GENERAL THORACIC SURGERY

DETECTION OF EARLY-STAGE LUNG CANCER: COMPUTED TOMOGRAPHIC SCAN OR CHEST RADIOGRAPH?

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Objective: Computed tomography has recently been proposed as a useful method for the early detection of lung cancer. In this study we compared the stage distribution of lung cancers detected by a computed tomographic scan with that of lung cancers detected by a routine chest x-ray film.

Methods: Two groups of patients with biopsy-proven non–small cell lung cancer were reviewed. In the first group of 32 patients, the tumors were detected by a computed tomographic scan. In a second group (n = 101), the lung cancers were detected on routine chest x-ray films. Patients with pulmonary symptoms or a history of cancer were excluded.

Results: There was no difference in age, sex, or cell-type distribution between the 2 groups. A significantly greater number of patients undergoing a computed tomographic scan had stage IA disease compared with those having an x-ray film. Of the 32 patients in the group having a scan, 10 had tumors 1 cm or less in size versus 6 of 101 in the group having a chest radiograph. Additionally, there was a significant reduction in advanced stage disease in the group having a scan.

Conclusions: In this retrospective study, a higher incidence of stage IA lung cancers and significantly fewer cases of more advanced disease were observed in patients screened with computed tomography than in those having a chest radiograph. These data suggest that computed tomographic screening may be of value in improving the survival of patients with non–small cell lung cancer. (J Thorac Cardiovasc Surg 2001;121:1053-7)

Lung cancer is the leading cause of cancer deaths in North America and most of the developed world. In the United States, approximately 172,000 new cases of lung cancer were diagnosed in 1999 and 158,000 deaths resulted from the disease in the same year.[1] Despite advances in surgical, medical, and radiation therapy over the past 3 decades, the overall 5-year survival remains 10% to 12%. Most patients present with advanced locoregional or disseminated disease for which therapy is frequently ineffective. In contrast, cure rates in the 70% range are often possible in patients with stage I disease and may exceed 80% in those with tumors measuring less than 3 cm.[2] Thus, the argument for early detection and its potential impact on survival seems self-evident. Recent evidence suggests that spiral computed tomography (CT) may increase the lung cancer detection rate by 4-fold to 10-fold compared with chest radiographs and that nearly 80% of detected lesions are stage I cancers.[3,4]

In the current study, we compared the stage distribution of a group of patients with non–small cell lung cancer (NSCLC) detected by CT scans with that of patients whose tumors were detected on a routine chest radiograph.

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Methods

A retrospective chart review was performed to identify all patients referred to the thoracic surgery service with biopsy-proven NSCLC who were asymptomatic at presentation. Two

Table I. *The distribution of surgical procedures among the CT and CxR groups*

	CT	*CxR*
Mediastinoscopy only	1	2
Segmentectomy	0	1
Lobectomy	30	93
Pneumonectomy	1	5

groups of patients were identified: a group whose lesions were detected by CT scan and another by chest radiography. Patients were included in the chest radiography group (CxR group) only if their chest radiograph was obtained as part of a routine examination or before elective non-pulmonary surgery. Patients were excluded if the chest radiograph was prompted by any upper or lower respiratory tract symptoms or if they had a prior malignant disease other than non-melanoma skin cancer.

In the CT group, 16 patients were referred to one of us (N.A.) through the Early Lung Cancer Action Project (ELCAP), a bi-institutional prospective lung cancer screening program established at Weill-Cornell Medical College and New York University in 1993. These 16 patients represent part of a group of 27 patients with screen-detected NSCLC previously reported by ELCAP.[3] An additional 16 patients were referred after CT scans done outside the ELCAP protocol.

Follow-up was obtained by direct patient contact either by telephone or in our lung cancer follow-up clinic. Follow-up was also obtained from the referring physicians if direct patient contact was not possible. Follow-up was complete through April 2000 in 100% of patients in the CT group and 92% of patients in the CxR group.

Statistical analysis. Mean and SD or percentages were used to describe each variable depending on whether the variable was continuous or categorical. A 2-tailed *t* test was used to compare continuous variables. The χ^2 or Fisher exact test was used to compare categorical variables. Survival for the CxR group was analyzed by means of the Kaplan-Meier product-limit method.

