

Mediastinal lymph node enlargement in idiopathic pulmonary fibrosis: relationships with disease progression and pulmonary function trends.

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Abstract

Background and objectives

Evidence of mediastinal Lymph Node Enlargement (LNE) on CT scan is a common finding in idiopathic pulmonary fibrosis (IPF). We sought to investigate whether the involvement of mediastinal lymph nodes is associated with accelerated disease progression, and explored the changes occurring in mediastinal lymph nodes during the radiological follow up of these patients.

Methods

This retrospective study included IPF patients referred to a single ILD centre in Italy. A consensus-based assessment of mediastinal LNE on chest CT scan was performed by two thoracic radiologists. Kaplan-Meier curves and multivariate Cox proportional hazards regression were used to assess hazard ratios for mortality and disease progression (defined as categorical FVC decline $\geq 10\%$). The annualized rates of change in functional parameters for each patient were calculated using mixed linear models.

Results

152 IPF patients were included in the analysis, of whom 135 (89%) received antifibrotic treatment for IPF during the study follow up. Patients having evidence of 3 or more enlarged mediastinal lymph nodes on baseline CT scan showed increased rates of mortality (HR 5.03, 95% CI 1.86-13.62, $p \leq 0.001$) and significant disease progression (HR 2.99, 95% CI 1.22-7.33, $p = 0.17$) as compared to patients without LNE, after adjusting for GAP stage. Among 62 patients with LNE who underwent a follow up CT scan of the chest and received antifibrotic treatment, 57 (92%) maintained evidence mediastinal LNE over time.

Conclusions

Diffuse mediastinal lymph node involvement predicts clinically meaningful functional deterioration in patients with IPF.

Background

Idiopathic pulmonary fibrosis (IPF), the most common and severe among idiopathic interstitial pneumonias, is a chronic disorder of unknown cause characterized by progressive scarring of the lung parenchyma leading to loss of lung function and ultimately death from respiratory failure despite treatment [1] [2]. The prognosis is poor, with a median survival of 3-5 years from the time of diagnosis [3]. Despite two antifibrotic drugs, nintedanib and pirfenidone, proved to slow down the functional decline in IPF [4,5], most patients still deteriorate despite treatment. As such, accurate monitoring of disease progression in IPF is crucial for predicting prognosis and optimizing management, including the appropriate timing of supportive care and the prompt referral for lung transplantation. Clinical findings, pulmonary function measures and computed tomography findings have been extensively studied to predict survival in IPF, either individually or by using composite scoring indices [6] [7] [8] [9], however prognostication remains challenging in the individual patient due to the heterogeneity of IPF and the significant intra-patient variability of the disease behaviour [10]. Measurement of forced vital capacity (FVC) via spirometry has been accepted as the most feasible and reliable tool to monitor disease progression in these patients in clinical practice as well as in randomized controlled trials [11] [12], however it has not been proved of great utility in predicting future loss of pulmonary function [13] [14]. Visual evaluation and computer-based quantification of high-resolution computed tomography (HRCT) lung parenchymal patterns of fibrosis have been demonstrated to be strong predictors of outcome, particularly in IPF patients [7] [9] [15][16][17], however their use in clinical practice is still limited. The evidence of mediastinal lymphadenopathies on chest CT scans in patients with interstitial lung disease (ILD) have drawn the attention of researchers over the years, due to the putative role played by inflammation and immunity processes in pulmonary fibrosis. The frequency of this finding has been reported in up to 70% of patients with a usual interstitial pneumonia pattern [18] [19], and in up to 58% of IPF patients [20][21]. Although the biology underpinning mediastinal lymph

node enlargement in these patients has never been clarified, the presence of LNE on chest CT scans has been associated with increased all-cause mortality in IPF and other ILD [22,23], suggesting a role as useful prognostic factor in fibrotic lung disease. An ongoing randomized clinical trial is currently exploring the efficacy of a human monoclonal antibody directed against the B-cell activating factor (BAFF) receptor on B cells in IPF patients (clinicaltrials.gov identifier NCT03287414). The study recognizes the presence of hilar/mediastinal lymphadenopathies on HRCT as one of the key inclusion criteria, based on the hypothesis that lymph node involvement may identify IPF patients with pronounced immune activation and who are therefore more likely to respond to the investigational treatment.

To date however, it is unknown whether the enlargement of mediastinal lymph nodes may be used to identify patients with more rapid functional deterioration, or to indicate response to currently available antifibrotic treatments.

In this study, we retrospectively evaluated the impact of LNE on mortality and disease progression in a cohort of IPF patients, and explored the changes occurring in mediastinal lymph nodes during the radiological follow up.

