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Interstitial lung abnormalities in treatment-naïve advanced non-small-cell lung cancer patients are associated with shorter survival

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Abstract

Objective—Interstitial lung diseases are associated with increased risk of lung cancer. The prevalence of ILA at diagnosis of advanced non-small-cell lung cancer (NSCLC) and its impact on overall survival (OS) remain to be investigated.

Materials and Method—The study included 120 treatment-naïve stage IV NSCLC patients (53 males, 67 females). ILA was scored on CT prior to any systemic therapy using a 4-point scale [0=no evidence of ILA, 1=equivocal for ILA, 2=suspicious for ILA, 3=ILA] by a sequential reading method previously reported. ILA scores of 2 or 3 indicated the presence of ILA.

Results—ILA was present in 17 patients (14%) with advanced NSCLC prior to any treatment (score3:n=2, score2:n=15). These 17 patients were significantly older (median age: 69 vs. 63, p=0.04) and had a heavier smoking history (median: 40 vs. 15.5 pack-year, p=0.003) than those with ILA score 0 or 1. Higher ILA scores were associated with shorter OS (p=0.001). Median OS of the 17 patients with ILA was 7.2 months [95%CI: 2.9-9.4] compared to 14.8 months [95%CI: 11.1-18.4] in patients with ILA score 0 or 1 (p=0.002). In a multivariate model, the presence of ILA remained significant for increased risk for death (HR=2.09, p=0.028) after adjusting for first-

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line systemic therapy (chemotherapy, p<0.001; TKI, p<0.001; each compared to no therapy) and pack years of smoking (p=0.40).

Conclusion—Radiographic ILA was present in 14% of treatment-naïve advanced NSCLC patients. Higher ILA scores were associated with shorter OS, indicating that ILA could be a marker of shorter survival in advanced NSCLC.

Keywords

Interstitial lung disease; lung cancer; computed tomography; advanced non-small-cell lung cancer; survival

INTRODUCTION

Lung cancer continues to be a leading cause of cancer death for both men and women in the United States [1]. Interstitial lung diseases, characterized by lung parenchymal damages due to various patterns of inflammation and fibrosis, were shown to be associated with the development of lung cancer, presumably because inflammation and fibrosis give rise to genetic damage which lead to lung parenchymal carcinogenesis and ultimately to cancer [2-6]. Interstitial lung diseases are also associated with smoking, which is one of the most clearly established risk factors and continued smoking is associated with shorter survival in patients with lung cancer [3, 4, 7-9]. Some prior reports have identified the similarities between the pathogenesis of interstitial lung diseases and smoking-related carcinogenesis, in the aspects of oxidative stress, mutagenesis, angiogenesis, and epithelial to mesenchymal transformation [2, 10, 11]. It is also well established that interstitial lung diseases may be exacerbated in lung cancer patients after local or systemic therapy which can adversely impact the clinical outcome [12-15]. However, the prevalence of interstitial lung diseases at the time of diagnosis and prior to initiation of treatment and the impact on survival among advanced lung cancer patients have not been systematically investigated.

Computed tomography (CT) of the chest has been the primary modality to noninvasively assess the presence and severity of interstitial lung diseases. Washko et al reported a sequential reading method for effective and efficient scoring of radiographic interstitial lung abnormalities (ILA) on chest CT using a 4-point scale [16, 17], which has been applied to study the frequency of ILA in smokers from the COPDGene study, participants in the Framingham Heart Study, National Lung Screening Trial participants and other clinical cohorts of subjects at risk of lung cancer [17-22]. The application of the ILA scoring method to a cohort of patients with established diagnosis of advanced lung cancer may contribute to defining the frequency and severity of ILA in these patients and assess the impact of ILA on clinical outcome of patients with advanced lung cancer.

The purpose of the study is to determine the prevalence of interstitial lung abnormalities (ILA) detected on baseline chest CT in advanced NSCLC patients prior to the initiation of anti-cancer therapy, and investigate the association between ILA and survival duration while adjusting for smoking and other clinical characteristics. The study was carried out to determine if advanced NSCLC patients with smoking history have higher ILA scores than

those without, and that patients with higher ILA scores have shorter overall survival compared to those with lower ILA scores.

MATERIALS AND METHODS

Patients

The study population included 120 patients with treatment- naïve stage IV (AJCC 7th edition) NSCLC who presented to the Dana-Farber Cancer Institute between August 2011 and July 2012, and had a baseline chest CT prior to the initiation of systemic therapy available for review. These 120 patients resulted from the selection of patients who satisfied these eligibility criteria. Clinical record of the demographics including age, gender, and race, clinical characteristics, and survival, as well as CT studies were retrospectively reviewed with the institutional review board approval. The patients in the study provided written informed consent. The specific items reviewed in the medical records included age, gender, and race, smoking history, pack years of smoking, histology, the presence or absence of distant metastasis (M1b or M1a disease), types of systemic therapy for lung cancer, and survival. Among the 120 patients, 83 patients received systemic chemotherapy, 28 received tyrosine kinase inhibitor therapy, and 9 patients received no systemic therapy.

CT scan of the chest

The standard clinical chest CT protocol at the DFCI utilized a 64-row MDCT scanner (Aquilion 64; Toshiba America Medical Systems, CA). Patients were scanned in the supine position from the cranial to caudal direction from the clavicles to the adrenal glands at end-inspiration. 100 mL of iopromide (Ultravist 300, 300 mg iodine/mL; Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ) was injected intravenously with an automated injector (Medrad, Pittsburgh, PA) at a rate of 3 mL/second, with a scan delay of 30 seconds, unless medically contraindicated. The parameters were as follows: 0.5 mm collimation, 120 kVp, 0.5-s gantry rotation time and table speed of 53 mm per rotation. Tube current was determined by dose modulation with noise index of 15.0 Hounsfield Units (HU).

Axial images (5 mm thickness) are reconstructed using standard and lung algorithms. For the purpose of ILA scoring, axial images reconstructed with a lung algorithm were reviewed on Picture Archiving Communication Systems (PACS) workstations (Centricity, GE Healthcare) with a window level of -700 HU and a window width of 1500 HU as previously described[16].

Scoring of ILA using a sequential reading method

Retrospective imaging review was performed on baseline chest CT obtained at the time of diagnosis of NSCLC and prior to the initiation of systemic therapy. The baseline CT scan performed within ±12 weeks of the date of diagnosis of NSCLC (median time from the date of diagnosis to baseline CT: -0.6 weeks, range: -11.6 to +11.9 weeks) was selected for each patient. For 9 patients who did not receive systemic therapy, a CT scan performed within ±12 weeks of the date of diagnosis of NSCLC was selected for each patient. When a patient underwent chest CT scans prior to and after the date of diagnosis that are within ± 12 weeks, the scan prior to the date of diagnosis was consistently selected for review.

