CHEST

Prognostic Impact of the Current Japanese Nodal Classification on Outcomes in Resected Non-small Cell Lung Cancer

Junji Ichinose, MD; Tomohiro Murakawa, MD; Haruaki Hino, MD; Chihiro Konoeda, MD; Yuta Inoue, MD; Kentaro Kitano, MD; Kazuhiro Nagayama, MD; Jun-ichi Nitadori, MD; Masaki Anraku, MD; and Jun Nakajima, MD

BACKGROUND: The prognosis of N2 non-small cell lung cancer (NSCLC) has been reported to be heterogeneous. The recently revised Japanese nodal classification subcategorizes N2 disease according to the tumor-bearing lobe. We evaluated the prognostic impact of the Japanese nodal classification and its ability to define favorable N2 disease in resected NSCLC.

METHODS: A total of 496 patients with NSCLC who underwent lobectomy with systematic lymph node dissection between 1998 and 2009 were analyzed retrospectively. N2 status was subdivided into N2a-1 and N2a-2, according to the Japanese nodal classification. Overall survival (OS), disease-free survival (DFS), and clinicopathologic features were compared between the two groups.

RESULTS: There were 67 cases with N2 disease. The outcome of resected N2a-2 NSCLC was far poorer than that of the N2a-1 group (5-year OS, 28% vs 62%, $P < .001$; 5-year DFS, 5% vs 35%, $P < .001$). Multivariate analysis revealed that pathologic N2a-2 was an independent prognostic factor (hazard ratio, 2.86; $P < .05$). Patients in the N2a-2 group showed more involved nodes and stations, less skip metastasis, and more locoregional recurrence than did patients in the N2a-1 group. The outcome of the N2a-1 group was satisfactory, and there was no significant difference in OS and DFS between N1 and N2a-1.

CONCLUSIONS: The Japanese nodal classification is able to identify a favorable N2 subgroup in resected NSCLC. Nodal staging by the Japanese system should be considered when a clinical trial of N2 disease is designed. CHEST 2014; 146(3):644-649

Manuscript received January 18, 2014; revision accepted April 1, 2014; originally published Online First May 8, 2014.

ABBREVIATIONS: DFS = disease-free survival; LN = lymph node; NSCLC = non-small cell lung cancer; OS = overall survival

AFFILIATIONS: From the Department of Thoracic Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

This study was presented at the 15th World Conference on Lung Cancer, October 27-30, 2013, Sydney, NSW, Australia.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Tomohiro Murakawa, MD, Department of Thoracic Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; e-mail: murakawa-tky@umin.ac.jp

DOI: 10.1378/chest.14-0159

The presence and extent of lymph node (LN) metastases are powerful prognostic factors in completely resected non-small cell lung cancer (NSCLC). Many studies have demonstrated that pathologic N2 NSCLC exhibits a heterogeneous prognosis. Various prognostic factors have been evaluated to identify a more accurate system than the current nodal classification.[1-16] *The General Rule for Clinical and Pathologic Record of Lung Cancer* was first published in 1978 and has been revised repeatedly by the Japan Lung Cancer Society to standardize the format of recording the operative notes and pathologic reports. The seventh edition[17] was revised in 2010, and it subcategorizes N2 according to the tumor-bearing lobe based on studies of the difference in patterns of the LN metastases[13,18] and on the validity of lobe-specific selective lymphadenectomy.[19,20] Few studies have validated this Japanese nodal classification.[16] In this study, we evaluated the prognostic impact of the Japanese nodal classification on resected NSCLC and investigated whether the patient groups with favorable N2 disease could be identified.

Materials and Methods

Patient Cohort

A total of 496 patients with NSCLC who underwent lobectomy with systematic LN dissection at our institute between 1998 and 2009 were analyzed retrospectively. Before the study, the research review board of the University of Tokyo Hospital examined and approved our research protocol in accordance with the Declaration of Helsinki (project approval No. 2406). All patients provided written informed consent for the review of their medical charts before the surgery. Patients who had evidence of small-cell carcinoma, distant metastases, dissemination, malignant effusion, or N3 disease were excluded. Patients who underwent neoadjuvant therapy or limited resection were also excluded. The definition of systematic nodal dissection followed the European Society of Thoracic Surgeons guidelines,[21] which recommended that at least three mediastinal nodal stations (always including the subcarinal nodes) should be excised. We excluded patients who underwent LN dissection that did not satisfy the criteria, such as LN sampling or lobe-specific LN dissection.

The preoperative examination for staging included a CT scan of the chest and upper abdomen, CT scan or MRI of the brain, and bone scintigraphy or ^{18}F fluorodeoxyglucose-PET scan. An LN $>$ 1 cm in its short axis on the CT scan was clinically determined to be metastatic. The definition of an abnormal LN based on PET scan followed the diagnosis of the radiologists. Clinical nodal staging was defined by the combination of the findings of CT and PET scans. The treatment plan for patients with clinical discrete N2 was made by a multidisciplinary team. We considered patients with clinical infiltrative N2 to have a contraindication for surgery. Evaluation of nodal status was based on CT scan, PET scan, or both during the study period, although recently, preoperative endobronchial ultrasound-guided transbronchial needle aspiration has become the preferred choice for clinically suspected N2 disease.

LN Assessment and Follow-up

The tumor stage was determined according to the seventh edition of the TNM staging system of the International Union Against Cancer,[22] and the histologic tumor type was determined according to the third edition of the World Health Organization classification.[23] All the dissected LNs were classified by the International Association for the Study of Lung Cancer node map,[24] and the number of resected and involved LNs of each station were confirmed on the pathologic report.

In the current Japanese nodal classification, the mediastinal nodal stations are subcategorized according to the tumor-bearing lobe (Table 1). Our systematic nodal dissection includes N2a-1 and N2a-2, but

TABLE 1] Japanese Nodal Classification for Resected Lung Cancer According to the Tumor-Bearing Lobe

Lymph Node Groups	Right Lung			Left Lung		
	Upper Lobe	Middle Lobe	Lower Lobe	Upper Division Segment	Lingual Segment	Lower Lobe
N2a-1	2R	2R	7	4L	4L	7
	4R	4R	8	5	5	8
		7	9	6	6	9
					7	
N2a-2	7	...	2R	7	...	4L
			4R			5
						6
N2b	3a	3a	3a	2L	2L	2L
	3p	3p	3p	3a	3a	3a
	8	8		3p	3p	3p
	9	9		8	8	
				9	9	

The rows of mediastinal nodes were extracted from the reference. Each number refers to the station of lymph nodes in the International Association for the Study of Lung Cancer node map.[24] This classification does not take into account the number of involved nodes. (Adapted from The Japan Lung Cancer Society.[17])