Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

A 20-year Follow-up of the International Early Lung Cancer Action Program (I-ELCAP)

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Conflicts of interest are listed at the end of this article.

See also the editorials by Grenier and by Sequist and Olazagasti in this issue.

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Background: The low-dose CT (≤3 mGy) screening report of 1000 Early Lung Cancer Action Program (ELCAP) participants in 1999 led to the International ELCAP (I-ELCAP) collaboration, which enrolled 31 567 participants in annual low-dose CT screening between 1992 and 2005. In 2006, I-ELCAP investigators reported the 10-year lung cancer–specific survival of 80% for 484 participants diagnosed with a first primary lung cancer through annual screening, with a high frequency of clinical stage I lung cancer (85%).

Purpose: To update the cure rate by determining the 20-year lung cancer–specific survival of participants diagnosed with first primary lung cancer through annual low-dose CT screening in the expanded I-ELCAP cohort.

Materials and Methods: For participants enrolled in the HIPAA-compliant prospective I-ELCAP cohort between 1992 and 2022 and observed until December 30, 2022, Kaplan-Meier survival analysis was used to determine the 10- and 20-year lung cancer–specific survival of participants diagnosed with first primary lung cancer through annual low-dose CT screening. Eligible participants were aged at least 40 years and had current or former cigarette use or had never smoked but had been exposed to secondhand tobacco smoke.

Results: Among 89 404 I-ELCAP participants, 1257 (1.4%) were diagnosed with a first primary lung cancer (684 male, 573 female; median age, 66 years; IQR, 61–72), with a median smoking history of 43.0 pack-years (IQR, 29.0–60.0). Median follow-up duration was 105 months (IQR, 41–182). The frequency of clinical stage I at pretreatment CT was 81% (1017 of 1257). The 10-year lung cancer–specific survival of 1257 participants was 81% (95% CI: 79, 84) and the 20-year lung cancer–specific survival was 81% (95% CI: 78, 83), and it was 95% (95% CI: 91, 98) for 181 participants with pathologic T1aN0M0 lung cancer.

Conclusion: The 10-year lung cancer–specific survival of 80% reported in 2006 for I-ELCAP participants enrolled in annual low-dose CT screening and diagnosed with a first primary lung cancer has persisted, as shown by the updated 20-year lung cancer–specific survival for the expanded I-ELCAP cohort.

In 1999, the initial results of the Early Lung Cancer Action Program (ELCAP) provided evidence supporting the benefit of annual low-dose CT as a screening modality for lung cancer in a predefined high-risk population (1). Starting in 1992, 1000 participants aged 60 years or older with a cigarette smoking history of at least 10 pack-years were prospectively enrolled in a cohort study that compared annual low-dose CT with annual chest radiography at two New York City institutions (2). Results of the baseline round of screening, reported in 1999 (1), found that 85% of the participants with newly diagnosed lung cancer detected with low-dose CT had

Abbreviations

ELCAP = Early Lung Cancer Action Program, I-ELCAP = International ELCAP

Summary

The estimated cure rate of 80% using the 10-year lung cancer–specific survival of 484 International Early Lung Cancer Action Program participants reported in 2006 has persisted after 20 years of follow-up in the expanded cohort of 1257 participants.

Key Results

- The estimated 10- and 20-year lung cancer–specific survival rates for the 1257 participants were 81% and 81%, respectively.
- The Kaplan-Meier lung cancer–specific survival plateau was reached 10 years after diagnosis.
- The 20-year follow-up provides an estimate of the cure rate achieved in annual screening programs using a well-defined protocol and comprehensive management system, which allows for identification of early lung cancer while it is still small and curable.

stage I lung cancer (*Lung Cancer TNM Classification*, 6th edition), while 82% of these low-dose CT–detected stage I cancers had not been identified on chest radiographs obtained at the same time as the low-dose CT scans. The results gave renewed hope to people at risk for lung cancer (3) and led to low-dose CT screening research throughout the world (4–7).

By 2006, the International ELCAP (I-ELCAP), a multinational collaboration (7), and the expanded New York Early Lung Cancer Action Program (NY-ELCAP) (8) provided sufficient long-term follow-up to estimate the cure rate in 484 participants diagnosed with a first primary lung cancer under annual screening among 31 567 participants using the 10-year Kaplan-Meier lung cancer–specific survival, which was 80% (95% CI: 74, 85) (9).

