



Interstitial lung abnormality in stage IV non-small cell lung cancer: A validation study for the association with poor clinical outcome

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ABSTRACT

Purpose: The presence of interstitial lung abnormality (ILA) at diagnosis of stage IV non-small cell lung cancer (NSCLC) patients has previously shown to be associated with shorter overall survival (OS). The present study aimed to validate the association between ILA and shorter OS in a larger cohort of treatment-naïve stage IV NSCLC patients.

Materials and methods: This study includes 484 patients (205 men and 279 women) with a pathological diagnosis of stage IV NSCLC with pretreatment baseline CT available for review. ILA was visually scored on the baseline chest CT with a 3-point scale (0 = no ILA, 1 = indeterminate for ILA, 2 = ILA) as published previously. Clinical characteristics and overall survival (OS) were compared in patients with ILA score 2 vs. those with ILA score 0 or 1.

Results: ILA was present (score 2) on baseline CT in 19 of 484 patients (3.9%, 95%CI 2.4–6.1%). Patients with ILA were significantly older ($p = 0.0008$) and more commonly male ($p = 0.03$) compared to those with ILA score 0 or 1. Patients with ILA score 2 showed significantly shorter OS compared to those with ILA score 0 or 1 (median OS 9.95 months vs. 16.95 months; $p = 0.0002$). In multivariate analyses, baseline ILA score 2 remained significant as a marker for shorter OS (HR = 2.09, $p = 0.004$) after adjustments for age (HR = 1.48; $p = 0.001$), gender (HR = 1.22, $p = 0.06$), and smoking (HR = 0.79; $p = 0.051$).

Conclusions: ILA on baseline CT at diagnosis of stage IV NSCLC patients was associated with shorter OS (HR = 2.09, $p = 0.004$), validating ILA as an independent marker for poor clinical outcome.

1. Introduction

Lung cancer is the leading cause of death in both men and women in the United States, occurs in approximately 234,000 patients and results in over 154,000 deaths annually [1]. Interstitial lung abnormality (ILA) is defined as nondependent changes affecting more than 5% of any lung zone and included non-dependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis on chest CT [2], suggestive of lung parenchymal damages due to various patterns of inflammation and fibrosis and now considered to included subclinical form of idiopathic pulmonary fibrosis (IPF) [3–5]. In the previous studies, ILA was

associated with increased all-cause mortality, possibly due to pulmonary fibrosis in the healthy participants of the Framingham Heart Study [2,6] and IPF is associated with increased risk for lung cancer development [7,8]. Our previous study investigated a cohort of 120 treatment-naïve stage IV non-small cell lung cancer (NSCLC) patients and reported that the presence of baseline ILA on CT prior to therapy was associated with shorter overall survival (OS), with the hazards ratio (HR) of 2.09 [4]. If the finding is reproduced and confirmed in a larger cohort, it may help provide further insights to optimize management of stage IV NSCLC with underlying ILA.

The purpose of this study was to validate the association between ILA and survival in a larger cohort of state IV NSCLC patients.

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2. Materials and methods

2.1. Study population

This study included 484 patients (205 men and 279 women, median age: 62 years, range: 23–95) with histologically confirmed stage IV NSCLC between August 2007 and July 2011 with pretreatment baseline chest CT scans available for review. The medical records and CT images were retrospectively reviewed with the IRB approval. The patients in the study provided written informed consent. Demographics including age, gender, race, clinical characteristics including smoking history, histological subtypes, and types of first-line systemic therapy for NSCLC, and survival were obtained from the medical records.

