Prognostic value of the initial chest high-resolution CT pattern in idiopathic pulmonary fibrosis

Olivier Le Rouzic[1,2], Sofiane Bendaoud[1,3], Cécile Chenivesse[4], Jacques Remy[1,3], Benoît Wallaert[1,2]

[1] Université Lille Nord de France, F-59000 Lille, France; [2] Clinique des Maladies Respiratoires, Centre de compétence Maladies Pulmonaires Rares, Hôpital Calmette, Centre Régional Hospitalier et Universitaire, F-59037 Lille, France; [3] Département de Radiologie Thoracique, Hôpital Calmette, Centre Régional Hospitalier et Universitaire, F-59037 Lille, France; [4] AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale, 47-83 Boulevard de l'Hôpital, F-75013, Paris, France

Abstract. *Background:* Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial pneumonia with a poor prognosis, and there is a clear need to identify factors predictive of disease progression and survival. Previous studies have suggested that patient survival may be associated with specific features on chest CT. Here, we evaluated the prognostic value of the initial high-resolution CT (HRCT) pattern according to the classification recommended by the most recent guidelines for IPF. *Methods:* A total of 66 patients diagnosed with IPF between 2000 and 2010 were included in this retrospective study. Patients were classified into three groups based on the pattern of their initial HRCT: definite usual interstitial pneumonia (UIP) (UIP_{def} n = 26), possible UIP (UIP_{poss}, n = 29), or inconsistent with UIP (UIP_{incons} n = 11). Epidemiological data, functional data, and patient survival were compared. *Results:* The median follow-up period was 48 months (range, 3–166 months) and the median survival time was 30, 52, and 44 months for UIP_{def}, UIP_{poss}, and UIP_{incons} groups, respectively (*NS*). Patients with UIP_{def} pattern HRCT were more likely to be former smokers ($p = 0.007$) in comparison with UIP_{incons}, to have a lower diffusing capacity of the lung for carbon monoxide in comparison with UIP_{poss} ($p = 0.01$) and to have a higher estimated systolic pulmonary artery pressure ($p = 0.002$). Patients with UIP_{incons} pattern HRCT were more likely to be younger ($p = 0.004$). *Conclusion:* There were no significant difference in survival between the three patient groups categorized by their initial chest HRCT pattern. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 353-359)*

Key words: idiopathic pulmonary fibrosis; radiological diagnostic, pulmonary function tests, high resolution computed tomography, prognosis

Abbreviations

HRCT   High-resolution computed tomography
IPF   Idiopathic pulmonary fibrosis
UIP   Usual interstitial pneumonia

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown cause, which is limited to the lung (1). The international recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS) stress that all clinical, radiological, histological, and functional data of suspected IPF patients should be analyzed by a multidisciplinary team in order to exclude other causes of interstitial pneu-

monia (1). The diagnosis can be established in the absence of lung biopsy if the clinical, radiological, and functional findings are compatible with IPF (1).

IPF has a poor prognosis. The median survival time following diagnosis has been estimated in different studies between 2 and 4.5 years (2). However, the disease course varies greatly among subjects. Some patients present with a disease that slowly progresses over several years, while others may have a rapidly deteriorating disease punctuated by exacerbations and accompanied by a high mortality rate (3). Despite extensive research, IPF remains an incurable disease and the only treatment proven to extend patient survival is lung transplantation (4). Recently, two drug therapies have been shown to reduce the deterioration of lung function in patients with IPF (5,6), highlighting the continuing need to identify markers to assess and predict the course of IPF and to determine the optimal time for lung transplantation.

Several studies have attempted to identify prognostic markers for the survival and disease course of patients with IPF (7). Patients with similar disease severity at the time of diagnosis can have very different outcomes. The deterioration of lung function over time remains the most reliable prognostic marker although at least six months of follow-up are required. This information is often not available during the initial patient assessment, suggesting the need for additional prognostic indicators.

The CT features of usual interstitial pneumonia (UIP) that characterize IPF include the presence of reticular abnormalities associated with honeycomb areas of cystic destruction occurring mainly in the basal and subpleural regions (1). However, these features are absent in 30% of IPF patients (8). Although high-resolution chest CT (HRCT) has been reported to have value in predicting the survival of patients with histologically diagnosed nonspecific interstitial pneumonia (9), there are few studies to support the prognostic value of the initial chest HRCT in IPF patients (10,11). Most of the studies focused on evaluation of grading systems of fibrosis (12-15). Recently Oda et al reported that HRCT fibrosis score was useful for predicting the clinical outcomes of IPF (16).

