Tumor stage at presentation plays an essential role in determining prognosis and managing the treatment of patients with a new diagnosis of non-small cell lung cancer (NSCLC). Clinical staging of regional lymph nodes typically relies on computed tomography (CT) of the chest, which uses size as the sole criteria to suggest metastasis. Although larger nodes have a greater probability for harboring tumor, the overall accuracy of CT is only approximately 60%.2,3 Some patients with early-stage NSCLC have enlarged regional lymph nodes that pathologically prove to be “reactive.” The prognostic significance of nodal size in these patients is uncertain. Recent studies in animal models have shown that primary tumors stimulate nodal lymphangiogenesis, causing enlargement of regional nodes before metastasis.4–8 These data suggested that patients with tumors and enlarged nodes may have a worse prognosis than those patients with normal size nodes, as the nodes were primed to accept tumor cells. Alternatively, enlarged reactive nodes in patients with early-stage disease can imply an immune response to the tumor, thus potentially conferring a degree of immunoprotection and improved outcomes.9,10 If the prognosis of pathological stage I (pStage I) NSCLC with reactive nodal enlargement (cN1-2) was different than that of patients with early-stage disease without enlarged nodes (cN0), then management changes could be made with the hope of improving outcomes. This retrospective study explored the International Association for the Study of Lung Cancer (IASLC) database to evaluate the prognostic significance of enlarged lymph nodes in patients with pStage I NSCLC.

**METHODS**

**Patient Population**

This study was approved by the IASLC Lung Cancer Staging Committee. A retrospective review of the tumor registry of the IASLC Staging Database was undertaken to identify all patients between January 1, 1990 and December 31, 2000 with clinical stage I, II (cT1-2N0-1M0 cases and excluding cT3N0M0), and IIIA (cT1-2N2M0 cases excluding cT3N1-2M0) who underwent resection and were proved to have pStage I NSCLC.11 The study group of 6995 subjects...
included 4772 men and 2003 women (sex not documented for 220 patients) with a median age of 67 years (range, 19–90 years).

Clinical Staging, Pathological Staging, Treatment, and Follow-Up

A clinical stage was assigned (cTNM) to all patients based on a combination of imaging studies, including plain chest radiographs and CT.

As per the entrance criteria, all patients had confirmed pStage I NSCLC (pT1-2N0M0) after attempted resection. No patient had preoperative therapy, although 222 of the 6995 patients were registered in databases submitted by clinical trial groups, and 287 had postoperative chemo- and/or radiotherapy. Follow-up data were recorded for all patients, with 95% followed at least 2 years or until death and 81% followed for at least 5 years or until death.

Defining Lymph Node Status

Lymph node categories (N) were recorded according to the AJCC Cancer Staging system, and regional nodes were considered enlarged and abnormal if they were larger than 1 cm in short axis on CT. All cases confirmed to be pN1 or pN2 after resection and the pathological examination were excluded from further study.

Statistical Analysis

Kaplan-Meier survival curves were performed and compared the survival probability between patients who had enlarged regional lymph nodes (cN1-2) but pStage I, and patients with normal size regional lymph nodes (cN0), and pStage I. Additional analysis was performed according to histology. These groups were compared with a log rank test generated using the SAS System for Windows Version 9.0 PHREG procedure. The survival time was defined as the time between the date of resection and the last follow-up or date of death.

RESULTS

Frequency of Enlarged Nodes among All Patients with pStage I NSCLC

This retrospective review of the IASLC database identified 6995 patients, 4772 men and 2003 women (220 sex unknown) with a mean age of 65 years (range, 19–90 years) with pathological stage I NSCLC. Of these patients, 859 (12%) had enlarged regional lymph nodes (cN1-2) but pStage I, and patients with normal size regional lymph nodes (cN0), and pStage I. Additional analysis was performed according to histology. These groups were compared with a log rank test generated using the SAS System for Windows Version 9.0 PHREG procedure. The survival time was defined as the time between the date of resection and the last follow-up or date of death.

