

# Change of Junctions Between Stations 10 and 4 in the New International Association for the Study of Lung Cancer Lymph Node Map

## A Validation Study from a Single, Tertiary Referral Hospital Experience

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**BACKGROUND:** Some tumors previously staged as N2 disease, using the Mountain-Dresler/American Thoracic Society (MD-ATS) map are staged as N1 per the new International Association for the Study of Lung Cancer (IASLC) lymph node (LN) map. We aimed to evaluate the effectiveness of the IASLC LN map in stratifying prognosis in patients with non-small cell lung cancer (NSCLC) and LN metastasis in nodal stations 4 or 10.

**METHODS:** Of 2,086 patients undergoing curative surgical resection for NSCLC, we searched for patients who had LNs harboring cancer cells in nodal stations 10 or 4 ( $n = 531$ ) and reclassified them into three different subgroups (N1 [N1 according to both the MD-ATS and IASLC maps], in-between [N2 according to the MD-ATS map but N1 by the IASLC map], and N2 [N2 according to both maps]) based on histopathologic results. We compared disease-free survival (DFS) among the three subgroups by using the Kaplan-Meier method and log-rank analysis.

**RESULTS:** Of 531 patients, 295 belonged to the N1 group, 66 patients belonged to in-between group, and 170 patients belonged to N2 group, according to the IASLC map. The cumulative DFS rates at 5 years for the N1, in-between, and N2 groups were 47%, 39%, and 29%, respectively. In multivariate analysis, LN ratio was identified as significant independent prognostic factor (hazard ratio, 2.877; 95% CI, 1.391-5.950;  $P = .004$ ).

**CONCLUSIONS:** The changed definition between N1 and N2 diseases by the IASLC LN map works well, as expected, in stratifying patient prognosis. Positive LN ratio may be more valuable than the nodal stations involved in predicting patient survival in resectable NSCLC.

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**ABBREVIATIONS:** DFS = disease-free survival; IASLC = International Association for the Study of Lung Cancer; LN = lymph node; MD-ATS = Mountain-Dresler modification of the American Thoracic Society; NSCLC = non-small cell lung cancer

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The map of the mediastinal and pulmonary lymph nodes (LNs), which was proposed by Mountain and Dresler and modified by the American Thoracic Society (MD-ATS map),<sup>1</sup> gained wide acceptance and became a standard for nodal staging in non-small cell lung cancer (NSCLC). However, the LN map has some shortcomings in terms of its clarity in describing specific nodal-station localization. Moreover, Japanese surgeons and oncologists continuous to use the Naruke map, as advocated by the Japan Lung Cancer Society.<sup>2</sup>

Recently, the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project revised a new LN map to provide more specific anatomic definition and to achieve international uniformity of LN status.<sup>3,4</sup> This new map renders important changes compared with the MD-ATS and Naruke maps.<sup>5</sup> One of the significant discrepancies in nomenclature between the MD-ATS and new IASLC maps is the junctions between stations 4 and 10 nodes. The previous

definition of the lower border of 4R was a horizontal line extending across the right main bronchus at the upper margin of the origin of the upper lobar bronchus. It is currently at the lower border of the azygos vein.

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Similarly, the definition of the lower border of 4L changed from a horizontal line extending across the left main bronchus at the upper margin of the origin of the upper lobe bronchus to the upper rim of the left main pulmonary artery.<sup>6</sup> Consequently some tumors staged as N2 or stage IIIA according to the MD-ATS map may be staged as N1 or stage II when adopting the new LN map.<sup>5</sup> To confirm the validity of N descriptors proposed by the IASLC, we compared the prognostic implication of the new IASLC LN map with those of the MD-ATS map in terms of disease-free survival (DFS) between patients classified into having stations 10 and 4 nodes.

## Materials and Methods

This retrospective study was approved by our institutional review board (approval #2012-05-095). Informed consent was waived.