With this in mind we initiated this study in order to determine the prognostic value of the initial chest HRCT findings for patients with IPF using

the reference classification of findings on chest HRCT recommended by the recent international statement on IPF (definite UIP, possible UIP, and inconsistent with UIP patterns) (1). Our primary objective was to assess the prognostic value for overall survival. Our secondary objective was to assess the prognostic value of HRCT for disease severity determined by the change in the initial, 6 month, and 12 month clinical and functional assessments at rest and during exercise.

Patients and Methods

Patients

We performed a retrospective study of IPF patients diagnosed between January 1st 2000 and December 31st 2010 at the center of rare pulmonary diseases of the University Hospital of Lille. From the clinic database, 97 eligible patients satisfied the diagnostic criteria for IPF of the international classification of the ATS and ERS (1). Patient characteristics and prognostic markers were obtained from the first assessment and from reassessments at 6 and 12 months. The epidemiological and clinical data included age at diagnosis, gender, smoking status, and body mass index (BMI). Patients were classified as non-smokers, ex-smokers (defined as past smokers of at least one cigarette per day for at least 12 months and who had stopped smoking at least 6 months before diagnosis), or active smokers. This database is registered at the National Commission on Information Technology and Civil Liberties (CNIL). Approval for the use of these data was provided by the Institutional Review Board of the French Learned Society for Pulmonology (CEPRO 2011-039).

Diagnosis of IPF

Diagnosis of IPF was established by a multidisciplinary team according to the international recommendations (1). The follow-up period was extended to December 31st 2014 in order to ensure that all surviving patients received a minimum of four years follow-up. Thirty-one patients were subsequently excluded: 9 had no definitive diagnosis because of contraindication to lung biopsy, 4 were lost to follow-up

and their survival status was unknown, 5 did not receive a first assessment, 3 had metastatic lung cancer and were treated with polychemotherapy, and 10 had a technically uninterpretable initial chest HRCT.

A final cohort of 66 IPF patients was selected for the analyses and subjects were assigned to three groups according to the classification of their initial chest HRCT: definite UIP pattern (hereafter abbreviated to UIP_{def}; n = 26, 39%), possible UIP pattern (UIP_{poss}; n = 29, 44%), and inconsistent with UIP pattern (UIP_{incons}; n = 11, 17%). A lung biopsy was not performed in 24 UIP_{def} and 17 UIP_{poss} patients if the clinical and functional test results agreed with the recommendations of the ATS and ERS (1). IPF diagnosis was obtained with surgical lung biopsy from upper and lower lobe in the 11 patients with UIP_{incons} pattern HRCT and histopathology feature was definite UIP. The date of diagnosis was defined as the date of the initial chest HRCT or the date of the lung biopsy (if performed). Overall survival was defined as the time from diagnosis until death from any cause, lung transplantation, or the end of the follow-up period.

Radiological classification

HRCT is an essential component of the diagnostic pathway in IPF. The actual classification is based on the analysis of four criteria: subpleural and basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis and absence of features listed as inconsistent with UIP pattern (1). When all four features were present, HRCT presents a definite UIP pattern. If honeycombing is absent and the three other features are present, HRCT presents a possible UIP pattern. In all other cases, HRCT is considered inconsistent with UIP pattern.

HRCT images were re-analyzed by two radiologists specialized in thoracic imaging, and one pulmonologist. The two radiologists and the pulmonologist were aware of the final diagnosis of IPF but were blinded to the patients' clinical, histological, and functional data. Each clinician independently reviewed all chest scans. The final classification of the scans was based on the majority opinion. If all three opinions differed, the scans were reanalyzed and a consensus reached.

Pulmonary function tests

Pulmonary function tests included forced vital capacity (FVC), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLco), and transfer coefficient for carbon monoxide (KCO). The SpO_2 nadir and the distance covered during a six-minute walk test (6MWT) were recorded. Cardiopulmonary exercise testing (CPET) was performed and peak oxygen consumption (VO_2), peak arterial oxygen pressure (PaO_2), and peak alveolar-arterial oxygen gradient ($P[A-a]O_2$), were recorded. The estimated pulmonary artery wedge pressure (transthoracic echocardiography) was also determined.

