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Lung
Cancer

Frontiers

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“The purpose of Lung Cancer Frontiers is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.”

The Debate on Lung Cancer Screening Increases

Screening Strategies for Early Detection of Lung Cancer. The Time is Now.

(Petty TL: JAMA 2000;284:1977-1980)

Current knowledge and available technology could change the outcome of lung cancer. But screening and even case finding in patients at high risk is still not recommended. No major medical organization in the United States recommends any form of screening for lung cancer. For this reason, lung cancer is not diagnosed until it is symptomatic and usually when it is in advanced and incurable stages. Assume that the following facts are true: In the year 2000, approximately 172,000 patients will be diagnosed as having lung cancer, which represents the most common fatal malignancy in both men and women in the United States (based on 1996 data),¹ and the 5-year survival rate will be only 15%, which is a generous estimate. Simple arithmetic results in 25,800 patients who will survive, and 146,200 patients who will have progressive, rapid, and painful deaths from lung cancer, often with bone and brain metastases. However, the survival rate in early-stage lung cancer, that is, *in situ* and stage IA, is 60%, which also is a conservative estimate. Thus, if all 172,000 patients could be diagnosed at this early stage, this would result in 103,200 survivors and 68,800 deaths in 2000. Diagnosing and treating lung cancer in the early stages of the disease could save tens of thousands of lives each year.

Historical Perspective

Why does current dogma state that screening for lung cancer is not beneficial? The answer comes from 3 related studies sponsored by the National

Cancer Institute (NCI) in the mid-1970's^{2,4} and a Czechoslovakian study.⁵ These 4 studies used standard chest radiology and sputum cytologic testing to identify persons with lung cancer. Although the resectability and survival rates were higher in at least 1 of the NCI studies,² overall mortality did not change.⁶ There are many problems with these studies.^{2,5} For instance, standard chest radiography, although beneficial in case finding,^{7,8} often does not identify early stages of disease. Also, in the mid-1970's, approximately 50% of the control group received chest radiographs as a part of standard practice.^{2,4} Thus, these studies included a control group that was “contaminated” by patients who also had chest radiographs during the study. An annual chest radiograph provides some lung cancer surveillance, albeit crude. In addition, the entry criteria into the NCI studies did not require history of heavy smoking. The criterion of smoking intensity only required the subjects to have consumed 20 cigarettes during the year before study entry. The mean pack-years of smoking was only 20.^{2,4}

Moreover, in the Johns Hopkins Lung Project, an analysis of molecular markers for cancer showed that a substantial number of patients determined to be free of cancer actually had evidence of cancer in their expectorated sputum specimens.⁹ Thus, this study shows that many cancers that could be detected with modern technology can be missed otherwise.

The Present Era

Recent studies^{10,11} using low-radiation, high-resolution computed tomography (CT) have shown that peripheral nodules as small as 3.0 mm can be detected and virtually all of these lung cancers could be resected.¹⁰ Computed tomography is the standard practice for detecting

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lung cancer in Japan, often by using mobile vehicles with CT scanners to screen for lung cancer in persons living in rural areas, even where smoking prevalence is relatively low.¹¹ It is well established that CT is far more sensitive and specific than conventional chest radiography in the diagnosis of early peripheral lung cancers, which are usually adenocarcinomas.¹⁰

Sputum cytologic testing has been successfully used in the United States to identify radiographically occult lung cancer of the central airways, including in a community hospital where the modern method of sputum cytopathologic testing has its roots.^{12,13} Lung cancer was diagnosed by sputum cytologic testing in 51 consecutive patients in whom chest radiographic results were normal.¹³ Most of these cancers (44/51) were squamous cell carcinomas. These patients were evaluated because of changing symptoms, heavy smoking, or occupational exposures. Forty-six (90.1%) of these patients had early-stage disease that could be treated with surgical intervention or with radiotherapy in an attempt to cure. Actual 5-years survival rate was 54.3% following either surgical or radiotherapy treatment.¹⁴ As expected, some patients had secondary or tertiary carcinomas, which also were identified by sputum cytologic testing in stages during which retreatment was possible. Many of these patients were cured of their cancer but later died from other causes.

Screening to identify lung cancer in its early stages has been extensively criticized on the basis of lead-time, length-time, and tumor selection biases.¹⁵ The very purpose of screening is to exploit the advantages offered by lead- or length-time.¹⁶ In other cancers, such as of the breast and prostate gland, treatment in early and even in so-called indolent stages has become the standard of care, thus improving survival. Clinical objectives also should include the detection and cure for lung cancer in its early, less invasive, and probably less virulent stages.¹⁶ Extensive evidence indicates that late-stage diagnosis or diagnosis of lung cancer on the basis of symptoms is not the correct approach to this most common fatal malignancy in men and women. New and aggressive approaches to early identification of lung cancer must be adopted.

