Connective tissue disease related fibrotic lung disease: HRCT patterns and pulmonary function indices as prognostic determinants

Appendix

HRCT protocol and image evaluation

HRCT was performed using 64- slice MDCT (Somatom Sensation 64, Siemens, Erlangen, Germany, n=134) or 4-slice MDCT (Siemens Volume Zoom, Siemens, Erlangen, Germany, n=34) in all cases. HRCT images were reconstructed at section widths of 1.5mm (4-slice) or 1mm (64-slice) using a high spatial frequency algorithm. All patients were examined in the supine position from lung apices to lung bases at full-suspended inspiration using standard acquisition parameters: 90 mA, 120kVp. All images were viewed at window settings optimized for assessment of lung parenchyma (window width, 1500–1600 HU; window level, -500 to -600 HU).

Six levels in each HRCT were pre-selected by an observer who was not involved in subsequent scoring of cases: 1) the aortic arch, 2) 1cm below the level of the carina, 3) the right pulmonary venous confluence, 4) the midpoint between 3 and 5, 5) 1cm above the dome of the right hemi-diaphragm and 6) 2cm below the level of the dome of the right hemi-diaphragm. The sixth level ensured that the posterior costophrenic recesses were evaluated.

All images were anonymized and reviewed at the pre-selected levels independently by two thoracic radiologists (NS and AD with 10 and 9 years experience respectively) using Digital Imaging Communications in Medicine viewing software (DicomWorks, version 1.3; *http://dicom.online.fr*) at standard window settings for visualization of the lung parenchyma (centre -500 HU, window width 1500 HU). Prior to scoring, each observer underwent familiarization with the HRCT

patterns described below, using 10 cases of CTD-FLD that were not subsequently used in the study. During the course of scoring the study cases, observers had no knowledge of lung function data or other clinical indicators of disease severity.

The presence and extent of the following parenchymal patterns based on the Fleischner Society's glossary of terms for thoracic imaging [1] with minor modifications, were evaluated 1) ground glass opacification - increased parenchymal density with preservation of the bronchial and vascular markings, with or without superimposed very fine texture but no obvious reticulation, 2) reticulation – criss-crossing linear opacities that are fine or coarse (including interlobular septal or intralobular septal thickening) with associated distortion of the lung architecture, 3) honeycombing – air-filled cystic spaces with irregular walls deemed not to represent traction bronchiectasis, 4) consolidation – a homogeneous increase in pulmonary parenchymal density obscuring the underlying vessels and 5) emphysema.

At each of the six levels, the total extent of disease was estimated to the nearest 5%. The relative proportions of each of the five patterns contributing to the total disease extent at each level were then recorded to the nearest 5%. Thus, at any level, the individual pattern proportions summed to 100%. The presence of traction bronchiectasis within each parenchymal pattern, with the exception of emphysema, was scored as follows: 0 – none, 1 – mild, 2 – moderate and 3 – severe, based upon the most severely affected airways in that pattern. A score of 1 was assigned when the severity of traction bronchiectasis was considered borderline. Grade 2 represented definite traction bronchiectasis but not considered severe. Grade 3 was assigned when traction bronchiectasis was definitely present and severe. Examples are given in figures 1-3. Observers also gave a radiologic diagnosis (either UIP, fibrotic NSIP or

indeterminate) for each patient based upon the pattern of disease on HRCT. This determination was made according to ATS/ERS guidelines [2].

Once the two observers had reviewed all HRCTs, the 5% most discrepant observations for total disease extent at each level and for each HRCT pattern score at each level were reviewed and a score was reached by consensus between the two observers. Observations, which were discrepant by more than one point on the traction bronchiectasis scale described above, were reviewed jointly and re-scored by consensus. All discrepant radiologic diagnoses were reviewed jointly and re-assigned by consensus.

