

Computed Tomography Morphological Phenotypes in Pulmonary Sarcoidosis

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*A thesis submitted to Imperial College London for the degree of
Doctor of Medicine (Research)*

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London

September 2022

STATEMENT OF ORIGINALITY

I declare that this thesis, which I present for consideration of the degree of Doctor of Medicine (research), is my own original work. Any data, figure, or text resulting from published or unpublished work of others has been duly credited.

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ABSTRACT

Sarcoidosis — the archetypal granulomatous disorder — while being a multisystem disease, clearly has a propensity to affect the lungs. The clinical presentation, imaging features, patterns of functional impairment and outcome of lung disease may vary significantly, leading to the not unreasonable suggestion that sarcoidosis is simply a convenient ‘umbrella’ term for what are, in fact, different disease entities. The investigations in this thesis have exploited *imaging* tests, and particularly high-resolution CT (HRCT), to explore the morphological aspects of lung disease in sarcoidosis.

The studies in the first section confirmed that chest radiography (CXR) ‘masks’ abnormalities that are more readily visible on HRCT – this was to be expected. However, a comparison between so-called CXR ‘stage’ and HRCT findings also revealed that a) parenchymal disease is present in a significant minority (40%) of patients with CXR stages 0/1 — that is, those with no CXR evidence of lung involvement and b) that fibrosis may be present on HRCT, albeit with varying prevalence, in all CXR stages. Further exploration uncovered a striking and *independent* linkage between specific morphological signs on HRCT— in particular traction bronchiectasis and honeycombing — and prognosis in sarcoidosis, a theme that is repeated in other fibrotic lung diseases.

In the final section, the aim was to gain consensus on the recognisable HRCT phenotypes in sarcoidosis. To this end, a Delphi study methodology was employed through which the opinions of a large body of international experts (thoracic radiologists & respiratory physicians) were garnered. The Delphi exercise identified *seven* key morphological/HRCT phenotypes divided roughly into non-fibrotic and fibrotic phenotypes. It is suggested that these phenotypes might, in the future, form the basis of a new

morphological classification which more accurately reflects variations in clinical presentation, patterns of functional impairment, natural history and outcome in patients with pulmonary sarcoidosis.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the assistance, encouragement, and guidance I received from many colleagues and friends at Royal Brompton Hospital.

First and foremost, I must thank my supervisor, Professor Desai. His unfaltering dedication and support have contributed to my success over the last two years in more ways than he will ever know. His energy, charisma and (very loud) singing from the adjoining offices have boosted me at times when I was low and I dare not mention the significant amount of time he spent scoring CT scans for my project. This body of work is undoubtedly a testament to his brilliant supervision. I am also privileged to have had the support and supervision of Professor Wells – a true giant in the field of interstitial lung disease. He has dedicated countless hours to imparting a mere fraction of his statistical and methodological wisdom on me and on most occasions, restrained himself to only mild sarcasm when responding to some of my more trivial queries. I am very grateful to Dr Xu for her expertise on all things related to data collection and would also like to thank Dr Kouranos for providing me with access to his patient data. I must also mention Dr Walsh and Professor Cullinan for co-supervising this project and thank them for their guidance along the way.

I owe thanks to my radiology colleagues at Royal Brompton Hospital – Professor Devaraj, Professor Padley, Dr Ridge, Dr Mirsadraee, Dr Semple, Dr Rubens, Dr Rawal and Dr Bartlett – all of whom have supported me in some shape or form during the course of my research.

Finally, I must thank my family. My wonderful parents and siblings, who have always encouraged me to be the best version of myself, pushed me to rise to every challenge and empowered me to bounce back when things have not gone to plan. Last, but not least, my wife Kristina, for her unconditional love and encouragement, and for looking after our two monsters during the last 2 years and more.

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ATS	American Thoracic Society
BHL	Bilateral hilar lymphadenopathy
BP	Bronchopulmonary (segment)
BTS	British Thoracic Society
CI	Confidence interval
CPI	Composite physiological index
CT	Computed tomography
CTAS	CT activity score
CXR	Chest (X-ray) radiograph
DICOM	Digital imaging and communications in medicine
DLco	Diffusing capacity of the lung for carbon monoxide
ECCS	European Community of Coal and Steel
ECG	Electrocardiogram
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HLA	Human leukocyte antigen
HR	Hazard Ratio
HRCT	High-resolution computed tomography
HRCT	High-resolution computed tomography
HU	Hounsfield Units
ICC	Intra-class correlation coefficient
IQR	Interquartile range
Kco	Transfer coefficient of the lung for carbon monoxide
MDCT	Multidetector row computed tomography
NSIP	Non-specific interstitial pneumonia
OR	Odds Ratio

PA	Pulmonary artery
PACS	Pictures archive and communication system
PET-CT	Positron emission tomography-computed tomography
PFT	Pulmonary function tests
PMF	Progressive massive fibrosis
PPFE	Pleuroparenchymal fibroelastosis
r	Sample correlation coefficient
RV	Residual Volume
SD	Standard Deviation
TBx	Traction bronchiectasis
TLC	Total lung capacity
UIP	Usual interstitial pneumonia
URL	Uniform resource locator
WASOG	The World Association of Sarcoidosis and Other Granulomatous Disorders
K	Kappa
K_w	Weighted Kappa

Section I | *Chapter 1*

Introduction

1.1 HISTORICAL OVERVIEW

The Englishman Sir Jonathan Hutchinson (4) is generally credited with describing the first case of what we now consider sarcoidosis. At the time, sarcoidosis was believed to be a novel dermatological condition. The publication in 1877 titled '*Illustrations of Clinical Surgery*' (5) described the case of a 58-year-old coal-wharf worker with '*a number of peculiar patches of dark purplish colour on his extremities*', which were tentatively described as an '*anomalous disease of skin of fingers, etc. (papillary psoriasis?)*'. In 1898, Hutchinson presented further cases of previously unseen dermatological disorders and, in so doing, described: '*...a skin disease which has...hitherto escaped special recognition. It may not impossibly be a tuberculous affection and one of the lupus family, but if so it differs widely from all other forms of lupus.*' In what should only be regarded as prescient, Hutchinson proposed that these cases might be manifestations of a single disease, tentatively named after one of his patients 'Mortimer's malady' (6).

In 1889, Ernest Besnier had similarly described violaceous swellings of the face and fingers in a single patient, which he believed were manifestations of lupus erythematosus, and coined the phrase 'Lupus pernio' (7). While acknowledging some similarities between his case and that of Mortimer's malady, he maintained that the presentations were sufficiently disparate for them to be considered separate entities. Later in the 19th century, Scandinavian dermatologist Cæsar Boeck was the first to describe the histopathological features of the mysterious cutaneous lesions previously reported by Hutchinson and Besnier. In a landmark article, the report was of '*sharply-defined tumour foci*' (8). The term 'sarkoid' was proposed on the mistaken notion that the disease was a tumour of connective tissue, an idea later abandoned by Boeck himself. In 1916, through his publication of 23

cases, Boeck demonstrated, for the first time, that sarcoidosis was a multi-system disorder, not restricted to the skin (9). Boeck was of the opinion that Mortimer's malady, lupus pernio and 'multiple sarcoid' were of the same character and, possibly, variants of tuberculosis.

There was a steady evolution in the understanding of sarcoidosis over the 20th century. In 1915 Kuznitzky and Bittorf (10) first reported the typical radiographic manifestations of pulmonary sarcoidosis describing the now well-recognised constellation of enlarged hilar lymph nodes and pulmonary infiltrates. Further reports including those by Heerfordt (11), Schaumann (12) and Löfgren (13) were also influential, with the latter describing a cluster of cases of so-called 'bilateral hilar lymphoma' and erythema nodosum giving rise to the eponymous Löfgren's syndrome.

In 1941, the Norwegian dermatologist, Ansgar Kveim, developed the first diagnostic test for sarcoidosis on noticing that an intradermal injection of sarcoid tissue produced granulomatous papules in individuals with sarcoidosis but not in controls (14). The Kveim test, as it became known was fine-tuned by Siltzbach by refining the sarcoid suspensions and antigens used for testing (15). For many decades the Kveim test was standard in the diagnostic armamentarium even though the exact pathophysiological mechanisms underlying the Kveim response remains a mystery (16).

1.2 ANATOMICAL CONSIDERATIONS

1.2.1 *Early Anatomical Studies of The Lungs*

A knowledge of *normal* — macroscopic and microscopic — lung anatomy is a pre-requisite for understanding radiology and the pathophysiology of sarcoidosis. The study of

pulmonary anatomy has long been of interest, dating back to the time of Vesalius who saw the lungs as '*soft, spongy, thin, light, airy flesh... filled with branches of vessels*'. Vesalius' view of the lung held forth until well into the 17th century with Marcello Malpighi's likening of lung structure to a honeycomb and his recognition of the sub-divisions of normal lung into lobules (17).

A deeper understanding of lung anatomy came with the production of lung casts: Thomas Willis described the presence of 'little lobes' surrounded by a 'membrane' (18), the earliest reference, perhaps, to the presence of pulmonary lobules. In 1872, Franz Schulze used animal models to describe, for the first time, the presence of alveoli, a feature further explored by Rindfleisch who defined the pulmonary acinus (i.e. the functional unit subtended by terminal bronchioles) (19).

1.2.2 General Lung Anatomy

Each lung occupies one hemithorax and is invested by two layers of pleura. The pleural layers are separated by approximately 10-20ml of pleural fluid which facilitates frictionless expansion and contraction of the lungs during respiration. The principal elements of lung anatomy (i.e. the interstitium, airways and vessels) which warrant further review are discussed in the sections that follow.

1.2.3 Pulmonary Interstitium

The interstitium comprises central and peripheral components. The peripheral interstitium lies deep to the visceral pleura as a network of fibrous connective tissue. These

fibres penetrate the surface of the lung constituting a well-defined network of fibrous connective tissue, referred to as the interlobular septa. At a microscopic level, delicate fibrous structures also intervene between the microscopic alveoli, forming so-called inter-alveolar septa (20, 21). Centrally, the axial connective tissue bundles arise from the hilar structures and radiate out towards the septa and, in reaching the periphery, serve to support the alveoli. Although it is convenient to describe the axial and peripheral interstitium separately it must be stressed that these two elements form a continuous network of fibres that support key functional aspects of the lung. In addition to its role in providing structural integrity, the pulmonary interstitium contains a complex network of pulmonary venous and lymphatic tributaries (see section 1.2.6, page 25) (20, 21).

Collagen is a key component of the pulmonary interstitium and exists in different forms (22). The subtype of collagen found in different anatomic regions varies according to function (23, 24). Thus, for example, type II collagen is the main constituent of the cartilaginous rings that provide the structural scaffold for the central airways but is also abundant in the axial and peripheral interstitium. Conversely, the finer connective tissues forming the basement membranes of the alveoli primarily comprise type V collagen which gives high-tensile strength (to withstand the forces generated by repeated expansion and contraction during breathing), while simultaneously permitting gas exchange (22-25). Fibroblasts and elastin are also important constituents of the lung interstitium, along with a host of other essential fibrillary proteins (26).

A knowledge and understanding of the axial and peripheral interstitium underpins interpretation of imaging studies and, in particular, high-resolution computed tomography (HRCT). In this regard, interlobular fibrous septa are particularly well-developed in the

subpleural lung and a few are rendered visible on HRCT, even in patients without established lung disease (27). Importantly, even in the periphery of the lung, normal interlobular septa are usually not visible on plain chest radiographs. However, in pathological states, for example pulmonary oedema, the interlobular septa become thickened and then, are readily identifiable. As a result, parenchymal diseases that have a predilection for the axial interstitium, such as sarcoidosis, can give rise to an irregular/nodular appearance of bronchovascular bundles on HRCT (28).

1.2.4 Airways

Broadly speaking, the lungs may be regarded as comprising a *conducting system* (made up of airways) and a *gas exchange system* (which occurs at the level of the alveolar-capillary membrane). The former is responsible for the delivery and extraction of gases, while the latter represents the interface between the atmosphere and circulation (29). The nomenclature of airways is based on their luminal diameter: those with a diameter greater than 1mm, which are reinforced by cartilage are termed bronchi, whereas the smaller, more distal, non-cartilaginous airways are called bronchioles. The airways and accompanying arteries divide dichotomously. The larger airways divide asymmetrically, varying in diameter and length, with the smaller more distal airways generally showing more symmetrical division. This variation in branching pattern is thought to reflect the change in functional characteristics: the central airways being responsible for gas conduction, while the distal airways responsible for gas exchange (30). Inhaled air travels through the upper respiratory tract, the trachea, into the main bronchi and then into ~16 generations of rapidly-dividing lobar, segmental and subsegmental bronchi and bronchioles. These airways are referred to

as conducting airways with the last generation of conducting airways being called terminal bronchioles.

Studies of microscopic anatomy reveal that as air travels further into the lungs (i.e. into the 17th-19th generation), the bronchioles are lined by occasional alveoli and these are aptly termed respiratory bronchioles. From generation 20 to 22, the airways become fully lined by alveoli and are termed alveolar ducts, which terminate as blind alveolar sacs (23rd generation) lined by alveoli (31). The entire unit of lung subtended by a terminal bronchiole is called the acinus (Figure 1.1) and is designed to maximise surface area for gas exchange. In adults, each acinus measures approximately 6 mm in diameter. However, in practical terms, the acinus is rarely appreciable on HRCT (32, 33).

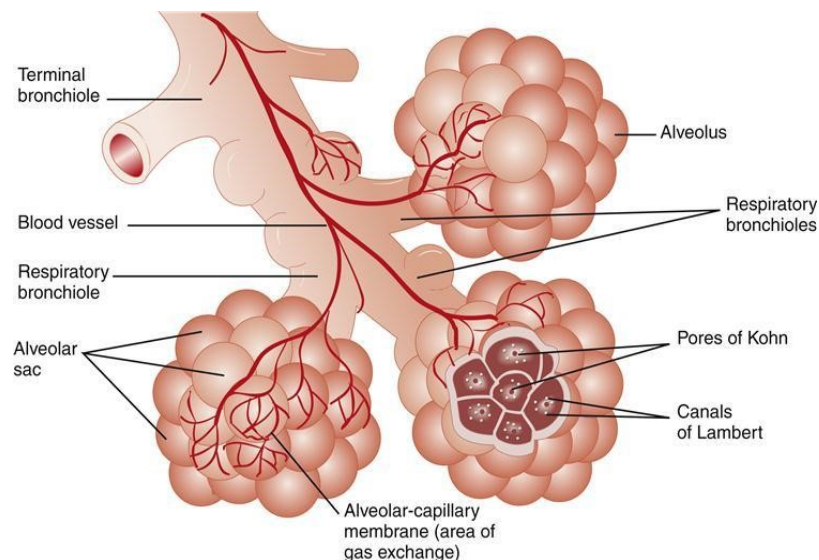


Figure 1.1 Schematic of the pulmonary acinus. The relationship between terminal bronchioles, respiratory bronchioles and alveolar structures is shown. From: 'Lower airway structures', basicmedicalkey.com

1.2.5 The Pulmonary Lobule

The pulmonary lobule (Figure 1.2), formerly termed the 'secondary' pulmonary lobule, is the basic unit of lung structure first described by William Snow Miller and defined as the smallest unit of lung bounded by connective tissue septa (17). The pulmonary lobule comprises a pre-terminal bronchiole, the corresponding acini (normally ~10, although numbers vary considerably) and the homologous pulmonary artery (17). Each pulmonary lobule has a roughly polygonal shape, measuring approximately 10-25mm, with lobules in the periphery generally more conspicuous than those in the centre. The central lobular airway has a diameter of approximately 1mm (17). It is worth noting, that in his seminal paper, Miller also described the primary pulmonary lobule (a unit of gas exchange distal to the respiratory bronchioles i.e. the alveolar ducts and sacs). In practice, primary pulmonary lobules are rarely referred to and for imaging purposes it is the secondary pulmonary lobule or simply 'pulmonary lobule', that is of significance (18).