Methods

Study population

All patients referred to the outpatient ILD clinics at Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome between January 2014 and November 2018 were retrospectively screened for inclusion in the study. Eligibility criteria were represented by a multidisciplinary diagnosis of IPF according to ATS/ERS/ALAT/JRS available diagnostic guidelines[1] [3] and the availability of a chest CT scan performed within one year from diagnosis. Patients were excluded if they had either concurrent pulmonary infection at the time of the CT scan, acquired immunodeficiency syndrome (AIDS), unstable chronic heart disease or history of malignancy with less than 5 years of negative follow up. Subjects with no available Pulmonary Functional Tests (PFTs) were also excluded. The study was reviewed and received approval by the local ethics committee of Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome.

Data collection and study groups

Baseline and follow up data were obtained from available medical records at the ILD outpatient clinic Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome up to April 2019. Demographics and medical history including smoking status, use of supplemental oxygen, antifibrotic treatment and comorbidities were collected. Baseline and follow up lung function data included absolute and percent predicted values of FVC and diffusion capacity for carbon monoxide (DL_{CO}). The Gender/Age/Physiology (GAP) score, that integrates patient-specific variables (sex, age, FVC, DL_{CO})[8], was calculated for each patient. Follow up time was calculated for each patient as the time interval between the first and the last functional test performed at the referral centre.

For the purpose of this study, study groups were defined according to the presence (LNE+) or absence (LNE-) of at least one mediastinal lymph node with short-axis diameter ≥ 10 mm on chest CT scan at baseline, as reviewed by thoracic radiologists.

Chest CT evaluation

The CT exams evaluated for this study were performed at different centres, with some variability in reconstruction parameters used and contrast medium administration. Since most of CT studies were performed for the analysis of the lung parenchyma, CT scans without contrast medium administration were the majority and were preferred for the analysis when available. Images with a maximum slice thickness of 5 mm (range: 1-5 mm), smooth reconstruction algorithm and soft tissue window setting (level 50/width 350 HU) were used for lymph node assessment. Mediastinal lymph node stations based on the International Association for the Study of Lung Cancer nomenclature were systematically assessed for enlarged lymph nodes [24]. Mediastinal lymph node measurements were provided using electronic calipers. Lymph nodes

with a short-axis diameter ≥ 10 mm were reported as enlarged, as previously described in papers focused on ILD [22,23]. The number and maximum short-axis diameter for each station as well as location (upper zones, lower zones, or both) of LNE were recorded. When available, follow up CTs were also reviewed for the presence of LNE to evaluate the longitudinal behaviour of LNE. Radiologic patterns were also assessed according to the current ATS/ERS/ALAT/JRS guidelines for diagnosis of IPF (UIP, probable UIP, Indeterminate for UIP and alternative diagnosis)[1]. All the evaluations were performed via consensus between two thoracic radiologists with expertise in ILD, blinded to clinical information of patients included in the study.

Statistical analysis

Assuming a survival rate of 70% in the group without mediastinal LNE over a follow up period of 2 years, a sample of 148 patients was calculated as required to provide the study with 90% power to detect a 2.26-fold increased mortality risk in the group with mediastinal LNE with a two-sided significance level of 5%. The effect size was chosen based on a previous study investigating the impact of mediastinal LNE on survival in IPF [22].

Descriptive statistics such as means with standard deviations and frequencies or percentages were used for continuous and categorical variables, respectively. Between-group comparisons of demographics and clinical data were performed using t-test for continuous variables and the chi-square test for categorical variables. Kaplan–Meier analysis with log-rank testing was performed to compare, across study groups, the rates of mortality from any cause during the follow up and the rates of disease progression as defined by a categorical FVC decline $\geq 10\%$ measured at the time of the last available pulmonary function assessment.

Cox proportional hazard regression analysis was used to calculate crude and adjusted hazard ratios and their 95% confidence intervals (CIs). Observed baseline and 12(± 4) months FVC and percent predicted DLco values were entered in a mixed linear model with fixed effects for presence of mediastinal LNE, time, gender, age and random effects for patient-specific intercept to predict the annualized rate of change in the parameters for each patient. The effect of mediastinal LNE on FVC and DLco changes over time was determined on the basis of the time-by-group interaction term from the mixed model. P-values less than 0.05 were considered statistically significant. SPSS (version 24, IBM, USA) was used for statistical analysis.

