Diameter of Non-small Cell Lung Cancer Correlates With Long-term Survival*

Implications for T Stage

Carlos M. Mery, MD, MPH; Anastasia N. Pappas, MSW, MPH; Bryan M. Burt, MD; Raphael Bueno, MD, FCCP; Philip A. Linden, MD; David J. Sugarbaker, MD, FCCP; and Michael T. Jaklitsch, MD, FCCP

Study objectives: To determine the effect of tumor diameter on the long-term survival of patients with stage I non-small cell lung cancer (NSCLC) within a large multi-institutional database, and to assess the accuracy of the T-descriptor threshold of 3 cm.

Design and patients: A total of 9,191 patients ≥ 20 years old with surgically treated stage I NSCLC ≤ 6 cm registered in the Surveillance, Epidemiology, and End Results database from 1992 to 1997 were included. The size of the nodule was grouped into six categories: < 1 cm (n = 191, 2%), 1 to 1.9 cm (n = 2,130, 23%), 2 to 2.9 cm (n = 2,851, 31%), 3 to 3.9 cm (n = 1,984, 22%), 4 to 4.9 cm (n = 1,161, 13%), and 5 to 6 cm (n = 874, 9%). Due to its limited sample size, subcentimeter nodules were not included in the survival analysis. Survival analyses were performed with Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards models.

Measurements and results: A total of 4,904 (53%) men and 4,287 women (mean ± SD age, 66.6 ± 9.4 years) with stage I NSCLC were analyzed. The use of lobectomies and pneumonectomies as surgical treatment instead of limited resections increased with the size of the tumor, from 62% in subcentimeter nodules to 96% in 5- to 6-cm tumors (p < 0.0001). Survival decreased with increasing size of the tumor (p < 0.0001). There was a significant survival difference when size groups were compared to tumors 1.0 to 1.9 cm: 2.0 to 2.9 cm (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.16 to 1.47), 3.0 to 3.9 cm (HR, 1.49; 95% CI, 1.32 to 1.69), 4.0 to 4.9 cm (HR, 1.82; 95% CI, 1.59 to 2.08), and 5.0 to 6.0 cm (HR, 2.04; 95% CI, 1.77 to 2.36). Survival was similar in tumors between 2.0 to 2.9 cm and 3.0 to 3.9 cm, and in tumors between 4.0 to 4.9 cm and 5.0 to 6.0 cm.

Conclusions: The T descriptor should be changed so that T1 is reserved for tumors < 2 cm. Further refinement of larger tumors into T2a (2 to 3.9 cm) and T2b (≥ 4 cm) should be considered.

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Key words: diameter; lung cancer; lung carcinoma; non-small cell lung cancer; size; staging; T stage; TNM

Abbreviations: CI = confidence interval; HR = hazard ratio; NSCLC = non-small cell lung cancer; SEER = Surveillance, Epidemiology, and End Results

Accurate staging of cancer helps define prognosis, guide therapy, and facilitate the development of new treatment strategies. The TNM staging system for all solid tumors was devised by Pierre Denoix1 between 1943 and 1952, using the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases to classify the progression of cancer. In 1974, the American Joint Committee on Cancer and the Union Internationale Contre le Cancer applied the TNM cancer staging system to lung cancer.2 T staging defines the primary tumor by size, airway location, and degree of local invasion. A 3-cm diameter of the primary tumor was chosen as the threshold to differentiate T1 from T2 tumors. This was largely due to observations over the previous 20 years that tumors > 3 cm on plain chest radiography had a worse prognosis than smaller tumors.

Two major revisions of the lung cancer staging
system have been published in 1986 and 1997. In 1986, N1 disease was moved from the stage I group into the stage II group, but there was no change in the size of the T descriptor. The latest revision to the system was published in 1997, based on 5,319 patients from databases provided by MD Anderson Cancer Center and the Lung Cancer Study Group. This revision found a significant survival difference between the population of patients with T1 cancers (i.e., all tumors ≤ 3 cm) and T2 cancers (i.e., all tumors > 3 cm). Therefore, the old grouping of stage I was divided into two subcategories, IA (T1N0M0) and IB (T2N0M0), based on the T descriptor. However, no analysis was provided of the adequacy of the 3-cm threshold, nor was there any analysis of survival as a function of smaller tumor sizes. The purpose of this analysis was to determine the effect of tumor diameter on the long-term survival of patients with stage I non-small cell lung cancer (NSCLC) within a large multi-institutional database and assess the accuracy of the T-descriptor threshold of 3 cm.