Visual CT scoring of ILA was performed using a sequential reading method with a 4-point scale system that has been previously described[16, 17]. CT scans were scored by 3 readers (board-certified radiologists with expertise in thoracic imaging; M.N., T.A., and H.H.) as "0", no evidence of ILA, "1", equivocal for ILA, "2", suspicious for ILA, and "3", ILA. *Equivocal* for ILA (Score of 1) was defined as focal or unilateral ground glass attenuation, focal or unilateral reticulation, and patchy ground glass abnormality (less than 5% of the lung). *Suspicious* for ILA (Score of 2) was defined as follows: nondependent ground glass abnormality affecting more than 5% of any lung zone, non-dependent reticular abnormality, diffuse centrilobular nodularity with ground glass abnormality, honeycombing, traction bronchiectasis, non-emphysematous cysts, architectural distortion. ILA (Score of 3) was defined as bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a sub-pleural distribution [16, 17]. In this cohort of patients with advanced NSCLC, the readers were instructed to disregard findings due to lung cancer involvement such as intraparenchymal metastasis and lymphangitic spread of tumor, based on the radiologic interpretation, when assigning scores for ILA.

In the sequential reading method, Radiologist 1 reviewed and scored all the CT studies (Fig. 1). Next, Radiologist 2 independently reviewed all the studies scored as 1, 2, or 3 by Radiologist 1, as well as randomly selected 20% of the studies with score 0 by Radiologist 1, being blinded to the scores by Radiologist 1. The studies with concordant scores by two radiologists received the final score based on the two reads. The studies with discordant scores by two radiologists were independently reviewed by Radiologist 3, who was blinded to the scores by Radiologists 1 and 2, and were assigned the final score with majority opinion as described previously [16, 17]. For each reader, the CT scans were presented in a different random order.

Statistical analysis

Associations between ILA scores and disease characteristics and demographics were assessed using Fisher's exact test for categorical variables and Kruskal test for continuous variables. The ILA scores of 2 or 3 were considered to indicate the presence of ILA. Overall survival (OS) was defined as the time from the date of diagnosis of NSCLC to the date of death of any cause. Patients who were still alive by the time of analyses were censored at the last known date of follow-up. The log-rank test was used to assess differences in the OS distributions between groups. Cox proportional hazards models were used to estimate hazard ratios (HRs), and multivariable analyses were performed using a stepwise regression. All *p*-values are two-sided and tests were conducted at the 0.05 level.

RESULTS

Patient characteristics and ILA scores

ILA was present in 17 patients (14%), with a score of 3 in two patients and a score of 2 in 15 NSCLC patients, while ILA scores were 1 in 52 patients and 0 in 51 patients. The summary of sequential reading in this study population is provided in Fig. 2.

Table 1 summarizes the patient demographics and disease characteristics of the study population, and the ILA scores on baseline chest CT prior at diagnosis. Significant associations were noted between higher ILA scores and older age (p=0.01), a history of smoking (p=0.03), and increased number of pack years of smoking (p=0.0002). When the patients were dichotomized with the ILA scores 2 or 3 versus 0 or 1, patients with scores 2 or 3 were significantly older (median age 69 vs. 63 years, p=0.04), and had significantly more pack years of smoking history (median: 40 vs. 15.5 pack years; p=0.003) compared to those with ILA scores 0 or 1. In a multivariable logistic regression model, only the pack years of smoking history remained significant predictor of ILA (p=0.03).

ILA scores and overall survival

At the time of the survival analysis, 71 of the 120 patients had died. The median follow-up time for all patients alive at the time of this analysis was 18.4 months [range for those who were alive: 2.1-23.7 months]. The patients with higher ILA scores had significantly shorter survival (median OS: 4.7 months for score 3, 7.7 months for score 2, 12.3 months for score 1, 18.2 months for score 0; p=.001)(Fig. 3). The median OS of the 17 patients with ILA score 2 or 3 was 7.2 months [95%CI: 2.9-9.4], which was significantly shorter compared to the median OS of 14.8 months [95%CI: 11.1-18.4] in 103 patients with ILA score 0 or 1 (p=0.002) (Fig.4-6).

Multivariable analyses were performed for OS using Cox regression, adjusting for ILA using the dichotomized groups with ILA scores 2 or 3 versus 0 or 1, as well as for age, categorical smoking history (never, former or current), the number of pack years of smoking, histology, and the types of first-line systemic therapy (chemotherapy, n=83; tyrosine kinase inhibitors, n=28; or no therapy, n=9) for NSCLC. Backwards stepwise regression was used to exclude non-significant variables, which resulted in the model including ILA and the first-line systemic therapy as significant predictors, while all the other variables including age and smoking were insignificant. Because of the known relationship between smoking and ILA as well as smoking and survival of lung cancer patients, the number of pack years of smoking was included in the final model along with ILA and the first-line systemic therapy; other variables were excluded because they were insignificant and not thought to be confounding factors. In this final model, the presence of ILA remained significant for increased risk for death (HR=2.09, p=0.028) after adjusting for the first-line systemic therapy (chemotherapy: HR=0.209, p<0.001; TKI: HR=0.130, p<0.001; each compared to no therapy) and pack years of smoking (HR=1.004, p=0.40).

DISCUSSION

ILA was present in 14% of stage IV NSCLC patients at the time of diagnosis of lung cancer. The presence of ILA was associated with heavier smoking history and older age as shown before [17, 21, 22]. Patients with ILA at diagnosis had significantly shorter overall survival, which remained significant after adjusting for other factors including the types of first-line systemic therapy for NSCLC and pack year smoking history, indicating that ILA could be an independent marker for survival in advanced NSCLC. To our knowledge, the prevalence of

ILA in stage IV NSCLC patients and its impact on survival have not been previously described.

The prevalence of ILA on chest CT was 14% in stage IV NSCLC at diagnosis in this study cohort, which is higher compared to 8% in 2416 smokers with at least 10 pack years history enrolled in COPDGene study, 9.7% among 884 cigarette smokers studied in NLST who had smoked at least 30 pack year, and 7% in 2633 participants in the Framingham Heart Study which included 1184 former smokers and 162 current smokers [17, 21, 22]. Of note, these prior studies utilized the essentially same scoring method and definitions for ILA as the method used in the present study. The higher prevalence of ILA among our NSCLC cohort compared to others without established diagnosis of lung cancer further supports the association between interstitial lung disease and lung cancer, because patients with underling ILA are more likely to develop lung cancer.