2.2. Imaging analysis

All CT images were evaluated for ILA on the Picture Archiving Communication Systems (PACS) workstation (Centricity, GE Healthcare, Waukesha WI) using a sequential reading method by three board-certified radiologists (TA, HH, MN) with a 3-point scale system as described previously [4,9,10]. CT scans were scored for ILA as “0”, no evidence of ILA; “1”, indeterminate for ILA; and “2”, ILA. ILA 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 [6,10,11]. Indeterminate for ILA (score 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). 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, as published before [4]. In the sequential reading method, Reader 1 reviewed and scored all the CT studies. Next, Reader 2 independently reviewed all the studies scored as 1 and 2 by Reader 1, and randomly selected 20% of the scans scored as 0 by Reader 1, without access to the scores by Reader 1. The studies with concordant scores by two radiologists received the final score based on the two scores. The studies with discordant scores by two radiologists were independently reviewed by Reader 3, who was blinded to the scores by Readers 1 and 2, and were assigned the final score with majority opinion, as described previously [4,9–11].

Clinical information was obtained from electronic medical record including smoking history, histological subtypes, and types of first cancer therapy, and survival, as well as date of death. In patients with ILA, the respiratory symptoms during the disease course were also collected from the medical records.

2.3. Statistical analysis

Comparisons between the groups with and without ILA were performed using a Wilcoxon rank sum test for continuous data, and a Fisher's exact test for categorical data. ILA Score 2 was considered to indicate the presence of ILA. 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 difference in the OS distributions between the groups. Cox proportional hazards models were used to estimate hazard ratios (HRs), and multivariable analyses were performed using stepwise regression. All tests conducted were two-sided at the 0.05 significance level.

Table 1
Patient characteristics and ILA scores.

Clinical characteristics		Score 0 or 1 (n = 465)	Score 2 (n = 19)	Total (n = 484)	P Value
Age	Median (years) [range]	62 [23–90]	69 [39–95]	62 [23–95]	0.0008
Gender	Male	192	13	205	0.03
	Female	273	6	279	
Race	White	398	17	415	0.2
	Asian	25	0	25	
	Black	28	0	28	
	Other	14	2	16	
Smoking	Never	107	3	110	0.8
	Former	301	14	315	
	Current	57	2	59	
Histology	Adeno	355	14	369	0.07
	Squamous	35	4	39	
	Others	75	1	76	
Systemic therapy	None	63	0	63	0.09
	Chemotherapy	336	14	350	
	TKI	66	5	71	

TKI: tyrosine kinase inhibitors.

3. Results

3.1. Clinical characteristics and ILA scores

Among 484 patients with stage IV, ILA was present in 19 patients with ILA score 2 (3.9%, 95%CI: 2.4–6.1%). There were 178 patients with ILA score 1 and 287 with ILA score 0. Clinical and disease characteristics in patients with ILA score 2 and those with ILA score 0 or 1 are summarized in Table 1. The presence of ILA was significantly associated with older age (median 69 vs. 62 years; $p = 0.0008$) and male gender (68%, 13/19 vs. 41%, 192/465; $p = 0.03$). There was no significant difference in race, smoking history, tumor histology, and types of first-line systemic therapy for NSCLC between patients with and without baseline ILA.

Among 19 patients with ILA, 10 patients (53%) experienced respiratory distress with worsening respiratory symptoms such as cough, shortness of breath, and hypoxia during the disease course.

3.2. ILA and overall survival

At the time of the analysis, 404 out of 484 patients had died. The patients with ILA score 2 had significantly shorter OS than those with ILA score 0 or 1 (median OS: 9.95 months [95%CI: 5.88–15.5] vs. 16.95 months [95%CI: 14.65–18.7]; $p = 0.0002$) (Figs. 1 and 2).

Multivariate regression analyses were performed to further study association between the presence of ILA and OS. Backwards stepwise regression was used to exclude non-significant variables, which resulted in the model including ILA score 2, age (as > 70 years versus ≤ 70 years, using the 75th percentile of the cohort); gender; smoking status (current or former smoker versus never smoker). The types of first-line therapy were not included in the model due to confounding with smoking history. In the multivariate model, baseline ILA score 2 remained significantly associated with shorter OS (HR = 2.09; $p = 0.004$), after adjusting for age (HR = 1.48; $p = 0.001$), gender (HR = 1.22, $p = 0.06$) and smoking status (HR = 0.79; $p = 0.051$).

