Lung Cancer in Young Patients: Higher Rate of Driver Mutations and Brain Involvement, but Better Survival

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INTRODUCTION

Lung cancer (LC) is the leading cause of cancer mortality worldwide. Despite advances in the treatment strategy, including surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy, 5-year survival is estimated as 9% to 20%.[1,2] During the past decade, LC incidence has been increasing and age at the time of diagnosis continues to decrease.[3,4] Median age at diagnosis is 70 years, and approximately 13% of all patients with LC are younger than age 50 years. Numerous studies have suggested that LC in young patients constitutes an entity with unique characteristics, such as a higher percentage of female patients, a lower rate of smoking history, a higher percentage of family history of LC, a higher rate of adenocarcinoma histology, and more advanced stage at diagnosis.[5-13] However, it is still controversial whether youthful patients with LC have better or worse outcomes.[14-16] In addition, most of the literature regarding young patients is associated with Asian cohorts, whereas less data about white communities are available.

Currently, a considerable percentage of patients with non–small-cell lung cancer (NSCLC) benefit from personalized therapy protocols that are based on the genomic profile of tumors.[17,18] Mutations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes affect the prognosis of patients. Recent studies have shown that young patients with NSCLC harbor more driver mutations than older patients. The rate of mutations documented in the young white population varies between articles and is approximately 20% to 30% for EGFR mutation and 10% to 20% for ALK rearrangement.[17-19]

There are conflicting data on whether younger patients with NSCLC achieve better or worse outcomes compared with the older population, yet most studies show that younger patients have better survival rates.[7-10] Identifying the clinicopathologic characteristics and making appropriate proactive molecular profiling of the youthful population can guide treatment strategy in the clinical setting. Therefore, in the current study, we carried out a comprehensive analysis of patient clinicopathologic features and clinical outcomes in both young (age ≤ 50 years) and older (age > 60 years) patients with NSCLC.

METHODS

Patients

Patients who were diagnosed and treated for LC in the Davidoff Cancer Center, Rabin Medical Center, Israel, were identified retrospectively between January 2010 and December 2015. Patients were sorted by age at diagnosis and divided into two groups: younger than age 50 years and older than age 60 years. Patients younger than age 50 years were used in previous studies.[5,8,14] As we intended to have clear discrimination from the older group, we included patients older than age 60 years. For every young patient, two older patients were enrolled (n = 62 and n = 124, respectively). Diagnosis was based on tumor pathology via surgical or biopsy specimen, or cytology examination via lung, lymph node aspiration, or pleural effusion. Exclusion criteria included patients with lung cancer other than NSCLC and those with non–pathologic-based diagnosis, or cases in which LC was combined with another type of malignancy. The study was approved by the ethical committee of Rabin Medical Center (approval no. 0391-14 RMC).

Data Collection

Medical records were reviewed retrospectively. Patient demographics, smoking history, personal and family history of cancer, medical history, body mass index at diagnosis, performance status, initial clinical presentation, time since presentation to tissue diagnosis, disease stage, histologic subtype, driving mutations, treatment, and survival data were recorded.

EGFR mutation status was analyzed using real-time polymerase chain reaction (PCR), narrow-spectrum next-generation sequencing (NGS), or broad, hybrid capture–based NGS assays. ALK rearrangements were assessed using immunohistochemistry or fluorescence in situ hybridization.

Statistical Analysis

Patients were observed until January 2017 or until the date of their death. We compared categorical

characteristics using the χ^2 test. Continuous variables were compared using an independent t test. Median survival was analyzed using the Kaplan-Mayer method with log-rank. A P value less than .05 was considered significant. Data were analyzed using SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

Between January 2010 and December 2015, 95 patients were diagnosed with LC at younger than age 50 years, accounting for 7.7% of all newly diagnosed patients. Sixty-two patients were included in the analysis (median age, 44.5 years). One hundred twenty-four patients age 60 years or older (median age, 68.0 years) were analyzed and compared with the younger cohort. Clinical characteristics of these patients are listed in Table 1.