A total disease extent score, total interstitial disease extent score, five parenchymal pattern scores and one traction bronchiectasis score was calculated for each patient as follows:

1. A *total disease extent score* was calculated for each patient by adding the total disease extent scores at all six levels and dividing by six.
2. Parenchymal pattern scores were calculated by multiplying the total disease extent score at each level (expressed as a percentage of the total lung at that level) by the parenchymal pattern score at that level (expressed as a percentage of the abnormal lung at that level). The results for each of the six levels were then averaged. For example, if total disease extent was graded as 50% at all 6 levels, and ground glass opacification was scored as 25% of the abnormality at each level, then the parenchymal pattern score for ground glass opacification would be [(.50)(.25) + (.50)(.25) + (.50)(.25) + (.50)(.25) + (.50)(.25) + (.50)(.25)]/6 = 0.75/6 = 0.125. As emphysema was considered as primarily an airway disease, a *total interstitial disease extent score* was

calculated by subtracting the total parenchymal pattern score for emphysema from the total disease extent score.

3. A *traction bronchiectasis score* for the entire lungs was calculated for each patient, as follows: a traction bronchiectasis score for each of the four interstitial patterns (all parenchymal patterns except emphysema) was first calculated. This was generated by adding the traction bronchiectasis scores for an individual pattern at each of the six levels. To prevent spurious underestimation of the severity of traction bronchiectasis in cases in which traction bronchiectasis is absent in a pattern at some levels (i.e. score = 0) but severe in others, the score was adjusted proportionately to a six-level score. For example, if traction bronchiectasis were graded as 2 in ground glass opacification in 5 out of the six levels, but was absent in ground glass opacification in the sixth level, then the score of 10 (2+2+2+2+2+0) would be adjusted by 6/5 to result in an adjusted score of 12. The traction bronchiectasis scores for each of the four interstitial patterns were then added to generate a total traction bronchiectasis score.

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722.
2. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of

directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304.

Radiologic diagnosis	Variable	Hazard ratio	95%CI	p value
NSIP (n=144)	Honeycombing	1.87	1.53-3.43	0.021
	Traction bronchiectasis	1.09	1.01-1.21	0.001
	DLco %Predicted	0.97	0.95 - 0.99	0.023
UIP (n=15)	Honeycombing	1.33	1.03-1.73	0.034
	Traction bronchiectasis	1.43	0.98-1.13	0.051
	DLco %Predicted	0.89	0.78-1.01	0.084

Table 1. Mortality expressed as hazards ratios for HRCT and pulmonary function indices on subgroup analysis of patients with a radiologic diagnosis of CTD-FLD and a radiologic diagnosis of NSIP and UIP.

Subgroup removed	Number of deaths removed	Number of patients remaining	Hazard ratio	95% CI	p value
RA (n=39)	18/48	129	6.89	1.64-20.97	0.008
SScl (n=32)	8/48	136	5.11	1.57-16.61	<0.001
MCTD (n=33)	11/48	135	6.31	1.94-13.12	<0.001
PM (n=33)	7/48	135	5.62	1.74-15.17	<0.001
SLE (n=17)	1/48	151	5.95	1.21-18.15	<0.001
Sjögren's (n=14)	3/48	154	6.09	1.93-10.29	<0.001

Table 2. Mortality expressed as hazards ratios for the traction bronchiectasis binary score following removal of each CTD subgroup.

Subgroup removed	Number of deaths removed	Number of patients remaining	Hazard ratio	95% CI	p value
RA (n=39)	18/40	129	2.65	1.00-6.94	0.042
SScl (n=32)	8/48	136	5.02	2.57-9.81	0.007
MCTD (n=33)	11/40	135	4.47	2.20-9.10	0.002
PM (n=33)	7/40	135	4.01	2.09-7.69	0.004
SLE (n=17)	1/40	151	4.61	2.45-8.69	0.002
Sjögren's (n=14)	3/40	154	3.88	2.02-7.42	<0.001

Table 3. Mortality expressed as hazards ratios for the honeycombing binary score following removal of each CTD subgroup.