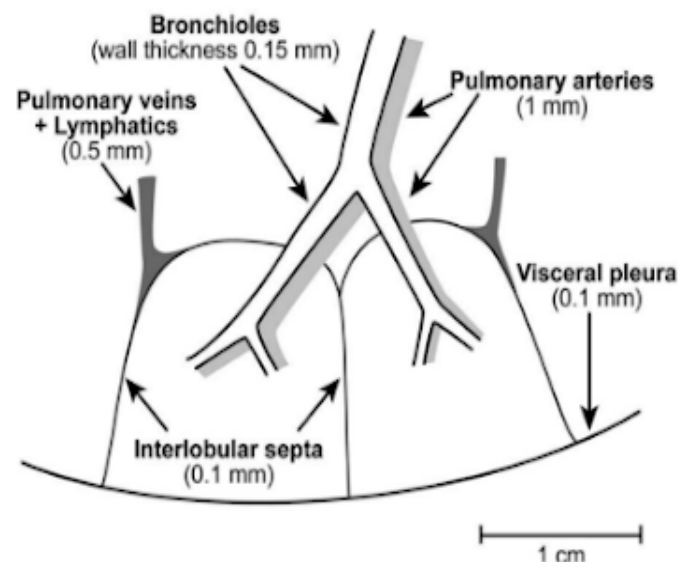


Figure 1.2 Stylised representation of two adjacent sub-pleural pulmonary lobules. The lobular airway and homologous pulmonary artery enter the lobule centrally. The venous and lymphatic drainage run within the interlobular septa (From: Raoof et al (34)).

1.2.5.1 The Pulmonary Lobule on HRCT

HRCT manifestations of many pulmonary diseases may be better understood by relating the distribution of abnormalities to the components of the pulmonary lobule and, in particular, to the interlobular septa, the centrilobular and lobular parenchymal structures. The interlobular septa, as described previously (see section 1.2.3, page 19), form part of the continuum between the peripheral and axial interstitium. Within the septa run the peripheral lymphatics and veins. Normal interlobular septa have a thickness of $\sim 0.1\text{mm}$ in the periphery of the lung and so, generally remain below the resolution limits of HRCT (35). Pathological processes characterised by thickened interlobular septa on HRCT can be regarded as a sign of disease centred either on veins, the lymphatic systems or interstitium (for example pulmonary oedema, lymphangitis carcinomatosa or sarcoidosis; Figure 1.3) (18, 36, 37).

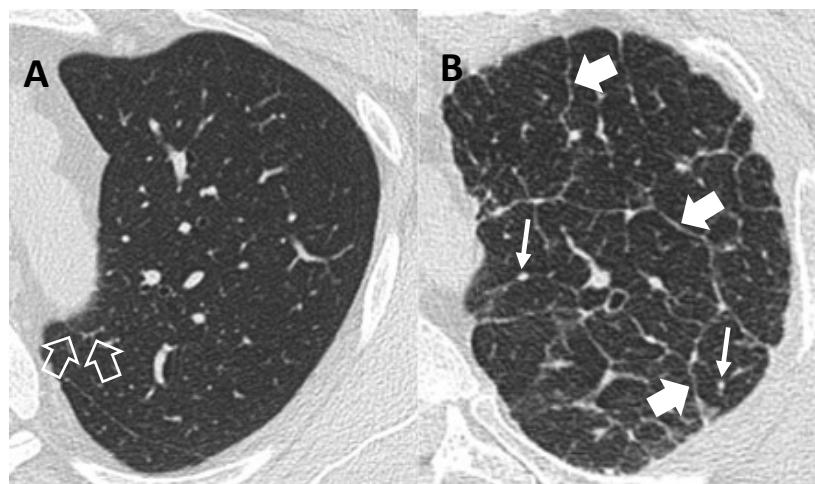


Figure 1.3 Targeted axial HRCT images through the left upper lobe in two patients: A) Normal lung with sub-segmental vessels and airways clearly seen; part of a pulmonary lobule is also visible with its thin inter-lobular septum (*open arrows*). **B)** Extensive interlobular septal thickening (*closed arrows*) in pulmonary sarcoidosis. The thickened septa highlight multiple pulmonary lobules. The lobular artery is visible as a 'dot' in a few lobules (*thin arrows*) but normal lobular airways are not visible.

The centrilobular region of the lobule contains the centrilobular bronchiole and accompanying artery. On HRCT, the centrilobular region is seen as a central 'dot' representing the lobular artery, which has a diameter of ~1mm (the limit of HRCT resolution). The walls of the lobular airways are too thin to be resolved and, in the absence of disease, generally not visible (18, 38). The lobular parenchyma refers to the functioning lung tissue surrounding the centrilobular region and is constrained by the interlobular septa. This tissue consists mainly of alveoli and the pulmonary capillary bed within the intralobular septa. Though these structures form a substantial component of the lung, they are often too small and lacking in contrast to be seen on HRCT (18, 19).

1.2.6 Pulmonary Vasculature

The lungs have a dual blood supply: the pulmonary arteries form the dominant supply of blood, while a smaller volume is received from the bronchial arteries. The main pulmonary artery, or pulmonary trunk, arises from the right ventricular outflow tract and divides into the right and left main pulmonary arteries. As with the airways, pulmonary arteries decrease in calibre as they become lobar, segmental and subsegmental vessels (39). The pulmonary arteries continue dividing in successive generations eventually supplying arterioles, pre-capillary vessels and ultimately the capillary bed (40). The capillary bed envelopes the alveoli and has a key role in gas exchange (41). After gas exchange, blood drains from the capillary bed through a series of venules and incrementally larger veins. It is worth noting that the pulmonary veins do *not* follow the centrilobular bronchovascular structures. Instead, venous channels course through the interstitium surrounding the

pulmonary lobule and join larger peri-segmental veins, which drain into the left atrium via the main (right and left) inferior and superior pulmonary veins (40, 42).

Bronchial arteries account for 1% of the cardiac output but play an important role in supplying the supporting structures of the lungs including the pulmonary arteries (43).

Bronchial artery anatomy is highly variable, with the most common configuration being two left sided arteries and one right sided artery arising from the descending thoracic aorta or intercostal arteries (43). They form a rich vascular network with corresponding pulmonary arteries at the level of the lobar and segmental bronchi. The majority of the bronchial artery supply drains via the aforementioned pulmonary venous system (40).

1.3 PATHOGENIC CONSIDERATIONS IN SARCOIDOSIS

Unravelling the pathogenesis of sarcoidosis is a challenge. The extant literature remains conflicted on how best to classify the pathogenesis of the disease, with many describing the condition as an 'immune paradox' (44-46). There has been speculation that sarcoidosis may have an auto-immune basis (46-49) while others have argued that the absence of a specific antigen/antibody reaction, the presence of anti-inflammatory cells within granulomas (46) and evidence of peripheral anergy (50) makes this unlikely. In the sections below the basic immunological responses in the human body are reviewed as relevant to sarcoidosis.

1.3.1 *Inflammatory & Immune Mechanisms in the Lung*

The inflammatory immune response in man is central to many disease processes and is a complex process involving a myriad of defence immune cells and chemical mediators (51-54). The immune response to pathogens is broadly divided into 'innate' and 'adaptive' pathways. The innate immune system is a non-specific, fast-acting process that detects antigens and attracts inflammatory cells to the region of concern. The lungs, and particularly the airways, are constantly exposed to inhaled pathogens and so immune regulation is particularly important. Dendritic cells and macrophages harboured in the airways, play a key role in the phagocytosis of antigens (55). In addition, these cells are responsible for triggering an immune cascade by secreting chemokines and cytokines promoting the accumulation of other inflammatory cells and also initiating the adaptive lymphocytic response (56).

Lymphocytes are present in abundance within the airway and lung parenchyma, and comprise two main populations: thymus-dependant (T) lymphocytes and bone-marrow dependant (B) lymphocytes (57). T lymphocytes are further subdivided into CD4+ (helper T cells) and CD8+ (cytotoxic T cells), with the former separated into Th1 and Th2 classes, based on their unique cytokine profiles (58). Th1 cells drive the cell-mediated immune response by producing pro-inflammatory cytokines such as IFN- γ and TNF- α , while Th2 cells produce cytokines which drive the humoral (antibody-mediated) immune response (59). It is important to note that there is constant interplay between the Th1 and Th2 systems, with each producing cytokines that may regulate one another (60). B lymphocytes are responsible for much of the humoral immunity by producing antibodies (immunoglobulins).

There has been a historical focus on the role of the adaptive immune response in the pathogenesis of sarcoidosis. For example, clonal proliferation of CD4⁺ T cells (61, 62) and dominant expression of cytokines TNF α and IFN γ is well-recognised and believed to be a defining feature of active sarcoidosis (63, 64). More recently, there has been some interest in the contribution of innate pathways to the pathogenesis of sarcoidosis. Increased levels of toll-like receptor 2 (TLR2) – an important innate receptor involved in antigen presentation – has been shown both in lung and circulating macrophages in patients with sarcoidosis (65, 66). Furthermore, TLR2 is expressed in lung epithelial cells and can be induced by TNF α and IFN γ (67), supporting the concept of an interplay between the adaptive and innate immune mechanisms in sarcoidosis. It perhaps goes without saying that there is a spectrum of inflammatory mechanisms at play with different components gaining dominance at different stages and some responsible for the development of chronic disease (68, 69).

1.3.2 Chronic Pulmonary Inflammation & Granulomatous Disease

The granulomatous diseases unsurprisingly involve the formation of granulomata. In many cases, granuloma formation is thought to be an antigen-driven process (70, 71). Circulating dendritic (antigen-presenting) cells identify and process pathogens, thereby triggering a cascade of immune responses, including Th-1 cell activation, B cell overactivity and immune complex formation. These foci of immunological activity recruit circulating monocytes into the lungs, where they differentiate into histiocytes and can coalesce to form multinucleated giant cells. Activation of histiocytes gives rise to the typical epithelioid appearance and, when arranged in compact groups, are recognised as granulomas. Granulomas are therefore ‘active’ sites, consisting of several enzymes, cytokines and various

immune cells (71). Histologically, granulomas are characterised by aggregates of epithelioid histiocytes, a peripheral cuff of lymphocytes and plasma cells and occasionally a necrotic core (Figure 1.4) (72-74).

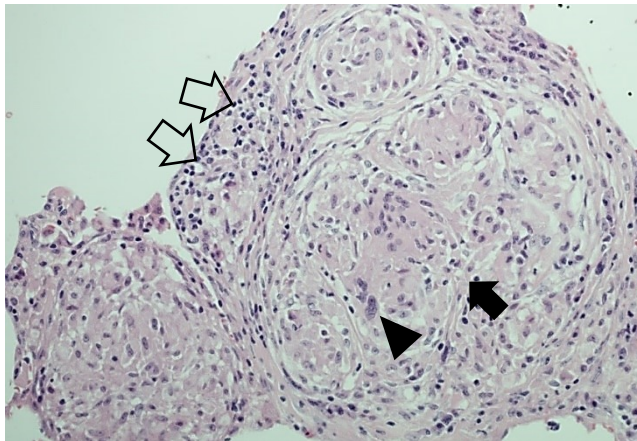


Figure 1.4 Classical non-necrotising granulomas in sarcoidosis (*solid arrow*; H&E stain; x200 magnification). Multinucleate giant cells (*arrowhead*) are flanked by a typical peripheral cuff of lymphocytes (*open arrows*). Image courtesy of Dr Alexandra Rice, Dept of Histopathology, Royal Brompton Hospital

It is noteworthy that the term 'granulomatous inflammation' covers a spectrum of findings, ranging from the focal granuloma described above to loose collections of inflammatory cells and histiocytes. It is also worth stressing that the presence of granulomas is a non-specific finding that may be encountered in myriad different scenarios: thus, necrotising granulomas may occur secondary to infections (e.g. mycobacterial or fungal), vasculitis (e.g. granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis), connective tissue diseases (rheumatoid arthritis) and other less common conditions (75-77). The differential diagnosis of non-necrotising granulomas is broad and includes sarcoidosis, hypersensitivity pneumonitis and pulmonary Langerhans' cell histiocytosis (78).

1.3.3 The Biology of Granulomata in Sarcoidosis

Non-caseating granulomas are the pathological 'calling-card' of sarcoidosis. However, the pathological appearances can vary depending on the stage of disease and disease activity (79-81). Non-granulomatous interstitial pneumonitis/alveolitis is frequently seen in the initial stages, and believed to be a forerunner of granuloma formation: a 'pneumonitis' is reportedly present in nearly two-thirds of open-lung biopsy specimens containing granulomas (82), is frequently present in transbronchial specimens (83) and is often accompanied by the presence of lymphocytosis on bronchioalveolar lavage (BAL), supporting its role in early inflammation (84).

With time, granulomas inevitably develop and are characterised by typical epithelioid aggregates, often surrounded by a peripheral mantle of lymphocytes. Immunohistochemistry studies have demonstrated that in sarcoid (as well as granulomatous infections), T-helper lymphocytes are present throughout the granuloma (84, 85). Importantly, while sarcoid granulomas are frequently described as non-necrotising, a variable degree of central necrosis is not unusual (81, 86). With more extensive necrosis, the pathological distinction from other diagnoses becomes more challenging (87). In addition, a variety of non-specific inclusions have also been demonstrated on histology, including Schaumann's (88), asteroid and Hamazaki-Wesenberg bodies (81).

In a subset of patients, there is progression to a fibrotic phenotype. Evidence suggests that cytokine profiles differ between the remitting and the progressive phenotypes, with higher TNF- α levels and lower TGF- β levels reported in the latter (89, 90). Furthermore, patients with progressive disease often show evidence of chronic activation of T effector cells, as evidenced by upregulated levels of PD1 (91). Despite identifying

differences in the cytokine milieu, the mechanisms driving the progression to fibrosis are poorly understood. For example, IFN γ levels have been shown to correlate with chronicity and severity in fibrotic sarcoidosis (92), despite this cytokine having an inhibitory effect on collagen deposition (90). Histologically, early fibrosis begins at the periphery of granulomas and serves to 'wall off' the active sites of disease. However, as deposition of collagen proceeds, there is more established mature fibrosis, obliterating the parenchyma and contributing to the functional decline (93).

1.4 PATTERNS OF INTRA-THORACIC DISEASE IN SARCOIDOSIS

An appreciation of the pathological distribution of disease in sarcoidosis has an important bearing on imaging features. In the following section, the common patterns of distribution are discussed.

1.4.1 *Nodal, Lymphatic & Parenchymal Sarcoidosis*

The commonest thoracic manifestation of sarcoidosis is lymph node enlargement, seen in up to 95% of cases at some stage and classically in a symmetrical hilar distribution with or without mediastinal involvement (94). Bilateral hilar and right paratracheal nodal enlargement, the so-called 'Garland Triad' (Figure 1.5), is another commonly recognised pattern of disease (95). With regard to parenchymal disease, sarcoid granulomata have a predilection for the bronchovascular bundles (Figure 1.6) and fibrous septa containing the pulmonary veins and lymphatics. In this way, granulomatous infiltrates characteristically follow a lymphatic distribution (96).