Results

Patient characteristics. Between January 1995 and March 2000, 133 patients were evaluated and treated for NSCLC detected by either a chest radiograph (n = 101) or CT scan (n = 32). The median age of the entire group was 66.5 years. There were 70 male and 63 female patients. No differences in demographic features were identified between the CT group and the CxR group or between the ELCAP and the non-ELCAP referred patients.

Surgical procedures. The distribution of surgical procedures in both groups is shown in Table I. Lobectomy was carried out in more than 90% of patients in both groups. Mediastinoscopy was the only procedure done in 1 patient in the CT group and in 2 patients in the CxR group. The in-hospital mortality for the entire group of patients was 1.5% (2/132).

Pathology. Tumors with nonsquamous histologic features were seen in 91% of the CT group (30/32) and in 74% (75/101) of the CxR group (Table II). The difference approached but did not achieve statistical significance ($P = .059$).

Maximal tumor size was determined by review of the pathology report. The mean tumor size was 1.84 cm in the CT group and 3.08 cm in the CxR group ($P = .0001$). Ten patients in the CT group had tumors that measured 1 cm or less compared with 6 patients in the CxR group. The CT group had a significantly higher proportion of T1 tumors than did the CxR group.

There was no significant difference between the 2 groups in the frequency of node-negative disease (77% CT group, 68% CxR group; $P = .3$).

Stage distribution. The stage distribution for the 2 groups is shown in Table III. Eighty-one percent of the patients in the CT group had stage I disease compared with 70% of patients in the CxR group ($P = .25$). However, a significantly greater number of patients had stage IA disease in the CT scan group (62.5%) than in the CxR group (39%) ($P = .02$). Overall, there was no statistically significant reduction in the number of patients with advanced stage disease (defined as stage IIA or above) in the CT group compared with the CxR group. However, there was a significant reduction in advanced stage disease ($P = .02$) in the CT group with the inclusion of stage IB cancers within "advanced stage disease."

Survival. Overall actuarial 5-year survival in the CxR group was 42%. Five-year survival was 84% for stage IA, 55% for stage IB, and 28% for all other stages combined. With a median follow-up of only 10 months, survival data for the CT group are not yet ready for analysis.

Discussion

Recent reports have suggested that CT may hold great promise in the detection of early-stage lung cancer compared with chest radiography.[3,4] In the ELCAP trial, 1000 participants were recruited over a 5-year period and screened by low-dose CT scans. Twenty-seven NSCLCs were detected on the baseline screen, of which only 7 were visible on a plain chest radiograph. Significantly, more than 80% of patients had stage IA disease.[3] A study from Japan, where lung cancer screening has been used over the past decade, showed that the lung cancer detection rate by CT scan was nearly 10-fold higher than that achieved by chest x-ray films.[4]

Table II. *Tumor histology among the CT and CxR patients*

	CT		*CxR*	
	No.	*%*	*No.*	*%*
Squamous	3	9	26	26
Adenocarcinoma	23	72	58	57
Bronchoalveolar	6	19	5	5
Large cell	—	—	6	6
Undifferentiated	—	—	6	6
Nonsquamous (overall)	29	91	75	74

Table III. *Stage distribution among the CT and CxR patients*

	CT		*CxR*	
	No.	*%*	*No.*	*%*
IA	20	62.5	39	38.6
IB	6	18.7	32	31.6
IIA	2	6.2	8	7.9
IIB	0	—	4	3.9
IIIA	3	9.3	16	15.8
IIIB	1	3	1	—
IV	0	—	1	—

In the present series, we have shown that patients in the CT detection group had significantly smaller tumors (1.8 vs 3.0 cm) than those in the CxR group. Additionally, 63% of patients in the CT group had stage IA disease in comparison with 39% in the CxR group. Since the 5-year survival of stage IA NSCLC frequently exceeds 80%, the detection of smaller and earlier stage tumors in the CT group is a significant finding.

However, these data should be interpreted with caution because of a number of factors. The present series is a retrospective study with its attendant limitations. The possibility of a selection bias in either group cannot be reasonably excluded. As previously stated, the patients in the CT group do not represent an entirely homogeneous group. Approximately 50% were referred through a well-designed screening protocol and the remainder represent random non-study cases. Similarly, patients in the CxR group are a highly selected group whose stage distribution may well have been different had they been referred through a CxR screening program. Only a well-designed prospective screening protocol can reliably resolve these issues.

