Computed Tomographic Screening for Lung Cancer

The Relationship of Disease Stage to Tumor Size

The International Early Lung Cancer Action Program Investigators*

**Background:** The relationship of lung cancer stage to tumor diameter has been identified as a prognostic indicator. We report on the stage-size relationship of these asymptomatic, latent lung cancer cases diagnosed by computed tomographic screening.

**Methods:** Baseline and repeat screening of 28,689 people following the International Early Lung Cancer Action Program regimen of screening has resulted in 464 diagnoses of lung cancer. Each case was characterized according to tumor diameter, consistency (solid, part solid, or nonsolid), and the presence or absence of identifiable metastases (N0 M0) at the time of diagnosis, regardless of whether it was delayed.

**Results:** For the 436 non–small cell carcinomas, the percentages of cases with no metastases (N0 M0) were 91%, 83%, 68%, and 55% for the categories 15 mm or less, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater, respectively. The gradients in the successive percentages of N0 M0 cases were significantly different (P=.02, 1-sided), except between the last 2 categories, and held for solid nodules, were suggestive for part-solid ones, but were not suggestive for nonsolid ones. For the 28 small cell carcinomas, the percentages of N0 M0 cases were 67% and 23% (P=.01, 1-sided), respectively, for those 25 mm or less compared with those greater than 25 mm.

**Conclusions:** Lymph node status has a strong relationship to tumor diameter for non–small cell and small cell cancers. The percentages of N0 M0 cases in screen-diagnosed lung cancers are much higher than previously reported in the Surveillance, Epidemiology, and End Results registry. These results provide direct evidence of a stage-size relationship in a screened population.

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**FOR STAGE I LUNG CANCER, tumor size has been identified as a prognostic indicator. It thus was incorporated into the International System for Staging Lung Cancer classification in 1986. Cases without identifiable lymph node metastases (stage I cases) were subdivided into stage IA and stage IB, according to the tumor being less or more than 30 mm in diameter. This refinement in staging has been continued, but all were based on registries of cases.** Since 1986, remarkable advances have occurred in computed tomography (CT) scanners. Submillimeter slicing can now be applied to the entire chest in a single breath-hold; as a result, lung cancer is being detected at a smaller size than in cases diagnosed before 1986. Further size-based subdivisions of stage I cancer have been suggested, also based on registry cases.

The introduction of CT screening leads to consideration of the prognostic value of tumor size in the context of diagnoses of asymptomatic (thus latent) lung cancers. Until now, registry data have been used to investigate disease stage in relation to tumor size for these smaller, latent cancers. Registry cases, however, do not expressly reflect the stage-size relationship of asymptomatic cases; registry cases typically come to medical attention because of symptoms, possibly metastasis induced, whereas latent cases are found in asymptomatic people.

We report the stage-size relationship of latent lung cancers diagnosed in our International Early Lung Cancer Action Program (I-ELCAP), which is dedicated to research on CT screening for lung cancer. These data provide for the first time, to our knowledge, direct evidence relevant to this issue.

**METHODS**

Following the I-ELCAP protocol, 28,689 asymptomatic men and women were enrolled and received baseline screening at 38 institutions throughout the world; among them,
22,991 repeat screenings have been performed. At enrollment, the median age was 61 years, median pack-years of smoking was 30, and 58% of the study participants were men. Baseline screenings were conducted in 1993 to 2004 and repeat screenings in 1994 to 2004. All participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols.

The I-ELCAP protocol defined the initial low-dose, noncontrast CT test and its positive result at both baseline and repeat screening. It also defined the recommended diagnostic workup following a positive result. The actual workup, however, was left to the discretion of each participant and the referring physician, but it was documented in the Web-based ELCAP Management System.

All screen-diagnosed cases of lung cancer are included in this report. They consist of cases in which the diagnostic workup was prompted by a positive result of the initial CT test on either the baseline or repeat screening, even if the interval to repeat screening was more than 12 months or the diagnostic workup was delayed, the latter by as much as 3 years. Thus, we excluded the interim-diagnosed cases, identified on the prompting of symptoms emerging between screenings. We focused on the first primary lung cancer that was diagnosed.

