Young lung cancer patients undergoing surgery: Comparison of clinicopathological characteristics and outcomes in patients aged ≤50 years versus >50 years

Rachel T. Leo, BA, Evert A. Sugarbaker, BS, Miles McAllister, BA, Anupama Singh, MD, Rafael R. Barcelos, MD, Ali Basil Ali, MD, Raphael Bueno, MD, Michael T. Jaklitsch, MD, Paula Ugalde Figueroa, MD, and Scott J. Swanson, MD

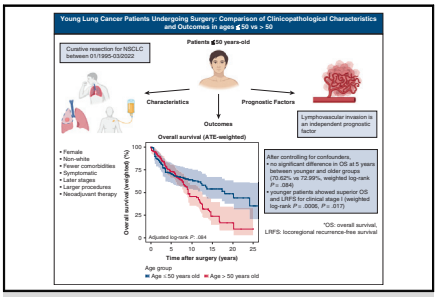
ABSTRACT

Objective: We investigated clinicopathologic characteristics, overall survival (OS), and locoregional recurrence-free survival of young surgical patients with non–small cell lung cancer.

Methods: Retrospective review of an institutional database of patients aged 50 years or younger undergoing resection for non–small cell lung cancer between January 1995 and March 2022. A control group of patients older than age 50 years was selected by stratified random sampling. Relevant characteristics were compared with Wilcoxon rank sum,χ^2 and Fisher exact tests. Propensity-score weighting was used to control for confounders. OS and locoregional recurrence-free survival were analyzed with Kaplan-Meier and Cox proportional hazards regression.

Results: We identified 196 patients aged 50 years or younger and 232 patients older than age 50 years. Median age was 46 years (interquartile range, 43-49 years) in the younger group and 69 years (interquartile range, 63-74 years) in the older group. Younger patients were more often women, non-White, and with fewer comorbidities. They more often presented with symptoms, stage III or IV disease, and more often received neoadjuvant therapy. In unweighted analysis, younger patients showed superior OS (log-rank $P < .0001$). After propensity score weighting for procedure type, histologic type, Charlson Comorbidity Index, and smoking status, there was no significant difference in OS at 5 years between younger and older groups (70.62% vs 72.99%; weighted log-rank $P = .084$). Younger patients showed superior OS (weighted log-rank $P = .0006$) and locoregional recurrence-free survival (weighted log-rank $P = .017$) for clinical stage I, but not any other stage. lymphovascular invasion was an independent risk factor for worsened OS and locoregional recurrence-free survival across ages.

Conclusions: Recognizing lung cancer as a differential diagnosis for patients aged 50 years or younger is crucial because this group shows superior outcomes for stage I disease. Lymphovascular invasion is an independent prognostic risk factor across age groups. (JTCVS Open 2025;24:409-22)



Graphical abstract.

CENTRAL MESSAGE

Young surgical patients with NSCLC show superior long-term outcomes, driven by stage I. We emphasize the independent prognostic significance of lymphovascular invasion across ages.

PERSPECTIVE

Identifying lung cancer in young patients with typical lung cancer symptoms and demographic risk factors is crucial because this group shows improved outcomes for stage I disease. Lymphovascular invasion is an independent prognostic risk factor across age groups irrespective of cancer stage, histologic type, and patient factors, emphasizing need for further investigation of its mechanisms.

Lung cancer remains a major public health issue, claiming more than 127,000 lives annually and approximately one-fifth of cancer-related deaths in the United States.[1] According to the Surveillance, Epidemiology, and End Results Program, lung and bronchus cancer is most frequently diagnosed among individuals aged 65 to 74 years, with a median age

From the Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, Mass.

Dr Singh is supported by the Jack Mitchell Thoracic Oncology Fellowship.

Approved by Mass General Brigham IRB Protocol #2023P000860 on April 19, 2023.

Received for publication May 21, 2024; revisions received Oct 30, 2024; accepted for publication Nov 27, 2024; available ahead of print Jan 18, 2025.

Address for reprints: Rachel T. Leo, BA, Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, 15 Francis St, Boston, MA 02215 (E-mail: rtleo22@gmail.com).

2666-2736

https://doi.org/10.1016/j.xjon.2024.12.008

Abbreviations and Acronyms

NSCLC = non–small cell lung cancer
CCI = Charlson Comorbidity Index
CT = computed tomography
OS = overall survival
LR = locoregional recurrence
LRFS = locoregional recurrence-free survival
LVI = lymphovascular invasion
VPI = visceral pleura invasion

at diagnosis of 71 years.[2] However, studies have shown a distinct lung cancer population that is aged 50 years and younger who are more likely to be women, never-smokers, and non-White. This cohort often presents with more advanced disease manifestations, including larger tumor sizes, nodal metastases, and receives more aggressive treatment.[3-12] We refer to this group as young lung cancer patients.

The prognosis for young lung cancer patients remains a subject of debate. Initial studies suggest comparable long-term outcomes to their older counterparts.[13-16] Other studies indicate improved survival and recurrence among younger patients.[5-7,9,11,17-20] Furthermore, few studies focus on individuals who have undergone surgical treatment for lung cancer or compare outcomes by cancer stage.

In this study, we review our lung cancer experience to investigate differences in clinicopathological characteristics and long-term outcomes between younger and older patients undergoing curative surgical resection for non–small cell lung cancer (NSCLC).

PATIENTS AND METHODS

Patient Selection

This study was approved by the Mass General Brigham Institutional Review Board under protocol #2023P000860; April 19, 2023, and informed consent was waived. We retrospectively reviewed our institutional database and identified patients who were aged 50 years and younger (younger group) and underwent curative resection for NSCLC between January 1995 and March 2022. A control group of patients older than age 50 years (older group) who underwent curative resection for NSCLC during the same time period was selected by stratified random sampling.[21-23] With this sampling method, all patients in our database older than age 50 years were stratified by age and randomly selected from strata to create a proportionate control group that was representative of the older population of patients with lung cancer. This approach ensured balanced comparisons between younger and older cohorts while proportionately representing the heterogeneity of the older patient population. For both younger and older groups, patients with a prior primary lung cancer diagnosed within 5 years of the surgery and those who underwent synchronous resection of nonlung cancer pulmonary metastases were excluded.

Data Collection

An electronic medical record system was utilized to collect patient demographics, operative details, pathology report, postoperative outcomes, and long-term follow-up data. All operations were performed at a single tertiary care hospital by a team of board-certified thoracic surgeons. Postoperative follow-up consisted of physical examination and surveillance computed tomography imaging at least every 6 months for the first 3 years and at least annually thereafter. Patients who were originally staged with the seventh edition of the American Joint Committee on Cancer staging system were reviewed and restaged according to the eighth edition.

