Natural History of Stage I Non-Small Cell Lung Cancer*

Implications for Early Detection

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Background: **Concern has been raised that early detection of lung cancer may lead to the treatment of clinically indolent cancers. No population-based study has examined the natural history of patients with stage I NSCLC who receive no surgery, chemotherapy, or radiation therapy. Our hypothesis is that long-term survival in patients with untreated stage I non-small cell lung cancer (NSCLC) is uncommon.**

Methods: **A total of 101,844 incident cases of NSCLC in the California Cancer Center registry between 1989 and 2003 were analyzed; 19,702 patients had stage I disease, of whom 1,432 did not undergo surgical resection or receive treatment with chemotherapy or radiation. Five-year overall survival (OS) and lung cancer-specific survival were determined for this untreated group, for subsets of patients who were recommended but refused surgical resection, and for T1 tumors.**

Results: **Only 42 patients with untreated stage I NSCLC were alive 5 years after diagnosis. Five-year OS for untreated stage I NSCLC was 6% overall, 9% for T1 tumors, and 11% for patients who refused surgical resection. Five-year lung cancer-specific survival rates were 16%, 23%, and 22%, respectively. Among these untreated patients, median survival was 9 months overall, 13 months for patients with T1 disease, and 14 months for patients who refused surgical resection.**

Conclusion: **Long-term survival with untreated stage I NSCLC is uncommon, and the vast majority of untreated patients die of lung cancer. Given that median survival is only 13 months in patients with T1 disease, surgical resection or other ablative therapies should not be delayed even in patients with small lung cancers.** ***(CHEST 2007; 132:193–199)***

Key words: early detection; non-small cell lung cancer; screening; survival

Abbreviations: BAC = bronchioloalveolar carcinoma; CI = confidence interval; CCR = California Cancer Registry; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; OS = overall survival

Lung cancer is the most common cause of cancer death worldwide. At the time of diagnosis, only one third of cases are surgically resectable. Even among patients with surgically resected stage I lung cancer, 5-year survival is only approximately 70%.[1] The dismal prognosis of patients with lung cancer can be attributed to the aggressive biology of the

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disease, reflected in clinically undetectable micrometastases. Early detection may decrease lung cancer mortality, and promising results have been recently reported from several ongoing clinical trials of screening with CT scanning, including a remarkable 88% 10-year survival among patients with screen-detected stage I lung cancer in the International Early Lung Cancer Action Program screening study.[2,3]

At the same time, there has been concern that screening may lead to the detection of cancers so indolent that they would never result in clinical consequences.[4] In the Mayo lung project chest radiography screening trial,[5] more lung cancers were detected in the screened group than the unscreened group, but lung cancer mortality was equal in both groups. These results suggested that the excess lung cancers detected by screening did not contribute to lung cancer mortality.[5] These cancers have been referred to as *pseudodisease*.[4]

Lung cancer pseudodisease would be expected to manifest as indolent early stage cancers. If pseudodisease were common, some of these tumors would be detected incidentally and some patients would forego treatment. We recently reported that at least 50% of treated stage I lung cancers are detected incidentally.[6] Other investigators[2] have speculated that almost all lung cancers < 2 cm that were not screen detected were incidentally detected. Two population-based studies[7,8] of patients with unresected stage I lung cancers reported a 5-year survival of 17% and an 8-year survival of 12%, but did not have information on cause of death, reason for not undergoing treatment, and whether patients were treated with certain nonsurgical treatments such as chemotherapy.

We set out to determine whether there were long-term survivors among patients with stage I lung cancer who did not undergo surgery, chemotherapy, or radiation therapy in a large population-based cohort. Our hypothesis was that the vast majority of patients with clinical stage I lung cancer die of lung cancer within 5 years if untreated. To test this hypothesis, we analyzed the clinical characteristics and survival of patients with untreated lung cancer in the California Cancer Registry (CCR) between 1989 and 2003.