Cure rates of different cancers are of increasing interest to screening participants and national public health policy authorities (10–14). The multinational Siracusa charter (12) defined cure of a cancer as "complete remission of a cancer regardless of the presence or absence of late sequelae of treatment." The cure rate is estimated by the plateau reached in a cancer-specific Kaplan-Meier survival curve, and the number of years to reach this plateau varies by type of cancer (12–14). For lung cancer, the consensus was that the plateau is reached 8–10 years after treatment (12–14).

The aim of this report is to provide the updated 20-year lung cancer–specific survival of participants diagnosed with lung cancer in the prospectively enrolled I-ELCAP cohort, following the I-ELCAP protocol of annual screening (15), with a view toward strengthening confidence in the previously reported cure rate (9). As the prevalence of lung cancer in screening participants with different exposures to cigarette smoking was previously examined (16,17), 20-year lung cancer–specific survival was separately estimated for participants with a smoking history of 30 pack-years or more, those with a smoking history of 10–29 pack-years, and those with a smoking history of less than 10 pack-years, including those who had never smoked cigarettes but had passive exposure to cigarette smoke.

Materials and Methods

This Health Insurance Portability and Accountability Act–compliant study was conducted in accordance with the Declaration of Helsinki and received approval from the institutional review board of the Western Institutional Review Board (approval no. 1106439) and the institutional review boards of participating institutions. All enrolled participants provided written informed consent.

Study Participants

All participants consecutively enrolled between 1992 and 2022 in I-ELCAP (15) were reviewed. I-ELCAP is a prospective multi-institutional cohort study. Institutional enrollment criteria differed. Individuals with a history of any cancer other than nonmelanotic skin cancer were excluded from enrollment in this cohort. Race was self-reported by study participants. Included in this report are all participants aged at least 40 years who had current or former cigarette use or who had never smoked but were exposed to secondhand tobacco smoke. Some study participants were previously reported, including the 484 participants in the previous 2006 publication (9), but to our knowledge, the 20-year follow-up results have never been reported.

All identified participants were those diagnosed with a first primary lung cancer, either non–small cell or small cell cancer, regardless of stage or type of treatment, diagnosed under annual screening, that is resulting from baseline and annual screenings performed 7–18 months after the previous screening or from interim lung cancer diagnoses identified between rounds of screening (15,18). Participants diagnosed with lung cancer had a firmly established diagnosis of lung cancer and documentation in the management system. Updates have been made for each participant on an ongoing basis and have also been provided at each of the 44 International Conferences on Screening for Lung Cancer held since 1999 (7).

Study Design

The principal investigators and study coordinators at each participating institution observed participants diagnosed with lung cancer and submitted follow-up information to the I-ELCAP coordinating center, as required by the common standardized protocol. Date and cause of death were obtained from the participant's physician, family members, and—in the United States—from the National Death Index.

Documented in the ELCAP Management System were: participant demographics, comorbidities, contact information, and referring physician information at enrollment; follow-up participant communications; low-dose CT findings; pathology findings; and treatment (19). The maximum tumor diameter of the lung cancer on axial, sagittal, and coronal CT images was measured on the last CT scan obtained before treatment. Lung cancer consistency was determined on the same pretreatment CT scan and was classified as solid or subsolid (part-solid or nonsolid) according to established criteria (15,20,21). For part-solid lung cancers, the maximum diameter of the largest solid component was also measured; when this diameter was more than 80% of the overall tumor diameter, tumor consistency was classified as solid (15). The I-ELCAP protocol required demonstration of growth of small nodules developed through a National Cancer Institute grant (R01-CA-78905; September 1999 to August 2002) since the beginning of the study (5,9,15,21). Reviews of

the I-ELCAP database were made for protocol compliance at the semiannual conferences since 1999, which included multiple expert pathology panel reviews (22).

The documented diagnoses, treatment, and posttreatment follow-up information for all participants diagnosed with lung cancer and staging were available in the I-ELCAP Management System so that staging could be updated according to the *Lung Cancer TNM Classification*, 8th edition (23).

