Screening for Lung Cancer

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The survival from bronchogenic carcinoma is highly dependent upon stage at the time of treatment. This is particularly true for squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, but holds true for small cell carcinoma as well. The problem presented to the medical profession has been to find a practical means of detecting lung cancer while it is still at an early stage. Three studies in progress have indicated that a larger proportion of the patients may be found to have early stage lung cancer when screened with a combination of chest X-rays and sputum cytology. However, the detection of these early stage cases has not yet been translated into an improvement in the overall mortality rate from lung cancer.

PROBLEM

The incidence of lung cancer has continued to climb dramatically throughout the last fifty years. In 1930, the incidence of lung cancer was approximately five per 100,000 men. In 1970 it was approximately 14 times as high with an incidence of 70 per 100,000. The American Cancer Society estimates that 122,000 people in this country will get lung cancer in 1981 and that 105,000 of them will die of this disease. Approximately one American will die of lung cancer every five minutes. The overall five-year survival from lung cancer in men is 8 percent. In large part, this is due to the fact that only 17 percent of lung cancers present clinically as localized disease. The remainder of the patients have either regional or distant metastases at the time of discovery [1].

The survival from bronchogenic carcinoma is highly dependent upon stage at the time of treatment. The American Joint Commission has devised a TNM system for bronchogenic carcinoma [2]. T stands for tumor, N for lymph node metastases, and M for distant metastases. In Stage I disease (local disease) the five-year survival from squamous cell carcinoma is approximately 38 percent, large cell carcinoma 31 percent, and adenocarcinoma 32 percent. In Stage II (regional) disease the five-year survival for squamous cell carcinoma drops to 16 percent, for large cell undifferentiated to 7 percent, and for adenocarcinoma to 8 percent. For Stage III disease (tumor which has invaded from the lung into the thoracic contents, or which has metastasized to the mediastinum or to distant viscera) the five-year survival for squamous cell carcinoma is 10 percent, for large cell undifferentiated carcinoma 5 percent, and for adenocarcinoma 3 percent [2].

Even small cell carcinoma can be broken into groups on the basis of the apparent...
extent of disease at the time of detection. In those patients with small cell carcinoma apparently localized to the chest after careful staging, who have been treated with a combination of radiotherapy and chemotherapy, there is a 50 percent complete remission rate and a 20 percent survival at two-plus years [3,4]. For patients with higher stage small cell carcinoma, there are only a few survivors at six months.

If the task is to reduce the mortality from cancer of the lung, there are only two ways to go about it.

1. Prevention. This would be the most desirable method. A host of environmental carcinogens capable of producing bronchogenic carcinoma have been described and continue to be identified. Perhaps the most important single factor in the incidence of lung cancer is cigarette smoking. Efforts to remove the carcinogens from the environment and stop people from smoking have obviously not been successful in preventing a rapid increase in the incidence of this disease. The Surgeon General's report in 1964 clearly pointed out the dangers of cigarette smoking, but the mortality from lung cancer 17 years later is 75 percent higher in men and 100 percent higher in women [1].

2. Effective Treatment of the Disease. Numerous studies have been undertaken in an attempt to find a modality of treatment which would be effective in high-stage lung cancer. A variety of drugs and radiotherapeutic regimens have been used against all the various subtypes of bronchogenic carcinoma. Even in small cell carcinoma, the most responsive to radiation and to chemotherapy, there has been very limited success with high-stage disease. With the other types of bronchogenic carcinoma, the success achieved has been even less.

Treatment of low-stage disease, however, has been relatively successful. The surgical treatment of squamous cell carcinoma, adenocarcinoma, and large cell undifferentiated carcinoma leads to a cumulative five-year survival rate of over 50 percent when these lesions are in Stage I at the time of treatment [2,5]. In an attempt to increase the percentage of bronchogenic carcinomas which are found as local disease at the time of detection, a number of screening programs have been employed. The various types of bronchogenic carcinoma present different problems in the screening process.

Squamous Cell Carcinoma

Squamous cell carcinoma begins in the basal layer of the bronchial epithelium of bronchi which are usually of subsegmental order or larger. This type of bronchogenic carcinoma, approximately 40 percent of lung cancers, passes through three stages: (1) pre-carcinoma or dysplastic stage, (2) pre-clinical stage of squamous cell carcinoma, and (3) clinical stage of squamous cell carcinoma [6].

