Long Term Evaluation of Quantitative Cumulative Irradiation in Patients Suffering From ILDS

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Abstract

Background

Interstitial lung diseases (ILD) are a heterogeneous group of infiltrating lung pathologies, requiring diagnosis and assessment, among which chest CT is of utmost importance. Nevertheless, the imaging modalities for the follow-up do not have formal guidelines and remain at the discretion of the clinician.

Methods

Our study restrospectively evaluated the indication of chest CT in a cohort of 129 ILD patients. The aim was to determine whether the realization of the imaging control had a true impact on clinical course and follow-up. We accept 3 different situations for justifying the indication of the CTs as clinical deterioration, decrease in pulmonary function tests (at least 10% drop in a parameter) and monitoring for oncological purposes. The other indications, mainly classical follow-up, were classified as “non justified”. We selected patients from our ambulatory care polyclinic at Liège University Hospital.

Results

We followed up a total cohort of 129 ILD patients. The mean number of CT scan per patient per year was 1.7±0.4 determining an irradiation in CT Dose Index (mGy)/year of 34.9±64.9 and an irradiation dose x length product in (mGy*cm)/year of 1095±1971. Around 40% of the routinely prescribed monitoring CT scans had no impact on the management of ILD and direct patient care, raising the question of inappropriate irradiation

Conclusion

Our study identifies overuse of chest CT scanner in the follow-up of ILD outside those performed for clinical exacerbation or oncological investigation. In the particular case of ILD exacerbation, CT-scan valuability stay high underlying the benefit of this validated strategy.

Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of parenchymal diseases of the lung, with highly variable clinical course and outcomes („„). The entire pulmonary architecture, including interstitium and alveoli, can be damaged, leading to an abnormal scaring process inducing at term a progressive lung fibrosis. The functional assessment of the evolution of ILDs is still challenging and is mainly based on pulmonary function tests (PFTs), and more particularly on lung volume and diffusion capacity decline. Indeed, over time, patients suffering from a progressive fibrosing ILD can experience a decline in lung function, principally characterized by a reduction in Total Lung Capacity (TLC) and Residual Volume (RV), sometimes evolving towards a true restrictive syndrome (TLC < 80%). Similarly, the forced vital capacity (FVC) and the maximal expiratory volume in 1 second (FEV1) are also generally

reduced, resulting in a global reduction of the lung volumes, without true obstructive syndrome. The lung diffusing capacity for carbon monoxide (DLCO) is also classically reduced, although this does not systematically correlate with the course of the pathology (). In the same way, multiple biomarkers have been developed over the time to help clinicians in the diagnosis and follow up of ILDs („).

Parallel to the biological and functional evaluation, chest high resolution CT (HRCT) has a central role in the diagnostic work-up and longitudinal follow-up of patients. Indeed, in addition to assessing the radiological patterns of ILDs, chest CT is of utmost importance in identifying the inherent progression of the disease, or sometimes in highlighting the appearance of concomitant processes, such as neoplastic pathology which can incidentally be uncovered in some patients (). In HRCT, image acquisition is obtained in supine position at the end of inspiration, or in some specific cases in sustained expiration. Additionally, prone position can sometimes be required to reduce any posterior alveolar collapse that can mimic ground glass opacities. During follow-up, a low irradiating protocol, referred as “low-dose” chest CT, can also be used (2 mSv versus 7mSv for the high-resolution scanner). Noteworthy, in the last few years, a new ILD phenotype characterizing patients with a progressive fibrosing interstitial lung disease (other than IPF) has been described by Cottin et al (), highlighting the undeniable utility of repeated thoracic HRCT evaluation. Of note, contrast utilization is mainly used to rule out pulmonary embolism in case of unusual or rapidly progressive dyspnea. Therefore, considering the extensive utility of chest CT in ILDs for diagnostic or monitoring purposes, it appears important to unveil the question of cumulative irradiation of patients engendered by the acquisition of CT images during follow-up, potentially generating long-term effects (stochastic effects). To the better of our knowledge, there is no standardized routine indication (out of significant clinical worsening) for reassessing chest CT in ILDs despite the increased risk of neoplasic occurrence ().