Materials and Methods

Data were obtained on 101,844 incident non-small cell lung cancer (NSCLC) cases in the CCR during the period from 1989 to 2003 with TNM staging data and complete follow-up data available. This included 19,702 stage I, 3,753 stage II, 10,429 stage IIIA, 22,285 stage IIIB, and 45,675 stage IV NSCLC patients. Recorded data included demographic information (age, gender, ethnicity), stage at presentation, histology, tumor size, tumor location, socioeconomic status, and vital status. Socioeconomic status is denoted as a single-index variable in CCR using statewide measures of education, income, and occupation as described previously.[9] Data were abstracted from medical and laboratory records by trained tumor registrars according to the California Tumor Registry.[10]

Tumor site and histology were coded according to criteria specified by the World Health Organization in International Classification of Diseases for Oncology.[11] Only histologically confirmed or cytologically confirmed NSCLC cases were included in the analysis. Tumors were identified using primary site and histology codes for NSCLC as follows: large cell carcinoma (8012, 8013, 8022, 8030, 8031), squamous cell carcinoma (8050–8052, 8070–8076), adenocarcinoma (8140–8239, 8260–8550), and bronchioloalveolar carcinoma (BAC) [8250–8254] as previously described.[12,13] Non-small cell histologies that were not identified with the above histologic codes and not coded as a metastatic lung lesion from a separate primary tumor were categorized as undifferentiated NSCLC, the majority of which were coded as 8010 (carcinoma not otherwise specified [NOS]), 8046 (non-small cell carcinoma NOS), or 8000 (neoplasm NOS), as previously described.[12,14]

Treatment during the first course of therapy was ascertained using available data from the CCR to determine whether patients underwent surgical resection, chemotherapy, or radiation therapy. Treatment data were available for 100,651 patients (98.8%), including 22,954 patients (22.3%) who did not receive any surgical, radiation, or chemotherapeutic treatment. Codes capturing the reason for not undergoing surgery reflected the following reasons: contraindications due to patient risk factors, patient died prior to planned surgery, recommended but not performed or refused by the patient, or because it was not part of the planned first course of treatment.

Cause of death was recorded according to the International Classification of Diseases criteria in effect at the time of death.[11] The last date of follow-up was either the date of death or the last date the patient was contacted. There was near-complete ascertainment of vital status by linkage to the California State mortality tapes and the National Death Index. There was no information on the extent of disease progression among survivors.

The subset of patients with stage I NSCLC who received no surgery, chemotherapy, or radiation treatment was analyzed. The clinical characteristics, including sex, age, histology, and tumor stage, of patients who were alive 5 years after diagnosis were compared to patients not surviving 5 years. A student t test was used to compare continuous variables. Pearson χ^2 test or Fisher exact test were used to compare categorical and dichotomous variables. Life tables and Kaplan-Meier curves were generated for all untreated stage I NSCLC patients, and for subsets of patients with stage I disease (*ie*, T1 or T2), or stage I patients who were recommended but did not undergo surgical resection. Overall survival was compared between two groups using Kaplan-Meier estimates, and comparisons between groups were analyzed with the log-rank test. Lung cancer-specific survival (*ie*, the proportion of patients who did not die from lung cancer) was compared for patients with stage I disease. All statistical analyses were conducted using software (SAS 9.1; SAS Institute; Cary, NC). Statistical significance was assumed for a two-tailed p value < 0.05.

Ethical Considerations

This research study involved analysis of existing data from the CCR database with no subject intervention. No identifiers were linked to subjects. Therefore, this study was approved by the

University of California Irvine Institutional Review Board under the category "exempt" status (#2004–3971).

Results

Information related to surgical treatment rendered on the primary tumor was available for 19,699 of the 19,702 stage I NSCLC patients (99.9%), among whom 16,184 (82%) underwent surgical resection (median overall survival [OS], 69 months; 95% confidence interval [CI], 67 to 71; 5-year OS, 54%). Of the remaining 3,515 patients, 1,432 patients (41%) did not receive chemotherapy or radiation therapy (Fig 1). Median overall survival among these untreated stage I NSCLC patients was 9 months (95% CI, 8 to 10 months) [Fig 2]. The estimated 5-year survival was 7%; 42 patients with untreated stage I NSCLC were alive 5 years after diagnosis. As summarized in Table 1, 26 of 42 untreated patients (62%) who were alive at 5 years were women, while 659 of 1,390 untreated patients (47%) who were dead by 5 years were women ($p = 0.06$). Patients who survived 5 years without treatment were younger at diagnosis than those who died (70 ± 1.6 years [SE], compared with 74 ± 0.3 years; $p = 0.004$). No statistically significant differences in socioeconomic status were detected between untreated patients surviving ≥ 5 years compared to those who died within 5 years of diagnosis ($p = 0.50$) [Table 1].

