of endoscopic ultrasound. Station 3a/p nodes are not indicated on this image. Stations 5 and 6 can often be seen during endoscopic ultrasound, whereas sampling is hazardous because of interposition of the great vessels.

Naruke and Mountain-Dresler modification of the American Thoracic Society maps.[15–17] The document[15] provides precise anatomic borders that should be taken into account also when diagnostics and staging are performed with EUS-FNA and/or EBUS-TBNA. With EUS, lymph nodes can be identified if they are located in the vicinity of the esophagus. The nodes to be identified with EUS are described in relation to vascular structures (including the aorta, the azygos vein, the left atrium, and the pulmonary artery) and the diaphragm.[18,19] With EBUS, the ultrasound window angle is much smaller, when compared with EUS (50–60 degree angle versus 150–180 degree angle), which makes the visualization and identification of large vessels or ultrasound landmarks easier with the latter. It has to be noted that endoscopic ultrasound is a dynamic investigation and that the back and forward and the rotational movement of the endoscope helps in the identification of structures and landmarks. In contrast to EUS, a bronchoscopic view into the airways is available during EBUS, which helps in the identification of the lymph node stations.[20]

Station 1 nodes are located caudal to the inferior margin of the cricoid but cranial to the incisura jugularis of the sternum and cranial to the clavicles bilaterally. Therefore, the supraclavicular nodes are also part of station 1. The latter can be felt by a clinical examination when enlarged; however, external ultrasound has shown to be useful for their localization, identification, and puncture.[21–24]

Although the paratracheal part of station 1 can be reached by EBUS-TBNA (1R/L; bilateral–the midline of the trachea serves as the border) or EUS-FNA (1L; left), the proposed anatomic borders cannot be recognized with endoscopic ultrasound. Because these nodes are localized extrathoracic, an endoscopic approach is very unpractical. The endoscopes are not stable for these very proximal stations making interpretation and sampling technically difficult and uncomfortable for the patient. Therefore, endoscopic ultrasound is of limited value for identification, delineation, and sampling of the paratracheally located station 1 nodes.

From station 2 onward, the lymph nodes have an intrathoracic localization. The inferior border of station 2L is the transverse plane through the superior border of the aortic arch (Figures 1 and 2). For 2R, the inferior border is then the intersection of the caudal margin of the brachiocephalic vein with the right-sided border of the trachea. The sagittal plane at the left tracheal wall now makes the difference between right and left. For endoscopic ultrasound node identification and delineation, these revised definitions are important. Ultrasonographic discrimination between stations 2 and 4 is evident, especially on the left side because the apex of the aortic arch can readily be visualized by either EUS-FNA or EBUS-TBNA. For the right-sided nodes, the margin simply follows this transverse plane, which can serve as a surrogate for the intersection of the trachea and brachiocephalic vein.

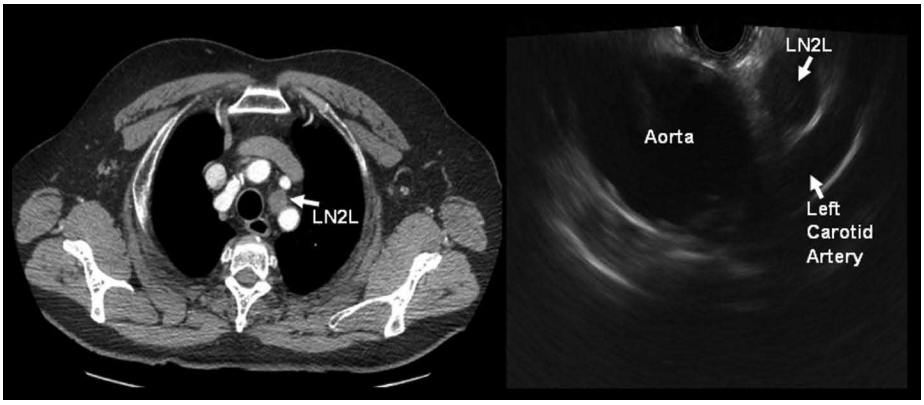

FIGURE 2. Computed tomography (CT) scan (left panel) and endoscopic curved-linear ultrasound (EUS) image (right panel) of lymph node (LN) station 2L. The inferior border of this lymph node is localized just cranial to the transverse plane through the superior margin of the aortic arch. On the computed tomography (CT) scan image, the lymph node is situated immediately adjacent to the trachea and ventrally to the esophagus. During endoscopic curved-linear ultrasound (EUS), the lymph node is found as a hypoechogenic sharp edged lesion just cranial to the transverse plane through the superior margin of the aortic arch. Note: the right side of the endoscopic ultrasound image (also for Figures 3–8) corresponds with the cranial (superior) side in the patient.

