0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2023.06.004

Lung: Research

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Recurrence After Complete Resection for Non-Small Cell Lung Cancer in the National Lung Screening Trial

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ABSTRACT

BACKGROUND The objective of this study was to evaluate patterns, predictors, and long-term outcomes of recurrent disease after complete resection for early-stage non-small cell lung cancer (NSCLC) using the National Lung Screening Trial (NLST).

METHODS The frequency of recurrence in patients with pathologic stage I-II NSCLC who underwent complete resection (lobectomy or bilobectomy) in the NLST was evaluated. Predictors of increased risk of recurrence were assessed by Fine-Gray competing risks regression.

RESULTS Of the 497 patients meeting study inclusion criteria, 94 experienced a recurrence—a rate of 4.9 (95% CI, 4.0-6.0) per 100 person-years. The 5-year cumulative incidence of recurrence was 20.1% (95% CI, 16.5%-23.9%). Most patients experienced recurrences at distant sites alone (n = 47 [50.0%]) or at both locoregional and distant sites (n = 30 [31.9%]). The median time from resection to recurrence was 18.8 (10.6-30.7) months. The incidence rate of recurrence was significantly lower among patients with lung cancer detected by low-dose computed tomography screening during one of the three screening rounds of the NLST when compared with patients with lung cancer detected by chest radiography screening and patients with lung cancer not detected by any form of screening (ie, those diagnosed after a negative or missed screening exam and those diagnosed during follow-up after the three screening rounds of the NLST were completed) ($P < .001$). Median survival (from the date of recurrence) of patients with pathologic stage I and stage II disease who had recurrences at locoregional, distant, or both sites was 63.0, 23.1, and 9.8 months and 28.9, 8.7, and 10.2 months, respectively.

CONCLUSIONS In this analysis of NLST participants with completely resected stage I-II NSCLC, the 5-year cumulative incidence of recurrence was 20%. Nearly 82% of recurrences were at distant sites and associated with poor survival.

(Ann Thorac Surg 2023;116:684-93)

Whereas recent advancements in the early detection of lung cancer through low-dose computed tomography (LDCT) screening have been shown to be associated with

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2023.06.004] on http://www.annalsthoracicsurgery.org.

Accepted for publication Jun 12, 2023.

*Ms Potter and Dr Costantino are co-first authors.

Presented at the Fifty-eighth Annual Meeting of The Society of Thoracic Surgeons, Virtual Meeting, Jan 29-30, 2022.

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significantly improved survival,[1,2] recurrence after curative-intent resection for early-stage disease remains a common and deadly problem. Previous studies have shown that 20% to 55% of patients have a recurrence within 5 years after curative-intent resection.[3-5] After recurrence is diagnosed, 3-year overall survival of patients is 24%.[6]

Although previous studies have examined rates of recurrence after resection for non-small cell lung cancer (NSCLC), most of these studies were single-institution studies[3,4] and grouped patients with early and later stages of disease together.[4] Importantly, it is unknown whether the findings of these previous studies truly reflect the patterns and risks of recurrence for patients undergoing curative-intent resection for early-stage disease, especially in a screen-detected population. With the increasing adoption of LDCT screening[7] and the corresponding increase in the number of early-stage, operable lung cancers diagnosed, studies are needed to better understand patterns and predictors of recurrence after curative-intent resection for early-stage disease. The objective of this study was to evaluate patterns, predictors, and long-term outcomes of recurrent disease after complete resection for early-stage NSCLC using the National Lung Screening Trial (NLST).

PATIENTS AND METHODS

DATA SOURCE. The NLST[1] is a randomized trial that compared the effectiveness of screening with LDCT vs chest radiography in reducing lung cancer mortality among individuals meeting requisite age and smoking history criteria. The 53,454 individuals enrolled into the study from 33 participating centers from 2002 to 2004 were observed until December 31, 2009. Of these individuals who were enrolled in the trial, 2058 were diagnosed with lung cancer. Data collected from the NLST include detailed demographic, tumor, and treatment characteristics and short- and long-term outcomes.

STUDY DESIGN. This retrospective study was approved by the Massachusetts General Hospital institutional review board. Patients who underwent complete resection (lobectomy or bilobectomy) for pathologic stage I-II NSCLC from 2002 to 2009 in the NLST were identified for analysis by *International Classification of Diseases for Oncology, Third Edition* histology and topography codes.[8] Patients who received induction therapy and patients diagnosed with pathologic stage IA NSCLC who underwent adjuvant therapy were excluded from this analysis. Staging data were classified with the eighth edition American Joint Committee on Cancer guidelines.[9] Of note, lung cancers diagnosed among participants in the NLST include those detected by LDCT screening (during one of the three screening rounds of the NLST), those detected by chest radiography screening (during one of the three screening rounds of the NLST), and those not detected by any form of screening during the trial period (ie, those diagnosed after a negative or missed screening exam and those diagnosed during follow-up after the three screening rounds of the NLST were completed). In this study, all participants in the NLST diagnosed with lung cancer, regardless of the method of detection, who met study inclusion criteria were included for analysis.