Results

Baseline characteristics of patients and comparison of study groups

One hundred eighty-one IPF patients from the ILD clinic registry were screened for eligibility (figure 1). Overall, twenty-nine patients were excluded for unavailability of CT scan within 12 months from diagnosis (n=21), history of thoracic malignancy (n=3), respiratory infection at the time of diagnosis (n=1) or for missing reports of baseline pulmonary function tests (n=4). One hundred fifty-two IPF patients in the ILD registry were therefore included in the analysis. Average clinical follow up time of the study population was 19.08 months (SD 12.8). The majority of IPF patients (n=94, 62%) had at least one LNE on CT performed within a year from diagnosis, while 58 patients (38%) had no LNE present. Within patient with mediastinal LNE, 62 (66%) had two or more mediastinal lymph node with short-axis diameter ≥ 10 mm, while 31 (33%) had 3 or more LNE. In this group, the mean short-axis diameter of largest lymph node was 12.4 mm (SD 2.4). LNE was predominantly distributed in paratracheal stations (n=93, 99% of LNE patients), while only 3 patients (3%) had LNE in the lower zones. The large majority of patients included in this study (n=135, 89%) received antifibrotic treatment for IPF during the follow up.

Baseline characteristics of the study groups by presence of LNE on baseline CT scan are reported in table 1. No significant differences were found at baseline between the two study groups as to demographics. Patients without LNE had lower GAP

stage ($p=0.038$) and higher DLco % predicted at baseline ($p=0.023$) as compared to LNE+ patients. Diabetes was a more frequent comorbidity among patients with LNE (25.8% vs 6.9%, $p=0.004$).

All-cause mortality

On univariate Kaplan-Meier analysis, IPF patients with evidence of mediastinal LNE on baseline CT scan of the chest had lower survival rates as compared to patients without LNE (median survival 37.8 months vs 44.5 months, log-rank $p=0.025$) (figure 2). This corresponded to a 2.65-fold increased risk of mortality for LNE+ patients on Cox proportional hazard analysis (95% CI 1.09-6.46, $p=0.032$) (table 2). After stratification of the study population by number of enlarged mediastinal lymph nodes, the involvement of three or more lymph nodes was found significantly associated with worse survival as compared to each of the other groups (Figure 2), with a 5.72-fold increased risk of mortality (HR 5.72, 95%CI 2.18-14.98, $p<0.001$). Within patients with mediastinal LNE at baseline, increasing dimensions of the largest lymph node were also associated with higher mortality (HR 1.17, 95% CI 1.04-1.32, $p=0.01$).

When hazard ratios were adjusted for GAP stage[8], only the presence of 3 or more mediastinal enlarged lymph nodes maintained a strong association with poorer survival (HR 5.03, 95% CI 1.86-13.62, $p\leq 0.001$)(table 2).

Pulmonary function

Time to significant functional decline defined as 10% absolute decline in FVC was not significantly different between patients with or without LNE (figure 3, table 2). On the other hand, patients with evidence of 3 or more mediastinal enlarged lymph nodes showed increased disease progression rates both on univariate analysis (HR 2.67, 95% CI 1.19-5.97, $p=0.017$) and after adjusting for GAP stage (HR 2.99, 95% CI 1.22-7.33, $p=0.17$)(table 2).

In order to further explore the association between mediastinal LNE and change in pulmonary function parameters, the annualized rates of change in absolute FVC and % predicted DLco were compared between patients with different degrees of lymph node involvement at baseline (figure 4, table 3). The rate of decline in FVC increased with the number of mediastinal lymph nodes involved and was largest in patients with 3 or more enlarged lymph nodes (-178 mL, SE 0.09), especially if compared to patients without LNE, who showed relative stability over 12 months (FVC change -4 mL, SE 0.07). However, the differences in the rates of change in FVC were not statistically significant as shown by the group-by-time interaction term in the model ($p=0.332$). The largest decline in DLco occurred in the group with 3 or more enlarged lymph nodes (-10.5%, SE 2.55) as compared with the other groups, although such difference did not meet statistical significance (group-by-time interaction $p=0.349$) (table3).

Longitudinal assessment of mediastinal LNE

117 patient cases who had available longitudinal imaging data were assessed for the presence of mediastinal LNE at the follow up CT scan. Average time difference between consecutive CT scans was 17.7 months (SD 10.4). LNE status did not change over time in 101 (86%) of these patients. Among the 48 patients without evidence of mediastinal LNE at baseline, 38 (79%) patients remained without mediastinal LNE at follow up, while among the 69 patients with baseline mediastinal LNE 63 (91%) maintained evidence mediastinal LNE over time. Among the 62 patients with baseline LNE who received antifibrotic treatment, 57 (92%) had mediastinal LNE at follow up. Mediastinal LNE disappeared in only 6 (9%) patients who had LNE at baseline, while 10 (11%) patients who did not have LNE at baseline developed LNE at follow up.

Discussion

In this study we retrospectively evaluated the impact of mediastinal LNE on survival and disease behaviour in patients with IPF followed up at a tertiary ILD centre in Italy. The results from our cohort suggest that a diffuse involvement of mediastinal lymph nodes in IPF patients is an independent predictor of both mortality and functional deterioration in these patients.