Statistical analysis

Survival analyses were performed with Kaplan–Meier survival curves and compared with the log-rank test. For the analysis, deaths and lung transplantations were recorded as events, and survival at the end of the follow-up period was recorded and treated as censored data. We used the Shapiro–Wilk test for normality of continuous data. Normally distributed data are presented as mean ± standard deviation (SD) and non-normally distributed data are presented as medians with the 25th and 75th percentiles. Comparisons between the three groups were performed with the nonparametric Kruskal–Wallis test. When the differences were significant, post hoc analysis was performed with Dunn's test and Bonferroni's correction to identify the groups responsible for the observed differences. A p value <0.05 was considered statistically significant. Inter-observer variations were globally assessed with Fleiss's multiobserver kappa coefficient and the results for each observer were compared using Cohen's kappa coefficient. All data were analyzed with R® version 3.1.1.

RESULTS

Description of the overall study population

The mean age at diagnosis was 66 years and the median follow-up period was 48 months (range, 3–166 months). Men accounted for 77% of the pa-

tients. Half of the patients were non-smokers, only one patient was an active smoker, and the mean cumulative smoking exposure was 27 pack-years. Of the 66 patients selected, 8 were alive at the end of the follow-up period and an additional four received lung transplants. The median survival in the overall population was 39 months (95% confidence interval [CI]: 22–70). Inclusion in the study was not homogeneous over time. Thus, when dividing the inclusion period into four equivalent time periods, 10 patients were enrolled between January 1, 2000 and October 1, 2002, 20 patients between October 2, 2002 and July 1, 2005, 25 patients between July 2, 2005 and March 31, 2008 and 11 patients between April 1, 2008 and December 31, 2010.

Group comparisons

Interobserver variation

The interobserver variation analysis revealed a good correlation, with a Fleiss kappa value of 0.622. The interobserver variations for the data provided by the pulmonologist and the most and least experienced radiologist showed good (kappa = 0.61) and moderate (kappa = 0.58) correlations, respectively. The data provided by the two radiologists also showed a good correlation, with a kappa of 0.66.

Demographic data

The comparison between the three groups of patients indicated that an initial UIP$_{incons}$ HRCT was associated with younger age and higher percentage of non-smokers (Table 1). There were significantly fewer smokers in the UIP$_{incons}$ group than in

the UIP$_{def}$ group (p = 0.027). Patients in the UIP$_{poss}$ group had a significantly higher BMI than those in the UIP$_{def}$ group (p = 0.016).

Survival

The median survival of patients in the UIP$_{def}$, UIP$_{poss}$, and UIP$_{incons}$ groups was 30 months (95% CI: 14–68), 52 months (95% CI: 38–61), and 44 months (95% CI: 32–Inf), respectively (Fig. 1). These differences were not statistically significant (p = 0.23). Moreover, no statistically significant differences were noted when comparing the survival of either the UIP$_{def}$ or the UIP$_{incons}$ groups versus the other two groups combined.
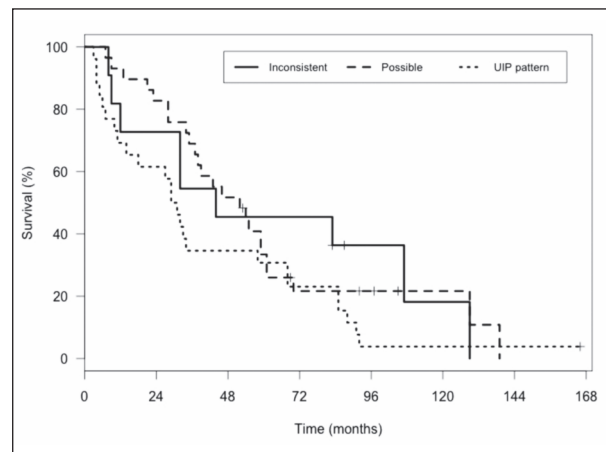

Fig. 1. Kaplan-Meier distribution of overall survival time according to radiological classification of the initial chest HRCT. Each cross represents the time at which one patient was censored. These patients were alive at the end of the study (December 31, 2014) and the cross indicates the follow-up time. The overall and pairwise survival differences were not statistically significant (log-rank test).

Table 1. Demographic data of radiologically classified IPF patients

	Definite UIP Pattern		Possible UIP Pattern		Inconsistent with UIP Pattern		P Value
	N	Values	N	Values	N	Values	
Age at diagnosis (year)	26	68.2 ± 6.3	29	66 ± 7.4	11	58.3 ± 7.4	.004[a,b]
Follow-up (months)	26	30 [10, 68]	29	52 [34, 61]	11	44 [22, 85]	.17
Sex ratio (M:F)	26	0.85	29	0.72	11	0.73	.52
Non-smokers (%)	26	35	29	48	11	91	.007[a,b]
Pack-years	15	20 [15, 35]	11	15 [10, 43]	1	29	.82
BMI (kg/m²)	25	27.3 ± 3.5	29	30.2 ± 3.7	11	28.6 ± 4.3	.01[c]

Data are presented as the mean ± SD or the median [25th, 75th percentiles].
BMI: body mass index.
[a]Significant difference between the UIP$_{def}$ and UIP$_{incons}$ groups.
[b]Significant difference between the UIP$_{poss}$ and UIP$_{incons}$ groups.
[c]Significant difference between the UIP$_{def}$ and UIP$_{poss}$ groups.

