Natural Course of Inoperable Lung Cancer*:

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Of more than 7,500 men with nonresectable lung cancer with extensive disease treated on various regimens assigned at random, 1,068 received the best possible supportive treatment without any specific chemotherapeutic agent. This group of patients was reviewed for information pertinent to the natural history of bronchogenic carcinoma. The prognosis for lung cancer patients is usually poor. Median survival time was related mainly to patient's status at entry into the study: performance status using the Karnofsky scale, cell type and extent of disease.

Bronchogenic carcinoma is a lethal disease with steadily increasing incidence especially in men, and high early mortality reported for treated and untreated patients, even for those with supposedly small, asymptomatic lesions. From 70 to 88 percent of consecutive, unselected bronchogenic carcinoma patients, when first seen in general hospitals, are found to have nonresectable lesions, about 12 to 15 percent of these patients after thoracotomy. Periodic x-ray film screening has revealed that survival after the last negative chest roentgenogram was so poor as to suggest that metastases in many cases have occurred before a pulmonary mass is detectable by present methods.

Multiple forms of therapy have been reported in the past, usually in small groups of patients and without adequate controls. Breslow has indicated that, "perhaps the underlying difficulty with the published reports is the tendency to present findings with the implied assumption that treated cases [sic] survive because of the treatment."

Evaluation of therapy, including chemotherapy, irradiation, and surgery, is impossible without knowledge of the natural course of lung cancer and possible variations in pattern of disease. A systematic attempt to evaluate the effect of therapy on patients with inoperable lung cancer was begun by the Veterans Administration Lung Cancer Study Group in February, 1958. More than 7,500 such patients have been studied in 13 series of controlled clinical trials. It was established that the use of the percentage of survival to a given point in time is a valid and objective method of assaying drug effectiveness in this disease. Patients were classified according to the extent of their disease as defined by either "limited" or "extensive" disease. Subsequent survival experience has indicated that these groups are, in fact, different. The length of median survival time is increased only slightly, if at all, by these various treatments. Cure is not effected, and the number of patients who benefit strikingly remains distressingly small. (Other reports will compare the effectiveness of various drug regimens with the present "control" group of patients.) The incidence of lung cancer is expected to increase from 68,800 deaths in 1972 to more than 85,000 in 1980. The lung cancer death rate in 1972 is 18 times as high for men as it was 40 years ago.

Materials and Methods

Studies conducted by the Veterans Administration Lung Cancer Therapy Group have been previously described. Treatment regimens for consecutive, unselected cases of nonresectable lung cancer were randomized separately for each hospital. The patients were first divided into two groups: (1) limited disease, or (2) extensive disease. "Limited disease" classification met the following criteria: the nonresectable tumor was limited to one hemithorax but may have included scalene nodes; the patient had received no previous radiation therapy and was in fairly good general condition; and the apparent tumor mass was totally encompassed in every portal for possible x-ray therapy. All other patients, not meeting these criteria, were placed in the...
"extensive disease" group. Within each group, therapeutic regimens were randomized from sealed envelopes, and in most cases, were double-blind since code names were used for drugs whenever possible.

During the first seven protocols 4,296 unselected, consecutive men admitted to the hospital with nonresectable lung cancer were placed on study between February, 1958, and January, 1966. All cases were proved, with slides being reviewed by the hospital pathologist, plus a panel of three pathologists who made their diagnoses independently. The Veterans Administration modification of the World Health Organization (WHO) classification of lung tumors was used. For purposes of this report, the several histologic categories were combined into five main groups, namely: (1) the differentiated epidermoid carcinomas, types 1a and 1b; (2) adenocarcinomas, types 3a, 3b, and 3c; (3) all types of large cell undifferentiated carcinomas in group 4, including the squamatoid tumors, type 1c; (4) small cell undifferentiated carcinomas, types 2a and 2b; and (5) all other categories, including sputum yielding definite malignant cells. At the start of therapy, most patients were classified by "performance status" (PS), using the Karnofsky scale (Table 1). Various treatments were assigned at random to these patients, and as a result, 1,068 became controls, i.e., they received the best possible supportive treatment, but no chemotherapy agent.