Clinical and Pathologic Stage

Clinical T status was defined by maximum tumor diameter on the last pretreatment CT scan (15); clinical N status was defined by lymph node location; N2 lymph nodes were defined as those with a short-axis diameter of more than 10 mm on pretreatment CT scans (15). Clinical stage I was defined as cT1a-c and cT2aN0M0 based on the last pretreatment CT scan. Pathologic T status was defined by maximum tumor diameter in the resected pathologic specimen: 10 mm or less (pT1a), 11–20 mm (pT1b), 21–30 mm (pT1c), and 31–40 mm or tumor with main bronchus involvement, invading visceral pleura or associated with atelectasis or obstructive pneumonitis (pT2a).

Many reports define stage I by using a hybrid definition of pathologic stage if resected or clinical stage if not resected. This means that the percentage diagnosed in stage I depends on the frequency of resection at any one institution. To avoid this bias, the clinical stage I definition was used, but the frequency of stage I using the hybrid definition was also provided.

Statistical Analyses

Statistical analyses were performed by a data scientist (R.Y.). Categorical variables were summarized as frequencies (percentages), continuous variables are presented as means ± SDs, and nonparametric variables are presented as medians and IQRs. Continuous variables for normal distribution were assessed with the Shapiro-Wilk test. Differences in demographic and sociomedical characteristics and CT findings were assessed using the χ^2 or Fisher exact tests for categorical variables and using the two-sample *t* or Wilcoxon rank sum tests for parametric and nonparametric continuous variables.

Using Kaplan-Meier survival analysis, 10- and 20-year lung cancer–specific survival rates were calculated for all participants diagnosed with a first primary lung cancer through annual screening (15,17) using documented follow-up from diagnosis to death or last contact until December 31, 2022, whichever came first. The 95% Hall-Wellner bands were also computed. Deaths within 30 days of surgery or other lung cancer–related treatment were considered lung cancer deaths. Kaplan-Meier lung cancer–specific survival was calculated separately for participants with clinical stage I lung cancer and for the hybrid stage I definition. It was also calculated separately for three different cigarette smoking categories: *(a)* those with a smoking history of less than 10 pack-years, including those who had never smoked cigarettes but had passive exposure to cigarette smoke; *(b)* those with a smoking history of 10–29 pack-years; and *(c)* those with a smoking history of 30 or more pack-years. Factors associated with time to lung cancer death were analyzed using the Cox proportional hazards model; both crude and adjusted hazard ratios with 95% CIs are reported. $P \leq .05$ was considered indicative of a significant difference. All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

Results

Participant Characteristics

Among the 89404 I-ELCAP screening participants enrolled in low-dose CT screening programs between 1992 and 2022, 62722 (70.2%) participants were screened in North America, 16082 (18.0%) were screened in Europe, and 10600 (11.8%) were screened in Asia. A total of 1257 (1.4%) participants were diagnosed with first primary lung cancer under annual screening; 684 (54.4%) were male, and 573 (45.6%) were female (Table 1).

At the time of diagnosis, the median age of these 1257 participants was 66 years (IQR, 61–72), with a median smoking history of 43 pack-years (IQR, 29–60). Median tumor diameter on the last pretreatment CT scan was 14.0 mm (IQR, 9.3–22.0 mm). Lung cancer consistency was solid for 1008 (80.2%) participants and subsolid for 249 (19.8%). Cancer cell type was adenocarcinoma in 843 (67.1%) participants, squamous cell carcinoma in 168 (13.4%), small cell carcinoma in 82 (6.5%), large cell carcinoma in 42 (3.3%), and carcinoid (both typical and atypical) in 27 (2.2%); other non–small cell types accounted for the remaining 95 (7.6%). Median follow-up in the 1257 participants was 105 months (IQR, 41–182). As of December 31, 2022, 212 (16.9%) participants had died of lung cancer; the rate of death from lung cancer was 18.8 deaths per 1000 person-years. Surgical resection was performed for 998 (79.4%) participants; it was performed within 1 month of diagnosis in 768 (77.0%), within 2–3 months of diagnosis in 179 (17.9%), within 4–6 months of diagnosis in 27 (2.7%), and more than 6 months after diagnosis in 24 (2.4%). Of the 998 surgical participants (Table 2), 142 (14.2%) underwent wedge resection, 82 (8.2%) underwent segmentectomy, 733 (73.4%) underwent lobectomy, 25 (2.5%) underwent bilobectomy, and eight (0.8%) underwent pneumonectomy; in eight participants (0.8%), the extent of surgery was not specified. The primary treatment for the remaining 259 (20.6%) participants was stereotactic body radiation therapy in 77 (6.1%), chemotherapy in 114 (9.1%), and concurrent radiation therapy and chemotherapy in 24 (1.9%); 44 (3.5%) participants underwent other treatments. The frequency of clinical stage I was 81% (1017 of 1257), which was higher than that using the hybrid definition (pathologic stage if resected, clinical stage if not resected) of 74.0% (930 of 1257).