Histology of patients with untreated lung cancer is listed in Table 1. BAC was more common among surviving patients (14% compared with 5%, $p = 0.018$), while squamous cell was more common among nonsurviving patients (33% compared with 17%, $p = 0.029$). There was no statistical difference in the proportion of patients with adenocarcinoma among surviving and nonsurviving patients (38% compared with 29%, $p = 0.20$). Surviving patients were more likely to have T1 tumors (57% compared with 39%, $p = 0.02$). The median survival of patients with T1 disease was 13 months (95% CI, 11 to 15 months); 24 of 571 patients (4%) with T1 disease were alive at 5 years, with an estimated 5-year survival of 9% (Fig 3, *top*, *a*). The median survival of patients with T2 disease was 8 months (95% CI, 7 to 8 months); 17 of 853 patients (2%) with T2 disease were alive at 5 years, with an estimated 5-year survival of 5%.

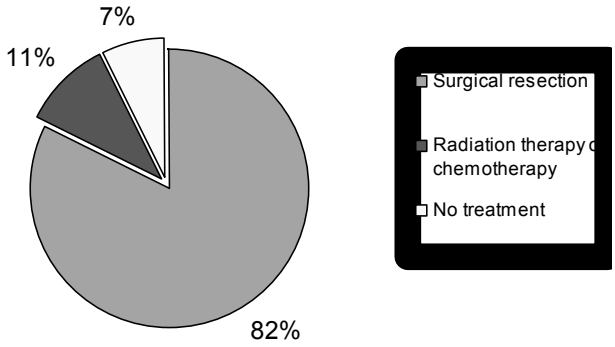

Figure 1. Treatment of patients with stage I NSCLC, as recorded in the CCR between 1989 and 2003.

Lung cancer-specific survival was analyzed for treated and untreated stage I NSCLC. Among patients with treated T1 NSCLC, the 5-year lung cancer-specific survival rate was 72%, with a median lung cancer-specific survival of 155 months (95% CI, 148 mo to upper limit not reached). Among patients with treated T2 lung cancer, the 5-year lung cancer-specific survival was 57%, with a median survival of 91 months (95% CI, 85 to 99 months). In contrast, the 5-year lung cancer-specific survival was 23% for patients with untreated T1 tumors and 12% for untreated T2 tumors. The median lung cancer-specific survival rates were 26 months (95% CI, 22 to 29 months) for patients with untreated T1 tumors and 10 months (95% CI, 9 to 11 months) for patients with untreated T2 tumors.

Among patients with T1 tumors ($n = 571$), those with tumors < 2 cm ($n = 264$) had improved OS (median OS, 15 months; 95% CI, 12 to 19 months; 5-year OS, 11%) compared with patients with tumors > 2 cm ($n = 307$; median OS, 12 months; 95% CI, 10 to 14 months; 5-year OS, 6%) [$p = 0.041$]. Lung cancer-specific survival at 5 years was 27% among patients with tumors < 2 cm and 20% among patients with tumors > 2 cm ($p = 0.003$).

Surgery was not performed because it was not part of the planned first course of treatment in 635 stage I patients (45%), because of contraindications due to patient risk factors in 317 patients (22%), and because it was recommended but not performed or refused by the patient in 455 patients (32%). Among untreated stage I NSCLC patients who were recommended but did not undergo lung resection, 28 patients (6%) were alive at 5 years, with a median survival of 14 months (95% CI, 13 to 17 months). The Kaplan Meier estimated 5-year survival for this group was 11% (Fig 3, *bottom*, *b*). Among untreated stage I NSCLC patients who were recommended but did not undergo lung resection, the 5-year lung cancer-specific survival was 22%, with a median lung cancer specific survival of 20 months (95% CI, 17 to 23 months).