Table 2. Prognostic candidates in radiologically classified IPF patients

	Definite UIP Pattern		Possible UIP Pattern		Inconsistent with UIP Pattern		p Value
	N	Values	N	Values	N	Values	
Pulmonary Function Tests							
FVC (%)	25	75 [60, 88]	29	78 [70, 95]	11	78 [64.5, 87]	0.37
Change in FVC at 1 year (%)	18	-2 [-9.8, 4.1]	27	-3 [-6, 4.5]	9	-2 [-5, 0]	0.9
TLC (%)	21	67.1 ± 13	28	72 ± 13.2	11	70.7 ± 14.5	0.52
DLco (%)	24	37.2 ±10.2	29	47.3 ± 12.2	11	46.2 ± 15	0.01 [a,b]
KCO (%)	24	68.2 ± 17.4	29	74.9 ± 12	11	68.3 ± 16	0.12
Cardiopulmonary Exercise Tests							
VO_2 peak (ml/kg/min)	14	16.9 ± 4.6	22	16.8 ± 3.2	10	17.5 ± 3.7	0.83
PaO_2 peak (mm Hg)	14	55.5 [46.7, 58.7]	22	59.9 [54.1, 66.3]	10	60.2 [47.6, 71.6]	0.16
$P(A-a)O_2$ peak (mm Hg)	14	58 [55.1, 69.3]	22	58 [50.1, 61]	10	55.4 [42.7, 63.5]	0.31
6-Minute Walk Test							
Distance (m)	18	329 ± 112	27	395 ± 90	9	422 ± 117	0.13
Change in distance at 6 months (m)	13	40 [10, 55]	21	-5 [-30, 35]	7	15 [-57.5, 40]	0.12
Change in distance at 1 year (m)	10	15 [0, 37.5]	20	-2.5 [-36.3, 46.3]	4	-35 [-67.5, 11.3]	0.62
Resting Blood Gases							
PaO_2 (mm Hg)	19	76.2 ± 11.6	28	84.2 ± 10.4	11	84.1 ± 12.9	0.08
$P(A-a)O_2$ (mm Hg)	19	28.4 ± 13.3	28	19.6 ± 9.3	11	18.3 ± 10.1	0.06
Transthoracic Echocardiogram							
sPAP (cm H_2O)	10	48.5 [36.5, 54]	17	30 [24, 33]	8	26 [24.3, 29]	.002[a,b]

Data are the mean ± SD or the median [25th, 75th percentiles].
FVC, forced vital capacity; TLC, total lung capacity; DLco, carbon monoxide diffusing capacity; KCO, carbon monoxide transfer coefficient; VO_2, oxygen uptake; PaO_2, arterial oxygen pressure; $P(A-a)O_2$, alveolar-arterial oxygen gradient; sPAP, systolic pulmonary arterial pressure.
[a] Significantly different between the UIP_{def} and UIP_{incons} groups.
[b] Significantly different between the UIP_{def} and UIP_{poss} groups.

There were no statistically significant differences among the three groups of patients in FVC, change in FVC at 1 year or exercise tests measures (Table 2). The DLco of patients in the UIP_{def} group was significantly lower than that of patients in the UIP_{poss} groups (p = 0.016). However, there were no differences in KCO values and in the change of DLco at 1 year. Patients in the UIP_{def} group had significantly higher estimated sPAP values than patients in the other two groups (p = 0.003) but the PaO_2 at rest and at peak exercise, and the resting $P(A-a)O_2$ were not different.

Discussion

The major finding of this study was establishing that the initial chest HRCT pattern is not a prognostic factor in IPF. This finding is consistent with previous studies of "radiologically" classified biopsy-proven IPF patients by Flaherty et al (10) and Sumikawa et al (11), which also did not show any statistically differences in survival. Similarly, Sverzellati et al. found that the chest CT was not predictive of disease evolution in IPF patients (8). However, neither the Sverzellati nor the Flaherty studies used the previous ATS/ERS reference classification (17).