To assess the radiation output, some parameters can be referred to.

The CTDI (acronym for Computed Tomography Dose Index, measured in mGy) is a standardized index that measures the radiation dose output applied to a patient per CT section. Another parameter is the dose x length product (measured in mGy x cm), which corresponds to the absorbed dose multiplied by the length explored and is a better reflection of the total dose delivered to the patient. It is important to differentiate measurable physical doses expressed in mGy (amount of energy locally deposited) and non-measurable doses expressed in mSv (quantification of effects and risk assessment). For chest CT, the conversion factor is 0.017 to convert n mGy in mSv (,).

Our study focused on the indication of monitoring chest CT in ILDs, and the potential impact that the control CT had on clinical course and follow-up, while balancing with the radiation dose experienced by the patient.

Material And Methods

Subject characteristics

We retrospectively selected patients from our ambulatory care polyclinic at Liège University Hospital. Those patients were recruited based on a clinical evaluation between July 2014 and July 2016. The diagnosis of ILD was made according to the international recommendations of the ATS (American Thoracic Association) (1), with an assessment based on respiratory function test (PFTs), chest HRCT, bronchoalveolar lavage (when available), as well as the clinical history of the patient. All cases had been discussed in the interstitial lung diseases multidisciplinary, composed of a pulmonologist, a specialist in pulmonary rehabilitation, a rheumatologist, a radiologist, a pathologist and a specialist in occupational medicine.

The protocol was approved by the ethics committee of Liège University Hospital, and all subjects gave written informed consent before their enrollment (Belgian number: B707201422832; ref: 2014/302). All methodswerre performedaccording to the relevant guidelines.

Pulmonary function tests

We performed lung function tests in the Liège University Hospital lab. All spirometric tests were measured using the pneumotachograph. The forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured in accordance with the recommendations of the European Respiratory Society (ERS) (). The result were expressed in milliliters and percent predicted. The Tiffeneau index or FEV1/FVC was expressed in percent. The total lung capacity (TLC) was measured by body plethysmography according to ERS recommendations. The DLCO and the DLCO/AV ratio were measured by the single-breath carbon monoxide gas transfer method and expressed as percent predicted.

Image acquisition

We used different CT scans to make the evaluation following the standard clinical workflow. The different models of CT were Siemens-Somatom Egde +, Siemens Emotion 16, General Electric Revolution, General Electric BrightSpeed.

Dosimetric evaluation

We collected the different data from the report generated by the CT-scan, displaying *Computed Tomography Dose Index* (CDTI, in mGy) and *Dose length Product* (DLP, in Gy*cm).

Clinical validity of HRCT indication

Radiological data were collected for each patient, including the number of total chest CT performed for the follow-up of ILD. We classified those examinations according to the justification that motivated the realization of the chest CTs, either emergency or routine evaluation. We collected the total administrated irradiation in CDTI and dose-length product. The dosimetric data were extracted from each scanner, collected and added-up individually, after an individual de-archiving work.

Evaluation of thoracic HRCT indication

We arbitrarily evaluated the validity of CT indication for each scanner. We separated them into two groups: justified indication or not justified indication. Our judgement was based on the examination motivation as written on the medical request by the prescriber, in order to evaluate the indication. We then analyzed the results of the chest CTs to see whether this had impacted the treatment or outcome for the patient, independently of the indication.

We specifically looked at 3 different situations for justifying the indication:

- Clinical deterioration (fever, desaturation)
- Significant decrease in PFTs (at least 10% drop in FVC)
- Monitoring for oncological purposes

The CT scans performed for systematic follow-up without any other criteria were marked as “not pre-justified”. For those examinations, we also checked whether new data collected after the completion of the scanner could have somewhat changed the management of the patient (ex: fortuitous discovery of a nodule/cancer, ILD progression requiring a therapeutic modification), redefining the *a priori* justification (that initially seemed “not justified”), to an *a posteriori* justification (that had in fact a true impact on management and was therefore finally truly justified)

In order to more accurately evaluate the impact of follow-up CT, we specifically analyzed a sub-group of ILD-patients who experienced a significant functional reduction (10% in a parameter in PFTs) and searched for correlation with CT indication or cumulative radiation.