**Materials and Methods**

The study cohort comprised the 9,191 patients > 20 years of age with surgically treated stage I NSCLC, tumors < 6 cm, and no history of lung malignancy included in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute from 1992 to 1997. The SEER database is a multi-institutional, community-based cancer registry containing clinical, pathologic, and survival-related data from 12 population-based cancer registries in the United States. Three hundred twelve patients were excluded for lack of tumor size data. No patient consent or institutional review board approval were obtained, as the data were collected from a public domain database of anonymous patient data.

Variables extracted from the SEER database included gender, age, race/ethnicity, marital status, histology and size of the tumor, stage, type of surgery, survival, and cause of death. Tumor size is originally determined by the SEER group from, in order of priority, pathology reports, endoscopic examinations, or radiographic reports. Stage is based on pathologic data, complemented with clinical data as needed.

The histology of the tumors was classified into six categories based on the International Classification of Diseases for Oncology (ICD-O):

1. Squamous cell carcinomas (8050–8123, 8562), adenocarcinomas (8140, 8141, 8250–8323, 8480–8550, 8572), large cell carcinomas (8012–8031), adenosquamous carcinomas (8560, 8561, 8140, 8141, 8250–8323, 8480–8550, 8572), unknown histology (8000, 8010, and missing values), and other tumors including spindle cell carcinomas, mucopidermoid malignancies, neuroendocrine tumors, and mixed malignant tumors.

Patients were grouped into five categories based on the size of the tumor: 1.0 to 1.9 cm, 2.0 to 2.9 cm, 3.0 to 3.9 cm, 4.0 to 4.9 cm, and 5.0 to 6.0 cm (6.0 cm inclusive). Patients with subcentimeter nodules were not included in the survival analysis due to the limited sample size (n = 191).

The relationship between categorical variables and each of the size groups was analyzed using χ² tests. Size as a continuous variable was compared among the different histology groups with the use of analysis of variance. Mortality was compared between each of the size groups by Kaplan-Meier estimates and log-rank tests.

**Results**

The study included 4,904 men (53%) and 4,287 women (mean age ± SD, 66.6 ± 9.4 years; range, 20 to 92 years) with surgically treated stage I NSCLC. The cohort was divided by size into the following categories:

- < 1.0 cm (n = 191, 2%), 1.0 to 1.9 cm (n = 2,310, 23%), 2.0 to 2.9 cm (n = 2,815, 31%), 3.0 to 3.9 cm (n = 1,984, 22%), 4.0 to 4.9 cm (n = 1,161, 13%), and 5.0 to 6.0 cm (n = 874, 9%).

Although mean tumor size was statistically larger among men (2.9 ± 1.3 cm) than women (2.7 ± 1.2 cm) (p < 0.0001), this is likely of no clinical significance. Size differed with histology of the tumor, with adenocarcinomas being significantly smaller than the other tumor types (p < 0.0001) [Table 1]. The use of limited resections decreased while the use of lobectomies and pneumonectomies increased with increasing size of the tumor (p < 0.0001) [Table 2].

Long-term survival decreased with tumor size (Fig 1). Lesions < 2 cm had significantly better survival than tumors ≥ 2 cm (p < 0.0001). The survival curves for tumors 2.0 to 2.9 cm and the survival curves for tumors 3.0 to 3.9 cm were very similar among themselves (p = 0.014). Similarly, the survival curve for tumors 4.0 to 4.9 cm was similar to the survival curve for tumors 5.0 to 6.0 cm (p = not significant).

Table 3 shows the 5-year survival and the mortality hazard ratios (HRs) for each size group using the 1.0- to 1.9-cm group as the reference. The results were unchanged after adjusting for age, gender, type of surgery, and histology. Five-year survival for patients with tumors < 2 cm in size was significantly better than for tumors of any larger size group (p < 0.0001 for all comparisons). Survival was similar between the groups including tumors 2.0 to 2.9 cm and 3.0 to 3.9 cm, and between the groups with tumors 4.0 to 4.9 cm.
4.9 cm and 5.0 to 6.0 cm. Five-year survival for patients with tumors < 4 cm was statistically better than that of patients with tumors ≥ 4 cm (HR, 1.52; 95% confidence interval [CI], 1.39 to 1.66; p < 0.0001). Figure 2 depicts the unadjusted mortality HRs for each group using 1.0 to 1.9 cm as the reference group.

