Clinical Presentation and Management of Patients with Carcinoma of the Lung: A 14-Year Experience

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Carcinoma of the lung has been steadily increasing since World War II, and the family physician can now expect to see a greater incidence of the disease in women and persons under age 50 years.

The clinical manifestations of carcinoma of the lung are described, based on a 14-year experience at the University of Michigan. Diagnostic procedures are outlined. The preferred treatment for carcinoma of the lung is pulmonary resection, combined, in appropriate situations, with mediastinal lymph node irradiation. Survival is dependent to some degree on the tumor cell type as well as the extent of metastasis.

A new immunotherapeutic adjunct to resection and irradiation is being developed. Five to ten-year survivors of resections for lung cancer and normal persons serve as lymphocyte donors. Transfer factor is extracted from these lymphocytes and injected into selected patients who have recently had resections for lung cancer. It is too soon to evaluate the results of this experiment, but it is hoped that immunotherapy using transfer factor will be of help to patients with carcinoma of the lung.

During the past 60 years there has been a marked increase in the incidence of carcinoma of the lung, with an estimated 85,000 to 92,000 persons in the United States dying of the disease each year.[1] With the total number of new cases expected to be about 102,000 in 1978, the family physician can well expect to encounter patients with carcinoma of the lung in the course of the year. This marked rise has been associated primarily with an increase in cigarette smoking, but also with environmental factors such as urban air pollution and exposure to certain industrial agents such as asbestos, chromium, and nickel. About 90 percent of all lung cancer is directly attributable to heavy cigarette smoking, ie, two to three packs a day for 20 or more years.

Thirty years ago the male-female incidence of lung cancer was almost 5:1, but with the increase in smoking among women which began during World War II, this ratio has been closing. Of the 92,000 deaths from lung cancer predicted for 1978, the American Cancer Society estimates 70,500 will

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0094-3509/79/061127-05$01.25

be men and 21,900 will be women, a ratio of approximately 3.5:1. A recent study by the Connecticut Cancer Registry revealed some even more startling figures.[2] Among persons aged 35 to 44, the first age group in which the effects of cigarette smoking are clearly evident, between 1970 and 1974 the male-female incidence was a little less than 2:1. In 1975, for the first time in Connecticut history there were more lung cancers among women than among men in the 35 to 44-year age group. The ratio was 0.9:1.

While the disease still has a higher incidence in the fifth through seventh decades of life, the evidence for its increase in younger age groups is mounting, and the family physician should be alert to the possibility of lung cancer occurring in men and women under the age of 50 years, particularly those who have been heavy smokers.

Clinical Manifestations

From a retrospective analysis of the case records of patients with carcinoma of the lung managed at the University of Michigan Medical Center over the past 14 years, it has been determined that patients with carcinoma of the lung may present in one of five ways.

1. *With one, some, or all of the symptoms of respiratory disease, ie, cough, sputum production, hemoptysis, chest pain, or wheeze.* Cough was the most frequent symptom, occurring in nearly 75 percent of the patients and is one of the major reasons for medical advice being sought. Worsening of an otherwise chronic cough, especially in association with a febrile illness, was not an infrequent occurrence. In many instances the cough was mistakenly attributed to smoking alone. Hemoptysis was the second most frequent respiratory symptom and occurred in nearly half of the patients. Hemoptysis usually took the form of blood streaked sputum in the early morning. On rare occasions hemoptysis as the presenting symptom occurred as an isolated event. In approximately one quarter of the patients in this group there was a history of either an acute febrile illness often called influenza, from which recovery had been slow and incomplete, or of a series of acute febrile illnesses with complete or incomplete recovery between episodes. Such a history of failure to make an anticipated recovery from an acute respiratory illness is strongly suggestive of carcinoma of the lung. Chest pain occurred in about 15 percent of the patients. The pain was commonly described as an intermittent discomfort lasting for hours at a time and worsening at night. As a rule, severe pain occurred in patients with chest wall involvement. Pleuritic chest pain was a rare occurrence. Wheeze as a presenting symptom occurred in less than one percent of the patients and usually was related to a tumor which had extended to the main bronchus, close to the main carina.

2. *With an abnormality detected on a chest roentgenogram made for routine purposes, but without symptoms.* This occurred in 15 to 25 percent of the patients undergoing pulmonary resection.

3. *With symptoms of extension of bronchial carcinoma such as cerebral or osseous metastases, hoarseness, jaundice, superior vena caval obstruction, or dysphagia, but without symptoms of a pulmonary disorder.* Approximately five percent of the patients presented in this manner.

