Early Lung Cancer Action Project: A Summary of the Findings on Baseline Screening

CLAUDIA I. HENSCHKE, a DOROTHY I. MCCAULEY, b DAVID F. YANKELEVITZ, a DAVID P. NAIDICH, b GEORGEANN MCGUINNESS, b OLLI S. MIETTINEN, a,c DANIEL LIBBY, a MARK PASMANTIER, a JUNE KOIZUMI, a NASSER ALTORKI, a JAMES P. SMITHa

aNew York Presbyterian Hospital-Weill Cornell Medical Center, New York, New York, USA; bNew York University Medical Center, New York, New York, USA; cMcGill University, Montreal, Canada

Key Words. Early Lung Cancer Action Project · CT screening

ABSTRACT

Purpose. The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low radiation dose computed tomography (low-dose CT) in persons at high-risk for lung cancer.

Methods. Since starting in 1993, the ELCAP has enrolled 1,000 asymptomatic persons, 60 years of age or older, with at least 10 pack-years (1 pack per day for 10 years, or 2 packs per day for 5 years) of cigarette smoking, no prior cancer, and medically fit to undergo thoracic surgery. After a structured interview and informed consent, baseline chest radiographs and low-dose CT were obtained on each subject. The diagnostic work-up of screen-detected noncalcified pulmonary nodules (NCN) was guided by ELCAP recommendations which included short-term high-resolution CT follow-up for the smallest nodules.

Baseline Results. On low-dose CT at baseline compared to chest radiography, NCN were detected three times as commonly (23% versus 7%), malignancies four times as commonly (2.7% versus 0.7%), and stage I malignancies six times as commonly (2.3% versus 0.4%). Of the 27 CT-detected cancers, 96% (26/27) were resectable; 85% (23/27) were stage I, and 83% (19 of the 23 stage I) were not seen on chest radiography. Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCN; 27 had a malignant and one a benign NCN. Another three individuals underwent biopsy outside of the ELCAP recommendations; all had benign NCNs. No one had thoracotomy for a benign nodule.

Conclusion. Baseline CT screening for lung cancer provides for detecting the disease at earlier and presumably more commonly curable stages in a cost-effective manner.

The Oncologist 2001;6:147-152

INTRODUCTION

In the United States, the cure rate of lung cancer is a dismal 10%, and the 5-year survival rate is only slightly higher than the cure rate. In stage I lung cancer, by contrast, the 5-year survival rate upon resection is as high as 70%; but if left unresected, that rate is again of the order of a mere 10% [1, 2]. While these rates imply that the cure rate of lung cancer can be substantially enhanced by screening and its associated earlier intervention, results of randomized trials have been interpreted as indicating that this is not the case [3].

This paradox points to the possibility that the negative results of the randomized trials were a consequence of flaws in their design, execution and/or analysis. To quantify the full effect of screening in a randomized trial, the experimental regimen of screening and early intervention is to be contrasted with no screening; close adherence to these regimes is to be achieved in the implementation of the protocol; the analysis is to focus on the ratio of the respective rates of death from lung cancer in the relevant subsegment of the total period of follow-up in which the full effect of screening and early intervention can be expected to prevail [4]. These requirements were not met in the one and only randomized trial that contributed to the various authoritative recommendations against roentgenographic (CXR) screening for lung cancer [3]. In that trial [5], the experimental regimen of CXR screening every 4 months was contrasted with the routine Mayo Clinic recommendation, which at that time...
was to perform annual screening for high-risk persons; the rates of adherence to these two regimens were about 75% and 50%, respectively [6], and the analysis never focused on the relevant subsegment of follow-up. Moreover, the experimental regimen of quarterly screening in the Mayo study was so weak that it led to the detection of resectable malignancy in only 29% of the cases of lung cancer [5].

Our review of the previous studies of lung cancer screening led us to the conclusion that resection of screen-detected early-stage lung cancer commonly is curative, and that this has already been demonstrated beyond question [1, 2, 4]. Inspired by the enhanced potential of computerized tomography (CT) in screening for lung cancer, we developed the study design to assess the usefulness of annual CT screening for lung cancer in 1992 [7] and started baseline screening in 1993. The principal objective of the Early Lung Cancer Action Project (ELCAP) was to assess the extent to which the screening shifts the distribution of diagnosed cancers toward smaller sizes and thus toward earlier stages. We refer to this as the diagnostic mission. An added major objective, the interventive mission, was to quantify the curability of lung cancer as it depends on tumor size and disease stage at diagnosis. Both of these objectives may be taken to refer to all lung cancers diagnosed under screening, irrespective of whether the diagnosis actually is prompted by the screening or interim symptoms. The diagnostic and interventive components jointly determine the overall rate of curability for cases detected under screening. To us, therefore, the real question remaining to be answered by the ELCAP is whether the diagnostic shift towards smaller and earlier-stage lung cancers and the resultant gain in curability are large enough to provide for cost-effective screening, given suitable specifications of both the screening regimen and its recipients.