The 10- and 20-year Lung Cancer–specific Survival

For all 1257 participants, the 10-year lung cancer–specific survival was 81% (95% CI: 79, 84) and the 20-year lung cancer–specific survival was 81% (95% CI: 78, 83) (Fig 1). For the 1017 participants with clinical stage I lung cancer (cT1a,b,cN0M0 or cT2aN0M0), the 20-year lung cancer–specific survival was 87% (95% CI: 85, 89) while for the 930 participants with stage I lung cancer defined by the hybrid

Table 1: Characteristics of 1257 I-ELCAP Participants with Lung Cancer

Characteristic	Finding
Sex	
Male	684 (54.4)
Female	573 (45.6)
Age at time of diagnosis (y)*	66 (40–92) [61–72]
Self-reported race	
Asian	58 (4.6)
Black	36 (2.9)
White	1160 (92.3)
Other†	3 (0.2)
Smoking history	
Never	77 (6.1)
Current	612 (48.7)
Former	568 (45.2)
No. of pack-years among participants with current or former smoking history*	43.0 [29.0–60.0]
Comorbidity	
Cardiac	84 (6.7)
Vascular	351 (27.9)
Chronic obstructive pulmonary disease	189 (15.0)
Diabetes	118 (9.4)
Cancers other than lung	214 (17.0)
Other diseases	423 (33.7)
No. of comorbidities*	1 [0–2]
Maximum nodule diameter on pretreatment CT scans (mm)*	14.0 [9.3–22.0]
Nodule consistency on CT prior to treatment	
Subsolid (part-solid and nonsolid)	249 (19.8)
Solid	1008 (80.2)
Cell type	
Adenocarcinoma	843 (67.1)
Squamous	168 (13.4)
Small cell	82 (6.5)
Large cell	42 (3.3)
Carcinoid (typical and atypical)	27 (2.2)
Other non–small cell types‡	95 (7.6)

Note.—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. I-ELCAP = International Early Lung Cancer Action Program.

* Data are medians, with ranges in parentheses and IQRs in brackets.

† "Other" includes American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, and unspecified.

‡ This includes mucoepidermoid, neuroendocrine, adenoid cystic, adenosquamous, and spindle cell or pleomorphic cell carcinoma.

Table 2: Treatment and Pathologic Stage of the 998 I-ELCAP Participants with Resected Lung Cancers

Pathologic Finding	No. of Findings
Treatment	
Surgical resection	998 (79.4)
Wedge resection	142 (14.2)
Segmentectomy	82 (8.2)
Lobectomy	733 (73.4)
Bilobectomy	25 (2.5)
Pneumonectomy	8 (0.8)
Unspecified	8 (0.8)
Radiation therapy	77 (6.1)
Chemotherapy	114 (9.1)
Radiation and chemotherapy	24 (1.9)
Other treatment, not specified	44 (3.5)
Median of maximum pathologic tumor diameter*	15 (11–21)
Nodule consistency on CT prior to treatment	
Subsolid (part-solid and nonsolid)	229 (22.9)
Solid	769 (77.1)
Cell type	
Adenocarcinoma	737 (73.8)
Squamous	141 (14.1)
Small cell	26 (2.6)
Large cell	40 (4.0)
Atypical carcinoid	4 (0.4)
Typical carcinoid	19 (1.9)
Non-small cell, not otherwise specified†	31 (3.1)
Pathologic stage (8th ed. TNM Classification)	
Stage 0 or I	
Tis-T1N0M0	675 (67.6)
T2aN0M0	148 (14.8)
Stage II	
N0‡	39 (3.9)
N1	47 (4.7)
Stage III	
N0‡	12 (1.2)
N1–N3	70 (7.0)
Stage IV	
N0‡	5 (0.5)
N1–N3	2 (0.2)

Note.—I-ELCAP = International Early Lung Cancer Action Program.

