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Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

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In 1993, the Early Lung Cancer Action Project (ELCAP) initiated a study of the early diagnosis of lung cancer in cigarette smokers with the use of annual screening with spiral computed tomography (CT).[1,2] The principal finding was that more than 80% of persons given a diagnosis of lung cancer as a result of annual CT screening had clinical stage I cancer.[3] This result has been confirmed by others[4] who have adopted the updated protocol.[5,6] The question remains, however, whether early intervention in such patients is sufficiently effective to justify screening large asymptomatic populations who are at risk for lung cancer.[7,8] We report the results of all patients in the study with stage I lung cancer detected with the use of spiral CT screening, including those who underwent surgical resection.

METHODS

Screening was defined according to the International ELCAP (I-ELCAP) protocol[6] so that data from participating institutions could be pooled. Each institution was required to document the initiation of screening in each participant and all subsequent screenings of that participant for as long as the screening continued, transmit the data and images to the coordinating center at Weill Medical College of Cornell University by means of the study's Web-based management system for CT screening for lung cancer,[9] submit pathological specimens to the coordinating center, and follow quality-assurance procedures specified by the protocol. All participants gave written informed consent, and the institutional review board at each participating institution approved the protocols (Fig. 1).

The protocol specified a common regimen of screening but allowed each participating institution to specify its criteria for enrollment. The regimen included the technical variables for the initial low-dose spiral CT scan, which were the same for the baseline and annual screenings. However, the definition of a positive result on the initial CT scan and the diagnostic workup leading to a diagnosis of lung cancer were different for the baseline screening and annual screening.

For baseline screening, a positive result on the initial low-dose CT scan was defined as the identification of at least one solid or partly solid noncalcified pulmonary nodule 5 mm or more in diameter, at least one nonsolid noncalcified pulmonary nodule 8 mm or more in diameter, or a solid endobronchial nodule.[10] If none of the noncalcified nodules identified met the study criteria for a positive result or if the test was negative, CT was repeated 12 months later. The diameter of the nodule was defined as the average of the length and width of the cross-sectional area of the largest nodule in the CT images. The consistency of the nodule was defined as solid if the nodule obscured the entire lung parenchyma, partly solid if it obscured part of the lung parenchyma, and nonsolid if it obscured none of the parenchyma.[11] If the result was positive, the type of workup depended on the diameter of the largest nodule. For nodules 5 to 14 mm in diameter, the preferred option was to perform another CT at 3 months; if the images showed growth of the nodule,[12] then biopsy, ideally by fine-needle aspiration, was to be performed, whereas if there was no growth, the workup was stopped. The other option was to perform positron-emission tomography (PET) immediately, and if the results were positive, biopsy was to be performed; otherwise, CT was to be performed at 3 months. For nodules 15 mm in diameter or larger (whether solid, partly solid, or nonsolid), immediate biopsy was an option in addition to the options already specified for smaller nodules. When infection was suspected, a 2-week course of antibiotics followed 1 month later by CT was an alternative to all the options mentioned,[13] and if no resolution or growth was observed, biopsy was to be performed; otherwise, the workup was stopped. For all participants for whom the workup was stopped or for whom the biopsy did not lead to a diagnosis of lung cancer, CT was to be repeated 12 months after the baseline CT.

For annual screenings, a positive result was considered to be any newly identified noncalcified nodule, regardless of size. If no new nodule was identified, CT was to be repeated 12 months later. If one or more new nodules were identified, the workup depended on the diameter of the largest nodule. If all nodules were less than 3.0 mm in diameter, or if the largest nodule was more than 3.0 mm but less than 5.0 mm in diameter, CT 6 or 3 months later, respectively, was to be performed. If no growth was seen in any of the nodules, the workup was stopped. If at least one of the noncalcified nodules was 5.0 mm or larger in diameter, then an immediate 2-week course of a broad-spectrum antibiotic was prescribed, followed 1 month later by CT. If the nodules showed no