Locoregional Recurrence

Recurrence was confirmed by histology and/or surveillance positron emission tomography/computed tomography imaging interpreted by a trained thoracic radiologist. Locoregional recurrence (LR) was defined as recurrence along the staple line, within the same lobe, or within ipsilateral lobar, hilar, or mediastinal lymph nodes. The date of recurrence was deemed to be the first radiologic presentation of a confirmed recurrence.

Statistical Analysis

Clinical and pathological characteristics of the younger and older groups were compared using the following tests: Wilcoxon rank sum test for continuous variables and χ^2 and Fisher exact tests for categorical variables.

Long-term oncologic outcomes analyzed were overall survival (OS) and LR-free survival (LRFS). A failure event in OS was death, whereas a failure event in LRFS was defined as death or LR, whichever came first. A propensity-score weighted analysis was used to adjust for clinically relevant confounding variables, including specimen type, histologic type, Charlson Comorbidity Index (CCI), and smoking status. To maintain an adequate sample size, propensity-weighting follows a propensity-score matching model without requiring the exclusion of cases.[24] OS and LRFS were evaluated using Kaplan-Meier analysis, and differences in survival between the younger and older groups were evaluated using log-rank hypothesis tests. Patients who were confirmed deceased with no known date of death and patients with no follow-up were excluded from OS analyses. Likewise, patients with no follow-up were excluded from LRFS analyses.

Multivariable Cox proportional-hazards regression models were used to evaluate the independent effect of clinically relevant variables on OS and LRFS by controlling for potential confounding variables. To prevent model overfitting, the number of variables included in each multivariable regression was limited such that at least 10 events occurred over the study period per variable. Patients with missing data in a variable included in a regression model were excluded from that regression analysis.

Statistical analyses were performed using Stata Statistical Software (StataCorp) and R Statistical Software version 4.2.1 (R Foundation for Statistical Computing).

RESULTS

A total of 3687 patients of all ages were identified: 196 (5.3%) patients aged 50 years or younger and 3491 (94.7%) older than age 50 years at the time of their surgery. One hundred ninety-six young patients were included in the younger experimental group, and 232 patients were included in the older control group for analysis. Median age was 46 years (interquartile range, 43-49 years; range: 18-50 years) in the younger group and 69 years (interquartile range, 63-74 years; range: 51-90 years) in the older group. A flow chart detailing cohort selection is shown in Figure 1.

Demographic and Clinical Characteristics

Differences in patient demographic and clinical characteristics are shown in Table 1. Younger patients were more often women (72% vs 58%; $P = .002$), non-White (15% vs 5.3%; $P < .001$), and never-smokers (31% vs

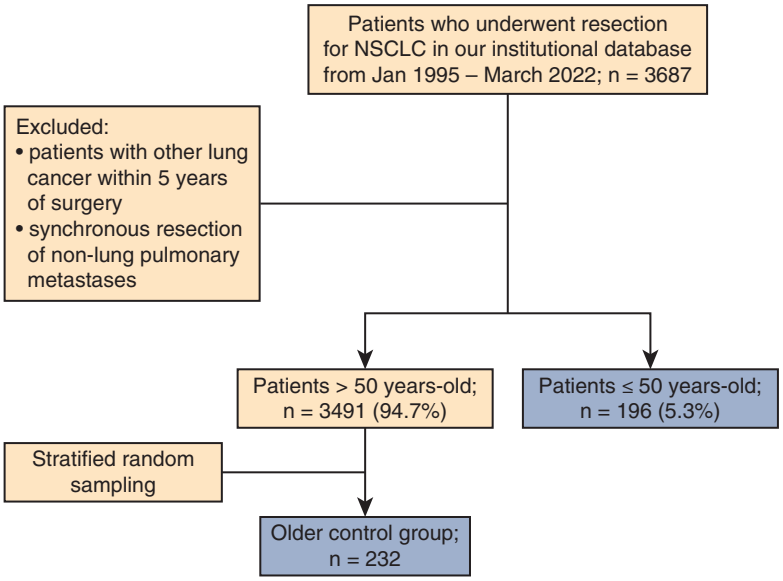


FIGURE 1. Exclusion criteria of overall cohort. *NSCLC*, Non–small cell lung cancer.

13%; $P < .001$) with fewer comorbidities ($P < .001$). Younger patients were also significantly more likely than older patients to be never smokers (31% vs 13%; $P < .001$) or current smokers (49% vs 19%; P .001). There was no significant difference in baseline pulmonary function (forced expiratory volume in 1 second, 0.89 [range, 0.75-1.03] vs 0.86 [range, 0.68-1.01]; $P = .164$).

Younger patients were more likely to receive a diagnostic scan for lung cancer prompted by typical lung cancer symptoms, such as dyspnea, cough, and chest pain (63% vs 40%; $P < .001$), whereas older patients were more likely to have a history of other cancer (32% vs 12%, respectively; $P < .001$) and thus more likely to receive a diagnostic scan during follow-up for other conditions. There were no significant differences between the 2 groups regarding types of symptoms at presentation or documented length of symptoms (Table E1).

Although older patients were more likely to present with clinical stage 0 or I disease (86% vs 73%; $P < .001$), younger patients were more likely to present with clinical stage III (15% vs 7.3%; $P = .013$) or clinical stage IV disease (3.6% vs 0.4%; $P = .026$) and were more likely to receive neoadjuvant treatment (20% vs 8.2%; $P < .001$).

Pathological and Operative Characteristics

Differences in pathological and operative characteristics are shown in Table 2. Younger patients were more likely to undergo lobectomies (62% vs 46%; $P = .009$). Older patients were more likely to receive segmentectomies (17% vs 9.7%; $P = .024$) and wedge resections (33% vs 22%; $P = .018$). Older patients more often had synchronous primary tumors (7.8% vs 0.5%; $P < .001$). Younger patients were more likely than older patients to have a nonadenocarcinoma and nonsquamous cell carcinoma subtype of NSCLC, such as large cell carcinoma (19% vs 7.3%; $P < .001$). Furthermore, younger patients were more likely to have a mixed adenocarcinoma histological subtype ($P < .0001$).

There were no significant differences between older and younger patients regarding pathologic staging. In the younger and older groups combined, 18 patients had pathological stage 0 disease at time of resection, including 14 pT0 patients who had previously received neoadjuvant therapy for clinical stage II through IV disease, and 4 pTis patients who had not received previous neoadjuvant therapy. There were also no significant differences in the presence of visceral pleura invasion (VPI) ($P = .6$) or lymphovascular invasion (LVI) ($P = .4$). Younger patients were more likely to receive adjuvant therapy (18% vs 15%, respectively, $P = .047$). There was no significant difference in hospital lengths of stay between the 2 groups, both with a median of 4 days.

Survival and Recurrence

Median follow-up for the entire study cohort was 72 months. In the unweighted Kaplan-Meier analysis, younger patients showed improved OS compared with older patients (log-rank $P < .0001$). After propensity-weighting for procedure type, histologic type, CCI, and smoking status, there was no significant difference in OS at 5 years between younger and older groups (70.62% vs 72.99%; weighted log-rank $P = .084$) (Figure 2).