Discussion

Our results show that long-term survival with untreated stage I NSCLC is uncommon. The esti-

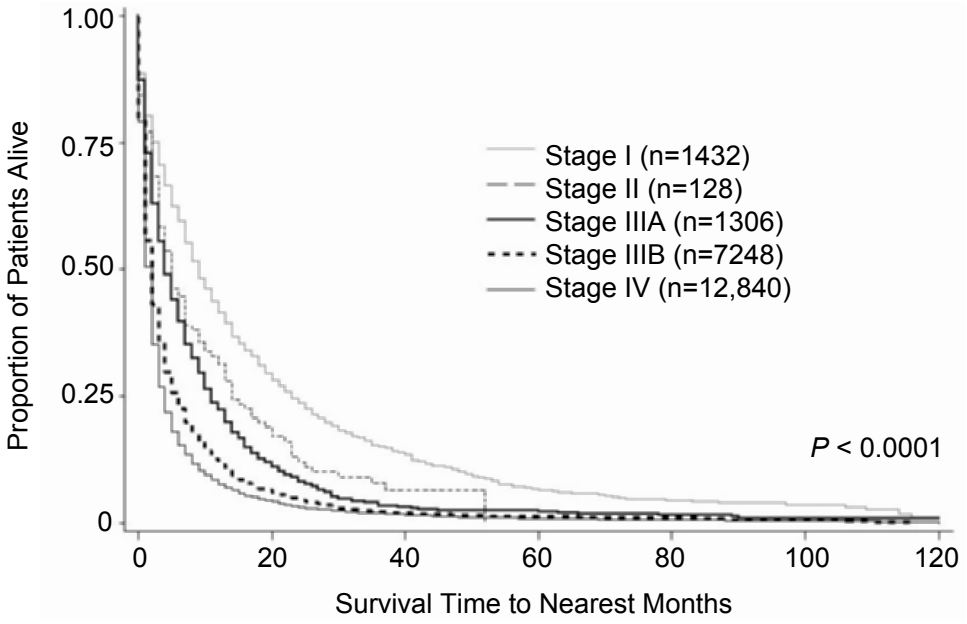

FIGURE 2. NSCLC in California from 1998 to 2003: overall survival for untreated patients with NSCLC, stage I-IV (n = 22,954). Five-year survival rates were 7% for stage I and 0% for stage II-IV.

mated 5-year survival of all untreated stage I patients in California during the study period was 7%, with a median survival of only 9 months. While many untreated patients did not undergo treatment due to underlying medical comorbidities, an estimated 89% of patients who were recommended to undergo surgical treatment but refused died within 5 years, with 78% of those patients dying of lung cancer.

Among patients who received no initial treatment, there were only 42 long-term survivors. As expected, patients who survived were somewhat younger than patients who died (70 years compared with 74 years) and were more likely to have smaller tumors. Long-term survivors were more likely to have BAC and less likely to have squamous cell carcinoma than nonsurvivors. BAC is a more clinically indolent subtype of NSCLC that is associated with improved long-term survival after surgical resection compared with other subtypes of NSCLC.[15] We recently reported that BAC is more common in patients with incidentally detected NSCLC.[6] The finding that BAC is more prevalent in survivors of untreated stage I NSCLC adds to existing evidence that at least some stage I BAC, which frequently appear on CT scan as semisolid nodules or ground-glass opacities, are clinically indolent lung cancers that might be of little clinical consequence.[15,16] Yet, these indolent tumors account for a very small proportion of stage I lung cancers overall and a minority of long-term survivors with untreated lung cancer.

Our findings are consistent with small institutional series[17,18] that reported few long-term survivors among patients with untreated stage I NSCLC. In a population-based study from Japan, Motohiro et al[7] reported that patients with stage I NSCLC had a 5-year survival rate of 17% without lung resection.

Table 1—*Clinical Characteristics of Untreated Patients With Stage I NSCLC (n = 1,432)**

Characteristics	Dead at 5 Years (n = 1,390)	Alive at 5 Years (n = 42)	p Value, *t* Test†
Female gender	659 (47)	26 (62)	0.064
Age, yr	74.4 ± 9.8	70.0 ± 10.1	0.0043
Histology			
Undifferentiated	380 (27)	10 (24)	0.61
Large cell	86 (6)	3 (7)	0.74
Squamous cell	453 (33)	7 (17)	0.029
Adenocarcinoma	403 (29)	16 (38)	0.20
BAC	68 (5)	6 (14)	0.018
T stage‡			
T1	547 (39)	24 (57)	0.02
T2	843 (61)	18 (43)	
Socioeconomic status			
Quintile 1 (lowest)	315 (23)	6 (14)	0.50
Quintile 2	276 (20)	8 (19)	
Quintile 3	320 (23)	13 (31)	
Quintile 4	252 (18)	6 (14)	
Quintile 5 (highest)	227 (16)	9 (21)	

*Data are presented as No. (%) or mean ± SD..