We first investigated the incidence of recurrence in the overall cohort. We also evaluated the incidence of recurrence stratified by pathologic stage and by the method of lung cancer detection (ie, by LDCT screening, by chest radiography screening, or not by any form of screening during the trial period [ie, those diagnosed after a negative or missed screening exam and those diagnosed during follow-up after the three screening rounds of the NLST were completed]). In addition, for patients diagnosed with pathologic stage IA NSCLC, we evaluated the incidence of recurrence stratified by histologic subtype (see Supplemental Table 1 for details) and by predominant nodule attenuation (eg, solid, ground-glass, or mixed solid and ground-glass nodule).

Recurrences were then grouped by type: locoregional, distant, or both. Locoregional recurrences included recurrences to the N1 lymph nodes, N2 lymph nodes, mediastinum, original lung, or pleura. Distant recurrences included recurrences to the adrenal gland, bone, brain, liver, contralateral lung, skin, or N3 lymph nodes. Patients with synchronous recurrences to locoregional and distant sites were considered to have both locoregional and distant recurrences. The time to recurrence was calculated as the months from resection to the first lung cancer recurrence.

The distributions of recurrences by recurrence type (eg, locoregional, distant, and both) and by recurrence site were assessed. Separate analyses were conducted by pathologic substage. Because some patients with stage IB and stage IIB NSCLC in the study cohort underwent adjuvant therapy, we examined the distribution of recurrences by recurrence type and site stratified by the receipt of adjuvant therapy. We also examined the distribution of the time from resection to recurrence by pathologic stage.

Next, we evaluated factors associated with an increased risk of recurrence. Lastly, we assessed overall survival of patients who did or did not have a recurrence after resection. For the subset of patients who did not have a recurrence, survival time in months was calculated from the date of resection to death from any cause. In the subset of patients who did have a recurrence,

TABLE Baseline Characteristics of Patients Who Underwent Complete (R0) Resection and Were Diagnosed With Pathologic Stage I-II NSCLC by Recurrence Status

Characteristic	No Recurrence	Recurrence	*P* Value
No.	403	94	
Age, y	64.0 (59.0-68.0)	62.5 (59.0-67.0)	.29
Sex			.22
Male	242 (60.0)	50 (53.2)	
Female	161 (40.0)	44 (46.8)	
Race			.003
White	370 (91.8)	86 (91.5)	
Black	31 (7.7)	5 (5.3)	
Other	0 (0.0)	3 (3.2)	
Unknown	2 (0.5)	0 (0.0)	
Pack-year smoking history	57.0 (44.0, 80.0)	60.0 (44.0, 82.0)	.62
Smoking status			.10
Former	196 (48.6)	37 (39.4)	
Current	207 (51.4)	57 (60.6)	
Prior history of cancer			.11
No	379 (94.0)	84 (89.4)	
Yes	24 (6.0)	10 (10.6)	
COPD			.058
No	362 (89.8)	77 (81.9)	
Yes	38 (9.4)	15 (16.0)	
Unknown	3 (0.7)	2 (2.1)	
Pneumonia			.42
No	314 (77.9)	70 (74.5)	
Yes	87 (21.6)	24 (25.5)	
Unknown	2 (0.5)	0 (0.0)	
Method of lung cancer detection			.39
LDCT screening	235 (58.3)	49 (52.1)	
Chest radiography screening	71 (17.6)	22 (23.4)	
Not by any form of screening during the trial period	97 (24.1)	23 (24.5)	
Grade			.088
Well differentiated	81 (20.1)	8 (8.5)	
Moderately differentiated	153 (38.0)	41 (43.6)	
Poorly differentiated	136 (33.7)	36 (38.3)	
Undifferentiated	9 (2.2)	1 (1.1)	
Unknown	24 (6.0)	8 (8.5)	
Tumor size, mm	17 (12-25)	20 (15-28)	.03
Lymph node evaluation[a]			
Lymphadenectomy	357 (88.6)	86 (91.5)	.42
Mediastinoscopy	64 (15.9)	22 (23.4)	.08
Pathologic T status			.44
T1a	37 (9.2)	6 (6.4)	
T1b	165 (40.9)	32 (34.0)	
T1c	85 (21.1)	27 (28.7)	
T2a	72 (17.9)	20 (21.3)	
T2b	18 (4.5)	5 (5.3)	
T3	26 (6.5)	4 (4.3)	
Pathologic N status			.001
N0	365 (90.6)	74 (78.7)	
N1	38 (9.4)	20 (21.3)	
Operation type			.89
Lobectomy	383 (95.0)	89 (94.7)	
Bilobectomy	20 (5.0)	5 (5.3)	
Adjuvant chemotherapy	57 (14.1)	21 (22.3)	

(Continued)

survival time in months was calculated from the date of recurrence to death from any cause.

STATISTICAL ANALYSIS. Baseline characteristics of patients who underwent complete resection for pathologic stage I-II NSCLC and did or did not have a recurrence were evaluated with the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables.