Like improvements in the radiographic diagnosis of lung cancer, the sensitivity and specificity of sputum cytologic testing has been improved by automated techniques. Also, the search for molecular markers from expectorated sputum cells may make lung cancer screening even more sensitive and specific than it is today.¹⁷

Case Finding in High-Risk Groups

Nearly 10 years ago, I proposed that lung cancer screening should be performed in patients who are at highest risk.¹⁸ It is well established that airflow obstruction as measured by spirometry in heavy smokers corresponds to 4 to 6 times increased prevalence of lung cancer compared with patients in whom airflow is normal.^{19,20} Kennedy et al,²¹ in a prospective study of patients who smoked 30 or more pack-years with any degree of airflow obstruction (as defined by a forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] ratio of <70% or an FEV₁ of <80% of predicted normal values), documented that sputum cytologic results were positive for cancer in 1.8% and for severe dysplasia in 0.3% of the patients. A yield of approximately 2.0% of lung cancer diagnoses is huge compared with the 0.5% diagnoses of breast cancer, which Salzmann et al²² pointed out in high-risk women screened by mammography. In addition, 25.0% of the patients were found to have moderate dysplasia.

A Mayo Clinic study revealed moderate dysplasia in only 2.9% of its patients.²³ The reason for the much higher yield of both cancer and moderate-to-severe dysplasia in the study by Kennedy et al²¹ is because of the selection of a high-risk cohort due to heavy smoking and coexistent chronic obstructive pulmonary disease (COPD). A follow-up of patients with moderate dysplasia from this series of patients²¹ has already yielded 4 additional cancers among 41 patients who received bronchoscopy of the 155 patients with moderate dysplasia as detected with sputum cytologic testing, (Timothy C. Kennedy, MD, oral communication, May 5, 2000). This follow-up searched for molecular markers of lung cancer in these subjects. These additional squamous cell cancers were all small intraepithelial lesions, and some were occult or subtle radiographically detected lesions. Three of the cancers were found by both white light and fluorescent bronchoscopy.²⁴ The fourth cancer was found only by fluorescent bronchoscopy. Light-intensified fluorescent endoscopy, as compared with white light bronchoscopy, can identify small foci of abnormal fluorescence in which a biopsy should be performed to more accurately detect the presence of cancer.²⁴ However, bronchoscopy using light-intensified fluorescent endoscopy is not yet widely available.

Other high-risk groups, such as patients with a previous lung cancer, individuals with significant occupational exposure such as asbestos workers, and patients with a strong family history of lung

cancer, also would be candidates for screening by CT and sputum cytologic testing.

Positron emission tomography also is not widely available, but in the future, it likely will be valuable to differentiate clearly between benign solitary nodules and those that are probably malignant.²⁵ Positron emission tomography also will be useful in staging and the identification of metastatic disease.²⁵

Economic Considerations

The cost to screen for early lung cancer and to cure and treat this disease is an important consideration. Hillner et al²⁶ reported that the cost for lung cancer diagnosis and treatment in the present era (1989–1991), when screening is not practiced, is approximately \$50,000 per patient (1990 dollars). In this study, the 2-year survival rate, in patients so diagnosed, was only 20%. Contrast this rate with a potential rate of 60% or more 5-year survival prediction of early diagnosed lung cancer. The true cost of early diagnosis needs to be established by prospective studies which should determine not only the costs of early identification and treatment but also whether the high end-of-life costs that patients now incur are also found in a cohort of patients with early-stage lung cancer, even if their survival is prolonged.

Lessons From the Lung Health Study

The Lung Health Study, a multicenter, randomized clinical trial of smokers with more than 10 pack-years and who were aged 35 to 60 years, showed that 57 patients (1%) died of lung cancer at the end of 5 years.²⁷ Late follow-up data indicated that a total of 227 (3.9%) of the original 5,887 patients enrolled in the Lung Health Study developed lung cancer (John E. Connett, MD, oral communication, October 10, 1999).

This study was designed to track the course and prognosis of patients with mild-to-moderate stages of COPD and the effect of smoking cessation on the rate of change of FEV₁. Stopping smoking improved FEV₁ followed by a slight decline in FEV₁ in sustained quitters. In patients who continued to smoke, the rate of FEV₁ decline was much more rapid. However, only 22% of patients who were randomly assigned to the smoking intervention group (with bronchodilator or placebo) actually succeeded in stopping smoking throughout the 5-year study, compared with 5% of patients who received ordinary care. Many of these patients with histories of heavy smoking would be candidates for yearly

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surveillance to detect the cytologic or molecular markers of lung cancer. Today, more lung cancer is found in former smokers than in current smokers.²⁸ Patients with moderate dysplasia also would be excellent candidates for chemoprevention studies, as would patients who were apparently successfully treated for early-stage lung cancer.²⁹

Lessons from Japan

A comparison of survival rates has been done in Niigata Prefecture in Japan.³⁰ Screening for tuberculosis using radiography has been a routine procedure in Japan because of a continuing high prevalence of the disease. During 1963 to 1977, before lung cancer screening became the norm, the 5-year survival rate was 33.7% for lung cancer cases discovered during tuberculosis radiographic screening.³⁰ This was a good result in cancer outcome compared with 15% or less survival in the United States at 5 years. A pilot study of screening for lung cancer during 1978 to 1986 in the same prefecture yielded a 51.8% 5-year survival rate.³⁰ The lung cancer screening program was expanded to the entire population of the prefecture in 1987 in which sputum cytologic testing was added to radiographic screening. From 1987 to 1992, the 5-year survival rate increased to 58.4%. In studies of surgery of radiographically occult lung cancer found by sputum cytologic testing, the 5-year survival rate was 80.4% for squamous cell carcinoma.³¹

Critics of lung cancer screening disapprove of the use of 5-year survival curves, but this same yardstick is used as a standard measurement for colon, breast, cervical, and prostate cancers. Why treat survival in lung cancer any differently?