In a subgroup analysis of outcomes by clinical stage, the younger group showed superior OS over the older group (79.00% vs 73.30% at 5 years; weighted log-rank $P = .0006$) and LRFS (69.70% vs 65.30% at 5 years; weighted log-rank $P = .017$) for clinical stage I (Figures

TABLE 1. Summary statistics of clinical characteristics

Characteristic	N	Older group (>50 y) (n = 232)	Younger group (≤50 y) (n = 196)	*P* value*	Weighted *P* value
Age (y)	428	69 (63-74)	46 (43-49)	**<.001**	**0**
Sex	428			**.002**	**.016**
Male		97 (42)	54 (28)		
Female		135 (58)	142 (72)		
Race/ethnicity	421			**.035**	.416
White		216 (95)	164 (85)	**<.001**	
Black or African American		5 (2.2)	13 (6.6)	**.022**	
Hispanic		4 (1.8)	7 (3.6)	.071	
Asian		3 (1.3)	8 (4.1)	.2	
Arabic		0 (0.0)	1 (0.5)	.5	
Smoking status				**<.001**	.654
Never		29 (13)	61 (31)	**<.001**	
Current		44 (19)	96 (49)	**<.001**	
Former		159 (69)	39 (20)	**<.001**	
Charlson Comorbidity Index	428	2.00 (2.00-3.00)	5.00 (3.00-6.00)	**<.001**	
FEV1 (% predicted)	401	0.86 (0.68-1.01)	0.89 (0.75-1.03)	.164	.281
Size on CT Imaging	418	2.00 (1.30-3.00)	2.10 (1.40-3.70)	**.003**	**.001**
Clinical stage by numerical group	426			**<.001**	**0**
Stage 0		18 (7.9)	1 (0.5)	**<.001**	
Stage 1a		150 (65)	124 (64)	.9	
Stage 1b		28 (12)	16 (8.2)	.2	
Stage 2		14 (6.0)	17 (8.8)	.3	
Stage 3		17 (7.3)	29 (15)	**.013**	
Stage 4		1 (0.4)	7 (3.6)	**.026**	
Neoadjuvant therapy	428	19 (8.2)	39 (20)	**<.001**	**0**

Values are presented as median (interquartile range) or n (%). Bolded *P* values indicate statistical significance. *FEV1*, Forced expiratory volume in 1 second; *CT*, computed tomography. *Wilcoxon rank sum test, Pearson Chi-squared test, or Fisher exact test.

3 and 4). None of the weighted OS or LRFS analyses for stage 0, 2, 3, or 4 differed significantly between younger and older groups, but OS for clinical stage 3 disease was closest to reaching significance (36.30% younger vs 60.20% older at 5 years; weighted log-rank $P = .082$) (Figures 3 and 4).

Multivariable Analysis

Factors influencing OS and LRFS in young patients on univariable analyses can be found in Table E2.

When analyzing the 2 age groups in a multivariable analysis after propensity-weighting for procedure type, histologic type, CCI, and smoking status, LVI was an independent risk factor for worsened OS and LRFS for both younger and older patients (Table E3). Pathologic cancer stage and receipt of adjuvant therapy were not independent risk factors for worsened OS or LRFS.

See Figure 5 for a graphical abstract of the study.

DISCUSSION

Our study reaffirms findings indicating that young lung cancer patients are more likely to be women, non-White, nonsmokers, and present with adenocarcinoma.[3-7,10-12] Approximately 5% to 10% of lung cancer cases occur in patients aged 50 and younger.[25,26] This is reflected in our institutional database, where 5.3% of lung resections in the younger group were performed for malignancy. This not only attests to the infrequency of young lung cancer patients but also highlights the scarcity of young patients presenting at a cancer stage typically amenable to surgical resection. Our study focused on the prognosis of this specific cohort who underwent curative resection for NSCLC.

Most patients (86% of older patients and 73% of younger patients) in our study had clinical stage I disease and lower, when surgical resection is the standard treatment. It is important to note that younger patients are more likely to harbor targetable driver mutations for treatment,[7,9] present at more advanced disease stages,[3,7,11] and begin their treatment sooner than older patients after first presentation.[7] In the 1990s, neoadjuvant therapy was rarely used for NSCLC, but by the early 2000s, landmark clinical trials began to support its application, especially for stage III disease. In our study, 3 patients with clinical stage III disease before 2000 (2 older and 1 younger) did not receive neoadjuvant

TABLE 2. Summary of pathological, surgical, and postoperative characteristics

Characteristic	n	Older group (>50 y) (n = 232)	Younger group (≤50 y) (n = 196)	*P* value*	weighted *P* value
Surgical primary specimen	428			**<.001**	.32
Wedge resection		76 (33)	44 (22)	**.018**	
Segmentectomy		40 (17)	19 (9.7)	**.024**	
Lobectomy		114 (49)	121 (62)	**.009**	
Pneumonectomy		1 (0.4)	6 (3.1)	.051	
Pancoast resection		1 (0.4)	6 (3.1)	.051	
Total lymph node count	425	4 (2-8)	6 (3-9)	.116	.232
Tumor size at pathology	428	1.90 (1.20-3.10)	2.00 (1.20-2.93)	.283	.59
Tumor focality	422			**<.001**	**0**
Single tumor		204 (88)	185 (94)	**.021**	
Synchronous primary tumors		**18 (7.8)**	**1 (0.5)**	**<.001**	
Multifocal disease		9 (3.9)	5 (2.6)	.4	
Histologic type	428			**.002**	.771
Adenocarcinoma		180 (78)	133 (68)	**.024**	
Squamous cell carcinoma		35 (15)	26 (13)	.6	
Other NSCLC		17 (7.3)	37 (19)	**<.001**	
Adenocarcinoma subtype	236			**<.001**	**.009**
Acinar		72 (51.4)	41 (42.7)	.233	
Lepidic		34 (24.3)	17 (17.7)	.262	
Micropapillary		4 (2.9)	1 (1.0)	.651	
Mixed		3 (2.1)	22 (22.9)	**<.0001**	
Papillary		10 (7.1)	5 (5.2)	.600	
Solid		17 (12.1)	10 (10.4)	.836	
Pathologic stage by numerical group	428			.276	**.001**
Stage 0		6 (2.6)	9 (4.6)	.3	
Stage 1a		134 (58)	112 (57)	.9	
Stage 1b		53 (23)	32 (16)	.092	
Stage 2		24 (10)	22 (11)	.8	
Stage 3		12 (5.2)	18 (9.2)	.11	
Stage 4		4 (1.7)	3 (1.5)	>.9	
Visceral pleura invasion	427	44 (19)	33 (17)	.6	.859
Lymphovascular invasion	426	28 (12)	29 (15)	.4	.074
Adjuvant therapy received	415	34 (15)	33 (18)	**.047**	**0**
Hospital length of stay	413	4 (2-6)	4 (3-5)	.693	.96