Among the prior studies that focused on lung cancer patients, Kawasaki et al retrospectively reviewed 711 surgically resected lung cancer patients and reported that 7.5% of them had idiopathic interstitial pneumonia (IPF)[23]. In the study, the diagnosis of IPF was made based on the radiological findings (diffusely distributed reticulonodular shadow, honeycombing, or reduction of lung volume) and also based on histology in some cases, while our study solely based on imaging findings to detect ILA and included a spectrum of CT findings of interstitial abnormalities rather than advanced fibrosis alone[16, 17]. The majority (483/711, 68%) of the patients had early stage lung cancer (373 stage I patients and 110 stage II patients) in this surgical cohort, while 6 of 60 (10%) patients with stage IV cancer in the cohort had IPF. The prevalence of 10% is relatively similar to our results of 14%, taking account their study focused on IPF which is associated with a more advanced form of fibrosis and honeycombing, while our study included a wider spectrum of interstitial findings seen in cases with ILA score 2. Among the 15 patients with ILA score 2, 13 patients had nondependent reticular and ground glass abnormalities predominantly in subpleural distribution, with (n=6) or without (n=7) traction bronchiectasis. The remaining 2 patients with score 2 had diffuse centrilobular nodularity with ground glass abnormality.

In a study of 555 patients with lung adenocarcinoma who underwent *EGFR*-mutation testing, preexisting interstitial lung disease was noted in 9.7% (30/309) of patients without *EGFR* mutation and in only 0.4% (1/246) of patients with *EGFR* mutation. One of the explanations of this marked difference could be due to that *EGFR*-mutant lung cancer is much more common among non-smokers[24]. In their study, the diagnosis of interstitial lung disease was based on clinical features, pretreatment chest CT results, and histological findings [2]. The prevalence of 9.7% among non-*EGFR* mutant patients is similar to the prevalence of ILA in our study. Their study is somewhat different because it utilized clinical features for the diagnosis of interstitial lung disease, while our study is based on CT findings and may include subclinical cases. The radiologic criteria can be different, while no details of the specific radiological criteria were provided in their report. The cohort includes only adenocarcinoma, which may also contributed to a lower prevalence. The study also adds an interesting insight about the different prevalence of interstitial lung disease among lung cancer patients with and without specific mutations, which warrants further investigation in genomically characterized cohorts with the information of smoking history.

The presence of ILA was associated with older age in univariate analysis, which is consistent with prior reports in general population and smokers and in lung cancer patients [2, 17, 21, 23]. Male gender and squamous cell histology were associated with IPF in lung cancer patients in two prior reports[23, 25], which was not noted in the present study. The difference could be due to different patient characteristics such as stage (predominantly early stage disease in the prior reports compared to stage IV alone in the present study). The difference between IPF and ILA can be another factor, since IPF represents a clinical syndrome associated with usual interstitial pneumonia (UIP) which is indicative of end-stage fibrotic lung disease characterized by areas of honeycombing, while ILA includes a spectrum of CT findings from early to advanced interstitial lung diseases[16, 17, 26]. Smoking history was associated with the presence of ILA, which was consistent with our hypothesis and the prior reports[2, 17, 21-23]. The close relationship between higher ILA scores and heavier smoking history in lung cancer patients was reproduced.

The shortened overall survival was noted among 4 groups of stage IV NSCLC patients categorized according to higher ILA scores. When dichotomized, patients with ILA had significantly shorter OS than those without, which remained significant in multivariate analyses. Kinoshita et al studied idiopathic interstitial pneumonia (IIP), diagnosed based on histological diagnosis of UIP or nonspecific interstitial pneumonia (NSIP), or radiological and/or clinical diagnosis of IPF. Among stage III, IV or recurrent lung cancer patients treated with chemotherapy alone, 22 patients with IIP had significantly shorter overall and progression-free survival compared to 276 patients without IIP, which shares similarity with our results[15]. In their study, IIP was diagnosed based on histological diagnosis of UIP or NSIP, or radiological and/or clinical diagnosis of IPF; other interstitial lung diseases that many manifest similar radiologic findings such as connective tissue disorders and hypersensitivity pneumonitis were excluded. Our scoring method is designed to capture most of the radiologic patterns of interstitial lung diseases and categorize them into 4 groups according to the degree of ILA rather than binary groups alone. Our results indicate that ILA scores on chest CT at diagnosis could be an additional marker for survival, which needs to be further investigated in a larger independent cohort.

The multivariable analysis demonstrated that ILA remained significant for increased risk of death after adjusting for other factors including the first-line systemic therapy and smoking history. ILA is an independent marker for shorter survival among these advanced NSCLC patients. Cigarette smoking is a well-established negative prognostic factor for NSCLC patients [7-9]. In a study by Janjigian et al of 2,010 patients with stage IIIB/IV NSCLC, more cigarette smoking, measured in pack years, was associated with shorter survival after diagnosis of stage IIIB/IV NSCLC[9]. Smoking was also shown to be associated with radiographic ILA in the prior studies[3, 17, 22], as in the present study in which patients with ILA had significantly higher number of pack years of smoking. Because of such prior knowledge, smoking history measured by pack years of smoking was included in the final multivariate model although it was not a statistically significant covariate. The result demonstrated that the significance of ILA as a marker for survival was independent of smoking history. This observation, as well as any interaction between ILA and smoking (which was insignificant in the present cohort), needs to be further studied in a larger number of patients.

The present study included all stage IV patients with histologically confirmed NSCLC regardless of the types of subsequent treatment for cancer. There were 9 patients in our cohort who did not receive systemic anti-cancer therapy, including 5 patients with score 1, 3 patients with score 2 and one patient with score 3. Although it is natural that the stage IV NSCLC patients without any systemic therapy has shorter survival, the presence of ILA remained significant in a multivariable Cox model adjusting for the types of the first-line systemic therapy. The study by Kinoshita et al exclusively studied patients who received chemotherapy alone and demonstrated similar results in terms of impact on IIP on OS, where NSCLC patients with IIP had a significantly shorter median OS (5.4 mos vs. 13.2 mos, P<0.001) than those without IIP[15]. Aubry et al studied 24 patients with IPF and lung cancer and reported that the survival of these patients were not different compared to an age-matched control group with lung cancer alone [25]. However, their study population was distinctly different from our cohort in that all patients had stage I-IIIa disease (56% with stage I, none with stage IV) and 92% of the patients were treated surgically. The results indicate that the impact of ILA on survival may be different according to lung cancer stage, and the analyses should be stratified according to stage in future studies.