The National Lung Health Education Program

Unfortunately, the great majority of smokers and particularly those with incipient stages of COPD are not seen by pulmonologists or other medical specialists. However, approximately 70% of all smokers do see a physician each year for various reasons.³² A new national healthcare initiative, known as the National Lung Health Education Program (NLHEP), has been launched to identify and treat patients with early mild-to-moderate stages of COPD.³³ The NLHEP encourages all primary care practitioners to perform spirometric testing in smokers older than 45 years and in anyone with cough, dyspnea, wheeze, or mucus hypersecretion.³⁴ The identification of patients with heavy smoking, that is, greater than 30 pack-years and previously undiagnosed airflow

obstruction, will provide large numbers of patients who also would be candidates for lung cancer screening.²¹

As learned from the Japan experience,^{30,31} most patients identified with lung cancer by screening will have early-stage resectable lesions. Computed tomography will provide a higher yield of detection than standard chest radiography.¹⁰ Follow-up of patients with moderate-to-high degrees of dysplasia will identify even more lesions. Hopefully, this new nationwide effort plus a change of attitude about screening will identify many more patients with lung cancer so a higher cure rate can be expected, compared with the dismal outcome when lung cancer is diagnosed as an incidental finding or on the basis of symptoms, which usually represents advanced and often metastatic stages of disease.

Recent reports following an annual meeting of the American Society of Preventive Oncology argued that modern imaging for tiny, early lung cancers often reveals “indolent cancers,”³⁵ citing a doubling rate of 1 year. The presenters argued that it would take 8 years for a 5 mm lesion to grow to 3 cm. But who would be comfortable watching a known lung cancer grow over 8 years or even 1 year? At what point would metastasis occur? Spontaneous regression of a proven lung cancer has not been reported.

Conclusion

Now is the time to screen for early-stage lung cancer since it has been shown that lung cancer screening ought to work.³⁶ By using radiography, screening heavy smokers with airflow obstruction (as determined by spirometry) with sputum cytologic testing for central lesions and CT for peripheral lesions, we can then identify and harvest “the low-hanging fruit.”³⁷ In addition, the cost of curative treatment for early-stage lung cancer can be determined and such effective screening strategies for early detection and treatment of lung cancer should begin to reduce the unnecessary morbidity and mortality of lung cancer. (References are available upon request).

Editor’s (TLP) comment: The above article, reproduced in its entirety from the *JAMA* Controversies Section, advocates case finding in patients at high-risk rather than screening in the whole adult smoking population. This is consistent with our understandings of where lung cancer is most prevalent, which is in heavy smokers with any degree of airflow obstruction (Kennedy TC, et al: Cytopathological analysis of sputum in patients with airflow obstruction and

“From 1987 to 1992, the 5-year survival rate increased to 58.4%. In studies of surgery of radiographically occult lung cancer found by sputum cytologic testing, the 5-year survival rate was 80.4% for squamous cell carcinoma.”

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significant smoking histories. *Cancer Res* 1996;56:4673-4678). The advantage of lung cancer surveillance in high-risk patients, is that the yield will be predictably 2% to 5% with early stage lung cancer, within five years of initial testing. Since smokers with airflow obstruction already have an established disease, i.e., COPD, there can be little argument that a further work-up to identify comorbidities is appropriate. Thus, reimbursement issues should disappear, or at least be minimal. Virtually all patients with heavy smoking and airflow obstruction also have cough and expectoration, i.e., symptoms, seeking a remedy. Most patients with lung cancer are symptomatic with chronic cough or spirometric abnormalities leading the list (Lange P, et al: Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. *Am Rev Respir Dis* 1990;141:613-617; Tenkanen L, et al: Smoking and cardiac symptoms as predictors of lung cancer. *J Chron Dis* 1987;40:1121-1128; Escalante CP, et al: Dyspnea in cancer patients. Etiology, resource utilization, and survival-implications in a managed care world. *Cancer* 1996;78:1314-1319).

The rebuttal from a family practitioner (Frame PS: Routine screening for lung cancer? Maybe someday, but not yet. *JAMA* 2000;284:1980-1983) repeated the same, age-old argument that the controlled clinical National Cancer Institute-supported trials of the mid-1970's failed to show an improvement in disease-specific mortality. This author failed to comment on the inherent flaws of these historical studies. The fundamental flaws in these earlier studies are basically four:

1. Screening was offered to all smokers, no matter how little they smoked; only 20 cigarettes had to be smoked in the year before screening to be included,
2. Non-screened or so-called control patients often had yearly chest x-rays, and thus some level of lung cancer surveillance,
3. Subjects did not have to demonstrate airflow obstruction to be screened, and
4. Only men were screened.

Thus, these studies have not dealt with high-risk patients. Also, newer imaging technologies currently available were not yet developed in that historical era.