The results of baseline screening have been published in The Lancet [8]. Here we present a summary review of these findings.

**Enrollment**

Enrollment into the ELCAP was confined to a cohort of 1,000 persons (522 at Cornell University Medical College and 478 at New York University Medical Center), 60 years of age or older with a history of at least 10 pack-years of cigarette smoking, no history of cancer (other than nonmelanotic skin cancer), and fit to undergo thoracic surgery. Fit to undergo thoracic surgery means that the candidate does not require oxygen and can hold his/her breath for up to 20 seconds while obtaining the CT scan.

Baseline screening, initiated in 1993, was completed in 1998. Of the 1,000 persons at high risk for lung cancer that were enrolled, 46% were females, 54% males; 91% were white, 5% African-American, and 2% Hispanic (2% other).

Median age at admission was 67 years, the median number of pack-years of smoking was 45, and the history of asbestos exposure was positive in 14%.

**The Screening Test**

The screening test was defined in terms of the equipment, how the images are viewed, and by whom they are read. Finally, the definition of the test also includes the results, both positive and negative for the test.

At baseline, a posterior-anterior and lateral standard CXR was obtained using Insight (Kodak; Rochester, NY) film. At baseline, low-dose CT (LDCT) images were obtained using a HighSpeed Advantage scanner (GE; Milwaukee, WI) film. At baseline, low-dose CT (LDCT) images were obtained using a HighSpeed Advantage scanner (GE; Milwaukee, WI) at 140 kVp, 40 mA, 2:1 pitch with a collimation (slice thickness) of 10 mm. The images, covering the entire lung region, were acquired in a single breath-hold at end-inspiration following hyperventilation, and they were reconstructed with overlapping 5-mm intervals.

While images were initially read on film, 12 images per film, the readings were done on monitors once they became available with the images being viewed one at a time using maximum magnifications. Two dedicated chest radiologists, each one blinded to the reading of the other, read the images. The respective findings with regard to the presence and number of nodules were separately recorded and then discussed, and the consensus findings were documented for the study. When the two readers could not reach a consensus, the case was presented to a third expert reader, and the adjudicated reading became the final one.

A positive test result at baseline was defined as the presence of one to six noncalcified nodules (NCN). If no NCN were identified, the result was classified as negative. Instances of more than six NCN, diffuse bronchiectasis and/or ground-glass opacities were classified as diffuse disease.

For all instances of positive results, defined characteristics of the relevant nodules were recorded: size (length and width), location (lobe), and calcification (benign, other). A nodule was classified as noncalcified if it did not show a “benign pattern of calcification” [9]. The following definitions were used: size was defined as the average of length and width.

Other measures were also obtained, but not analyzed for purposes of this paper. They were: distance from the costal pleura, shape (round, non-round), edge (smooth, non-smooth), and texture (pure ground-glass, other); location as peripheral if any part of the nodule was within 2 cm of the costal margin, otherwise central; shape as round if the nodule’s width-to-length ratio was greater than two-thirds, otherwise non-round; and texture as pure ground-glass if the nodule did not obscure the lung parenchyma and had no solid component, otherwise “other.”
POST-TEST WORK-UP

Recommendations were made for the work-up of positive results of baseline and annual repeat screening. However, it was not a requirement for the validity of the ELCAP that these recommendations be followed, as long as the final diagnosis became firmly established. Thus, the decision as to how to proceed was left to the referring physician, and the actual work-up was recorded. If malignancy was diagnosed and resectable, lobectomy was coupled with complete mediastinal lymph node dissection and labeling of all lymph node stations, and the inflated lung was palpated for any additional nodules. All cytologic and histologic findings from any biopsy or surgical procedure were documented.

For the instances in which NCN were detected on the baseline LDCT, additional deployment of a standard-dose, diagnostic CT scan of the chest with high-resolution imaging (HRCT) of the nodule(s) was recommended for management purposes. For all nodules detected on HRCT, the same nodule characteristics previously specified were documented. If the HRCT demonstrated benign calcifications not identified in the LDCT, both in terms of extent and distribution, in a nodule with smooth edges whose size was less than 20 mm, the nodule was considered to be benign.