In the pre-carcinoma phase, the presence of a lesion can be detected only by finding dysplastic cells in sputum. This has been done on relatively few occasions. Saccomanno [7] described the progression of changes from dysplasia to frank cancer. The duration of this period is long, at least several years in the few reliable studies which have been published.

The pre-clinical phase of squamous cell carcinoma begins with the detection in the sputum of malignant squamous cells. At the first appearance of these cells, the patients are asymptomatic and the plain chest X-ray is not revealing. A number of workers studying the rather unusual examples of squamous cell carcinomas resected during this phase in their development have shown that there is a broad range in the extent of tumor in this phase. It progresses from in-situ carcinoma in the surface epithelium to in-situ carcinoma in the submucosal glandular epithelium to invasion
of the bronchial wall and extension to hilar or even mediastinal lymph nodes before signs or symptoms are produced. A number of reports have indicated that squamous cell carcinoma found in the pre-clinical phase has a high resectability and potential curability rate [5]. There are problems related to the finding of tumors in this early stage of their clinical course [8]. Careful localization with fiberoptic bronchoscopy is required [9,10]. Extension of even very early squamous cell carcinoma to proximal or lobar bronchial margins, the presence of multifocal disease appearing either synchronously or subsequently, and the extent of underlying pulmonary disease in this group of patients create problems for the surgeon attempting to treat such lesions conservatively [11]. Nevertheless the results of treatment in this stage are among the best achieved for bronchogenic carcinoma. In 89 patients reported by Melamed [12], Pearson [13], Woolner [14], Lerner [15], Martini [16], Carter [11], and their respective associates, 81 percent underwent resection for cure and 76 percent were alive at the time the cases were reported.

The signs and symptoms of the clinical stage of squamous cell carcinoma are produced by the growth of the primary tumor to produce obstruction of the bronchus in which it arises. Most of the course of the disease has preceded the first clinical appearance of squamous cell carcinoma. Even at this stage, squamous cell carcinoma may still be at Stage I by the American Joint Commission definitions and surgical treatment may still lead to a cure rate of over 38 percent. However, the majority of squamous cell carcinomas found in the clinical phase are at higher stage.

Adenocarcinoma

Unlike squamous cell carcinoma in which a combination of X-rays and sputum cytology are useful for the early detection of the lesion, adenocarcinomas are found in the periphery of the lung where they are not likely to shed malignant cells into the sputum, and therefore are detected on X-ray. Mass X-ray screening has not been very successful. The Philadelphia Lung Cancer Detection Program, using small films, was unable to demonstrate an improvement in survival in their patients detected by screen as opposed to those who presented with lung cancer [17]. Newer screening methods have been tried and have at least yielded peripheral adenocarcinomas which are at a lower stage for treatment.

RESULTS OF SCREENING STUDIES

Baker and his associates [18] reported the surgical experience in treating the patients found in a screening program for over 10,000 men—half of whom had chest X-rays and half of whom had chest X-rays and sputum cytologic studies. Thirty-nine patients underwent resection for cure, an overall resectability rate of 55 percent. Five patients had Stage 0 disease clinically and are well after a median followup period of 36 months. Twenty-six patients had Stage I disease pathologically. Seventy-seven percent of them are free of disease after a median followup period of 36 months. The other patients have developed second primary tumors. Three of seven patients with Stage II disease have survived for 40 to 50 months. Only two of 17 patients with Stage III disease have survived. All nine patients with small cell carcinoma are dead after a median interval of eight months. The results indicate that a screening process such as this will increase the proportion of patients who are at low stage who have a better prognosis.

Melamed and his associates [5] have reported a similar experience from a similar screening program. Forty percent of the patients detected had Stage I disease and 87 percent of these patients were alive at the time of the report. Only two of the 62 pa-
tients with Stage I bronchogenic carcinoma who were treated by resection had died of lung cancer. These authors estimate that the probability of survival for true Stage I lung cancer is better than 90 percent at five years.

Taylor et al. [19] report a parallel study being carried out at the Mayo Clinic. They too find that the screened group contains approximately 50 percent of cases which are localized and low stage as determined pathologically after pulmonary resection. Only 21 percent of the control cases fall into this favorable category.

All three of these studies have been undertaken in an effort to determine the feasibility of screening to detect cancer of the lung at a curable stage. None of these studies has yet been able to demonstrate a difference in the overall survival rate between screened and control groups. In part, this may be due to the fact that the followup period is not sufficiently long at this time. Only time will tell whether a true reduction in mortality consistent with that predicted by the detection of low-stage disease cases can be achieved or whether the disease has only been detected earlier in a course which is unaltered.

