Metastasis to Subsegmental and Segmental Lymph Nodes in Patients Resected for Non-Small Cell Lung Cancer: Prognostic Impact

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Background. We investigated the prognostic significance of segmental and subsegmental (level 13 and 14) lymph nodes metastasis in patients with resected non-small cell lung cancer (NSCLC).

Methods. The pattern of lymph nodal metastasis was analyzed in 124 patients with pN1 NSCLC. Long-term outcomes were compared for 390 pN0, 124 pN1, and 82 pN2 consecutive patients submitted to planned pulmonary resection for NSCLC between 2000 and 2006. The pN1 status was stratified into 3 groups according to the highest level of lymph node involvement: level 10 (hilar); level 11+12 (lobar + interlobar); and level 13+14 (segmental + subsegmental).

Results. The 5-year overall survival (OS) rates for pN0, pN1, and pN2 patients were 93%, 66%, and 25%, respectively. The highest level of lymph node involvement was a significant prognostic indicator; the 5-year OS rate for level 13+14, level 11+12, level 10 pN1, and pN2 was 81%, 58%, 48%, and 25%, respectively. Significant differences were recorded in long-term outcome when pN0 and pN1 level 13+14, pN1 level 13+14, and pN1 level 11+12, pN1 level 11+12 and pN1 level 10 were compared ($p < 0.05$). The median number of examined level 13+14 lymph nodes was 2 (range 0 to 6) and 57% pN1 patients had metastasis at level 13+14 lymph nodes.

Conclusions. The highest level of lymph node metastases may be used to stratify outcome of patients with pN1 disease. Routine examination of level 13+14 lymph nodes is to be recommended to correctly identify patients at risk of relapse and predict long-term prognosis.

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Non-small cell lung cancer (NSCLC) causes more deaths worldwide than any other cancer [1]. Today, the overall survival rate at 5 years for patients with NSCLC is still low (under 20%), but patients with completely resected NSCLC have a considerably better prognosis [2]. Correct staging of the tumor is fundamental in treatment planning and to express a long-term prognosis.

The lymph node (LN) pathologic status is a cornerstone of the staging system and the stronger determinant of prognosis [3]. The current staging system distinguishes 4 conditions of LN involvement, from N0 (absence of nodal involvement) to N3 (involvement of supraclavicular or controlateral mediastinal nodes) [4]. It is obvious that the more accurate is the sampling or dissection of the nodal stations the more realistic is the consequent staging of the disease. For the definition of a pN0 diagnosis, histopathologic examination of hilar and mediastinal lymphadenectomy specimens should include at least 6 LNs; 3 out of 6 should be mediastinal including the subcarinal LNs and the other 3 should be N1 level LNs [4]. Surgeons and pathologists should attend to these criteria or can extend the dissection to a greater number of lymphatic stations and nodes.

Among the so called "N1 level lymph nodes," the actually followed nodal map depicts 5 different nodal levels or stations: hilar (level 10); interlobar (level 11); lobar (level 12); segmental (level 13); and subsegmental (level 14). During lung cancer staging, levels 10, 11, and 12 are easily and frequently sampled or dissected by the surgeon, whereas levels 13 and 14 are accessed by the pathologist during the specimen (lobe or lung) sampling. We investigated the presence of level 13 and 14 LNs and the prognostic value of metastasis to these nodes in a population of patients resected for primary lung cancer.

Patients and Methods

For the present study we retrospectively analyzed the patients submitted to anatomic lung resection and hilar-mediastinal LN dissection for NSCLC at out institution between January 1, 2000 and December 31, 2006. Only patients affected by single NSCLC, without previous intrathoracic or extrathoracic malignancies, with no

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history of thoracic surgery and not submitted to induction therapies were considered. All the included patients had received hilar-mediastinal LN dissection according to the minimal criteria for lung cancer staging described by the TNM Classification of Malignant Tumours, 7th Edition [4]. Following the above restrictions, 596 patients were identified and are the focus of the present paper.

Among 596 patients, 570 lobectomy and 26 pneumonectomy associated with hilar and mediastinal LNs dissection were carried out. According to the pathologic N status, there were 390 pN0, 124 pN1, and 82 pN2 patients. Among 82 patients with pN2 disease and 124 with pN1 disease, 48 and 24 received adjuvant chemotherapy, respectively.