If those criteria were not met by all of the NCN detected in the subject, the ELCAP protocol recommended further work-up according to the size of the largest nodule:

A) For NCN 5 mm or less in size (average of length and width), follow-up by HRCT 3 months later, and given no growth, at 6, 12, and 24 months. If no growth was noted over 2 years, the nodule was considered to be benign.

B) For NCN 6-10 mm in size, assessment on a case-by-case basis of the possibility of obtaining a biopsy using either percutaneous transthoracic CT-guided fine-needle aspiration or video-assisted thoracoscopic biopsy procedures. For instances of no biopsy, follow-up for growth, as described above.

C) For NCN 11 mm or more in size, biopsy according to current standards of care, by fine needle aspiration, video-assisted thoracoscopy, bronchoscopy, or a combination of these.

RESULTS

Chest radiography found 68 subjects with one to six NCN, among whom fewer than half (33) actually had a nodule on LDCT. The remaining 35 subjects had false-positive chest radiography-detected nodules as they were not real but merely apparent ones caused by a confluence of shadows. LDCT identified 233 subjects as having one to six NCN; in only 33 of these subjects was the nodule(s) also apparent on chest radiography.

Following the ELCAP recommendations, biopsies were performed on 28 of the 233 subjects with NCN; 27 had a malignant nodule and one had a benign one. Another three individuals underwent biopsy outside of the ELCAP recommendations; all had benign nodules. No one had thoracotomy for a benign nodule. The diagnostic work-up was based on the size and appearance of the nodules. Those of suspicious appearance with non-smooth edges, for the most part NCN 10 mm or larger in size, were identifiable on the LDCT or baseline HRCT, and immediate biopsy was confidently recommended for these. In smaller nodules, documented growth was recommended as a prerequisite for biopsy, based on follow-up HRCT when compared with baseline HRCT. Additionally, given the concern about overdiagnosis, that is, the detection of malignancies whose growth is so slow that death is caused by diseases other than lung cancer, we determined growth per se, as well as the rate of growth in the smaller malignancies, using careful HRCT measurements [10, 11]. The growth rate of the smaller malignancies was all within the known range for malignant tumors of the lung [12-14] (Fig. 1).

Among the 233 subjects with one to six NCN found on LDCT, 27 (12%) had a nodule-associated malignancy. Among the 68 subjects with one to six NCN found on chest radiography, only seven (10%) were found to have a malignancy; therefore, 20 (74%) of the CT-detected malignancies were not seen on chest radiography. On the other hand, all of the chest radiographic-detected malignancies were detected on LDCT. Of these 27 CT-detected malignancies, 85% (23) were stage I and 83% (19/23) of them were missed on chest radiographs. The sizes of the CT-detected malignancies were 2-5 mm for one, 6-10 mm for 14, 11-20 mm for eight, and greater than 20 mm for four.

Pathologically, one of the nodule-associated malignancies was classified as an atypical carcinoid, one as a squamous-cell carcinoma, three as mixed squamous-adenocarcinoma, three as bronchioloalveolar carcinoma, two malignancies (in one lobe) were found in one person, one of them classified as adeno-squamous carcinoma and the other as bronchioloalveolar carcinoma, and the remaining 18 were classified as adenocarcinoma.

DISCUSSION

In summary, on baseline screening, NCN were detected three times as commonly (23% versus 7%), malignancies four times as commonly (2.7% versus 0.7%), and stage I malignancies six times as commonly (2.3% versus 0.4%). Careful assessment of growth, and more particularly, growth rates prior to any invasive procedures permitted identification of
Figure 1. HRCT obtained at time of initial detection of the left upper lobe NCN (A). Repeat HRCT of the nodule obtained 20 days later (B). Three-dimensional reconstruction of the nodule at time of the initial CT (C) and three months later (D). Initial volume was 240 mm$^3$ and on repeat CT, it was 314 mm$^3$, a marked change of 31% when compared with the normal variation of 2%. The resulting doubling time was 51 days. The growth is best documented by viewing the nodule at both times on the same grid (E).
the malignancies without anyone undergoing lobectomy for benign disease. We thus showed that baseline screening markedly enhanced the detection of small NCN and confirmed our expectation that, relative to traditional chest radiography, CT-based screening markedly enhances the detection of lung cancer at earlier and more curable stages relative to what is known to prevail in the absence of screening.

