High Resolution CT in Diffuse Lung Disease

W. Richard Webb

Dept of Radiology, University of California of San Francisco, San Francisco

The development of high-resolution CT (HRCT) in recent years has revolutionized our ability to detect and characterize diffuse pulmonary disease. Using HRCT, lung morphology can be assessed in detail.

HRCT TECHNIQUE

High-resolution CT techniques attempt to optimize the demonstration of lung architecture.[14] The use of thin collimation (1-2 mm) and image reconstruction with a high-resolution algorithm are essential in obtaining HRCT.[1] Additional modifications of technique can improve image quality further, but are not necessary. These include increasing the kVp or mA scan settings in order to reduce image noise, and targeting image reconstruction to a small field of view.[2,5-8]

The average skin radiation dose associated with HRCT scans has been compared to that of conventional CT.[9] Using a scan technique of 120 kVp, 200 mA, 2 sec, the mean skin radiation dose was 4.4 mGy for 1.5 mm HRCT scans at 10 mm intervals, 2.1 mGy for scans at 20 mm intervals, and 36.3 mGy for conventional 10 mm scans at 10 mm intervals. Thus, HRCT scanning at 10 and 20 mm intervals, as is done in clinical imaging, results in 12% and 6%, respectively, of the radiation dose associated with conventional CT.

Recently, the utility of "low-dose" HRCT (120 kVp, 20 mA, and 2 second scan time) has been evaluated.[10] Image quality is generally not as good as with standard HRCT technique, but low-dose scans may be adequate for the follow-up of patients with an established diagnosis.

Most patients who have HRCT in our institution for the diagnosis of suspected restrictive lung disease or who have diffuse lung disease of unknown type, have scans performed at 2 cm intervals from lung apices to bases in both the supine and prone positions. Some dependent lung collapse is often seen in both normals and abnormals, and having scans in both positions allows us to differentiate this finding from true pathology. Patients with suspected obstructive disease have scans performed at 1 cm intervals from the lung apices to bases in the supine position only.

The use of HRCT following expiration, or dynamic ultrafast high-resolution CT (DUHRCT) in which a rapid series of ultra. fast HRCT scans are obtained during a forced inspiratory and expiratory maneuvers, can demonstrate dynamic morphologic and lung attenuation changes associated with airways obstruction.[11]

NORMAL HRCT FINDINGS

Struetures as small as 0.2 to 0.3 mm can be seen on HRCT images; this level of resolution allows the imaging of lung anatomy at the level of the secondary pulmonary lobule.[2,8,12,13] Within the peripheral lung, interlobular septa measuring 100 μm or 0.1 mm in thickness are at the lower limit of HRCT resolution,[13] but nonetheless can sometimes be seen on HRCT scans performed in vitro.[12] These are better seen within the peripheral lung than in the central lung, as septa are better developed in this location. On clinical HRCT in normal patients, a few interlobular septa can often be seen, but they tend to be inconspicuous.[8] Numerous clearly defined interlobular septa are usually abnormal.

The central portion of the 'secondary lobule, referred to as the lobular core or centrilobular region,[14] contains the pulmonary artery and bronchiolar branches which supply the lobule. The pulmonary artery supplying a secondary lobule measures approximately 1 mm in diameter, while intralobular acinar artery branches measure 0.5 mm in diameter, vessels of this size are easily seen using HRCT. The visibility of bronchi or bronchioles on HRCT is determined by their wall thickness rather than their diameter. As an approximation, the thickness of the wall of a bronchus or bronchiole measures from 1/6 to 1/10th of its diameter.[15] Thus, for a 1 mm bronchiole supplying a secondary lobule, the thickness of its wall measures approximately 0.15 mm; the wall of a terminal bronchiole measures only 0.1 mm in thickness, and that of an acinar bronchiole only 0.05 mm. Bronchioles are below the resolution of HRCT technique for a tubular

ABNORMAL HRCT FINDINGS

Numerous pathologic studies have shown that HRCT accurately depicts lung anatomy and pathology. Generally speaking, HRCT findings of lung disease can be considered in 4 groups or categories, which reflect the histologic abnormalities present. These are 1) reticular opacities, 2) nodular opacities, 3) increased lung opacity, and 4) decreased lung opacity or cystic opacities.