Values are presented as median (interquartile range) or n (%). Bolded *P* values indicate statistical significance. *NSCLC*, Non–small cell lung cancer. *Wilcoxon rank sum test, Pearson χ^2 test, Fisher exact test.

treatment, with 1 receiving adjuvant therapy. Given the limited number of patients eligible for neoadjuvant treatment, we believe this would not significantly influence our analysis.[27,28] Currently, the American Cancer Society recommends yearly lung cancer screening scans for current and past smokers who are aged 50 to 80 years.[29] Given that younger patients do not qualify for yearly screening scans, our cohort demonstrated that young patients were more likely to undergo diagnostic scans due to lung cancer symptoms and thus more likely than older patients to present with clinical stage III or IV disease. Furthermore, using the SEER database, Thomas and colleagues[6] reported that young patients, aged 40 years and younger, were more likely to undergo surgery at each stage compared with patients older than age 40 years ($P = .0054$ to $< .0001$). This may further contribute to the observation that younger surgical patients more often present with clinical stage III or IV disease.

Existing research yields conflicting findings regarding long-term survival in young versus older patients. Although some studies suggest comparable OS between age groups,[13-16] most of the current literature reports young patients exhibiting superior long-term outcomes postsurgery

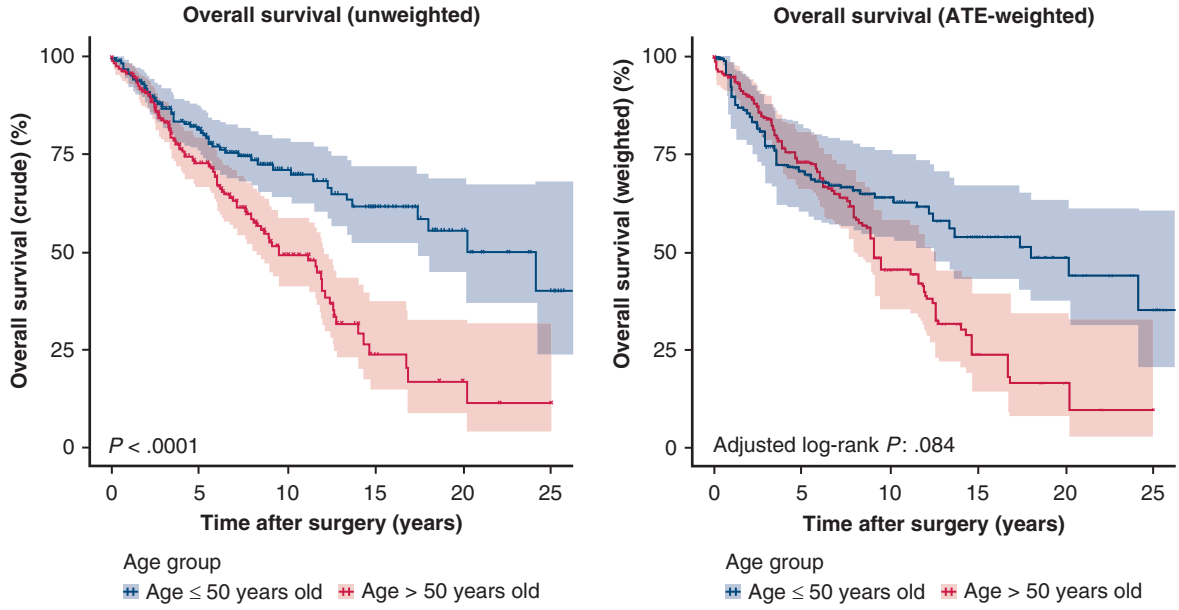


FIGURE 2. Unweighted and propensity-score weighted Kaplan-Meier curves with 95% CI for overall survival.

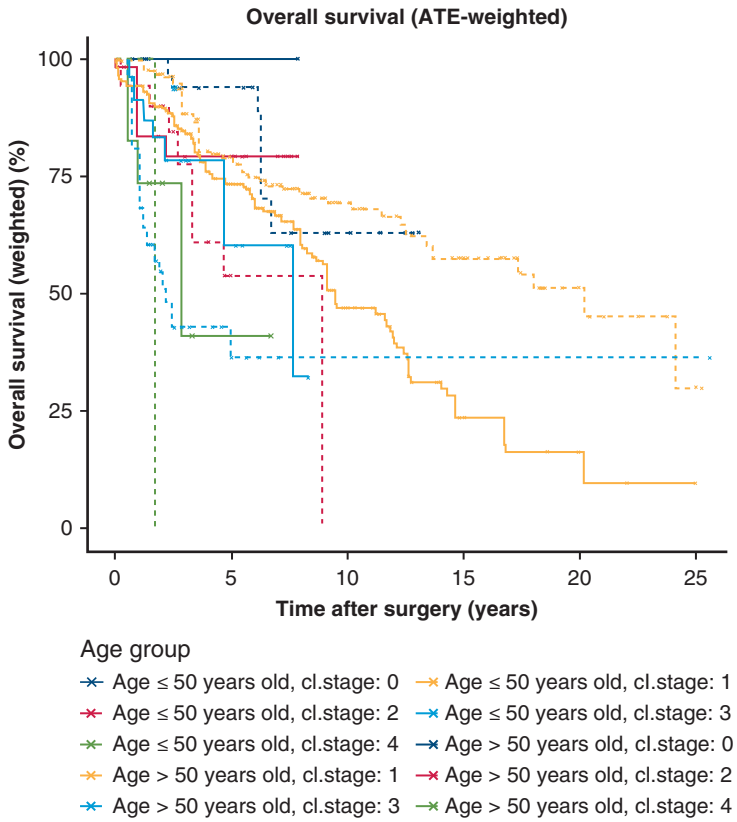


FIGURE 3. Propensity-score weighted Kaplan-Meier curve for overall survival, stratified by clinical stage and age group. For patients aged 50 years or younger, the 5-year overall survival rates and 95% CI by clinical stage were as follows: Stage 0 (100.0%; CI, 100.0%-100.0%), Stage I (79.0%; 95% CI, 66.5%-93.8%), Stage II (79.2%; 95% CI, 56.3%-100.0%), Stage III (36.3%; 95% CI, 18.7%-70.4%), and Stage IV (40.9%; 95% CI, 12.9%-100.0%). For patients older than age 50 years, the 5-year overall survival rates and 95% CIs by clinical stage were: Stage 0 (93.8%; 95% CI, 85.2%-100.0%), Stage I (73.3%; 95% CI, 65.3%-82.3%), Stage II (53.8%; 95% CI, 27.5%-100.0%), and Stage III (60.2%; 95% CI, 35.6%-100.0%).