The rate of recurrence in the study cohort was defined as the ratio of the number of recurrences to the number of person-years at risk for recurrence. The 2- and 5-year cumulative incidences of recurrence after resection were estimated by cumulative incidence functions. Differences in the cumulative incidence of recurrence between different groups were assessed by the Gray test.[10]

To identify factors associated with an increased risk of recurrence for patients in the study cohort who underwent curative resection, we used a multivariable Fine-Gray competing risks regression model.[6] The covariates included in this model were patient age, sex, race, comorbidities (ie, chronic obstructive pulmonary disease, adult-onset asthma, pneumonia), smoking pack-year history, smoking status (current vs former), prior history of cancer, histologic type, tumor size, tumor grade, tumor location, pathologic N status, and method of lung cancer detection (ie, by LDCT screening, by chest radiography screening, or not by any form of screening during the trial period). We chose to use a Fine-Gray model because it allows us to evaluate the risk of recurrence in the presence of competing risks. For example, after lung cancer resection, patients may die of cancer or of other causes before a recurrence can develop. Patients who die before they have a recurrence can influence the estimate of the probability for development of a recurrence. To account for this competing risk, the Fine-Gray model estimates a hazard function that adjusts for covariates for each failure (eg, recurrence vs death). Overall survival of patients who did or did not have a recurrence was evaluated by the Kaplan-Meier method.

The proportional hazards assumption was assessed with no violation identified. All P values $< .05$ were considered to be statistically significant. Statistical analyses were performed on version 17.0 of the Stata/MP software for PC (StataCorp LLC).

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY COHORT. A total of 497 patients underwent complete resection and were diagnosed with pathologic stage I-II NSCLC (Supplemental Figure). The 30-day mortality rate was 1.0% (n = 5) and the 90-day mortality rate was 1.8% (n = 9). During a median follow-up of 4.0 years, 94 patients had a recurrence—a rate of 4.9 (95% CI, 4.0-6.0) per 100 person-years. The 2- and 5-year

cumulative incidences of recurrence were 12.2% (95% CI, 9.4%-15.3%) and 20.1% (16.5%-23.9%), respectively. Baseline characteristics of patients who did or did not have a recurrence after complete resection for NSCLC are detailed in the Table.

INCIDENCE OF RECURRENCE STRATIFIED BY PATHOLOGIC STAGE. Of the 388 patients diagnosed with pathologic stage I disease, 66 had a recurrence—a rate of 4.2 (95% CI, 3.3-5.4) per 100 person-years. For patients diagnosed with pathologic stage I disease, the 2- and 5-year cumulative incidences of recurrence were 10.2% (95% CI, 7.4%-13.6%) and 17.9% (14.0%-22.1%), respectively.

Of the 109 patients diagnosed with pathologic stage II disease, 28 had a recurrence—a rate of 7.5 (95% CI, 5.2-10.8) per 100 person-years. For patients diagnosed with pathologic stage II disease, the 2- and 5-year cumulative incidences of recurrence were 20.2% (95% CI, 13.1%-28.4%) and 28.2% (19.6%-37.4%), respectively.

INCIDENCE OF RECURRENCE STRATIFIED BY METHOD OF LUNG CANCER DETECTION, HISTOLOGIC SUBTYPE, AND PREDOMINANT NODULE ATTENUATION. Of the 497 patients in the study cohort, 284 (57.1%) were diagnosed with lung cancer detected by LDCT screening (during one of the three screening rounds of the NLST), 93 (18.7%) were diagnosed with lung cancer detected by chest radiography screening (during one of the three screening rounds of the NLST), and 120 (24.2%) were diagnosed with lung cancer either after a negative or missed screening exam or during follow-up after the 3 screening rounds of the NLST were completed (here on out referred to as lung cancers not detected by any form of screening during the trial period). Supplemental Table 2 shows the baseline characteristics of patients in the study cohort stratified by the method of lung cancer detection. Supplemental Table 3 shows the incidence of recurrence stratified by the method of detection for the overall cohort and a subset of patients diagnosed with pathologic stage IA disease. The incidence of recurrence was highest for patients diagnosed with lung cancers not detected by any form of screening during the trial period and lowest for patients diagnosed with lung cancers detected by LDCT screening.

For patients diagnosed with pathologic stage IA NSCLC, the incidence of recurrence stratified by histologic subtype and by predominant nodule attenuation is shown in Supplemental Table 4 and Supplemental Table 5, respectively.

DISTRIBUTION OF RECURRENCE AFTER LOBECTOMY BY RECURRENCE TYPE AND SITE. Figure 1 shows the distribution of recurrences after lobectomy by recurrence type for each pathologic substage. For all pathologic substages evaluated, recurrences developed most commonly at distant sites and least commonly at locoregional sites.

