Quantitative computed tomography detects interstitial lung diseases proven by biopsy

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Abstract. *Background:* The Quantitative chest CT (QCT) is emerging as a promising tool in the assessment of interstitial lung disease (ILD). However, the precise relationship between QCT parameters and the fibrosis detectable in lung tissue, remains to be established. *Objectives:* The aim of this study was to compare QCT and histopathological features in patients with ILD. Moreover we verified if the QCT assessment is similar in patients with or without a ILD diagnosis proven by a biopsy. *Methods:* Twenty patients affected by ILD who underwent a chest CT and, later, a lung biopsy, were enrolled. Patients were divided according to the histopathological findings (IPF vs sarcoidosis) in two groups (respectively bIPF and bSarc). Other 20 patients with a radiological diagnosis of IPF were included in a control group (rIPF). All CTs were post-processed with a free software (Horos) in order to obtain an ILD quantitative assessment. *Results:* There were no differences in terms of gender, smoking habit and spirometric values between patients' groups. rIPF subjects were older than the other: 70 vs 59 and 47 years (p<0.001). A different distribution of QCT parameters was observed between bIPF and bSarc (p<0.01) while it was comparable within bIPF and rIPF. *Conclusions:* QCT parameters were similar in subjects affected by the same type of ILD detected with biopsy and with CT alone. These findings make stronger the assumption that QCT can identify the presence of pulmonary fibrosis and, ultimately, that it can represent an useful and effective tool to assess ILD. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 16–20)*

Key words: Quantitative Computed Tomography, idiopathic pulmonary fibrosis, sarcoidosis

Introduction

The severity of pulmonary fibrosis is one of the most important factor influencing the risk of mortality in patients affected by interstitial lung diseases (ILD) (1-3). The respiratory function tests are often used in clinical practice to assess ILD but they are affected by an unsatisfying reproducibility (4-7). Moreover, in patients with severe ILD it is not always possible to perform such tests due to the poor compliance.

Chest computed tomography (CT) is the gold standard for the assessment of the extent (and, as a consequence, severity) of pulmonary fibrosis (8). Semi-quantitative radiological scores were developed to evaluate lung impairment and its impact on pa-

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tients' survival. However, these methods are usually complex, time-consuming, and only few radiologists are able to perform them (8). Additionally, semi-quantitative scores show a low inter-rater agreement in the evaluation of pulmonary fibrosis even among the most experienced radiologists (9).

In the last years, many software have been developed to analyze the presence and the extension of pulmonary fibrosis in subjects with idiopathic pulmonary fibrosis (IPF) or ILD related to other diseases (e.g. systemic sclerosis, rheumatoid arthritis, sarcoidosis etc) (10-12). Their limited spread, especially in clinical practice, is manly due to the fact that these programs are very expensive and difficult to use. Recently, free and open source software (i.e. OsiriX and Horos) proved to be suitable for obtaining a quantitative analysis of severity and extent of pulmonary fibrosis. This makes the extensive use of quantitative CT (QCT) possible in clinical practice and multi-center trials (13-15).

QCT consists of a voxel-wise analysis of the distribution of pulmonary attenuation (i.e. the absorption of X-rays passing through the lung) values. The parameters which describe univocally such distribution are called QCT indexes (QCTi). The most relevant QCTi are kurtosis, skewness and mean lung attenuation (16). Many Authors showed that they are related to the extent of pulmonary fibrosis, pulmonary function and mortality risk (11, 13, 17-19). However, as far as we know, it has been never investigated whether or not the QCT identifies the presence of pulmonary fibrosis confirmed by histological examination, differentiating it from other diffuse lung affections (i.e. sarcoidosis).

The main aim of this study is to verify if QCT indexes in patient with IPF proven by lung biopsy (bIPF) are similar to those observed in patients with diagnosis of IPF according to clinical and radiological criteria (rIPF). Furthermore, QCT of subjects with sarcoidosis diagnosed on the basis of histological findings (bSarc) were compared to those ones of the above mentioned groups.

Methods

All subjects with a IPF who underwent a surgical biopsy in a referral center between 2004 and 2014 were enrolled (bIPF) (20). Two control groups were considered. The first one included IPF subjects who had not an histological diagnosis (rIPF). Radiological and clinical features of these patients were assessed by expert radiologists and respiratory physicians. Patients with lung sarcoidosis (radiological stage ≤3) proven by the histological exam (performed between 2004 and 2014) constituted the other control group (bSARC).