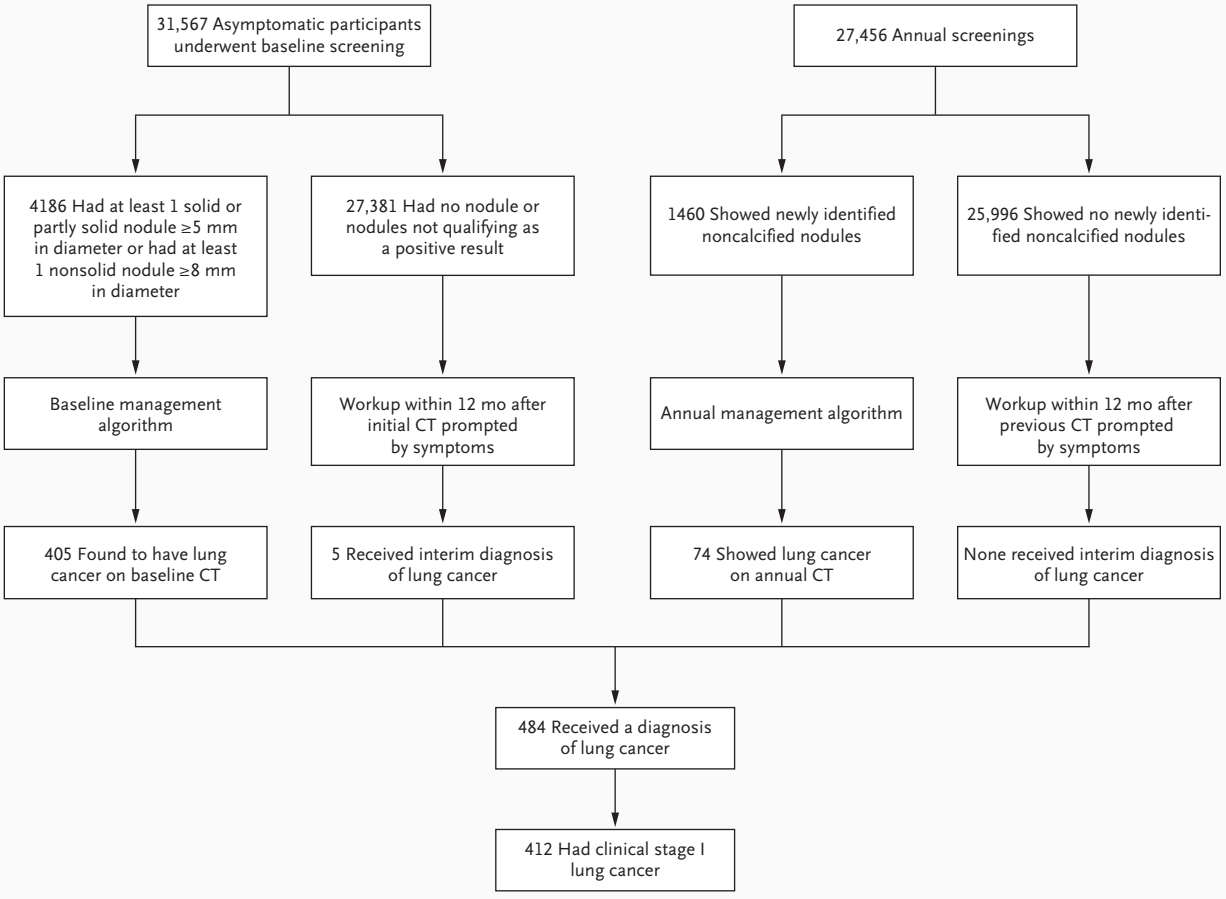


Figure 1. Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT.

A description of the I-ELCAP management algorithm for baseline CT and repeated CT screening is available in the study protocol.[6]

resolution or growth, biopsy was to be performed; otherwise, the workup was stopped. PET was an alternative to immediate biopsy; if the result was positive, biopsy was to follow. If the result was indeterminate or negative, CT was to be performed 3 months later, and if the scans showed growth, biopsy was to follow. Otherwise, the workup was stopped. For all patients for whom the workup was stopped or when biopsy did not result in a diagnosis of lung cancer, CT was to be repeated 12 months after the previous annual CT.

The protocol provided recommendations for the diagnostic workup in participants with a positive result on CT, with the decision regarding how to proceed left to each participant and the referring physician. The I-ELCAP protocol did not require that its recommendations for the workup of a nodule be followed, but it did require a firmly established final diagnosis of lung cancer and documentation of the workup in the management system. After the diagnosis of lung cancer was established, the type of intervention, if any, was left to the discretion of the participant and the physician. Documentation in the management system of the timing and type of intervention, if any, and follow-up with respect to manifestations of spread or death up to 10 years after diagnosis, were required.

A total of 31,567 asymptomatic men and women underwent baseline screening between 1993 and 2005 (median, 2001). The participants, who were 40 years of age and older, were at risk for lung cancer because of a history of cigarette smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to secondhand smoke without having smoked themselves; in Azumi, Japan, they participated as part of the annual health screening program (Table 1). All partici-

Table 1. I-ELCAP Participants, According to the Smoking Status, Exposure to Secondhand Smoke, and Occupational Exposures.