Clinical information was obtained from the in-patient medical record. Pathologic staging was revised and expressed according to the TNM Classification of Malignant Tumours, 7th Edition [4]. Follow-up data were recorded from the out-patients medical charts or phone contact. The local ethics committee approved the design and waived need for an informed consent by each patient because of the retrospective nature of the study. In particular, the status of the lymph node tumor spread among patients affected by pN1 disease was studied.

Lymph Node Dissection and Collection

The hilar and mediastinal LNs ipsilateral to the cancer were resected en-bloc during surgery before the lobe or lung resection and assigned in a standardized manner to the respective stations according to the Mountain-Dresler modification of the American Thoracic Society map [3] . The removed LNs were fixed overnight with a 10% formalin solution and sent to the pathology department. Because of the difficulties encountered during some lobectomy procedures (middle lobe and lower lobes resection) to correctly separate N1 level 11 from level 12 lymph nodes, we proposed a variation of the N1 lymph nodes level classification (Table 1). According to this new scheme, level 11+12 lymph nodes (the lymph nodes of the "interlobar/lobar level") were collected together, fixed overnight with a 10% formalin solution and sent for pathologic evaluation. After lymph nodes dissection, lobe or lung resection was carried out. The resected specimen (lobe or entire lung) was fixed overnight with 10% formalin. Levels 13 and 14 LNs (segmental and subsegmental LNs, the new "segmental level" nodes) were identified and collected from the formalin-fixed surgical specimen (lobe or lung) during its dissection by the pathologist. An expert pathologist (R.B.) carried out by his own, or in which he supervised each procedure of dissection of the surgical specimen by the pathologist in training. All the tissue specimens collected during surgery or by pathologist dissection were separately embedded with paraffin and processed. In particular, the LNs were included into separated tissue blocks and processed for histopathologic and immunohistochemical evaluation for the presence of metastatic disease. Each tissue block of lymphoid tissue of more than 3-mm diameter with a fibrous capsule was defined as a lymph node. Pathologic N1 disease diagnosis was posed when metastatic cancer was demonstrated to the N1 (at each station from 14 up to10) level LNs, with no demonstration of metastasis at the N2 level. When LN metastases were observed at multiple levels, the higher one involved was considered as the advanced one. The total number of patients with LNs present, the number of LNs dissected, and the number of metastatic LNs were accurately collected.

Table 1. New Proposed Scheme for N1 Lymph Node Level Description

Previous Classification [5]	New Proposed Classification
Hilar zone	"Hilar zone"
Level 10	Level 10
Level 11	"Interlobar/Lobar zone"
Peripheral zone	Level 11+12
Level 12	"Segmental zone"
Level 13	Level 13+14
Level 14	

Follow-Up and Statistical Analysis

After surgery each patient was followed up at the outpatient structure every 4 months with physical examination and the execution of a whole body computed tomographic (CT) scan. The CT and positron emission tomography was carried out in the case of suspected recurrence at CT scanning and sequent biopsy when feasible was carried out to confirm the recurrence. In the case of recurrence, its date was calculated as the mean time between the date of the radiologic exam showing the recurrent disease and the date of the previous negative control.

Disease-free survival (DFS) was considered as the period of time occurring from the date of surgical resection of the disease and the date of the demonstration of recurrent disease. Overall survival (OS) was considered as the period of time occurring from the date of surgical resection of the disease and the date of death. Statistical analyses were carried out by computed software (Statistica version 9; Statsoft Inc, Tulsa, OK).

Kaplan-Meier DFS and OS curves were calculated for patients affected by pN0, pN1, and pN2 disease. Patients affected by pN1 disease were stratified according to the higher level of metastatic LNs (pN1 level 10, pN1 level 11+12, and pN1 level 13+14). The log-rank test was applied to calculate the statistical difference between the groups survival. Clinicopathologic parameters of patients with pN0, pN1, and pN2 disease were compared by the use of the χ^2 test. Variables detected to affect prognosis at univariate analysis were tested in a multivariate analysis by a Cox-proportional regression model. Differences were considered significant if the p value was less than 0.05.

Results

Clinicopathologic Characteristics of pN1 Patients Compared With pN0 and pN2 Patients

Among the entire population, the median age at surgery was 68 (range 44 to 83) years, with a male to female ratio of