Tumor Size Is a Determinant of Stage Distribution in T1 Non-Small Cell Lung Cancer*

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**Study objective:** Despite renewed interest in early detection of lung cancer, the relationship between tumor size and survival remains controversial. The objective of this study was to evaluate the relationship between size and stage in patients with T1 (<3.0 cm) non-small cell lung cancer (NSCLC).

**Patients and methods:** A retrospective review of a lung cancer database from 1995 to 2003 identified 503 patients with completely resected invasive NSCLC with tumors ≤3 cm. All clinical and pathologic characteristics were recorded. Univariate associations between nodal status and other prognostic factors were explored by χ² and t tests. The independent effect of tumor size >2 cm vs ≤2 cm on the risk of nodal disease was analyzed using a logistic regression model.

**Results:** Of the 503 patients, 324 patients (64.4%) had stage IA disease, 52 patients (10.3%) had stage IB disease, 37 patients (7.4%) had stage IIA disease, 15 patients (3%) had stage IIB disease, 43 patients (8.6%) had stage IIIA disease, 24 patients (4.8%) had stage IIIB disease, and 8 patients (1.6%) had stage IV disease. One hundred patients (19.9%) had nodal metastases. The mean (± SD) tumor size of cases without nodal disease was 1.90 ± 0.67 cm, compared to 2.18 ± 0.69 cm for node-positive tumors (p = 0.0003; 95% confidence interval [CI] for mean difference, 0.13 to 0.43). Forty-eight of 308 patients (15.6%) with smaller carcinomas (<2.0 cm) compared to 52 of 195 patients (26.7%) with carcinomas >2.0 cm had nodal metastases (p = 0.002). Exploratory multivariate analysis revealed that only tumor size (≤2.0 cm [referent] vs >2.0 cm) affected nodal status and thus stage (adjusted odds ratio, 2.0; 95% CI, 1.3 to 3.1; p = 0.002).

**Conclusions:** Primary invasive NSCLC >2.0 cm was twice as likely to have nodal metastases than carcinomas ≤2.0 cm. Our results suggest that in lung cancer smaller lesions may represent earlier stage disease. These results also suggest the need for further subclassification by tumor size within the current International Union Against Cancer/American Joint Committee on Cancer stage I, with tumors <2 cm in size contained in a separate substage. This refinement may help to better clarify which patients might benefit from novel adjuvant or neoadjuvant therapeutic interventions.

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**Key words:** CT scan; lung cancer; stage

**Abbreviations:** BAC = bronchioloalveolar carcinoma; CI = confidence interval; NSCLC = non-small cell lung cancer; OR = odds ratio; UICC/AJCC = International Union Against Cancer/American Joint Committee on Cancer

Approximately 170,000 new cases of lung cancer are diagnosed each year in the United States, and 160,000 patients die of their disease.¹ Fewer than 15% of patients present with stage I disease, in which surgical resection results in a 5-year survival of 60 to 80%.² The improved survival following surgical resection in patients with stage I disease has rekindled interest in lung cancer screening in order to detect smaller and potentially more curable lesions. Several studies³–⁷ have explored the value of low-dose spiral CT as a screening modality for lung cancer. Advocates of low-dose spiral CT believe that detection of small lesions will lead to a significant stage shift (to earlier stage disease) with improved survival, while...
critics of this approach argue that tumor biology rather than size is the key determinant of stage, thus negating the merits of screening.5–11

Although tumor size is an important characteristic in the current International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system,2 the relationship between size and stage within the T1 (tumor ≤ 3 cm in greatest dimension) group is uncertain. The current study was designed to evaluate the relationship between size and stage distribution in completely resected pathologically staged invasive T1 (≤ 3.0 cm) non-small cell lung cancer (NSCLC).