Ideally, the detection of earlier stage disease will translate into improved survival for patients with NSCLC. However, the anticipated survival benefit may reflect lead-time bias or over-diagnosis. Lead-time bias can be addressed only after survival data in the CT group have matured sufficiently to allow meaningful conclusions. Over-diagnosis implies that early detection uncovers slow-growing, indolent tumors that may never present a serious clinical menace. Conceptually, the idea of NSCLC behaving in a "benign" way is anathema to nearly all clinicians dealing with this disease. The issue of over-diagnosis has been elegantly addressed by Flehinger, Kimmel, and Melamed,[5] who collected data on all patients with stage I disease detected in 3 randomized trials for lung cancer screening sponsored by the National Cancer Institute.[6-8] Although the majority of stage I tumors were surgically resected, a number of patients (n = 45) either declined or were not offered resection because of medical ineligibility. Five-year survival for surgically treated patients with stage I cancer was 70%, whereas it was only 10% for the medically treated patients; nearly 80% of deaths in the latter group were related to lung cancer. The authors noted that if "dormancy" was a biologic feature of NSCLC, the surgically and nonsurgically treated patients would have had similar survivals.

In the current series we have observed a significant reduction in advanced stage disease (stage IB and above) in the CT group compared with the CxR group. These data suggest that CT screening may be of benefit in improving the survival of patients with NSCLC.

Currently, no recommendations exist for screening for lung cancer, either with sputum cytology or with plain chest radiography. This policy is largely based on 3 clinical trials whose results were reported almost 2 decades ago. Two of these studies reported no additional benefit for sputum cytology as a screening modality compared with chest radiography alone.[7,8] The third study (The Mayo Lung Cancer Project) resulted in a recommendation against radiographic screening for lung cancer.[6] However, flaws in the design and execution of this study have called into question the validity of its final conclusion. The findings from the recently published ELCAP trial suggest that low-dose CT scanning may be of substantial benefit in screening high-risk groups for lung cancer. The cost-effectiveness of large-scale screening for lung cancer with CT scans is unknown at present. This important issue should be addressed in a large, population-based trial before a clear recommendation for CT screening can be advocated.

The overlap in patients and authors not withstanding, this report represents work by its authors only. The methods and conclusions presented here are not those of the ELCAP investigators as a whole.

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Discussion

Dr Joseph S. Friedberg *(Philadelphia, Pa).* Dr Altorki, the conclusion of your abstract states that CT scans yield a higher incidence of stage IA and significantly fewer patients with more advanced disease than that achievable by chest radiography. This statement is supported by the ELCAP study and other published reports but, from a scientific standpoint, I am not sure your data support this conclusion. Your study was a retrospective review of patients with biopsy-proven lung cancer initially detected by either CT or chest radiography. Your statistics indicate that the mean size difference in the nodules detected by the 2 modalities was significantly different. However, the actual mean size is basically 2 cm for the CT nodules and 3 cm for the chest radiography nodules. Thus, my first question is this: Did any of the patients with nodules detected by CT scan also have chest radiograms and, if so, what percentage of those patients had nodules visible on CT but not on chest radiography? Only a demonstration that the stage IA tumors were visible on CT but not on plain chest films would support your conclusion that the CT scans were responsible for this finding.

In support of your argument, however, are observations we have made at the University of Pennsylvania with respect to incidental nodules found in patients evaluated for lung volume reduction surgery. Since 1995, approximately 250 patients have been set up for this procedure. This group of patients had an average smoking history of 30 to 60 pack-years and were otherwise similar to your group of patients with lung cancer. All of these patients had both chest radiographs and CT scans. Twenty-six of the 250 were found to have suspicious nodules by radiographic criteria and, to date, 23 have undergone excisional biopsies. Unlike other reports, only 4 of the 23 nodules were cancer and the remainder were predominantly *Mycobacterium avium intracellulare* infections or scars. Two thirds of the 26 nodules were visible only on CT scan and not on plain chest radiographs, including 3 of the 4 primary lung cancers. To a great extent, this was a function of the small size of the nodules, many less than 1 cm. Thus, in effect, approximately 10% of this high-risk group had suspicious radiographic findings on CT scan, of which only a third were visible on plain films. Approximately 2% had lung cancers, of which only one quarter were identified on plain chest x-ray films. In this setting, all radiographs were nonspecific, but the CT scans certainly proved more sensitive than plain chest x-ray films as a screening test.