Discriminating left and right-sided nodes has clinical implications (N2 versus N3). In most of the cases, there is no discussion about the position because the presence and the size of the nodes as seen and measured on the CT scan also help the endoscopist in the identification. However, it can be that similarly enlarged nodes are found in this region and that attention is needed for making the difference between N2 and N3. As a general rule, it can be said that EUS-FNA can only reach the left paratracheal lymph node stations. With EBUS-TBNA, both stations can be approached while no clear endoscopic or ultrasonographic landmarks are available to discriminate left and right. Although the bronchoscopic image helps during EBUS-TBNA, the left side of the trachea never identifies as a straight plane. The large arteries (e.g., subclavian artery or the aortic arch) cannot help much because their position relative to that sagittal plane is variable. In addition, the smaller ultrasonography window of EBUS-TBNA also makes the visualization of the anatomic ultrasound landmarks is more limited.

Station 3 lymph nodes are defined with an anterior part being the prevascular nodes and a posterior part being the retrotracheal nodes. The craniocaudal extent goes for both from the sternal notch down to the main carina. Although the prevascular station 3A can be visualized with EBUS as laying ventrally from the large vessels, there are no anatomic ultrasound landmarks to recognize the superior border of this lymph node station. Sampling station 3A by endoscopic ultrasound is impossible because of the interposition of the large vessels (Figure 3). This contrasts with station 3P, which is situated in between the pars membranacea of the trachea and the vertebrae (Figure 3). It can be seen and sampled by both EUS-FNA and EBUS-TBNA. Although there is no ultrasound landmark for the superior margin of 3P either the inferior margin being the main carina level corresponds with the level of the main stem or left pulmonary artery during EUS and can be seen as an anatomic structure during EBUS. The margin between 3P and 2/4L is the left posterior tracheal corner, which is identifiable by EUS-FNA or EBUS-TBNA. The margin between 3P and 2/4R is the right posterior tracheal corner that can be identified during EBUS-TBNA.

Station 4 lymph nodes are—as station 2 nodes—located paratracheally but situated caudal to the transverse aortic arch plane. The sagittal plane on the left side of the trachea is—identical as discussed for the station 2 nodes—the margin between left and right. By consequence, EUS-FNA in general cannot approach a right paratracheal node. The comments made to discriminate between 4R and 4L with EBUS-TBNA are identical to those for stations 2. However, what can be helpful for the endoscopist is that 4R nodes are situated posterior to the superior vena cava and/or ascending aorta, both presenting as large vessels with a vertical course, which can be readily visualized by EBUS-TBNA. The inferior margins of station 4 nodes have been redefined with important clinical implications, also for endoscopic ultrasound. The pleural reflection no longer serves as the border between stations 4 and 10. Station 4L has now an inferior border defined by the superior rim of the left main pulmonary artery and a lateral margin defined by the aortopulmonary ligament (Figures 1 and 4). With both EUS-FNA and EBUS-TBNA, the cranial rim of the left main pulmonary artery can be visualized. The aortopulmonary ligament is invisible for ultrasound.

Station 4R's inferior border has now been redefined as the inferior border of the azygos vein. This new definition is better because the anatomic margin being the pleural fold is invisible for conventional or endoscopic imaging, whereas the azygos vein is always visible. During EBUS-TBNA, it typically presents in the right tracheobronchial corner as a kidney-shaped vessel (Figure 5). By consequence, EBUS-TBNA now can be used more confidently to discriminate between mediastinal 4R and hilar 10R nodes. The 4R nodes are by consequence characterized by their position just dorsally from the superior caval vein and/or aorta and medially but not distally to the azygos vein.