TABLE Continued

Characteristic	No Recurrence	Recurrence	*P* Value
Adjuvant radiation therapy	4 (1.0)	5 (5.3)	
Histologic type			.33
Adenocarcinoma	185 (45.9)	53 (56.4)	
Lepidic adenocarcinoma	48 (11.9)	7 (7.5)	
Squamous cell carcinoma	104 (25.8)	21 (22.3)	
Adenosquamous cell carcinoma	10 (2.5)	0 (0)	
Large cell carcinoma	18 (4.5)	6 (6.4)	
Tumors formerly classified as bronchioloalveolar carcinoma, excluding lepidic adenocarcinoma	14 (3.5)	2 (2.1)	
Other	24 (6.0)	5 (5.3)	
Tumor location			.88
Left upper lobe	51 (12.7)	12 (12.8)	
Left lower lobe	99 (24.6)	18 (19.1)	
Right upper lobe	70 (17.4)	15 (16.0)	
Right middle lobe	24 (6.0)	6 (6.4)	
Right lower lobe	157 (39.0)	43 (45.7)	
Mainstem bronchus	1 (0.2)	0 (0.0)	
Unknown	1 (0.2)	0 (0.0)	

[a]Categories are not mutually exclusive. Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). COPD, chronic obstructive pulmonary disease; LDCT, low-dose computed tomography; NSCLC, non-small cell lung cancer.

Figure 2 shows the distribution of recurrences after lobectomy by site for each pathologic substage. Of patients diagnosed with pathologic stage IA disease, 48 patients experienced recurrence; the most common site of recurrence for these patients was the contralateral lung (n = 21 [43.8%]).

For patients diagnosed with pathologic stage IB disease who received adjuvant therapy, the most common sites of recurrence were the contralateral lung (n = 2 [40.0%]), ipsilateral lung (n = 2 [40.0%]), and brain (n = 2 [40.0%]). For patients diagnosed with pathologic stage IB disease who did not receive adjuvant therapy, the most common sites of recurrence were the brain (n = 5 [38.5%]) and ipsilateral lung (n = 5 [38.5%]). The most common site of recurrence for patients diagnosed with pathologic stage IIA disease was the contralateral lung (n = 2 [50.0%]). The most common site of recurrence for patients diagnosed with pathologic stage IIB disease who received adjuvant therapy was the bone (n = 6 [35.3%]), and the most common sites of recurrence for patients diagnosed with pathologic stage IIB disease who did not receive adjuvant therapy were the ipsilateral lung (n = 2 [28.6%]), adrenal gland (n = 2 [28.6%]), and bone (n = 2 [28.6%]; Figure 2).

PATTERNS IN THE TIMING OF CANCER RECURRENCE AFTER LOBECTOMY. The median number of months from resection to recurrence after lobectomy for pathologic stage IA, IB, IIA, and IIB disease were 22.9 (interquartile