### *Patient Population*

From 2008 to 2011, a total of 2,086 consecutive patients with primary NSCLC underwent curative surgery at our institution, and complete pathologic staging was available for these patients. All patients received the resection of a primary tumor and complete mediastinal and hilar LN dissection. Among those, 736 patients had LN metastases in the N1 or N2 region (pN1 or pN2) based on the MD-ATS map. Of these 736 patients, we excluded 147 with a prior history of malignant disease, those receiving induction chemotherapy or radiotherapy before curative resection, or those with incomplete resection or microscopic or macroscopic residual disease. Then, we additionally excluded 58 patients with pN1 or N2 disease involving LNs other than stations 10 or 4.

Two chest radiologists (one with 10 and one with 5 years of chest CT scan interpretation experience) reviewed both axial and coronal CT images of the final cohort of 531 patients. Before imaging and surgical correlation for nodes of our interest, we made sure the nodes seen on transverse CT images were located in the peribronchial area on coronal images, by adopting a cross-reference technique (indicating LNs on transverse and coronal images) on picture archiving and communication systems monitors (Figs 1, 2). Individual nodal stations identified on CT images were matched carefully with surgically dissected nodes by reviewing medical records. Pathologic results of the matched nodes were recorded. Thus, we tried to deter mismatching of one nodal station seen on CT imaging with the adjacent nodal station on surgery. In consideration of the proposals of the IASLC staging committee,<sup>3,4,6</sup> involved nodal stations on CT scans were reclassified into three subgroups: (1) N1 nodes by both the MD-ATS map and the IASLC map (N1 group), (2) N2 nodes by the MD-ATS map but reclassified nodes as N1 by IASLC map (in-between group), and (3) N2 nodes by both the MD-ATS map and the IASLC map (N2 group) (Figs 1, 2).

### *Preoperative Staging*

Noninvasive clinical staging was conducted with chest CT scans and integrated PET-CT scans in all patients. At our institution, for patients with preoperatively proven NSCLC, cervical mediastinoscopy was

routinely performed regardless of the observed findings on CT or PET-CT scans. The mediastinoscopy was waived in following patients: those who were not the candidates for neoadjuvant concurrent chemoradiation therapy for subsequent surgery because of old age or comorbidities (n = 29) and those who underwent endobronchial ultrasound with transbronchial needle aspiration (n = 25). Patients with negative mediastinal nodes underwent directly thoracotomy, whereas those with positive nodes received neoadjuvant therapy and subsequent thoracotomy.

### *Surgical Approach*

The surgery was performed for the affected lung, consisting of segmentectomy, lobectomy, bilobectomy, and pneumonectomy. Segmentectomy was performed only for high-risk patients. All patients received complete mediastinal and hilar LN dissection. The LN dissection criteria include the exploration of the fissures, the hilus of the lung, and all of the ipsilateral mediastinal LN zones and en bloc removal of all LNs.

### *Analysis of Metastatic LNs*

The surgeons labeled the dissected LNs by numbering the nodes based on the LN map. A pathologist with 17 years' experience in lung cancer diagnosis evaluated the nodes and recorded the absence or presence of tumor cells in the nodes according to how they were numbered in the surgical field by using hematoxylin-and-eosin staining of the specimens.

The number of positive LNs for cancer cells from each defined anatomic nodal location was recorded. The LN ratio was defined as the ratio of positive LNs divided by the total number of harvested LNs.<sup>7</sup> The presence of extracapsular extension of the positive LNs was also assessed.

### *Follow-up and Survival*

Postsurgical therapy was administered at the discretion of physicians in charge, and the adjuvant therapy included radiation, chemotherapy, or chemoradiotherapy. The adjuvant treatment was administered in the event of histologically positive N2 status at the surgery, positive multi-N1 status, the presence of extracapsular extension of positive LN, or a positive resection margin at the time of pathologic staging.

After the completion of treatment, patients were followed up at 3-month intervals with chest CT scans to identify any disease recurrence for the following 12 months. Chest CT scans were followed up at 6-month

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