The reason why the patients with higher ILA scores have shorter survival remains to be investigated. It is possible that the patients with underlying ILA at diagnosis of lung cancer requires smaller tumor burden to develop significant respiratory distress that leads to significant clinical deterioration compared to those without ILA. The study by Kinoshita et al demonstrated similar response rates to chemotherapy between patients with and without IIP (72.3 vs. 69.2%)[15], which partly supports this hypothesis. Another important factor is the acute exacerbation of preexisting interstitial lung disease during therapy, which was noted 13.6% (3/22) in NSCLC patients with IIP in the prior study [15]. In a study of lung cancer patients with interstitial lung disease, acute exacerbation was noted more frequently in patients with UIP (a more advanced form of pulmonary fibrosis and would be scored as 3 in our system) compared to those with non- UIP[27]. The change of the degree of ILA over time during systemic therapy in advanced NSCLC patients and its impact on survival remains to be further investigated.

Limitations of the present study include retrospective design with patients treated at a single institution, and a relatively small number of patients (n=17) with ILA at diagnosis. The slice thickness of CT images was 5 mm, which is not ideal for the detailed assessment of interstitial lung abnormalities due to decreased sensitivity for subtle ILA and therefore adds another limitation. High-resolution CT images without intravenous contrast agent are more favorable for the purpose, however, were not available for the present study cohort of advanced lung cancer patients undergoing cancer follow-up scans as the clinical routine. ILA was determined based on CT findings on sequential reading method, and histological confirmation was not obtained. Although it is ideal to have histological diagnosis of interstitial lung diseases, it is not commonly possible in stage IV lung cancer patients due to lack of histologic specimen of non-tumor bearing lung parenchyma. Among the 17 patients with ILA, 14 had died at the time of analysis. Death was primarily related to lung cancer in 12 patients. Two patients died due to acute respiratory distress syndrome, which was clinically thought to be related to pneumonia. While it is possible that underlying ILA contributed to death in patients with cancer-related death and those with ARDS, detailed

analyses of this question were not possible in this retrospective study, which adds another limitation to the study. The results of the study, especially the impact of ILA scores on survival, need to be validated in a larger cohort.

In conclusion, ILA was present on chest CT at diagnosis in 14% of stage IV NSCLC patients, and was more common in older patients with heavier smoking history. The presence of ILA was associated with shorter overall survival even after adjusting for other factors including the types of first-line systemic therapy and smoking. The results are indicative that ILA scores could be an additional independent marker for survival among advanced NSCLC patients, if reproduced in a larger independent cohort.

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REFERENCE

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30. [PubMed: 23335087]
2. Fujimoto D, Tomii K, Otoshi T, et al. Preexisting interstitial lung disease is inversely correlated to tumor epidermal growth factor receptor mutation in patients with lung adenocarcinoma. Lung Cancer. 2013; 80:159–164. [PubMed: 23419507]
3. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002; 165:277–304. [PubMed: 11790668]
4. Bouros D, Hatzakis K, Labrakis H, Zeibecoglou K. Association of malignancy with diseases causing interstitial pulmonary changes. Chest. 2002; 121:1278–1289. [PubMed: 11948064]
5. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2012; 18:1028–1040. [PubMed: 22772564]
6. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420:860–867. [PubMed: 12490959]
7. Toh CK, Wong EH, Lim WT, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis. Chest. 2004; 126:1750–1756. [PubMed: 15596669]
8. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. Chest. 2004; 125:27–37. [PubMed: 14718417]
9. Janjigian YY, McDonnell K, Kris MG, et al. Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. Cancer. 2010; 116:670–675. [PubMed: 20029977]
10. King TE Jr. Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011; 378:1949–1961. [PubMed: 21719092]
11. Nathan N, Thouvenin G, Fauroux B, Corvol H, Clement A. Interstitial lung disease: physiopathology in the context of lung growth. Paediatr Respir Rev. 2011; 12:216–222. [PubMed: 22018034]
12. Sato T, Teramukai S, Kondo H, et al. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014 May; 147(5):1604–1611.e3. [PubMed: 24267779]

13. Voltolini L, Bongiolatti S, Luzzi L, et al. Impact of interstitial lung disease on short-term and long-term survival of patients undergoing surgery for non-small-cell lung cancer: analysis of risk factors. Eur J Cardiothorac Surg. 2013; 43:e17–23. [PubMed: 23129356]
14. Sato T, Teramukai S, Kondo H, et al. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. Lung Cancer. 2014 Jan.83(1):112. [PubMed: 24199683]
15. Kinoshita T, Azuma K, Sasada T, et al. Chemotherapy for non-small cell lung cancer complicated by idiopathic interstitial pneumonia. Oncol Lett. 2012; 4:477–482. [PubMed: 23741246]
16. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene Study. Acad Radiol. 2010; 17:48–53. [PubMed: 19781963]
17. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011; 364:897–906. [PubMed: 21388308]
18. Doyle TJ, Washko GR, Fernandez IE, et al. Interstitial lung abnormalities and reduced exercise capacity. Am J Respir Crit Care Med. 2012; 185:756–762. [PubMed: 22268134]
19. Xu JF, Washko GR, Nakahira K, et al. Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. Am J Respir Crit Care Med. 2012; 185:547–556. [PubMed: 22246178]
20. Doyle TJ, Dellaripa PF, Batra K, et al. Functional Impact of a Spectrum of Interstitial Lung Abnormalities in Rheumatoid Arthritis. Chest. 2014 Jul; 146(1):41–50. [PubMed: 24305643]
21. Hunninghake GM, Hatabu H, Okajima Y, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013; 368:2192–2200. [PubMed: 23692170]
22. Jin GY, Lynch D, Chawla A, et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. Radiology. 2013; 268:563–571. [PubMed: 23513242]
23. Kawasaki H, Nagai K, Yokose T, et al. Clinicopathological characteristics of surgically resected lung cancer associated with idiopathic pulmonary fibrosis. J Surg Oncol. 2001; 76:53–57. [PubMed: 11223825]
24. Nishino M, Hatabu H, Johnson BE, McLoud TC. State of the art: response assessment in lung cancer in the era of genomic medicine. Radiology. 2014; 271:6–27. [PubMed: 24661292]
25. Aubry MC, Myers JL, Douglas WW, et al. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. Mayo Clin Proc. 2002; 77:763–770. [PubMed: 12173712]
26. Nishino M, Itoh H, Hatabu H. A practical approach to high-resolution CT of diffuse lung disease. Eur J Radiol. 2014; 83:6–19. [PubMed: 23410907]
27. Kenmotsu H, Naito T, Kimura M, et al. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. J Thorac Oncol. 2011; 6:1242–1246. [PubMed: 21623239]

Highlights

- Interstitial lung abnormalities were present in 14% of stage IV NSCLC patients
- ILA was more common in older patients with heavier smoking history
- ILA was associated with shorter survival after adjusting for smoking and therapy
- ILA could be an additional independent marker for survival in advanced NSCLC