Gender distribution showed a slight predominance of female patients in the younger cohort (56% v 46% in the older group). A decreased ratio of ever-smokers in the young cohort was demonstrated (64% v 76%, respectively; $P = .081$), with a significantly lower median number of pack years (35 years v 62 years; $P < .001$). The younger cohort had lower rates of personal cancer history (5% v 22%, respectively; $P < .001$), with no cancer type predominance, and similar rates of family history of LC. Performance status at diagnosis was demonstrated to be similar between both cohorts. As expected, the older cohort had more comorbidities at the time of diagnosis, mostly cardiovascular disease. These patients also suffered from more lung diseases compared with the younger cohort (12% v 28%, respectively; $P = .02$), mostly chronic obstructive pulmonary disease.

Course of Disease

Disease presentation did not differ between the two age groups. Both cohorts demonstrated similar average time since clinical presentation to diagnosis (1.99 months v 1.53 months, respectively; not significant [NS]), and stage at

diagnosis was similar in both groups (stage IV: 53.2% v 46.7%, respectively; NS). Initial tumor size was similar (4.43 cm v 4.44 cm, respectively; NS).

The majority of patients in the older cohort had the initial tumor mass located in the upper lobes of the lungs (50% in the right upper lobe and 29% in the left upper lobe) in comparison with the younger cohort which had more diversity in initial tumor location (24% left upper lobe, 25% right upper lobe, 25% right lower lobe; $P < .001$).

Adenocarcinoma was the most common histopathology in both age groups (77% v 75%, respectively), followed by squamous cell carcinoma (14% v 14%, respectively; Table 2). A significantly greater percentage of younger patients developed brain metastases during their disease course (39% v 25%, respectively; $P = .04$). In both groups, approximately 67% of patients with brain metastases developed the brain metastasis later in the disease course. In the younger age group, 39% of patients had one and 52% had multiple—more than two—brain metastases. Similar percentages were observed in the older age group: 43% had one brain metastasis and 43% had multiple brain metastases.

Analyzing only patients who harbored an EGFR mutation, we found that young EGFR-positive patients were more likely to develop brain metastases during their disease course than older patients (71% v 36%, respectively; $P < .001$).

Treatment Modalities and Survival Rates

Molecular profiling was performed in 69% of patients in both age groups. A similar percentage of patients underwent PCR and NGS evaluation in both groups (approximately 15% and 53%, respectively). Sixty-four percent of patients had molecular testing performed around the time of diagnosis in both groups and 26% underwent analysis after disease progression. Additional testing after negative PCR results was performed more frequently in the younger cohort (34% v 24%, respectively; $P = .16$), and

TABLE 1. Clinical Characteristics of Young (age ≤ 50 years) Versus Old (age ≥ 60 years) Patients

Clinical Characteristic	Patients Age ≤ 50 Years (n = 62)	Patients Age ≥ 60 Years (n = 124)	P
Age at diagnosis, years, median (range)	44.5 (19-50)	68.0 (60-80)	< .001
Male, No. (%)	27 (43)	67 (54)	.214
BMI (kg/m^2)	24.2	26.2	.016
Ever cigarette smokers, No. (%)	40 (64)	94 (76)	.081
Mean pack years (range)	35 (5-120)	62 (2.5-200)	< .001
Personal cancer history, No. (%)	3 (5)	28 (22)	.002
Family history of LC, No. (%)	6 (10)	11 (9)	1.0
PS, No. (%)			.49
0-1	56 (90)	113 (91)	
2-4	3 (5)	10 (8)	

Abbreviations: BMI, body mass index; LC, lung cancer; PS, performance status.

