Early Detection of Lung Cancer

Clinical Conference from the University of Iowa
College of Medicine

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Dr. Rhodes: Our topic today is early detection of lung cancer. This discussion would have been totally inappropriate 50 years ago. In his recent review of lung cancer, Dr. Alton Ochsner states that as a medical student in 1916, he and fellow students were called to the autopsy room to see a very rare disease—primary bronchogenic carcinoma of the lung. This was the first case Ochsner had seen and one of a few cases reported at that time. He did not see another case until 1936, when he saw nine cases, all in men who had been heavy smokers since World War 1. Today lung cancer is of epidemic proportions. Dr. Richardson will present the case.

Dr. Richardson: Our patient is a 55-year-old man who saw his local physician one year ago because of recurrent cough, productive of occasional blood-streaked sputum over the preceding two months. He was a 70-pack year smoker, but otherwise was asymptomatic. A chest x-ray film, shown in Figure 1, was unchanged from previous films. The calcified lesion in the right lower lung field had been unchanged for 20 years, and the remainder of the film was felt to be normal. Repeated sputum cytologies were negative. Fiberoptic bronchoscopy revealed a small pedunculated endobronchial lesion in a subsegment of the superior segment of the left lower lobe. Brush biopsy of this lesion was conclusive for carcinoma as we see in Figure 2, which is a millipore filtered specimen taken from brush biopsy. These cells are obviously malignant; there is marked variation in nuclear size, abnormal nuclear chromatin pattern, and enlarged multiple nucleoli. At thoracotomy, the lesion was well-localized. There were no positive mediastinal nodes. Left lower lobectomy was performed without complication. In Figure 3, we see a section of the resected tumor, a large cell undifferentiated carcinoma. After operation, the patient received a VA chemotherapy protocol consisting of alternate months of amethopterin and cyclophosphamide. When last seen three weeks ago, he was well, with no evidence of recurrence and no significant drug toxicity. Even though this tumor seemed well localized, our prognosis must remain guarded because of the uniformly poor prognosis of all undifferentiated lung tumors. Of all techniques for early diagnosis of lung cancer, fiberoptic bronchoscopy seems to have the greatest potential. In-

FIGURE 1. Chest x-ray film with nipple markers. Calcified granuloma at right base was present unchanged for several years.
indeed, it was for the early diagnosis of lung cancer that Ikeda initially developed the fiberoptic bronchoscope in the mid 1960s. This instrument allows direct visualization to the subsegmental level of all bronchial segments and biopsy, under fluoroscopic control, even beyond this level. Table 1 shows our initial results with fiberoptic bronchoscopy. Of the first 200 patients examined at the University of Iowa Hospitals, 130 proved to have primary lung cancer, of which 77 had a visible endobronchial tumor. Of this last group, 71, (92 percent) had a brush biopsy which was positive for malignancy. Fifty patients had no obvious endobronchial lesion, but had a radiologic lesion which was possible to brush under fluoroscopic control. Out of this group, 39 (78 percent) had a brush biopsy specimen which was positive for malignancy. Three patients in whom it was not possible to perform a brush biopsy had bronchial washings which were negative. Out of the total of 130 patients with carcinoma of the lung, 110 (85 percent) had cytologic proof of malignancy established by brush biopsy through the broncho-fiberscope. These results compare very favorably with the original series with bronchoscopy by Ikeda using curette and forceps biopsy through the fiberoptic bronchoscope. He established a positive diagnosis in 89 percent of all patients who eventually were proved to have carcinoma of the lung.

Of three patients whose initial chest x-ray findings were regarded as normal, only the patient presented today had a resectable lesion. All three had hemoptysis. Even with the fiberoptic bronchoscope technique, the only hope, it seems to me, is earlier diagnosis, which is the topic of today’s discussion.

**Dr. Rhodes:** Thank you Dr. Richardson. One approach that has been studied fairly extensively in an attempt to detect lung cancer in an earlier stage is the use of x-ray film screening at periodic intervals. Dr. Zavala will tell us about the results of these studies.

**Dr. Zavala:** When one speaks of bronchogenic carcinoma and the results of therapy, we have not progressed very far down the road since the days of calomel and leeching. During the past two years, Dr. Richardson and I have performed flexible fiberoptic bronchoscopies on over 500 patients with chest lesions suggestive of malignancy. The more acquainted one becomes with lung cancer, the more discouraged one becomes. The survival statistics are utterly dismal.