Enlarged Nodes in 859 Patients with pStage I (cT1-2N1-2M0; pT1-2N0M0)

There were 704 men and 129 women (26 sex unknown) with a mean age of 65 years (range, 33–83 years) reported to have cN1 or N2 disease and thus clinical stage II (n = 367) or IIIA (n = 492), but all were later proved to be pStage I (Table 1).

The histology of the tumors is shown in Table 2. The estimated median and 5-year survival are 107 months and 62%, respectively (Figure 1 and 2).

Normal Size Nodes in 6136 Patients with Pathological Stage I Disease (cT1-2N0M0; pT1-2N0M0)

There were 4068 men and 1874 women (194 sex unknown) with a mean age of 65 years (range, 19–90 years). None of these patients was reported to have enlarged regional

TABLE 1. Overall Clinical Versus Pathological Stage

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Total</th>
<th>IA</th>
<th>IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6995</td>
<td>3248</td>
<td>3747</td>
</tr>
<tr>
<td>IA</td>
<td>3277</td>
<td>2747</td>
<td>530</td>
</tr>
<tr>
<td>IB</td>
<td>2859</td>
<td>289</td>
<td>2570</td>
</tr>
<tr>
<td>II A</td>
<td>79</td>
<td>54</td>
<td>25</td>
</tr>
<tr>
<td>II B (T3 excluded)</td>
<td>288</td>
<td>26</td>
<td>262</td>
</tr>
<tr>
<td>III A (T3N1-2 excluded)</td>
<td>492</td>
<td>132</td>
<td>360</td>
</tr>
</tbody>
</table>

TABLE 2. Histology of Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Pathology N0</th>
<th>Clinical N0</th>
<th>Clinical N1–N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6995</td>
<td>6136</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3438</td>
<td>3119</td>
</tr>
<tr>
<td>BAC</td>
<td>303</td>
<td>287</td>
</tr>
<tr>
<td>Squamous</td>
<td>2748</td>
<td>2293</td>
</tr>
<tr>
<td>Large cell, NOS</td>
<td>291</td>
<td>252</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>92</td>
<td>73</td>
</tr>
<tr>
<td>Large cell, neuroendocrine</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Mixed non-small cell</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Non-small cell, NOS</td>
<td>102</td>
<td>96</td>
</tr>
</tbody>
</table>

BAC, bronchioalveolar carcinoma; NOS, not otherwise specified.

FIGURE 1. Survival for patients with pathological stage I non-small cell lung cancer. Clinical N0 versus clinical N1–N2. Median survival times were 102 and 107 months for patients with clinical stage I and II–III A (excluding T3N0M0), respectively (hazard ratio 1.16, p = 0.01), shown in the Kaplan-Meier survival curve. The survival curves converge at 8 years postsurgery. The 95% confidence limits for the median survival time (MST) estimates are shown in parentheses.
lymph nodes and thus were both clinical and pathological stage I (Table 1). The histology of the tumors is shown in Table 2. The estimated median and 5-year survival rates are 102 months and 67%, respectively.

Statistical Comparison
Survival for patients with enlarged versus normal nodes was statistically different favoring the cN0 patients (hazard ratio 1.16, \( p = 0.01 \)), although the survival curves converge at 8 years postsurgery (Figure 1). Analysis was also performed according to histology. There was a statistically significant difference in survival (RR 1.35, \( p = 0.0017 \)) among nodal status groups for adenocarcinoma (including bronchioalveolar carcinoma (BAC)), but no difference for other histologies (Figure 3) in general and no difference among squamous cases in particular (data not shown).

### FIGURE 2.
Non-contrast computed tomography scan of the thorax shows a cavitary right upper lobe non-small cell lung cancer and enlarged right paratracheal (Station 4R) lymph node (arrow). Mediastinoscopy was performed, and there was no evidence of lymph node metastasis on pathological evaluation. All nodes were reactive.

