Analysis of Survival in 400 Surgically Resected Non-small Cell Lung Carcinomas: Towards a Redefinition of the T Factor

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Introduction: The tumor, node, metastasis (TNM) system has been recognized internationally as the standard for staging disease extension, but despite the improvements of the 1997/2002 international staging system, there may be marked differences in postoperative 5-year survival rates within each stage. There is controversy about the impact of tumor size itself as a variable unrelated to stage.

The objective of this study was to analyze the influence of tumor size on the survival in patients with surgically resected non-small cell lung carcinoma (NSCLC).

Methods: Between August 1985 and January 2006, 400 patients underwent pulmonary resection with a curative intention for non-small cell lung carcinoma. Patients were excluded if they had received neoadjuvant chemotherapy. The clinicopathological records of each patient were examined for prognostic factors such as age, sex, left or right side cancer, histology, tumor location, tumor size, clinical nodal stage number, and distribution of metastatic nodes.

Results: Operative mortality was 2.2% for lobectomy and 18% for pneumonectomy (p < 0.05). Adenocarcinoma was the most common tumor type (n = 245, 61.2%). Surgery was considered a complete resection in 341 patients (85.2%). When only patients without neoplastic hilar or mediastinal metastases (pN0) were included, the difference in survival was significantly different in terms of tumor size on the survival in patients with surgically resected non-small cell lung carcinoma (NSCLC).

Key Words: Non-small cell lung cancer, TNM classification, Mediastinal metastases.

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The tumor, node, metastasis (TNM) system has been recognized internationally as the standard for staging disease extension. It has been revised repeatedly over the last 30 years. The last revision was the sixth edition in 2002 and remained unchanged since the fifth edition, by the International Union against Cancer (IUCC) and the American Joint Committee on Cancer. Changes included in previous revisions comprise the following: subdivision of stages I and II into A and B, and addition of T3N0M0 to stage IIB. Despite the improvements of the 1997/2002 international staging system, there may be marked differences in postoperative 5-year survival rates within each stage. Currently, efforts are being made to collect data to generate the seventh edition of the TNM Classification of Malignant Tumors which is due to be published early in 2009.

The availability of more accurate imaging methods allows now the detection of much smaller lesions. Tumor size is a factor that has not changed since the initial staging system of 1973 and the cutoff value of 3 cm is still in use to discriminate between T1 and T2 tumors. However, controversy has arisen over the impact of tumor size itself as a variable unrelated to stage and a potential subdivision of stage I in terms of tumor size has been considered. In fact, the prognostic effect of tumor size in patients without involvement of mediastinal lymph nodes (pathologic N0) has not been clearly defined.

Tumor size may also impact on the degree of local and regional spread. It may mean that even in the absence of enlarged lymph nodes in the computed tomography (CT) scan, larger tumors could require invasive staging to exclude mediastinal invasion. Although mediastinoscopy is currently suggested in the presence of a negative CT scan for staging “large” tumors and adenocarcinomas, the exact impact of histology and size of the primary lesion on regional invasion still needs to be determined.
The objective of this study was to analyze the influence of tumor size on the survival in patients with surgically resected non-small cell lung carcinoma (NSCLC). Our hypothesis is that tumor size is an independent variable and that risk of mortality increases with the increase of the tumor size in every TNM stage of NSCLC.

MATERIALS AND METHODS

Between August 1985 and January 2006, 400 patients underwent pulmonary resection with a curative intention for NSCLC in the British Hospital in Buenos Aires. Patients were excluded if they had exhibited small cell lung cancer or a rare histologic type or if they had been included in a neoadjuvant chemotherapy protocol. Patients were included only after institutional review board approval. They were retrospectively analyzed and all data were obtained from the medical records. Survival status was obtained from telephone interview and/or medical records.

Preoperative staging was performed according to the TNM classification system of the International Union Against Cancer using chest CT and abdominal CT or ultrasonography in all patients. Brain CT or magnetic resonance imaging was done only in case of clinical suspicion of brain metastases. In cases of uncertain clinical or radiologic findings, further examinations were performed to exclude extrapulmonary metastases. Mediastinal and hilar lymph node status was assessed as positive if the chest CT showed that the shorter axis of any node was larger than 1.0 cm. Positron emission tomography (PET) scan was not routinely performed. Mediastinoscopy has not been performed routinely in this series unless the CT scan demonstrated mediastinal lymph node enlargement. The clinicopathological records of each patient were examined for prognostic factors such as age, sex, right or left side cancer, histology, tumor location (upper or lower), tumor size, cN number, and distribution of metastatic nodes.