TABLE 2. Disease Course in Young (age ≤ 50) Versus Old (age ≥ 60 years) Patients

Disease Course	Patients Age ≤ 50 Years (n = 62)	Patients Age ≥ 60 Years (n = 124)	P
Initial presentation, No. (%)			.48
Cough	20 (32)	32 (26)	
Pneumonia	10 (16)	19 (15)	
Other	9 (14)	19 (15)	
Incidental	7 (11)	27 (22)	
Chest pain	5 (8)	5 (4)	
Hemoptysis	5 (7)	8 (8)	
Skeletal pain	4 (6)	14 (11)	
Neurologic symptoms	4 (6)	7 (6)	
Time since clinical presentation to diagnosis, months	1.9	1.5	.36
Tumor size, cm	4.4	4.4	.98
Location of primary tumor, No. (%)			< .001
RUL	16 (26)	62 (50)	
RML	4 (6)	5 (4)	
RLL	16 (26)	11 (9)	
LUL	15 (24)	37 (30)	
LLL	7 (11)	3 (2)	
Disease stage, No. (%)			.69
I	8 (13)	12 (10)	
II	5 (8)	9 (7)	
IIA	10 (16)	30 (24)	
IIB	6 (10)	15 (12)	
IV	33 (53)	48 (47)	
Histopathologic type, No. (%)			.86
Adenocarcinoma	48 (77)	93 (75)	
Squamous cell	9 (15)	18 (15)	
Undifferentiated	5 (8)	13 (10)	
Brain metastasis, No. (%)	24 (39)	31 (25)	.04
No. of brain metastasis, No. (%)			.7
One	9 (14)	13 (10)	
Two	2 (3)	4 (3)	
Multiple (≥ 3)	12 (19)	13 (10)	
Molecular analysis, No. (%)			
Any	43 (69)	86 (69)	1.0
PCR	7 (11)	24 (19)	.63
NGS	32 (52)	69 (56)	.87
Driver mutation, No. (%)			
EGFR mutation	14 (23)	22 (18)	.4
ALK translocation	8 (13)	2 (2)	.002
Other mutations detected	17 (27)	29 (23)	.45
Treatment change upon molecular testing	24 (39)	27 (22)	.002

TABLE 2. Disease Course in Young (age ≤ 50) Versus Old (age ≥ 60 years) Patients (Continued)

Disease Course	Patients Age ≤ 50 Years (n = 62)	Patients Age ≥ 60 Years (n = 124)	P
Treatment, No. (%)			
Lung resection	24 (39)	36 (29)	.24
Radiotherapy	40 (64)	76 (61)	.73
Chemotherapy	42 (68)	87 (70)	.73
Targeted therapy	30 (48)	29 (23)	< .001

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; LLL, left lower lobe; LUL, left upper lobe; NGS, next-generation sequencing; PCR, polymerase chain reaction; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

molecular testing affected treatment decisions more for younger patients (39% v 22%, respectively; P = .002).

Younger patients were more likely to harbor driver mutations—EGFR mutations were more common in the younger cohort (23% v 18%, respectively; P = .4), as well as ALK translocations (13% v 2%, respectively; P = .002) as shown in Table 2 and Figure 1. Additional mutations, such as c-MET, KRAS, HER2, TP53, MYC, BRAF, BRCA1, BRCA2, CTNNB1, ERBB2, APC, and others, were found in similar percentages in both patient groups upon molecular testing (27% v 23%; P = .4)

Treatment modalities were fairly similar in both cohorts, including the rate of patients who received neoadjuvant

FIG 1. Percentage of patients with driver mutations in different age groups (age < 40, 41-50, 61-70, and 71-80 years). One hundred eighty-six patients were divided into four age groups. Age group 19-40 years included 16 patients, of which three (19%) had an epidermal growth factor receptor (EGFR) mutation and four (25%) had anaplastic lymphoma kinase (ALK) rearrangement. Age group 41-50 years included 46 patients, of which 11 (24%) had an EGFR mutation and four (19%) had ALK rearrangement. Twenty percent patients had EGFR mutation in the age group 60-70 years, which included 79 patients, but only 1% had ALK rearrangement. The percentage of EGFR mutation was reduced to 13% in the age group 71-80 years, which included 45 patients, with 2% ALK rearrangement found

chemotherapy and adjuvant chemotherapy and patients who received radiotherapy. The younger cohort had a higher rate of lung resection (39% v 29%, respectively; P = .2) and a higher rate of treatment with targeted therapy (48% v 23%, respectively; P < .001) as indicated in Table 2.