Predicting the course of IPF represents a historical challenge for clinicians. Current risk prediction models, robustly developed using data from large randomized clinical trials, may not be suitable for individual prognostication in the real life heterogeneous IPF populations. Furthermore, no parameters have shown to be useful in predicting future trends of functional decline, the hallmark of progressive disease in IPF [13]. Mediastinal lymph node enlargement on CT scan has been recently investigated as a prognostic biomarker in IPF and other fibrotic ILD, for reflecting pathobiological mechanisms of activated immune response that may be relevant to easily stratify patient with at risk of poorer outcome. Sin and colleagues [22] demonstrated that mediastinal LNE was a strong, independent predictor of mortality in a retrospective cohort of 132 patients with IPF. Adegunsoye and colleagues [23] nicely reported the association of several features of mediastinal lymphadenopathies with disease severity and higher risk of mortality or hospitalization in patients with a variety of forms of ILD, including IPF, IPAF (interstitial pneumonia with autoimmune features), CTD-ILD (connective tissue disease-associated interstitial lung disease) and unclassifiable ILD, suggesting a role for mediastinal lymph node assessment in ILD prognostication beyond specific etiology.

In our cohort, a “diffuse” lymph node involvement - as defined by 3 or more enlarged mediastinal lymph nodes - was strongly associated with lower survival rates, in line with previous findings. Sin and coworkers [22] demonstrated the impact of mediastinal LNE on survival in an equally-sized IPF cohort with comparable size and similar proportion of patients showing lymph node enlargement on CT. Notably though, the large majority of patients in our study received antifibrotic treatment after diagnosis, suggesting that the presence of multiple mediastinal lymphadenopathies may predict poorer prognosis despite treatment.

Importantly, our study provided first evidence as to the relationships between mediastinal LNE and disease progression expressed by means of functional decline. The involvement of 3 or more lymph nodes involved was found to be associated with an increased risk of disease progression as defined by significant drop ($\geq 10\%$) in percent predicted FVC, suggesting that diffuse mediastinal LNE represent a marker of more aggressive disease behaviour in these patients. Patients with higher number of lymph nodal stations involved also showed decreased annual trends of pulmonary function and gas diffusion capacity, although the slopes of change were not found significantly different as compared to patients with no or lesser lymph node involvement. Whilst our study was not powered to detect the impact of LNE on continuous change in pulmonary function parameters in a treated IPF population with reduced progression rates, these findings further support the hypothesis that major lymph node involvement predicts future functional deterioration.

The longitudinal evaluation of mediastinal LNE in a subpopulation with follow up imaging data showed that such finding is stable over time in most patients despite currently available antifibrotic treatment, which seems to preclude the role of LNE as a marker of response to treatment. Indeed, further studies are needed to clarify the pathobiological mechanisms at the basis of this prevalent finding in IPF patients. The study of histological features of LNE may help shed a light on the immune processes involved and whether a subset of patients exists where such pathways are paramount for driving disease progression.

The main limitations of our study are represented by its retrospective nature and the small size of our cohort. Nevertheless, the study was adequately powered based on previously reports of mortality hazard ratio for IPF patients with LNE [22], which increases the robustness of our results. Another theoretical limitation consists in the heterogeneity of CT reconstruction protocols and contrast medium administration, as the exams have been performed in different centres.

In conclusion, we demonstrated that the presence of diffuse mediastinal lymphadenopathy on CT scan is independently associated with higher risks of mortality and clinically significant disease progression in a cohort of IPF patients despite antifibrotic treatment. Altogether, our results support the utility of mediastinal LNE in the risk stratification of the heterogeneous IPF population. Ongoing trials and future research will eventually clarify the pathobiology of mediastinal lymphadenopathy in IPF and if such finding may be useful to identify patients responding to treatments targeting specific immune pathways.

Declarations

Ethics approval and consent to participate:

The study was reviewed and received approval by the local ethics committee of Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome. The need to receive an informed consent from all patients was waived due to the retrospective nature of the study.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

Dr. Sgalla reports personal fees from Boehringer Ingelheim outside the submitted work; Dr. Calvello reports personal fees from Boehringer Ingelheim, outside the submitted work; Dr. Varone reports personal fees from Boehringer Ingelheim, personal fees from Roche, outside the submitted work; Dr. Iovene reports personal fees from Menarini, personal fees from Boehringer Ingelheim, outside the submitted work; Dr. Richeldi reports personal fees and other from Boehringer Ingelheim, grants and personal fees from InterMune, personal fees from Cipla, personal fees from Vertex, other from AstraZeneca, other from GlaxoSmithKline, other from Sanofi-Aventis, other from Celgene, other from Prometic, other from Roche, other from Takeda, during the conduct of the study.