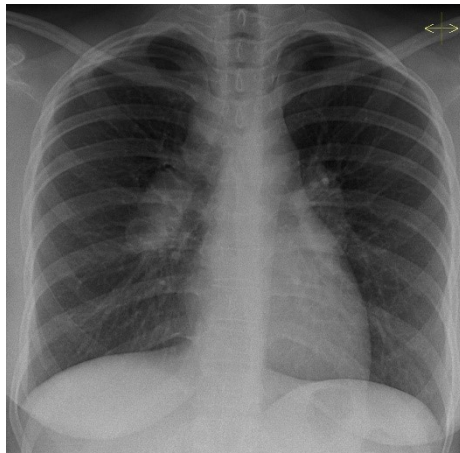


Figure 1.5 PA chest radiograph of a patient with typical bilateral hilar and right paratracheal nodal enlargement ('Garland Triad').

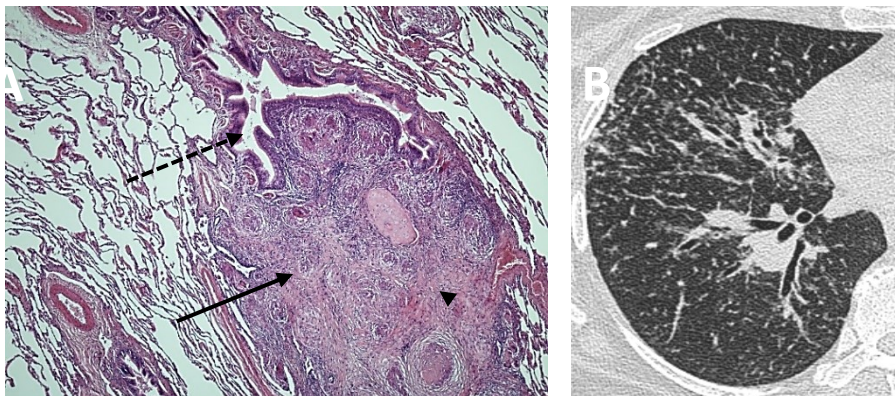


Figure 1.6 Histopathological and radiological findings in two patients with classical peribronchovascular disease: A) Haematoxylin and Eosin, viewed at x40 magnification, of a non-necrotising granuloma (solid arrow) adjacent to a bronchiole (dotted arrow) with evidence of early fibrosis (arrowhead). Image courtesy of Dr Alexandra Rice, Dept of Histopathology, Royal Brompton Hospital. B) HRCT axial section demonstrating peribronchovascular, perifissural and subpleural micronodules

In the nodular form of sarcoidosis patients present with characteristic peribronchovascular, subpleural and septal micronodules (97). Less commonly, granulomas may coalesce to form larger masses, mimicking alveolar consolidation (Figure 1.7) (97).

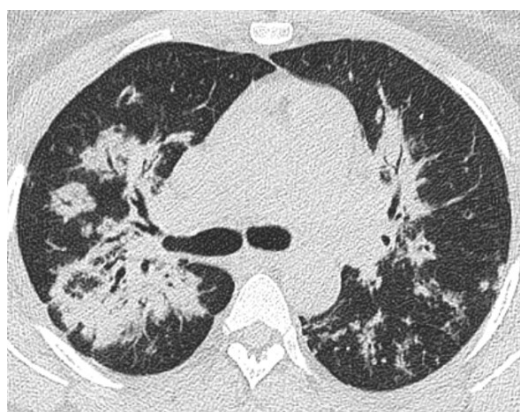


Figure 1.7 Axial slice of a HRCT demonstrating alveolar consolidation representing coalescent non-necrotising sarcoid granulomas

1.4.2 Airway Involvement in Sarcoidosis

Sarcoidosis may affect both the upper and lower airways. Sarcoidosis of the upper respiratory tract includes nasopharyngeal, laryngeal and tracheal disease and occurs in approximately 2-3% of sarcoidosis patients; sinonasal and laryngeal disease accounts for most cases (98, 99) and generally presents with non-specific symptoms (e.g. nasal 'stuffiness' or blockage) (98) while laryngeal sarcoidosis presents with more typical upper airways symptoms of hoarseness, dysphagia and in severe cases, stridor (100). Tracheal sarcoidosis is rare and descriptions are limited to a few case reports (101, 102). Symptoms are related to either tracheal stenosis (102) or tracheal dystonia (i.e. tracheal collapse on expiration) manifesting as dyspnoea, wheeze and/or stridor (101).

Bronchial involvement in sarcoidosis was first described at autopsy by Bernstein et al in 1929 (103). A number of cases have been reported since then (104) and the presence of submucosal granulomas on endobronchial biopsy is now recognised as a common finding (105). Despite the prevalence of endobronchial granulomas, disease is rarely severe enough to cause symptoms (106) although, not surprisingly, symptomatic disease is seen if granulomatous inflammation and oedema result in airway narrowing (107): a retrospective study of 2500 patients identified bronchial narrowing of >50% in only 0.7% of sarcoidosis cases (108). By contrast, bronchial distortion is a feature commonly seen in the later stages of sarcoidosis, where extensive granulomatous infiltration and traction bronchiectasis, secondary to fibrosis, result in airway distortion (109, 110).

Small airways disease is an underappreciated manifestation of pulmonary sarcoidosis and is best identified on expiratory phase CT scans (111). On HRCT obstructive small airways disease manifests as a mosaic attenuation pattern (112), the extent of which

correlates with an obstructive lung function profile (113, 114). Patients with small airways disease most frequently present with worsening dyspnoea, cough and wheeze (115).

1.4.3 Vascular Involvement in Sarcoidosis

The occurrence of vascular disease in sarcoidosis warrants brief discussion. In a study of 128 open lung biopsies, just under 70% had evidence of granulomatous pulmonary angiitis and small vessel occlusive disease (116). These findings mirrored those of a subsequent post-mortem study, in which vascular involvement was related to the extent of parenchymal disease (117). Although sarcoid granulomas are seen in small and large vessels alike, a systemic vasculitis is generally considered rare (118). In the entity of necrotising sarcoid granulomatosis, there are sarcoid-like granulomas, necrosis and vasculitis. However, this is rare and poorly-understood, with current consensus that this is either a subtype of sarcoidosis or possibly a separate disease entirely (119).

The above notwithstanding, pulmonary hypertension is an increasingly recognised complication of sarcoidosis and a harbinger of increased mortality (120). The true prevalence of sarcoidosis-associated pulmonary hypertension (SAPH) is unclear, but estimates range from 5.7% of unselected patients (121) to 74% in patients with end-stage fibrosis (122). Nunes et al., found that pulmonary artery hypertension may be present even in patients with early-stage sarcoidosis (i.e. with limited parenchymal involvement), supporting the theory that interstitial lung disease alone cannot account for the development of SAPH (123). The pathophysiology of SAPH is uncertain; indeed even in the World Health Organization (WHO) classification, SAPH is categorised as ‘pulmonary

hypertension with unclear multifactorial mechanism' (124). That said, it is postulated that causes of SAPH can be categorised as either 1) pre-capillary causes: due to destruction of the distal capillary bed, vasculopathy, veno-occlusive disease and extrinsic compression of pulmonary vessels or less frequently, 2) post-capillary sarcoid-associated left ventricular dysfunction (125).

1.4.4 Pleural Disease

Clinically-relevant pleural disease is uncommon in sarcoidosis. That said, granulomatous involvement of the visceral pleura appears to be common on histopathological examination (126). Pleural sarcoidosis with effusions is certainly uncommon, reportedly occurring in under 5% of cases (127, 128) and, it must be stressed that the presence of an effusion does not necessarily equate with pleural involvement *per se*: hence, in a study of 181 patients with sarcoidosis, Huggins et al. found five patients with pleural effusions and, of these, only two were confirmed secondary to pleural sarcoidosis (127). Furthermore, a proportion of pleural effusions in patients with sarcoidosis are confirmed biochemically to be transudates and are therefore probably best explained by cardiac involvement and consequent failure (129).

1.5 EPIDEMIOLOGY OF SARCOIDOSIS

1.5.1 Global Incidence & Prevalence

Sarcoidosis has a worldwide prevalence. Methods to estimate incidence and prevalence vary considerably but, that said, it is believed that there are notable geographic

differences (130). Arkema and colleagues (131) analysed population data from the Swedish National Patient Register and reported an incidence of 11.5/100,000 per year and a prevalence of 160/100,000. European estimates of incidence and prevalence are significantly lower (132, 133): for example, in the UK there are approximately 5/100,000 new diagnoses per year (134). In addition to geographical variations there are important ethnic differences (135). A recent population-based study by Baughman and colleagues (136) examined the US National Healthcare database and reported an incidence of 17.8/100,000 per year in African-Americans, compared with 8.1/100,000 per year in white individuals and 3.2/100,000 per year in Asians. The higher incidence among African-Americans echoed the findings of a previous American cohort study, in which a fourfold higher incidence (compared with Caucasians) was reported (137). The reasons for such racial differences remain unclear. One possible explanation may be in the relative profusion of granulomata: Burke et al. found a significantly higher density of granulomata among African-Americans compared with their Caucasian counterparts, even after adjusting for CXR stage (138). The authors proposed that such a difference may reflect a more intense immune reaction to an, as yet unidentified antigen, among African-Americans, consequent on complex genetic associations underlying sarcoidosis (139-141).

Differences in socioeconomic status may also be important (142). The American Thoracic Society (143) and the American College of Chest Physicians in a 1995 Working Group report (144) have previously highlighted racial and ethnic differences in a variety of lung disorders related to variables including socioeconomic status. Factors such as occupational exposures, housing and lifestyle have also been implicated in the development and severity of sarcoidosis and are indirectly linked to ethnicity (145).

1.5.2 Age and Sex

Data on the age and sex predilection for sarcoidosis also vary. In some studies, the rate of sarcoidosis is reportedly higher among women (135, 146). For instance, Hillerdal and colleagues found an incidence rate of 21.7 per 100,000 per year among women, compared with 16.5 per 100,000 per year among men (146). They also showed that older women were more likely to have symptomatic disease. Similarly, in a study of newly-diagnosed sarcoidosis, conducted over 5 years, there was a higher incidence among African-American women compared with men (39.1 versus 29.8 per 100,000 per year respectively) (135). By contrast, several other studies have found no gender difference (134, 147-149). Interestingly, there is also emerging evidence suggesting that the age of disease onset may vary by sex. A number of European studies have reported an earlier age of onset among men, by as much as a decade (146, 150-153). The reasons for this difference are poorly-understood, but theories include differences in occupational exposures and also the potential influence of hormonal protection in women (154).

Another point of interest is the reported increase in the peak age of disease onset. For example, Arkema et al conducted the largest population-based epidemiology study in sarcoidosis and found that the peak age of incidence is now 30-55 years (130, 131), contrasting with the 20-45 year peak quoted in the 1999 Sarcoidosis Consensus Statement (155) and also supported by older epidemiological studies (146). The reasons for these changes are unclear. However, Arkema and colleagues have suggested that the differences might be attributable to variations in study design. For example, earlier studies from the 1900's had adopted less reliable mass radiographic screening methods to assess disease incidence and perhaps not surprisingly, revealed lower rates of screening for older subjects

(146, 156). An ageing population may also explain the rise in peak incidence. However, against this, a recent retrospective Japanese study demonstrated that even when adjusting for population dynamics, the age of disease onset had increased over the 40 year study period (157). In addition, there seem to be racial differences in the age of presentation. Rybicki et al observed an annual peak incidence of 107 per 100,000 among African American females aged 30-39 years and 89/100,000 among African American males aged 30-39 years. By comparison, the peak incidence in Caucasians was a decade later (40-49 years) (135). In addition to presenting at a younger age, African Americans presented with more advanced disease (135).

1.5.3 Mortality

The quoted mortality rate in sarcoidosis varies from <1% to 8%, depending on multiple factors including age, ethnicity, site and severity of disease (134, 158, 159). In England, studies of national death certificate data from 2008 reported an age-adjusted 'all-cause' mortality of 4.2 per million but with 2.3 per million directly attributed to sarcoidosis (160). An almost identical rate is evident from US data (161). By contrast, an older study of a Japanese cohort demonstrated a significantly lower mortality of 0.1 per million (162); interestingly, sarcoid-related mortality in Japan is primarily attributed to cardiac involvement which contrasts with data from US and Europe, where respiratory complications appear to predominate (163).

A US-based population study by Swigris et al., found an increase in the age-adjusted mortality rate over time (161). In this study, the greatest increase was among non-Hispanic African-American females, in contrast to a recent population study by Mirsaeidi and

colleagues, which found that mortality was undoubtedly highest in African-Americans, but with a rate that has remained unchanged over the studied 12-year period, in contrast to the Caucasian population in whom rates have increased (164). The reasons for the described mortality trends are not entirely apparent although changes in coding practices, variable disease severity and an ageing population are likely contributory factors (163).

1.6 RISK FACTORS FOR SARCOIDOSIS

Despite its recognition as a disease entity in the late 19th Century, the aetiology and pathogenesis of sarcoidosis have never been fully elucidated. However, analysis of the data accrued to date provides some glimpse into the possible risk factors.

1.6.1 Obesity

The Black Women's Health Study of nearly 60,000 African-American women declared that obesity at baseline (defined as a body mass index [BMI], over 35 kg/m²), at 18 years of age, was associated with an increased risk of sarcoidosis over a 16-year observation period (hazards ratio, HR=1.42, 95% CI=1.07–1.89), when compared to those with a normal BMI of 20-25 kg/m² (165). In a similar fashion, a subsequent study examined the role of obesity in 116,000 predominantly white females and again found a markedly increased risk of disease among obese individuals (HR=1.74; 95% CI 1.26–2.40) (166). Both studies also demonstrated that from the age of 18, a cumulative weight gain of 25kg in the African American population and 30kg in a predominantly Caucasian cohort, were associated with an increased risk of sarcoidosis. The mechanisms by which obesity increases the risk of

developing sarcoidosis is unclear. However, one hypothesis is that the pro-inflammatory state reported in obesity drives granuloma formation (167, 168).

1.6.2 Smoking

The role of smoking in the pathogenesis of sarcoidosis has long been questioned. In one multicentre study of 706 newly-diagnosed sarcoidosis patients and matched controls, the ACCESS research group demonstrated that 'ever-smoking' was associated with a 35% reduction in the odds of developing disease (Odds ratio, OR=0.65, 95% CI 0.51-0.82) (169). Similarly, a more recent case-control study by Ungprasert et al, identified a lower risk of sarcoidosis in current smokers (OR=0.34, 95%CI=0.23-0.50) compared with non-smokers, while former smokers had a similar risk to that of non-smoking subjects (OR=0.68; 95% CI=0.45–1.01) (170). Interestingly, in another retrospective study smoking was a risk factor for ocular sarcoidosis (OR=5.25, 95% CI=1.58-17.41). However, the results were based on a relatively small sample size (171). The mechanism by which smoking might protect against granulomatous diseases is unclear. Blanchet et al performed an *in vivo* study of mouse models and observed that exposure to nicotine reduced the release of tumour necrosis factor, and IL-10 and IFN- γ expression in hypersensitive environments (172). The authors concluded that the inhibitory effect of nicotine may, at least partly, account for the protective effect of smoking in hypersensitivity pneumonitis and, indeed, this may be a shared mechanism with sarcoidosis.

Importantly, not all studies have revealed a negative association with smoking and sarcoidosis onset. For instance, in a case-control study including 98 patients with newly diagnosed sarcoidosis, Gupta and co-workers found no significant association with smoking

or environmental smoke exposure and sarcoidosis (173). Interestingly, another case control study of 60 patients, while demonstrating that sarcoidosis occurred more frequently in smokers, found no difference in the extent, course or outcome of disease between smokers and non-smokers (174).