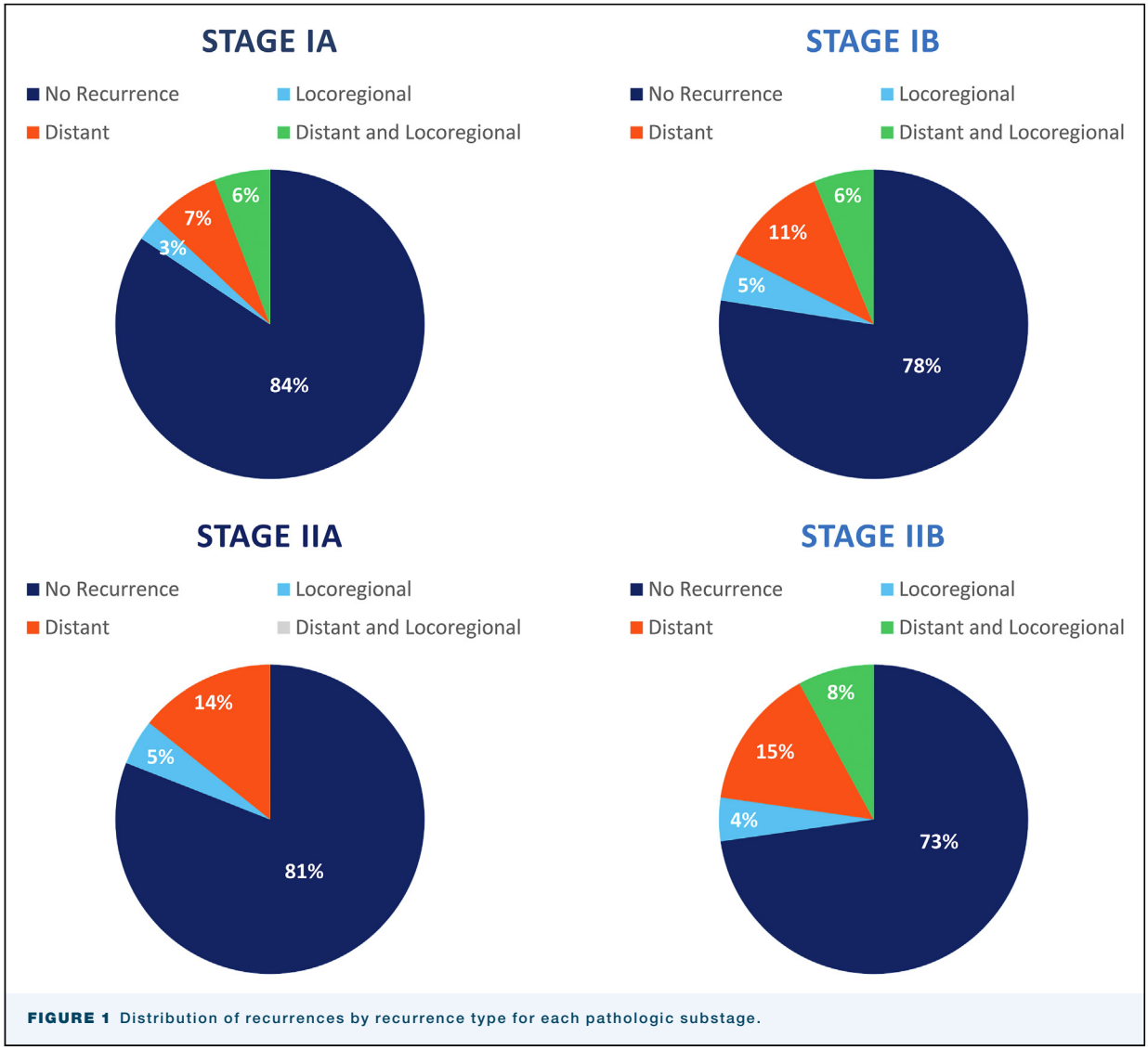

FIGURE 1 Distribution of recurrences by recurrence type for each pathologic substage.

range [IQR],10.9-34.7) months, 20.1 (IQR, 13.0-27.6) months, 30.6 (IQR, 22.4-38.0) months, and 12.8 (IQR, 8.3-22.1) months, respectively. The distribution of the time from resection to recurrence by pathologic stage is shown in Figure 3. Of note, for pathologic stage I and stage II disease, nearly 27.3% and 39.2% of recurrences developed during the first year after resection. However, 66.7% and 60.7% of recurrences still developed in patients diagnosed with pathologic stage I and stage II disease during the 1 to 4 years after resection, respectively.

PREDICTORS OF AN INCREASED RISK OF RECURRENCE AFTER LOBECTOMY. Predictors of an increased risk of recurrence after lobectomy included increased tumor size (subdistribution hazard ratio [SHR], 1.02; 95% CI, 1.00-1.05; $P = .047$), greater number of smoking pack-years (SHR, 1.01; 95% CI, 1.00-1.02; $P = .03$), and pathologic N1 status (SHR, 2.35; 95% CI, 1.31-4.24; $P = .004$; Supplemental Table 6). Compared with lung cancers detected by LDCT screening, lung cancers detected by chest radiography (SHR, 1.11; 95% CI, 0.62-1.98; $P = .73$) and lung cancers detected during follow-up (SHR, 1.42; 95% CI, 0.76-2.66; $P = .28$) had a similar risk of recurrence.

OVERALL SURVIVAL OF PATIENTS WHO DID NOT HAVE A RECURRENCE AFTER COMPLETE RESECTION. Figure 4 shows the overall survival of patients in the study cohort diagnosed with pathologic stage I and stage II NSCLC who did not have a recurrence. The 5-year overall survival of patients who underwent lobectomy for pathologic stage I disease and did not have a recurrence was 89.6% (95% CI:, 85.3%-92.8%). The 5-year overall survival of patients who underwent lobectomy for pathologic stage II disease and did not