I recently reviewed several extensive surveys, which, I think, tell the true story about bronchogenic carcinoma. The Philadelphia project was a ten-year study of 6,136 men, 45 years of age or older. Seventy millimeter chest photofluorograms were taken and symptom questionnaires were administered to these men every six months during the ten years of this survey. All had normal x-ray film findings initially. In spite of these findings, the survival rate was only eight percent among 94 proved cases. The length of survival was related more closely to the tumor doubling time than to the type of therapy used.

**Dr. Kasik:** Did they have a control group?

**Dr. Zavala:** No, they did not, but the London study did have a control group. The London study dealt with the value, or I should say the lack of value, of chest radiographs for early lung cancer detection. Their test group consisted of 29,723 men, aged 40 years and over. These men had chest x-ray films taken every six months for a period of three years. A
EARLY DETECTION OF LUNG CANCER

similarly constituted control group consisted of 25,311 men who had chest x-ray films initially, then once again at the end of the study period. There was no significant difference in the annual mortality between the test and the control groups; none whatsoever. It was concluded that large scale, six-month-interval chest radiographs did not alter the mortality from lung cancer.

A Canadian survey, done at the Hamilton Tumor Clinic, of 594 consecutive lung cancer patients yielded the startling figure that 50 percent of this group were dead in 5.67 months, and that at the end of five years, only 5.2 percent were alive and well, regardless of the type of therapy given.

A conclusion may be made from these studies: regardless of chest x-ray films at six-month intervals, symptom questionnaires at six-month intervals, or the best therapy at our disposal, the five-year survival rate remains about 6 percent.

We need to select our type of therapy more carefully. Mediastinoscopy does offer help in screening patients as candidates for operation. A negative mediastinal node biopsy is fairly good evidence that the patient is a candidate. Chemotherapy has proved disappointing, with the possible exception of cyclophosphamide (Cytoxan) to treat oat cell carcinoma, but I hasten to add that it has not changed the overall mortality. Radiotherapy is occasionally helpful in alleviating pain from bony metastases, but it also can do harm. We have to remember that there is a loss of lung function involving the irradiated area and a danger of postirradiation pneumonitis. Immunotherapy offers some interesting and potentially hopeful possibilities.

One obvious solution to lung cancer lies in its prevention, but efforts to eliminate smoking have failed rather miserably. The biggest increase has been in teenage girls, ages 12 to 18 years. In this group, the percentage of smokers rose sharply from 8.4 in 1968, to 13.3 in 1972.

Dr. Rhodes: How do bronchograms fit into the picture of early lung cancer detection?

Dr. Zauala: Enthusiasm for bronchography has varied. It tends to lose its effectiveness as a diagnostic tool in a patient who has had previous insults with infection, such as chronic bronchitis. We often cannot tell whether the structural changes are due to inflammation or tumor. At present, it is used rather selectively. Successful bronchography is dependent on the material and the technique used. The perfect medium would have the following features: (1) a high density for radiopacity; (2) complete absence of toxicity; (3) ease of administration; (4) a high degree of structural resolution; and (5) non-interference of pulmonary function. The routine usage of iodized oil (Lipiodol, Dionosil) often produces an inflammatory response due to the iodine content. The oily material has a packing and filling effect rather than a coating effect, and it may remain in the tracheobronchial tree for months or years. Furthermore, it frequently causes a decrease in pulmonary function, abnormal blood gas values and some loss of compliance.

Recently, Tantalum has appeared on the scene. Tantalum powder meets all of the requirements for successful bronchography except for one area of potential concern, which is its retention in the smaller airways. It has a density 16 times greater than iodine or barium and, therefore, requires only a small amount to coat the tracheobronchial tree. One milliliter is the usual amount used. Tantalum is totally inert. It produces no interference with pulmonary function and no changes in blood gas values.

Dr. Rhodes: Have you been using bronchograms routinely when you perform bronchoscopy?

Dr. Zauala: No, we have not. Four years ago, I routinely used selective bronchography. The additional information gained was of little help. Many of the patients were smokers and had distortion of their bronchial trees, which we were often unable to differentiate from malignancy. Also, we found that vigorous brushing can tear up the bronchial mucosa and produce edema, bronchospasm and small clots. Therefore, we had to do the bronchography prior to the brush biopsy, if it was to give us any help.

Dr. Rhodes: Dr. Richardson, you worked with Dr. Ikeda in Japan. Do they use selective bronchograms?