For all subjects other inclusion criteria were: age >18 years; availability of chest CT images; pulmonary function test performed within four weeks from CT scans; written informed consent provided.

All chest CT images were analyzed with a free open-source software (Horos 64-bit, downloadable from www.horosproject.org; date of last access 30 April 2017) in order to obtain the quantitative indexes. The algorithm was the same previously described (21). The QCT indexes (QCTi) taken into account were: kurtosis (Kurt), skewness (Skew), Mean Lung Attenuation (MLA), standard deviation (SDev) and fibrosis ratio (FR). Except for the latter one, all QCTi were calculated both in whole (tQCTi) and parenchymal (pQCTi) as reported by Ariani et al (22).

Collected data were analyzed with R software (version 3.3.3). Non parametrical test were applied as appropriate. In particular, Mann-Whitney test investigated the differences between the subgroups. A p-value <0.05 was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki.

Results

The study population consisted in 40 patients clustered in 3 subgroups. Subjects with bIPF , rIPF and sarcoidosis were respectively 10, 20 and 10. Patients characteristics are summarized in Table 1. In both IPF subgroups (bIPF and rIPF) male and smokers prevalence was higher than that one observed in the sarcoidosis subgroup. The majority of IPF patients had a restrictive respiratory pattern requiring oxygen therapy. There were no significant differences between group bIPF and rIPF except for the mean age (59 vs 70 yrs; p = 0.0105).

The QCTi of bIPF and rIPF were not significantly different (p>0.05). All QCTi, except for tMLA and pMLA, showed a different distribution between bSarc vs group bIPF or rIPF (p < 0.05) (Fig 1).

Table 1

	bIPF	bSarc	rIPF	p<0.05
Sample size	10	10	20	-
Age, mean±SD (yrs)	59±10	47±12	70±8	bIPF vs rIPF bIPF vs bSarc rIPF vs bSarc
F:M	5:5	7:3	4:16	rIPF vs bSarc
Smoke (no:curr:former)	3:3:4	6:2:2	2:2:16	rIPF vs bSarc
FVC, mean±SD (%)	81±19	99±6	91±25	bIPF vs bSarc
FEV1, mean±SD (%)	78±27	98±3	91±26	-
TLC, mean±SD (%)	90±16	116±9	82±19	rIPF vs bSarc bIPF vs bSarc
DLco, mean±SD (%)	53±23	-	58±16	-
Dlco/VA, mean±SD (%)	75±35	-	82±21	-
Oxigen therapy (yes:no)	4:6	0:10	12:8	rIPF vs bSarc

Legend: bIPF: patients with an histological diagnosis of IPF; rIPF: patients with a radiological diagnosis of IPF; bSarc: patients with an histological diagnosis of Sarcoidosis; FVC- forced vital capacity; FEV1: Forced Expired Volume 1 s; TLC: Total Lung Capacity; DLco: carbon monoxide diffusing capacity; DLco: carbon monoxide diffusing capacity / Alveolar Volume.

Discussion

In this study we investigated QCTi in IPF patients assembled in two groups, depending on how the diagnosis was based either on biopsy or radiological findings . We did not find statistical differences in QCTi between those two subgroups. In order to verify the actual capacity of QCTi to distinguish ILD from normal lung we would like to study patients without pulmonary fibrosis at the histological exam. Of course, in our database there were not healthy patients who received a lung biopsy. So we took into account patients without fibrotic lesions at the histological exam. The most consistent and homogeneous group was represented by subjects affected by pre-fibrotic lung sarcoidosis (radiological stage ≤3).

