OCCUPATIONAL CANCER

Early Diagnosis of Lung Cancer

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INTRODUCTION

If early diagnosis of a disease is taken to mean that an incurable illness is converted to a curable one, then it is clear that more than 90% of the people who develop lung cancer are not diagnosed early. Even chest surgeons have stopped exhorting their colleagues to find this disease earlier, for our current methods of detecting the disease as well as the type of host who is prone to develop this dread malignancy are inadequate.

The clinical diagnostic methods that are available include the time-honored history and physical examination, the chest roentgenogram, cytologic study of sputum, bronchoscopy, biopsy of accessible lesions (including the method of mediastinoscopy) and thoracotomy. I have listed these in increasing order of technologic sophistication. With the exception of the least expensive chest film and cytologic examination of sputum, these methods also are listed in order of increasing cost.

If we wait for the patient to seek medical attention, his 5-year cure rate for lung cancer—from experience—will be less than 10%. Therefore, efforts have been directed at screening large populations in order to diagnose a larger proportion of cases early enough to improve the cure rate.

SCREENING FOR LUNG CANCER

A useful screening procedure should be simple, inexpensive, convenient, reliable, sensitive and specific. In addition, it should provide a significant yield of curable disease, improve the cure rate and have a favorable cost-to-benefit ratio. The only procedure that has been adequately and repeatedly tested for lung cancer so far is the semiannual chest roentgenogram (1-4), beginning with the Philadelphia Pulmonary Neoplasm Research Project (PNRP) (1). The semiannual chest film is simple, inexpensive, convenient and fairly reliable. While its specificity is good, sensitivity is low, the yield of curable disease is poor and it provides very little improvement in the cure rate. Finally, the cost-to-benefit ratio does not seem to be favorable, but this is a societal rather than scientific judgment.

Semiannual questionnaires about respiratory symptoms were evaluated in the PNRP; the unpublished data have shown that symptoms are insensitive, nonspecific or both. Semiannual sputum cytologic examinations have been studied in only one uncontrolled investigation (4); the results were bad. Controlled studies of cytologic screening at 4-month intervals are in progress (5-6). Although it is too early to assess them, a presentation by Robert Fontana, MD on the Mayo Lung Project (from the State-of-the-Art Conference on Screening for Lung Cancer, sponsored by the National Cancer

Institute in Reston, Virginia, September, 1978) indicates no significant impact on the lung cancer mortality rate. Since sputum cytologic examinations at 4-month intervals cannot presently be evaluated, this discussion will be limited to an assessment of the semiannual chest film and the reasons for its failure.

EFFICACY OF THE SEMIANNUAL CHEST FILM

Estimates of sensitivity and specificity of this procedure have been made in two investigations. The American Cancer Society-Veterans Administration study (4) of approximately 14,000 older men in domiciliary homes, estimated the sensitivity of the chest x-ray to be 42% and specificity at 98%. In the PNRP, unpublished data indicate a sensitivity of 61% in 121 cases of lung cancer (72% in 67 complaint cases) and specificity of 96%; this study took a systematic sample of 97 men from among 5,906 who did not develop lung cancer in the 10-year observation period. These figures show that sensitivity is not very good and, what is worse, the ratio of false positives to true positives is about 3:1 or higher; thus, many men who do not have lung cancer are subjected to clinical evaluation and its attendant anxiety.

The ultimate test of a screening procedure depends on how it affects the cure rate and the population mortality rate; a controlled trial is required in which a screened population is compared with an unscreened, radomized population of similar characteristics. Only Brett (2) has evaluated the semiannual chest film with a controlled trial and it could be criticized because the two populations were not obtained by randomization. Be that as it may, the 5-year survival rate of men with lung cancer in his screened group was 15% vs 6% in the control group (Table 1), a difference which was not statistically significant at the 0.05 level.

TABLE 1. - Results of a 3-year Study of Semiannual Chest X-ray Screening Among Industrial Workers Aged 40-65 in NW London (2)

Characteristic	Screened	Unscreened
Population size	29,723	25,311
No. developed lung cancer	101	77
Lung cancers resected	44%	29%
Cases with 5-yr survival	15%*	6%*
Lung cancer mortality rate (per 1,000/yr)	0.7	0.8

* chi-square, Yates' correction = 2.28, df=1, "p" less than 0.05

Even if the difference were statistically significant, it would have to be interpreted in the light of the "lead-time" afforded by screening. Lead-time is the interval between the time the cancer is detected by the screen and when it would have been found without screening. If this interval becomes part of the survival time, then the screened cases will appear to have better results even though death has not been deferred. To

evaluate the contribution of lead-time to the survival rate, we need to know the length of the lead-time. There are no good data, yet some unpublished data from the PNRP suggest that the median lead-time is more than one year and it varies tremendously according to the growth rate of the individual cancer.

In view of the problem with lead-time and other problems regarding the type of disease uncovered by screening—which might result in the inclusion of a disproportionate percentage of favorable cases—the screening procedure should have a significant impact on the population mortality rate for lung cancer if it is to be considered effective. In Brett's controlled study, there was little impact on the annual mortality rate: 0.7/1,000 in the screened group vs 0.8/1,000 in the control group. This poor result is supported by equally poor figures in the other three studies; therefore, it can be concluded that semiannual chest x-rays have very little value in screening for lung cancer.

There are five reasons for the failure of the semiannual chest film: the nature of lung cancer, the nature of the host, the peculiarities of the patient with lung cancer, the nature of current medical practice and the multifocal nature of lung cancer.