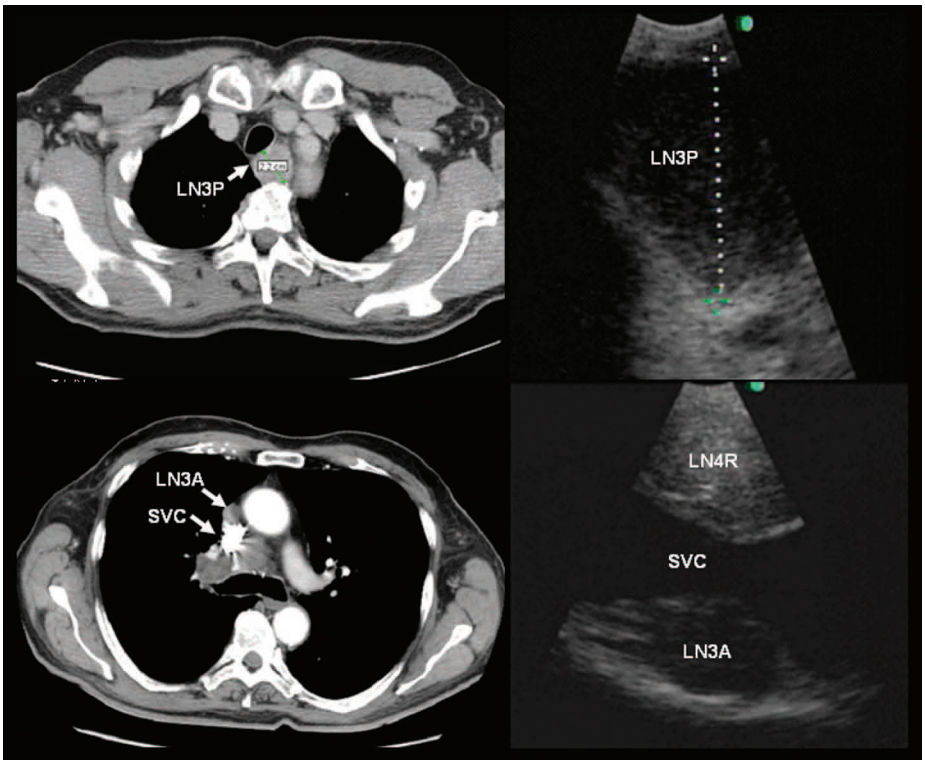

FIGURE 3. Computed tomography (CT) scan and endobronchial curved-linear ultrasound (EBUS) image of lymph node stations 3A and 3P. Station 3P (upper panel) is located just behind the trachea (left panel) and reaches from the apex of the lung down to the main carina. 3P can be identified and sampled with endobronchial curved-linear ultrasound (EBUS) (right panel) or endoscopic curved-linear ultrasound (EUS). There are no ultrasound landmarks to identify the upper border of this lymph node station. Station 3A (lower panel) is on the right situated anterior to the superior vena cava (SVC) and on the left anterior to the left carotid artery. Although 3A can be seen with endobronchial curved-linear ultrasound (EBUS), sampling is impossible.

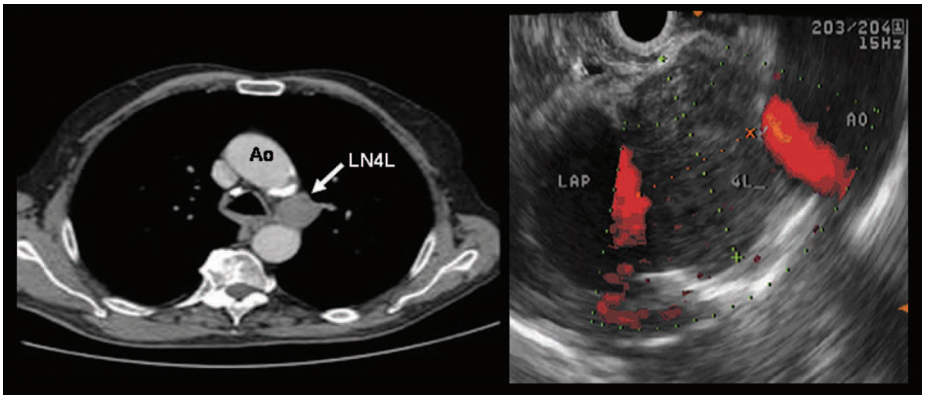

FIGURE 4. Computed tomography (CT) scan and endoscopic curved-linear ultrasound (EUS) image of lymph node station 4L. Both the superior and inferior border of lymph node station 4L can be accurately identified by endoscopic ultrasound (right panel) being the transverse planes through the superior border of the aorta (Ao) and left pulmonary artery, respectively (LAP). The lateral border of this station being the ligamentum arteriosum is invisible both on computed tomography (CT) and during endoscopic ultrasound.