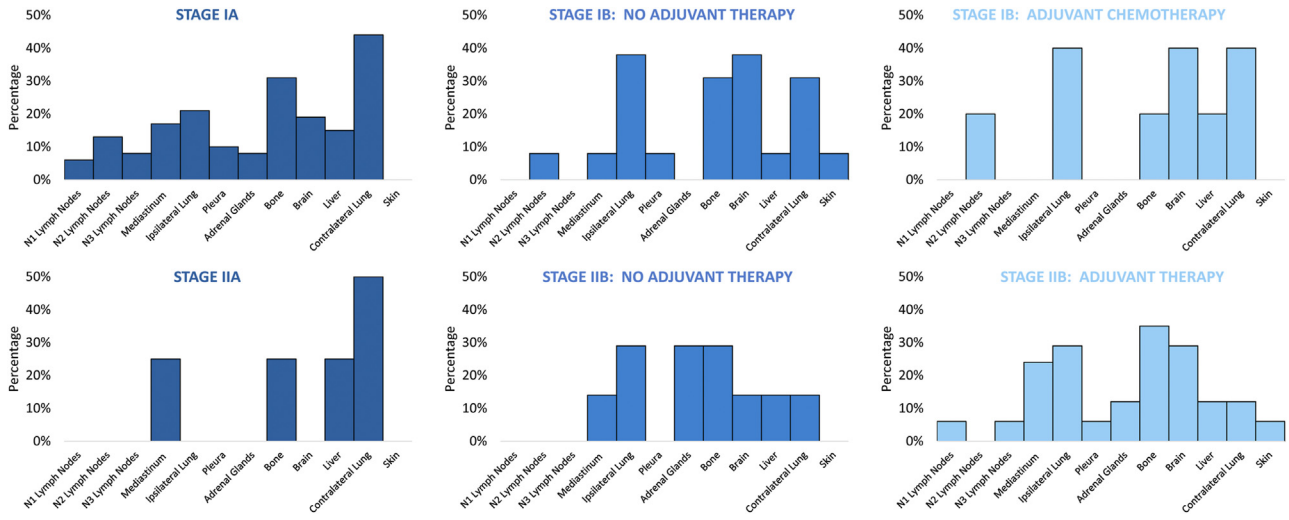

FIGURE 2 Sites of recurrence stratified by pathologic substage and the receipt of adjuvant therapy. Sites are not mutually exclusive (ie, patients may have had recurrence to both the brain and the liver).

have a recurrence was 83.6% (95% CI, 85.3%-92.8%). There were no statistically significant differences in overall survival of patients diagnosed with pathologic stage I vs stage II NSCLC who did not have a recurrence (log-rank, $P = .23$).

OVERALL SURVIVAL OF PATIENTS WHO DID HAVE A RECURRENCE AFTER COMPLETE RESECTION. Figure 5 shows the overall survival from the date of recurrence for patients in the study cohort diagnosed with pathologic stage I and stage II NSCLC who had a recurrence stratified by recurrence type. The median time from recurrence to death from any cause for patients diagnosed with pathologic stage I and stage II NSCLC was 28.9 (IQR, 15.6-not applicable) months and 10.2 (IQR, 1.9-24.8) months, respectively.

COMMENT

In this analysis of patients who underwent complete resection and were diagnosed with pathologic stage I or stage II NSCLC in the NLST, we found that the 5-year cumulative incidence of recurrence after resection was 20.1%. Although approximately 30% of recurrences developed during the first year after resection, approximately 65% of recurrences developed during the 1 to 4 years after resection. Patients with larger tumors, greater

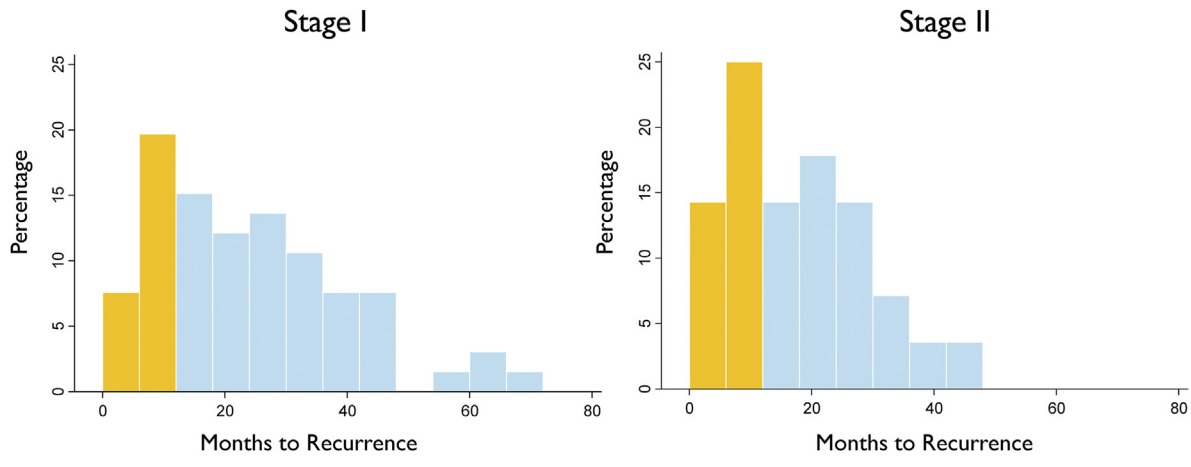

FIGURE 3 Distribution of the time from resection to recurrence by pathologic stage. Each bar represents a 6-month interval. The y-axis is the percentage of recurrences. The x-axis is the time from resection to recurrence. The orange bars indicate recurrences during the first year after resection. The light blue bars indicate recurrences >1 year after resection.

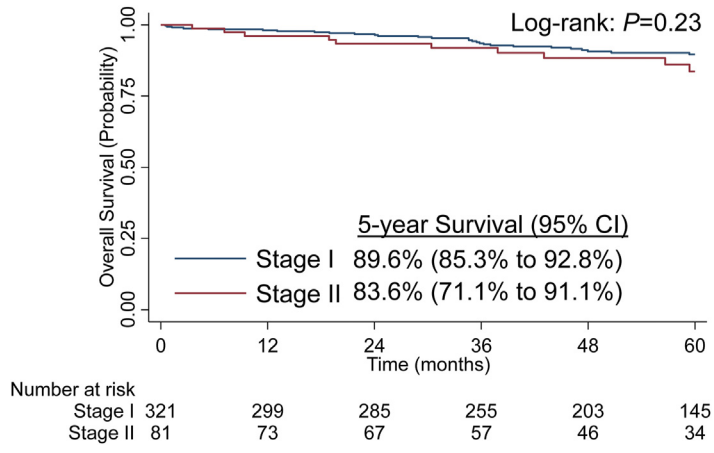

FIGURE 4 Overall survival of patients who did not have a recurrence stratified by pathologic stage. Of note, one patient who died intraoperatively was excluded from this analysis.

pack-year smoking history, and pathologic N1 disease were at greatest risk of recurrence. Median overall survival after recurrence, regardless of whether it was a locoregional or distant recurrence, was poor.