Materials and Methods

The Thoracic Surgery Tumor Registry at the Weill Medical College of Cornell University served as the initial database. A retrospective review of this tumor database identified 600 patients with non-small cell carcinomas with primary tumors measuring ≤ 3.0 cm who underwent mediastinoscopy followed by lobectomies without preoperative therapy between 1995 and 2003. Inclusion criteria included complete pathologic staging according to the UICC/AJCC staging scheme with complete mediastinal lymph node dissection and availability of all pathologic materials. Seventy cases with incomplete nodal staging or incomplete pathologic material were excluded. Five hundred thirty cases were reviewed by one author (D.B.F.), and tumors were classified according to the current World Health Organization classification of lung tumors.12 Of note, this classification scheme defines bronchioloalveolar carcinoma (BAC) as an adenocarcinoma without histologic evidence of stromal, vascular, or lymphatic invasion. Given the particular behavior of this adenocarcinoma subtype, 16 identified BAC cases were excluded. Eleven cases of typical carcinoid tumor, atypical carcinoid tumor, or salivary gland-type tumors were also excluded.

The 503 remaining cases form the basis for this study. Given the growing and controversial interest in the prognostic significance of micrometastatic disease in locoregional lymph nodes, histologic sections from all 406 light microscopically negative peribronchial lymph nodes were stained with anti-cytokeratin AE1/AE3 and calretinin antibodies. Patient gender as well as gross tumor size and pathologic subtype were also recorded.

Statistical Analysis

Univariate associations between nodal status (positive/negative) and other prognostic factors were explored by the χ2 test (gender, histology, tumor size categories) and the t test (age, tumor size continuous). The independent effect of tumor size > 2 cm vs ≤ 2 cm on the risk of nodal disease was analyzed using a logistic regression model, controlling for gender (male [referent] vs female), and histology (adenocarcinoma [referent] vs squamous cell/large cell carcinoma). As well, a restricted logistic model was run only for patients with adenocarcinoma. The use of an a priori cutoff point of 2 cm was suggested by previous work13 that demonstrated a statistically significant effect of tumor size (≤ 2 cm vs > 2 cm) on 5-year survival in resected stage IA NSCLC. The current study was designed as a hypothesis-generating study, and all of the analyses described below should be treated as exploratory. All p values are two sided, with statistical significance evaluated at the 0.05 level. Ninety-five percent confidence intervals (CIs) were calculated to assess the precision of the obtained estimates. All analyses were performed using software (SAS Version 9.1; SAS Institute; Cary, NC). This study was approved by the institutional review board of the Weill Medical College of Cornell University.

Results

Patient characteristics and tumor histology are presented in Table 1. Tumors measured from 0.2 to 3.0 cm (median, 2.0 cm). Three hundred ninety-one tumors were T1, 83 tumors were T2 (visceral pleural invasion), 4 tumors were T3 (chest wall invasion), and 25 tumors were stage T4 (intralobar satellite lesions). Of the 503 cases, 100 patients (19.9%) had nodal disease including three adenocarcinoma cases measuring 2.1, 2.3, and 2.6 cm, which were considered N0 on histology but upstaged to N1 following the identification of 2.0-, 2.2-, and 2.3-mm metastatic foci on cytokeratin immunohistochemical stains. Of the 503 patients, 324 patients (64.4%) were found to have stage IA disease, 52 patients (10.3%) had stage IB disease, 37 patients (7.4%) had stage IIA disease, 15 patients (3%) had stage IIB disease, 43 patients (8.6%) had stage IIIA disease, 24 patients (4.8%) had stage IIIB disease, and 8 patients (1.6%) had stage IV disease. Stage distribution according to tumor size is illustrated in Figure 1.

The mean (± SD) tumor size of cases without nodal disease was 1.90 ± 0.67 cm, while the mean tumor size of cases with nodal disease was 2.18 ± 0.69 cm (p = 0.0003; 95% CI for mean difference, 0.13 to 0.43). Forty-eight of 308 patients (15.6%) with smaller carcinomas (≤ 2.0 cm) compared to 52 of 195 patients (26.7%) with carcinomas > 2.0 cm had nodal metastases (p = 0.002). Of the 48 cases with tumors ≤ 2.0 cm with nodal metastases, 28 cases were N1+ and 20 cases were N2+. Of the 52 cases > 2.0 cm with nodal metastases, 23 were N1+, 27 were N2+, and 2 were N3+.

As shown in Table 2 in an exploratory multivariate analysis, only tumor size ≤ 2.0 cm (referent) vs > 2.0 cm, but not gender or histology, affected nodal status and thus stage (p = 0.002). In short, tumors > 2.0

<table>
<thead>
<tr>
<th>Table 1—Patient Characteristics (n = 503)*</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Mean age (range), yr</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell</td>
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<tr>
<td>Large cell</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
cm appeared twice as likely to have nodal disease as compared to carcinomas ≤ 2.0 cm in greatest dimension.