The most recent review article on screening for lung cancer (Patz EF, Jr., et al: Screening for lung cancer. *New Engl J Med* 2000;343:1627-1633) again presents the same arguments against screening for early lung cancer. This is a scholarly

review of the issues and nicely discusses the lead-time bias, length-time bias, and tumor biology biases inherent to all screening studies. Earlier, the same author reported that size of lesion does not equate with age of lesions. Smaller lesions may already be metastatic at time of diagnosis of lung cancer, and larger lesions may remain localized. (Patz EF, Jr., et al: Correlation of tumor size and survival in patients with stage 1A non-small cell lung cancer. *Chest* 2000;117:1568-1571). In this citation, however, excellent survival was achieved in spite of tumor size, with the actual survival of 80% at five years and the probability of further long-term survival for over 15 years, which would remain very high. The reason is that all of these cancers were stage 1A, regardless of size. **This is just the point in lung cancer testing. Find early stage lung cancer, treat it, and cure it.** In this latest review, the authors advise, "...only carefully monitored studies should enroll patients for lung cancer screening." I could not agree more.

Economic Projections (Hypothetical):

The economic prospects of targeted case finding are interesting and are presented in Table 1. In this Table, it is argued that if 200 patients with chronic airflow obstruction and heavy smoking are tested for lung cancer, at a cost of approximately \$400 per subject, it will cost \$80,000 to try to identify early lung cancer, for a yield of approximately ten patients over five years. These cost estimates are based on the projections that CT scans during low utilization times, such as evenings, could cost \$250 each. Sputum cytology may cost \$50 to \$75, and other costs, including spirometry and services of a healthcare coordinator, approximately \$75 per patient screened.

Not testing these same 200 patients costs nothing, of course. But, over five years, the same estimated ten lung cancers will emerge, of which only the one of three who will have attempts at cure will survive five years. The cost of surgery or radiation for the three salvageable patients at an estimated \$20,000 per patient, will be \$60,000. An earlier study (Hillner BE, et al: Costs of care associated with non-small-cell lung cancer in a commercially insured cohort. *J Clin Oncology* 1998;16:1420-1424) reported that the cost of palliative care in nine patients not cured is nearly \$50,000 per patient, for a total expense of \$450,000 in the patients not cured. This study of lung cancer economics was done in the mid-1990's. Thus, actual palliative costs today would probably be higher in 2001 dollars. The interim

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Table 1:
Lung Cancer
Detection in 200
High-Risk Patients
(Age > 45,
30 pack-years,
FEV₁ < 70%).

	Screened	Not Screened
Cost of screening (200 patients=200x\$400)	\$ 80,000	\$ 0
Cancers detected in 5 years	10	10
Cost of treatment (10 patients)	\$ 200,000	(3 patients) \$ 60,000
Cost of one rescreening (190 patients in 4 yrs =190x\$400)	\$ 76,000	(interim costs unknown)
Cost of yearly follow-up (8 patients cured=8x\$400x4)	\$ 12,800	(interim costs unknown)
Palliative care for patients not cured (2 patients)	\$ 100,000	(9 patients) \$450,000 or more
Total costs	\$ 468,800	\$510,000 or more
5 year survival	8	1

Table 2:
Potential Flaws in
Hypothetical
Economic Projections
Shown in Table 1.

Screened (n=200)	Not Screened (n=200)
May cost more than projections	May take >5 years
May refuse intervention	May die of non-cancer cause

“Thus, the total cost of testing for early stage lung cancer and treatment for the projected eight survivors of 200 patients, compared with no screening with a projected survival of one patient, are approximately equal, or slightly greater if a second rescreening is done.”

costs in this hypothetical untested population, is difficult to estimate, but the dollar amount could be considerable.

In this hypothetical example, the cost of treating the ten lung cancers found in early stages will be an estimated \$200,000 based upon projected surgery or radiation therapy costs. Rescreening of 190 patients on one occasion within five years would cost an additional \$76,000. With two rescreenings the costs would elevate another \$76,000, but probably more lung cancer would be found. Yearly follow-up of the 8 patients treated for cure would cost \$12,800. Based on 1990 estimates, the cost of palliative care at approximately \$50,000 per patient, would be \$100,000. Thus, the total cost of testing for early stage lung cancer and treatment for the projected eight survivors of 200 patients, compared with no screening with a projected survival of one patient, are approximately equal, or slightly greater if a second rescreening is done.

Of course, these economic considerations remain a hypothesis. They could be pursued in

any community, prospectively, however. The advantages of such a descriptive study would be to learn the true cost and outcome of early identification of lung cancer in high-risk patients compared to identification by accident or by symptoms.

Potential flaws in Table 1 above are shown in Table 2.

Five-Year Survival and Later Outcome of Patients With X-ray Occult Lung Cancer Detected by Sputum Cytology.

(Bechtel JJ, et al: *Lung Cancer* 2000;30:1-7)

Background: A cohort of 51 consecutive patients with roentgenographically occult lung cancer, identified by sputum cytology and confirmed by bronchoscopy was reported previously.

Table 3.
Second Primary Lung
Cancer Cases.