RETICULAR OPACITIES

Thickening of the interstitial fiber network of the lung by fluid, fibrous tissue, or because of interstitial infiltration by cells, results in an increase in reticular lung opacities as seen on HRCT. Reticular interstitial abnormalities can often be characterized according to their relation to secondary lobular structures.

Interlobular septal thickening occurs in patients with a variety of interstitial lung diseases, and in the presence of interstitial fluid, fibrosis, or cellular infiltration. In the peripheral lung, thickened septa measure 1-2 cm in length and are often seen extending to the pleural surface; in the central lung, the thickened septa can outline lobules which are 1-2.5 cm in diameter and appear polygonal in shape. Such visible lobules commonly contain a central dot-like or branching artery.

Septal thickening can be smooth, nodular, or irregular in contour in different pathologic processes. Pulmonary edema results in smooth septal thickening; lymphangitic spread of tumor characteristically results in smooth, nodular, or "beaded" thickening,[16-18] while "beaded septa" or septal nodules can also be seen in patients with sarcoidosis and coal workers pneumoconiosis.[19-22] Septal thickening is not common in patients with interstitial fibrosis, except for those with sarcoidosis and asbestosis;[23] when visible, septal thickening due to fibrosis is often irregular in appearance.

When interlobular septa are visible, and lobules are well outlined, it is important to note whether the lobules are normal in shape and appearance or whether they are distorted. Thickened septa without architectural distortion is characteristic of edema, lymphangitic spread, or infiltration, while distortion strongly suggests fibrosis.

Intralobular interstitial thickening represents an abnormality of the intralobular interstitium, perhaps occurring in relation to small arterial or bronchiolar branches or in the periphery of acini.[7,12] This finding is most common can be seen in patients who have fibrosis, and is visible as a fine network of lines.[7,12]

Honeycombing reflects extensive fibrosis with lung destruction, and results in a cystic, reticular appearance on HRCT which is characteristic.[12,24] When honeycombing is present, normal lung architecture is distorted, and secondary lobules are difficult or impossible to recognize. The cystic spaces of honeycombing can range from several mm to several cm in diameter, and are characterized by thick, clearly definable, fibrous walls.

Centrilobular opacities[25-27] can reflect peribronchovascular interstitial thickening such as occurs in patients with fibrosis or interstitial infiltration, or can reflect bronchiolar abnormalities. For example, centrilobular (peribronchiolar) abnormalities have been reported as early HRCT findings in patients with asbestosis[28] and silicosis,[29] and can also be seen in patients with pulmonary edema, sarcoidosis[19,30] histiocytosis X,[31] and hypersensitivity pneumonitis [32]. In some of these conditions, the presence of centrilobular abnormalities reflects peribronchiolar inflammation or air-space disease. In patients with small airways diseases such as panbronchiolitis,[26] cystic fibrosis,[27] and bronchiolitis, centrilobular opacities and bronchiolar wall thickening have been seen. On HRCT, centrilobular abnormalities can appear as an abnormal prominence of the centrilobular artery or bronchiole because of peribronchovascular interstitial thickening or as a nodular opacity. The appearance of "tree-in-bud" is often indicative of airways disease or inflammation, as in cystic fibrosis or endobronchial spread of TB.[33]

NODULES

Nodules as small as 1-2 mm in diameter can be detected on HRCT in patients with a variety of diseases. Nodules can be "perilymphatic", random, or centrilobular in distribution in different diseases and recognizing one of these distributions can be important in differential diagnosis.[34] **"Perilymphatic" nodules** affect the peribronchovascular, interlobular septal, subpleural, and centrilobular interstitial compartments, and are usually due to sarcoidosis, which tends to have a peribronchovascular and subpleural predominance,[19,22,30,35-37] silicosis and coal-worker's penumoconiosis, which predominates in the subpleural and centrilobular regions,[20,21,29,38] and

lymphangitic spead of tumor, which is typically peribronchovascular and septal.[8,18,39] Nodules with a **random distribution** are most typical of milary tuberculosis[33] and hematogenous metastases.[40] **Centrilobular nodules,** often reflect bronchiolar or peribronchiolar abnormalities,[41] and can be seen in silicosis and coal-worker's pneumoconiosis,[29] asbestosis,[42] endobronchial spread of tuberculosis[13,33] or other causes of bronchopneumonia, hypersensitivity pneumonitis[32,43], airways diseases, respiratory bronchiolitis, bronchiolitis obliterans or bronchiolitis obliterans with organizing pneumonia (BOOP), and pulmonary edema.[41]