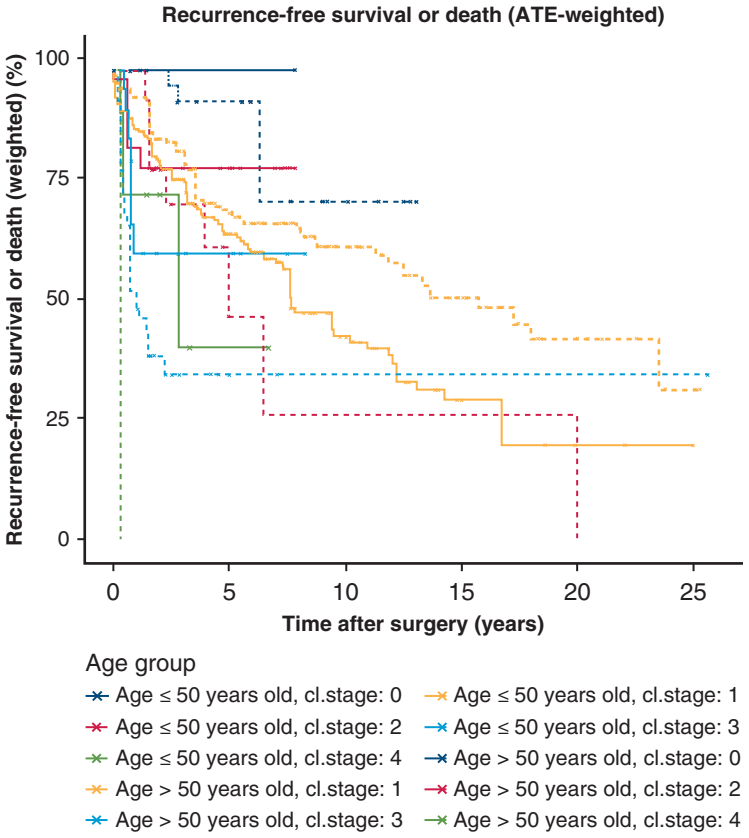


FIGURE 4. Propensity-score weighted Kaplan-Meier curve for locoregional recurrence-free survival, stratified by clinical stage and age group. For patients aged 50 years or younger, the 5-year locoregional recurrence-free survival rates and 95% CIs by clinical stage were as follows: Stage 0 (100.0%; 95% CI, 100.0%-100.0%), Stage I (69.7%; 95% CI, 57.7%-84.1%), Stage II (79.3%; 95% CI, 56.4%-100.0%), Stage III (35.3%; 95% CI, 18.7%-66.5%), and Stage IV (40.9%; 95% CI, 12.9%-100.0%). For patients older than age 50 years, the 5-year locoregional recurrence-free survival rates and 95% CIs by clinical stage were: Stage 0 (93.3%; CI, 84.1%-100.0%), Stage I (65.3%; 95% CI, 56.1%-75.9%), Stage II (47.6%; 95% CI, 22.6%-100.0%), and Stage III (61.1%; 95% CI, 39.4%-94.7%).

compared with their older counterparts.[11,12,18,20] Studies suggest that the improved survival in young patients is driven by a pronounced benefit at earlier cancer stages, though these studies are not limited to patients undergoing surgical resection.[5-7,9,17,19] Our study found that improved OS and LRFS in younger patients is driven by stage I disease. After propensity-weighting, younger patients showed superior OS and LRFS compared to older patients, specifically for clinical stage I disease. This suggests that the survival advantage for younger patients is independent of the factors we controlled for. The reasons for this advantage are not entirely clear. Although we used the CCI to account for comorbidities, this system may not fully capture their influence on survival. The severity and nature of these conditions can significantly influence outcomes, and older patients have shown to be more likely to die from causes other than lung cancer. Comorbidities may also indirectly affect survival by influencing treatment decisions because patients with higher comorbidity burdens are less likely to receive guideline-concordant treatment at earlier stages.[7]

In analyses from nonsurgical national database studies, older age was a significant predictor of mortality.[6,7] In our unweighted univariable analyses, age was not a significant risk factor for worsened OS or LRFS (Table E2). Furthermore, we initially observed a significant difference in OS between younger and older groups (log-rank $P < .0001$). However, after applying propensity score weighting, this difference became nonsignificant (weighted log-rank $P = .084$). This suggests that the weighted variables (procedure type, histologic type, smoking status, and comorbidities) indeed diminish the effect of age on survival outcomes. Notably, the weighted OS curves are time-dependent and cross evidently at 9 and 75 months. Older people experience lower mortality rates between 9 and 75 months after surgery and more likely to die of causes other than lung cancer over time (Figure 2).[7]

In their multivariable Cox-regression analyses, Dell'Amore and colleagues[11] indicated that larger tumor size was an independent negative prognostic factor for young patients with surgically treated NSCLC. Furthermore, in