Program	Participants (N=31,567)
	no. (%)
Azumi Health Care Program in Japan	
Current or former smokers	3,087 (10)
Persons who had never smoked with exposure to secondhand smoke	3,299 (10)
Programs in the United States, Europe, Israel, and China	
Current or former smokers	23,052 (73)
Persons who had never smoked	
Occupational exposure*	1,690 (5)
Exposure to secondhand smoke with or without family history of lung cancer	439 (1)

* This category includes exposure to asbestos, beryllium, uranium, or radon.

pants were considered fit to undergo thoracic surgery. A total of 27,456 annual screenings were conducted between 1994 and 2005 (median, 2002), each of which was performed 7 to 18 months after the previous screening. At baseline, the median age of the participants was 61 years (range, 40 to 85), and the median number of pack-years of smoking was 30 (range, 0 to 141); on annual CT, the median values were an age of 62 years (range, 41 to 86) and 35 pack-years (range, 0 to 141). Among the participants, 13% (4186 of 31,567) who underwent baseline CT and 5% (1460 of 27,456) who underwent annual CT had a positive result that required immediate further workup. A biopsy of a pulmonary nodule as recommended in the protocol was performed in 535 of the participants with a positive result on the baseline or annual CT and led to a diagnosis of malignant disease in 492 of the participants (lung cancer was diagnosed in 479 and lymphoma or metastases from cancers other than lung cancer in 13) and no evidence of malignant disease in 43. The diagnosis was classified as having been identified during baseline screening when the nodule was first identified on the baseline CT, even for cases not meeting the criteria for a positive result, regardless of when the diagnosis was made. When the nodule was first identified on an annual CT, it was attributed to the annual screening. If the result on the baseline or annual CT was negative and a diagnostic workup was subsequently prompted by suggestive symptoms (or incidental findings) before the next scheduled annual CT, the finding was classified as an interim diagnosis. To fully document interim diagnoses of lung cancer, the protocol required that each enrolled participant who had not returned for the next scheduled screening be contacted 1 year after the previous screening. If contact could not be made either directly or through relatives of the participant, the referring physician was contacted to ascertain whether a diagnosis of lung cancer had been made.

We determined the distribution of the baseline and annual screenings and the resulting diagnoses according to age and median pack-years of cigarette smoking (Table 2). Each diagnosis of lung cancer was classified according to clinical stage with the use of standard criteria based on the clinical examination and the results of imaging.[14] The presence or absence of lymph-node (N) and distant metastases (M) was assessed on the most recent CT obtained before diagnosis and from PET (performed in 166 of the 484 participants who received a diagnosis of lung cancer). The cancer was classified as N0M0 if on CT the widths of all mediastinal lymph nodes were less than 10 mm and no hilar lymph nodes or distant metastases were identified (and PET, if performed, showed no abnormal uptake). For the purpose of this study, stage I cancers included those classified as N0M0 with more than 1 adenocarcinoma so long as all adenocarcinomas were 30 mm or less in diameter.[6]

The specimens obtained from participants who underwent surgical resection were examined at each institution according to the I-ELCAP pathology protocol,[15] which specified the preparation of the specimen and the findings that were to be documented by the pathologist at the hospital where the resection was performed. The protocol also specified the review process: a five-member pathology-review panel consisting of expert pulmonary pathologists was to reach a consensus diagnosis for each case of cancer and identify lymph-node involvement, additional cancers, and pleural, lymphatic, vascular, bronchial, and basement-membrane invasion by the cancer. For 22 of the 411 participants who underwent resection (5%), specimens could not be obtained from a nonparticipating hospital, and the panel therefore reviewed the detailed surgical and pathological reports for the relevant information.

All patients given a diagnosis of lung cancer were followed annually by the principal investigator and by the study coordinator at each participating institution, who submitted the information

Table 2. Frequency Distribution of Lung-Cancer Diagnoses on Baseline and Annual CT Screening, According to Age and Median Pack-Years of Cigarette Smoking.

Age	Baseline Screening			Annual Screening		
	Smoking History	No. Screened	Diagnosis of Lung Cancer	Smoking History	No. Screened	Diagnosis of Lung Cancer
	median pack-yr		*no. (%)*	*median pack-yr*		*no. (%)*
40–49 yr	15	4,066	8 (<1)	20	1,324	1 (<1)
50–59 yr	28	9,948	67 (1)	30	6,678	7 (<1)
60–69 yr	38	12,184	206 (2)	40	11,879	29 (<1)
70–79 yr	38	4,840	116 (2)	40	6,692	33 (<1)
80–86 yr	30	529	13 (2)	37	883	4 (<1)
Total	30	31,567	410 (1)*	35	27,456	74 (<1)

* The number includes five participants with interim diagnoses.

required by the protocol to the coordinating center. When a participant was known to have died, the date and cause were obtained from the participant's physician, family members, or both. Death resulting from treatment was considered to have been caused by lung cancer. Follow-up from diagnosis to death from lung cancer, the last contact, or May 30, 2006, whichever came first, was documented for each participant. The duration of follow-up ranged from 1 to 123 months (median, 40).