Longitudinal evaluation

Patients had a follow-up from their first pulmonology or rheumatology consultation to their last consultation (at the time of the study) or to their death.

Statistical analysis

The Kolomoronov Smirnov test is used to test the normality of quantitative data. The results of the comparative analyze are obtained from the student's unpaired T test when the data are parametric and from the Mann Whitney test when the distribution is not normal. The results are considered significant at the 5% uncertainty level ($p < 0.05$). Calculations are performed using TIBCO Statistica® 13.5.0 software. Another part of the statistical study was carried out using Prism and Statistica software.

Results

Patients’ characteristics

Patients’ characteristics are listed in Table 1. The cohort consisted of 129 patients. Mean age was 63 years old, with a male predominance (61.2%), and smoking predominance (58.9%) (Table 1). The main

represented diagnosis were NSIP, IPF, CTD-PF and sarcoidosis (30%, 26%, 31% and 18% respectively) (Fig. 1).

Figure 1: **Diagnosis repartition of ILDs in our cohort. NSIP**: Nonspecific interstitial pneumonia **RBILD**: Respiratory bronchiolitis interstitial lung disease; **UIP**: Usual interstitial pneumonia; **COP**: Cryptogenic organizing pneumonia; **CTD-PF**: Conjunctive tissue disease-pulmonary fibrosis

Table 1
Patients characteristics

	n = 129
Male n (%)	79 (61.2%)
Mean Age (± SD)	3.7 (± 2.3)
Active smokers n (%)	58.9% (76)
Mean follow-up in years (± SD)	3.7 (± 2.3)
FVC ± SD (% predicted)	81 (± 19)
FEV1 ± SD (% predicted)	81(± 20)
DLCO ± SD (% predicted)	54 (± 20)
KCO ± SD (% predicted)	82 (± 25)
TLC ± SD (% predicted)	77 (± 17)

Table 1: **Patients' demographics and functional respiratory parameters. PFT** : pulmonary function test; **VC** : vital capacity; **FEV1**: forced expiratory volume ; **DLCO**: diffusing lung capacity for carbon monoxide; **KCO**: transfer coefficient for carbon monoxide for the lung; **SD** : standard deviation

The pulmonary function tests globally identified as expected a restrictive syndrome (initial average TLC at 77%) with a marked alteration in diffusion (DLCO 54% at the beginning of treatment) in the majority of cases. The average follow-up duration was approximately 3.7 years. By the end of monitoring, 7% of patients had developed lung cancer (and 2 hematologic cancers) and 32.6% (n = 42) died.

The average number of CT-scans performed per patient was 2.6 scans over the first year of follow-up. Thereafter, patients benefited from approximately 1 CT scan per year, reaching a mean sum of 4.5 CT-scans after 3 years of follow-up and 6.4 CT-scans on the overall follow-up (Table 2). The irradiation undergone is substantial, with a CDTI at 27.3 ± 20.2, 54.5 ± 64.9 and 67.8 ± 52.2 (mGy) and a dose-length product of 897 (± 595), 1582 (± 908), 2192 (± 1474) (mGy* cm) respectively after 1 year, 3 years and at the end of the total average care. Globally, we calculated a mean irradiation of 34.9 mGy and 1095 mGy*cm per patient per year.