INCREASED LUNG OPACITY

Air-space consolidation, by definition, occurs when alveolar air is replaced by fluid, cells, or other material.[25] On HRCT, consolidation results in an increase in lung opacity associated with obscuration of underlying vessels. Among patients with chronic diffuse infiltrative lung disease, the most common causes of this pattern include chronic eosinophilic pneumonia and BOOP.[44,45]

"Ground-glass opacity" is nonspecific term referring to a hazy increase in lung opacity which is not associated with obscuration of underlying vessels. This finding can reflect the presence of a number of diseases, and can be seen in patients with either minimal interstitial thickening or minimal air-space filling.[7,46,47] It can reflect minimal thickening of the alveolar interstitium, alveolar wall thickening, or the presence of fluid or cells filling the alveoli. Thus, it can be seen in patients with mild or early interstitial disease or alveolitis

Although "ground-glass" opacity is a nonspecific finding, its presence is very significant. This finding usually indicates an acute, active, and potentially treatable process,[47] such as pulmonary edema, alveolitis, desquamative interstitial pneumonitis (DIP),[7,48] active idiopathic pulmonary fibrosis,[46,49] pneumonia (particularly pneumocystis carinii pneumonia,[50] alveolar proteinosis,[51] hypersensitivity pneumonitis,[32,52] and sarcoidosis.[19,53] Because of its association with active lung disease, the presence of this finding often leads to lung biopsy, depending of the clinical status of the patient.

DECREASED LUNG OPACITY AND CYSTIC LESIONS

Honeycombing, as described above, results in cystic abnormalities which can be precisely characterized and localized on HRCT.[12,24,54] Honeycomb cysts are often peripheral in location, and are characterized by thick, clearly definable walls.

Emphysema is accurately diagnosed using HRCT, and this technique is more sensitive than conventional CI or plain radiographs in detecting the presence of this abnormality.[12,39,55-57] Emphysema results in focal areas of very low attenuation which can be easily contrasted with surrounding, higher attenuation, normal lung parenchyma if sufficiently low window means (< 600 H) are used. Emphysemal is usually distinguishable from honeycombing because areas of emphysematous destruction lack a visible wall, while honeycomb cysts are characterized with thick walls of fibrous tissue.

Lung cyst is a term which is used to describe to a thin-walled (usually < 3 mm), well defined and circumscribed air-containing lesion, 1 cm or more in diameter. Lymphangiomyomatosis and histiocytosis X often produce multiple lung cysts which have an appearance on HRCT which is usually quite distinct from that of honeycombing.[31,58-63] The cysts have a thin but easily discernable wall, ranging up to to a few millimeters in thickness. Associated findings of fibrosis are usually absent or much less conspicuous than they are in patients with honeycombing. In these diseases, the cysts are usually interspersed within areas of normal appearing lung. In patients with histiocytosis X, the cysts can have bizarre shapes because of the fusion of several cysts or perhaps because they represent ectatic and thiek-walled bronchi.

Bronchiectasis is diagnosed with a high degree of accuracy using HRCT.[64,65] Types of bronchiectasis can be distinguished, but this is not commonly of clinical significance.

Decreased lung attenuation, not reflecting the presence of cystic lesions or emphysema can sometimes be recognized on HRCT in patients who have diseases which produce air-trapping, poor ventilation, or poor perfusion.[27,66] The areas of decreased lung attenuation which are seen on HRCT can be focal, lobular or lobar, or multifocal. The term "mosaic perfusion" has been used to refer to patchy lung attenuation resulting from perfusion abnormalities [67]. In patients with air-trapping, this appearance can be enhanced by using dynamic expiratory HRCT or by obtaining expiratory scans.[11,68-70]

CLINICAL UTILITY OF HRCT

HRCT may show parenchymal abnormalities in patients with normal radiographs, and because it provides an accurate assessment of the pattern and distribution of lung disease, it may allow confident diagnosis in patients with normal or nonspecific findings on the radiograph.[5,6,17,22,30,38,59,63,71-77] HRCT may also be able to distinguish areas of active alveolitis from irreversible fibrosis[46,78,79] and be a helpful guide to the optimal type and site of lung biopsy.[38,80] The clinical utility and indications for use of HRCT therefore may be reviewed in terms of its ability to detect lung disease, to categorize it, to assess disease activity, and as a guide to lung biopsy.