Since a ≤ 3.0 cm non-small cell carcinoma can be T2 or even T4 on the basis of pleural invasion or presence of satellite lesions, ie, features reflecting biological behavior rather than simply size, a restricted exploratory multivariate model was performed on the 391 ≤ 3.0-cm T1 carcinoma cohort to evaluate for a potentially different result. The adjusted odds ratio (OR) [for tumor size > 2.0 cm] from this restricted model was essentially unchanged (OR, 1.89; p < 0.019) [Table 3].

We also evaluated adenocarcinomas ≤ 3.0 cm. The exploratory logistic regression model performed on the 399 adenocarcinomas revealed that only tumor size (> 2.0 cm vs ≤ 2.0 cm), but not gender, was significant, with an adjusted OR of 1.70 (95% CI, 1.03 to 2.81; p = 0.038). Investigation of the influence of size on the 308 T1 adenocarcinomas failed to maintain statistical significance (p = 0.204). However, the adjusted OR of 1.48 and the associated 95% CI (0.81 to 2.73) still demonstrated a trend toward an effect for tumor size > 2.0 cm.

**DISCUSSION**

While few would argue with the premise that size is a major determinant of survival in lung cancer, controversy exists as to the role of size within the T1 category. This issue has important implications for lung cancer screening as well as for future refinements of the lung cancer staging system. If the expected survival with a subcentimeter tumor is no different than that with a 3.0-cm tumor, the ability of CT scans (as opposed to plain chest radiographs) to detect these small lesions may not translate into a meaningful survival benefit. While many groups have performed retrospective studies examining the effect of tumor size on stage, curability, and patient survival with conflicting results,13–28 several findings require individual comments.

Heyneman and colleagues15 performed a retrospective analysis of 620 patients with pathologically proven NSCLC measuring ≤ 3 cm. They determined that there was no significant relationship between size and the distribution of the disease stage and that it followed that CT screening may not result in a shift to an earlier disease-stage distribution. However, the study was performed over a 20-year period, included very few non-stage I patients and within stage I very few subcentimeter cancers. This study may not reflect the current screening population and thus may be inappropriate to base conclusions on the merits of screening from such analysis.

Wisnivesky and colleagues18 demonstrated an improved curability for smaller lesions within stage IA utilizing the Surveillance, Epidemiology, and End Results database. Survival analysis was carried out to 12 years, a compelling argument against lead-time bias. These results are in concordance with our previous analysis of 244 resected stage IA patients that demonstrated an improved survival for patients with ≤ 2-cm NSCLC compared to stage IA patients with larger tumors (> 2 cm).13 This reported finding served as the basis for the exploration of the 2.0-cm tumor size cutoff point in the current study.

The current study differs from previous work in several ways. All patients underwent resection with a mediastinal lymph node dissection, and surgical material was reviewed by a pulmonary pathologist, with particular attention to stage-related issues such as

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**Table 2—Determinants of Stage in ≤ 3.0 cm Invasive NSCLC by Logistic Regression Model (n = 503)**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Gender*</td>
<td>1.19</td>
<td>0.76–1.88</td>
<td>0.450</td>
</tr>
<tr>
<td>Histology†</td>
<td>0.95</td>
<td>0.55–1.65</td>
<td>0.853</td>
</tr>
<tr>
<td>Tumor size‡</td>
<td>2.00</td>
<td>1.25–3.13</td>
<td>0.002</td>
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*Male (referent) vs female patients.
†Adenocarcinoma (referent) vs squamous cell/large cell.
‡≤ 2 cm (referent) vs > 2 cm.