### FIGURE 3.
Survival for pathological stage I according to histology. Survival curves with 95% confidence limits for the median survival time (MST) estimates are shown in parentheses.

Non-invasive imaging plays an integral role in staging and facilitating management in patients with a new diagnosis of lung cancer. These studies typically include a thoracic CT through the adrenal glands, a head CT or magnetic resonance imaging, a bone scan, and, at many institutions, a positron emission tomographic (PET) scan. The most common site of lung cancer metastasis is the regional lymph nodes, which are considered abnormal on CT when nodes are larger than 10 mm in diameter in short axis. However, it is well established that benign reactive lymph nodes may be enlarged and metastatic lymph nodes may be of normal size.5,13–15

When lymph nodes are enlarged on CT in patients with a new diagnosis of NSCLC, they are considered to contain metastasis, although 37% to 43% of enlarged lymph nodes on CT are negative by pathological evaluation.13,14,16 Although PET imaging may reduce the number of false-positive CT scans,15,17,18 enlarged nodes are still usually biopsied before resection. Thus, although imaging provides a road map to target regional nodes sampled at mediastinoscopy or thoracotomy, it is not sufficient for making treatment decisions.

The clinical significance of enlarged reactive nodes remains unclear. Some investigators have suggested that non-malignant lymph node enlargement can be the result of preexisting inflammatory processes. Alternatively, lymph node expansion is attributed to the growth of new lymphatic capillaries and dilatation of lymph sinuses and vessels that are stimulated by tumor-secreted cytokines such as vascular endothelial growth factors (VEGF)-A, -C, and –D.4 –7,19 –23 The effect of lymphangiogenesis results in increased blood flow to the lymph nodes, which can potentially increase seeding of subsequent metastases.4 –8 Lynhphangiogenesis in NSCLC is associated with an increased incidence of regional lymph node metastasis.24 –26 Furthermore, expression of VEGF-C and -A in the primary NSCLC has been shown to be a significant prognostic factor.25 If this were the case, then one would predict patients with enlarged, reactive nodes would do worse than patients with normal sized nodes.

This study showed that enlarged nodes are uncommon in patients with pathologically proved early-stage disease and that overall survival differences in nodal size groups for all patients with NSCLC are not clinically meaningful. Early survival differences were observed among nodal size groups in patients with adenocarcinoma; however, median survival exceeded 10 years for these patients, and there was insufficient follow-up beyond 7 years for the patients with cN1-2 pN0 adenocarcinoma to reach conclusions about long-term survival for this specific subgroup.

The overall findings most likely result from the fact that lymph node enlargement can be caused by a spectrum of diseases, not just tumors. Although enlarged nodes may have been caused by the tumor, they may have predated the onset of their NSCLC and be unrelated. Regardless, size of nodes does not seem to be useful in stratifying patients with early-stage NSCLC, and nodal sampling is required for accurate pathological staging in all cases, irrespective of cN category.

This study has several fundamental limitations, particularly because the data were collected and analyzed retro-
spectively. Although this is the largest lung cancer database ever recorded and standard terminology was requested, there would be variations in nomenclature and classification. In addition, whereas patients’ clinical stages were recorded, the exact size of nodes is unknown, and we can only conclude that patients with NSCLC and enlarged nodes do not have any different outcome than patients without evidence for adenopathy. Other limitations are that we only had overall survival and did not have disease-specific survival data; postsurgical treatment regimens were not uniform; there was no standard requirement of nodal sampling at surgery; and pathologic examination of reselected nodes varied among institutions. Additional follow-up, which may shed further light on the findings, has been requested.

In conclusion, despite these limitations, this study analyzed a large number of patients from an international database and found that enlarged regional lymph nodes in all patients with pStage I NSCLC was uncommon and did not have clear prognostic significance.

REFERENCES