Dr. Richardson: Yes, Dr. Ikeda routinely does prebronchoscopy, segmental or subsegmental bronchograms in patients who have a lung lesion so that he can identify its specific location. Thus, he can direct the biopsy curette more easily under fluoroscopic control. We have been able to get the brush into the lesion in all but 3 of our first 130 cases of lung cancer without such a road map, but perhaps in those 3 cases it would have been helpful to have performed bronchography beforehand.

Dr. Rhodes: I think that we can summarize by saying that x-ray films taken every six months are not the answer. When we see the lesion on x-ray film, we are seeing a late stage of the disease. If you assume that a lung cancer starts from one cell, then by the time the lesion becomes a 1 cm nodule, 20 generations will have occurred, or an increase to about a million cells. When the lesion becomes radiographically apparent, it has already gone through 80 percent of its lifespan and is not curable by resection in over 90 percent of cases. One other fact that came out of the Philadelphia x-ray film study...
was that the risk of developing lung cancer approached 10 percent in persons smoking a pack a day for 40 years.

Dr. Bedell, would you tell us about screening cytology?

Dr. Bedell: A potential approach would be to do sputum cytologies on people at high risk at regular intervals. In several centers in England, Brazil and the United States, where careful sputum studies are collected from people with chest lesions suspected of being cancer, about two-thirds of the cancers are detected on sputum cytology. You will note from the figures given previously, when bronchoscopy and brush biopsy are added, the percentage of positive results goes up significantly. There are several problems with doing routine sputum cytologies. First, it requires a well-trained cytologist. Next, it takes anywhere from 30 to 45 minutes to arrive at a negative answer. In the groups where cytology was added to chest x-ray film studies, 15,000 patients in the VA Hospital study, and 3,000 patients at the University of Chicago, cytology did not greatly improve the yield of early resectable carcinomas from x-ray film findings alone, and we have already heard that the yield from x-ray film studies was very poor. The verdict on sputum cytology is that it is not a sensitive method for the early diagnosis of carcinoma of the lung. Apparently, these malignancies commence and grow very rapidly so that in a given patient, cytology can be negative at one point in time and positive six months later, at which time the lung carcinoma is already too far advanced for resection.

Dr. Kasik: What was the percentage of false negative and false positive findings?

Dr. Bedell: The percentage of false positive findings is 0.5 percent, so the chances of a positive result being due to inflammation are quite small. I think in our series that we have had only one or two false positive results from patients. Is that right, Dr. Richardson?

Dr. Richardson: We have had two patients with cytology highly suggestive of cancer who later proved to have organized pneumonia. One problem is the patient with a positive sputum cytology on whom there is no recognizable lesion on chest x-ray film. So far, these patients have not been subjected routinely to fiberoptic bronchoscopy in any series of which I am aware. Repeated bronchoscopy every few months might be necessary to localize the lesion.

Dr. Rhodes: What is the best way to collect a sputum specimen for cytology?

Dr. Bedell: It has to be sputum from the lower respiratory tract. Some people have trouble coughing up sputum, so having them breathe a heated aerosol substance enables most to cough. The sputum should be coughed directly into 95 percent alcohol, because exposure to the air for just a few seconds causes cellular degeneration.

Dr. Zavala: There is evidence of a cumulative positivity rate with repeated sputa specimens. How many sputa cultures would you recommend on a patient suspected of having carcinoma?

Dr. Rhodes: The yield of return after three diminishes. I think the ultimate role of cytology is still uncertain. There are case reports of patients having positive sputum for three to five years before any lesion appears on x-ray film. If we had techniques with which we could localize the lesion prior to its becoming radiographically evident, we might be able to do something to increase survival rates. One aspect of technology that might increase the diagnostic yield of sputa is the capability of computers to screen the cytology and select "suspicious" slides, which would then be examined by a cytotechnician and pathologist.

One thing we have to ask ourselves is, "are all these contortions of any benefit?" If we can find lung cancer earlier by x-ray film screening or cytology, are we going to do anything to improve the length of survival of the patient?

Dr. Kasik: I am skeptical that there is any method currently available by which we can reduce the death rate from bronchogenic carcinoma. Obviously, a case with a well localized tumor should be resectable, but a tumor that is highly invasive but resectable may have small, invisible metastases. The single most important factor in the survival of patients with bronchogenic carcinoma is the malignancy of the tumor. A patient who has a slow growing tumor which is less malignant than average has a long period, relatively speaking, to have his tumor discovered and resected before it metastasizes. I suspect that if one were able to observe a large group of patients with bronchogenic carcinomas from the very beginning, he would find that highly malignant tumors become unresectable very quickly, and low grade malignancies remain resectable for months. This means that for the patient with a highly malignant tumor, a program of screening every six months is not suitable. Since you do not know who is to develop a highly malignant lesion, it would mean that you would have to screen everyone at a much more frequent interval.