1.6.3 Occupational Exposures

The notion that sarcoidosis might be a response to an, as yet, unidentified inciting agent is logical. Accordingly, in the ACCESS study, environmental factors that predispose to sarcoidosis were investigated (169). The study reviewed a list of potential exposures including insecticides, birds, home/work air conditioning and mould, as putative aetiological agents. The findings were intriguing if not entirely illuminating! For example, 'musty odors' at work increased the risk of sarcoidosis 1.6 times, a finding supported by a subsequent sibling study which identified a 78% increased risk of sarcoidosis (OR, 1.78; 95% CI, 1.32 to 2.40) in those exposed to musty odours for >1 year (175). The mechanism by which mould and damp induce sarcoidosis has yet to be defined, but one theory is that fungal cell walls trigger an exaggerated immune response leading to granuloma formation (176).

The potential role of dust particles in the pathogenesis of sarcoidosis has also been explored. In this regard, studies of 9/11 World Trade Centre emergency staff and construction workers have shed some light on this field (177-179). Jordan et al., demonstrated that individuals involved in the more intensive rescue and recovery activities had an increased risk of sarcoidosis, while exposure to the dust-cloud alone (a highly-alkaline mixture comprising concrete, gypsum, anhydrite and many man-made fibres (180)), was not considered a risk factor (179). Other potential occupational dust exposures have

also been suggested. For instance, two large Swedish studies found an association between silica exposure and sarcoidosis (180, 181). Importantly, these studies did not outline the method by which patients were defined as having sarcoidosis and so, it is not clear how the diagnosis was made in the presence of significant silica exposure. Indeed silicosis has a clinical presentation not dissimilar to sarcoidosis with clinicians having to resort to a detailed occupational history and steroid-responsiveness to distinguish between the two (182, 183). Similarly, a study of death certificates over a 10-year period in the USA found that metal workers had a higher sarcoidosis mortality odds ratio compared with other occupations, perhaps signifying the importance of metal dust exposure (184).

Overall then, although associations vary from study-to-study, there is a general consensus that occupational exposures to inorganic airborne respiratory irritants may be important in the aetiology of sarcoidosis.

1.6.4 Infection

In much the same way as with occupational factors, the possible aetiological role of infection needs considering. Indeed, possible linkages between sarcoidosis and mycobacterial infection have long been postulated. A recent meta-analysis examined 58 case-control studies using cytological and histological methods to analyse the presence of infectious organisms in tissue from patients with sarcoidosis (185). The authors demonstrated that mycobacterial species (OR 6.8, 95%CI 3.73-12.39) and *Propionibacterium acnes* (OR 18.80, 95% CI 12.62-28.01) were both significantly associated with the development of sarcoidosis. Given the superficial similarity of histopathological findings and the occasional presence of mycobacterial remnants in sarcoidal tissue *Mycobacteria*

tuberculosis complex and non-tuberculous variants have been implicated in the pathogenesis of sarcoidosis (185, 186). Furthermore, historical reports of mycobacterial disease existing contemporaneously or preceding the onset of sarcoidosis have supported this theory (187-190). That said, to this day, a causal link between mycobacterial infection and sarcoidosis remains a matter of conjecture.

Seasonal variations in the incidence of sarcoidosis have been reported. For example, a study by Ungprasert and colleagues identified new diagnoses of sarcoidosis over a 37 year period and found that the age and sex-adjusted disease incidence was lowest in autumn and highest in winter (191). The authors concluded that the observed seasonal differences may be related to variation in unidentified environmental antigens. They also proposed that sunlight exposure might account for some of the variation due to its role in upregulation of vitamin D3 and calcium levels (192). However, this does not explain why the incidence rate was higher in winter than in summer. Furthermore, results from other studies are somewhat discordant, with some having observed a higher incidence of sarcoidosis in different seasons (193, 194), while another observed no seasonal variation at all (195).

1.6.5 Genetic Associations and Familial Sarcoidosis

Familial clustering in sarcoidosis was first recognised in 1923 by Martenstein (196) and has been reported frequently since (197-199). Indeed, international surveys report that just over 10% of cases in the Netherlands (200) and up to 6% of cases in the UK are familial (201). A familial predisposition has understandably spawned a search for genetic associations in sarcoidosis. A large twin study in a Danish and Finnish population showed that, compared with the general population, monozygotic twins with an affected co-twin

had an 80-fold increased risk of developing sarcoidosis, compared with a 7-fold increased risk among dizygotic twins (202). The finding that monozygotic twins are more often synchronously affected than dizygotic twins supports the notion that genetic susceptibility may be important in the pathogenesis of sarcoidosis. Moreover, as discussed previously, racial difference in sarcoidosis prevalence may also be related to genetic susceptibility, although race-related health differences must be interpreted with caution due to confounders including environmental exposures and socio-economics status (203).

Though a detailed discussion of the genetic associations in sarcoidosis is beyond the scope of this thesis, it is worth reviewing a few of the key findings in the literature and, in this regard, 'candidate gene' studies are important. This methodology involves exploring associations with candidate genes selected based on their suspected role in pathogenesis (204). In sarcoidosis, the human leukocyte antigens (HLAs) have been the centre of gene association studies given their role in antigen presentation and granuloma formation. Based on these studies, a number of HLA haplotypes have been implicated: for example, HLA-A1 (205) and HLA-B8 (205, 206) have been linked to sarcoidosis susceptibility, while HLA-DR3 (207) and HLA-DQ2 (208) are associated with the acute form of sarcoidosis with a better prognosis. In addition, a number of non-HLA candidate genes have also been identified, such as the angiotensin-converting enzyme gene (209) and specific chemotactic agent genes (210, 211). More recently, genome wide association studies (GWAS) have become the method of choice for genetic studies, allowing the identification of associations irrespective of disease mechanism (212). A number of chromosomal regions have been identified as possibly linked to sarcoidosis susceptibility. However, research is on-going and the exact clinical significance of these findings has yet to be elucidated (213-215).

It is clear then that, while there is undoubtedly a familial component to sarcoidosis, no single gene has been attributed to disease onset. Instead, it seems highly likely that genetic susceptibility may result from a complex interplay between several candidate genes.

1.7 CLINICAL CONSIDERATIONS IN SARCOIDOSIS

Sarcoidosis is the archetypal granulomatous multi-system disorder. The pattern of organ involvement and severity of disease inevitably dictates the clinical presentation. In this regard, a discussion centred on key clinical features, diagnosis, pulmonary function and imaging is pertinent.

1.7.1 *Clinical Presentation*

It is salutary to note at the outset that just under half of all patients with sarcoidosis are entirely asymptomatic, sometimes presenting serendipitously because of incidental findings on radiographs (216). In these cases, hilar nodal enlargement is generally the predominant finding, with occasional pulmonary infiltrates also recognised (94). Non-specific constitutional symptoms, including fatigue, low-grade fever, malaise and weight loss are reported by around 1/3 of patients (155). Not surprisingly therefore, diagnosis is often delayed or not infrequently, missed (217). With this in mind, the ATS/ERS/WASOG Sarcoidosis Consensus Statement proposes that the presence of such symptoms, along with an unexplained cough and shortness of breath, should prompt investigations for sarcoidosis, particularly for patient groups with a known high prevalence of sarcoidosis (e.g. African-Americans and Scandinavians) (155). In the remainder, symptoms tend to be organ-specific.

In this regard, because lung involvement is by far the most common manifestation, pulmonary symptoms dominate (218). Accordingly, the clinical manifestations of sarcoidosis have traditionally been divided into those that are pulmonary from others that are extra-pulmonary. Against this, a recent European multicentre study examined 2163 Caucasian patients with the aim of identifying disease phenotypes in sarcoidosis. The investigators found that, based on patterns of organ involvement, clinical presentation could be 'clustered' into the following groups: musculoskeletal-cutaneous, pulmonary and intrathoracic nodes, abdominal (renal/splenic/hepatic), ocular-cardiac-cutaneous-CNS, and extrapulmonary sarcoidosis (219).

1.7.2 Lung disease in sarcoidosis

Pulmonary involvement in sarcoidosis occurs, to a greater or lesser degree, in ~90% of patients and overwhelmingly accounts for the morbidity and mortality. Respiratory symptoms, when present, include breathlessness, cough and chest pain which trouble 30-50% of patients and, perhaps not surprisingly, tend to be more severe in those with extensive parenchymal and airway involvement (155). In contrast to other fibrotic interstitial lung diseases, features such as inspiratory crackles and finger clubbing are uncommon. Pleural effusions, pneumothoraces and pleural thickening are uncommon findings (94).

The severity of pulmonary disease varies considerably: at the mild end, patients may be entirely asymptomatic and, as mentioned above, only identified incidentally on radiographs or occasionally biopsy, performed for another reason. With more severe disease (which occurs in approximately 5%), there is advanced pulmonary fibrosis and this

accounts for most of the morbidity and mortality (220, 221). Mycetomas and pulmonary hypertension are frequent complications of end-stage fibrotic disease and also harbingers of increased mortality (222-224). Sarcoid associated pulmonary hypertension (SAPH) is an increasingly recognised complication of end-stage pulmonary fibrosis and is particularly prevalent in patients with chronic exercise intolerance (225). SAPH should be considered in patients with worsening hypoxaemia and reduction in diffusing lung capacity for carbon monoxide (Dlco) disproportionate to the amount of pulmonary disease.

Mycetomas are masses of fungal — most frequently *Aspergillus* — mycelia that occupy intrapulmonary cavities and are reported in ~2% of patients with advanced pulmonary sarcoidosis (226, 227). Many mycetomas are quiescent and only identified on imaging. However, occasionally mycetomas can present with life-threatening haemoptysis (224, 228). Although chronic pulmonary aspergillosis is associated with a worse prognosis in patients with sarcoidosis, the reduced survival is attributable to the associated severe fibrosis, rather than the fungal disease itself (229). Indeed, deaths from mycetoma-related life-threatening haemoptysis are rare (230) although admittedly, survival data in this cohort of patients are noticeably lacking.

1.7.3 Lymphoid System

Intra-thoracic lymph node enlargement is one of the ‘trademark’ pathological and radiological features of sarcoidosis: bilateral hilar lymph node enlargement (BHL), alone or with mediastinal involvement (figure 1.5), is seen in as many as 95% of patients (94, 95, 158). That said, this finding is not confined to sarcoidosis and it is important to consider fungal disease, mycobacterial infection and malignancy (particularly lymphoma) as

alternative diagnoses. Importantly, a study of 100 patients with BHL found that in the absence of symptoms, the diagnosis is almost always sarcoidosis (231). Needless to say, other patterns of nodal enlargement also occur. Thus, in a radiographic study of 62 patients, 75% of patients had nodal enlargement within right paratracheal or aortopulmonary stations, while 20% had subcarinal or anterior mediastinal involvement (95). Bilateral hilar and right paratracheal nodal enlargement – the so-called ‘Garland Triad’ – was the commonest pattern of involvement, seen in 37% of cases (95).

Sarcoid nodal enlargement is not always limited to the mediastinum; indeed extra-thoracic lymph node enlargement has been observed in up to one third of patients (232). Importantly, when nodal involvement is extensive, sarcoidosis can be difficult to distinguish from lymphoma. To add further complexity, lymphoma and sarcoidosis can co-exist, although there are conflicting views on the prevalence of sarcoidosis-associated cancer (233, 234). Importantly, the presence of lung disease, respiratory symptoms, high angiotensin converting enzyme (ACE) levels and asymptomatic BHL seem to favour a diagnosis of sarcoidosis, although in cases with uncertainty, histological assessment is mandatory (235).

Nodal calcification is common in sarcoidosis and its presence is linked with chronicity. Nodal calcification is seen in 3% of cases after 5 years and 20% after 10 years (236). Interestingly, the frequency of nodal calcification in sarcoidosis is comparable to that of tuberculosis, although, the ‘pattern’ and distribution of calcification differs (Figure 1.8). In sarcoidosis, calcification is most frequently focal, while in TB the entire lymph node is involved and nodes are often reduced in size due to necrosis (237). So-called ‘egg-shell

calcification' is an infrequent finding in both conditions and is more commonly seen in silicosis and coal workers' pneumoconiosis (238).

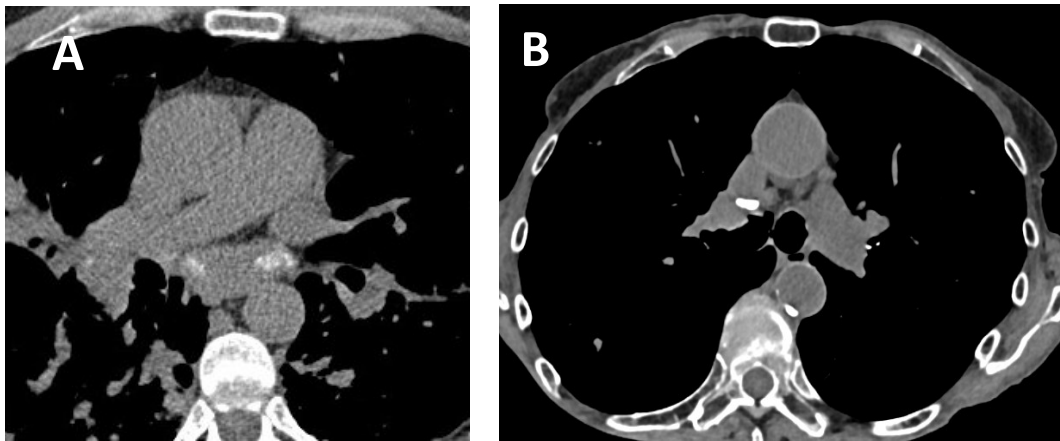


Figure 1.8 Nodal calcification in sarcoidosis and tuberculosis. (A) CT image below the level of the carina in sarcoidosis. There is classical 'milky' or 'icing sugar' calcification in enlarged nodes contrasting with **(B)** a patient with a history of previous tuberculosis; note that the small node is completely calcified and of higher density than in sarcoidosis.

Perhaps not surprising, given its role in the reticuloendothelial system, splenic involvement is frequently demonstrated on autopsy in patients with sarcoidosis. However, clinical disease related to splenic involvement is rare (239).

1.8 DIAGNOSIS & ASSESSMENT IN SARCOIDOSIS

Based on the 1999 International Consensus Statement, there are three principle criteria for securing a diagnosis of sarcoidosis: i) a compatible clinical picture, ii), histological demonstration of non-caseating granulomas and iii) exclusion of other diseases masquerading with the same clinical and histological findings (155). In 2020, two major sarcoidosis diagnostic guidelines were published: firstly, the British Thoracic Society (BTS) Statement on pulmonary sarcoidosis (240) and the Official American Thoracic Society (ATS)

Guidelines for Sarcoidosis (182). If nothing, these documents, published over 20 years after the 1999 statement, highlighted the striking paucity of evidence-based literature in sarcoidosis. Indeed, much of the guidance is based on expert opinion and experience. An important change in the BTS guideline is that, with typical CT findings and presenting symptoms, a confident diagnosis of sarcoidosis can be made without the need for biopsy confirmation (240). Similarly, the statement suggests that radiographic appearances supporting a clinical diagnosis of Lofgren's syndrome negate the need for histological confirmation even in the absence of CT (240). By comparison, the ATS guidelines focus on areas of uncertainty around detection and diagnosing sarcoidosis (182). Surprisingly, this guidance provides no recommendation on the imaging diagnosis of *pulmonary* sarcoidosis, instead concentrating on the role of lymph node sampling and the detection and evaluation of extrapulmonary disease (182).

The above notwithstanding, identifying a '*compatible clinical picture*' is critical for securing a sarcoidosis diagnosis. More often than not, this is dependent on a combination of clinical suspicion (essentially reliant on clinician experience) and results of specific investigations (Table 1.1). Pulmonary functions tests are almost *de rigueur* in the assessment of patients with suspected sarcoidosis. Functional evaluation at presentation is important not only to ascertain the severity and 'pattern' of functional impairment (obstructive versus restrictive versus mixed) but also as a baseline for follow-up (155, 240).