ID #	Initial Cancer Cell Type	Initial Cancer Location	Second Cancer Found After Initial Therapy	Second Cancer Cell Type	Second Cancer Location	Rx Second Cancer	Sputum	Total Survival	Status
Surgical Treatment									
R.M.	SQ	LUL	10 mos.	SQ	RUL	S	Positive	148 mos.	L
D.G.	SQ	LUL	13 mos.	SQ	RUL	S	Negative	122 mos.	L
L.D.	SQ	RUL	16 mos.	SQ	LUL	R	Positive	159 mos.	D
E.E.L.	SQ	LLL	31 mos.	SQ	LUL	R	Positive	144 mos.	D
J.H.	SQ	RUL	51 mos.	SQ	LLL	R	Positive	88 mos.	D
J. McB	AD	RLL	52 mos.	AD	LLL	R	Positive	88 mos.	D
J.P.	SQ	RUL	111 mos.	SQ	RUL	R	Positive	167 mos.	L
Radiation Therapy									
J.J.	SQ	RUL	6 mos.	OAT	BILAT	CH	Negative	7 mos.	D
D.L.	SQ	RUL	17 mos.	SQ	RUL	S	Negative	120 mos.	D
R.S.	SQ	RUL	23 mos.	AD	RUL	S	Positive	-	-
R.S.	(#3 tumor)		34 mos.	OAT	LLL	CH	Positive	40 mos.	D
J.M.	SQ	RUL	9 mos.	SQ	LLL	R	Positive	29 mos.	D

Cell type: SQ=squamous cell cancer, AD=adenocarcinoma, OAT= oat or small-cell
Rx: S=surgery, R=radiation, CH=chemotherapy
Status: L=living, D=deceased

Methods: All patients have now been followed beyond 5 years and the causes of death ascertained.

Results: The actual 5-year survival of 27 patients who were resected for cure was 74% including death for all causes. The 5-year survival of all patients who received either surgery or radiation in an attempt to cure was 54.3%. Twelve secondary cancers were found by sputum cytology; eight of these patients have died.

Conclusions: Sputum cytology can be useful in the identification of early-stage lung cancer in patients at high-risk where the chances of cure are favorable.

Editor's (TLP) comment: This is a follow-up report of the original Grand Junction study, reported in *Lung Cancer Frontiers*, 1996:2:6-7. (For the original article see: Bechtel JJ, et al: Outcome of 51 patients with roentgenographically occult lung cancer detected by sputum cytologic testing: A community hospital program. *Arch Intern Med* 1994;154:975-980). This late follow-up shows the type and location

of 12 patients with a second or third cancer from the patients in the original surgical treatment group (n=27), or radiation therapy group (n=19) (See Table 3).

Now all patients have survived beyond five years. The late survival curve of 27 subjects surgically treated, is presented in Figure 1. Those treated with either surgery or radiation are shown in Figure 2. Finally, the longest survival observation period, up to more than 180 months, is presented in Figure 3. Note that there are no late cancer deaths beyond 95 months.

This further follow-up indicates a better survival than when lung cancer is diagnosed conventionally and deals with the lead-time, length-time objection. The bottom line is that both primary and recurrent cancers can be cured when identified early. Cure is more common with surgery compared with radiation therapy.

This community-based study should not be construed as a screening study. Nearly all patients had symptoms of cough and expectoration or had an occupational exposure,

“Sputum cytology can be useful in the identification of early-stage lung cancer in patients at high-risk where the chances of cure are favorable.”

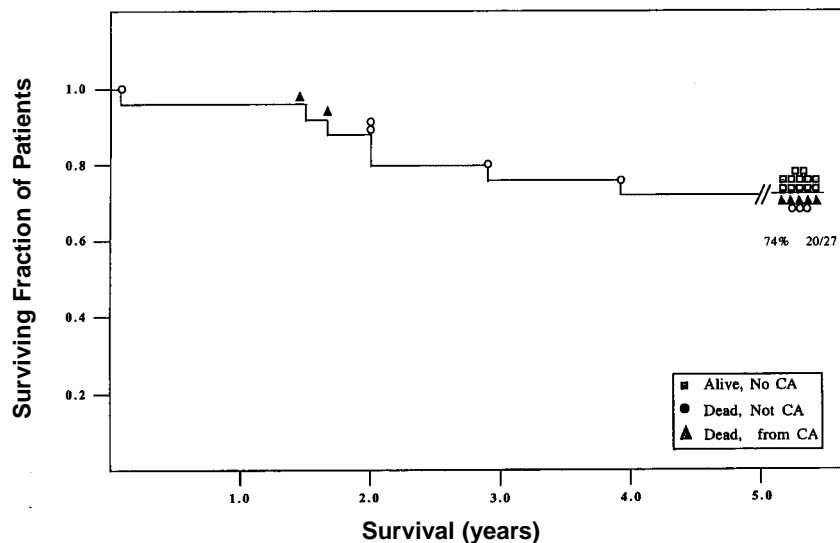


Figure 1: Survival of 27 Patients Treated Surgically.

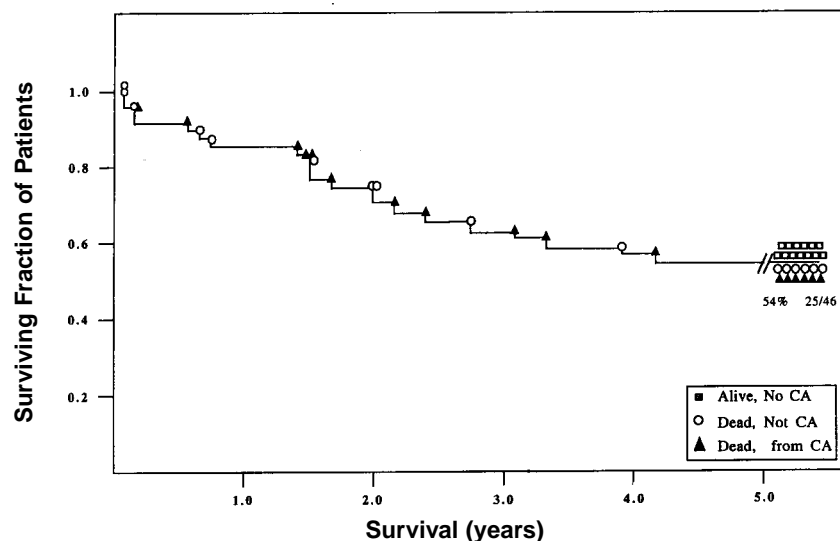


Figure 2: Survival of 46 Patients Treated With Either Surgery or Radiation.