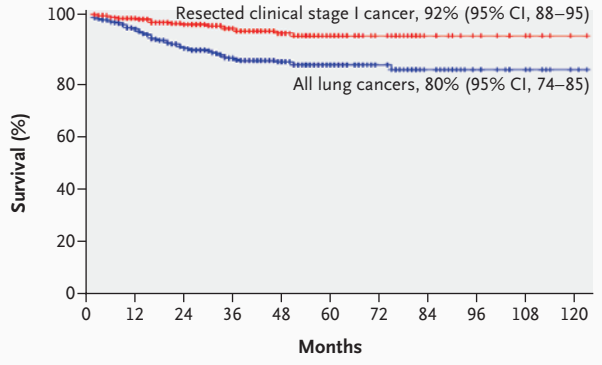
Kaplan–Meier curves were calculated for lung-cancer–specific survival as of the date of diagnosis, irrespective of the type of treatment, including no treatment, for all participants with lung cancer, irrespective of the stage of the cancer, and for the subgroup with clinical stage I cancer. Survival curves were also calculated for participants who underwent resection of clinical stage I cancer within 1 month after diagnosis and those who did not receive treatment. On the basis of these curves, we estimated the 10-year survival rates. The curves were constructed with the use of SAS statistical software (version 8), which also produced the standard error for the estimates.

RESULTS

Baseline screening of 31,567 asymptomatic persons who were at risk for lung cancer and annual screening of 27,456 resulted in the diagnosis of lung cancer in 405 and 74 participants, respectively (Fig. 1). Another five participants received interim diagnoses of lung cancer that were prompted by the development of symptoms within 12 months after the baseline screening. Of these 484 participants given a diagnosis of lung cancer, 411 underwent resection; 57 received radiation, chemotherapy, or both; and 16 received no treatment. Because survival rates among the participants who underwent baseline screening and those who underwent annual screening did not differ significantly, Kaplan–Meier estimates of lung-cancer–specific survival were calculated for all 484 participants (Fig. 2). The estimated 10-year survival rate for all participants, regardless of tumor stage and treatment, was 80% (95% confidence interval [CI], 74 to 85); as of May 2006, 75 of the 484 participants had died of lung cancer, including 2 who died within 4 weeks after surgery, yielding an operative mortality rate of 0.5% (2 of 411 participants).

Of the 484 participants who received a diagnosis of lung cancer, 412 (85%) had clinical stage I lung cancer. In this subgroup, the estimated 10-year survival rate regardless of treatment was 88% (95% CI, 84 to 91); as of May 2006, 39 of these 412 patients had died of lung cancer. Of these 412 participants, 375 had undergone surgical resection (284 lobectomy, 60 wedge resection, 21 segmentectomy, and 10 bilobectomy); 29 did not undergo resection but received chemotherapy, radiation, or both; and the remaining 8 did not receive treatment. Figure 2 also shows the lung-cancer–specific survival rate among the 302 participants who underwent resection within 1 month after diagnosis, among whom the estimated 10-year survival rate was 92% (95% CI, 88 to 95). All eight untreated patients died within 5 years after diagnosis.

Among the 412 participants with clinical



No. at Risk											
All participants	484	433	356	280	183	90	50	28	16	9	2
Participants undergoing resection	302	280	242	191	120	59	34	18	12	7	1

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

Table 3. Types of Cancer among 412 Participants with Clinical Stage I Lung Cancer Detected on Baseline or Annual CT Screening.

Type of Cancer	Diagnosed on Baseline Screening (N = 348)	Diagnosed on Annual Screening (N = 64)
	no. of participants	
Adenocarcinoma		
Bronchioloalveolar subtype	20	1
Other subtypes	243	30
Squamous cell	45	14
Adenosquamous	3	0
Non–small-cell*	5	2
Neuroendocrine		
Atypical carcinoid	2	1
Large cell	15	8
Small cell	9	7
Other	6	1

* If this cell type cannot be differentiated, the category is known as "not otherwise specified."

stage I cancer, the distribution according to the type of cell is shown in Table 3. The median tumor diameter was 13 mm at baseline and 9 mm on annual CT. The pathology-review panel confirmed the diagnosis of clinical stage I cancer in the specimens obtained from the 375 participants who underwent resection according to World Health Organization criteria of 2004.[16] With regard to spread or invasion (Table 4), the panel identified lymph-node metastases (hilar or ipsilateral mediastinal) in 28 participants (7%) and more than one cancer, either in the same or in different lobes, in another 35 (9%). Among the remaining participants, each with a solitary cancer, the panel identified invasion of the pleura in 62 (17%); bronchial, vascular, or lymphatic invasion or a combination in another 28 (7%); invasion of the basement membrane alone in 203 (54%), and no invasion in the remaining 19 (5%). (Because of rounding, percentages may not total 100.) Thus, of the 375 participants who underwent resection, 347 had pathological stage I cancer, and their estimated 10-year survival rate was 94% (95% CI, 91 to 97).