Approximately 85% of patients with advanced stage disease in both cohorts received first-line treatment and 49% received second-line treatment. Of treatment-naïve patients, 15% did not receive treatment because of late-stage presentation and low performance status. Younger patients received more targeted therapy—both lines—compared with patients in the older cohort (first line: 41% v 19%, respectively; P = .01; second line: 56% v 28%, respectively; P = .02). Similar percentages of patients received chemotherapy in both lines. Of younger and older patients, 14% and 20%, respectively, ever received immunotherapy in the course of their treatment. Older patients had a higher rate of dose reduction throughout the course of their treatment (12% v 37%, respectively; P < .01).

Median survival of patients age 50 years or younger was longer than median survival of patients older than age 60 years (34 v 21 months, respectively; P = .1), but was not significant. Substratification of patients into smaller age groups demonstrated that the youngest patients (age < 40 years) had the highest median survival (59 months; Fig 2).

Among patients with a driver mutation, younger patients had better median survival, but this was not statistically significant (33 v 25 months; P = .4).

Among patients who developed brain metastases, patients in the younger age cohort had better survival (24.5 v 18 months; P = .4). Furthermore, in those with no brain metastases, younger patients also had better survival, but the difference was much greater (59 v 21.6 months; P = .18).

DISCUSSION

The current study strengthens the need for defining young patients with LC as a subentity. Our retrospective study confirms the results of previous studies[7,10,18-22] that indicate that younger patients have a higher rate of driver mutations and may have better prognosis. Here, we report a higher incidence of brain metastasis among young patients and,
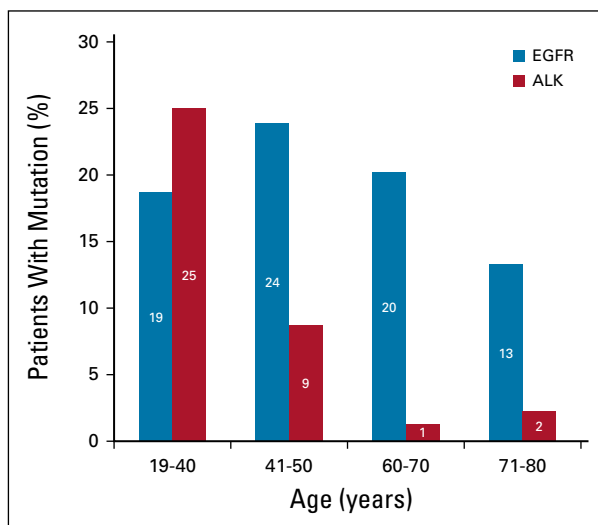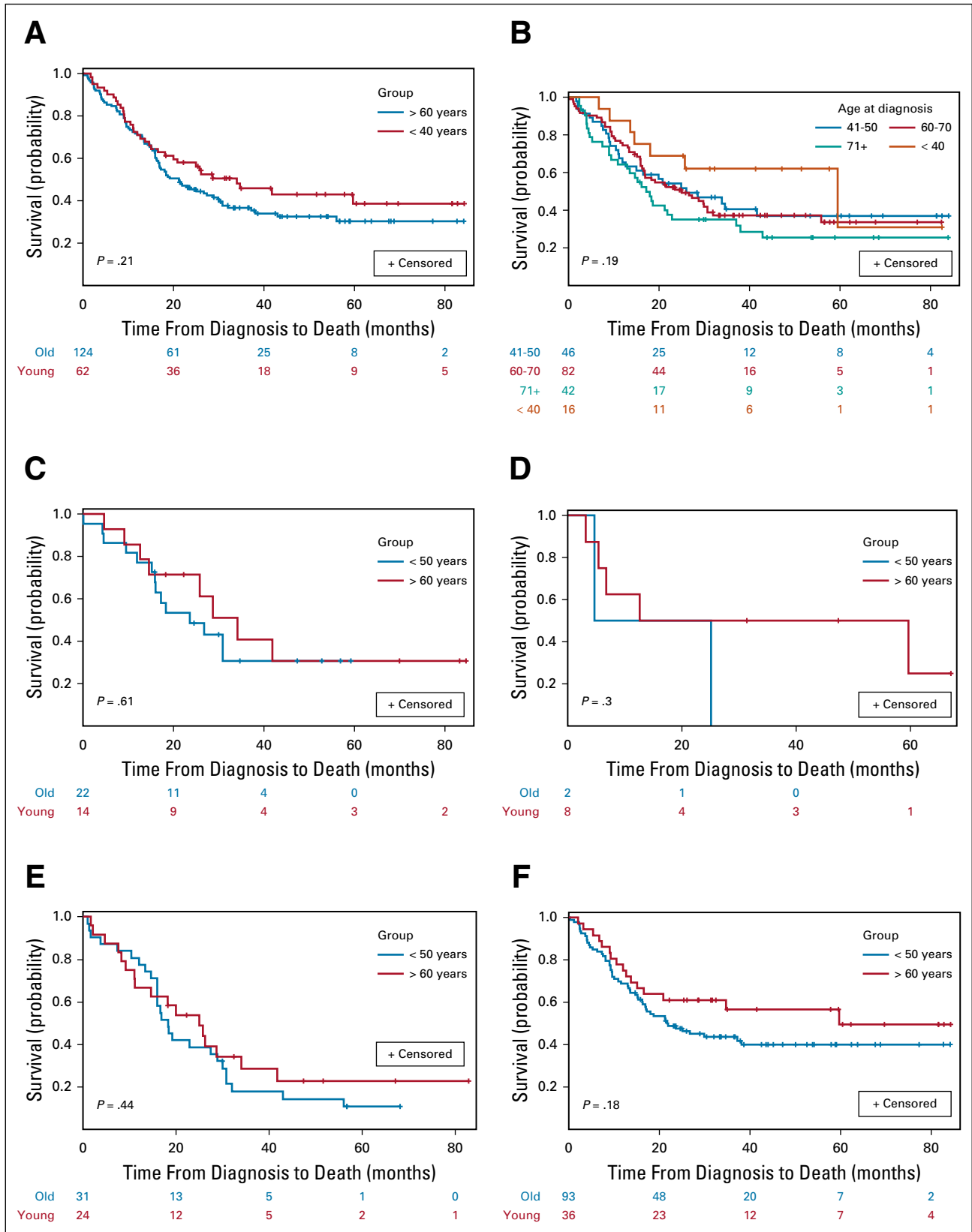
FIG 2. Survival comparison of older versus younger patients in different patient groups: (A) Kaplan-Meier curve of all patients divided into two age groups: 62 patients younger than age 40 years (n = 28 censored) and 124 patients older than age 60 years (n = 44 censored). Median survival for the younger group was 34 months and 21.2 months for the older group. *P* = .19. (B) Kaplan-Meier curve of all patients divided into four age groups:

more commonly, among mutation-bearing patients. This may suggest the need to search for both molecular targets and brain metastases early in the course of disease. Deeper investigation may lead to a more tailored treatment and a better outcome for patients, and is especially important in the younger population.

In the eastern population, EGFR mutations are more common in nonsmoking women.[5-13] Our cohort, which was comprised of white patients, demonstrated that younger patients harbored more targetable driver mutations compared with older patients (34% v 18%; P = .01), including a higher rate of EGFR and ALK gene alterations. The difference in prevalence of targetable mutations was much more prominent for ALK translocations, as they were prominent in the young (13%) and almost not found in the old (2%). Sacher et al,[21] in 2016, demonstrated similar results in the white population, with a 59% increased risk of targetable genotypes in patients younger than age 50 years. This interesting finding suggests that NSCLC in the young might represent a biologically distinct subgroup of tumors and highlights the importance of urgent molecular analysis of tumors to identify targetable mutations for personalized treatment. Moreover, we found that, although young and old patients underwent similar molecular investigations, in younger patients, therapy had twice as much impact on treatment strategy. The high rate of ALK translocation in the younger population deserves additional investigation in the white population as the rate of ALK positivity in our country is 7%, similar to previous reports.[23]

Our study shows that younger patients developed more brain metastases in the course of their disease, also described in previous reports.[24-26] Duell et al[25] recently reported that brain metastases are frequent among younger patients (age < 65 years), females, never smokers, and patients with early-disease stage. Our study did not demonstrate any gender predominance in patients who developed brain metastases, but in both age groups they were significantly more likely to harbor EGFR mutations. This was more significant in patients younger than age 50 years; (55% in the young; 31% in the old; P = .03). Our cohort was too small for multivariable analysis to answer whether driver mutation or age was the main factor that affected brain metastasis development; however, it has been described

that brain metastases are more likely to occur in patients with driver mutations, such as EGFR and ALK.[27,28]

Brain magnetic resonance imaging is not a standard of care in the treatment of LC, including a lack of formal recommendation within the younger cohort (National Comprehensive Cancer Network). We found that, in both age groups, two thirds of patients had metastases detected later in the disease course, indicating a higher index of suspicion in patients even after normal initial brain imaging.