Table 2
CT scan analysis

Number of CT/patient	**6,34 ± 4,12**
Low dose CT/patient	0,5 ± 1
% Low dose CT/patient	8 ± 18.5
Injected CT scan/patient	1 ± 2
% Injected CT scan/patient	17 ± 23
Emergency CT scan/patient	0,5 ± 1
% Emergency CT scan/patient	6.7 ± 31
% Justified emergency CT scan	94.2%
a priori = posteriori	
Number of routine CT scan	5,6 ± 3,5
% Justification a priori of routine CT scan	57 ± 32
% Justification a posteriori of routine CT scan	60 ± 34
Number of CT scan over	2.6 ± 1.5
1 year	4.5 ± 2.5
3 years	6.4 ± 4.1
On the overall follow up	
Number of mean CT scan/patient/year	1.7 ± 0.4
Irradiation CDTI (mGy) /patient over	27.3 ± 20.2
1 year	54.5 ± 64.9
3 years	67.8 ± 52.2
On the overall follow up	
Irradiation DLP (mGy*cm)/patient over	897 ± 595
1 year	1582 ± 908
3 years	2192 ± 1474
On the overall follow up	
Irradiation in CDTI (mGy)/year	34.9 ± 64.9
Irradiation in DLP (mGy*cm)/year	1095 ± 1971

Table 2

Data concerning the number CT scans performed and their irradiation consequences in *Computed Tomography Dose Index* (**CDTI**, in mGy) and *Dose length Product* (**DLP**, in Gy*cm)

Further analysis were achieved by classifying patients into sub-populations (annex 1), according to the lung disease progression based on PFTs. We separated patients with stable PFTs and patients with a drop of at least 10% of the absolute value in one PFT parameter (FVC or FEV1). Our findings highlighted a relationship ($p < 0.05$) between the patients presenting a deterioration in lung function parameters such as FEV1 and FVC and the percentage of *a posteriori* justified CT scans, whereas correlation with justification for *a priori* CT-scans was (nearly but) not reaching statistical significance. However, this rationale reasoning is not present for parameters such as the drop in DLCO (annex 2) except for the DLP, probably because of the variations of the DLCO.

Of interest, PFT decline (assessed by FVC, FEV1 or DLCO) was not associated with a significant increase in total DLP. Interestingly, this progressive subpopulation did not benefit from more emergency, contrast-enhanced or low-dose CT scans than patients without progressive disease.

Considering the entire studied population (n = 820 CT scans), we noticed a low prescription rate in low dose CT-scans (68 CT scans = 8%) or emergency CT-scans (68 CT scans = 8%), versus a slightly larger number of injected CTs (138 CT scans = 17%).

Discussion

To the best of our knowledge, there is nowadays no dedicated longitudinal observational study on quantification and justification of radiation doses in patients with ILDs. Our study demonstrated that patient did not experience a harmful over-irradiation over the time. Nevertheless, we noticed that overall justification of the chest CT-scans was weak, out of those dedicated for acute clinical deterioration, which are in line with guidelines recommendations in the event of an ILD exacerbation ().

Our population is like what is generally seen in chronic ILD populations, with an increase prevalence of CTD-PF due to the bias induced by the recruitment in our hospital, as a tertiary center. The demographic characteristics are in line with those classically seen in patients suffering from ILD (,).

In our study, clinicians performed an average of 1.7 scans / year / patient. We therefore observed a concordance between the *a priori* indication and the *a posteriori* validity of the scanners. The approach showed us that, overall, 56.9% of scanners were justified *a priori*, whereas 60.15% of them were justified *a posteriori*. We therefore defined the unjustified CT-scanner as a CT-scanner performed systematically without clear clinical indication or expected result inducing no specific clinical or therapeutic response. In our study, we therefore identified that 40% of the performed CT-scans were not justified.

As indicated by the ERS guidelines, which define an ILD exacerbation based on a drop in FVC or DLCO or the need for oxygen support, PFT is seen as a useful parameter (). Therefore, PFTs and their degradation over time, such as a drop of 10% or more in FEV1 or FVC, represent an interesting monitoring tool which

allows us to study the evolution of ILDs, and could possibly lead to a therapeutic implication in our patients. Based on the ERS recommendations defining significant deterioration in DLCO and FVC, we tried to correlate the number of CT-scans performed with the drop in FVC and DLCO experienced by some patients over the time. Interestingly, we didn't identify any specific correlation between those parameters, neither for FVC or DLCO. The absence of correlation possibly due to the low number of acute exacerbation that will only slightly increase the number of CT scans (). The drop of DLCO is

Facing those observations, we raise the question of the cost-effectiveness of the routine CT-scans in patients suffering from chronic ILD. Indeed, it emerges that a significant number of CT-scans are prescribed without any diagnostic and therapeutic consequences, suggesting that clinicians are performing some of those explorations in a procedural way, regardless of the result of the PFTs modification over the time. The question of the occurrence of lung cancer in this specific populations has to be addressed in order to define the most relevant way to follow those patients.