To test the hypothesis that prognosis for tumors in the size range of 2.0 to 2.9 cm were more similar to tumors 3.0 to 3.9 cm than they were for tumors < 2 cm, we compared the overall survival between each size group and its respective smaller one, using the smaller one of the two as the reference (Table 4). The greatest difference in survival was seen between the 1.0- to 1.9-cm group and the 2.0- to 2.9-cm group. According to the measured HR, patients with tumors 2.0 to 2.9 cm have approximately a 30% higher probability of dying at any point in time than patients with tumors 1.0 to 1.9 cm, suggesting a better breakpoint in the T descriptor (i.e., T1 < 2 cm, T2 ≥ 2 cm). The next greatest difference was seen between patients with tumors 3.0 to 3.9 cm and those with lesions 4.0 to 4.9 cm, with the latter group having a 22% higher probability of dying from all causes than the former. Patients with lesions 2.0 to 2.9 cm had a relatively similar survival than those with tumors 3.0 to 3.9 cm, and those with lesions 4.0 to 4.9 cm had a statistically similar survival than those with tumors 5.0 to 6.0 cm. Subcentimeter nodules had no significant difference in survival from 1.0- to 1.9-cm tumors. Therefore, consideration should be given to a three-way break in size description with T1 ≤ 2 cm, T2a 2.0 to 3.9 cm, and T2b ≥ 4 cm. Five-year survival for tumors > 4 cm in this study (44 to 46%) was slightly better than pT3N0M0 tumors (involving chest wall, diaphragm, mediastinal pleura, pericardium, or main bronchi) in the Mountain4 database used for the 1997 revision in TNM staging (38%).

Table 4 shows the 5-year survival and mortality HRs for patients, classifying them into three groups: 2.0, 2.0 to 3.9 cm, and 4.0 to 6.0 cm. Figure 3 depicts the survival curves for these groups.

**Discussion**

The TNM staging system for lung cancer was developed in 1974 using 3 cm as the threshold
between T1 and T2 tumors based on observations on survival according to the size of tumors on plain chest radiographs. Despite the interval advances in surgical techniques, adjuvant therapy, and imaging technology (ie, CT), this specific threshold has not been revisited in either of the two revisions that the staging system has undergone in 1986\(^3\) and 1997.\(^4\)

A mathematical model favors a 2-cm diameter breakpoint for tumor nodules. Assuming these nodules grow as spheres, the volume of a sphere is calculated by the equation: 

\[
\frac{4}{3} \pi r^3
\]

Using 10 \(\mu\)m as the diameter of a cancer cell,\(^7\) a 2-cm nodule can accommodate 8 billion cancer cells if no necrosis is present. A 3-cm nodule is one and a half times larger in diameter but contains 3.4 times as many cancer cells, since this size difference is on the elbow of the exponential curve (Fig 4). In accordance with this reasoning, staging systems for most other nonophthalmic solid tumors for which prognosis is related to size (ie, breast, pancreas, thyroid, oral cavity, oropharynx, salivary gland, anal, and vulvar cancer) employ a 2-cm cutoff as the difference between T1 and T2 lesions.\(^8\) The T-size descriptor of some of these cancers, such as thyroid cancer, has been recently modified to include such a threshold.\(^9\) The staging of some of these malignancies also incorporates a second cutoff point in size to differentiate between T2 and T3 lesions similar to our recommendation.

Clinical data clearly confirm the association of tumor size and mortality for NSCLC. However, the literature is currently divided on the size thresholds that define prognosis and staging. Most prospective data correlate survival best with tumor size < 2 cm, although small prospective and retrospective trials\(^10–18\) can be found to support a 3-cm threshold. Studies\(^10–12\) published in the 1960s and 1970s showed a survival benefit for patients with tumors \(\leq 2\) cm when compared with larger lesions. More recent studies\(^13–16\) have demonstrated similar results. A prospective, multi-institutional study\(^16\) conducted in Spain by the Bronchogenic Carcinoma Co-operative Group of the Spanish Society of Pneumology and Thoracic Surgery included 1,020 patients with complete resection by thoracotomy of pathologic early stage NSCLC (pT1-T2N0M0). Intervals were statistically created to best define survival ranges. These intervals included 0 to 2 cm, 2.1 to 4 cm, 4.1 to 7 cm, and \(\geq 7\) cm. Five-year survival rates were 63%, 56%, 49%,

### Table 4—Mortality HRs for Size Comparing Each Size Group With the Next Smaller Size Group Using the Smaller Group as Reference

<table>
<thead>
<tr>
<th>Size Groups, cm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 to 1.9</td>
<td></td>
</tr>
<tr>
<td>2.0 to 2.9</td>
<td>1.30 (1.16–1.47)*</td>
</tr>
<tr>
<td>3.0 to 3.9</td>
<td>1.14 (1.03–1.27)*</td>
</tr>
<tr>
<td>4.0 to 4.9</td>
<td>1.22 (1.07–1.39)*</td>
</tr>
<tr>
<td>5.0 to 6.0</td>
<td>1.12 (0.97–1.30)</td>
</tr>
</tbody>
</table>

\*p < 0.05.