Median survival of patients with brain metastases was worse in patients in both age groups. Having metastasis affected young patients' survival more than older patients, as younger patients who did not develop brain metastasis had the best median survival (59 months with no metastasis v 25 months with brain metastasis). This difference was not observed in the older cohort in which developing brain metastasis or not did not much affect survival (21 months v 18 months). These findings may suggest a different mechanism of metastatic seeding or underlying tumor biology.

There have been conflicting data about the survival and prognosis of young patients with LC. Some studies have shown prognosis to be worse for younger patients, indicating a more aggressive disease, such as the recent large study by Sacher et al.[21] Others have shown that there was no significant difference in survival[5]; however, it has mostly been demonstrated that younger patients have better prognosis[7-11] and this effect was more prominent in early-stage disease.[7,10,11] In our study, we concluded that median survival was longer in patients in the younger cohort, but this was not significant, likely because of the small number of patients. When separately analyzing patients younger than age 40 years, we found their survival to be even better than that of older patients, which further supports our finding. The longer survival in the younger cohort was consistent also when normalizing for driver mutations. We could not conclude any difference in survival between patients who presented with early or advanced disease as a result of the paucity of patients.

Interestingly enough, primary tumors were more commonly found in the upper lobes of the lung in patients in the older cohort, whereas in the younger group they were more

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FIG 2. (Continued). 16 patients younger than age 40 years (n = 9 censored), 46 patients age 41-50 years (n = 19 censored), 82 patients age 60-69 years (n = 32 censored), and 42 patients older than age 70 years (n = 12 censored). Median survival for the youngest group was 59.6 months, 26.1 months for those age 41-50 years, 25 months for those age 60-69 years, and 17.2 months for the oldest age group. Significance: P = .2. Kaplan-Meier curves of driver mutation–positive patients: (C) Kaplan-Meier curve of epidermal growth factor receptor (EGFR) mutation–positive patients: 14 patients were younger than age 50 years (n = 6 censored) and 22 patients were older than age 60 years (n = 8 censored). Median survival was 33.5 months for younger patients and 22.8 months for older patients. Significance: P = .61. (D) Kaplan-Meier curve of anaplastic lymphoma kinase (ALK) rearrangement–positive patients: eight patients were younger than age 50 years (n = 3 censored) and two patients were older than age 60 years (n = 0 censored). Median survival was 35.5 months for younger patients and 14.4 months for older patients. Significance: P = .3. (E) Patients who developed brain metastases: 24 patients were younger than age 50 years (n = 7 censored) and 31 patients were older than age 60 years (n = 4 censored). Median survival was 24.6 months for younger patients and 18 months for older patients. Significance: P = .4. (F) Patients who did not developed brain metastases: 36 patients were younger than age 50 years (n = 20 censored) and 93 patients were older than age 60 years (n = 40 censored). Median survival was 58.8 months for younger patients and 21.6 months for older patients. Significance: P = 0.

equally distributed. This may be associated with smoking-related lung cancer, which has an upper lobe tendency.

Our study had several limitations. First, it included a small sample size of young patients. Moreover, data collection and analysis were retrospective and included only one medical center. Limited information was available regarding risk factors, such as occupation, exposure to asbestos, and detailed genetic background.

In conclusion, our study indicates that young patients harbor a higher rate of driver mutations and have an increased incidence of brain involvement. Although we observed no significant difference in overall survival, which could be a result of the small number of younger patients, yet we noticed a trend for better survival in patients in the younger cohort, which could be explained by the higher rate of mutation and respective targeted treatment. This highlights the importance of genetic background assessments and considering LC as a possible diagnosis in young symptomatic patients in clinical settings.

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Manuscript writing: All authors

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