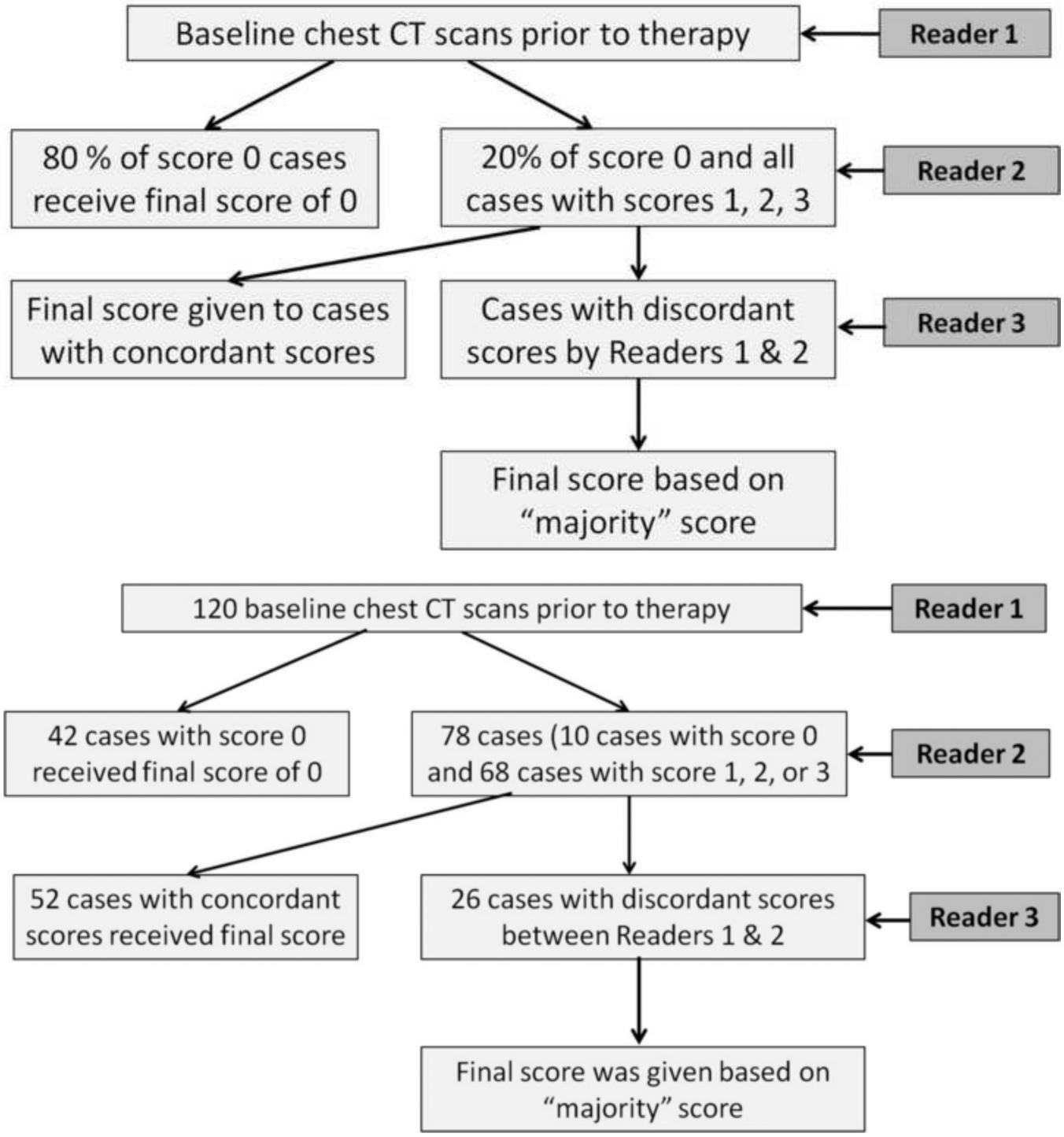

Fig. 1.
Flowchart of the sequential reading method

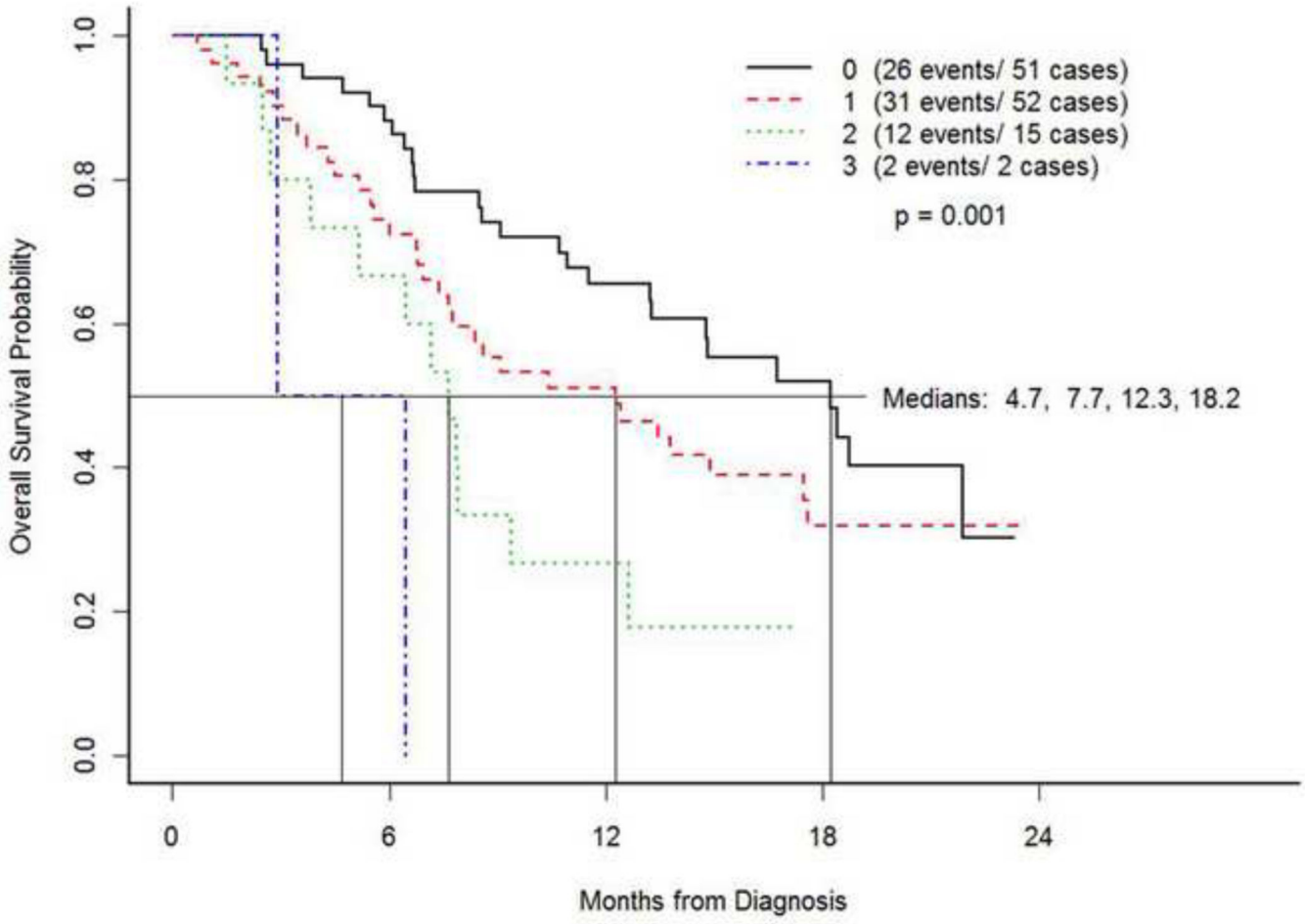

Fig.2. Summary of the sequential reading

Among all 120 cases read by Reader 1, 78 cases including 10 randomly selected scores 0 cases were read by the 2nd reader. Among them, 26 cases (26/78, 33%) had discordant scores between Readers 1 and 2, where the discordance were by 1-point scale difference in all cases and included scores 0 vs. 1 in 10 cases, scores 1 vs. 2 in 