DISCUSSION

In making decisions about instituting CT screening for lung cancer, a major consideration is the outcome of treating a cancer detected on screening. In our study, the estimated 10-year lung-cancer–specific survival rate among the 484 participants with disease diagnosed on CT, regardless of the stage at diagnosis or type of treatment (including no treatment), was 80% (95% CI, 74 to 85) (Fig. 2). Among the 412 participants with clinical stage I lung cancer — the only stage at which cure by surgery is highly likely — the estimated 10-year survival rate was 88% (95% CI, 84 to 91), and among those with clinical stage I lung cancer who underwent surgical resection within 1 month after the diagnosis, the rate was 92% (95% CI, 88 to 95). The diagnosis of lung cancer of one type or another was verified by a panel of five expert pulmonary pathologists. In our series, the operative mortality rate was low — 0.5% — and was less than the 1.0% reported with lobectomy in a large cooperative study.[17]

Sobue et al.[18] reported a 5-year survival rate of 100% in their series of 29 patients who underwent resection after pathological stage I cancer was detected on CT. Before CT screening, reports based on registries showed 10-year survival rates of 80% among 17 patients with pathological stage I lung cancer 20 mm or less in diameter[19] and 93% among 35 patients with pathological stage I cancer less than 10 mm in diameter.[20] The National Cancer Institute's Surveillance, Epidemiology, and End

Table 4. Extent of Spread of Cancer in 375 Participants Who Underwent Resection of Clinical Stage I Lung Cancer According to Whether Cancer was Detected on Baseline or Annual CT Screening.

Extent of Spread	Diagnosed on Baseline Screening (N=320)	Diagnosed on Annual Screening (N=55)
	no. of participants	
Metastases to lymph nodes	22	6
No metastases to lymph nodes		
More than 1 cancer	29	6
Solitary cancer with invasion		
Pleural invasion	51	11
No pleural invasion but lymphatic, vascular, or bronchial spread (or a combination)	24	4
Basement membrane only	175	28
Solitary cancer without invasion	19	0

Results (SEER) registry, the largest U.S. cancer registry, reported an 8-year survival rate of 75% among patients with pathological stage I cancer with nodules less than 15 mm in diameter who had undergone resection.[8] Although the lung cancers in these three series were not detected on CT screening, most were presumably incidentally detected on imaging performed for other reasons in people who had no symptoms of lung cancer.

CT screening according to the I-ELCAP regimen can detect clinical stage I lung cancer in a high proportion of persons when it is curable by surgery. In a population at risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer. In comparison, in the United States at present, annually approximately 173,000 persons are diagnosed with lung cancer and 164,000 deaths are attributed to this disease,[21] so that approximately 95% of those who are diagnosed with lung cancer die from it.

Are these results sufficiently effective to justify screening people who are at risk of lung cancer? As compared with mammographic screening for breast cancer, for lung cancer the rates of detection among the participants in this study who were 40 years of age and older were 1.3% on baseline CT screening and 0.3% on annual screening (Table 2), values that were slightly higher than those for the detection of breast cancer (0.6 to 1.0% on baseline screening) and similar to those for annual screening (0.2 to 0.4%) among women 40 years of age and older.[22] The rate of cancer detection depends on the risk profile of those undergoing screening; the higher the risk, the more productive the screening. Thus, as expected, CT screening of the original participants in ELCAP, who were former and current smokers 60 years of age and older,[1,2] was more productive in detecting lung cancer (detection rates, 2.7% on baseline screening and 0.6% on annual screening) than among participants in the expanded study. The cost of low-dose CT is below $200,[23-26] and surgery for stage I lung cancer is less than half the cost of late-stage treatment.[26,27] Using the original ELCAP data and the actual hospital costs for the workup, we found CT screening for lung cancer to be highly cost-effective.[23] Other estimates of the cost-effectiveness of CT screening for lung cancer for various risk profiles[24-26,28] are similar to that for mammography screening.[29,30]