According to the recent BTS statement, imaging tests plays an important role at diagnosis and, where indicated, follow-up (240). Plain chest radiography (CXR) and particularly high-resolution computed tomography (HRCT) are usually requested to document the presence and extent of pulmonary disease. Furthermore, radiographic

appearance can influence biopsy decisions, with guidance suggesting that typical stage I and II disease can be sufficient for diagnosis without histology (155). While there is no specific guidance, HRCT is commonly requested at baseline in addition to CXR, to confirm the presence of lung disease, to characterise disease more accurately (see section 1.11.3, page 68) and to quantify its extent (241).

Recommended Initial Assessment of Patients with Sarcoidosis	
1)	History (including comprehensive occupational & exposure history)
2)	Physical Examination
3)	Full blood count (white blood cells, red blood cells, platelets)
4)	Serum biochemistry (urea and electrolytes, calcium, liver function tests, creatinine)
5)	Serum ACE levels
6)	12-lead ECG
7)	CXR for all patients
8)	HRCT if there is clinicoradiological discordance or atypical clinical/radiographic findings
9)	Consider PET-CT to assess 'disease activity' in cases where there is diagnostic uncertainty, particularly when cardiac sarcoidosis is suspected
10)	Cardiac MRI and echocardiogram if cardiac sarcoidosis is suspected
11)	Ophthalmic review if there are eye symptoms

Table 1.1 Summary of recommended baseline evaluation from the 2020 BTS Clinical Statement (240). ACE = angiotensin converting enzyme, ECG = electrocardiogram, CXR = chest X-ray, HRCT = high-resolution CT, PET-CT = positron-emission tomography CT.

1.9 NATURAL HISTORY & PROGNOSIS IN SARCOIDOSIS

The clinical course of sarcoidosis varies considerably, making management challenging. That said, the majority of patients with sarcoidosis generally have a favourable outlook (1, 146, 242, 243). In one study of 960 sarcoidosis patients, there was spontaneous remission in 62% and a further 19% improved on corticosteroid treatment (244). The remaining 19% developed chronic or progressive disease, but importantly, only 15% of these patients had received treatment (244). In a more recent subset analysis of 205 patients with biopsy-proven sarcoidosis from the ACCESS study, 46% were not on treatment at baseline and of those on treatment, only 47% remained so at 2-year follow-up (245). Relapse in sarcoidosis reportedly ranges from 13-74% (246, 247). In most cases, relapses typically occur within 1 month to 1 year of treatment being reduced or discontinued (248). However, studies of disease recurrence are limited by disparities in the definition of relapse. For example, in some cases, 'recurrent disease' may be considered an acute exacerbation (249), while in others the disease may have merely been suppressed by the medication and never really been under remission *per se* (248).

The clinical 'phenotype' in sarcoidosis may provide clues to prognosis. For instance, in acute sarcoidosis, presenting as Lofgren's syndrome, prognosis is excellent with over 90% of patients undergoing spontaneous remission (250) and, in the absence of systemic symptoms, these patients may be managed without treatment (240). The Scadding CXR stage, may also provide prognostic information (see also section 1.11.1.3, page 58) (1): Scadding himself showed that higher radiographic stage — characterised by pulmonary infiltrates and signs of fibrosis — were associated with a lower likelihood of radiographic resolution at five years (1). A more recent study of 212 patients showed that, although

infrequent, progression from a lower to higher CXR Stage was associated with higher mortality (251). Importantly, even among those with chronic disease, it is generally only the 5% of patients with the most severe fibrotic disease (sometimes co-existent with pulmonary hypertension) who account for the greatest morbidity and mortality in sarcoidosis (220, 221). A study of death certificates in the United States also reported higher mortality in older patients with sarcoidosis and in those of African-American heritage (161); an explanation for the former perhaps is the higher prevalence of co-morbidities (251). Swigris et al also suggested that age may be an independent risk factor for pulmonary fibrosis in sarcoidosis (161).

1.10 FUNCTIONAL EVALUATION IN SARCOIDOSIS

It goes without saying that functional tests are central to clinical management. The patterns of functional impairment in patients with sarcoidosis vary considerably: impairment of gas transfer (252), as well as restrictive (123, 253, 254), obstructive (112, 114, 123, 253-256), and mixed (257, 258) patterns are all reported. In non-fibrotic (i.e. CXR stages I to III) disease, pulmonary function tests (PFT) are most commonly normal (240, 259, 260). In those with abnormal lung function, the most frequent pattern of abnormality is a reduction of gas transfer, or more specifically, the diffusing capacity of the lung for carbon monoxide (DLco) (260-262). While a depression of DLco usually indicates parenchymal disease (252) it is important not to forget that, in sarcoidosis, this may also reflect pulmonary vasculopathy (225). Accordingly, a falling DLco in the context of otherwise stable parenchymal disease should raise the suspicion of sarcoidosis-associated pulmonary hypertension (240).

A restrictive pattern is the commonest deficit on spirometry (253), observed in two-thirds of patients with advanced (stage IV) disease. Obstructive and mixed patterns are also recognised, occurring in one-third and a fifth of advanced cases respectively (263). In sarcoidosis, the pathophysiology of obstruction is debated. One proposition is that endobronchial granulomatous infiltration and airway hyper-reactivity drives airway obstruction (264). Of interest, in this regard, was the finding by Hansell et al that airflow obstruction was most strongly linked with the CT extent of reticulation (generally a marker of *interstitial* lung disease) (114). Thus, *they* concluded that the extent of fibrosis was the most important determinant of airflow obstruction in sarcoidosis. Despite these mixed signals, suffice to say, an obstructive pattern has been associated with increased morbidity, stage IV disease and a poorer outcome (255). In addition to DLco, forced vital capacity (FVC) may be useful in monitoring disease progression in sarcoidosis (240). Although there are no agreed thresholds defining a significant change, a reduction of 10% from baseline is generally considered an appropriate threshold for decline in lung function (240).

The prognostic value of functional tests in sarcoidosis has been explored. Lamberto and colleagues examined PFTs in patients stratified according to CXR severity and saw that, irrespective of the presence or absence of fibrosis, resting DLco was a strong predictor of exercise-induced desaturation (265). The percentage predicted DLco is the best single correlate of disease severity/extent in ILD (266) and is known to be predictive of mortality in IPF (267). Moreover, a disproportionate reduction in DLco may be an important marker of pulmonary hypertension, a known sequela of severe sarcoidosis and a harbinger of increased mortality (254).

Recently, Walsh and colleagues (221) have shown that when combined with other variables, PFTs could be used to reliably indicate prognosis in sarcoidosis. The composite physiological index (based on predicted values for FVC, FEV₁ and DLco) was combined with extent of fibrosis scores and pulmonary diameter on HRCT to clearly separate patients into high and low-risk groups (268). This stratification is potentially useful for determining those who might benefit from treatment. However, a subsequent study by Kirkil et al was unable to reproduce the correlation between CPI and death and found that the extent of fibrosis and the presence of pulmonary hypertension (as identified by right heart catheterisation) were the only predictors of mortality (220).

1.11 IMAGING IN SARCOIDOSIS

Since the discovery of the X-ray, radiology has played a central role in respiratory medicine. Historically, chest radiography has been the mainstay of radiological diagnosis and complemented by the development of computed tomography (CT) in the 1970's. A decade later, high-resolution CT (HRCT) revolutionised the imaging of the lungs and, in particular, the diffuse interstitial lung diseases (269). In clinical practice, CXR and HRCT remain the 'work-horse' radiological investigations.

1.11.1 Plain Chest Radiography

1.11.1.1 Historical & Technological Considerations

In November 1895, Wilhelm Conrad Röntgen made the fundamental observation that, when passing an electric current flow in a partially-evacuated glass cathode ray tube, a

platinocyanide plate situated nearby emitted light in a process now termed 'fluorescence' (270). A similar effect was seen with photographic plates and Röntgen noted that some materials obstructed the process more than others. This led him to postulate that this was caused by a hitherto unknown form of radiation, which he called 'X-radiation'. The realisation that X-rays could penetrate the human body and, more importantly, be used to generate an image, led to the relatively rapid expansion and incorporation of X-ray technology into medical practice. Indeed, it was a mere 6 months after Röntgen's Nobel prize-winning discovery that the American physician Francis H Williams, working at the Boston City Hospital, began to explore the 'Röntgen examination' and who, by 1898, had described the first radiographic signs of a variety of intrathoracic diseases including tuberculosis and emphysema (271).

The plain CXR remains one of the commonest imaging tests in the investigation of pulmonary diseases. There are undoubted advantages to the humble CXR: firstly, there is the relative simplicity of the technology. Secondly, there is the benefit of widespread availability. Finally, and maybe most importantly, the issue of radiation dose: the radiation burden of a CXR is often the standard by which other radiological tests are compared. However, with these advantages, it is also important to stress the downsides. One problem is that the CXR is simply a 2-dimensional representation of 3-dimensional anatomy; anatomical superimposition is therefore a key limitation. Another issue is that, in comparison with CT, contrast resolution is poor – accordingly the various 'shades of grey' seen on CT, which allow the observer to distinguish tissues of differing attenuation, are not present on CXR. Not surprisingly then, the CXR has poorer diagnostic capabilities than CT, and this is particularly true in the arena of interstitial lung diseases.

1.11.1.2 Plain CXR in Sarcoidosis: Historical Attempts at Classification

The common CXR abnormalities in pulmonary sarcoidosis are related to the presence of nodal and/or parenchymal disease (128). Nodal enlargement is the classical and most common CXR manifestation of sarcoidosis; bilateral symmetrical hilar lymph node enlargement, alone or with enlargement of mediastinal nodes, is seen in as many as 95% of patients at some stage (94, 95, 158). The typical distributions of nodal enlargement and the patterns of nodal calcification have been described previously (see section 1.7.3, page 47). Pulmonary disease in sarcoidosis was first described as a radiographic feature in 1915, by Kuznitsky and Bitorf (10). Since then, there have been attempts to characterise or group the radiographic findings. For example, Nitter et al., sub-divided the pulmonary findings of sarcoidosis into nodular (measuring 3-5mm) and 'miliary' (~1mm in diameter) lesions (272). They observed that those with a miliary nodular pattern were most likely to resolve. A little later, Smellie and Hoyle in 1960 suggested four categories of parenchymal infiltration in sarcoidosis: i) coarse nodular shadows (3-5mm), ii) fine nodular shadows (1-3mm), iii) fine 'stippling' and, finally, iv) scattered or localised patchy opacities (273). They observed that the fine nodular pattern was the most frequent presentation. An obvious issue (and limitation) of such categorisation is the use of non-standard terminology which undoubtedly would lead to significant interobserver disagreement. In this regard, in a study of 70 cases, Citron proposed the terms 'mottling', to describe the coarse radiographic pattern consisting of larger nodules, and 'stippling', to describe the finer nodular pattern (274). He also found a proportion of patients presenting with 'cloudy shadowing' with surrounding fine nodules which they proposed were caused by a confluence of acinar opacities. In addition to the findings described above, it was clear that a proportion of patients would insidiously progress to fibrosis. Scadding and Mitchell described middle and upper zone 'dense' fibrosis

and 'fibrotic contracted lungs' on CXR, which were believed to be a consequence of persistent pulmonary infiltrates (275). It was also noted that the dense fibrotic masses might simulate a pattern of progressive massive fibrosis, more commonly encountered in the pneumoconioses. Importantly, they observed that although progressive clinical symptoms and typical radiographic appearances were suggestive of fibrotic disease, the two were not always concordant.

1.11.1.3 'Staging' of Sarcoidosis on CXR

A natural and understandable development in sarcoidosis were the attempts to derive a 'staging' system based on radiographic appearance (276). In one proposal, Nitter suggested that patients might be grouped as follows: stage I, bilateral hilar lymph node enlargement but without parenchymal involvement; stage II, bilateral hilar lymph node enlargement with accentuation of perihilar markings; stage III, diffuse pulmonary nodules varying from 3 to 5 mm in diameter; stage IV, disseminated miliary nodules and stage V, fibrotic changes (272). This study not only highlighted the fact that patients presented with variable clinical / radiographic severity but also set the stage for subsequent attempts at staging sarcoidosis. Five years later, Wurm, Reindell and Heilmeyer evaluated a large cohort and demonstrated that plain radiographic staging correlated with clinical course and, importantly, prognosis (277). The authors proposed a division into three stages: stage I, bilateral hilar lymph node enlargement; stage II, bilateral hilar lymph node enlargement with parenchymal involvement and stage III, end-stage disease with irreversible fibrosis. Importantly, it was suggested that patients followed serially, generally transitioned from stage I through to III, thus supporting the notion of a 'staging system'. A plethora of other

staging systems have since been proposed (1, 243, 276, 278, 279), largely all superseded by the one proposed by Scadding (1).

Scadding retrospectively reviewed the records and radiographic presentations of 136 patients over a 5-year period (1), noting that patients presented with '*various types of intrathoracic change*' that might be divided into four distinct groups: Group 1=enlarged hilar lymph nodes only; Group 2=mottled shadowing in the lungs with enlarged hilar lymph-nodes; Group 3=mottled shadowing in the lungs without enlarged hilar nodes and Group 4=fibrosis (figure 1.9).

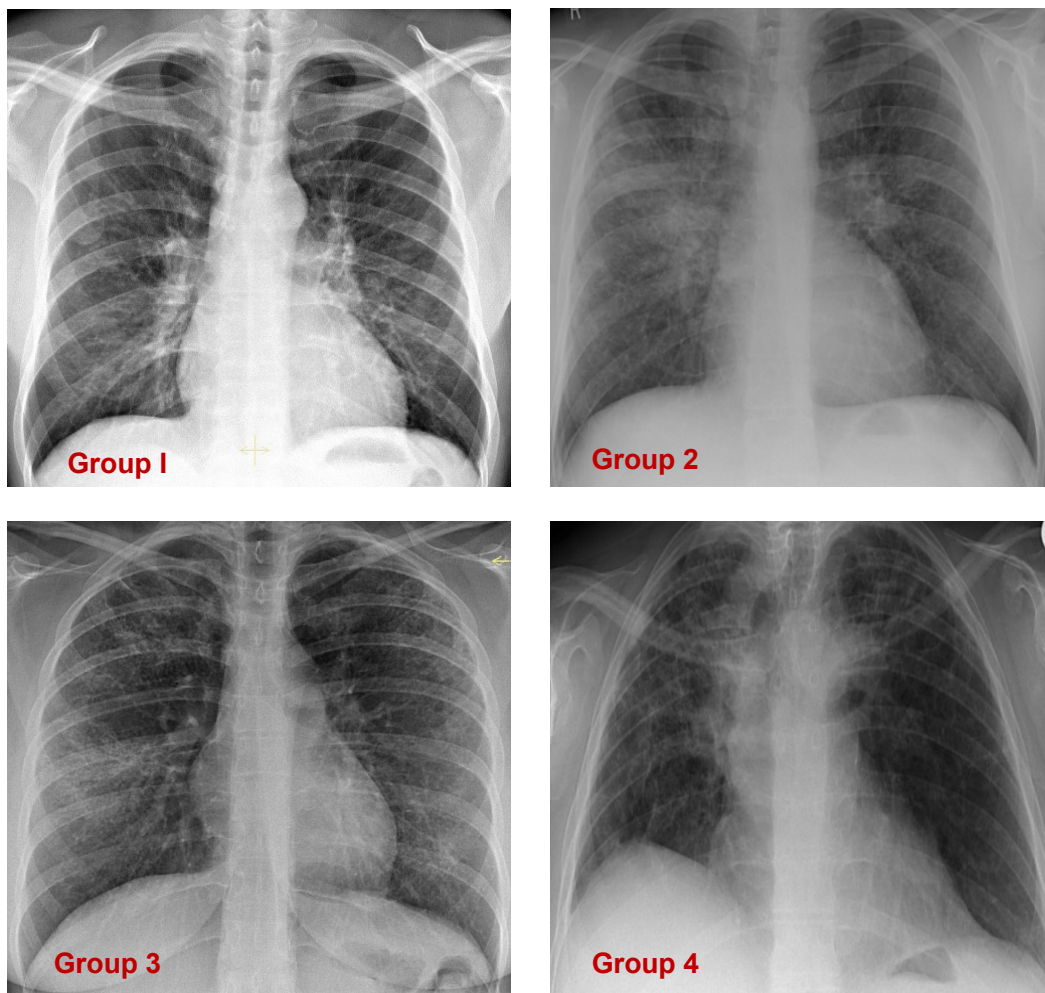


Figure 1.9 Scadding CXR Groups. Group 1, enlarged hilar lymph nodes with otherwise normal lung parenchyma; Group 2, enlarged hilar lymph nodes accompanied by “mottled shadowing in the lungs”; Group 3, “mottled shadowing in the lungs” without enlarged hilar nodes; and Group 4, overt fibrosis.