Station 5 lymph nodes are situated laterally to station 4L nodes with the ligamentum arteriosum as anatomic border. The inferior edge is similar for both, whereas the cranial edge is not. Although 4L nodes are situated caudal to the superior border of the aortic arch, station 5 nodes are located caudal to the inferior border of the aortic arch (Figure 6). Because the ligamentum arteriosum cannot be discerned by means of ultrasound, the differentiation between 4L and 5 can be difficult, especially when both stations contain suspect lymph nodes. Station 5 nodes can be identified by EUS-FNA and EBUS-TBNA although the latter is often more demanding. Because of the interposition of aortic arch or pulmonary artery, station 5 can only be punctured in selected patients with enlarged nodes.

Station 6 mediastinal lymph nodes are located lateral to the ascending aorta and aortic arch, in between the transverse planes at the superior and inferior border of the aortic arch (Figure 6). These nodes can most often be identified by means of EUS-FNA, whereas this is not always possible with EBUS-TBNA. The nodes in station 6 can only be punctured by a transaortal approach.[25]

The subcarinal area or station 7 nodes have an inferior border that is redefined. On the left side, this is the superior border of the lower lobe bronchus, and on the right side, this is the inferior border of the intermediate bronchus. The lymph nodes in this station can be seen and biopsied by both EUS-FNA and EBUS-TBNA. Formerly, an anterior and posterior part of this node was recognized. This was meaningful because a cervical mediastinoscopy cannot reach the posterior part of this station. With EUS-FNA and EBUS-TBNA, the entire subcarinal area can be approached. Although identification of the nodes in this station is easy for both EUS-

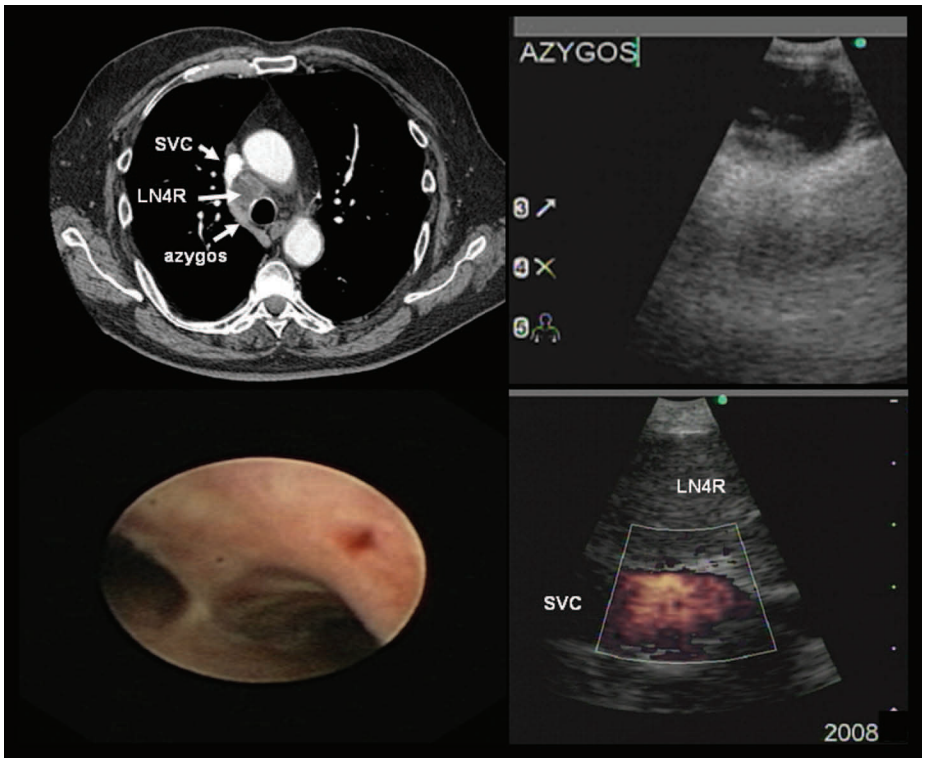

FIGURE 5. Computed tomography (CT) scan, endobronchial curved-linear ultrasound (EBUS) image of lymph node station 4R, and the corresponding endobronchial view. The lower border of the azygos vein is an ultrasound landmark structure making the difference between 4R and 10R nodes. This vein is localized in the tracheobronchial corner on the right and is typically kidney shaped during identification with endobronchial curved-linear ultrasound (EBUS) (upper panel, right). The lymph nodes are then visualized just superior to and/or medially from the azygos vein as hypoechogenic sharp edged structures lying just posterior to the superior vena cava (SVC) or aorta. The puncture for endobronchial curved-linear ultrasound with transbronchial needle aspiration (EBUS-TBNA) is classically performed at or just above the tracheobronchial corner, leaving behind a small bloody puncture lesion (lower panel-left).