The findings of this study provide several important additions to the literature. First, we found that lung cancers detected by LDCT screening (during one of the three screening rounds of the NLST) had a lower incidence of recurrence compared with lung cancers detected by chest radiography screening (during one of the three screening rounds of the NLST) and lung cancers not detected by any form of screening during the trial period. This finding may be attributed to the greater proportion of indolent or slower growing lung cancers in the LDCT screening group, as evidenced by the increased proportion of lepidic adenocarcinoma and well-differentiated disease in patients diagnosed with lung cancers detected by LDCT screening (see Supplemental Table 2). In addition, patients with lung cancers detected by LDCT screening had smaller tumors compared with patients with lung cancers detected by chest radiography screening or during follow-up and thus may have had a lower likelihood of micrometastatic disease present at the time of diagnosis. Second, whereas the incidence of recurrence was lowest in patients diagnosed with lung cancers detected by LDCT screening, the 5-year cumulative incidence of recurrence was still 17.0% for these patients, suggesting that recurrence does remain a notable risk even for patients diagnosed with screen-detected lung cancer.

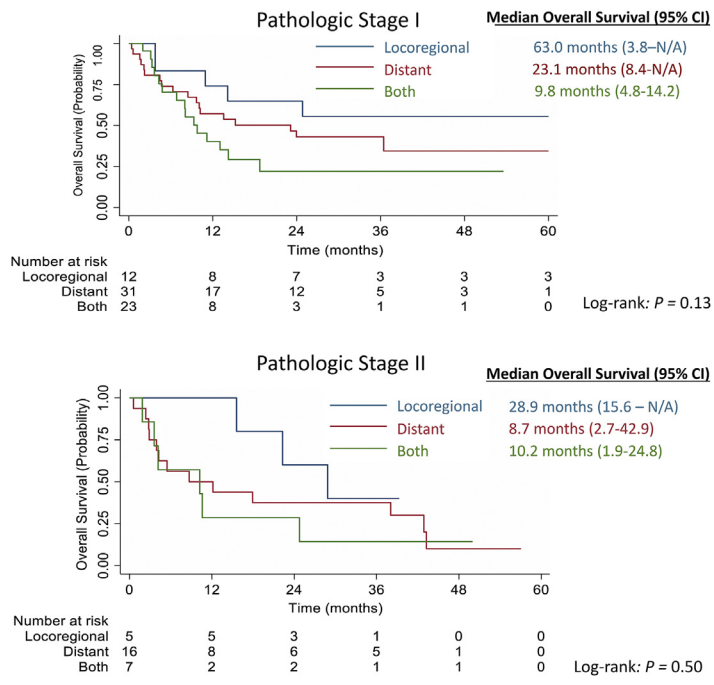

FIGURE 5 Overall survival after recurrence stratified by the type of recurrence and pathologic stage. The x-axis is the time from recurrence to death from any cause. (N/A, not applicable.)

Our finding that greater pack-year smoking history, larger tumor size, and the presence of nodal disease were associated with a significantly higher risk of recurrence for patients in our study cohort is consistent with previous literature.[4,11] In addition, we found that approximately 65% of recurrences developed during 1 to 4 years after resection. This finding corroborates the findings from previous studies reporting that elevated risks of recurrence persist for up to 4 years after resection.[6,12] Notably, this finding raises the question of whether current postoperative surveillance strategies appropriately reflect the risk of recurrence for patients undergoing curative-intent resection for early-stage disease. Perhaps, for some patients at higher risk of recurrence, more intense surveillance beyond 2 years may be warranted, and further investigation on optimal surveillance strategies is needed.

Several randomized trials have recently evaluated the use of immunotherapies[13,14] and targeted therapies[15] in the neoadjuvant and adjuvant setting to reduce the risk of lung cancer recurrence and to improve survival of patients undergoing resection for stage IB-IIIA resectable lung cancers. Based on the findings of CheckMate 816,[14] the National Comprehensive Cancer Network now recommends that all patients with resectable tumors ≥4 cm or node-positive disease undergo evaluation for induction nivolumab plus chemotherapy.[16] In addition, based on the results of the ADAURA trial[15] and Impower010,[13] the National Comprehensive Cancer Network recommends adjuvant osimertinib for resected stage IB-IIIB *EGFR*-positive NSCLC and adjuvant chemotherapy followed by atezolizumab for resected stage IIA-IIIB *EGFR*-negative

NSCLC.[16] Whereas the NLST preceded the advent of these therapies, it is likely that if patients in our cohort had access to present-day neoadjuvant and adjuvant immunotherapies and targeted therapies, the incidence of recurrence may have been lower than we observed in our cohort. In addition, there are several new salvage treatment strategies for recurrent disease that were not available at the time of the NLST, such as chemoradiotherapy followed by durvalumab for patients with recurrence to the N2 or N3 lymph nodes based on the Pacific Trial regimen,[17] which may have improved outcomes for some patients diagnosed with recurrent disease in our cohort. However, most patients (62%) in our cohort were diagnosed with pathologic stage IA disease, for which there are currently no Food and Drug Administration-approved adjuvant therapies.