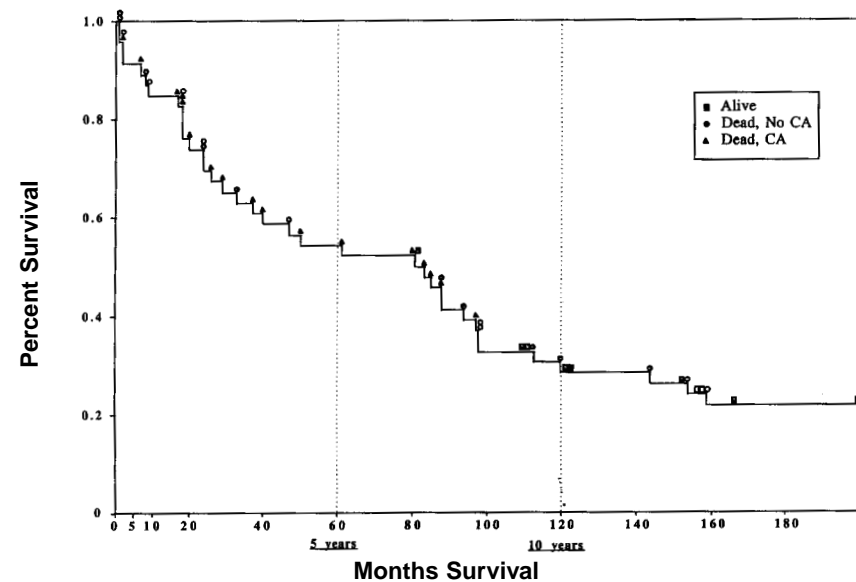


Figure 3. Long-term Survival of 46 Patients Treated With Either Surgery or Radiation.

a family history of lung cancer, or combinations. All but two were smokers. 85% had spirometric abnormalities. Thus, this is a cohort of high-risk individuals identified by sputum cytology where there was no radiographic evidence of lung cancer on standard chest x-rays. One patient had a small malignant nodule identified by CT, which was biopsied and later resected.

Historical Vignette on Mesotheliomas

Wagner made the first histological description of malignant mesothelioma in 1870. He described a case of so-called “tubercle-like” lymph adenoma of the pleura (Wagner E: Das tuberkelähnliche Lymphadenom. *Arch Heilkd* 1870;11:495-525). Five similar cases were published by Klemperer and Rabin in 1931 (Klemperer P, Rabin CB: Primary neoplasms of the pleura. A report of five cases. *Arch Pathol* 1931;11:385-412). A literature review by Saccone and Coblenz in 41 patients diagnosed from approximately 46,000 autopsies, was made later (Saccone A, Coblenz A: Endothelioma of the pleura. *Am J Clin Pathol* 1943;13:188-207). The tumor was originally referred to as an endothelioma, but discrimination of a metastatic pleural spread from a non-small cell lung cancer was not always clear. In this review, the authors mentioned a report from 1767 by Lieutaud of two similar tumors. The term “pleuroma” was first suggested, but later “mesothelioma” became the finally accepted term. An extensive report on the characterization and histogenesis as a pathogenic entity of localized pleural mesothelioma was published in 1942 by Stout and Murray (Stout AP, Murray MR: Localized pleural mesothelioma. Investigation of its characteristics and histogenesis by the method of tissue culture. *Arch Pathol* 1942;34:951-964). Since these observations, many case reports have been published, in which the difficulty of diagnosis and the occupational relationship have been discussed (Gloyne SR: Two cases of squamous carcinoma of the lung occurring in asbestosis. *Tubercle* 1935;17:5-10; Wedler HW: Uber den Lungenkrebs bei Asbestose. *Dtsch Arch Klin Med* 1943;191:189-209; Cartier P: Abstract of discussion. *Arch Indust Hyg Med* 1952;5:262).

Source: Giaccone G, Baas P: Chapter 42: Mesotheliomas. Raghavan D, et al (Eds), *Textbook of Uncommon Cancer*. 2nd Ed. 1999; John Wiley & Sons Limited. Chichester, NY. pp 523-535.

Outcome of Bronchial Carcinoma *In Situ*.

(Venmans BJW, et al: *Chest* 2000;117:1572-1576)

Introduction: The proportion of patients with carcinoma *in situ* in whom invasive cancer will develop is not known. It is important for clinical decision making to know the outcome of these lesions. The same applies for studies assessing the effectiveness of chemoprevention treatment or endobronchial therapy.

Methods: The records of patients with a bronchial carcinoma *in situ* who had undergone autofluorescence bronchoscopic examinations at regular intervals during a follow-up period for at least 6 months were reviewed. Data were examined for the outcome of carcinoma *in situ*, and for the detection, course, and bronchoscopic findings of neoplastic lesions at other bronchial sites.