* Numbers in parentheses are the IQR.

† The 31 non–small cell unspecified carcinomas includes mucoepidermoid, neuroendocrine, adenoid-cystic, adenosquamous, sarcoma, and spindle cell or pleomorphic cell carcinoma.

‡ Includes multiple primaries with the same cell type in the same lobe, ipsilateral lobe, and contralateral lung.

definition of stage I, it was 87% (95% CI: 85, 89). The survival rate reached a plateau after 10 years of follow-up. When excluding the 22 adenocarcinoma in situ and minimally invasive adenocarcinoma (previously classified as bronchioloalveolar carcinoma) cases, the 20-year lung cancer–specific survival for the remaining 1235 participants was 80% (95% CI: 78, 83).

In the 998 participants who underwent surgical resection, 20-year lung cancer–specific survival was 87% (95% CI: 85, 90). In the 181 participants with the earliest pathologic stage

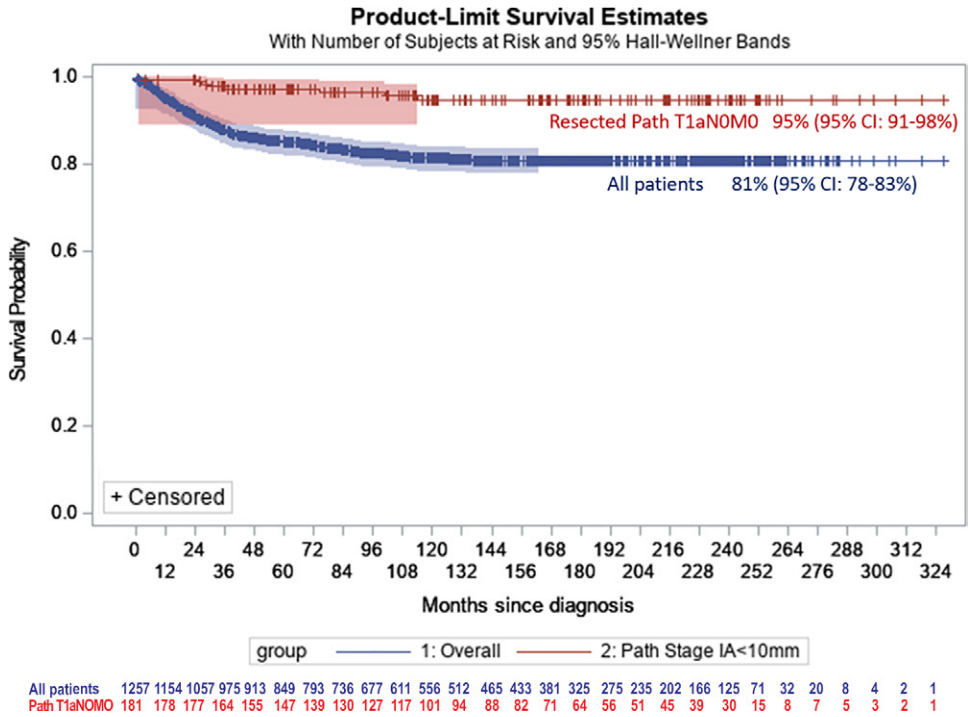

Figure 1: Kaplan-Meier curve shows lung cancer–specific survival for all 1257 participants with lung cancer and for the 181 participants undergoing resection with resulting pT1aN0M0 and tumor size of 10 mm or less in the pathology specimen.

of pT1aN0M0, it was 95% (95% CI: 91, 98) (Figs 1, 2). The 20-year lung cancer–specific survival was 83% (95% CI: 80, 86) in the 769 participants with resected solid cancers and 100% in the 228 participants with resected subsolid cancers. Of the 228 subsolid cancers, 71 (31%) were pathologic TisN0M0.