### Table 5—Five-Year Survival and Mortality HRs for Each of Three Size Groups (< 2.0 cm, 2.0 to 3.9 cm, \(\geq 4.0\) cm) Using the < 2.0-cm Size Group as Reference

<table>
<thead>
<tr>
<th>Size Groups, cm</th>
<th>Five-Year Survival, %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0 cm</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>2.0 to 3.9</td>
<td>55</td>
<td>1.35 (1.22–1.50)*</td>
</tr>
<tr>
<td>4.0 to 6.0</td>
<td>45</td>
<td>1.88 (1.67–2.10)*</td>
</tr>
</tbody>
</table>

\*p < 0.0001.

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22033/ on 06/26/2017)

**Figure 3.** Survival as a function of size group (< 2 cm, 2.0 to 3.9 cm, and \(\geq 4\) cm)

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22033/ on 06/26/2017)

**Figure 4.** Mathematical relationship between tumor diameter and number of cells.
and 38%, respectively. The differences in survival between all groups were statistically significant, and tumor diameter of 3 cm was not found to be an adequate threshold for prognosis. There are some studies\textsuperscript{17,18} suggesting that a 3-cm threshold is best suited to stratify survival in NSCLC; however, these data are largely retrospective and based on comparatively small study populations.

In our study 9,191 patients registered in the SEER database with surgically treated stage I NSCLC were studied to determine the effect of tumor size on survival and to determine the most reflective measurement of T1 with regard to prognosis. It is the largest study of its kind to challenge the definition of T1 in the current TNM staging system for NSCLC.

The SEER database is a multi-institutional community-based cancer registry containing clinical, pathologic, and survival-related data from 12 population-based cancer registries in the United States. Its base population (14% of the US population) adequately represents the population of the United States. Measures of poverty and education are comparable between the population covered by the SEER program and the general US population. However, the SEER population tends to have a higher proportion of urban and foreign-born people than the overall United States.

In this study, size of the tumor proved to be an independent predictor of survival among patients with stage I NSCLC. Tumors $\geq 2$ cm were associated with a progressive decrease in survival, even after adjustment of significant covariates. The difference in survival between tumor groups $\geq 2$ cm in diameter was not as significant as the difference between each of these groups and the groups of tumors $< 2$ cm. Likewise, the 5-year survival curves or the 2- to 2.9-cm and 3- to 3.9-cm group were quite similar. These data support the use of a 2-cm cutoff for the T1 descriptor, as it more accurately stratifies survival than the 3-cm cutoff in the present staging system.

Some studies have also proposed including an upper threshold for the T descriptor in NSCLC. Watanabe et al\textsuperscript{19} found a significant survival difference between patients with tumors 3.1 to 5 cm (5-year survival, 61%; $n = 94$) and those with tumors $> 5$ cm (5-year survival, 46%; $n = 43$) [$p < 0.05$]. They suggested dividing the T2 group into T2a and T2b subgroups using 5 cm as a threshold. Similarly, based on other studies, Ginsberg\textsuperscript{20} suggested changing the T1/T2 threshold to 5 cm, instead of the current 3 cm. In our study, there was no significant difference in survival between tumors 4.0 to 4.9 cm and tumors 5.0 to 6.0 cm.

The limitations of this study reflect the nature of its design. By virtue of being the result of a multi-institutional cancer registry, data are heterogenous, strict quality control is difficult, and other important covariates such as location of tumor, pathologic analysis of lymph nodes, significant comorbidities, associated symptoms, and details of adjuvant therapy are not available. In the SEER database, size is obtained from pathology reports, when available, and complemented by endoscopic and radiologic data. Since all patients included in this study underwent surgical resection, it is assumed that the diameter of the lesion is based on pathologic examination, although this cannot be confirmed.

It is clear from the previous studies and the results of this analysis that survival in NSCLC is affected by size as a continuum, with smaller tumors providing better prognosis than larger tumors. However, specific size thresholds are necessary to create a staging system for comparison between patients and studies, and prediction of prognosis.

Based on the results of this study and most of the prior studies, the T descriptor should be revised to include 2 cm as a threshold given the survival differences and the possibility of these patients benefiting from more limited resections than patients with larger tumors. Patients with larger tumors (4 cm according to our analysis) have a significantly different survival than patients with lesions $< 4$ cm and should probably not be included in the same staging group. A three-tiered T descriptor for lung cancer (T1, $< 2$ cm; T2a, 2 to 3.9 cm; T2b, $\geq 4$ cm) may provide a more appropriate estimation of the real survival distribution by size of patients with NSCLC.

\section*{References}
cation system in a retrospective analysis of 169 patients. Thyroid 2004; 14:65–70