All surgeries were performed by the same three surgeons and with the same sampling techniques. In all the patients intrapulmonary nodes (groups 11,12, and 13) and hilar nodes (group 10) were sampled. For right thoracotomies sampling of groups 7, 4R and 2R was performed in every case and for left thoracotomies sampling included groups 5, 6, and 7. For pneumonectomies and lower lobectomies sampling of groups 8 and 9 was included. All the cases antedated 1997 were reviewed and classified according the new Mountain’s node map. After surgery a final pathologic stage was stated based on the operative findings. Histologic typing was determined according to the World Health Organization classification.11 Lymph nodes were numbered and classified following Mountain’s classification.12

Surgical resection was considered complete if all of the following criteria were present: free resection margins proved microscopically; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension of the tumor; and the highest mediastinal node removed were negative.13

The postoperative follow-up of patients was based on regular visits, quarterly chest radiographs and a yearly chest CT. Patients with operative or inhospital mortality, defined as death occurring within 30 days after the operation or during hospitalization, respectively, were included in this study. Disease-free interval was defined as the difference between the day of surgery and the date of the first recurrence or, in the absence of recurrence, the last day of follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 statistical software. The analysis of differences in categorical outcomes was determined using the $\chi^2$ test or Fisher exact test. Logistic regression models were used to ascertain the association between individual factors and survival. Probabilities of disease free survival rates were estimated using the Kaplan–Meier method. Cox proportional hazards regression models were used to ascertain the association between individual factors and survival. Their joint effect was assessed in a multivariable Cox analysis. Statistical significance was assumed at $p < 0.05$.14 The selection of a 15-mm cutoff value was based on previous reports suggesting that resected tumors smaller than 1.5 cm have better survival in stage IA.6,7

RESULTS

Four hundred patients were included (298 males, 74.5%, median age 61.1 ± 9.9 years). Median follow-up was 44.7 months (rank, 1–229 months). In the first decade (1985–1995), 142 were treated and in the second period (1996–2006) patients included were 248.

A solid parenchymal opacity ($n = 268, 67.0\%$) and an indeterminate lung nodule ($n = 122, 30.5\%$) were the most common radiologic findings. The tumor was right-sided in 235 (58.7%), and peripheral in 292 patients (73.0%). Lobectomy was performed in 301 patients (75.2%) and pneumonectomy in 84 patients (21.0%). The remaining procedures were bilobectomies ($n = 12$) and multiple excisions. The length of stay in the intensive care unit was 1.18 ± 3.8 days and hospital stay was 3.9 ± 5.9 days long. Complications occurred in 118 patients (29.5%). Operative mortality was 2.2% for lobectomy and 18% for pneumonectomy ($p < 0.05$). Clinical staging of patients is shown in Table 1. Patients in stage IV were nine and they had fully resected solitary brain metastases and locally circumscribed disease and were considered surgically treatable.

Adenocarcinoma was the most common type ($n = 245, 61.2\%$) (Table 2). Surgery was considered a complete resection in 341 patients (85.2%).

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>$n$</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>124</td>
<td>31.0</td>
</tr>
<tr>
<td>IB</td>
<td>159</td>
<td>39.8</td>
</tr>
<tr>
<td>II A</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>II B</td>
<td>52</td>
<td>13.0</td>
</tr>
<tr>
<td>III A</td>
<td>47</td>
<td>11.8</td>
</tr>
<tr>
<td>III B</td>
<td>7</td>
<td>1.8</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>2.3</td>
</tr>
</tbody>
</table>

TABLE 1. Clinical TNM Staging Distribution of Patients
Recurrences were seen in 137 patients during follow-up. Distant recurrences were the most common ($n = 99$, 72.3%), with 13 cases of unrelated second tumors (9.5%).

Survival according pathologic TNM stages is shown in Table 3, and survival for pathologic stages is shown in Figure 1. The 5-year survival of pathologic stage IA was 85.9%. When only patients without neoplastic hilar, mediastinal, or distant metastases (pN0M0) and with a complete resection were included, the difference in survival was significantly different in terms of tumor size ($\log \text{rank} = 6167, p = 0.013$) (Figure 2).

Univariate analysis for the group of pN0 patients showed survival was not significantly affected by age, sex, side, or adenocarcinoma histology. Survival was shorter when the T factor was higher and the tumor size was larger (Table 4). In the multivariate analysis, tumor size and the T factor were found to have maintained its independent prognostic effects on overall survival (Table 5). Among patients with pN0 tumors smaller that 15 mm in diameter, 5-year survival was 95% whereas patients with tumors bigger than 16 mm in diameter had a 5-year survival of 65% ($p < 0.0001$).

**DISCUSSION**

The current study shows an increased relative risk of lung cancer mortality that correlates with tumor size in patients with different TNM stages of resected non-small cell lung carcinoma.