The 20-year lung cancer–specific survival for the three categories of cigarette smoking was *(a)* 85% (95% CI: 78, 91) in 136 participants who had a smoking history of less than 10 pack-years, including those who had never smoked cigarettes but had passive exposure to cigarette smoke; *(b)* 83% (95% CI: 77, 89) in 196 participants with a smoking history of 10–29 pack-years; and *(c)* 79% (95% CI: 77, 82) in 925 participants with a smoking history of at least 30 pack-years ($P = .26$) (Fig 3). After adjusting for sex and age, there was no evidence of a difference in the risk of lung cancer death among participants who had smoked for at least 30 pack-years when compared with participants who had a smoking history of less than 10 pack-years, including those who had never smoked (hazard ratio, 1.2; 95% CI: 0.65, 2.17; $P = .59$) and participants who had smoked for 10–29 pack-years (hazard ratio, 1.3; 95% CI: 0.82, 2.22; $P = .25$).

Discussion

Among 89 404 participants in the International Early Lung Cancer Action Program (I-ELCAP) annual program of low-dose CT screening, 20-year lung cancer–specific survival for 1257 (1.4%) participants diagnosed with a first primary lung cancer under annual screening was 81% (95% CI: 78, 83), and in the subset of 181 participants who underwent surgical resection and had T1aN0M0 lung cancer confirmed via pathology, 20-year lung cancer–specific survival was 95% (95% CI: 91, 98) (Fig 1). The survival rate reached the plateau after 10 years of follow-up, and the 10-year lung cancer–specific survival for all 1257 participants was 81% (95% CI: 79, 84). These updated survival rates allow us to confirm our previously reported estimated cure rate of 80% reported in 2006 based on the 10-year lung cancer–specific survival of 484 participants (9). This high cure rate was anticipated using a mathematic model prior to the start of the Early Lung Cancer Action Program (ELCAP) screening program in 1992 (24), as well as the initial ELCAP stage distribution reported in 1999 (1). To reach this high cure rate of 80%, however, requires that low-dose CT screening follows a well-defined regularly updated protocol for the work-up of CT findings, a comprehensive data management system for the entire screening program, and training to ensure appropriate follow-up and adherence to continued annual screening (21).

Lung cancer cure rates achieved in screening programs have received increased attention as low-dose CT screening has begun to be implemented globally (10–14,23,25,26). For lung cancer, the consensus is that the survival curve plateau for estimating the cure is reached 8–10 years after treatment (12–14). To the best of our knowledge, no other studies have reported 20-year lung cancer–specific survival for low-dose CT screening programs. Sufficiency of 10 years of follow-up to reach the plateau had been demonstrated by the I-ELCAP 10-year lung cancer–specific survival of 80% for the original 484 participants in 2006 (9) and again by the 10-year survival of 81% (95% CI: 79, 84) for the 1257 participants in this report. The plateau is also evident in the 10-year lung cancer–specific survival of 73.4% among stage I participants in the National Lung Screening Trial (27). The 10-year survival in the National Lung Screening Trial is lower due to many factors, including that screenings were performed from 2002 to 2008, that screenings

were limited to a maximum of two annual rounds and thus were predominantly baseline cases, and that there was a lack of consensus in the work-up protocol among the 33 participating institutions (28), as detailed in a previous report (29). In summary, the 20-year follow-up provides strong added empirical support of the consensus that 8–10 years of follow-up after diagnosis is sufficient to estimate cure rates for lung cancer (12–14).