Let us say that a protocol were devised in which 1,000 heavy smokers between the ages of 50 and 60 years of age had chest x-ray films and bronchoscopy twice a year. What could you expect to find? Based on the Philadelphia study, about 1 percent of these patients would develop a bronchogenic car-
EARLY DETECTION OF LUNG CANCER

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cinoma per year. This means that one could expect to find ten carcinomas each year, but also that there would be a total of 1,990 unrewarding bronchoscopies per year. The cost of such a procedure would be extremely high, and would require a bronchoscopist for bronchoscopy of about six patients a day the year round.

In closing, let me say that I think my major function at this symposium has been to be very skeptical that there is anything we can do to reduce the death rate of bronchogenic carcinoma by an aggressive program of diagnosis using the currently available technology. The way to solve this problem is to educate the public not to smoke cigarettes.

Dr. Rhodes: Dr. Kasik brought out many interesting points. There have been retrospective studies looking at the results of finding carcinoma in situ and the problem of positive sputa cytology in patients with normal chest x-ray films. Woolner et al recently reviewed the 28 cases of patients with bronchogenic carcinoma seen over a 23-year period at Mayo Clinic in which the tumor had apparently not extended beyond the bronchial wall. The patients complained of cough and either hemoptysis or obstructive pneumonia. Ten had normal x-ray film findings. Of the 26 who survived operation, 23 had a five-year cure. Bell, on the other hand, reported 12 patients with positive cytology and negative findings on x-ray films seen at the University of Washington over ten years. Six developed clinical and x-ray film evidence of tumor, but none of the tumors was resectable. I recently heard Edward Beatle of Memorial Hospital, New York, report on 27 such patients. In the nine in whom the tumor was located and resected, the patients have a 60 percent, five-year survival. So retrospective studies report from 85 percent to as low as 0 percent, five-year survival in patients with positive cytology and negative findings on x-ray films seen in this series of doctors in London who quit smoking from 1951 to 1966. The incidence of lung cancer in men who continued to smoke increased over this 15-year period, while the incidence of death from lung cancer in the physicians who quit smoking, decreased significantly. On this basis, he felt that people who had been smoking as long as 30 years, who then stopped smoking, reduced their risk of incidence of lung cancer approaching that of a nonsmoker by eight to nine years after stopping smoking.

Dr. Rhodes: Can we use bronchoscopy on all high-risk patients?

Dr. Richardson: Yes, I think it is, indeed, technically feasible. If we have adequate technical assistance and an adequate number of bronchoscopes and bronchoscopists, I think that we could screen everyone who comes in over the age of 40 years who had smoked 20 pack years or more, even without symptoms or without evidence of an abnormality on chest x-ray film.

Dr. Zavala: I empathize with Dr. Richardson’s enthusiasm for routine fiberoptic bronchoscopy. It is time consuming, but I think in some respects it may be rewarding. At least it should be explored. I do want to point out, though, that many bronchogenic carcinomas begin in the periphery of the lung beyond the range of the bronchoscope, where they lie silently for a long period. The farther the tumor is from the central bronchi, the more difficult it becomes to make a diagnosis because they do not cause early symptoms and the more inoperable they are when we finally do make a diagnosis. Therefore, in this group of patients, routine bronchoscopy by our present fiberoptic techniques is not going to result in an early diagnosis. I would estimate that approximately 40 to 50 percent of all bronchogenic carcinomas are located in the periphery of the lung at the time of diagnosis.
REFERENCES

Beginnings of Modern Astronomy

Nicholas Copernicus (1473-1543) was born in the Polish town Torun on the River Vistula. At the age of eighteen he went to the Polish University of Krakow where he studied astronomy. He continued at Bologna University. Then he went on to study medicine at the University of Padua. At thirty-two he settled in Ermland. Shortly before he died, his book De Revolutionibus Orbium Coelestium was published. It stated, quite clearly, that the sun was the center of a planetary system, had a number of smaller "planets" moving round it and the earth was only one of these. Far from being stationary and central, the earth was in a huge "orbit", millions of miles away from the sun, travelling at a great speed. The publication, long delayed, was a small tragedy. Copernicus sensed that the Church would take exception to his revolutionary theory. As he admits in his preface, explaining the delay: "The scorn which was to be feared on account of the novelty and the absurdity of the opinion impelled me for that reason to set aside entirely the book already drawn up."