4. Discussion

The current study validates the association of the presence of ILA on baseline CT scan with poor clinical outcome in a larger cohort of 484 stage IV NSCLC patients. This study showed that the patients with ILA

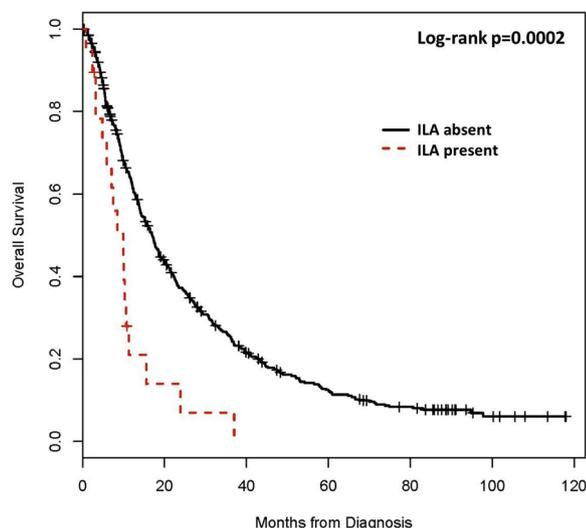


Fig. 1. Overall survival of patients with and without ILA using Kaplan-Meier estimate. Patients with baseline ILA had significantly shorter OS compared to those without (median OS: 9.95 months [95%CI: 5.88–15.5] vs. 16.95 months [95%CI: 14.65–18.7]; $p = 0.0002$).

score 2 had significantly shorter OS than those without ILA (9.95 vs 16.95 months, $p = 0.0002$), similar to our previous results (median OS: 7.2 vs 14.8 months, $p = 0.001$) [4]. These findings indicate the reproducibility of the association, and applicability of our study approach and method in patients with advanced NSCLC.

The findings were consistent with previously reported results [8,12–14]. Kinoshita et al investigated patients with NSCLC who were treated with chemotherapy alone, including 22 patients with idiopathic interstitial pneumonia (IIP) in comparison of 276 patients without IIP, and showed that those with IIP had significantly shorter median progression free survival (PFS) (3.1 vs 6.6 months, $P < 0.001$) and OS (5.4 vs 13.1 months, $P < 0.001$) [13]. Kanaji et al investigated 218 patients with advanced NSCLC and showed median PFS and OS in patients with ILD were significantly shorter than those without ILD (PFS: 3.9 vs 6.4 months, $P = 0.0007$, and OS: 8.8 vs 17.7 months, $P = 0.001$) [12]. Their findings are consistent to our findings (OS: 9.95 vs 16.95 months, $p = 0.0002$). A study by Fujimoto et al also showed association of ILD with shorter OS, investigating 770 patients with NSCLC of stage IIIB and IV who were treated with chemotherapy, and revealed that pre-existing ILD was seen in 3.8% (29/770) and which was one of the independent predictors of shorter OS (HR 1.90, $P < 0.001$) [14].

The prevalence of ILA varies among different cohorts probably due to multiple factors including tumor histology and stage. The protocols and qualities of CT scans as well as interpretations by radiologists are other factors that may influence the prevalence. The prevalence of baseline ILA was 3.9% in patients with stage IV NSCLC, which is similar to the result (3.8%) reported in the study of advanced NSCLC by

Fujimoto et al [14]. Hunninghake et al reported that the prevalence of ILA was 7% (177/2633) among the supposedly healthy participants in the Framingham Heart study cohorts [11]. Kawasaki et al investigated 711 patients with lung cancer including NSCLC and small cell lung cancer (SCLC), and the prevalence of idiopathic pulmonary fibrosis (IPF) was 7.5% (53/711) [7]. Our previous study showed that 14% of stage IV NSCLC patients (17/120) had ILA on pretreatment CT scan [4]. In a study by Kanaji et al, they investigated 218 patients with pathologically confirmed NSCLC of stage IIIB and IV and showed the prevalence of ILD was 24.3% (53/218) [12]. However, regardless the ranges of the prevalence in different studies, the higher prevalence of baseline ILA in men and in an older age population noted in the present cohort has been reproducibly noted in other studies of lung cancer patients [4,7,15,16] further confirming the risk factors of the underlying ILA among lung cancer patients.