HRCT in the Detection of Lung Disease

The chest radiograph remains the first and foremost imaging technique used in the assessment of patients with suspected diffuse infiltrative lung disease. However, the radiographs is normal in 10- 16% of patients with biopsy-proven disease.[81-82] Abnormal conventional CT or HRCT in patients with normal chest radiographs have been reported in a number of patients with chronic infiltrative lung diseases, including asbestosis,[71-74] sarcoidosis,[22-30] lymphangioleiomyomatosis,[63] fibrosing alveolitis,[76] lymphangitic carcinomatosis,[17] desquamative interstitial pneumonia,[83] and hypersensitivity pneumonitis.[83] The sensitivity of HRCT in detecting lung disease has been compared to that of the radiograph in patients with biopsy-proven sarcoidosis, lymphangioleiomyomatosis and lymphangitic carcinomatosis.[17,22,30,63] On the average, looking at all the patients assessed in these studies, the sensitivity of the radiograph in detecting infiltrative lung disease was 80% compared to 94% for HRCT. HRCT not only allows greater sensitivity in demonstrating infiltrative lung disease, it also allows greater specificity in distinguishing normal from abnormal lung parenchyma. This was evaluated in a recent study by Padley et al.[84] In their study the specificity in correctly identifying the normal subjects was 82% for the radiograph and 100% for high-resolution CT. Thus high-resolution CT is indicated not only in patients with suspected lung disease and normal radiographs but also in patient with questionable radiographic abnormalities or with radiographic findings not in keeping with the clinical or functional abnormalities.

HRCT can also be helpful in determining what type of parenchymal abnormality is responsible for clinical and functional impairment in patients with more than one abnormality. Dyspneic smokers with idiopathic pulmonary fibrosis may have impairment in gas transfer but normal or near-normal spirometric measurements of lung function. These patients are difficult to assess objectively because the radiograph may not show evidence of emphysema and the pulmonary function tests may be misleading.[85] HRCT can identify the presence and extent of emphysema and fibrosis as well as their relative contribution to the clinical and functional abnormalities and therefore be valuable in the assessment of these patients.[57,85,86]

Differential Diagnosis of Lung Disease

Mathieson et al[38] compared the accuracy chest radiography and CT in the prediction of specific diagnosis in 118 consecutive patients with chronic diffuse infiltrative lung disease. The radiographs and CT scans were assessed independently by three observers without knowledge of clinical or pathologic data. The observers made a confident diagnosis on 23% of radiographic and 49% of CT interpretations. This diagnosis was correct with 77% and 93% of those readings, respectively ($p>.001$). Thus, a confident diagnosis was made more than twice as often on the basis of CT scans than on the basis of chest radiographs, and the CT-based diagnosis was more often correct.

Grenier et al[87] compared the diagnostic accuracy of chest radiography and HRCT in 140 consecutive patients with chronic diffuse infiltrative lung disease. Three independent observers listed the three most likely diagnoses and recorded the degree of confidence they had in their choice. The percentages of high confidence diagnosis by each of the three observers that were correct on the basis of the chest radiograph were 29%, 34% and 19%, respectively, as compared to 57%, 55%, and 74%, respectively on the basis of the HRCT ($p<.001$ for each comparison). The interobserver agreement for the proposed diagnosis was also significantly better with HRCT than with conventional radiography.

On the basis of the results of these studies, HRCT is indicated in the assessment of patients with suspected infiltrative lung disease in whom the combination of clinical and radiologic findings does not allow a confident diagnosis. Although HRCT is a morphologic and not a histologic tool, in some cases it does allow a definitive diagnosis.