Criticisms of our estimated cure rate in 2006 (9) were biases due to length time, overdiagnosis, and lead time biases, as described by Morrison (30). Length bias is introduced, as slower-growing cancers are more frequently detected in the asymptomatic participants presenting for screening, while participants with aggressive cancers may have symptom-prompted diagnoses outside of screening rounds (30). Thus, to determine lung cancer–specific survival, it is important to include all lung cancers diagnosed by screening as well as those diagnosed in between screening rounds. Length bias was demonstrated in the Dutch-Belgian Lung Cancer Screening (NELSON) trial (31), as the frequency of stage I diagnoses decreased as symptom-prompted diagnoses in between rounds of screening increased when longer intervals were used between screening rounds. In both our 2006 report and our current report, we included all lung cancers diagnosed at baseline and annual screening rounds, as well as all those diagnosed between screening rounds. Overdiagnosis bias, a severe form of length bias, occurs when screening reveals cancers that would otherwise never have exhibited clinical symptoms, leading to a diagnostic work-up in the patient's lifetime (30). Overdiagnosis in I-ELCAP was mitigated by the requirement to demonstrate growth of small nodules using growth assessment developed through a National Cancer Institute grant (R01-CA-78905; September 1999 to August 2002) which was incorporated from the beginning in the I-ELCAP protocol (5,9,15,21). There were also expert pathology panel reviews of I-ELCAP lung cancers (22), and these expert panel members stimulated the development of the revised adenocarcinoma classification (32). Further, analysis of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated the low rate of overdiagnosis (33); the National Lung Screening Trial protocol, which did not require growth assessment prior

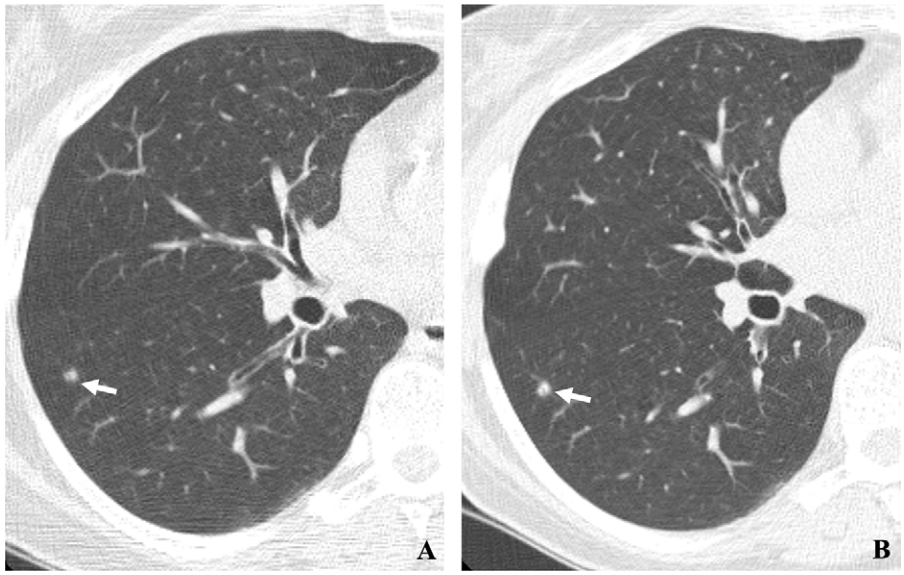

Figure 2: **(A, B)** Two annual repeat low-dose CT scans in a woman who was 60 years old at baseline enrollment in 1999. At baseline enrollment, she was currently smoking and had a 30-pack-year smoking history. No nodules were identified on baseline low-dose CT scans. On the sixth annual low-dose CT scan **(B)**, a right lower lobe solid nodule (arrow) measuring 4.5 mm in maximum diameter was identified. The nodule could be identified in retrospect on the prior annual CT scan (arrow in **A**), when it measured 2.0 mm in maximum diameter. Estimated tumor volume doubling time was 161 days. Lobectomy was performed 2 months later, and diagnosis of stage 1aN0M0 moderately differentiated adenocarcinoma measuring 6.0 mm in maximum diameter was made. Expert pathologic panel review (22) of the pathologic specimen updated the diagnosis to adenocarcinoma with mixed subtype (80% acinar, 20% bronchoalveolar carcinoma components) with 5 mm of invasion.