Of interest, we've demonstrated that only a small proportion the CT scans were low dose CTs. While it seems obvious to explore lung parenchyma through high resolution CT-scans during the initial evaluation and diagnosis work-up, it is reasonable to assume that systematic imaging during follow-up low dose could be achieved with low-dose acquisition CTs specifically for lung cancer screening purpose (10). Considering low dose CT scans for basic monitoring could imply a reduction in the irradiation of our patients. Of note, only a minority of the images are contrast-enhanced CT scans.

In our study, it appears that few CT scan were performed in an emergency setting (8%), which is in keeping with the low prevalence of acute exacerbation of ILDs corroborated in literature 4–20% ().

This study is the opportunity to raise a specific concern focusing on the accurate evaluation of the benefit/risk balance of multiple CT scan evaluation in patients suffering from chronic fibrosing ILD. Indeed, it appears that PFTs and clinical evaluation can help to quantify sufficiently, in a routine-based follow-up, the evolution of the disease. Therefore, global irradiation could possibly be reduced by individuating the imaging acquisition modalities to each patient and situation. Of interest, we've noticed that the majority of not-routinely-based CT-scans (ie. Emergency CTs or CTs consecutive to clinical or functional deterioration) are justified on a clinical basis, highlighting the absolute usefulness of chest CTs in this precise context. Moreover, the concept of accurate follow-up through CT imaging must be put into perspective with lung cancer screening. Indeed, systematic lung cancer screening is not specifically recommended in ILD patients and is committed to personalized and individualized work-up. More specifically, ILD patients exhibit an increased risk of developing lung cancer (smoking history, scaring process, use of immunosuppressive agents,). Therefore, clinicians have to be cautious to reduce global cumulated irradiation over the time due to their ILD follow-up. Implementing a public health perspective, the overall increase in health care costs implies a rationalization of the use of complementary examinations in chronic diseases.

Out of economic considerations, it is important to note that the average irradiation level was 34.9 mGy and 1095 mGy * cm per year and per patient (18.6 mSv), which remains high enough to induce stochastic

effects after a few years. The incidence of lung cancer in the general population is 100/100000 inhabitants (i.e., 1% / year) (). In smokers, the risk of having lung cancer is 10 to 30 times higher than in a non-smoker population (). In a review of the literature, the percentage of lung cancer with patients suffering from ILD is 9.8–20% depending of the time of follow-up, the risk globally increasing over the time (). In our study, the global level of lung cancer is similar to what is seen in literature (7%), with a median follow up of 3.7 years (). In the literature, to the best of our knowledge, there are nowadays no long-term studies reporting the effects of radiation on the lung or breast. Such a study would be welcomed but would require a larger population associated to a longer follow-up.

Limitations

Our study faces some limitations. Firstly, it was a monocentric retrospective study, and the population was quite small. PFTs and measurements of the various parameters (FEV1, FVC, TLC, DLCO, KCO) and their deterioration over time occurs between the start and the end of treatment. Some patients can experience initial severe deteriorations modified with specific dedicated therapy modifying disease behavior. The question of Chest CT imaging for ILD follow-up is also a tool for disease severity and evolution assessment.

Conclusion

Thoracic imaging through chest CT is the cornerstone in the evaluation of chronic fibrosing lung diseases. Our retrospective study highlighted that routinely follow-up HRCT did not demonstrate an undeniable clinical utility. The cumulated irradiation is acceptable whereas the occurrence of lung cancer is in line with what is seen in the ILD population. Further prospective studies will have to demonstrate the potential value of HRCT in lung cancer screening in order to guide clinicians in their daily practice. Moreover, dedicated AI-based automatized tools in order to increase the accuracy of fibrosis quantification are highly needed in order to be combined with clinical and PFT parameters.