4. *With nonspecific symptoms such as anorexia, weight loss, fatigue, and dyspepsia.* The overwhelming majority of these patients also had an associated abnormality on the chest roentgenogram, but did not have associated respiratory symptoms. This group represented about five to ten percent of the patients.

5. *With neural or humoral manifestations such as hypertrophic pulmonary osteoarthropathy, myopathy, (myasthenia-like syndrome and polymyositis), migratory thrombophlebitis, Cushing syndrome, hypercalcemia, hypoglycemia, and peripheral neuropathy, or with other unusual manifestations such as spontaneous pneumothorax, exacerbation of diabetes mellitus, or recurrence of inguinal hernia.* This represents a very small number of patients (one to three percent).

Roentgenographic Findings

In all of the patients with bronchogenic carcinoma, chest roentgenogram was abnormal, and the abnormality was suggestive of tumor in over 75

percent of them. There were several roentgenographic patterns noted which correlated reasonably well with the histologic cell type. The exact incidence of the various roentgenographic patterns was difficult to ascertain since many patients had advanced disease when first seen. A peripheral mass on chest roentgenogram was found to occur most often in association with adenocarcinoma or large cell undifferentiated tumors and was observed in 40 to 75 percent of the cases. The sizes of the peripheral mass as measured on the chest roentgenogram varied from 1.0 to 6.0 cm in diameter. Cavitation of peripheral masses occurred about five percent of the time. Evidence of bronchial obstruction as manifested by obstructive pneumonitis, loss of lung volume, or segmental or lobar consolidation was most frequent in patients with squamous cell carcinoma, occurring in roughly one half of the patients with squamous cell carcinoma. A hilar abnormality was frequently seen in these patients as well. Roentgenographic evidence of mediastinal widening or of a mediastinal mass was more characteristic of oat cell carcinoma than of any other cell type.

Diagnostic Studies

In addition to the various roentgenographic studies, especially laminography used in the diagnosis of carcinoma, cytologic examination of the sputum and bronchoscopy were routinely employed in the evaluation of patients with suspected tumors of the lung.

Cytologic examination of the sputum was very useful in these patients as tumor cells were found in over 50 percent of the patients with proven carcinoma of the lung.

Bronchoscopy should be carried out, preferably by the operating surgeon, in all patients suspected of having a tumor in the lung. Direct visualization of the tumor or positive biopsy findings or *both* were obtained in 70 percent of the patients. In addition to actual assessment of the tumor, other valuable information was obtained at the time of bronchoscopy. The length of the normal bronchus proximal to the tumor, status of the carina, presence or absence of rigidity of either mainstem bronchus as well as any anatomical variants may be assessed. In patients with peripheral pulmonary lesions beyond the reach of the bronchoscope, the technique of bronchial brushing yielded the diagnosis of carcinoma 48 percent of the time.

Excision of lymph nodes in the supraclavicular fossa was performed on any patient with palpable cervical lymph nodes or in those patients without palpable nodes but with a centrally located tumor as judged by bronchoscopy or a peripheral lesion greater than 3 cm in diameter.

Treatment

The preferred treatment for bronchogenic carcinoma is surgical resection. Unfortunately, approximately 60 percent of all the patients with bronchogenic carcinoma evaluated at the University of Michigan from 1959 through 1972 were not candidates for resection when first seen. The contraindications to pulmonary resection included phrenic nerve paralysis, recurrent laryngeal nerve paralysis, superior vena caval obstruction, malignant pleural effusion, malignant tracheoesophageal fistula, extrathoracic metastatic disease (cerebral, scalene node, hepatic, osseous), oat cell carcinoma, poor pulmonary function, or poor general condition of the patients.[3]

During this 14-year interval, 510 other patients did undergo operation for bronchogenic carcinoma at the University of Michigan Medical Center. Only 51 (ten percent) of these patients were found to have unresectable lesions. The operations performed and mortality rate for each type of procedure are listed in Table 1.

The absolute five-year survival for the entire group of patients was 36.7 percent. The ten-year survival rate was 14.4 percent. No patient undergoing exploration alone or noncurative resection survived five years. The average survival of these patients was 7.5 months.