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Drs. Henschke and Yankelevitz report receiving royalties from Cornell Research Foundation as inventors of methods to assess tumor growth and regression on imaging tests for which pending patents are held by Cornell Research Foundation and licensed to General Electric. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The following investigators participated in I-ELCAP: *Joan and Sanford I. Weill Medical College of Cornell University, New York:* C.I. Henschke (principal investigator), D.F. Yankelevitz, D.I. McCauley; *Azumi General Hospital, Nagano, Japan:* S. Sone, T. Hanaoka; *Center for the Biology of Natural Systems, City University of New York at Queens College, Queens:* S. Markowitz, A. Miller; *LungenZentrum Hirslanden, Zurich:* K. Klingler, T. Scherer, R. Inderbitzi; *Clinica Universitaria de Navarra, Pamplona, Spain:* J. Zulueta, L. Montuenga, G. Bastarrika; *National Cancer Institute Regina Elena, Rome:* S. Giunta, M. Crecco, P. Pugliese; *H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL:* M. Tockman; *Hadassah Medical Organization, Jerusalem, Israel:* D. Shaham; *Swedish Medical Center, Seattle:* K. Rice, R. Aye; *University of Toronto, Princess Margaret Hospital, Toronto:* H. Roberts, D. Patsios; *Christiana Care Helen F. Graham Cancer Center, Newark, DE:* T. Bauer, J. Lally; *Columbia University Medical Center, New York:* J.H.M. Austin, G.D.N. Pearson; *New York University Medical Center, New York:* D. Naidich, G. McGuinness; *State University of New York at Stony Brook, Stony Brook:* M. Rifkin, E. Fiore; *Maimonides Medical Center, Brooklyn, NY:* S. Kopel; *Roswell Park Cancer Institute, Buffalo, NY:* D. Klippenstein, A. Litwin, P.A. Loud; *State University of New York Upstate Medical University, Syracuse:* L.J. Kohman, E.M. Scalzetti; *North Shore–Long Island Jewish Health System, New Hyde Park, NY:* A. Khan, R. Shah; *Georgia Institute for Lung Cancer Research, Atlanta:* M.V. Smith, H.T. Williams, L. Lovett; *Mount Sinai School of Medicine, New York:* D.S. Mendelson; *Jackson Memorial Hospital, University of Miami, Miami:* R. Thurer; *Memorial Sloan-Kettering Cancer Center, New York:* R.T. Heelan, M.S. Ginsberg; *Holy Cross Hospital Cancer Institute, Silver Spring, MD:* F. Sullivan, M. Ottinger; *Eisenhower Lucy Curci Cancer Center, Rancho Mirage, CA:* D. Vafai; *New York Medical College, Valhalla:* T.A.S. Matalon; *Mount Sinai Comprehensive Cancer Center, Miami Beach, FL:* S.-L. Odzer; *Fifth Affiliated Hospital (Zhuhai Hospital), of Sun Yat-Sen University, Zhuhai, China:* X. Liu; *Dorothy E. Schneider Cancer Center, Mills-Peninsula Health Services, San Mateo, CA:* B. Sheppard; *St. Agnes Cancer Center, Baltimore:* E. Cole; *Our Lady of Mercy Medical Center, Bronx, NY:* P.H. Wiernik; *Evanston Northwestern Healthcare Medical Group, Evanston, IL:* D. Ray; *Karmanos Cancer Institute, Detroit:* H. Pass, C. Endress; *Greenwich Hospital, Greenwich, CT:* D. Mullen; *Sharp Memorial Hospital, San Diego, CA:* M. Kalafer; *City of Hope National Medical Center, Duarte, CA:* F. Grannis, A. Rotter; *ProHealth Care Regional Cancer Center, Waukesha and Oconomowoc Memorial Hospitals, Oconomowoc, WI:* M.K. Thorsen, R. Hansen; *Comprehensive Cancer Center, Desert Regional Medical Center, Palm Springs, CA:* E. Camacho; *St. Joseph Health Center, St. Charles, MO:* D. Luedke; **Coordinating Center:** C.I. Henschke, N. Altorki, A. Farooqi, J. Hess, D. Libby, D.I. McCauley, O.S. Miettinen, J. Ostroff, M.W. Pasmantier, A.P. Reeves, J.P. Smith, M. Vazquez, D.F. Yankelevitz, R. Yip, L. Zhang, K. Agnello; **Pathology Review Panel:** D. Carter, E. Brambilla, A. Gazdar, M. Noguchi, W.D. Travis.

REFERENCES

1. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105.

2. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screening. Cancer 2001;92:153-9.

3. Henschke CI, Yankelevitz DF, Smith JP, et al. CT screening for lung cancer: assessing a regimen's diagnostic performance. Clin Imaging 2004;28:317-21.

4. Henschke CI, Yankelevitz DF, Miettinen OS, I-ELCAP Investigators. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. Arch Intern Med 2006;166:321-5.

5. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS, ELCAP Group. Screening for lung cancer: the Early Lung Cancer Action approach. Lung Cancer 2002;35:143-8.

6. International Early Lung Cancer Action Program protocol. (Accessed September 29, 2006, at http://www.IELCAP.org.)

7. Henschke CI, Yankelevitz DF, Smith JP, Miettinen OS. The use of spiral CT in lung cancer screening. In: DeVita VT, Hellman S, Rosenberg SA, eds. Progress in oncology 2002. Sudbury, MA: Jones and Barlett, 2002.