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Authors' contributions

Conceptualisation of the study: GS, ARL, FV. Data collection: NG, MRC. Analysis of radiological data: AF, ADC. Statistical Analysis: GS. Writing of study manuscript: GS. Review of study manuscript: BI, FV, ARL. Study supervision: LR, RM. All authors have read and approved the manuscript.

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Not applicable.

Abbreviations

LNE - Lymph Node Enlargement

IPF - Idiopathic Pulmonary Fibrosis

FVC - Forced Vital Capacity

HRCT - High-resolution computed tomography

ILD - Interstitial Lung Disease

PFTs – Pulmonary Function Tests

DLco - Diffusion capacity for carbon monoxide

GAP - Gender/Age/Physiology

IPAF - Interstitial pneumonia with autoimmune features

CTD-ILD - Connective tissue disease-associated interstitial lung disease

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Tables

Table 1 - Baseline characteristics of patients without (LNE-) or with (LNE+) mediastinal lymph node enlargement on CT scan of the chest. Data are expressed as counts (%) or mean with standard deviation. Reported p-values were obtained via t-test for independent samples or Pearsons' Chi-squared test as applicable. BMI=body mass index; FVC=forced vital capacity; DLco=diffusion lung capacity for carbon monoxide; 6MWD=6-minute walk distance; COPD=chronic obstructive pulmonary disease; OSAS= obstructive sleep apnea syndrome; GERD=gastroesophageal reflux disease; GAP=gender age physiology.

	N available observations	LNE- (n=58)	LNE+ (n=94)	p value
Age, years	152	76 (7.3)	74.7 (7.6)	0.277
Sex	152			0.627
1. Male		45 (77.6)	76 (80.9)	
2. Female		13(22.4)	18 (19.1)	
Smoking history	148			0.599
1. Current		0 (0)	1 (1.1)	
2. Former		34 (60.7)	60 (65.2)	
3. Never smoker		22 (39.3)	31(33.7)	
BMI	140	28.2 (3.9)	27.31 (4.5)	0.244
Use of oxygen therapy	137			0.405
No		51 (91.1)	70 (86.4)	
Yes		5 (8.9)	11(13.6)	
HRCT pattern	136			0.504
UIP		27 (52.9)	32 (37.6)	
Probable UIP		14 (27.5)	7 (8.2)	
Indeterminate for UIP		7 (13.7)	3 (3.5)	
Alternative diagnosis		3 (5.9)		
Anti-fibrotic treatment	150			0.064
1. No treatment		6 (10.5)	9 (9.7)	
2. Pirfenidone		30 (52.6)	32 (34.4)	
3. Nintedanib		21 (36.8)	52 (55.9)	
Follow up time (months)	140	21.2(13.4)	18.1 (12.4)	0.166
FVC volume, L	141	2.6 (0.7)	2.56 (0.73)	0.737
FVC % predicted	152	85.6 (21)	80.3 (19.5)	0.118
DLco % pred	142	58.9 (23.2)	50.1 (21.7)	0.023
SaO ₂ % at rest	142	94.4 (2.2)	94.7 (2.7)	0.563
Comorbidities				
1. COPD	152	4 (6.9)	5 (5.3)	0.732
2. Emphysema	152	5 (8.6)	13 (13.8)	0.334
3. OSAS	152	6 (10.3)	8 (8.5)	0.704
4. Chronic heart disease	152	17 (29.3%)	32 (34)	0.544
5. Pulmonary hypertension	152	2 (3.4)	12 (12.8)	0.054
	152	16 (27.6)	30 (31.9)	0.573
	152	2 (3.4)	4 (4.3)	0.804
	205	4 (6.9)	24 (25.8)	0.004
GERD				
Anxiety/Depression				
Diabetes				
GAP Index	148			0.038
1. Stage I		25 (43.9)	35 (38.5)	
2. Stage II		30 (52.6)	40 (44.4)	
3. Stage III		2 (3.5)	16 (17.6)	
LNE number				
1. 1			32 (34)	
			31 (33)	
			31 (33)	

2. 2			
3. ≥ 3			
Larger LNE (mm)	113	-	12.4 (2.4) <0.001

Table 2 - Cox proportional hazard regression analysis for all-cause mortality and disease progression. Disease progression was defined as death or absolute forced vital capacity (FVC) decline $\geq 10\%$. *Values of HR were adjusted for GAP (Gender, Age, Physiology) stage index. **within LNE+ patients.