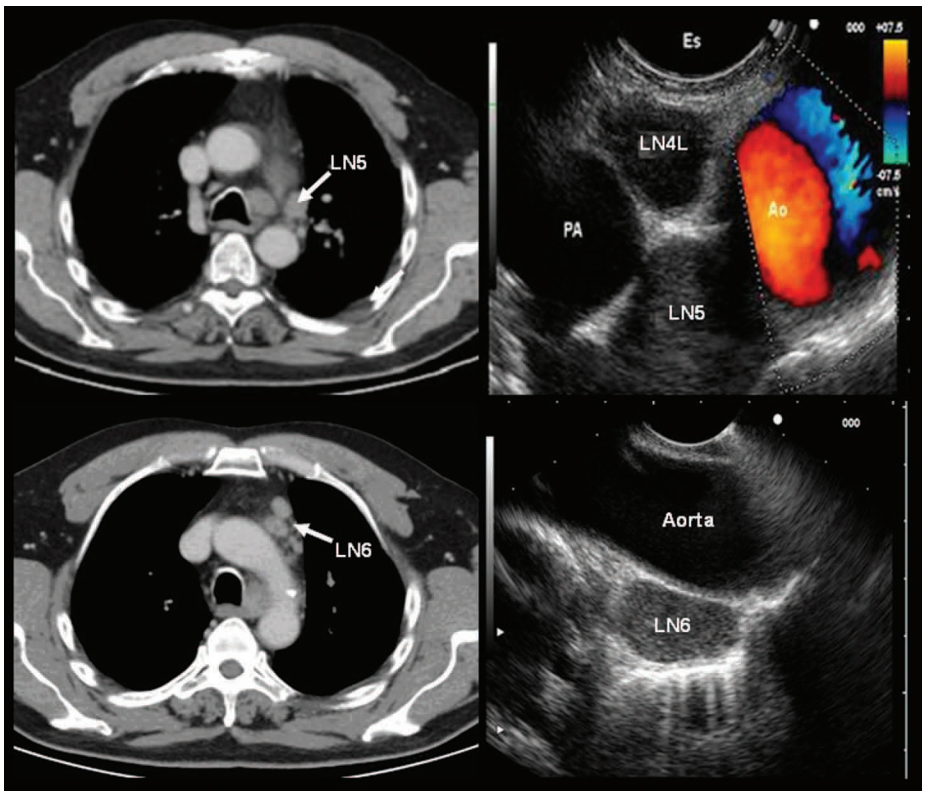

FIGURE 6. Computed tomography (CT) scan and endoscopic curved-linear ultrasound (EUS) images of lymph node stations 5 (left upper panel; white arrow) and 6 (left lower panel, white arrow). The inferior border of station 5 is the superior rim of the left pulmonary artery (right upper panel). The inferior border of the aortic arch is the frontier between stations 5 and 6. The superior border of station 6 (right lower panel) is the transverse plane through the superior border of the aortic arch. Although these stations and their borders can be identified by means of EUS and endobronchial curved-linear ultrasound (EBUS), sampling without transpassing the great vessels is often impossible.

FNA (the nodes lay just dorsally to the origin of the left pulmonary artery and cranial to the left atrium) and EBUS-TBNA (by means of the endoscopic view), the delineation of the inferior border by means of endoscopic ultrasound is, however, not easy (Figure 7). With EUS-FNA, the left atrium is generally seen as the anatomic border above which the