**Table 3—Determinants of Stage in ≤ 3.0 cm Invasive T1-Only NSCLC by Logistic Regression Model (n = 391)**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Gender*</td>
<td>0.90</td>
<td>0.53–1.53</td>
<td>0.687</td>
</tr>
<tr>
<td>Histology†</td>
<td>0.98</td>
<td>0.52–1.87</td>
<td>0.951</td>
</tr>
<tr>
<td>Tumor size‡</td>
<td>1.89</td>
<td>1.11–3.22</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Male (referent) vs female patients.
†Adenocarcinoma (referent) vs squamous cell/large cell.
‡≤ 2 cm (referent) vs > 2 cm.
pleural invasion and presence or absence of satellite lesions. Thus, all cases were meticulously staged. We have also excluded cases of BAC. As currently defined, BAC is a carcinoma without stromal, vascular, or lymphatic invasion. Despite a propensity to multifocality and thus “high stage,” BAC has a more favorable survival rate than invasive carcinoma. As researchers and clinicians grapple with this entity and perhaps consider BAC an in situ lesion and precursor to invasive carcinoma, it was decided not to include such cases in this statistical analysis.

Additional tissue sections and immunohistochemical analysis of light microscopically tumor-free peribronchial lymph nodes were also performed to allow for accurate staging. Only 3 of 399 patients were found to have micrometastases after additional sections and immunohistochemical stains. These results merely strengthen our belief and that of others29,30 that histologically negative lymph nodes are essentially tumor free and of no clinical import. But it should be noted that this undertaking was not equivalent in scope to published sentinel node studies.27 31 Furthermore, since up to 10% of lymph node metastases skip peribronchial lymph nodes and appear first in mediastinal (American Joint Committee on Cancer N2) lymph nodes,32,33 a complete nodal examination would, in this cohort, require deeper levels and immunohistochemical stains to be performed on at least three additional tissue blocks (right and left level 4 and level 7 lymph nodes) per case rendering at least 15 slides per case for an additional 6,000 study slides. Although we acknowledge the limitation of not examining the mediastinal lymph nodal stations by immunohistochemistry, there seems to be little rationale that immunohistochemistry-detected mediastinal lymph node disease would be more prevalent than that detected in the N1 stations.

Our exploratory results suggest that further subclassification by tumor size within the current UICC/AJCC stage I is warranted particularly as it relates to peripheral adenocarcinomas, the most common lung cancer in the United States. Based on the 399 3.0-cm or smaller adenocarcinomas, an odds ratio of 1.70 (for size > 2.0 cm) with a p value of 0.038 lends statistical support to limiting T1 tumors to 2.0 cm or less. A lack of statistical significance, despite the presence of a trend toward an effect for size > 2.0 cm, with the T1 adenocarcinomas may be due to the small sample size of node positive patients in this group (53/308). These findings may have implications beyond the issue of substaging within the UICC/AJCC scheme.

Since most studies showed that low-dose CT scanning is more sensitive than chest radiographs for detecting early lung cancer and detected carcinomas have a median tumor size of 1.5 cm,3–6 these data suggest that earlier diagnosis may improve patient outcome. Although this work did not examine the cause-specific survival of patients with lung cancer ≤ 2.0 compared to those with carcinomas > 2.0 cm, the size-dependent stage shift refutes the argument that finding the tumors earlier has no clinical benefit. Yet whether CT screening lowers lung cancer mortality is at present unknown and will remain so until the completion of several ongoing prospective trials.

While this study cannot offer insights into the biological factors that affect patient survival, statistical analysis performed on the 391 T1 carcinomas demonstrates that the adjusted OR for size > 2.0 cm changed from 2.0 (based on all 503 patients, p = 0.002) to 1.89 (p = 0.019). This result may indicate that biological factors other than tumor size may determine patient stage. These findings are not surprising and only serve to emphasize that while smaller carcinomas are less likely to have nodal metastases (26.7% of carcinomas > 2.0 cm had nodal spread at the time of definitive surgical resection), and, as a consequence, lower stage, still 15.6% of ≤ 2.0-cm carcinomas had nodal metastases. This result is similar to that reported by others.

In conclusion, this study suggests that primary invasive non-small cell lung carcinomas > 2.0 cm are twice as likely to have nodal metastases as carcinomas ≤ 2.0 cm. Although these findings are only exploratory and require validation in an independent study, the results suggest further support for the theory that small lesions represent early stage disease and that further subclassification by tumor size within the current UICC/AJCC stage I may be warranted. This refinement may help to better clarify which patients might benefit from novel adjuvant or neoadjuvant therapeutic interventions. Additionally, the findings suggest that CT screening may result in a shift toward an early stage distribution.

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