Admittedly, Scadding's observations (summarised in Table 1.2), broadly mirror those summarised above, but show that the likelihood of CXR and symptomatic resolution was closely related to CXR group. For example, 82% of those in Group 1 had normal radiographs at 5 years, while there were no cases of radiographic resolution in Group 4. Similarly, only a single patient in Group 1 had symptoms at 5 years (3%), compared with 74% of those in Group 4. Finally, sarcoidosis-related deaths were only observed in patients stratified to Group 4.

Group	Number of patients	Clinical Features at 5 years					
		Normal X-ray	Abnormal X-ray			Dead	
		No symptoms	No symptoms	Mild symptoms	Severe symptoms	Sarcoidosis	Other
1	32	27	4	1	0	0	0
2	40	23	2	11	3	0	1
3	37	16	6	8	6	0	1
4	27	0	0	9	11	6	1

Table 1.2 5-year follow-up of 136 patients stratified by radiographic group. (From "*Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation*" (1).

Since the initial proposal an additional group, Group 0 (representing radiographically-occult disease), has been added (Table 1.3). It is worth noting at the outset that Scadding himself made no assertion that patients could be 'staged' based on radiographic appearance, rather he described phenotypes that could be separated based on disease behaviour. However, rather curiously, the term Scadding 'stage' has since been used ubiquitously in the literature and somewhat erroneously as we will discuss.

CXR 'stage'	Findings	Approx Frequency (%)
0	Normal CXR	5-10
I	Bilateral hilar lymph node enlargement (BHL)	50
II	BHL and pulmonary infiltrates	25-30
III	Pulmonary infiltrates without BHL	10-12
IV	Advanced pulmonary fibrosis	5

Table 1.3 Scadding radiographic scoring of sarcoidosis, with approximately frequencies as demonstrated by subsequent studies (1-3)

1.11.1.4 Limitations of CXR Staging

Staging of sarcoidosis, based on CXR observations, has significant limitations. Firstly, there is the not inconsiderable issue of observer variation. In a study assessing changes in CXR appearance following treatment, Baughman et al, found only 'moderate' (closer to 'fair') interobserver concordance (weighted Kappa=0.43) for baseline radiographic stage (280). A second problem is that CXR staging is imprecise (281-283). Indeed, one flaw highlighted by phenotyping patients in this manner, has been the inability to accurately distinguish between the absence (CXR stage III) and presence (CXR stage IV) of fibrosis, a potentially important clinical/prognostic cut-off (1). Another issue in this field is the use of the word 'staging', akin to the way it used for cancer management, which is misleading since there is no predictable progression between the proposed groups. Siltzbach described outcomes in 311 patients based in New York and saw that 54% of those with stage 1 had completely clear radiographs after 2 years, while the remaining were either stable or had progressed (243). Secondly, and again in contrast with malignant disease, there is no

evidence that patients systematically progress through the stages — for instance, the small minority with radiographic stage II who progress to fibrosis do not necessarily go through stage III disease (146). A further point to note is that the individual stages are not homogeneous. Hence, only a proportion of those with stage IV disease actually fare poorly, while the rest survive with so called “burnt-out” disease (220). It has also been shown that within stage IV, patients can be divided into at least three distinct CT subgroups that correlate with lung function profiles (109). This of course means that ‘lumping’ patients into a single radiographic group may limit the ability to target treatment to those who need it most.

A major practical issue is that the Scadding CXR stages also correlate poorly with function indices (283, 284), patient-reported disease severity (245, 285) and the need for long-term treatment (245). In a subgroup of 205 patients from the ACCESS study who were evaluated over an 18-24-month period, only treatment at baseline and dyspnoea were independent predictors of chronic therapy and there was no association with CXR stage (245). Finally, there is the ever-present concern of lower sensitivity of CXR, so that conceivably, parenchymal disease in patients with radiographic stage 0 or I can be missed (284, 286). Indeed, Drent and colleagues found that almost 30% of patients with CXR stage 0/I disease had parenchymal abnormalities on HRCT, with the majority having objective evidence of functional impairment (284).

1.11.2 Computed Tomography

The advent of CT in the 1970s revolutionised medical imaging (287). However, a significant amount of early work contributed to its development (288, 289). In brief, the technique of tomography, generates a cross-sectional representation through an object: the earliest iteration was linear tomography, patented in early 1922 (290). The key principle is that by moving an X-ray tube and detector in opposite directions about a 'fulcrum', it is possible to take an image that encompasses the entire plane of the object (Figure 1.10). The first clinical linear tomographic images were obtained in the late 1940s by Vallebona (291). The obvious drawbacks of linear tomography were the blurring of points above and below the focal point (fulcrum) and also the slow acquisition time. Clearly this was not an efficient method of obtaining cross-sectional imaging of the body.

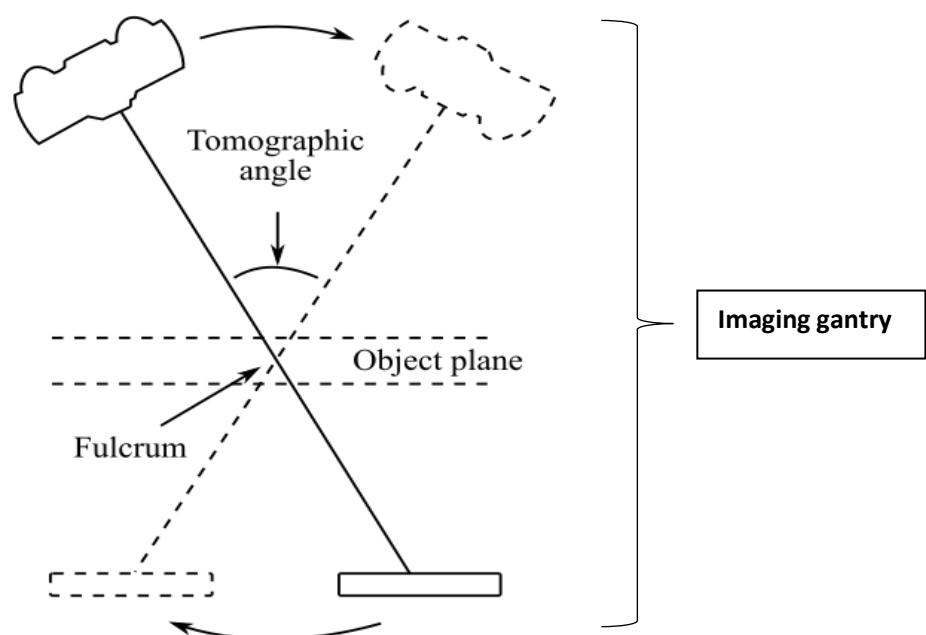


Figure 1.10 Illustration of the basic principle of linear tomography. The X-ray tube and detector move in opposite directions about a fulcrum which is set at the desired plane within the object being imaged.

1.11.2.1 The Physics of Computed Tomography

In October 1971, British engineer Sir Godfrey Hounsfield conceptualised and then created the first commercially viable computed tomography (CT) scanner (292). Hounsfield demonstrated that by positioning an X-ray source and a detector on opposite sides of a rotating gantry, it was possible to obtain transaxial images from multiple X-ray projections around a subject. Using mathematical algorithms developed over the preceding decade by Alan Cormack (293), Hounsfield was able, after acquiring the attenuation data, to produce an anatomical CT image. The CT image 'slice' comprises a matrix of 2-dimensional picture elements (pixels) corresponding to a dimensional volume element (voxel). Each pixel is assigned an attenuation value which is a summation of *all* physical components (soft tissue, bone, air etc.) in the corresponding voxel. Elements *partially* filling the voxel contribute *in part* to the attenuation value of the visualised pixel; a phenomenon known as 'partial volume averaging' (Figure 1.11) (294).

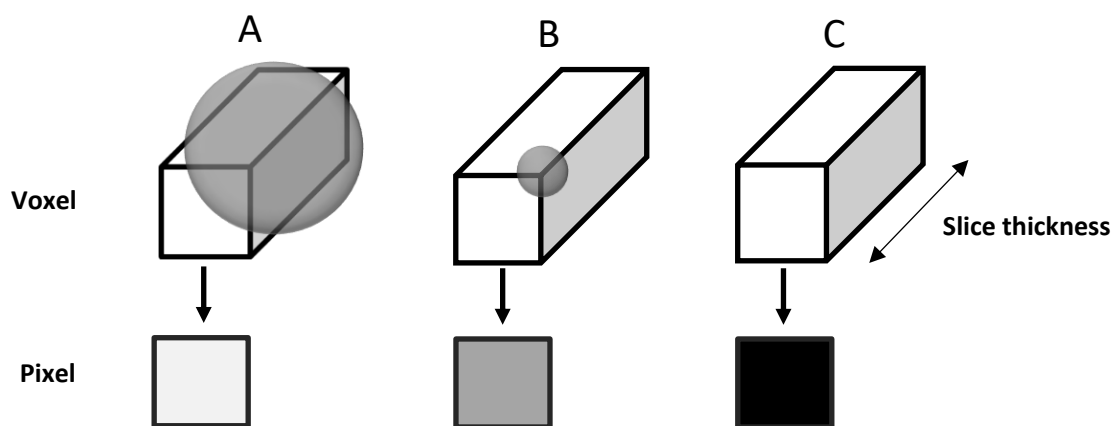


Figure 1.11 Illustration of 'volume averaging': the picture element (pixel) seen on-screen is assigned an attenuation value that is an average of *all* elements in the corresponding voxel being imaged. **A)** a mass almost completely occupies the volume element (voxel) and the corresponding pixel is therefore assigned a high attenuation value. **B)** A small nodule occupies a small part of the voxel and the pixel is assigned an intermediate attenuation value (closer to the attenuation of air in lung). **C)** There are no lesions within the imaged voxel and the corresponding pixel appears of low attenuation (lung density).

Thick (1cm) slice acquisitions result in significant partial voluming and loss of fine detail. Conversely, narrow slice acquisitions (1mm) reduce voxel thickness and accordingly improve spatial resolution. Importantly, successive generations of CT technology have resulted in modern-day scanners that feature multiple arrays of detectors and two X-ray sources. These developments mean that CT scanners are now capable of acquiring large volumes of data, with narrow collimation, within very short periods of times.

The data generated from the CT scanner comprises a series of attenuation values which, using a scaling factor, are assigned CT numbers (Hounsfield Units, HU) that can be displayed as an image (295). In this method, water is arbitrarily assigned a value of 0 HU and each CT number is then attributed a grey scale value, thereby generating the final image (292). In order to optimise interpretation, images are manipulated using 'windowing' to show the desired CT numbers. A 'window centre' is selected at the approximate HU of the tissue of interest (-500HU being optimal for lung parenchymal assessment and +10 to -20 HU for mediastinal structures) and a 'window width' is specified which governs the number of grey scale values displayed above and below the window centre; a narrow width gives an image of high contrast whereas a wider width produces a 'flatter' image.

1.11.2.2 Image Quality – Spatial resolution, Contrast Resolution & 'Noise'

CT image quality is greatly influenced by the key parameters of spatial resolution, contrast resolution and 'noise' (296). Spatial resolution describes the ability of an imaging system to distinguish (or 'resolve') two objects lying in close proximity (296). The technique of high-resolution CT (HRCT) was developed to optimise spatial resolution for accurate depiction of detailed lung parenchymal anatomy (297). The HRCT technique utilises narrow

collimation (typically 1mm but ranging from 0.6-1.5mm) and a dedicated high-spatial-frequency (bone) reconstruction algorithm, which contribute to increasing spatial resolution.

Contrast resolution refers to the ability of a system to distinguish differences in physical density and depends on two main factors: 1) the intrinsic differences in density between the tissues and 2) the 'noise' in the system. Structures can be difficult to distinguish if they are of similar density to surrounding tissues and especially if there is excessive background noise. Quantum noise or 'mottle', is a random phenomenon caused by fluctuations in the flux of X-ray photons reaching the detector. The presence of quantum noise reduces the ability to distinguish different densities. The severity of noise in an image can be reduced by increasing the mA — which increases the number of photons reaching the detector. However, the obvious drawback is an increase in patient dose. Image quality is therefore a fine balance between signal-to-noise. While reducing the size of the imaging voxel will maximise spatial resolution, it also reduces the amount of signal (or photons) within each voxel thus reducing the SNR and hence the contrast resolution. It is clear then that contrast and spatial resolution are intimately linked in CT imaging. Thankfully, the lung is an intrinsically high-contrast organ and therefore narrow collimation techniques can be used without significantly compromising contrast resolution.

1.11.2.3 Temporal Resolution and Interspaced vs. Volumetric Scanning

Another important component of image quality is temporal resolution, or more simply, the time needed to acquire an image. Historically, CT scanners suffered from poor

temporal resolution and it was not possible to acquire a full volumetric image of the lung during a single breath-hold. Instead, representative 'slices' of the lungs were taken at 10-20mm intervals to create a sample of the total lung volume; a technique known as 'interspaced' acquisitions, which had the benefit of reducing motion artefact associated with low temporal resolution early generation scanners and also offered a method of 'sampling' the lung parenchyma while reducing radiation dose.

The development of multidetector row CT (MDCT) machines was a significant step in the evolution of this technology. MDCT machines allow much faster acquisition using helical (constant table motion during image acquisition) or step-and-shoot techniques; these scanners facilitate imaging of the entire lung volume within a single breath-hold. These so called 'volumetric' studies have become the gold-standard of parenchymal imaging due to the ability to: 1) completely assess the lungs and thorax, 2) view contiguous structures allowing better definition of anatomical structures and pathology, 3) reconstruct data in multiple planes and 3) perform precise slice-by-slice comparison between studies performed at different time-points. The major downfall of volumetric scanning is the higher radiation dose compared with interspaced techniques. That said, various dose reduction techniques have considerably reduced this problem and in general, the advantages of volumetric imaging now outweigh the diminishing radiation dose (297-299).

1.11.3 HRCT Features of Pulmonary Sarcoidosis

The variable imaging appearances of sarcoidosis have been widely studied and reported (104, 300-312). The subsections below revise not only the common, but some of the more unusual features of sarcoidosis.

1.11.3.1 Nodal Enlargement

Intra-thoracic lymph node enlargement is one of the cardinal findings in patients with sarcoidosis: symmetrical hilar nodal enlargement is seen in up to 95% of cases (94) (Figure 1.12). CT is certainly more sensitive for identifying mediastinal nodal enlargement than CXR. However, a study of 25 patients with pulmonary sarcoidosis found that despite being better at demonstrating the *extent* of nodal involvement, there was no clear advantage over plain CXR for confirming the *presence* of nodal disease (313). Not surprisingly, nodal calcification is better depicted on CT. The different patterns of nodal calcification have been discussed previously (see section 1.7.3, page 47).