	Mortality				Disease progression				
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	
LNE + (vs LNE -)	2.65 (1.09-6.46)	0.032	2.39 (0.96-5.95)	0.062	1.75 (0.9-3.39)	0.097	1.87 (0.93-3.76)	0.078	
Number of LNE (vs 0)	1.49 (0.42-5.3)	0.538	1.1 (0.27-4.5)	0.894	1.43 (0.54-3.83)	0.472	1.65 (0.61-4.47)	0.326	
	1	1.62 (0.54-4.84)	0.386	1.55 (0.52-4.66)	0.436	1.41 (0.63-3.17)	0.405	1.53 (0.67-3.52)	0.313
	2	5.72 (2.18-14.98)	<0.001	5.03 (1.86-13.62)	0.001	2.67 (1.19-5.97)	0.017	2.99 (1.22-7.33)	0.017
	≥ 3								
Larger LNE** (mm)	1.17 (1.04-1.32)	0.01	1.14 (0.99-1.29)	0.058	1.05 (0.89-1.23)	0.57	0.93 (0.84-1.18)	0.928	

Table 3 - Annualized rates of change in Forced Vital Capacity (liters) and DLco (% predicted) across patients with different grade of involvement of mediastinal lymph nodes on baseline CT scan. LNE- = without mediastinal lymph node enlargement; LNE 1-2 = with 1 or 2 enlarged lymph nodes; LNE ≥ 3 = with 3 or more enlarged lymph nodes. Data are means of predicted values (baseline-12 months) derived from linear mixed models. p Values are for group \times time interaction. p Values <0.05 were considered statistically significant.

	12-month mean difference (SE)			p value
	LNE - n=58	LNE 1-2 n=63	LNE ≥ 3 n=31	
FVC (liters)	-0.04 (0.073)	-0.095 (0.073)	- 0.178 (0.094)	0.332
DLco (% predicted)	-3.49 (2.35)	- 3.99 (2.12)	- 10.5 (2.55)	0.349

Figures

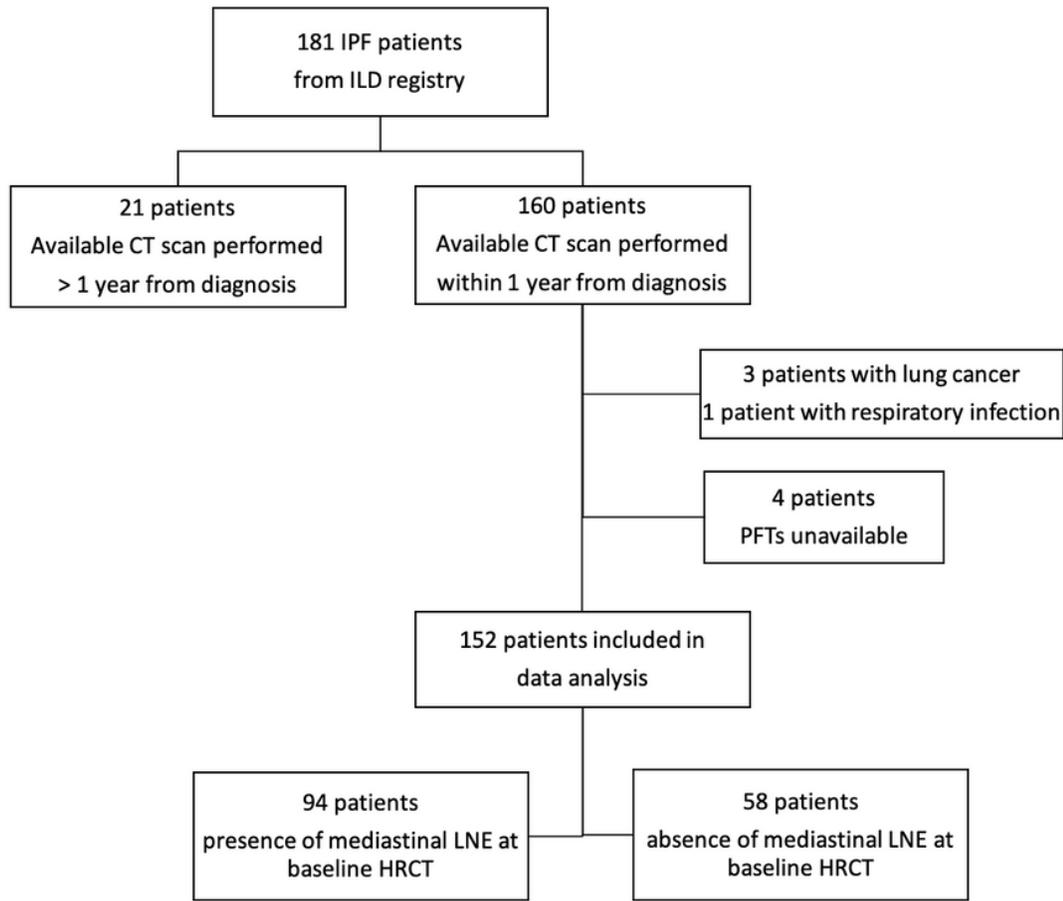


Figure 1

Flowchart of patient selection for the study.