14 cases, and scores 2 vs. 3 in 2 cases. These 26 cases were read by Reader 3, and final scores were assigned based on the majority score. (For example, if the scores were 1, 2, 2 in the sequential read, the final score 2 was given to the case.) All 26 cases had a concordant score by two of the three readers, and there was no case with 3 different scores by three readers.

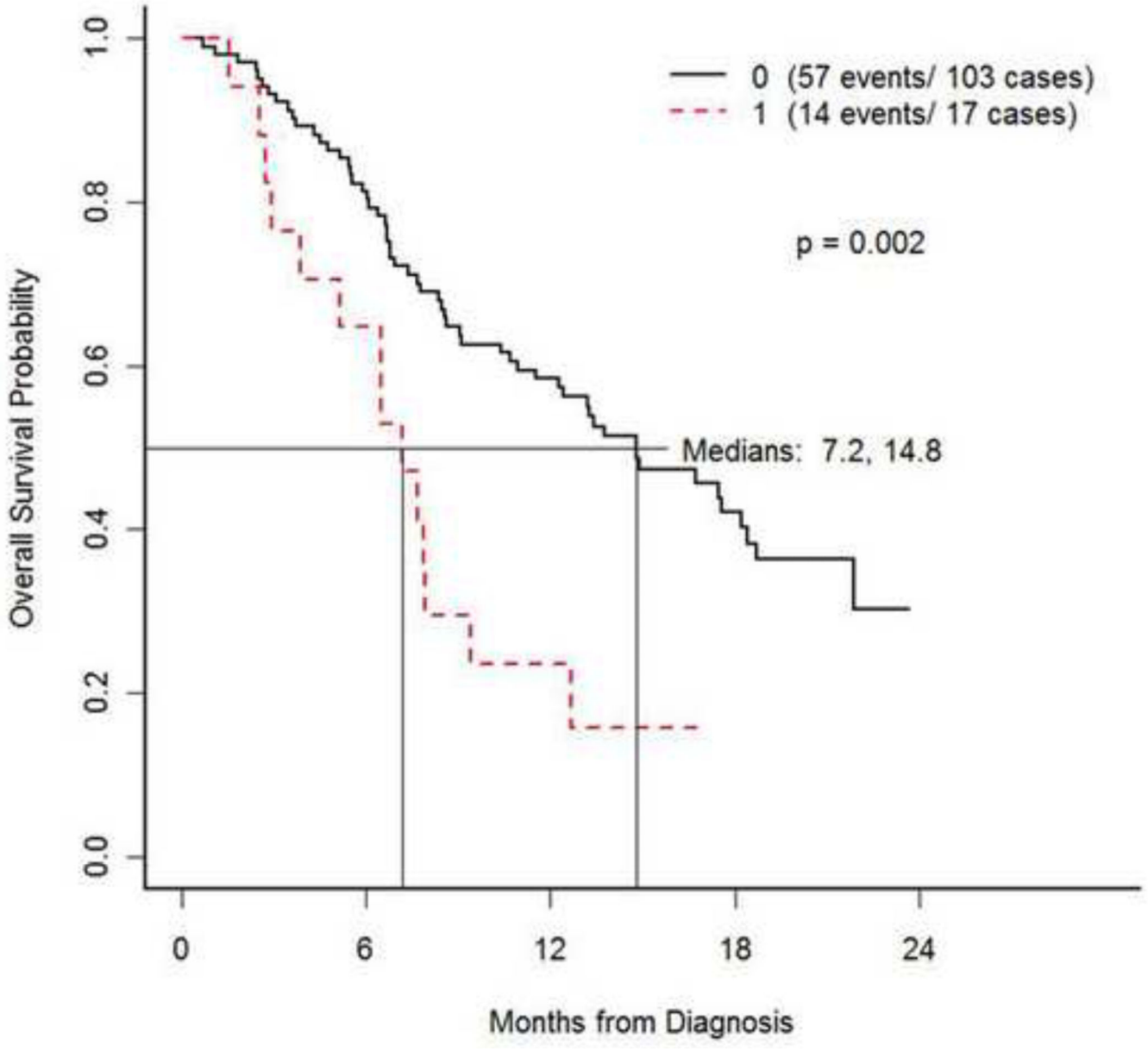

Fig. 3.
Overall survival of 4 groups of patients categorized by ILA score 0, 1, 2 and 3