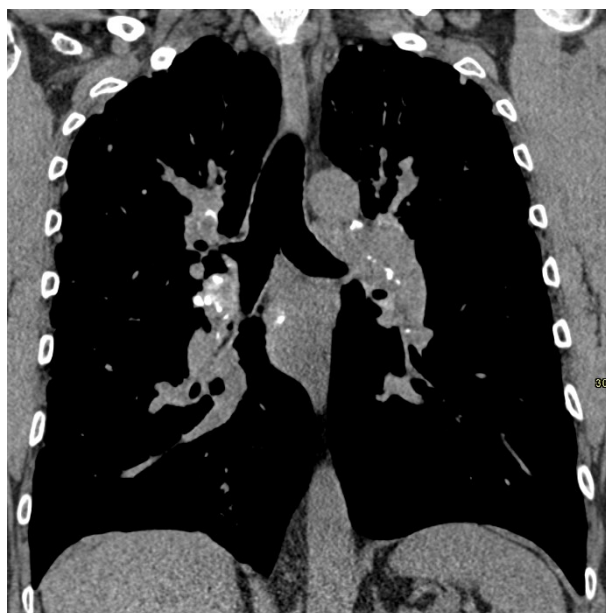


Figure 1.12 Symmetrical (calcified) hilar lymph nodes typical of sarcoidosis

1.11.3.2 Parenchymal Manifestations

Parenchymal manifestations of sarcoidosis are innumerable but can be broadly thought of as those that are 'classical' and those that are 'atypical'. The typical findings are those that occur frequently and in the correct clinical setting may facilitate a confident diagnosis of sarcoidosis. The atypical findings are less frequently encountered and, importantly, are less specific for a diagnosis, commonly mandating further investigations.

A nodular pattern is the commonest manifestation of pulmonary parenchymal sarcoidosis (241, 262, 314). The micronodular pattern (defined as nodules <3mm (315)) is perhaps the most frequent (Figure 1.13a). In classical cases, nodules are symmetrically distributed with a predilection for the mid/upper zones. Additionally, there is propensity for nodules to cluster around the central peribronchovascular structures, the fissures and subpleural lung (312, 316). These findings reflect the archetypal perilymphatic granulomas seen on histology (316, 317). Sharply demarcated centrilobular micronodules are a less common, but recognised finding in sarcoidosis, representing peribronchiolar granulomas (316). A 'miliary' pattern, characterised by randomly distributed micronodules, is another less common manifestation of pulmonary sarcoidosis (Figure 1.13b) (318). In a small proportion of patients (<25%), sarcoid interstitial granulomas may coalesce to form larger nodules measuring 1-4cm in size and appear as ill-defined irregular lesions within the perihilar or peripheral regions (319-321). These may or may not contain air bronchograms and they very rarely cavitate (319). Some of these lesions can be surrounded by small satellite nodules giving an appearance known as the "galaxy sign" (Figure 1.13c) (322).

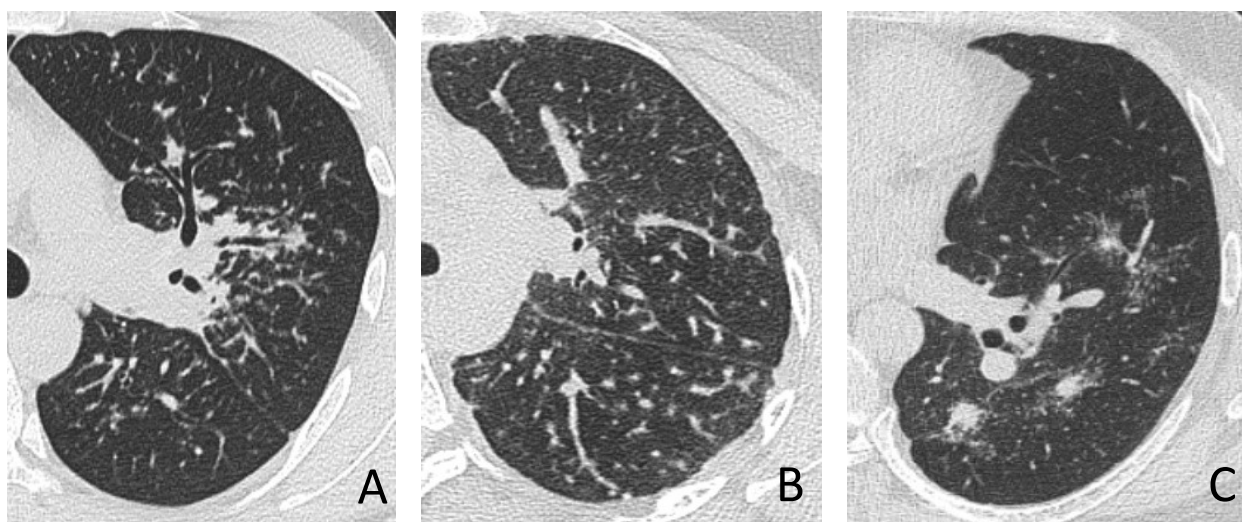


Figure 1.13 Typical nodular patterns in pulmonary sarcoidosis: A) micronodular pattern with a central peribronchovascular distribution, **B)** micronodular pattern with a 'miliary' (or *random*) distribution **C)** macronodular pattern with surrounding small satellite nodules ('galaxy' sign)

As discussed previously (see section 1.9, page 52), 10-30% of patients with sarcoidosis follow a chronic progressive course (155), with a proportion developing clinically-significant fibrosis. Different fibrotic subtypes have been described in sarcoidosis, but the classic fibrotic picture is of striking bronchocentric mid- and upper zone parenchymal distortion (Figure 1.14), with posterior retraction of the hila, traction bronchiectasis and linear bands of opacity extending from the hila to the periphery (109). Patients with advanced fibrosis may also have associated pulmonary hypertension manifesting as an enlarged pulmonary trunk and peripheral pulmonary arteries larger than their accompanying airway (125, 225, 323). On occasion, patients with overt fibrosis in the upper zone, develop areas of bullous 'destruction' or cavitation. Patients who develop advanced fibrotic disease can exhibit fibrotic cysts, bullae and cavities. Not surprisingly, some cases are complicated by fungal colonisation (mycetoma). Importantly, the presence of chronic mycetoma (identified in 2% of all pulmonary sarcoidosis patients) may confer a poor prognosis (324).



Figure 1.14 Fibrotic pattern in pulmonary sarcoidosis characterised by classical upper zone predominant bronchocentric fibrosis. There is architectural distortion and traction bronchiectasis (more severe on the right)

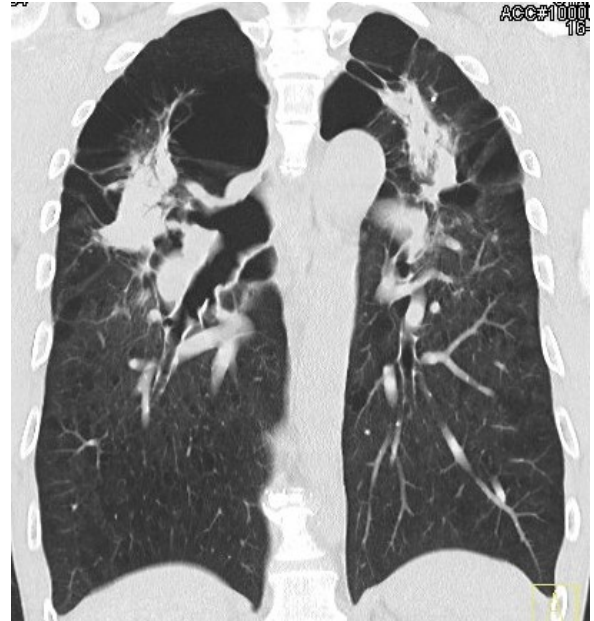


Figure 1.15 Fibrotic 'PMF' pattern in pulmonary sarcoidosis characterised by coalescent 'mass-like' peribronchovascular consolidation with airway distortion and fibrosis resembling progressive massive fibrosis

A pattern of consolidation — often erroneously termed 'air-space' or 'alveolar' sarcoid — can simply reflect excessive thickening of the interstitium (97, 309, 325-328) and may be found in a peripheral non-segmental distribution exhibiting air bronchograms (325, 329). In 1970, Freundlich proposed that the consolidation was a manifestation of conglomerate interstitial granulomas compressing the alveolar spaces, rather than an abnormality originating from the airspaces *per se* (309) and is supported by pathological findings (327). In more advanced cases of sarcoidosis, central peribronchovascular disease may coalesce to form larger mid and upper zone 'mass-like' areas of consolidation associated with airway distortion and variable fibrosis, closely resembling a pattern of so-called progressive massive fibrosis seen in pneumoconiosis (Figure 1.15) (97, 308).

Ground-glass opacification on CT, defined as hazy increased opacity of the lung *without* obscuration of bronchovascular structures (315), as the sole or predominant HRCT pattern, is uncommon in sarcoidosis (Figure 1.16) (307, 330, 331). Historically, this appearance was believed to represent a ‘sarcoidosis-related alveolitis’ but CT-pathological correlative studies by Nishimura and colleagues have shown that clusters of small interstitial granulomas (below the resolution of HRCT) were largely responsible for the appearance and, more to the point, there was no evidence of an alveolitis as such (309, 321).

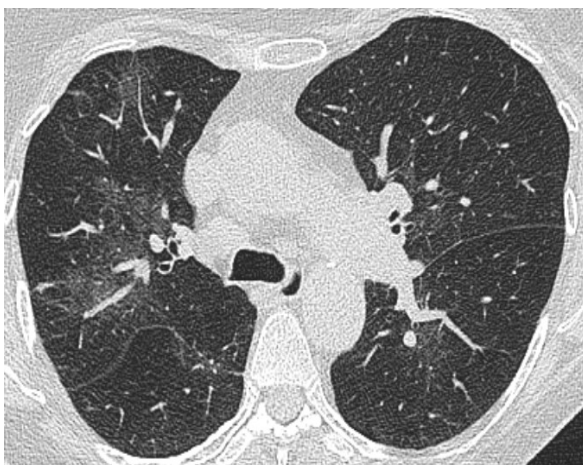


Figure 1.16 Groundglass pattern in pulmonary sarcoidosis, previously thought to represent ‘sarcoidosis-related alveolitis’, but now understood to represent interstitial granulomata below the resolution of CT.



Figure 1.17 Pulmonary sarcoidosis manifesting as linear opacities representing interlobular septal thickening

A pattern of interlobular septal thickening has been described as the predominant finding in only 15-20% of cases in small historical series (319, 320, 332). Interlobular septal thickening is thought to represent granulomatous infiltration of the interstitium and, if/when present, tends to predominate in the mid and upper zones (97) (Figure 1.17).

Honeycombing, a cardinal feature on pathology and HRCT in usual interstitial pneumonitis (UIP), is uncommon but recognised in advanced pulmonary sarcoidosis (109). Importantly, in sarcoidosis, the distribution of honeycombing is typically in the mid-to-upper zones, unlike the lower zone predominance recognised in a UIP pattern. However, occasionally the distinction is not straightforward on imaging (figure 1.18): for instance, Collins et al., reviewed 25 patients with histologically-confirmed sarcoidosis with probable or definite UIP on HRCT or histology. They proposed the term ‘combined sarcoidosis and IPF’, arguing that patients with sarcoidosis and a UIP pattern often followed the clinical trajectory of those with idiopathic pulmonary fibrosis (IPF). However, the issue of whether this finding on CT represents the co-existence of IPF in sarcoidosis or a true manifestation of sarcoidosis is unclear (333).

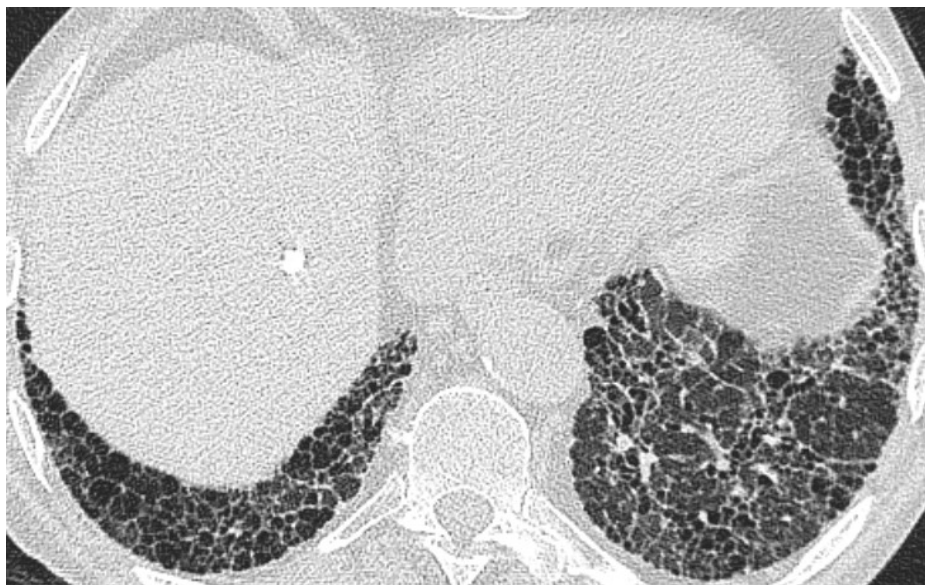


Figure 1.18 UIP pattern in pulmonary sarcoidosis, characterised by basal predominant subpleural reticulation, traction bronchiectasis and honeycombing. Note that in pulmonary sarcoidosis, honeycombing, when present, is often mid and upper zone predominant (unlike the example above which is basal-predominant and radiologically indistinguishable from UIP secondary to IPF).

Small airways disease, presenting as a pattern of mosaicism (with air trapping on expiration) is an uncommon CT finding in sarcoidosis (figure 1.19) (111, 113, 114). Although the exact pathophysiological mechanisms remain unclear, this finding is thought to be a manifestation of bronchiolar obstruction secondary to granulomatous infiltration (334). In sarcoidosis, small airways disease is mostly seen in the context of other parenchymal involvement. However, in some cases, the mosaic pattern is recognised in the absence of other findings (335).

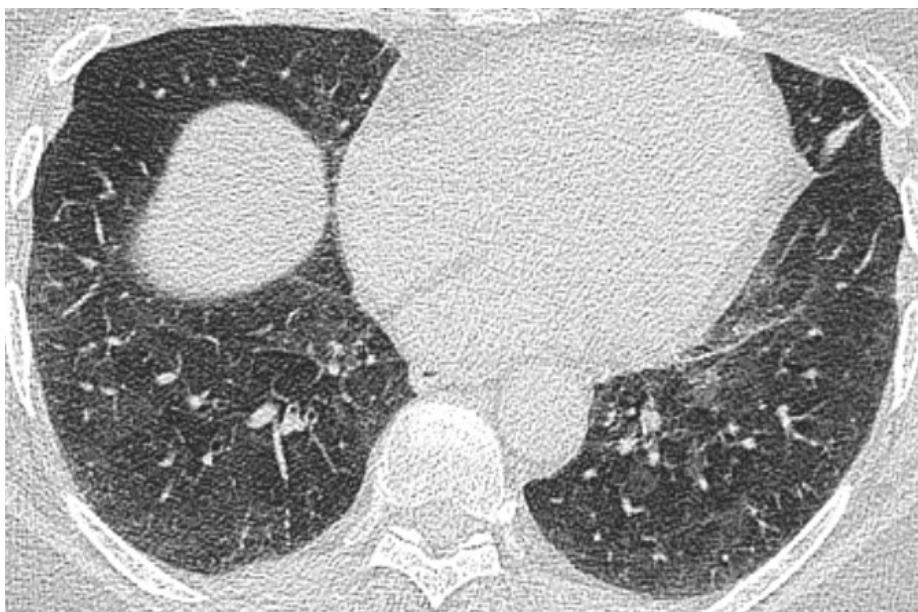


Figure 1.19 Mosaic pattern in pulmonary sarcoidosis, comprising lobules of low attenuation indicate air trapping.