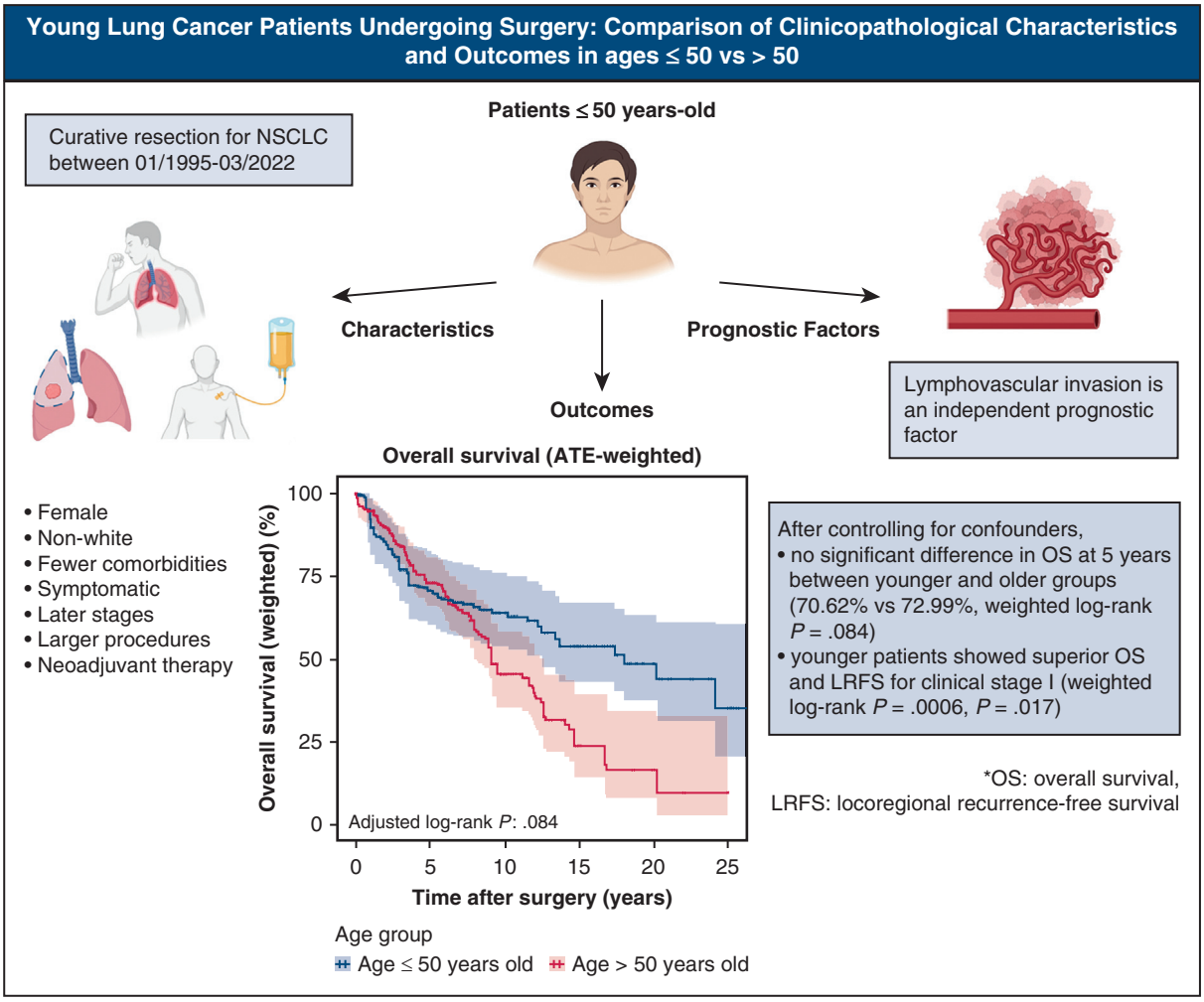


FIGURE 5. Graphical abstract.

their univariable analyses, risk factors for worsened long-term survival in young patients included larger procedures, more advanced TNM stage, and receipt of neoadjuvant therapy, which our analyses mirror. Additional risk factors for worsened OS from our univariable analysis for young patients include CCI, history of previous cancer, VPI, and LVI. Risk factors for worsened LRFS for young patients include CCI, former smoking, multiple lobes resected, VPI, and LVI.

After controlling for potential confounding variables, our multivariable analyses did not deduce any risk factors unique to younger patients. However, we found a significant association between LVI and worsened OS and LRFS in both age groups. The independence of LVI as a prognostic factor reinforces its role as a biological marker of tumor aggressiveness. LVI involves complex interactions between tumor cells and their microenvironment, including endothelial cells and the extracellular matrix, where cancer cells may have initiated dissemination from the primary tumor.[30,31] The presence of LVI may indicate that the tumor has resisted normal physiological pathways like lymphangiogenesis, leading to resistance to standard treatments. Our analyses indicate that the mechanisms of LVI adversely influences survival outcomes, irrespective of cancer stage, receipt of adjuvant therapies, histologic type of cancer, and patient comorbidities and smoking history.

Although the capability of LVI to develop recurrence and metastases is well established,[32] its influence on young lung cancer patients is understudied. In breast and colorectal cancer literature, LVI positivity has been consistently clinically associated with younger patients.[33-36] Younger age may be associated with an increased likelihood of encountering lymphatic ducts and small vessels, whereas older cancer patients experience lymphatic aging.[37] Future

studies may consider exploring the influence of LVI in younger patients.

Limitations

This is a single-institution retrospective review, where investigation inherently involves incomplete data documentation and limitations on sample size. The stratified random sampling method may have resulted in minor deviations from the true population parameters of older patients undergoing resection for NSCLC at our institution. Furthermore, the definition of young patients as those aged 50 years and younger and older patients as those older than age 50 years leaves room for exploring more refined age subgroups with a large surgical dataset. Despite these limitations, our study used a large, granular database allowing us to explore associations with detailed characteristics such as VPI and LVI, which are often unavailable in national databases.