In our study, the patients with UIP_{incons} pattern HRCT were younger and more often women (non NS) and non-smokers (than UIP_{def}), which is in agreement with the results of Flaherty et al. (10) and Lynch et al. (18). However, conflicting data were recently reported by Quadrelli et al., who found that patients with radiologically UIP_{def} were younger (19). Their study population included patients with UIP associated with a connective tissue disease, which affects women and younger subjects more frequently than do idiopathic forms of the disease (20). Nevertheless, this seems an unlikely explanation for the difference in age association, because the proportion of patients with pulmonary fibrosis associat-

ed with a connective tissue disease in the Quadrelli et al. study was similarly low in both groups of patients.

Our findings on the resting PFTs of patients with UIP_{def}, UIP_{poss}, and UIP_{incons} patterns on initial HRCT are consistent with those of previous studies. We found no significant differences in FVC at diagnosis or in the decline in FVC at 12 months after diagnosis between groups. However, the median decrease in FVC in the overall population at six months (3%) was statistically significant confirming the disease progression in our patients. Du Bois et al. showed that the minimal clinically important difference in FVC at 6 months was between 2% and 6% (21). We found that the mean DLco value for patients with UIP_{def} pattern HRCT was significantly lower than that of the other patients, which is consistent with the earlier findings of Flaherty et al (10) and Lynch et al (18). The DLco results in our UIP_{poss} and UIP_{incons} groups may be skewed by the non-inclusion of more severely affected patients in whom a lung biopsy could not be performed, but our results are sufficiently in line with earlier studies to suggest this is not the case. The low DLco of the UIP_{def} group was associated with a lower PaO_2 and a higher alveolar-arterial gradient at rest, which was not observed by Lynch et al.(18) In addition, the estimated PAP was higher in the UIP_{def} patient group in our study, indicating possible changes in the pulmonary vascular bed (22).

To our knowledge, there have been no other studies of the remaining functional parameters, either at rest or during exercise, comparing patients with UIP_{def}, UIP_{poss}, and UIP_{incons} patterns on initial HRCT. Du Bois et al. showed that the risk of death at 12 months was not increased for IPF patients with 6MWT distances of 350 m or longer (23). In our study, patients in the UIP_{def} group did not have a significantly increased risk of death despite covering less than 350 m. It is interesting to note that the UIP_{def} group had the shortest 6MWT distance (NS), even though the three groups showed no differences in peak VO_2 or peak $P(A-a)O_2$ during the CPET (they did not show any difference in 6MWT distance neither). The first 6MWT distance may have been underestimated for these patients, because the distance covered at 6 months was substantially, although insignificantly, higher than at diagnosis. The ATS has reported a similar increase of up to 17% be-

tween the first and second 6MWT distances, which they attribute to a learning effect (24). Indeed, the 6MWT distance for our patients returned to baseline at 12 months, suggesting that the difference at 6 months was due to such a learning effect. The results of the CPET revealed an impaired aerobic capacity in the overall population, associated with a decrease in peak PaO_2 and an increase in peak $P(A-a)O_2$. The differences between the groups in our study were not statistically significant; however, these data are consistent with an earlier study (25).

There was good interobserver agreement among the radiologists and pulmonologist who assigned patients to the three groups according to their HRCT scans (26). In their study of CT diagnoses in IPF patients, Sverzellati et al. obtained a moderate agreement (kappa coefficient of 0.4) among the three analyzing radiologists but they used a different type of classification (8). The better agreement in our study probably reflects the more uniform interpretation of colleagues who routinely work together.

There is a possibility of selection bias in our study due to the exclusion of patients lost to follow-up for whom no survival data were available, and of patients for whom the diagnosis could not be confirmed with a lung biopsy. Therefore, the proportion of patients with IPF and UIP_{incons} pattern HRCT could have been underestimated. Nevertheless, the proportion of patients in our study with UIP_{incons} HRCT (17%) was comparable to those in the studies of Thomeer et al. (27), Quadrelli et al. (19), and Flaherty et al. (10) who reported proportions of 12.6%, 42%, and 36%, respectively. Moreover, the proportion of our patients with metastatic lung cancer (3/109; 2.7%) is also consistent with data showing an excess risk of lung cancer in patients with IPF (28). Therefore, these biases are unlikely to have significantly affected our results.

Conclusions

In conclusion, the initial chest HRCT pastern is not a prognostic factor for IPF. These data, if confirmed, suggest that patients with UIP_{def} and UIP_{incons} pattern initial HRCT have similar survival prognosis, emphasizing the importance of initiating management of patients with UIP_{incons} HRCT immediately after diagnosis.

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