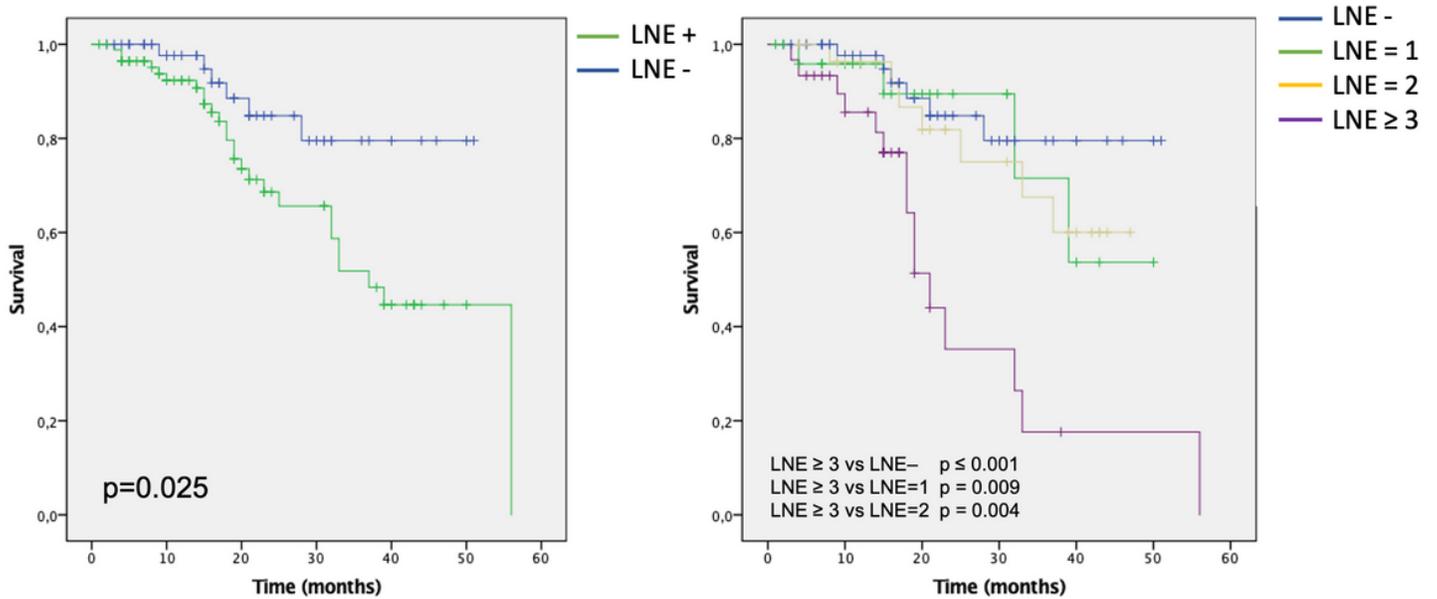


Figure 2

Kaplan-Meier curves of mortality for patients with (LNE+) or without (LNE-) mediastinal lymph node enlargement (left) and for patients stratified according to the number of mediastinal enlarged lymph nodes (right). P values were obtained via log-

rank test.