A total of 464 cases of lung cancer were screen diagnosed, 376 and 88 of the diagnoses prompted by a positive result of the initial CT test at baseline and on repeat screening, respectively. Each screen-diagnosed case of lung cancer was characterized according to tumor diameter, consistency, and the presence or absence of identifiable lymph node or distant metastases at the time of diagnosis by 1 of 3 experienced chest radiologists (C.I.H., D.F.Y., or Dorothy I. McCauley, MD) at the I-ELCAP Coordinating Center. Tumor diameter was derived as the average of its length and width measured on the pathologic specimen, if available; otherwise, it was measured on the CT images closest in time to diagnosis. Nodule consistency was classified as solid, part solid, or nonsolid on the basis of these same images. It was defined as solid if the nodule obscured the entire lung parenchyma within it (Figure 1) or subsolid if it did not. We further subdivided subsolid nodules into part solid if it obscured part of the lung parenchyma within it (Figure 2) and nonsolid if it obscured none of the parenchyma within it (Figure 3).

Biopsy specimens were submitted to experts for independent reading; cytology specimens to an expert cytologist (Madeleine Vazquez, MD) and histologic specimens to our 5-member Pathology Review Panel (Darryl Carter, MD, chair, Elizabeth Brambilla, MD, Adi Gazdar, MD, Masayuki Noguchi, MD, and William Travis, MD) for reading according to the I-ELCAP pathology protocol. Histologic diagnosis superseded the cytologic one when both were available. For purposes of this report, we used the consensus diagnoses of these experts, following the 2004 World Health Organization criteria. Among the 464 cases, there were 436 diagnoses of non–small cell carcinoma and 28 diagnoses of small cell carcinoma.

Lymph node status was based on the surgical findings when available; otherwise, it was based on the CT (and positron emission tomography, if done) test performed closest in time to the recommendation for biopsy, identical to the reporting in the National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results (SEER) registry. Hilar and mediastinal lymph nodes were classified as metastatic if the short axis on CT was greater than 10 mm or the positron emission tomographic scan showed any uptake. It was classified as N0 (no metastases), N1 (only ipsilateral peribronchial, hilar, and/or intrapulmonary metastases), N2 (ipsilateral mediastinal and/or subcarinal metastases, no contralateral), or N3 (contralateral mediastinal and/or hilar, scalene, or supraclavicular metastases). Status of distant metastases was classified as M0 (absent) or M1 (present). Staging was based on the postsurgical findings in 368 (84%) of the 426 cases of non–small cell carcinoma and in 8 of the 28 cases of small cell carcinoma. For these 376 resected cases, the presurgical and postsurgical stages were identical for 335 (89%) of them. Of the 41 cases in which there was disagreement, 37 were presurgical N0 but postsurgical N1 to N3, and 4 were presurgical N1 to N2 but postsurgical N0.

We classified the tumors in the following categories of diameter: 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. We focused principally on the frequency of N0 M0 status in these categories. Because it was well established that the frequency of N0 M0 decreases with increasing tumor size, we used the 1-sided test for assessing significant differences between the size categories. Statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

**Table 1** gives lymph node status by tumor size for 436 diagnosed cases of non–small cell lung cancer. The proportions of cases with no metastases (N0 M0) were 85% overall and 91%, 83%, 68%, and 55% for the respective size categories of 15 mm or smaller, 16 to 25 mm, 26 to 35 mm, and 36 mm or greater. The gradients in the successive percentages of N0 M0 were significantly different ($P=0.02$, 1-sided), except between the last 2 categories. Of the 370 cases classified as N0 M0, 323 (87%) were based on postsurgical staging.

**Table 2**, like Table 1, addresses lymph node status in relation to tumor size in those 436 cases of non–small cell lung cancer, but separately according to nodule consistency. The declining trend in the frequency of N0 M0 status with increasing size of the tumor is evident for solid nodules, suggestive for part-solid ones, but not suggestive for nonsolid ones. All non–small cell patho-
logic classifications were represented by the cancers presenting in solid nodules, whereas only adenocarcinoma (bronchioloalveolar or mixed subtype) was found in those presenting as part-solid and nonsolid nodules. For solid nodules, the proportions of N0 M0 cases of adenocarcinoma and squamous cell carcinoma were not significantly different (81% vs 79%, respectively; \( P = .69 \)).