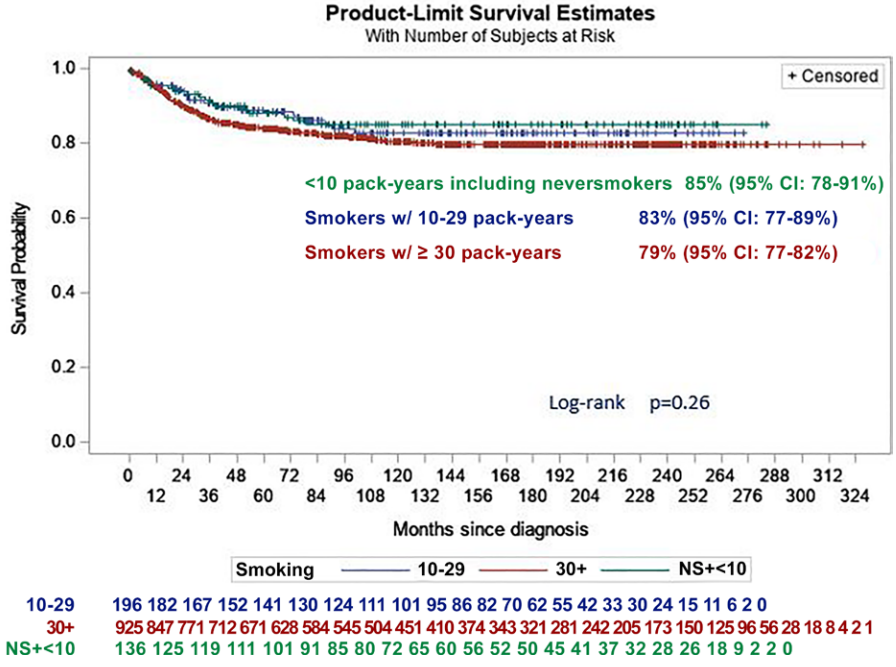

Figure 3: Kaplan-Meier curve shows lung cancer–specific survival for all 1257 participants with lung cancer, organized by smoking categories (participants who never smoked or who smoked less than 10 pack-years, participants who smoked 10–29 pack-years, and participants who smoked at least 30 pack-years).

to diagnosis, revised its estimate of overdiagnosis to 3% when excluding the nonsolid cancers (34); and Raz et al (35) reported that patients with untreated clinical stage I lung cancer in the California Cancer Registry had a 5-year all-cause survival of 7% (median survival, 9 months). To further address concerns about overdiagnosis, we presented 20-year survival separately for resected solid and subsolid lung cancers and showed that lung cancer–specific survival remained high after excluding adenocarcinoma in situ and minimally invasive adenocarcinoma as had been done in the National Lung Screening Trial survival analysis (34). We avoided lead-time bias, as we did not compare the survival rates achieved under screening with those achieved in the absence of screening.

Our study had limitations. First, a limitation of long-term follow-up is that advances in CT and PET technology, as well as other diagnostic and treatment innovations that improve outcomes, are not fully recognized. Second, staging has changed from the 6th to the current 8th edition of *Lung Cancer TNM Classification* (23); however, because we had an ongoing management system for data and image acquisition, we were able to review the images and treatment reports of all participants diagnosed with lung cancer to update the *Lung Cancer TNM Classification*, 8th edition, criteria. Third, compliance with the annual screening protocol was variable among the institutions, as illustrated by the reports from the Pamplona (25) and Valencia (26) sites; however, training and monitoring using a common management system, as well as follow-up reporting of I-ELCAP results at each semiannual conference (7), were important for protocol compliance. Fourth, only 556 of the 1257 participants with lung cancer had more than 10 years of follow-up data, which might have affected the precision of the survival estimates; however, the estimates include about three times the number of participants used to make the 2006 estimate of 80%, which had only two participants with 10 years of follow-up data (9).

In conclusion, the estimated cure rate of 80% reported in 2006 based on the 10-year survival of 484 participants in I-ELCAP diagnosed with a first primary lung cancer under annual low-dose CT screening has persisted after 20 years of follow-up in the expanded I-ELCAP cohort of 1257 participants and enables us to confirm the benefit of annual low-dose CT screening. Future focus should be on identifying lung cancer even earlier, perhaps during the first 20 doublings rather than the last 20 doublings, as can currently be achieved using low-dose CT. Blood biomarkers and new imaging tests will continue to improve. We eagerly await new innovations that can be rapidly evaluated by comparison with low-dose CT using the ELCAP approach.

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