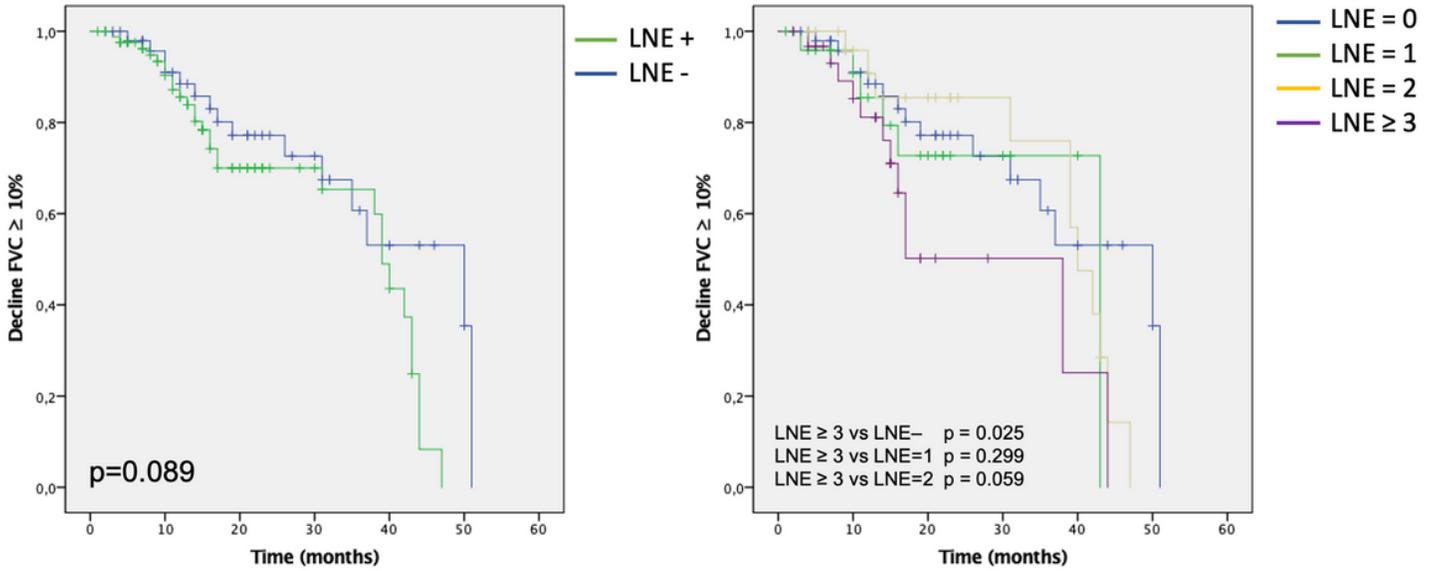


Figure 3

Kaplan-Meier curves of disease progression, expressed as absolute decline of predicted forced vital capacity (FVC) $\geq 10\%$ for patients with (LNE+) or without (LNE-) mediastinal lymph node enlargement (left) and for patients stratified according to the number of mediastinal enlarged lymph nodes (right). P values were obtained via log-rank test.

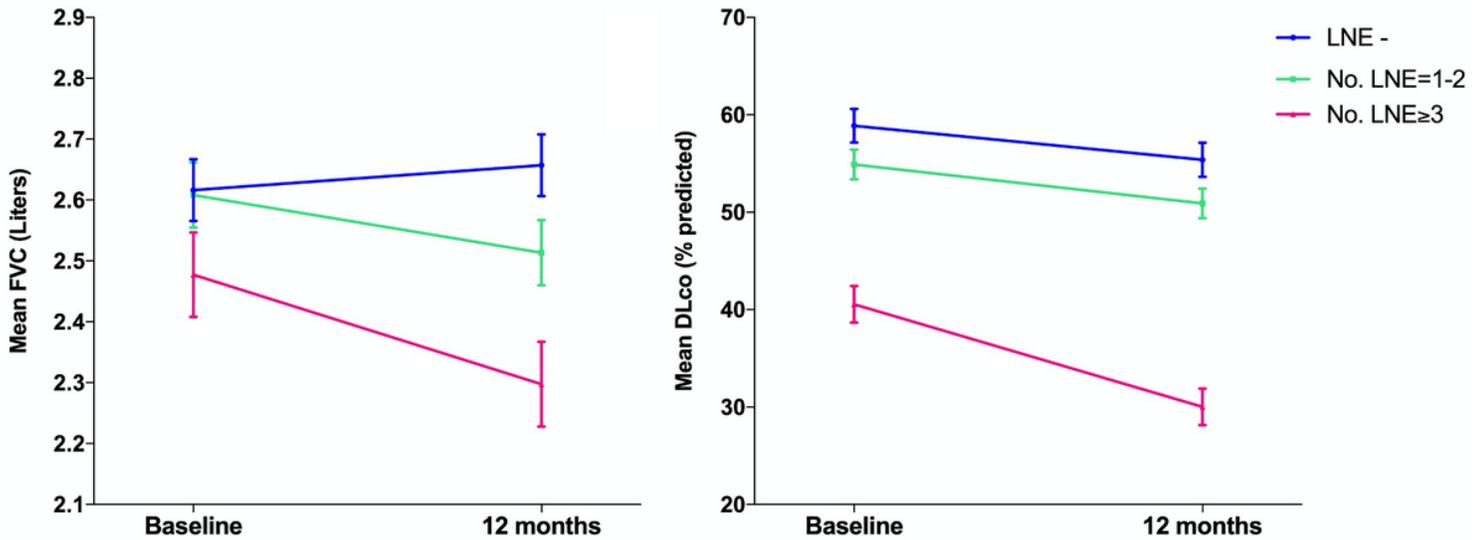


Figure 4

Predicted annual change in Forced Vital Capacity (FVC) and Diffusion Capacity of CO (DLco) for patients with different grade of involvement of mediastinal lymph nodes on baseline CT scan. LNE- = without mediastinal lymph node enlargement; LNE 1-2 = with 1 or 2 enlarged lymph nodes; LNE ≥ 3 = with 3 or more enlarged lymph nodes. Data are predicted mean values with standard error bars. No significant group \times time interactions were found (p=0.332 and p=0.349 respectively).