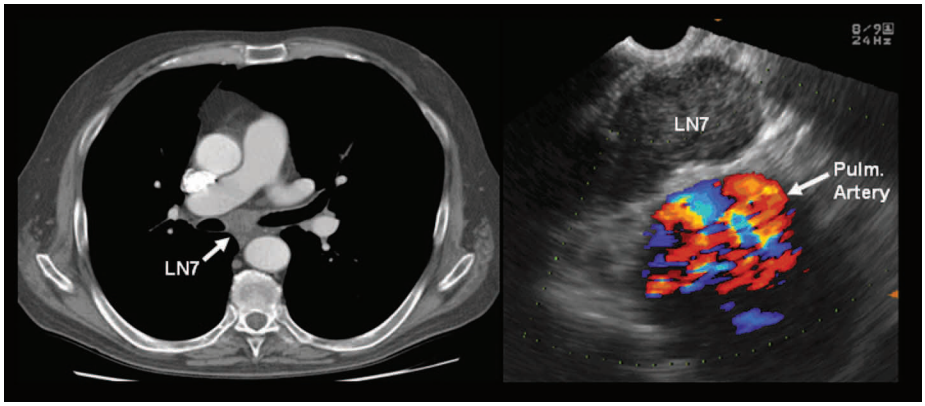

FIGURE 7. The subcarinal station shown on CT scan (left panel) can easily be visualized with both endoscopic curved-linear ultrasound (EUS) (right panel) but of course also with endobronchial curved-linear ultrasound (EBUS). During endoscopic curved-linear ultrasound (EUS), the subcarinal station identifies as a round, hypoechogenic sharply edged structure located in between the esophagus and the pulmonary artery. The upper rim of this artery corresponds in general with the main carina and is helpful during endoscopic curved-linear ultrasound (EUS). The main carina is visualized by means of endoscopy during endobronchial curved-linear ultrasound (EBUS). The inferior border is the roof of the lower lobe bronchus on the left and the bottom of the bronchus intermedius on the right. There are no unique ultrasound features that correspond to this definition although endoscopy during endobronchial curved-linear ultrasound (EBUS) is helpful.

subcarinal nodes are situated, although this is with the new definition probably too restrictive. The relation of the left atrium or pulmonary artery to the bronchus intermedius and the left lower lobe bronchus, the latter being the newly defined inferior borders of station 7, can be variable. With EBUS-TBNA, the delineation of the inferior border is possible because this investigation allows a simultaneous bronchoscopic view of the bronchial tree although there are no distinct corresponding ultrasound landmarks.

Stations 8 and 9 are the paraoesophageal and pulmonary ligament nodes, respectively, and are situated inferior to the inferior margins of station 7 lymph nodes. The superior border of these lymph nodes is as such defined by the inferior margin of the subcarinal area. Station 8 nodes are located along the left atrium, whereas station 9 nodes are lying within the pulmonary ligament. Although the latter is a structure that cannot be seen with endoscopic ultrasound, station 9 nodes are located just cranial to the diaphragm, which is readily identifiable with EUS-FNA. Stations 8 and 9 lymph nodes can be thus approached by means of EUS-FNA. Occasionally, station 8 nodes can be found by EBUS-TBNA. However, and as suggested above, one has to take into account the inferior stretch of the subcarinal nodes making this station in addition to station 9 becomes invisible for EBUS-TBNA. When performing EUS-FNA, one cannot confuse a lesion or lymph node with the esophagus. When performing EBUS-TBNA, the esophagus can be seen as a multilayered structure with a hyperechogenic line in the middle corresponding with air not to be misinterpreted as a lymph node (Figure 8). The discrimination between the left- and right-sided nodes is the midline. Although no formal ultrasound characteristics for the midline are available, the relative position of the endoscope to the descending aorta can help.

The hilar nodes of station 10 are situated immediately adjacent to the mainstem bronchus but caudal to the inferior border of azygos vein on the right and superior rim pulmonary veins and artery on the left. These nodes can be seen and sampled by EBUS-TBNA. The inferior margin of station 10R is the interlobar region. There is no unique ultrasound feature that defines that border, but because a bronchoscopic view is available during EBUS-TBNA, the secondary carina or the upper lobe split off can serve as surrogate here. EUS-FNA has been thought to be unable to see and sample hilar stations. However, there is no doubt that in certain cases, station 10 nodes located medially from the main stem bronchi can be assessed. Endoscopists should be aware of this because misinterpretation could lead to overstaging.[26] Once the secondary carina is reached, station 11 lymph nodes (or interlobar nodes) are encountered. From this station on, the nodes can only be approached by EBUS-TBNA and not by EUS-FNA. These nodes are located just underneath the mucosa of the secondary carina on the left. There is a division between 11s and 11i on the right side. The former indicate the nodes between upper lobe and intermediate bronchus, the latter are situated in between middle and lower lobe ultrasound landmarks are not available; however, the synchronous endoscopic view enables the identification of the relevant lobe split offs.

Once the lobar bronchi originate, then station 12 is reached. Again, there are no unique ultrasound borders, only the endoscopic view can help for guidance. Stations 13 and 14 are segmental and subsegmental nodes. Frequently, the EBUS-TBNA endoscope is too large to approach the segments and subsegments and their lymph nodes.