The diagnostic distribution was markedly shifted toward earlier stages and smaller sizes as we found 22 (80%) of the 27 nodule-associated malignancies to be of stage IA. This is in marked contrast to 7% of all those diagnosed with lung cancer as seen by the cases in the End Results and Surveillance Registry, a national registry sponsored by the National Cancer Institute. The mobile CT screening study by Sone et al. [15] also showed that LDCT markedly enhanced the detection of malignancies; 10 times as many were detected on CT as on CXR. Their overall malignancy rates were lower than ours, predominately due to the fact that they screened individuals from the general population, not high-risk people.

Translation of this diagnostic distribution to its corresponding overall rate of curability under screening requires information on the stage- and size-specific rates of curability. The 5-year survival rate of stage IA non-small-cell malignancies of size less than 20 mm, detected by CT, has been reported to exceed 90% [16, 17] suggesting a curability rate of these malignancies in excess of 80%. Curability of the screen-detected small but later-stage non-small cell and limited stage small-cell malignancies is yet to be quantified.

As these results and inferences mainly pertain to very small lesions, the question of overestimation on the grounds of potential “overdiagnosis” is prone to arise. Convincing evidence against overdiagnosis for lung cancer detected by traditional radiography was given by Flehinger et al. [1] and Sobue et al. [2]. But as the CT-detected lesions are distinctly smaller, the concern remains legitimate; and indeed, it was a concern of ours. In an effort to avoid the problem, we naturally have been very careful with the pathologic (cytologic and histologic) criteria for rule-in diagnosis of malignancy; but beyond this, we had interim growth in all cases, and this was supplemented by documentation of further growth before biopsy. As it turned out, all cytologic diagnoses of malignancy (rule-in) were confirmed by the histologic specimens from surgery; and further, all of the calculated rates of growth were in accord with those of definite cancers of the lung [12-14]. Ultimately, once there are sufficiently many cases that, for various reasons, were not resected within the ELCAP and its “sister” projects, it will be possible to empirically estimate the proportions overdiagnosed (specific to size), if any.

Following the ELCAP recommendations, only a single biopsy of a benign NCN, 18 mm in size, was performed. Another three subjects underwent biopsy despite the ELCAP recommendations for follow-up HRCT as no growth could be documented, and all of these had a benign nodule. No subject had lobectomy for a benign NCN. Thus, our recommendations, intended to prevent overuse of invasive procedures and their attendant morbidity and cost, turned out to be quite successful.

For evaluation of annual CT screening for lung cancer, our baseline results must be supplemented by the results of annual repeat LDCT screenings in the subjects in whom no malignant nodules were detected on baseline screening. This will provide data on the frequency of finding new nodules, the frequency with which these are malignant, and, eventually their cure rate. We expect to find few instances of new nodules with a rate of about five malignancies per 1,000 subjects on each 1-year repeat CT screening, with the majority of these in nodules whose size is 10 mm or less. We are pursuing this repeat screening in all subjects whose baseline screening was negative or positive with a diagnosis of benign nodules.

We plan to incorporate smoking cessation programs into our future screening program, as we found that review of the LDCT with those subjects who were still smoking provided considerable motivation for smoking cessation [18]. Additional considerations for future investigations, in conjunction with future CT screenings, include chemoprevention and perhaps even chemotherapy, possibly administered by inhalation rather than oral or intravenous methods.

Even if a given regimen of CT screening for lung cancer, perhaps a variant of the one addressed in the ELCAP, serves to raise the overall rate of curability for lung cancer among the screenees, this does not in and of itself justify the use of that regimen of screening. It needs to be applied on indications such that the prospect of early diagnosis and its associated curability translate to a gain in life expectancy sufficient to justify the cost of the “screening” that is, of the screening test together with the result-contingent definitive diagnostics. The issues here are somewhat complex, but it is evident that, with suitable specifications of both the screening and its recipients, the cost of life-year saved can be as low as $10,000 or even lower [19]. Such a cost per life-year saved is well below that for existing programs of screening for breast cancer [20] or cervical cancer [21] and well below the benchmark of $50,000 used in the U.S.

The particulars of potential screening for lung cancer constitute, at present, an actively evolving topic in respect to all of its principal elements—the screening test(s), the diagnostic work-up of screening positives, intervention on early cancer, and identification of suitable candidates for
screening. The accruing evidence from the ELCAP and others [22], while still insufficient, is continuing to heighten the prospects for cost-effective screening for the cancer that is now the main cause of cancer deaths in both genders.

REFERENCES


ACKNOWLEDGMENT

Supported in part by Eastman-Kodak Corporation, General Electric Corporation (New York, NY), and National Cancer Institute grant (R01-CA-63393).