For small cell lung cancers, all presenting as solid nodules, the trend in the percentage of N0 M0 status by tumor size is strongly apparent (Table 3). Because of the small number of cases, we pooled the data and compared only those 25 mm or less with those larger than 25 mm. The proportions of N0 M0 cases were significantly different: 67% (10/15) and 23% (3/13), respectively (\( P = .01 \), 1-sided).

**COMMENT**

Among cases of non–small cell lung cancer diagnosed in asymptomatic persons by CT screening, we find lymph node status to have a strong relationship to tumor diameter for cancers that present as solid nodules. Among the few cases of small cell lung cancer, all presenting as solid nodules, a relationship between lymph node status and tumor diameter was also seen.
The relationship of lymph node status to tumor size was not apparent for cancers that presented as nonsolid nodules, whereas it was suggestive for those that presented as part-solid nodules. Cancers that present as nonsolid nodules are noninvasive adenocarcinomas or adenoacinar–mixed subtype with a small invasive component and thus have not yet spread to the lymph nodes, as demonstrated by Noguchi et al.12

The percentages of N0 M0 cases specific to categories of tumor diameter for non–small cell lung cancer in this report are much higher than those reported from the Surveillance, Epidemiology, and End Results (SEER) registry data, which were 54%, 46%, 34%, and 18%, respectively (Figure 4).6 The trend, however, was evident in the SEER data as well. It was not apparent in the analysis of a smaller registry13 for reasons explained in subsequent publications.14,15 Nevertheless, results from that same registry were used as part of the justification for performing a large randomized controlled trial.16 We have now demonstrated the prognostic significance of tumor size directly.

Table 1. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter*

<table>
<thead>
<tr>
<th>Tumor Diameter, mm</th>
<th>≤15</th>
<th>16-25</th>
<th>26-35</th>
<th>≥36</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0 M0</td>
<td>234</td>
<td>98</td>
<td>27</td>
<td>11</td>
<td>370</td>
</tr>
<tr>
<td>N1 M0</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>N2 M0</td>
<td>19</td>
<td>10</td>
<td>8</td>
<td>4</td>
<td>41</td>
</tr>
<tr>
<td>N3 M0/M1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total (% of N0 M0)</td>
<td>258</td>
<td>118</td>
<td>83</td>
<td>40</td>
<td>436</td>
</tr>
</tbody>
</table>

*For tumor diameter ≤15 vs 16-25, P = .02; for 16-25 vs 26-35, P = .02; and for 26-35 vs ≥36, P = .17.

Table 2. Lymph Node Status of 436 Cases of Non–Small Cell Lung Cancer at Diagnosis by Tumor Diameter and Separately According to Nodule Consistency

<table>
<thead>
<tr>
<th>Nodule Consistency and Lymph Node Status</th>
<th>Tumor Diameter, mm</th>
<th>≤15</th>
<th>16-25</th>
<th>26-35</th>
<th>≥36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 M0*</td>
<td>169 (86)</td>
<td>65</td>
<td>18</td>
<td>6</td>
<td>235</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
<td>18</td>
<td>12</td>
<td>9</td>
<td>62</td>
</tr>
<tr>
<td>Total (% of N0 M0)</td>
<td>232 (100)</td>
<td>83</td>
<td>30</td>
<td>45</td>
<td>297</td>
</tr>
<tr>
<td>Part solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 M0*</td>
<td>48</td>
<td>22</td>
<td>5</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total (% of N0 M0)</td>
<td>49 (98)</td>
<td>24</td>
<td>6</td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>Nonsolid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 M0*</td>
<td>40</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (% of N0 M0)</td>
<td>40 (100)</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>58</td>
</tr>
</tbody>
</table>

The pattern confirmed herein suggests the usefulness of finding latent cancers at small sizes. Most lung cancers without evidence of lymph node metastases are curable, with the curability rate being higher at smaller sizes.5,6 This suggests that tumor diameter also serves as a prognostic indicator for curability, perhaps even for micrometastases not detectable by our current techniques.
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REFERENCES