†Mean age comparison, *t* test; all other comparisons, χ^2 test or Fisher exact test.

‡T1 is defined as tumor size < 3 cm; T2 is defined as tumor size ≥ 3 cm or pleural invasion.

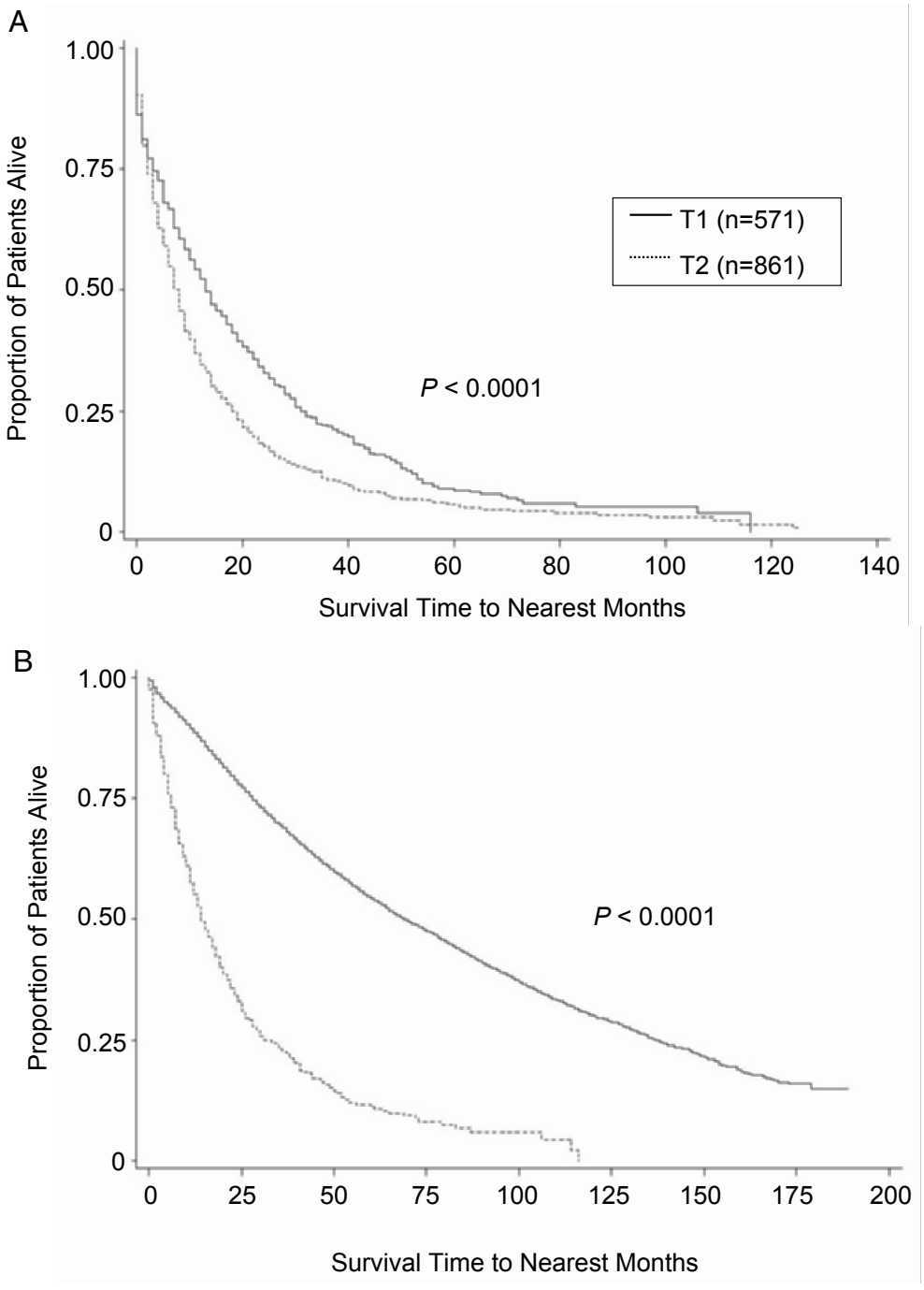

FIGURE 3. *Top*, *A*: Overall survival for untreated stage I NSCLC patients stratified by T stage. Five-year survival rates were 9% for T1 (n = 571) and 5% for T2 disease (n = 861). *Bottom*, *B*: Overall survival for untreated stage I NSCLC patients. Solid line, patients receiving surgery (n = 16,184); Dashed line, untreated patients who refused surgery (n = 455). Five-year survival rates were 54% for patients receiving surgery and 11% for patients who refused surgery.

Yet many patients in that study received radiation therapy or chemotherapy, likely resulting in an overestimation of the survival of untreated patients. Our study is the first large population-based study that included information on chemotherapy and radiation therapy, as well as information on cause of death and reason for not undergoing treatment.

This study has important implications for the treatment of stage I NSCLC. First, treatment of stage I lung cancer should not be delayed. Median survival without treatment was only 9 months overall and 13 months for T1 tumors. In contrast, the 5-year survival for patients with surgically resected stage I NSCLC is 60 to 80% in clinical studies,[1,19] and 54%

in this population-based analysis of unselected patients. Moreover, surgical mortality for lobectomy is on average $< 4\%$,[20] and $< 1\%$ at high volume centers.[21] In experienced hands, lobectomy or sublobar resection can be performed safely in patients with multiple comorbidities and advanced age.[22,23] In patients who are not surgical candidates, ablative procedures should be considered.

Our results also suggest that lung cancer pseudodisease is relatively uncommon. Although this study does not address patients with screen-detected lung cancers, it is probable that the majority of patients with stage I NSCLC in this study were asymptomatic. At least 50% of patients with surgically resected stage I NSCLC are incidentally detected, and it is likely that almost all lung cancers < 2 cm were incidentally detected.[2,6] The International Early Lung Cancer Action Program investigators[24–26] recently reported a remarkable 88% 10-year survival for stage I cancers detected by screening CT scan in their study; even among tumors < 2 cm, the size of most lung cancers detected on screening CT scan, long-term survival is uncommon without treatment. Only 14 of 264 patients with tumors < 2 cm were alive at 5 years without any treatment, with an estimated 5-year survival of 11%. Moreover, the large majority of these patients died of lung cancer.