LIMITATIONS. There are several limitations of this study. First, although the findings of this study provide valuable insight into the predictors and risks of recurrence in a screen-detected population, these findings may not be generalizable to all patients and may not reflect the risk of recurrence in populations outside of the NLST eligibility criteria. Second, adequate nodal dissection during lung cancer resection is critical to ensure accurate pathologic nodal staging and receipt of adjuvant therapy. However, the NLST does not include data on the number of lymph nodes removed or the specific lymph node stations sampled. Third, several factors that have been shown to be associated with increased risks of recurrence, including size of the invasive component of the tumor,[18] tumor mutations (eg, *KRAS* mutation, P53 deficiency),[19,20] lymphatic-vascular invasion,[21] visceral pleural invasion,[22] and postoperative complications,[23] are not available in the NLST. Fourth, given that the contralateral lung was a common site of recurrence for patients in our cohort, there may be concern that these recurrences were actually metachronous primary lung cancers. However, the NLST does capture data on whether patients had a subsequent primary lung cancer. Importantly, in the study cohort, 5% of patients had a subsequent primary lung cancer during follow-up, which is on par with the incidence of second primary lung cancer reported among patients with initial primary lung cancer in previous studies.[24,25] This suggests that the high rate of recurrences to the contralateral lung does reflect true recurrences and not metachronous primary lung cancer. Lastly, there are no data on the method by which lung cancers diagnosed during follow-up, after the 3 screening rounds of the NLST were completed, were detected. These lung cancers may have been detected incidentally. However, it is possible that some of these lung cancers were detected by screening, as some patients may have continued screening even after the 3 screening rounds of the NLST were completed.

CONCLUSION. In this national analysis of the NLST, we found that the 5-year cumulative incidence of recurrence after complete resection was 20.1%. The incidence of recurrence was lower for patients with lung cancers detected by LDCT screening compared with patients with lung cancers detected by chest radiography screening or not by any form of screening during the trial period (ie, those diagnosed after a negative or missed screening exam and those diagnosed during follow-up after the three screening rounds of the NLST were completed). Whereas nearly 30% of recurrences developed during the first year after complete resection, 65% of recurrences occurred during 1 to 4 years after complete resection.

The authors thank the National Cancer Institute for access to NCI's data collected by the National Lung Screening Trial (NLST). Data for the present study were obtained through the Cancer Data Access System (CDAS #: NLST-922).

FUNDING SOURCES

The authors have no funding sources to disclose.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Lung Cancer Screening Is Just Part of the Equation for Improving Survival for Early-Stage Lung Cancer

INVITED COMMENTARY:

The National Lung Screening Trial definitively demonstrated improved survival for patients with lung cancer who were screened with annual low-dose computed tomography.[1] As a result, the US Preventive Services Task Force recommends annual screening for lung cancer with low-dose computed tomography in adults 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Despite the proven benefit of early detection of lung cancer, the recurrence rate after curative-intent resection for early-stage lung cancer remains as high as 20% to 55%.[2] In this issue of *The Annals of Thoracic Surgery*, Potter and colleagues[2] demonstrate that participants in the National Lung Screening Trial who underwent complete resection for stage I-II non-small cell lung cancer (NSCLC) had a 5-year cumulative incidence of recurrence of 20%. Not surprisingly, 82% of the recurrences were at distant sites, which has a strong association with poor overall survival. This important point emphasizes that early detection of lung cancer is just part of the equation for improving survival for resectable early-stage NSCLC. Potter and colleagues also reconfirmed key risk factors for recurrence after complete resection of early-stage NSCLC, such as larger tumors, greater pack-year smoking history, and pathologic N1 disease. To better augment the survival advantage of early lung cancer detection, these risk factors must be effectively mitigated in addition to performing high-quality surgical resection.

In recent years, several randomized clinical trials have demonstrated improved survival with the use of perioperative immunotherapy and targeted therapy in patients with stage IB-IIIA resectable NSCLC.[3,4] The National Comprehensive Cancer Network now recommends that all patients with resectable NSCLC tumors ≥4 cm or node-positive (N1 or N2) disease should undergo evaluation for neoadjuvant nivolumab plus chemotherapy.[5] For adjuvant therapy, the National Comprehensive Cancer Network recommends adjuvant osimertinib for completely resected stage IB-IIIB NSCLC in patients with an exon 19 or 21 *EGFR*