Since over 90 percent of the patients undergoing curative resection had either squamous cell carcinoma or adenocarcinoma, only these patients were analyzed with regard to lymph node involvement. Postoperative mediastinal irradiation was given to patients with evidence of metastasis to the mediastinal lymph nodes. The absolute five-year survival among those patients with mediastinal metastases who received postopera-

Table 1. Operative Mortality Rates in 510 Patients With Bronchogenic Carcinoma

	Mortality %
Lobectomy	5.0
Pneumonectomy	6.0
Segmentectomy	8.3
Thoracotomy only	1.6

Table 2. Five-Year Survival Rates With Bronchogenic Carcinoma

Procedure, Metastases	Overall Survival (%)	Squamous cell Carcinoma (%)	Adenocarcinoma (%)
Operation			
Lobectomy	38	46	38
Pneumonectomy	30	38	7
Metastases			
None	51	55	45
Hilar only	31	45	0
Mediastinal			
Radiation therapy	23	30	13
No radiation therapy	0	0	0

tive mediastinal irradiation was 23 percent. Of interest was the fact that, in the entire 14-year period of study, all 26 patients who had mediastinal metastases but did not receive postoperative mediastinal irradiation were dead within five years after resection (Table 2).

The authors' experience suggests that cell type is an important factor in determining the prognosis in patients with bronchogenic carcinoma, especially if there is evidence of lymph node involvement. Patients with squamous cell carcinoma as a group had a greater five-year survival than patients with adenocarcinoma of the lung (43 vs 28 percent). The difference in survival between the two was even more striking when there were hilar or mediastinal lymph node metastases. The five-year survival rate in patients with squamous cell carcinoma and hilar metastases treated by pulmonary resection alone was 45 percent; it was 30 percent in patients with mediastinal metastases who underwent pulmonary resection, mediastinal lymph node dissection, and postoperative radiotherapy. In contrast are the poor results in patients with adenocarcinoma and lymph node metastases. No patient who had adenocarcinoma with hilar metastases survived five years following pulmonary resection, and only 13 percent with mediastinal metastases lived five years following resection, mediastinal node dissection, and postoperative irradiation.

Since the results of curative resection in bronchogenic carcinoma have been disappointing, an immunotherapy program has been instituted at the University of Michigan for patients who have had these operations.

There are several reasons to suggest that immunotherapy might be a useful adjunct to pulmonary resection. Tumor antigens and tumor immunity have been identified in patients with lung cancer.[4] In many patients with bronchogenic carcinoma, severe immunodeficiency has been shown to exist prior to operation.[5] In fact, a relationship between immunocompetence and prognosis in lung cancer patients has been demonstrated by Israel and associates.[6] These authors found that patients with a good general immunocompetence had a relatively good prognosis, whereas those patients with poor general immunocompetence had a reduced survival rate despite curative resection, with all other factors being equal.

Because pulmonary neoplasms are often contaminated with microorganisms and, in addition, may be quite fibrous, tumor antigens per se have been hard to demonstrate in lung cancer victims. Nevertheless, there have been a number of relevant studies implying their presence. Stewart and Hollingshead have demonstrated a delayed type of cutaneous hypersensitivity to lung cancer extracts in lung cancer patients.[4,7] This implies that there is potential for the development of cell-mediated immunity in lung cancer patients.

Transfer factor is a soluble dialyzable material of less than 10,000 molecular weight, extracted from sensitized lymphocytes. Administration of transfer factor to nonsensitized individuals has been shown to stimulate cell-mediated immunity.[8] It has been used to treat a wide variety of diseases characterized by deficient cell-mediated immunity, such as congenital immunodeficiency syndrome, disseminated intracellular infections caused by viruses and fungi, and certain malignancies, such as malignant melanoma and osteogenic sarcoma.[9] Transfer factor has not been used previously in the treatment of bronchogenic carcinoma.

A group of patients who survived five to ten years after pulmonary resection for bronchogenic carcinoma served as lymphocyte donors from which transfer factor was extracted. It was postulated that this group of patients survived because they had developed effective cell-mediated immunity. Another donor source was a group of normal individuals who may have natural cell-mediated immunity against neoplasms.

Only patients undergoing curative resection were admitted to the study. Preoperatively, the patients underwent immunologic evaluation which consisted of application of skin test antigens and in vitro lymphocyte testing. One month following resection or completion of radiation therapy, the patients were randomly divided into three groups and every three months they have been given one of the following: nonspecific transfer factor from normal persons, transfer factor obtained from long-term survivors of pulmonary resection for lung cancer, or a placebo. Their immunologic profile is repeated prior to each injection. The injections will be continued every three months for an indefinite period of time.

Although this study is still in its preliminary phase, immunotherapy with transfer factor may hold promise for the future for those patients who now die of bronchogenic carcinoma following "curative" pulmonary resection.

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