Abbreviations

CTD-PF
Connective tissue disease associated pulmonary fibrosis
ILD
interstitial lung disease
IPF
Idiopathic pulmonary fibrosis
CT
computed tomography
HRCT
high resolution Computed tomography
CTDI

computed Tomography Dose Index
DLP
dose x length product
TLC
total Lung Capacity
RV
residual Volume
FVC
forced vital capacity
FEV1
maximal expiratory volume in 1
VC
vital capacity
DLCO
diffusing lung capacity for carbon monoxide
KCO
transfer coefficient for carbon monoxide for the lung
NSIP
nonspecific interstitial pneumonia
RBILD
respiratory bronchiolitis interstitial lung disease
UIP
usual interstitial pneumonia
COP
cryptogenic organising pneumonia
CTD-PF
conjunctive tissue disease-pulmonary fibrosis
SD
standard deviation

Declarations

Ethics approval and informed consent to participate

The protocol was approved by the ethics committee of Liège University Hospital, and all subjects gave written informed consent before their enrollment (Belgian number: B707201422832; ref: 2014/302).

Availability of data and materials

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

Consent for publication

All the authors consent for the publication

Competing of interests

For this article, all the authors don’t have any conflict of interests

Authors contributions

J berg collected the data, made the data base and wrote the article. J Guiot helped and supervised for the writing of the article.

M.Henket made the statistics

AN Frix helped for the translation.

All the author reviewed the article.

Acknowledgments

Retrospective study.

all the patients were followed with care and relevant guidelines and regulations.

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Figures

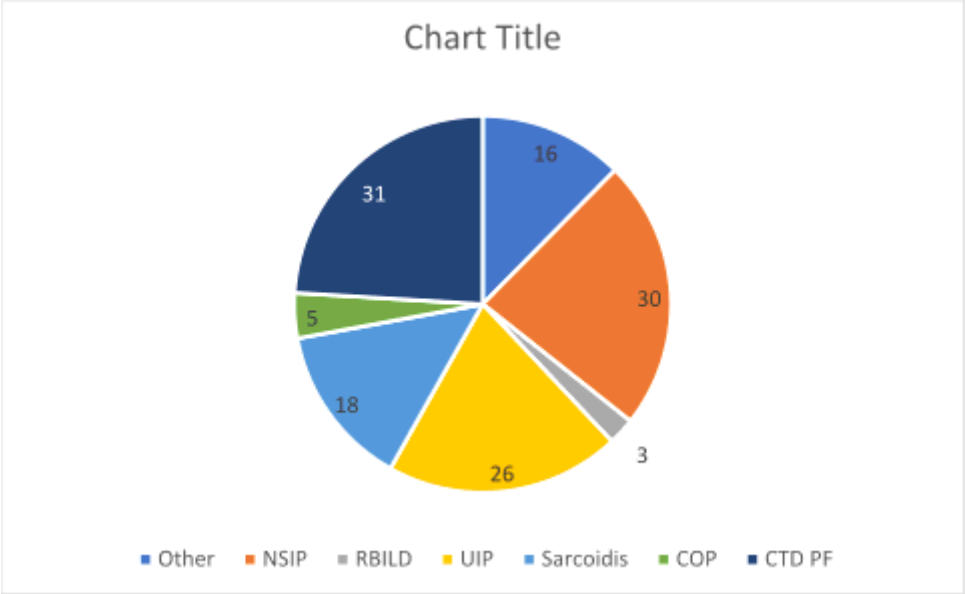

Figure 1

Diagnosis repartition of ILDs in our cohort. NSIP: Nonspecific interstitial pneumonia **RBILD**: Respiratory bronchiolitis interstitial lung disease; **UIP**: Usual interstitial pneumonia; **COP**: Cryptogenic organizing pneumonia; **CTD-PF**: Conjunctive tissue disease-pulmonary fibrosis