TNM stage is the most important prognostic factor in resected NSCLC\cite{15,16} but in the last few years, research has begun to focus on the influence of tumor size, even within the same stage.\cite{1,5,7,8} This concern has been somehow reflected in the 1997 reclassification of stages, with the subdivision of stage I into IA (T1: tumors 3 cm or less in its greatest diameter) and IB (T2, tumors larger than 3 cm).\cite{3} This restaging resulted in survival differences throughout several studies.\cite{7,17} Nevertheless, controversy remains about using 3 cm as the cutoff value (maintained by Mountain’s classifica-

**TABLE 2.** Population Distribution by Histologic Type ($n = 400$)

<table>
<thead>
<tr>
<th>Histology</th>
<th>$n$</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>245</td>
<td>61.3</td>
</tr>
<tr>
<td>Squamous</td>
<td>92</td>
<td>23</td>
</tr>
<tr>
<td>Bronchioloalveolar carcinoma</td>
<td>19</td>
<td>4.7</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>38</td>
<td>9.5</td>
</tr>
</tbody>
</table>

**TABLE 3.** Two- and 5-Year Survival by Pathological Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>$n$</th>
<th>2-yr Survival (%)</th>
<th>5-yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>95</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>IB</td>
<td>103</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td>IIA</td>
<td>8</td>
<td>85</td>
<td>57</td>
</tr>
<tr>
<td>IIB</td>
<td>66</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>IIIA</td>
<td>86</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>IIIIB</td>
<td>28</td>
<td>62</td>
<td>33</td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>35</td>
<td>11</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Survival according pathologic staging of NSCLC ($n = 400$).

**FIGURE 2.** Survival according the size of the tumor ($n = 400$).
tion) to define tumor size, as it may prove to be inadequate to predict differences in survival. It becomes particularly relevant now that the efforts to achieve early diagnosis are allowing the diagnosis of very small tumors. Several studies have reported tumor size may have an independent predictive value on survival in stage I patients. Birim et al.18 studied 130 patients with stage I NSCLC and concluded that a tumor smaller than 2 cm in diameter predicts a longer survival, and Riquet et al.19 have found a significant difference in survival for resected T1N0M0 NSCLC depending on tumor size (5-year survival, 77, 62.8, and 62.9% for tumors measuring 0.5–1 cm, 1.1–2 cm, and 2.1–3 cm, respectively). Nevertheless, these findings are not consistent and other researchers have not identified an independent effect of tumor size on survival.6,20,21 In a previous study in a very homogeneous group of patients (T1N0M0 tumors), Lyons et al.22 reported that patients with stage I tumors measuring less than 1.5 cm in diameter had a better survival suggesting that tumor size is an independent predictive variable that defines different categories of stage IA. That would be especially important to better define candidates for future studies on adjuvant chemotherapy whose results are still very contradicting and result in different recommendations about adjuvant chemotherapy for stage I in different association’s guidelines.23-25 The different results suggesting evidence or absence of evidence of decreased risk of recurrence in patients with stage I receiving chemotherapy26-30 may be dependent on the apparent homogeneity of the population studied (stages IA and IB), which in fact may be not so homogeneous if T1 tumors are different when they are smaller. This could also explain the 5-year survival differences reported on this population, which has been published from 9031 to 63%.32

The impact of tumor size seems not to be restricted to small tumors and has been also shown in larger tumors. In this regard, it has been suggested that stages IIA and IB should be merged into one unique category.33 In our pN0 patients, the multivariate analysis has revealed that tumor size and the T factor are the only independent factors associated with shorter survival (Table 5). The T categories “less than 3 cm” and “more than 3 cm” seems to be too broad supporting the need of a new revision of lung cancer staging system. In that direction, the International Association for the Study of Lung Cancer established its Lung Cancer Staging Project in 1998. The recommendations of this committee for changes to the T, N, and M descriptors include additional cutoffs for tumor size, with tumors more than 7 cm moving from T2 to T3 and the possibility that T2b N0 M0 cases should be moved from stage IB to stage IIA, T2a N1 M0 cases from stage IIIB to stage IIA, and T4 N0–1 M0 cases from stage IIIB to stage IIIA. Such changes, if accepted, will involve a reassessment of existing treatment algorithms.4,34

In our patients, survival following the traditional TNM system showed similar figures to those reported in many series5,6,17,35 although for stage IIIA survival was 37%,
around 10% higher than the survival reported by Goya et al. (19.3%)30, Naruke et al.7 (23.6%), and Jassem et al.33 (15%). Whether this represents a more strict selection of patients for surgery, ethnic differences or heterogeneity in the different series containing tumors of different sizes in the same stage is rather unclear.

In conclusion, our data suggest that tumors over 15 mm are associated with an increased risk of mediastinal metastases and with shorter 5-year survival in all TNM categories. Current TNM categories are not sufficiently discriminatory and the T factor requires to be reevaluated in further revisions of the TNM classification.

REFERENCES