Results: Progression to carcinoma occurred in five of nine patients (56%) with a carcinoma *in situ*. Eight neoplastic lesions were detected at other sites in four of the nine patients (44%). In earlier biopsy specimens of two sites that later showed a severe dysplasia and a carcinoma, only normal epithelium was found. Biopsies had been performed at these sites because they were assessed as suspicious during autofluorescence bronchoscopy.

Conclusion: The majority of sites showing a carcinoma *in situ* progressed to invasive carcinoma. A considerable portion of the patients had neoplastic lesions at other bronchial sites. The fluorescence pattern of the bronchial mucosa may reflect early changes that are not found at histopathologic examination, but which may progress to neoplastic growth.

Recent Studies of Lung Cancer Biomarkers.

A molecular biomarker workshop was held in Liverpool, England in October, 1999. Its purpose was to help develop a “European strategy for developing lung cancer molecular diagnostics in high-risk populations.” One of the important conclusions from the workshop is that now is the time to actively move toward concerted research efforts for early detection of lung cancer using both advances in imaging technologies and molecular biomarkers. Such studies may be employed on sputum or scrapings of the oral mucosa, bronchial lavage,

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and bronchial biopsies to estimate the degree of lung cancer risk in an individual, and to ultimately provide biomarkers for early identification. Biomarkers of dysplasia, which indicate premalignant clones may also help guide chemoprevention trials. The full report of this Conference will be available in a forthcoming issue of the journal, *Lung Cancer*.

A study was completed (Man YG, et al. Phenotypically different cells with heterogeneous nuclear ribonucleoprotein A2/B1 overexpression show similar genetic alterations. *Am J Respir Cell Mol Biol* 2000;23:636-645) in an effort to understand the relationship of the early detection marker, hn RNP A2/B1, with the molecular changes that have been associated with lung carcinogenesis. Using a series of 20 resected lung cancer cases, we immunostained with the monoclonal, 703D4 that recognizes hn RNP A2/B1. The entire tissue for each case was fully mapped as to the type of tissue differentiation: normal, hyperplastic, dysplastic, or neoplastic. The immunostaining status (positive or negative) was scored. All of the available regions of normal, hyperplastic, and neoplastic cells were then microdissected and extracted for DNA. All of the foci of discrete differentiation were then evaluated with a series of 14 probes that included microsatellites and allelic-loss markers to sites that have been previously reported to be associated with lung cancer.

The results demonstrated a statistically significant association of hn RNP A2/B1 expression with molecular alterations that was independent of histology. Many of the molecular events that were found in hn RNP-expressing areas of neoplastic tissue were also found in normal-appearing areas overexpressing hn RNP A2/B1. In the cases that could be analyzed by virtue of changes in the methylation status of the androgen receptor gene, the foci of tissues with these extensive molecular changes appeared to be clonal. This data strongly suggests that these areas that overexpress hn RNP A2/B1 and have multiple genetic changes are caught up in field carcinogenesis. In the discussion of this paper, we speculate that these field changes may be of more clinical significance when they occur in the setting of cells being exfoliated from the basement membrane, as opposed to when they occur in the setting of a terminally differentiated tissue.

Editorial (TLP) comment: Both CT and electron beam imaging can detect early peripheral lesions. Molecular biomarkers are needed to identify tiny malignant nodules, which may be present among many nodules, often benign, that

can be visualized with the new and ever-changing technologies. Biomarkers are also needed for central lesions that are not identified by computer imaging techniques, in order to indicate which patients should have bronchoscopic explorations to identify tiny intraepithelial central lesions. Today, accurate cytopathology is not widely available, and the value of sputum cytology varies with the experience of the cytopathologist. Automated, reliable, high-throughput sputum biomarker tests will ultimately replace cytomorphological techniques.

The Multidisciplinary Approach to Lung Cancer.

(Bensadoun ES: University of Kentucky, Lexington, KY)

There will be an estimated 164,000 new cases of lung cancer in the United States in 2000. Of all the new cases of non-small cell lung cancer, only about 25% to 30% will be diagnosed at an early stage and will be candidates for potentially curative surgery. The remainder of the new cases with locally advanced non-small cell lung cancer (stage IIIA and IIIB), and those patients with limited small cell lung cancer will receive some form of multimodality therapy consisting of surgery, chemotherapy, and/or radiation. Although early-stage lung cancer has traditionally been treated with surgery alone, a recent phase II trial showed promising results with preoperative chemotherapy (Pisters K, et al: Induction chemotherapy before surgery for early-stage lung cancer: A novel approach. *J Thorac Cardiovasc Surg* 1999;119:429-439). This led to the initiation of a prospective randomized phase III clinical trial, (The Intergroup Study S9900), comparing surgery alone to preoperative chemotherapy plus surgery in patients with stage IB, stage II, and in selected cases of stage III non-small cell lung cancer. The results of this ongoing trial may serve to broaden the indications for multimodality therapy to include early-stage lung cancer.

The future of lung cancer therapy appears to be heading towards regimens that will integrate surgery, chemotherapy, radiation, and in the not too distant future, immunotherapy, gene therapy, and other biological agents. If one accepts the notion that the care of lung cancer patients is becoming increasingly complex and often requires the input of multiple physicians, then a multidisciplinary clinic would seem to be the ideal setting for delivering this multidisciplinary care. This form of clinic, which is still relatively

new to the field of lung cancer, has been firmly established in the management of other solid malignancies.