8. Henschke CI, Wisnivesky JP, Yankelevitz DF, Miettinen OS. Screen-diagnosed small stage I cancers of the lung: genuineness and curability. Lung Cancer 2003;39:327-30.

9. Reeves AP, Kostis WJ, Yankelevitz DF, Henschke CI. A Web-based data system for multi-institutional research studies on lung cancer. Presented at the 87th annual meeting of the Radiologic Society of North America, Chicago, November 25–30, 2001. abstract.

10. Henschke CI, Yankelevitz DF, Naidich D, et al. CT screening for lung cancer: suspiciousness of nodules at baseline according to size. Radiology 2004;231:164-8.

11. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley DI, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053-7.

12. Kostis WJ, Yankelevitz DF, Reeves AP, Fluture SC, Henschke CI. Small pulmonary nodules: reproducibility of three-dimensional volumetric measurement and estimation of time to follow-up CT. Radiology 2004;231:446-52.

13. Libby DM, Wu N, Lee IJ, et al. CT screening for lung cancer: the value of short-term CT follow-up. Chest 2006;129:1039-42.

14. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.

15. Vazquez M, Flieder D, Travis W, et al. Early Lung Cancer Action Project pathology protocol. Lung Cancer 2003;39:231-2.

16. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, eds. World Health Organization classification of tumours: pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon, France: IARC Press, 2004.

17. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ASOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-20.

18. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911-20.

19. Buell PE. The importance of tumor size in prognosis for resected bronchogenic carcinoma. J Surg Oncol 1971;3:539-51.

20. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120-9.

21. Cancer facts and figures: statistics, 2005. Atlanta: American Cancer Society, 2005. (Also available at http://www.cancer.org.)

22. Quality determinants of mammography. In: Clinical practice guideline no. 13. Rockville, MD: Agency for Health Care Policy and Research, 1994:82-6. (Publication no. 95-0632.)

23. Wisnivesky JP, Mushlin A, Sicherman N, Henschke CI. Cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest 2003;124:614-21.

24. Miettinen OS. Screening for lung cancer: can it be cost-effective? CMAJ 2000;162:1431-6.

25. Marshall D, Simpson KN, Earle CC, Chu C. Potential cost-effectiveness of one-time screening for lung cancer (LC) in a high risk cohort. Lung Cancer 2001;32:227-36.

26. *Idem.* Economic decision analysis model of screening for lung cancer. Eur J Cancer 2001;37:1759-67.

27. Riley GF, Potosky AL, Lubitz JD, Kess-

ler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. Med Care 1995;33:828-41.
28. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. Chest 2002;121:1507-14.
29. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. JAMA 1995;274:881-4. [Erratum, JAMA 1996;275:112.]
30. Rosenquist CJ, Lindfors KK. Screening mammography beginning at age 40 years: a reappraisal of cost-effectiveness. Cancer 1998;82:2235-40.

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CORRECTION

Clarification of Funding of Early Lung Cancer Study

To the Editor: In our article[1] published in the October 26, 2006, issue of the *Journal,* one of the disclosed sources of funding was the Foundation for Lung Cancer: Early Detection, Prevention and Treatment, which provided partial support for our research. For full transparency we wish to inform you that $3.6 million (virtually all of the Foundation's funding) was contributed in 2000 through 2003 as an unrestricted gift by the Vector Group, the parent company of Liggett Tobacco, which manufactures cigarettes.

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References

1. The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-1771.

CORRECTION

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

Survival of Patients with Stage I Lung Cancer Detected on CT Screening . The disclosure statement (page 1769) should have read as follows: ``Drs. Henschke and Yankelevitz report receiving royalties from Cornell Research Foundation as inventors of methods to assess tumor growth and regression on imaging tests for which pending patents are held by Cornell Research Foundation and licensed to General Electric. No other potential conflict of interest relevant to this article was reported.´´ The article has been corrected on the *Journal*'s Web site at www.nejm.org.

CORRECTION

Clarifying Enrollment Procedures in the Trial of CT Screening for Lung Cancer

To the Editor: I would like to clarify the selection process leading to the inclusion of the patients in the previous report on survival in the trial of computed tomographic (CT) screening for lung cancer (Oct. 26, 2006, issue).[1] The process at 37 of the 38 participating sites was as follows. People interested in participating in the trial were first interviewed and were administered a precoded questionnaire by the study staff. The data from the questionnaires were entered, and data entry was checked, according to the standard protocol used at each center. The data were then transmitted electronically to the coordinating center. There, eligibility was assessed by means of a computer algorithm, and those who did not meet the eligibility criteria were excluded (Figure 1). At the 38th site, the questionnaire was not administered, and therefore all the needed data were not recorded before enrollment.