Our study has several limitations. First, registry data only include information on the initial course of treatment. Patients could have had additional treatments late in the disease course. For example, a patient with early stage lung cancer who initially was untreated may have received palliative treatments after disease progression. We estimate that any bias introduced by including patients with late treatments would be very small and would result in slight overestimation of survival.

Next, untreated patients are more likely to have medical comorbidities that preclude treatment, leading to a high rate of death from causes other than lung cancer. While we did not have information in our database on comorbidities, we had information on the reason a patient did not undergo surgical resection and on cause of death. Even among patients who were recommended to undergo surgery but refused, the number of long-term survivors was small. Moreover, the estimated lung cancer specific mortality at 5 years was 78%. Among patients in poor health at high risk for lung resection, consideration should be given to nonoperative means of tumor ablation such as stereotactic radiotherapy.[27,28]

Another limitation of this study is that we do not have information on if or how the mediastinum was staged, either surgically by mediastinoscopy or radiographically by positron emission tomography. It is likely that at least some patients clinically staged as stage I NSCLC had stage II or III disease. As a result, the survival estimate for untreated stage I disease may be underestimated in this study.

This is the largest study of untreated stage I NSCLC reported to date. Our results underscore the therapeutic benefit of surgical resection for early stage lung cancer. Despite ongoing controversy regarding overdetection of clinically insignificant lung cancers with screening, untreated lung cancer is a fatal disease in the great majority of patients with stage I disease. While our study is observational, a randomized study of treatment of stage I NSCLC would be unethical to perform. Results from ongoing clinical trials of CT screening will provide important information on the benefit of treatment of screen-detected cancers relative to the harm caused by treating clinically indolent cancers.[24]

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