The following brief description at the multidisciplinary lung cancer clinic at the University of Kentucky will serve as an example of this type of multidisciplinary clinic. The clinic meets once a week with thoracic surgeons, pulmonologists, medical oncologists, and radiation oncologists in attendance. New patient referrals are usually seen in the morning, while follow-up visits are in the afternoon. The new referrals are triaged to the most appropriate specialist for the initial evaluation. Following the initial consultation, the clinic physicians informally discuss the case, and if necessary, the patient can be seen by a second specialist the same morning or afternoon.

An integral part of the clinic is the multidisciplinary conference, which is held at noon on the day of the clinic. In attendance are the thoracic surgeons, pulmonologists, medical oncologists, radiation oncologists, radiologist, pathologist, and clinic nurses. Each new referral is formally presented to the group and the radiological and pathological studies are reviewed. The case is discussed with regards to diagnostic and/or treatment options, including possible eligibility for clinical trials. The treatment options sometimes follow standard guidelines. However, in certain cases, the patients fall into particular subgroups where the best treatment is not known. In these instances, patients are encouraged to participate in clinical trials. However, if no clinical trial exists or if a patient is ineligible, then an individualized plan is formulated based on the best evidence available. In addition to new cases, the follow-up of previously seen cases is also discussed with regards to postoperative staging, the need for adjuvant therapy, and the management of any treatment or disease-related complications. The multidisciplinary conference allows for the thorough review and discussion of each case, and serves to diminish the influence of individual physicians' biases on final treatment decisions.

Why establish a multidisciplinary clinic? A patient with lung cancer will often require multiple consultations before a definitive treatment plan can be formulated. These multiple visits are difficult on the patients, and the scheduling can sometimes take several weeks. In a multidisciplinary clinic setting, once a diagnosis of lung cancer has been confirmed, a preoperative evaluation can be done by the pulmonologists and the surgeon can see the patient that same day. Any further testing can be completed within a week. Surgery can often be scheduled the

following week. If the patient is not a surgical candidate, then the medical oncologist and/or radiation oncologist can see the patient that day, and a treatment plan can be decided upon and usually begun within a week. The multidisciplinary clinic setting facilitates the scheduling and coordination of any multi-modality treatment regimen, whether it is combined radiation and chemotherapy for limited small cell cancer, preoperative radiation in a patient with a superior sulcus tumor, or preoperatively chemotherapy in selected patients with locally advanced lung cancer. In addition, it allows a patient to see multiple physicians in one place and at one time and receive a treatment recommendation from a group of physicians with expertise in lung cancer that same day. This "one stop shopping" is convenient for the patient, and most importantly, should reduce the time from diagnosis to the start of definitive treatment by streamlining the consultation process.

We live in an age where patients are becoming increasingly educated as healthcare consumers and will often seek out multiple opinions before making decisions regarding their health. From a patient's perspective, the multidisciplinary clinic provides a convenient place where patients can obtain the latest information about lung cancer and have their questions answered by multiple experts in the field. Most importantly, the multidisciplinary clinic provides access to information, to state-of-the-art therapy, and to clinical trials. There are no known studies which evaluate specific outcomes as a result of participation in multidisciplinary lung cancer clinics. However, studies of multidisciplinary breast cancer clinics have shown an increase in patient satisfaction and a shorter time from diagnosis to the start of treatment (Gabel M, et al: Multidisciplinary breast cancer clinics. Do they work? *Cancer* 1997;79:2380-2384). Although based on anecdotal evidence, it is clear to this author that there are patients who have benefited greatly from this multidisciplinary consultative approach.

Once the decision to form a multidisciplinary clinic has been made, the first task is to assemble a group of physicians who have an interest in lung cancer and who can work well together. Physicians attending this clinic should include at a minimum, a pulmonologist, a thoracic surgeon, a medical oncologist, a radiation oncologist, a radiologist, a pathologist, and a palliative medicine specialist. Once each member has made a commitment to the multidisciplinary clinic, then an assessment of the other requirements for a successful clinic can be made. Essential clinic

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staff includes a nurse coordinator, nurses, social workers, a research nurse, and a data manager. A suitable location for holding the clinic is also important. The clinic should have a layout that allows for easy consultation among physicians. Once the group has been formed, it will be necessary to select a director and perhaps a co-director who will have as their main goals:

- Smooth day-to-day operation of the clinic,
- Growth of the clinic (increasing patient numbers), and
- Development of a marketing program to inform the public about the new clinic.

The overall goals of the clinic should be to:

- Provide patients with information on the latest therapeutic options for lung cancer,
- Provide access to and facilitate entry into clinical trials,
- Serve as a support system for patients and their families, and
- Function as a resource to physicians in the community.

There will be an estimated 156,900 deaths due to lung cancer in the United States in 2000. The hope is that new advances in treatment will reduce the mortality due to lung cancer. However, one should not forget the role of prevention and early detection in the fight against lung cancer. The multidisciplinary clinic should take the lead in these preventive and early detection efforts by sponsoring educational programs that increase lung cancer awareness in the community, by providing smoking cessation programs for smokers, and by promoting early detection programs. In this respect, the multidisciplinary clinic serves not only as a treatment center, but also as the focal point of a comprehensive strategy against lung cancer.

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