CONCLUSIONS

We conducted a single-institution retrospective study reviewing nearly 3 decades of lung cancer cases to investigate differences between younger patients (aged 50 years and younger) and older patients (older than age 50 years) undergoing surgical resection for NSCLC. Younger patients were more likely to be women and non-White and presenting with typical lung cancer symptoms. Additionally, younger patients showed improved OS and LRFS for clinical stage I disease independently of procedure type, histologic type, comorbidities, and smoking history. The effect of LVI as a prognostic factor warrants further investigation with larger sample sizes and multi-institutional data.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Key statistics for lung cancer. American Cancer Society. Accessed December 22, 2024. https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html
2. Cancer stat facts: lung and bronchus cancer. National Cancer Institute. Accessed December 22, 2024. https://seer.cancer.gov/statfacts/html/lungb.html
3. Gadgeel SM, Ramalingam S, Cummings G, et al. Lung cancer in patients <50 years of age: the experience of an academic multidisciplinary program. *Chest*. 1999;115(5):1232-1236. https://doi.org/10.1378/chest.115.5.1232
4. Maruyama R, Yoshino I, Yohena T, et al. Lung cancer in patients younger than 40 years of age. *J Surg Oncol*. 2001;77(3):208-212. https://doi.org/10.1002/jso.1096
5. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. *J Thorac Oncol*. 2010;5(1):23-28. https://doi.org/10.1097/JTO.0b013e3181c41e8d
6. Thomas A, Chen Y, Yu T, Jakopovic M, Giaccone G. Trends and characteristics of young non-small cell lung cancer patients in the United States. *Front Oncol*. 2015;5:113. https://doi.org/10.3389/fonc.2015.00113
7. Arnold BN, Thomas DC, Rosen JE, et al. Lung cancer in the very young: treatment and survival in the national cancer data base. *J Thorac Oncol*. 2016;11(7):1121-1131. https://doi.org/10.1016/j.jtho.2016.03.023
8. Sacher AG, Dahlberg SE, Heng J, Mach S, Janne PA, Oxnard GR. Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer. *JAMA Oncol*. 2016;2(3):313-320. https://doi.org/10.1001/jamaoncol.2015.4482
9. Suidan AM, Roisman L, Belilovski Rozenblum A, et al. Lung cancer in young patients: higher rate of driver mutations and brain involvement, but better survival. *J Glob Oncol*. 2019;5:1-8. https://doi.org/10.1200/JGO.18.00216
10. Galvez-Nino M, Ruiz R, Pinto JA, et al. Lung cancer in the young. *Lung*. 2020;198(1):195-200. https://doi.org/10.1007/s00408-019-00294-5
11. Dell'Amore A, Monteverde M, Martucci N, et al. Surgery for non-small cell lung cancer in younger patients: what are the differences? *Heart Lung Circ*. 2015;24(1):62-68. https://doi.org/10.1016/j.hlc.2014.07.054
12. Park B, Lee G, Kim HK, et al. A retrospective comparative analysis of elderly and younger patients undergoing pulmonary resection for stage I non-small cell lung cancer. *World J Surg Oncol*. 2016;14(1):13. https://doi.org/10.1186/s12957-015-0762-8
13. Icard P, Regnard JF, de Napoli S, Rojas-Miranda A, Dartevelle P, Levasseur P. Primary lung cancer in young patients: a study of 82 surgically treated patients. *Ann Thorac Surg*. 1992;54(1):99-103. https://doi.org/10.1016/0003-4975(92)91150-1158
14. Mauri D, Pentheroudakis G, Bafaloukos D, et al. Non-small cell lung cancer in the young: a retrospective analysis of diagnosis, management and outcome data. *Anticancer Res*. 2006;26(4B):3175-3181.
15. Hanagiri T, Sugio K, Uramoto H, et al. Results of surgical treatment for lung cancer in young adults. *Int Surg*. 2008;93(1):50-54.
16. Sugio K, Ishida T, Kaneko S, Yokoyama H, Sugimachi K. Surgically resected lung cancer in young adults. *Ann Thorac Surg*. 1992;53(1):127-131. https://doi.org/10.1016/0003-4975(92)90771-u
17. Nugent WC, Edney MT, Hammerness PG, Dain BJ, Maurer LH, Rigas JR. Non-small cell lung cancer at the extremes of age: impact on diagnosis and treatment. *Ann Thorac Surg*. 1997;63(1):193-197. https://doi.org/10.1016/s0003-4975(96)00745-x
18. Tian DL, Liu HX, Zhang L, et al. Surgery for young patients with lung cancer. *Lung Cancer*. 2003;42(2):215-220. https://doi.org/10.1016/s0169-5002(03)00286-1
19. Lara MS, Brunson A, Wun T, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a California Cancer Registry analysis. *Lung Cancer*. 2014;85(2):264-269. https://doi.org/10.1016/j.lungcan.2014.04.007
20. Trojnar A, Domagala-Kulawik J, Sienkiewicz-Ulita A, et al. The clinicopathological characteristics of surgically treated young women with NSCLC. *Transl Lung Cancer Res*. 2022;11(12):2382-2394. https://doi.org/10.21037/tlcr-22-443
21. Elfil M, Negida A. Sampling methods in clinical research; an educational review. *Emerg (Tehran)*. 2017;5(1):e52.
22. Suresh K, Thomas SV, Suresh G. Design, data analysis and sampling techniques for clinical research. *Ann Indian Acad Neurol*. 2011;14(4):287-290. https://doi.org/10.4103/0972-2327.91951
23. Byng D, Thomas SM, Rushing CN, et al. Surveillance imaging after primary diagnosis of ductal carcinoma in situ. *Radiology*. 2023;307(1):e221210. https://doi.org/10.1148/radiol.221210
24. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424. https://doi.org/10.1080/00273171.2011.568786
25. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. *Transl Lung Cancer Res*. 2018;7(3):220-233. https://doi.org/10.21037/tlcr.2018.05.06
26. Veness MJ, Delaney G, Berry M. Lung cancer in patients aged 50 years and younger: clinical characteristics, treatment details and outcome. *Australas Radiol*. 1999;43(3):328-333. https://doi.org/10.1046/j.1440-1673.1999.433666.x
27. Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med*. 1994;330(3):153-158. https://doi.org/10.1056/NEJM199401203300301

28. Kalvapudi S, Vedire Y, Yendamuri S, Barbi J. Neoadjuvant therapy in non-small cell lung cancer: basis, promise, and challenges. *Front Oncol*. 2023;13:1286104. https://doi.org/10.3389/fonc.2023.1286104
29. Lung cancer screening guidelines. American Cancer Society. Accessed December 10, 2023. https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/lung-cancer-screening-guidelines.html
30. Kariri YA, Aleskandarany MA, Joseph C, et al. Molecular complexity of lymphovascular invasion: the role of cell migration in breast cancer as a prototype. *Pathobiology*. 2020;87(4):218-231. https://doi.org/10.1159/000508337
31. Fujimoto N, Dieterich LC. Mechanisms and clinical significance of tumor lymphatic invasion. *Cells*. 2021;10(10):2585. https://doi.org/10.3390/cells10102585
32. Higgins KA, Chino JP, Ready N, et al. Lymphovascular invasion in non-small-cell lung cancer: implications for staging and adjuvant therapy. *J Thorac Oncol*. 2012;7(7):1141-1147. https://doi.org/10.1097/JTO.0b013e3182519a42
33. Kuhn E, Gambini D, Despini L, Asnaghi D, Runza L, Ferrero S. Updates on lymphovascular invasion in breast cancer. *Biomedicines*. 2023;11(3):968. https://doi.org/10.3390/biomedicines11030968
34. Dufour O, Houvenaeghel G, Classe JM, et al. Early breast cancer in women aged 35 years or younger: a large national multicenter French population-based case control-matched analysis. *Breast*. 2023;68:163-172. https://doi.org/10.1016/j.breast.2023.02.004
35. Song YJ, Shin SH, Cho JS, Park MH, Yoon JH, Jegal YJ. The role of lymphovascular invasion as a prognostic factor in patients with lymph node-positive operable invasive breast cancer. *J Breast Cancer*. 2011;14(3):198-203. https://doi.org/10.4048/jbc.2011.14.3.198
36. Inoki K, Sakamoto T, Takamaru H, et al. Predictive relevance of lymphovascular invasion in T1 colorectal cancer before endoscopic treatment. *Endosc Int Open*. 2017;5(12):E1278-E1283. https://doi.org/10.1055/s-0043-117952
37. Shang T, Liang J, Kapron CM, Liu J. Pathophysiology of aged lymphatic vessels. *Aging (Albany NY)*. 2019;11(16):6602-6613. https://doi.org/10.18632/aging.102213

Key Words: young patients, lung cancer, lung cancer surgery, survival outcomes, lung cancer prognosis

TABLE E1. Summary of symptoms and presentation of lung cancer for the younger and older groups

Characteristic	N	Older group (age >50 y) (n = 232)	Younger group (age ≤50 y) (n = 196)	*P* value*
Concurrent cancer	428	17 (7.3)	17 (8.7)	.6
History of other cancer	428	75 (32)	24 (12)	**<.001**
Diagnostic scan prompted by symptom	402	84 (40)	121 (63)	**<.001**
Confirmed symptomatic presentation	292	47 (24)	95 (99)	**<.001**
Symptom: Fatigue	142	8 (17)	21 (22)	.5
Symptom: Cough	142	29 (62)	68 (72)	.2
Symptom: Back pain	142	5 (11)	9 (9.5)	>.9
Symptom: Dyspnea	142	20 (43)	44 (46)	.7
Symptom: Hemoptysis	142	4 (8.5)	14 (15)	.3
Symptom: Pleuritic chest pain	142	12 (26)	30 (32)	.5
Symptom: weight Loss	142	5 (11)	10 (11)	>.9
Length of symptoms (mo)	128			>.9
≤6		29 (59)	46 (58)	>.9
6-12		9 (18)	16 (20)	>.9
>12		11 (22)	17 (22)	>.9

Values are presented as n or n (%). Boldface type in the *P* values column indicates statistical significance. *Pearson χ^2 test; Fisher exact test.