The nature of lung cancer — Experience shows that this cancer is a particularly vicious tumor. Most cases have a short volume doubling time (ie, rapid growth rate) as shown in Table 2

TABLE 2 - Distribution of Tumor Volume Doubling Times of Lung Cancers Appearing as Round Lesions on Serial Chest Films (7)

Doubling time, months	Number (%)
0-	1 (2)
1-	5 (0)
2-	9 (17)
3-	7 (13)
4-	8 (15)
5-	7 (13)
6-	4 (8)
7-	3 (6)
8-	2 (4)
9-	2 (4)
10-	2 (4)
11-	1 (2)
12+	1 (2)
Total	52 (100)

and it metastasizes early (Table 3).

TABLE 3 - Prevalence of Metastases at Autopsy by Interval From Resection to Death in 125 Men with Resected Lung Cancer (8)

Interval, months	No. of cases	No. of metastases (%)
1	44	16 (44)
2-5	27	18 (67)
6-11	20	17 (85)
12+	34	28 (82)
Total	125	79 (63)

Doubling time is inversely related to survival (Table 4).

TABLE 4 - Survival By Tumor Doubling Time in 20 Men with Round Lung Cancers Subjected to Resection (9)

Doubling time	No. of cases	Median survival, months
0.9-2.9 mos.	7	32
3.0-6.9	7	40
7.0-10.0	6	71

Furthermore, lung cancers usually are not detected until they are at least one centimeter in diameter and often larger (7). A majority of lung cancers whose growth rates have been measured have doubling times of less than 6 months (Table 2); therefore, during a 6-month interval between screenings, most tumors double in volume from one to more than six times, and a cancer that is missed at one examination may be quite large at the next (10). Studies of rates of cancer growth suggest that by the time a tumor reaches a diameter of 1 cm, the tumor has passed through the first two-thirds to three-fourths of its lifetime (7,9,10).

The nature of the host — Noncompliance with procedure is a serious obstacle to the success of any screening program and man is not noted for his response to such efforts. In the PNRP we found that the average probability of a patient having two consecutive semiannual chest films was 57%; at the end of 10 years only 18.5% of those who were still eligible (ie, those who were still alive and in contact with the project) had made early scheduled visits (11). And worse, the risk of lung cancer was higher in noncompliant men than in compliant ones (Table 5) (12), a phenomenon which was not limited to the risk of lung cancer but involved the risk of death regardless of cause.

TABLE 5 - Probability of Older Men Developing Lung Cancer in the Second Through Tenth Years of Observation, by Degree of Compliance in the First Year (12).

Compliance*	Number	(%)	Developed lung cancer	(% prob.**)
yes	4,302	(73)	73	(1.98)
no	1,562	(27)	45	(3.48)
Total	5,864	(100)	118	(2.36)

* made 2nd semiannual visit in first year
** computed by actuarial method; adjusted for age, race and smoking habits at start of observation ("p" less than 0.01)

The peculiarities of the patient with lung cancer — People who develop this disease tend to be elderly. The median age of men with this disease in the PNRP was 64 and this was not attributable to any maldistribution by age of the 6,027 men in the project; indeed, the study population tended to be slightly younger than the male population of Philadelphia at the time our group was assembled (13).

Inasmuch as 25% of the lung cancer cases were aged 70 or over, we have learned to be cautious about recommending major chest surgery in such men because the postoperative risk exceeded the 5-year cure rate of such individuals in Philadelphia teaching hospitals during the time of the project (Table 6) (14).

TABLE 6 - Operative Death and 5-year Survival Rates Among 968 Men Operated on for Lung Cancer* by Age in Philadelphia Teaching Hospitals, 1956-65 (14)

Age	Distribution	Operative deaths**	5-year survival
50	15.6%	9.3%	18.7%
50-59	35.9	9.5	14.4
60-69	38.4	12.9	13.7
70+	10.1	19.4	12.2
Total	100.0%	11.8%	14.6%

* includes thoractomies with and without resections
** within 30 days

In addition, many patients with lung cancer are poor risks for thoracic surgery because

they have other serious diseases associated with advanced age or smoking; particularly, chronic obstructive lung disease. We have noted that the risk of lung cancer is also higher in men with chronic cough than in those without this symptom of chronic obstructive lung disease (Table 7) (12).

TABLE 7 - Probability of Older Men Developing Lung Cancer in 10 Years by Presence or Absence of Chronic Cough at the Start of Observation (12)

Chronic cough	Number (%)	Developed lung cancer* (%)
yes	1,756 (29)	58 (2.98)
no	4,271 (71)	63 (2.05)
Total	6,027 (100)	121 (2.41)

* computed by actuarial method and adjusted for age, race and smoking habits at start of observation ("p" less than 0.05)

The nature of current medical practice — Not all physicians who are charged with the care of patients with lung cancer are equipped to provide the best management. In the PNRP, delay was attributable to the patient's physician in 6% of the cases.

The multifocal nature of lung cancer — Even after we have successfully treated a small proportion of people with lung cancer, there are still some who will develop a second lung cancer; especially, those who continue to smoke. The prognosis for them is not as good the second time (15). The explanation for this propensity for a second tumor is readily apparent from Auerbach's extensive studies of the bronchial mucosa (16) and is to be expected a priori since cigarette smoke and industrial carcinogens bathe the mucosa of the entire bronchial tree.

CONCLUSIONS

While the periodic chest roentgenogram has many of the characteristics of a good screening instrument, it is not adequate to reduce the mortality rate of bronchogenic carcinoma in populations at risk. Some of this failure is due to inadequacy of the screening method itself, but failure is due as well to the character of the disease, the nature of the host, current medical practice and available therapy. If screening is to have an impact on this disease in the global population at risk, it must deal with numerous problems that are unrelated to the particular screening method.

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