Shorter OS in lung cancer patients with baseline ILA may be partially explained by an association with acute exacerbation of ILD or higher frequency of drug-associated pneumonitis [12,14,17]. In the study by Fujimoto et al, 6% of patients (44/770) developed pneumonitis during the therapy, and that preexisting ILD was independently associated with higher incidence of pneumonitis (OR: 2.99, $P = 0.008$) [14]. Sakurada et al investigated 459 patients with lung cancer and revealed that preexisting ILD was a risk factor for drug-associated pneumonitis (OR: 5.38, $P < 0.01$) [17]. Acute exacerbation of ILD or drug-associated pneumonitis may have important contribution to the lower disease control rate due to interruption or termination of treatment, resulting in shorter survival [12], indicating the importance of radiographic ILA assessment at baseline before initiating therapy in advanced NSCLC patients. More than half of the patients with ILA in the present study experienced respiratory distress with worsening respiratory symptoms during the disease course, however, the observation can be due to multiple factors including underlying ILA, drug effects, tumor progression, and other complications such as pneumonia.

There were several limitations in this study, including retrospective study design with a cohort collected from a single institution. This study evaluated clinical oncologic chest CT scans without dedicated high-resolution CT, which may underestimate the prevalence of milder ILA. The diagnosis of ILA was based on CT image findings without pathologic confirmation. However, we used established sequential reading method for CT evaluation to increase the accuracy of diagnosis, and the results were correlated with pathological findings in the previous studies [18,19]. Additionally, in most patients presenting with stage IV NSCLC, it is difficult to obtain histological analyses of ILA. The causes of death in patients with ILA were of great interest to further assess the impact of baseline ILA in lung cancer mortality; however, the information was limited in this retrospective cohort and the issue needs to be better evaluated in future prospective studies.

In conclusion, the current study validated that baseline ILA was significantly associated with shorter OS. The presence of baseline ILA could be regarded as a reproducible prognostic marker in patients with advanced NSCLC. These findings suggest that the radiographic assessment for ILA on baseline CT is important for patients presenting with

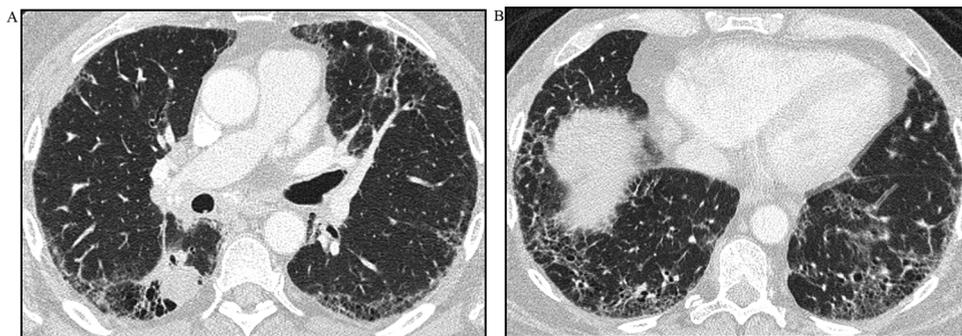


Fig. 2. A 55-year-old male smoker with stage IV adenocarcinoma of the lung, with a primary tumor in the right lower lobe (A) and osseous metastasis. Pre-treatment chest CT (A, B) demonstrated underlying interstitial lung abnormalities (ILA) with subpleural interlobular septal thickening, traction bronchiectasis, and volume loss in bilateral lungs predominantly in lower lobes. The patient had worsening shortness of breath and died at 10 months since the diagnosis of lung cancer.

stage IV NSCLC, and radiologists' interpretation of ILA may help optimize clinical management and outcome of the advanced lung cancer patients.

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