According to Goldin (16), quantitative image analysis of chest CT would have been useful in detecting the nature of parenchymal abnormality. This statement is confirmed by the difference of QCTi that we have observed in subjects with fibrotic (bIPF
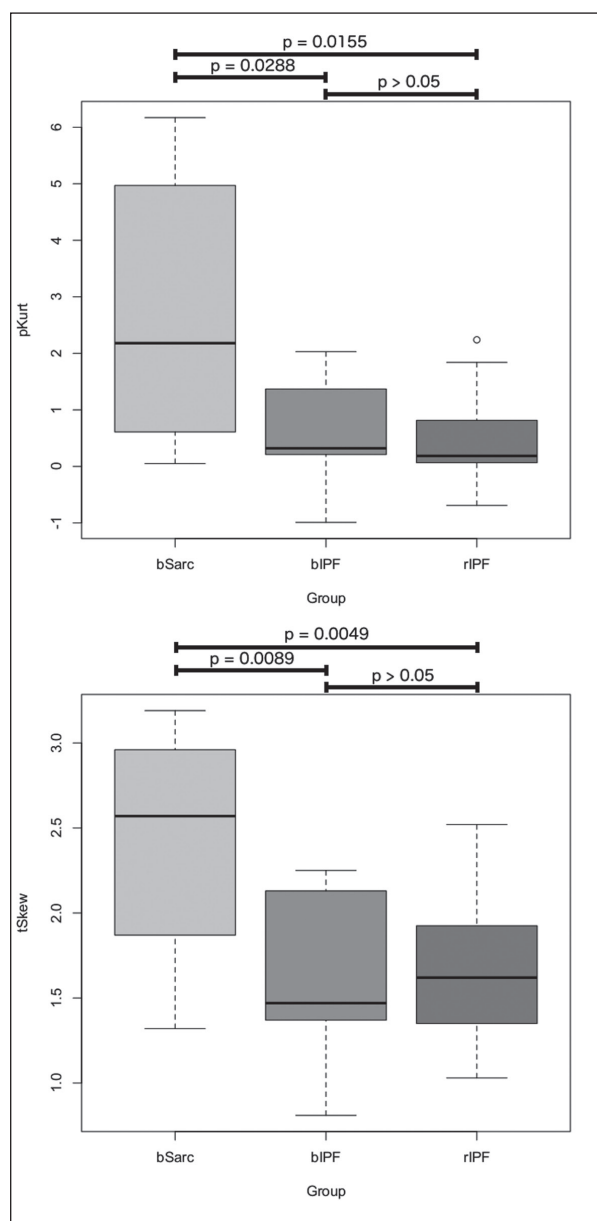

Fig. 1. Box-and-whiskers plots showing the differences of parenchymal kurtosis (pKurt) and total Skewness (tSkew) distribution between the three subgroups. [Legend: bIPF: patients with an histological diagnosis of IPF; rIPF: patients with a radiological diagnosis of IPF; bSarc: patients with an histological diagnosis of Sarcoidosis]

or rIPF) and non fibrotic lung diseases (pre-fibrotic lung sarcoidosis) proven by biopsies.

In order to have a final confirmation of the ability of QCT to detect lung fibrosis we would have compared bIPF with healthy subjects who received a biopsy. In clinical practice it is virtually impossible

to find subjects fulfilling these criteria: given the associate mortality (20), biopsies are reserved for those patients with extremely high suspicion of having a lung disease (23). Even if it is impossible to establish a direct comparison, there is a relevant difference between QCTi we observed and those reported in scientific literature. For example, Sverzellati et al. (24) found that in normal subjects MLA and skewness, were respectively of -837 HU and 3.5 (values very far from ours: -719 HU and 1.5). It therefore seems reasonable to assume that low values of skewness (and kurtosis) correspond to the actual presence of pulmonary fibrosis (i. e. proven by lung biopsies). This is the first study which verify, even if partially, this hypothesis and therefore we consider it a crucial element in favor of the criterion validity of QCT.

QCT in IPF or secondary ILDs (e.g. ILD related to systemic sclerosis) is going to become crucial in the approach to diffuse lung diseases. The software that we used in this study is free and the operator-independent algorithm we applied can be easily learnt (22). Moreover, our findings confirm that QCTi are, potentially, the best parameters in ILD assessment both in clinical practice and trials.

This study has several limitations. Firstly, the small number of enrolled patients. This is mainly due to the low propensity, in daily practice, to perform a surgical lung biopsy. However the results are quite convincing even from the statistical point of view. Secondarily, the two control groups (rIPF and bSarc) are not matched perfectly. Patients with rIPF are older than those with bIPF. This difference could be explained since surgical biopsy is more likely performed in younger patients having, usually, less severe comorbidity. The dissimilarities between the bIPF and bSarc can be brought back to the epidemiological, functional and prognostic characteristics of IPF and sarcoidosis.

In conclusion, this study provides the first evidence that QCT indices correlate with the actual presence of pulmonary fibrosis.

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