Another major concern regarding screening for lung cancer is the economic feasibility of such a program. Chest X-rays and sputum cytologies are relatively expensive procedures when compared with a Pap smear or a stool analysis for occult blood. Obviously, there is a real need to identify a high-risk group of patients who should be subjected to this costly screening process and to lower its cost. Major efforts have been made in both areas, but there is nothing which appears ready for clinical application at this time.

In summary, much has been learned about the natural history of lung cancer. All this information suggests that the therapeutic modalities which are currently available can be very effective when used at an early stage of the disease. They also show the ineffectiveness of these techniques when used in late-stage disease. Unfortunately, over 80 percent of lung cancers present at an advanced stage. In the absence of an effective preventive program, screening to detect early-stage lung cancer appears to offer the only hope for improved survival from this disease. The very real needs at this time are for refinement in the identification of a truly high-risk group, and for more economical ways of screening.

REFERENCES

1. Cancer Statistics, 1981. CA—A Journal for Clinicians 31:13-28, 1981
2. Carr DT, Mountain, CF: Staging lung cancer. In Lung Cancer. Edited by MJ Straus. New York, Grune and Stratton, 1977, pp 151-161
3. Greco FA, Richardson RL, Snell JD, et al: Small cell lung cancer. Complete remission and improved survival. Am J Med 66:625-630, 1979
4. Maurer LH, Tulloh M, Weiss RB, et al: A randomized combined modality trial in small cell carcinoma of the lung. Cancer 45:30-39, 1980
5. Melamed MR, Flehinger BJ, Zaman MB, et al: Detection of true pathologic stage I lung cancer in a screening program and its effect on survival. Cancer 47:1182-1187, 1981
6. Carter D, Eggleston JC: Tumors of the lower respiratory tract. Fascicle 17, Atlas of Tumor Pathology. Washington, DC, Armed Forces Institute of Pathology, 1980, pp 70-95
7. Saccomanno G, Archer VE, Auerbach O, et al: Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 33(1):256-270, 1974
8. Tyers GFO, McGavran MH: Diagnostic and therapeutic challenges following the cytologic diagnosis of in situ carcinoma of the lung. Chest 69(1):33-38, 1976
9. Marsh BR, Frost JK, Erozan YS, et al: Occult bronchogenic carcinoma. Endoscopic localization and television documentation. Cancer 30:1348-1352, 1972
10. Marsh BR, Frost JK, Erozan YS, et al: Flexible fiberoptic bronchoscope—its place in the search for lung cancer. Trans Amer Broncho-esophagological Assn 53:101-110, 1973
11. Carter D, Marsh BR, Baker RR, et al: Relationship of morphology to clinical presentation in ten cases of early squamous cell carcinoma of the lung. Cancer 37:1389-1396, 1976
12. Melamed MR, Koss LG, Cliffton EE: Roentgenologically occult lung cancer diagnosed by cytology: Report of 12 cases. Cancer 16: 1537, 1963
13. Pearson FG, Thompson DW, Delarue NC: Experience with the cytologic detection, localization and treatment of radiologically undemonstrated bronchial carcinoma. J Thorac Cardiovasc Surg 54: 371-382, 1967
14. Woolner LB, David E, Fontana RS, et al: In situ and early invasive bronchogenic carcinoma: Report of 28 cases with postoperative survival data. J Thorac Cardiovasc Surg 60:275-290, 1970
15. Lerner MA, Rosbach H., Frank HA, et al: Radiologic localization and management of cytologically discovered bronchial carcinoma. New Engl J Med 264:480-485, 1961
16. Martini N, Beattie EJ Jr, Cliffton EE, et al: Radiologically occult lung cancer: Report of 26 cases. Surg Clin N Amer 54:811-823, 1974
17. Weiss W, Boucat KR, Cooper DA: The Philadelphia pulmonary neoplasm research project. Survival factors in bronchogenic carcinoma. JAMA 216:2119-2123, 1971
18. Baker RR, Marsh BR, Ball WC Jr, et al: Screening for bronchogenic carcinoma. The surgical experience. J Thorac Cardiovasc Surg 78:876-882, 1979
19. Taylor WF, Fontana RS, Uhlenhopp MA, et al: Some results of screening for early lung cancer. Cancer 47:1114-1120, 1981