TABLE E2. Unweighted univariable Cox proportional-hazards estimates in young patients (aged 50 years or younger) for overall survival and locoregional recurrence-free survival (not all variables examined are shown)

Variable	Hazard ratio	*P* value*	95% CI
Overall survival			
Age (continuous)	0.99	.684	0.93-1.05
Charlson Comorbidity Index	1.23	**<.001**	1.10-1.38
FEV1 (% predicted)	0.25	.075	0.05-1.15
Smoking status			
Former	1.73	.171	0.79-3.80
Current	0.43	**.039**	0.19-0.96
Previous cancer	2.21	**.049**	1.00-4.85
Total tumor size on imaging	1.31	**<.001**	1.19-1.45
Clinical T stage			
cT3	4.53	**.001**	1.86-10.99
cT4	6.05	**<.001**	2.49-14.72
Clinical N stage			
cN1	3.49	.092	0.82-14.89
cN2	6.03	**<.001**	2.82-12.87
Clinical M stage			
cM1a-cM1c	4.70	**.011**	1.42-15.52
Clinical cancer stage			
IIIa-IIIb	6.66	**<.001**	3.17-13.99
IVa-IV	7.43	**.001**	2.16-25.49
Procedure			
Pneumonectomy	5.45	**.014**	1.40-21.20
Pancoast resection	5.66	**.034**	1.14-28.05
Histologic type			
Squamous cell	0.52	.279	0.16-1.70
Other NSCLC	0.52	.222	0.18-1.48
Presence of VPI	3.81	**<.001**	1.94-7.45
Presence of LVI	5.53	**<.001**	2.76-11.08
Adjuvant therapy received	3.70	**<.001**	1.84-7.42
Neoadjuvant therapy received	6.92	**<.001**	3.49-13.72
Pathologic total size	1.28	**<.001**	1.15-1.42
Pathologic T stage			
pT2-pT2b	1.66	.186	0.78-3.51
pT3	7.86	**<.001**	2.84-21.75
pT4	3.79	.074	0.88-16.37
Pathologic N stage			
N1-N2	5.04	**<.001**	2.41-10.55
Pathologic M stage			
M0			
M1a-M1c	18.24	**<.001**	4.07-81.77
Pathologic cancer stage			
IIa-IIb	3.06	**.018**	1.21-7.74
IIIa-IIIb	8.28	**<.001**	3.79-18.10
Locoregional recurrence-free survival			
Age (continuous)	1.00	.932	0.94-1.05
Charlson Comorbidity Index	1.06	**.029**	1.01-1.11
FEV1 (% predicted)	0.32	.096	0.08-1.23
Smoking status			
Former	1.23	**<.001**	1.13-1.34
Current	0.80	.542	0.40-1.63
Total tumor size on imaging	1.25	**<.001**	1.14-1.36

(Continued)

TABLE E2. Continued

Variable	Hazard ratio	*P* value*	95% CI
Clinical T stage			
cT3	1.13	**.038**	1.01-1.26
cT4	2.47	**.016**	1.19-5.14
Clinical N stage			
cN1	3.27	**<.001**	1.79-5.97
cN2	2.43	**.038**	1.05-5.60
Clinical cancer stage			
IIa-Iib	0.73	.664	0.17-3.05
IIIa-IIIb	3.23	**<.001**	1.72-6.05
IVa-IV	2.80	**.011**	1.27-6.18
Procedure			
Pneumonectomy	3.99	**<.001**	2.02-7.87
Pancoast resection	4.51	**<.001**	2.47-8.25
Multiple lobes resected	3.98	**<.001**	1.99-7.97
Histologic type			
Squamous cell	0.91	.831	0.38-2.17
Other NSCLC	0.97	.947	0.45-2.10
Presence of VPI	4.77	**<.001**	2.23-10.20
Presence of LVI	6.27	**<.001**	3.40-11.55
Adjuvant therapy received	5.85	**<.001**	2.89-11.88
Neoadjuvant therapy received	3.77	**.028**	1.15-12.34
Hospital length of stay	5.53	**<.001**	2.44-12.54
Pathologic total size	3.89	**.026**	1.17-12.91
Pathologic T stage			
pT3	4.50	**.014**	1.35-14.98
pT4	6.44	**<.001**	2.59-16.05
Pathologic N stage			
N1-N2	4.79	**.05**	1.00-22.96
Pathologic M stage			
M1a-M1c	5.20	**.027**	1.20-22.42
Pathologic cancer stage			
IIa-IIb	7.02	**.002**	2.00-24.65
IIIa-IIIb	10.65	**.001**	2.49-45.48

FEV1, Forced expiratory volume in 1 second; *NSCLC*, non–small cell lung cancer; *VPI*, visceral pleura invasion; *LVI*, lymphovascular invasion. *Boldface type in the *P* values column indicates statistical significance.

TABLE E3. Multivariable Cox proportional-hazards estimates of the younger and older groups for overall survival and locoregional recurrence-free survival after propensity-score weighting

Variable	Older group (age >50 y)			Younger group (age ≤50 y)		
	Multivariable regression			Multivariable regression		
	Hazard ratio	*P* value*	95% CI	Hazard ratio	*P* value*	95% CI
Overall survival						
Pathologic cancer stage						
I	0.208	.091	0.034-1.285	0.247	.112	0.044-1.385
II	0.424	.404	0.057-3.172	0.646	.645	0.101-4.131
III-IV	–	–	–	0.677	.691	0.099-4.646
Presence of LVI	3.517	**.006**	1.439-8.597	3.208	**.009**	1.330-7.733
Adjuvant therapy received	0.989	.981	0.385-2.538	0.626	.289	0.263-1.488
Locoregional-recurrence free survival						
Pathologic cancer stage						
I	0.288	.17	0.049-1.705	0.307	.193	0.052-1.822
Stage II	0.570	.574	0.080-4.041	0.740	.761	0.107-5.125
III-IV	–	–	–	0.758	.792	0.096-5.985
Presence of LVI	3.605	**.004**	1.521-8.542	3.727	**.002**	1.617-8.592
Adjuvant therapy received	1.096	.84	0.449-2.672	0.744	.502	0.315-1.761

LVI, Lymphovascular invasion. *Boldface type in the *P* values column indicates statistical significance.