DISCUSSION AND CONCLUSION

Accurate assessment of the mediastinal and hilar lymph nodes is important for patients with non-small cell lung cancer in whom no metastasis are found outside the thorax or in the pleural space or contralateral lung.[1,27] The reason is that lymph node metastases have an impact on the choice of

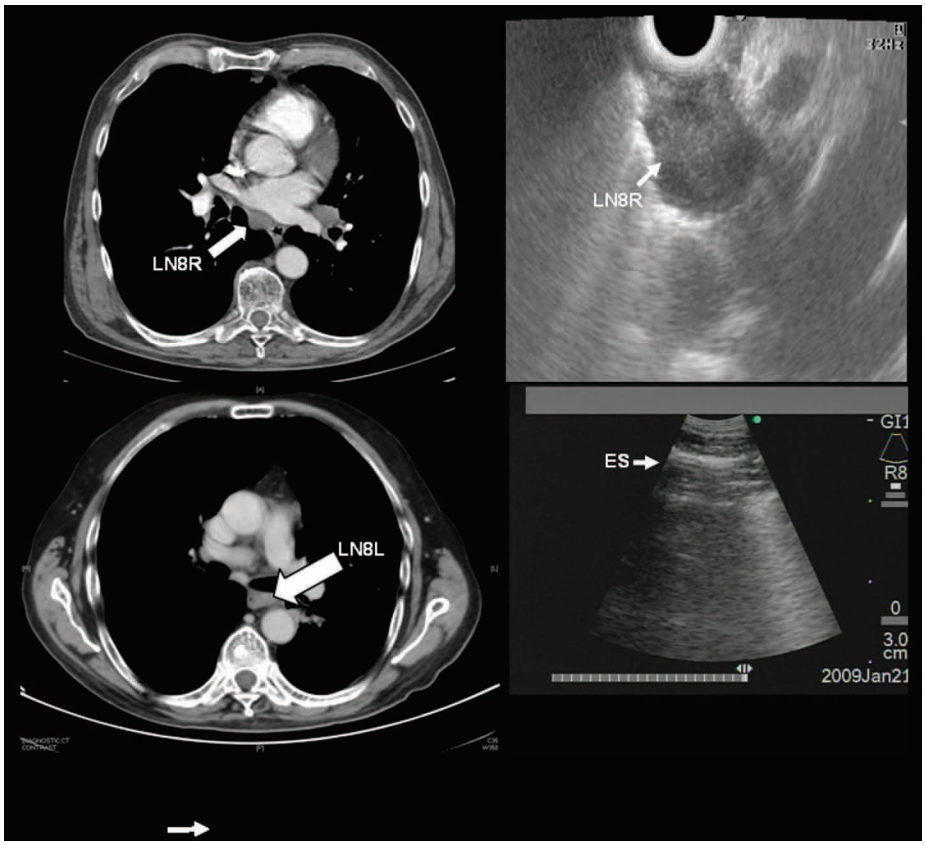

FIGURE 8. Typical computed tomography (CT) images (left upper and lower panel) of node stations 8R and 8L. The ultrasound visualization of these stations was performed here with the endoscopic curved-linear ultrasound (EUS) scope (8R: right upper panel). There are no specific ultrasound landmarks to identify the borders of these lymph node stations although the inferior margin of both stations 8 and 9 is the diaphragm, which is readily identifiable with endoscopic curved-linear ultrasound with fine-needle aspiration (EUS-FNA) but not endobronchial curved-linear ultrasound with transbronchial needle aspiration (EBUS-TBNA). The esophagus is visualized by endobronchial curved-linear ultrasound (EBUS) as a longitudinal structure with a hyperechogenic band (right lower panel).

therapy and prognosis. The correct identification of the lymph node stations is crucial to avoid overstaging and understaging. In particular, a correct mediastinal lymph node staging refers not only to making a difference between N0-1, N2, or N3 disease but also to a good assessment of the extent of lymph node metastasis (single station versus multiple stations).

In this document, we describe and discuss the reach and limits of endoscopic ultrasound in the precise delineation and approach of thoracic lymph nodes according to the new tumor, node, metastasis-classification of lung cancer and the new definition of IASLC thoracic lymph node map.[15] We are aware that the recognition of the borders of the different lymph node stations by endoscopic ultrasound is subjected to individual variations, but the findings described in this document should apply to a majority of the patients and have been summarized in Table 1.