In this day and age, a major issue is cost. Given that you only reviewed patients who were sent for surgical resection, we have no idea how many patients were screened and what the incidence was of benign nodules detected by the screening. Could you tell us approximately how many patients were screened or subjected to biopsy for benign disease for every cancer detected? Roughly, what sort of cost per tumor detected would you estimate for each modality?

To prevent prohibitive expense, what criteria do you recommend as an indication for CT screening, and can you foresee any supplemental assays to increase the specificity of radiographic screening?

The National Cancer Institute issued a press release on April 11, 2000, which is aimed at addressing questions regarding the current status of CT screening for lung cancer. It states: “Promising evidence from several studies shows that the scans can detect small lung cancers, but detecting these early tumors has not been proven to reduce the likelihood of dying from lung cancer, the gold standard for any cancer screening test.” On the other hand, I would concur with the statement from your manuscript that “the argument for early detection and its potential impact on survival seems self-evident.” That said, however, you do report 3 of 32 cancer-related deaths for your patients with CT-detected lung cancers at a median follow-up of 10 months. Although this statistic in and of itself is not significant, I think it does support the National Cancer Institute’s call to establish increased survival as the bottom line.

Dr Altorki. Dr Friedberg, thank you for your comments. You posed several questions and I will try to answer them all.

You first asked whether these lesions were also visible on a chest x-ray film. I can answer that question in 2 ways. One is to say that our ELCAP series, which is not the subject of the present report, showed that lung cancer was visible on chest films in only 7 of the 27 patients with lung cancer. In the current series, some of the patients in the CT group did not have chest x-ray films, so it is hard for me to answer your question specifically.

You inquired about the overall denominator of the patients screened and how many had benign lesions. Again, I stress, this is not a screening study. The screening study by ELCAP comprised 1000 patients. Two hundred fifty were found to have nodules, and 27 of them had cancer. The great majority of the nodules that you see on a CT scan are going to be benign nodules, and the number of cancers you find will vary depending on the entry criteria and how strict you are with respect to the population being screened. If you look at the population screened in Japan, where the minimal age is 40 years to enter the screening study, the incidence of cancer will be much lower than in our studies. Our own age limit is 60 years, because we try to focus on the relatively high-risk population.

The cost issues are obviously very important. The low-dose fast CT screen can be done at our institution for close to $200. I think that as the technology improves, the cost will decrease further.

The issue about whether or not screening will improve survival is both a medical and a political issue. I will not discuss the political issues. However, the main argument presented by the epidemiologists and statisticians is that lung cancer detected at an early stage may be cancer that might not otherwise be a clinical menace. I think few physicians in this room believe that statement to be true. It is important that we address the argument from the standpoint of advanced disease, because advanced disease is not going to be subject to a lead-time bias or an over-diagnosis bias. If the disease detected by CT is less advanced, then fewer patients will die. I think CT scanning will prove to be an effective screening modality.

Dr Hani Shennib *(Montreal, Quebec, Canada).* Did you evaluate the pathologic staging of your cancers? Have you seen an upstaging or downstaging in comparison with what you have noted on a chest radiograph and a CT scan? Is there a difference in the upstaging between a CT scan and a chest x-ray film?

Dr Altorki. I have not looked at that, because we used the pathology report to measure the tumor size. The data are obviously available, but I cannot comment on them.

Dr E. Carmack Holmes *(Los Angeles, Calif).* I just want to remind you of some data from the Lung Cancer Study Group, 821 study, in which about 800 patients with T1 N0 lesions detected by chest x-ray films were randomized to receive lobectomy or less than lobectomy. In this population with lesions measuring 1 cm or larger, detected on chest x-ray films, more than 50% had benign lesions at the time of thoracotomy. That speaks to the issue here. I think lesions that are detected by spiral CT and are less than 4 or 5 mm in diameter are probably going to have a much higher incidence of benignity than the experience in the Lung Cancer Study Group.

Dr Altorki. That is an important point. As we explore this modality further, as I believe we should, we need to establish the criteria for operating. Obviously if every nodule seen results in an operation, then the cost and disadvantage to the patient will be tremendous.