For participants who received a diagnosis of lung cancer after baseline screening, study records were reviewed by the steering committee at one of its twice-yearly meetings. This review included confirmation of eligibility for the study — that is, asymptomatic status at the time of enrollment. If the symptoms resulting in exclusion had been present at enrollment but had not been recorded, the participant was excluded post hoc. This was the case for three patients among the 37 sites. Other features relevant to overall survival or survival itself were not used as a basis for exclusion. At the 38th site, at which symptoms at enrollment had not been documented, eight participants were excluded on the basis of preexisting disqualifying symptoms, and one was excluded because pathological confirmation of lung cancer was not received by the coordinating center (Figure 1). The symptomatic status of participants who did not receive a diagnosis of lung cancer was not reviewed, since this information had no bearing on the research question addressed by the study.

Except for the 12 patients excluded after enrollment (the 3 from the 37 sites at which the screening questionnaire had been administered and the 9 from the 38th site, at which the questionnaire was not administered), no patients were excluded from the study after they had been enrolled on the basis of the computer algorithm.

Inclusion of these 12 patients changes the 10-year survival rate for patients with lung cancer from the 80% (95% confidence interval [CI], 74 to 85) reported previously for 484 patients to 81% (95% CI, 75 to 86) for 496 patients. The other reported findings are not changed.

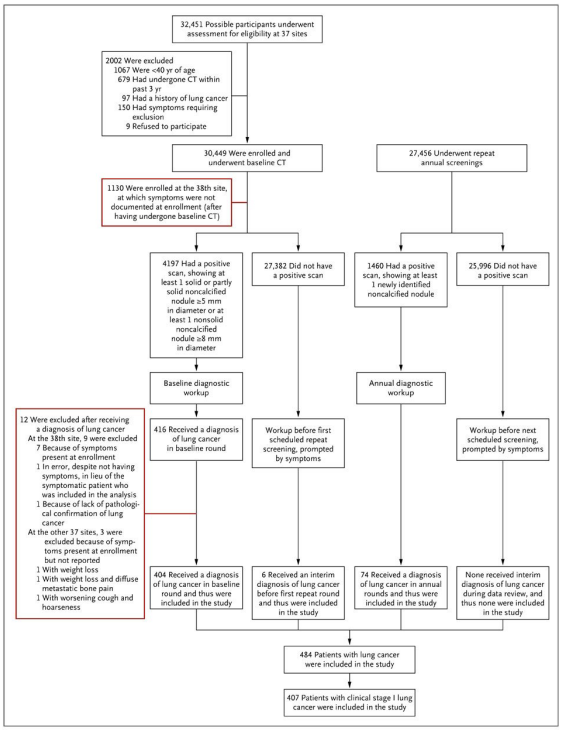
The article also reported that eight patients with clinical stage I lung cancer remained untreated and died within 5 years after diagnosis. However, only three had a pathological diagnosis of stage I lung cancer. Another four had stage I disease confirmed on CT, but further workup was delayed despite repeated promptings, and pathological diagnosis was made only after the cancer had progressed to stage IV. The remaining patient had a solitary nodule on baseline CT that grew at a rate consistent with primary lung cancer, refused biopsy and treatment, and died of lung cancer 6 months after the last CT showing lung cancer. Thus, all eight patients died from lung cancer within 5 years after their actual or potential diagnosis during stage I.

Since, however, pathological diagnosis of lung cancer was required by the International Early Lung Cancer Action Project (I-ELCAP) investigators, I should have classified four of the eight patients as having stage IV lung cancer and the remaining patient who had not received a pathological diagnosis during stage I as having an interim diagnosis. The remaining 483 patients received an antemortem pathological diagnosis of their lung cancer. Thus, the correct number of patients who were untreated and had a diagnosis of stage I lung cancer is 3, not 8, and the total number of patients who had clinical stage I lung cancer is 407, not 412 (Figure 1).

These corrections increased the 10-year Kaplan–Meier survival rate for clinical stage I lung cancer from 88% to 90%. The overall Kaplan–Meier survival rate remained the same, since all patients with any stage of lung cancer were included in that analysis.

Figure 1. Supplement to the Previously Published Figure 1, Showing the Numbers of Patients Enrolled and Evaluated at the 38th Site as Compared with the Numbers at the Other 37 Sites.

The ``31,567 Asymptomatic participants [who] underwent baseline screening´´ in the previously published Figure 1 comprises the ``30,449 [participants who] were enrolled and underwent baseline CT´´ at 37 sites plus the ``1130 [participants who] were enrolled at the 38th site,´´ minus the ``12 [participants who] were excluded´´ (30,449+1130–12=31,567). CT denotes computed tomography.



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References

1. The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-1771. [Erratum, N Engl J Med 2008;358:1862, 1875.]