**RESULTS**

Of these patients with nonresectable lung cancer,

**Table 1—"Performance Status" (Karnofsky scale)**

<table>
<thead>
<tr>
<th>Criteria of Performance Status (PS)</th>
<th>100</th>
<th>90</th>
<th>80</th>
<th>70</th>
<th>60</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>0</th>
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<td>Able to carry on normal activity; no special care is needed.</td>
<td>Normal; no complaints, no evidence of disease.</td>
<td>Ability to carry on normal activity; minor signs or symptoms of disease.</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
<td>Cares for self; unable to carry on normal activity or to do active work.</td>
<td>Requires occasional assistance, but is able to care for most of his needs.</td>
<td>Requires considerable assistance and frequent medical care.</td>
<td>Disabled; requires special care and assistance.</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent.</td>
<td>Very sick; hospitalization necessary; active supportive treatment is necessary.</td>
<td>Moribund, fatal processes progressing rapidly.</td>
<td>Dead.</td>
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<td>Unable to work; able to live at home, care for most personal needs a varying amount of assistance is needed.</td>
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<tr>
<td>Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.</td>
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FIGURE 1. Median survival varies directly with performance status (PS) at entry into study. (Lung cancer patients with extensive disease receiving only symptomatic care.)

There were 293 patients with "limited disease" who received no specific therapy, with a two-year survival rate of 3.8 percent. Of 775 nonresectable lung cancer patients with "extensive disease" who received no specific therapy, 0.9 percent survived two years, clearly indicating that survival was related to extent of disease at diagnosis. Of 667 patients with lung cancer in the extensive disease group who received no specific therapy, and where PS at entry to study was known, median survival was directly related to the PS (Fig 1). Thus, patients with a PS of 90 percent at entrance into the study had a median survival of 22 weeks; those with 60 percent had a median survival of 9 1/2 weeks; and those with 40 percent, a median survival of 4 1/2 weeks. Clearly, survival appears related to the patient's general condition at the first visit or time of diagnosis.

Of 488 patients in this study receiving only symptomatic nonspecific therapy and classified by cell type histologically, those patients with adenocarcinoma had the longest median survival (13 weeks), followed by those with squamous cell carcinomas (9 1/2 weeks), confirming an earlier study. In the present study, the median survival of patients with either large cell undifferentiated carcinoma or small cell undifferentiated carcinoma was 6 weeks (Fig 2). The importance of PS persists for each cell type, however (Fig 3).
These data emphasize the usually dismal prognosis of lung cancer of any cell type. Men with adenocarcinoma of the lung tend to live twice as long as those with undifferentiated small cell carcinoma when survival is measured from either the first symptom or date that histologic diagnosis was made. Cell type usually affects survival after lung resection, emphasizing the importance of this factor regardless of the mode of therapy used, although no effect was noted by Shields.

DISCUSSION

There are a number of reports in the literature dealing with the natural course of untreated carcinoma of the lung. Ariel et al reported that 527 untreated patients with bronchogenic carcinoma had an average survival of 6.2 months from the time of diagnosis. Tinney reported a survival of six months from the time of diagnosis in 315 patients with carcinoma of the lung. Buchberg et al reported a somewhat longer survival of 9.1 months in 443 untreated patients. Garland et al found an average survival of 3.2 months from the time of diagnosis in 275 untreated patients.

The importance of data of this type in assessing the results of various therapeutic regimens is obvious. It is, however, difficult to compare one study with another without evaluation of the variables involved. Feinstein has ably pointed out the difficulties inherent in interpreting data of this type and proposed a staging system for cancer based on clinical as well as anatomic criteria.

The present study emphasizes the need for such an approach. A number of factors were studied for their influence on survival by the Veterans Administration Lung Cancer Study Group. Among the most significant of these were: (1) extent of the disease ("limited" vs "extensive"); (2) PS of the patient; and (3) cell type of the tumor. Cell type has long been recognized as important to survival not only in untreated patients, but in those treated surgically. However, the data presented indicate that meaningful survival data must include all three of these variables. The close relationship of median survival to initial PS is documented for the first time.

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REFERENCES