Although translation of the new anatomic definitions in ultrasound landmarks is straight forward for a large number of stations, cautiousness is warranted in several instances. The reason is that the proposed IASLC-definition is based on anatomic/surgical data that were correlated with CT scan data, whereas ultrasound data were not considered. When the proposed borders are to be identified with either EUS-FNA or EBUS-TBNA, a number of elements should be taken into account. Although we advice to perform EUS and EBUS investigations in a standardized manner by seeking all nodes detectable from either the esophagus or large airways to detect potential metastases, it is clear that the CT scan (or F-18 fluorodeoxyglucose-positron emission tomography/CT scan) will always guide the endoscopist to find the nodes. It quite often happens that a single mediastinal lymph node station is suspect by its size and that it can be reached easily. In those cases, there can be no discussion about the lymph node station as it is defined by its unique localization on the CT scan.

However, when nodes are identified in multiple stations, the endoscopist has the task and responsibility to provide a correct identification and sampling. For quite a number of lymph nodes, these margins can be recognized; for example, there is the transverse plane on top of the aortic arch to make the difference between stations 2 and 4. Similarly, the azygos vein, which is easily identified by means of EBUS, is a recognizable border making the difference between 4 and 10. However, in some cases, delineation of the lymph node station by ultrasound is not unambiguous. Because there are no ultrasound landmarks corresponding with the sagittal plane on the left tracheal border, making the difference between N2 and N3 nodes can be a challenge. With EBUS-TBNA and also with EUS-FNA, hilar station 10 nodes that are located medially from the main bronchi can be overinterpreted as subcarinal nodes, which would implicate an upstaging of the patient with important therapeutic and prognostic consequences.[26] Therefore, we advise that endoscopists make a detailed and systematic protocol of the EUS or EBUS procedure and document it at least with relevant ultrasound

TABLE 1. Endoscopic Ultrasonography According to the Proposed Lymph Node Map Definition in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer

	EUS-FNA		EBUS-TBNA	
Margin Identifiable	**Superior**	**Inferior**	**Superior**	**Inferior**
1	−	−	−	−
2RL	−	+	−	+
3a	−	+	−	+
3p	−	+	−	+
4R	−	−	+	+
4L	+	+	+	+
5	+	+	(+)	(+)
6	+	+	(+)	(+)
7	+	−	+	+
8RL	−	+	+	−
9RL	−	+	−	−
10	−	−	+	+
11	−	−	+	+
12–13–14	−	−	−	−

The different thoracic lymph node stations and the ability of EUS-FNA and EBUS-TBNA to identify the newly defined upper and lower anatomical borders. "−" means that the newly defined lymph node station borders cannot be found by means of endoscopic ultrasound, "+" means that the newly defined lymph node station borders can be found by means of endoscopic ultrasound, and "(+)" means that the newly defined lymph node station borders can be found by means of endoscopic ultrasound, but that the nodes themselves are often out of the visibility range of the endoscope. Note that visualization of the newly defined borders of the nodes does not necessarily mean the nodes can be sampled by fine-needle aspiration, as is the case for nodes in stations 5 and 6.

EUS-FNA, endoscopic curved-linear ultrasound with fine-needle aspiration; EBUS-TBNA, endobronchial curved-linear ultrasound with transbronchial needle aspiration; TNM, tumor, node, metastasis.

images or video's together with the correlating images on the CT scan. It is important that, in case of doubt, a surgical verification of the endoscopic findings should be considered.

Not all borders have the same importance, for example, the difference between stations 8 and 9 will virtually never have therapeutic implications. The same holds for the inferior border of station 7, which is not recognizable with EUS-FNA, and probably hardly with EBUS-TBNA. Similarly, the difference between stations 10 and 11 is not relevant for clinical staging; however, it can have consequences for the extent of resection needed because involvement of station 10 will probably result in a higher rate of pneumonectomy.

Another issue is the risk for false-positive clinical staging in case of a centrally located lung tumor. It could be that during mediastinal sampling, regardless the technique, tumor instead of lymph node is taken by accident. Although this is probably very rare, its prevalence remains poorly documented in the literature.[28]

Areas of continuing controversy regarding the lymph nodes metastases, outside the above mentioned problems, include the assessment of intranodal versus extranodal disease, the detection (and significance) of isolated tumor cells and micrometastasis, and the need for systematic lymph node dissection versus a less extensive lymph node sampling.

In conclusion, recognition of the new anatomic borders by EUS-FNA and EBUS-TBNA is relevant to correctly stage the patient with lung cancer. Although these borders and thus the exact lymph node stations can be identified in a large number of cases, there is a degree of uncertainty in some. The clinician should be aware of these when making a clinical interpretation.

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