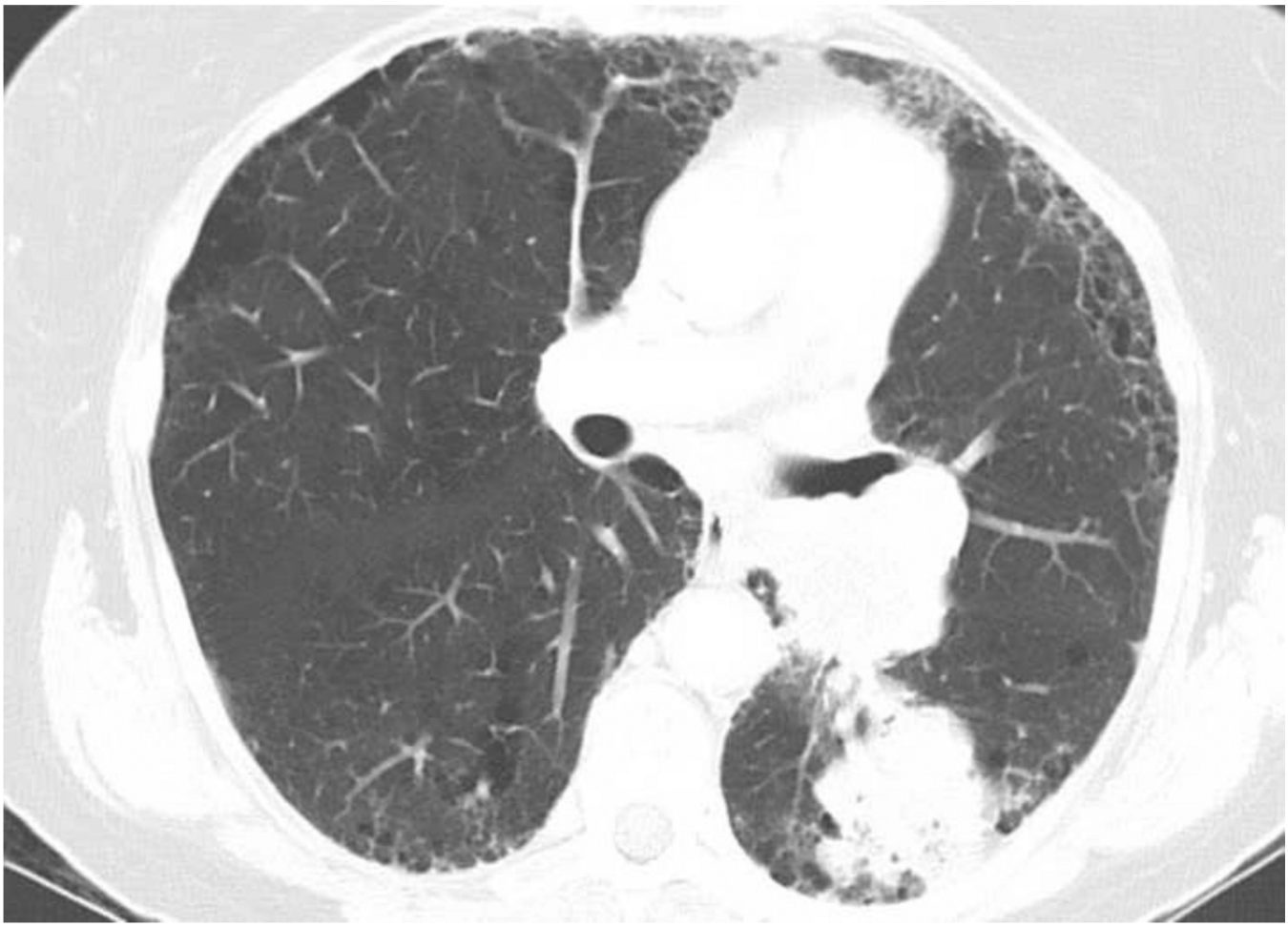

Fig. 4.
Overall survival of patients dichotomized using ILA score of 0 or 1 versus score of 2 or 3.

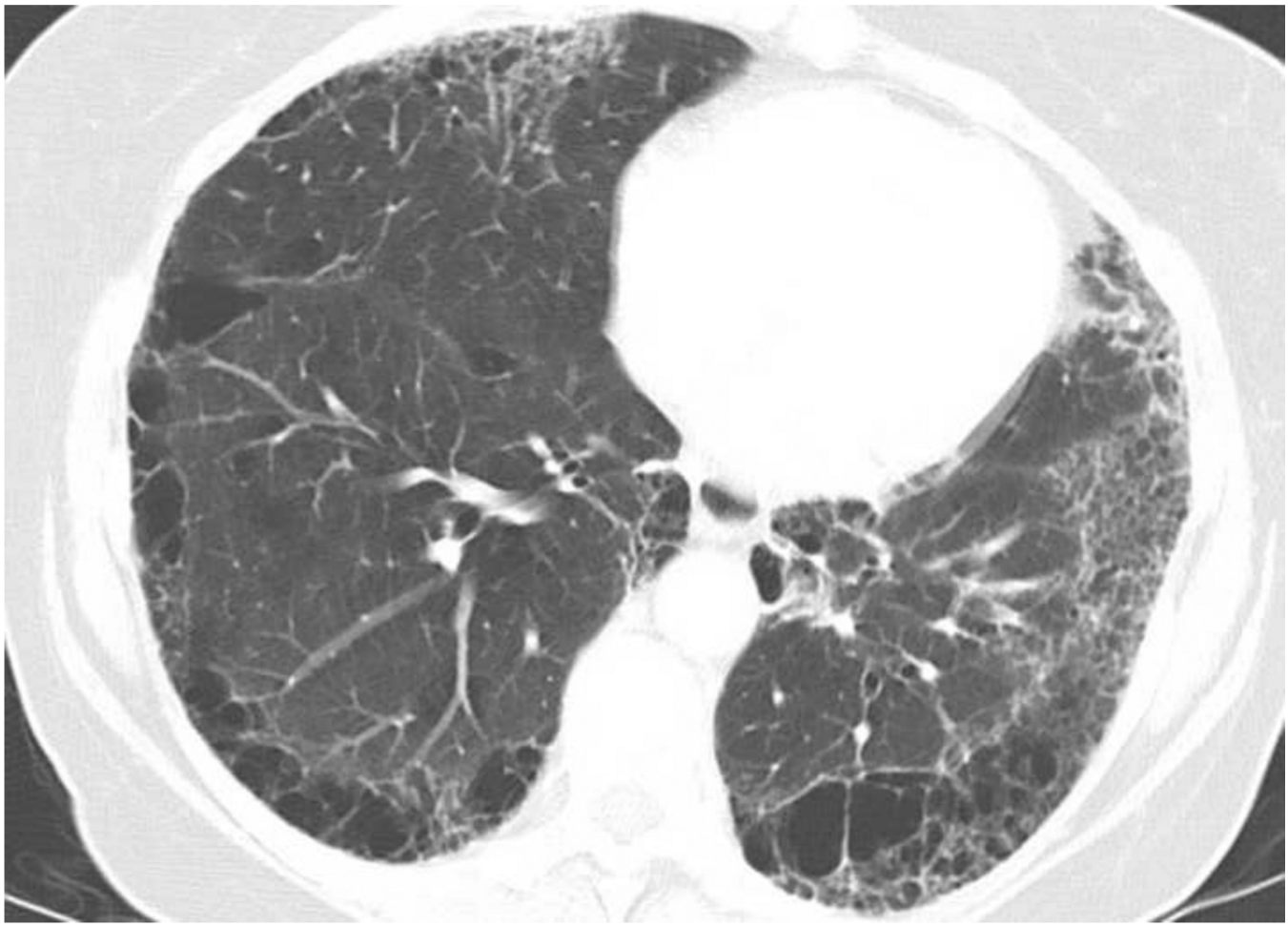

Fig. 5.