HRCT IN THE ASSESSMENT OF DISEASE ACTIVITY

HRCT may play a role in the assessment of disease activity and response to treatment in patients with diffuse infiltrative lung disease.[19,46,78,79]

In idiopathic pulmonary fibrosis, both long-term survival and response to treatment with corticosteroids correlate with the histologic changes. The best response to steroids is observed in patients with active alveolitis and mild fibrosis.[88-90] Although open lung biopsy provides the gold standard for the estimate of the degree of alveolitis, it has two limitations: it is invasive and it only assesses a small area of the lung which may not be representative of the overall process. Muller et al [46] correlated the CT scans with pathologic determinants of disease activity in 12 patients with idiopathic pulmonary fibrosis. Disease activity was assessed by the presence of areas of ground-glass density on CT. Five patients with marked disease activity pathologically and five of seven patients with mild disease activity were correctly categorized by both observers. The capacity of HRCT for distinguishing irreversible fibrosis from acute alveolitis in most patients with idiopathic pulmonary fibrosis has been recently confirmed by Hansell et a.[78] In a recent study, nearly 90% of patients with ground-glass opacity had disease activity on biopsy.[47]

Lynch et al[19] showed in a small number of patients with sarcoidosis that localized areas of hazy increased density (ground-glass opacities) correlated with active alveolitis as assessed by gallium-67 scans. Nodules on HRCT correlated with the presence of granulomata.[19,22] Currently it is thought that alveolitis rather than granuloma formation leads to fibrosis in these patients.[91] Follow-up HRCT in two patients who improved clinically with steroid therapy showed marked decrease in the ground-glass opacities and in the nodularity.[19] A more extensive follow-up of the HRCT findings was recently reported by Brauner et al.[53] They compared the HRCT findings during the active phase with those after improvement in 20 patients with pulmonary sarcoidosis. They demonstrated that nodules, ground-glass opacities and consolidation represent potentially reversible inflammatory changes. Septal lines, nonseptal lines, and lung distortion, on the other hand, remained unchanged or increase on follow-up scans.

HRCT as a guide to the type and site of lung biopsy

Most chronic infiltrative lung diseases have a patchy distribution within the lung parenchyma, areas of normal parenchyma being interspersed between areas of active disease and areas with irreversible fibrosis. HRCT is helpful in determining the kind of diagnostic procedure most likely to yield the diagnosis and, if biopsy is required, the area is most likely to yield the correct diagnosis.[5,6,38,80]

The two chronic diffuse infiltrative lung diseases that can be consistently and reliably diagnosed on the basis of the findings of bronchial or transbronchial biopsy are lymphatic spread of tumor and sarcoidosis.[92] Diagnosis of interstitial pneumonia, fibrosis, chronic inflammation, nonspecific reaction and normal lung that are based on the findings of transbronchial biopsy are unreliable and often entirely misleading.[92] Mathieson et al[38] compared the accuracies of chest radiography and CT in the prediction of whether transbronchal biopsy was likely to yield a diagnostic-quality specimen. Three independent observers correctly predicted that a transbronchial biopsy was indicated with 65% of radiographs and 87% of CT scans ($p < .001$). An open lung biopsy was correctly suggested by the radiographic findings in 89% of cases and on the basis of the CT findings in 99% of cases ($p < .001$).

When open lung biopsy is indicated, CT is helpful in guiding the surgeon to the optimal biopsy site.[80] In order to make the correct diagnosis at open lung biopsy, the specimen must include tissue from a representative area of lung and areas of extensive honeycombing must be avoided. This can be particularly difficult in cases of idiopathic pulmonary fibrosis because the most severe honeycombing is subpleural.[24] Disease distribution usually cannot be assessed adequately from the conventional radiography but it can easily be determined with CT.

Follow up of a known disease

In patients with a diffuse interstitial lung disease who are being treated, HRCT can be used instead of chest radiographs to follow the course of the disease. In patients with sarcoidosis and idiopathic pulmonary fibrosis, HRCT has proven valuable in this regard.[19,53,93-95] Progression or regression of disease can be followed using this technique.

Conclusions

HRCT is able to define lung anatomy at the secondary lobular level and define a variety of abnormalities in patients with diffuse lung diseases. Evidence from numerous studies indicates that HRCT can play a

major roie in the assessment of diffuse infiltrative lung disease and is indicated clinically (1) in patients with signs and symptoms suggestive of diffuse lung disease but normal or nonspecific radiographic findings, (2) in patients in whom the combination of clinical and radiographic findings does not allow a confident diagnosis, (3) in patients in whom the radiographic findings or pulmonary function tests are not in keeping with the clinical history or symptoms, (4) in patients with more than one parenchymal abnormality, e.g., emphysema and idiopathic pulmonary fibrosis, (5) before lung biopsy as a guide to the optimal type and site of biopsy, (6) In patient with infiltrative lung disease in whom complications (e.g., infection) are suspected.

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