Survival Analysis of Untreated Patients With Non-Small-Cell Lung Cancer*

Eduard Vrdoljak, MD; Kornelija Miše, MD; Damir Sapunar, MD; Ante Rozga, PhD; and Matko Marušić, MD, PhD

The survival rate analysis of 130 patients with non-small-cell lung cancer who did not receive any specific anticancer therapy showed no statistically significant differences in the survival rates between various TNM combinations classified into stage groups II, IIIa, IIIb, and IV, as proposed by Mountain in 1989 and adopted by the American Joint Committee on Cancer. Following these findings, based on survival probabilities, two distinctive staging groups could be distinguished. The first stage group was composed of only the T1, 2N0, M0 combination, and the second of all other TNM combinations. In a purely biologic sense of tumor growth, the lymph node involvement appeared to be the crucial factor determining the length of survival.

(Chest 1994; 106:1797-1800)

Key words: non-small-cell lung cancer; staging; survival; TNM classification; untreated patients

Lung cancer is a major cause of cancer death throughout the world, in both developed and developing countries.1 It is estimated that, at current incidence rates, there will be 590,000 new cases of lung cancer each year in the world.2 The incidence of lung cancer is increasing rapidly in both sexes.3 To ensure mutual understanding between researches, four decades ago Pierre Denoix proposed the TNM system for the classification of the anatomic extent of disease in patients with cancer.4 In addition to its role as an accurate communication about the patient’s status, the purpose of this staging is to aid in the selection of treatment, in the estimation of the probability of cure and survival, and in the comparison of the results from different clinical treatment studies.

The most important factor in designing a meaningful staging system is to identify and give proportional weight to those factors that reliably and validly predict the survival of a patient. All studies regarding the survival of patients with lung cancer were done after they had received one or more therapeutic modalities. In this study, we describe the survival rate analysis of patients with non-small-cell lung cancer who did not receive any type of therapeutic modality. These results add to the understanding of the real biologic behavior of lung tumors and/or host tumor relationship.

METHODS

Patients

The patients reviewed in this report were newly diagnosed as having non-small-cell lung cancer. This study was conducted over an 8-year period, from 1980 to 1987 in Clinical Hospital Split, Split, Croatia. The group was composed of 120 (92.3%) male and 10 (7.7%) female patients who ranged in age from 41 to 86 years, with a median age of 60 years. The male-female ratio in our study is 12:1, and is significantly different from the 3:1 ratio seen in the United States of America. The male-female ratio for patients with lung cancer in the United States has decreased from 6:1 in 1950 to 3:1 recently.5 In our Croatian population, the male-female ratio is 8:16 to 10:1 (unpublished data collected from 1973 to 1983).

The possible reason for that difference in ratios is that in our population, women are smoking less frequently and less number of cigarettes, and also that they were slightly more acceptable for the specific oncologic therapy. Although there are biologic differences between epidermoid carcinoma (61 cases, 46.9%), large-cell carcinoma (34 cases, 26.2%), and adenocarcinoma (35 cases, 26.9%), they were all combined in one survival study.

Distribution of different types of non-small-cell carcinomas in this study were similar to those already published.1,2 Small-cell carcinoma cases were excluded because of the large difference between non-small-cell lung cancers and small-cell carcinoma of the lung.8 Histologic classification of the lung cancer used in this study was recommended by the World Health Organization in 1977.9 To assess the anatomic extent of the disease, the standard clinical-diagnostic examination was used. This diagnostic workup included a medical history, physical examination, routine and special radiographs, computed tomographic scans, endoscopic examinations, including bronchoscopy, esophagoscopy, thoracentesis, and other examinations, including those used to demonstrate the presence of extrathoracic metastasis. The anatomic extent of the disease in each patient was classified into TNM categories following the staging system reported by Mountain et al.8

All patients included in this study were untreated, ie, they did not receive any specific anticancer therapy. It is difficult to explain why 130 patients in a single hospital went untreated over an 8-year period (from 1980 to 1987) while during that same period there were 1,236 newly diagnosed cases of lung carcinoma. Many of these patients had low sociocultural backgrounds with strong opinions about cancer as an incurable disease. Some patients refused therapy because they were afraid that it would drastically change the quality of their "remaining" years. Some patients simply did not accept the presence of lung cancer, denying the disease.
Statistical Analysis

Kaplan-Meier product limit estimate of the survivor function was generated along with associated statistics for each group. To compare survival distributions, we used four nonparametric tests: Peto/Wilcoxon, Gehan's Wilcoxon, Log Rank Test, and Cox Mantel test. The significance level was set to 0.05, as usual. Student's t-test was used to test the differences in the mean survival times between various TNM and stage groups. The results were almost the same as those obtained with nonparametric statistics.