62-year-old, female with stage IVB NSCLC with 27 pack year history of smoking. Baseline chest CT at diagnosis demonstrated bilateral fibrosis in multiple lobes with honeycombing and traction bronchiectasis in subpleural distribution (a, b), which was scored as 3 (ILA). The mass in the left lower lobe represents the primary tumor (a). Also note underlying emphysema. The patient was subsequently treated with systemic therapy using carboplatin and pemetrexed. The patient experienced progressive disease and significant increase of dyspnea over the course of 6 months, with oxygen saturation of 82% on room air, requiring 3 liters of oxygen at rest. The overall survival since the diagnosis of NSCLC was 6.5 months.

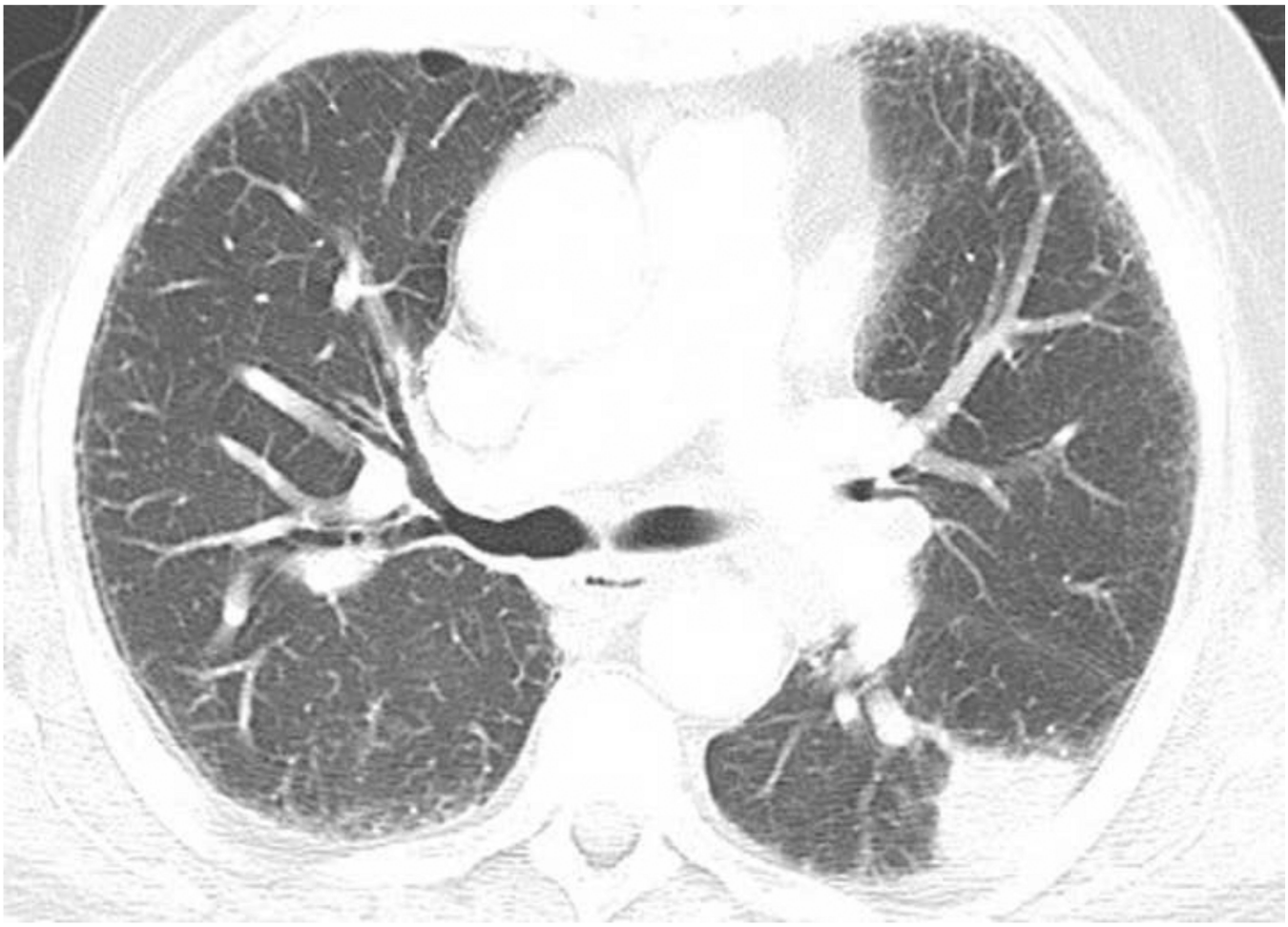

Fig.6.

77-year-old male with stage IVB adenocarcinoma of the lung with 100 pack year history of smoking. The baseline chest CT at diagnosis demonstrated non-dependent reticular and ground glass abnormalities in both lungs with subpleural distribution, without definite honeycombing, which was scored as “2” (suspicious for ILA) in the sequential reading. The wedge-shaped mass in the left lower lobe represent primary lung cancer. The patient subsequently received carboplatin and pemetrexed therapy for lung cancer, and died with progressing lung cancer at 7.7 months since diagnosis.

Table 1

Interstitial lung abnormalities (ILA) scores and patient characteristics

Clinical characteristics		ILA score					
		Score 0 (n=51)	Score 1 (n=52)	Score 2 (n=15)	Score 3 (n=2)	Total (n=120)	P value
Age (range)		60 (25-90)	64 (39-85)	70 (39-89)	55.5 (50-61)	64 (25-90)	0.01*
Gender	Male	23	21	9	0	53	0.38
	Female	28	31	6	2	67	
Race	White	42	47	15	2	106	0.89
	Asian	4	2	0	0	6	
	Black	4	2	0	0	6	
	Other	1	1	0	0	2	
Smoking	Never	20	8	1	0	29	0.03*
	Former	23	30	10	1	64	
	Current	8	14	4	1	27	
Pack years of smoking (range)		10 (0-60)	30 (0-100)	40 (0-180)	38.5 (27-50)	20 (0-180)	0.0002*
Distant metastasis	Present	39	43	11	2	95	0.75
	Absent	12	9	4	0	25	
Histology	Adeno	47	43	15	1	106	0.19
	Squamous	2	3	0	0	5	
	Other[#]	2	6	0	1	9	
Systemic therapy	Chemo	33	39	10	1	83	0.004*
	TKIs	18	8	2	0	28	
	None	0	5	3	1	9	

[#]Includes 7 patients with NSCLC NOS (not otherwise specified), one patient with large cell carcinoma and one patient with sarcomatoid carcinoma.