RESULTS

Survival curves (cumulative proportional survival) according to TNM subsets for patients with non-small-lung carcinomas are shown in Figure 1. If the lung tumor did not involve hilar or peribronchial lymph nodes and did not have distant metastasis (T2,N0,M0, stage I of disease according to American Joint Committee on Cancer8) patients had a significantly better survival rate than patients in other TNM combinations investigated in this study. All other TNM subsets investigated had similar survival rates. Statistically significant differences in survival rates (p<0.05) were found between T2,N1,M0 subset of stage II and T2,N1,M1, T2,N2,M1, and T3,N2,M0 subsets of stages IIIa and IV. However, T2,N1,M0 subset of stage II of the disease did not show statistically significant differences in the survival rates when compared with TN,M subsets from other stage groups, namely T2,N2,M0, T2,N0,M1, and T3,N2,M1 (stage IIIa and stage IV).

The number of untreated patients with non-small-cell lung cancer and median survival according to the different TNM subsets that have been investigated in this study are shown in Table 1. Because of the small number of patients with diagnosed lung cancer that constitute T1,N0,M0 group, and also that a small number of them were untreated, the T1,N0,M0 subset has not been included in this study.

Figure 2 presents the survival relationship between the two newly created stage groups based on the analysis of 130 untreated patients with non-small-cell lung cancer as presented in Figure 1. Namely, this analysis condensed T2,N0,M0 subset into one stage and all other TNM subsets into the other stage. This simplification clearly disclosed the existence of statistically significant differences (p<0.001) in survival rates between those two stage groups. Medium survival rate for group 2 (Fig 1) was 17 months, while medium survival rate for group 2 patients was 8 months.

| Table 1—Number of Untreated Patients With Non-Small-Cell Lung Carcinoma and Median Survival According to the Different TNM Subsets Included in This Study |
|-----------------|----------------|----------------|
| TNM Subset | No. of Patients | Median Survival, mo |
| T2, N0, M0 | 9 | 17 |
| T2, N1, M0 | 31 | 11 |
| T2, N2, M0 | 9 | 10 |
| T2, N0, M1 | 7 | 7.50 |
| T2, N1, M1 | 18 | 5.25 |
| T2, N2, M1 | 22 | 4.50 |
| T3, N2, M0 | 8 | 7.25 |
| T3, N2, M1 | 16 | 6.50 |
| Total | 130 | 9.00 |
**DISCUSSION**

The American Joint Committee on Cancer has adopted the TNM classification originally proposed by Mountain et al.\(^5\) This staging system, primarily based on surgical findings and the anatomic extent of the cancer, has recently been revised.\(^6\) The TNM classification is based on the anatomic extent of the disease.\(^7\) Various TNM categories were grouped into appropriate combinations to create a small number of stages of the disease.\(^8,10\)

The staging system is primarily based on the survival probability of patients who have lung cancer. All survival rate analyses on which the staging system is based were done with patients with lung cancer who had received one or more therapeutic modalities. In contrast, we studied a group of patients with lung cancer who had not received any specific anticancer therapy.

The results presented in this report are, therefore, not complementary to the results that have been presented on this subject before.\(^5,10,12,13\) We showed that there were no statistically significant differences (p<0.05) in the survival rates between TNM combinations classified into stage groups II, IIIa, IIIb, and IV, if patients had not received any specific anticancer therapy (Fig 1). These findings indicate that specific anticancer therapy (surgery, radiotherapy, and chemotherapy) that is used to treat patients with lung cancer is perhaps the major factor in creating the staging groups. In other words, the tumors treated with different anticancer therapeutic modalities tend to change their biologic presentation. If that was the case, the survival rates of patients would not present the biologic potential of lung tumor or/and host tumor relationship, that is in many ways a black box for our current knowledge.

Therefore, an untreated group of patients with lung cancer should represent the real biologic behavior and the potential of the tumor. Our results also showed that in the group of untreated patients with lung cancer, following survival analysis results and survival rates, only two distinctive staging groups could be distinguished. The first group includes tumors in T1,2 status with no involvement of lymph nodes by lung cancer (situation when disease is localized in the lung, T1-2, N0, M0, stage I in 1989 Mountain-proposed staging system). The other stage group includes all other TNM combinations (stages II, IIIa, IIIb, and IV [Fig 2]). According to these findings, we concluded that lymph node involvement with lung cancer is a major predicting survival factor if patients are not treated with specific anticancer therapy.

**REFERENCES**

2. Stanley KE. Lung cancer and tobacco: a global problem. Can-
cer Detect Prevent 1986; 9:83-9
8 Mountain CF, Carr DT, Anaderson WAD. A system for the clinical staging of lung carcinoma. AJR 1974; 120:130-38
11 Carr DT, Mountain CF. The staging of lung cancer. Semin Oncol 1974; 1:229-34
12 Mountain CF. Value of the new TNM staging system for lung cancer. Chest 1989; 96(suppl):47S-95