1.11.3.3 Structure-Function Evaluation on CT

The relationships between morphological abnormalities on HRCT and functional indices have been explored previously (114, 123, 314, 336). Earlier studies explored basic CT features and associations with lung function parameters. For instance, Hansell et al., semi-quantitatively scored patterns on CT scans in 45 patients with pulmonary sarcoidosis and

compared them with lung function tests (114). Three dominant HRCT features were identified: decreased attenuation (as part of a mosaic attenuation pattern), reticulation and nodules. Curiously, the authors found that the extent of reticulation, seen in more advanced disease, was the variable most strongly linked to airflow obstruction, superseding CT features of small airways disease. In a smaller study of 27 patients, Bergin and colleagues took an alternative approach to CT quantification by categorising CT appearances into five broad subtypes (normal, segmental airspace disease, mass-like opacities, nodules and parenchymal distortion) and then scoring the extent of parenchymal involvement in each case (311). The authors found that CT patterns could suggest the *type* of lung function abnormality, while disease extent predicted the *severity* of the deficit. Müller et al, in a study of 27 patients, focused predominantly on disease extent, rather than individual patterns and showed that the extent of parenchymal involvement on CT, scored to the nearest 5%, correlated with pulmonary function impairment (332). A further structure-function study performed at a similar time also found a significant, but weak correlation between disease extent on CT and functional impairment, but found no link between individual CT patterns and lung function, in contrast to Hansell et al. (114, 319). All of these early studies have limitations, not least the very small patient cohorts thereby limiting the power to show meaningful differences between CT groups. In addition, due to the nature of the scanning technology at the time, scans were limited to relatively thick slices with interspaced acquisitions. While interspaced acquisitions are clinically-acceptable for diagnostic purposes, there is the potential to underestimate disease extent (269). Against this, a plus for the studies discussed above was that interobserver variation was within clinically acceptable limits (114, 236, 311). Overall, if nothing, these early studies paved the way for future explorations of CT in this field.

In 2000, Abehsera and colleagues conducted a retrospective review of 80 CT scans with proven sarcoidosis (109). The investigators exclusively examined patients with pulmonary fibrosis, identifying three main CT patterns: bronchial distortion, honeycombing and reticulation. Not surprisingly, a pattern of honeycombing was most often associated with restrictive lung function indices and, in contrast to the earlier Hansell study, the linear pattern was associated with the least functional impairment. However, a major limitation of this study was that patients were selected for inclusion based on CXR evidence of fibrosis (i.e. stage IV). As discussed in section 1.11.1.4 (page 61), this method of patient selection is potentially flawed as it is likely to exclude patients with subtle fibrosis below the resolution of CXR. More recent studies have also explored the relationship between CT features and pulmonary functional impairment with somewhat conflicting results (123, 241, 255, 262, 284, 314, 336, 337). For example, a study of 80 patients with newly-diagnosed pulmonary sarcoidosis found that only ground-glass opacification and consolidation on CT were associated, albeit weakly, with lung function impairment, while profusion of lung nodules had no bearing on lung function (262). By comparison, Drent and colleagues, found significant associations between several HRCT patterns (for instance, bronchovascular thickening, nodules, septal lines and pleural thickening) and indices of lung function (284). Benamore and colleagues developed a scoring system to quantify disease activity using CT (314). The authors showed that the sum of the CT extent scores for nodules, interlobular septal thickening, groundglass opacity and consolidation (termed the 'CT Activity Score', CTAS) not only correlated with surrogate markers of disease activity but also predicted FVC response to treatment in a subset of patients. However, as with all of these studies, the sample for the subgroup analysis was small and consisted of only 29 patients receiving treatment.

It is clear then that there is wide variation in the findings of CT structure-function studies performed to date. As we have illustrated, researchers have focused largely on common manifestations of sarcoidosis (consolidation, reticulation, ground-glass opacification and nodules), but other features such as traction bronchiectasis, mosaicism and honeycombing (to name a few) have seldom been investigated. Moreover, studies are invariably limited in sample size presumably due to the relatively low prevalence of sarcoidosis (134).

1.11.3.4 CT Phenotyping in Sarcoidosis

Many authors have explored the potential for CT phenotyping in sarcoidosis (286, 311, 314, 319, 336, 338, 339). Brauner and colleagues, in a longitudinal observational study, compared baseline CT scans performed in 20 patients with active disease with subsequent scans performed during remission (320). They demonstrated that nodules and consolidation are mostly reversible CT features, while reticulation and parenchymal distortion are often irreversible. Subsequent studies have predominantly focused on identifying 'active' disease, as a method of determining which patients might benefit from treatment (314, 336, 339). A recent study by Benamore et al examined HRCT scans in 100 patients and compared the extent of nodules, ground-glass opacity, interlobular septal thickening and consolidation with surrogate markers of disease activity (314). They identified that the extent of ground-glass opacification and consolidation were weak, but significant predictors of treatment response, while their own proposed composite score (the 'CT activity score') was a stronger predictor. However, phenotyping patients according to disease activity is not always useful. For example, the acute form of sarcoidosis (Lofgren's syndrome) is highly active but is also

renowned for having an excellent prognosis and seldom requiring treatment (340). Similarly, current sarcoidosis guidelines suggest that in the absence of symptoms, 'active' disease alone is not an indication for therapy (240).

1.12 RATIONALE FOR THIS PROJECT

SECTION I: *Chest Radiographic (CXR) Staging, Relationship between CXR Stage & CT Appearances and Outcome*

Plain CXR and HRCT are the mainstays of imaging assessment in patients with suspected and established sarcoidosis. Historically, and perhaps for reasons of simplicity, CXR 'staging' has formed part of clinical evaluation when managing patients with sarcoidosis. However, for a variety of reasons that have been discussed in this chapter, the use of the word staging for the variable CXR appearances, is both inappropriate and misleading. Against this, HRCT characterisation of parenchymal disease in sarcoidosis is evidently more precise. Surprisingly though, there has been no formal comparison, in large cohorts between CXR and HRCT appearances. Thus, for instance, the morphological correlates on CT of patients with CXR stage III (parenchymal disease alone) and CXR stage IV (lung fibrosis) sarcoidosis are not known. Consequently, whether there are structural, functional and prognostic separations 'buried' within the different CXR stages is also unknown.

AIMS I:

- *To determine observer variation in a large cohort of patients with sarcoidosis for i) CXR staging AND ii) characterisation and quantification of HRCT patterns*
- *To evaluate the relationships between individual CXR stages and HRCT appearances in sarcoidosis*
- *To compare & contrast the functional and prognostic separations based on CXR staging and HRCT appearances in patients with sarcoidosis*

SECTION II: *Classification Based on CT ‘Phenotypes’*

It should be clear from the preceding discussions in this chapter that sarcoidosis, the paradigm of a granulomatous disease, is a complex disorder and something of an enigma. The aetiology of sarcoidosis has been a matter of conjecture since the late 19th century. However, a number of indicators — notably, the multiplicity of morphological CT manifestations, the differing physiological profiles and the highly-variable natural history — seem to suggest that the label, *sarcoidosis*, is simply a convenient ‘umbrella’ term capturing what are, in effect, separate diseases. Put simply, there has been a historical tendency to ‘lump’ different morphological phenotypes under the one, supposedly convenient, diagnostic label of sarcoidosis. This contrasts with the practice of ‘splitting’ in other diffuse interstitial lung diseases and, particularly, the idiopathic interstitial pneumonias. In large measure, this is attributable to the tradition of basing key separations between disorders on histopathological differences: however, in sarcoidosis, biopsy appearances do *not* necessarily predict the disparate CT features, variable physiological manifestations nor the differing outcomes. Following on then, one of the key (and somewhat surprising) issues in sarcoidosis is that there has never been any attempt to ‘classify’ on the basis of the widely differing CT phenotypes.

AIMS II:

- *To reach agreement among international experts (radiologists and physicians), employing Delphi methodology, on the existence of key morphological sub-types (or ‘phenotypes’) in sarcoidosis as a prelude to developing a new system of classification*
- *To ascertain observer agreement for CT phenotypes*

Section I | *Chapter 2*

General Methodology

2.1 Introduction

This chapter details the methodology and aspects common to the different projects in this thesis. The nature of the study population and the methods of patient selection are addressed. The key outcome variables are described together with the statistical analyses.

2.2 Study Setting, Design & Patient Selection

Consecutive patients were culled from the database of the Sarcoidosis Unit at Royal Brompton Hospital, one of the largest in Europe, caring for over 4000 patients. Patients reviewed at the hospital between 2007 and 2014 were retrospectively identified; this methodology was chosen to facilitate analysis of a sufficiently large number of cases with adequate follow-up.

The criteria for inclusion were: i) a high-confidence diagnosis of sarcoidosis; ii) evidence of lung parenchymal involvement and iii) the availability of baseline chest radiography (CXR) and high-resolution CT (HRCT) performed within 90 days of one another. This time interval was chosen to be inclusive of patients who had a short time delay between CXR and HRCT due to the referral pathway and was deemed acceptable given the indolent nature of sarcoidosis. The diagnosis of sarcoidosis was based on criteria jointly proposed by the American Thoracic Society (ATS), European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) (341); namely, a clinical presentation compatible with a diagnosis of sarcoidosis, the demonstration of non-caseating granulomas (or, in the absence of histopathological confirmation, the clinical and/or radiological features of Scadding CXR stage I or II disease)

and the exclusion of other diseases with similar histopathological appearances. Lung parenchymal sarcoidosis was confirmed by the presence of typical CXR or HRCT appearances and/or evidence of pulmonary functional impairment. All patients had full baseline lung function tests, however those with tests performed contemporaneously with imaging (defined as within 90 days) formed another subset for analysis. Patients with sub-optimal or poor quality CXR or CT imaging, cardiac predominant disease, extensive thoracic surgery, absence of demonstrable pulmonary disease and those with only a 'low confidence' diagnosis at multidisciplinary review were excluded.

374 consecutive patients with a suspected diagnosis of pulmonary sarcoidosis were selected. 85 were excluded based on the pre-defined exclusion criteria (Figure 2.1). The final cohort comprised 289 patients; 207 of which had contemporaneous lung function tests, forming a subset for further analysis. Demographics for the final patient cohort are presented in Table 2.1.

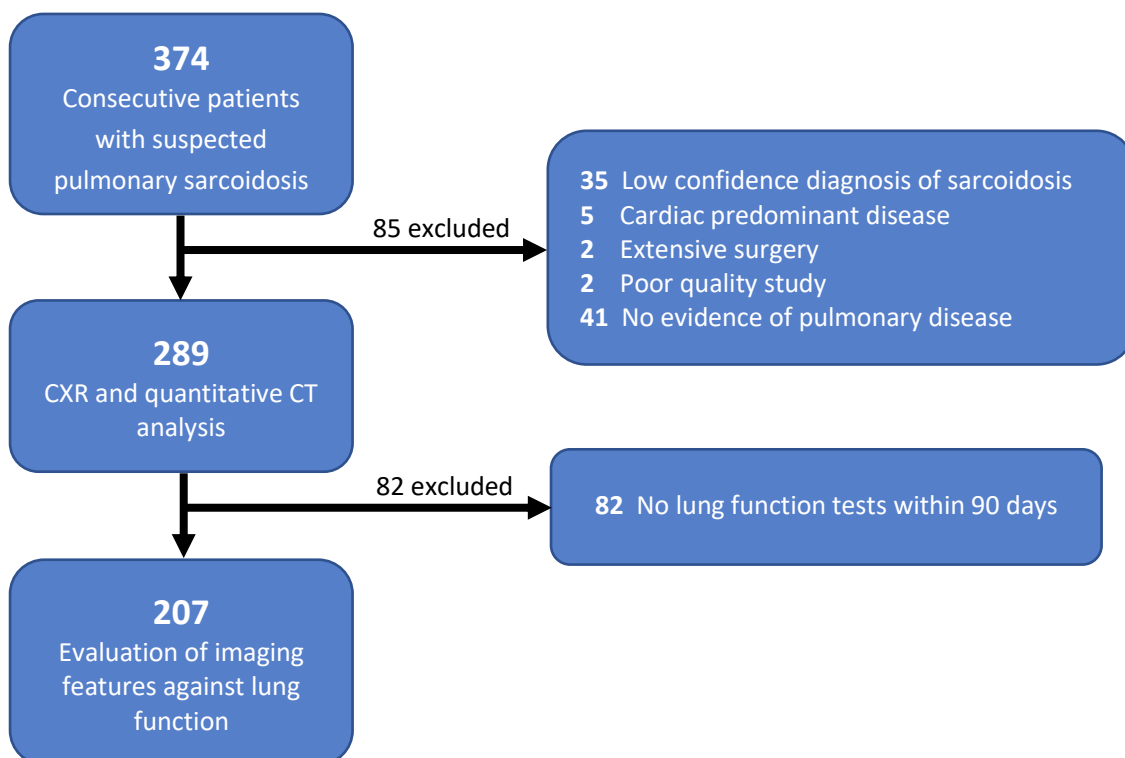


Figure 2.1 Consort diagram outlining the selection of study

PARTICIPANT CHARACTERISTICS	
Total	289
M:F	159:130 (55:45)
Median age at presentation	47 years (IQR, 39-56 years)
Died	50 (17)
Median age at death	61 years (IQR, 57-70 years)
CT acquisition protocols	
<i>Volumetric HRCT</i>	173 (60)
<i>Interspaced HRCT</i>	116 (40)

Table 2.1 Demographic data in 289 patients with sarcoidosis. Data are numbers of patients with percentages in parentheses or median values with interquartile ranges (IQR)

All identifiable clinical and imaging data were anonymised at the point of access by the chief investigator and study patients were assigned a random unique identifier. Co-investigators were provided access only to the anonymised datasets.

2.3 CHEST RADIOGRAPHY (CXR) AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT)

2.3.1 CXR and HRCT Acquisition

All CXRs (n=289) were performed in the postero-anterior projection and for clinical purposes in an outpatient setting. All CXRs were pre-loaded in a dedicated, secure worklist folder on the Trust's Pictures Archive and Communication System (PACS) to facilitate the review process. All CXRs were reviewed on Digital Imaging and Communications in Medicine (DICOM)-compatible screens.

The overwhelming majority of patients (280/289 [96.9%]) were scanned at Royal Brompton Hospital on a 64 slice multidetector row CT scanner (Somatom Sensation, Siemens, Erlangen, Germany) whereas, for organisational / logistic reasons, 9/289 (3.1%) had baseline imaging at the referring institution within 3 months of review at Royal Brompton Hospital. Externally performed studies were acquired on different CT scanners with slight variations in acquisition protocol, but all deemed acceptable for assessment of lung parenchymal abnormalities. Patients were scanned in the supine position with breathing suspended at full inspiration using either an interspaced (1.0-1.5 mm slice thickness with a 10 mm inter-slice gap; n=116/289 [40%]) or volumetric (0.625-1.6mm slice thickness volumetric acquisition; n=173/289 [60%]) HRCT protocol. All images for review were reconstructed using high-spatial-frequency ('bone') algorithms and reviewed on window setting: window centre, -550 HU; window width, 1500 HU.

2.3.2 *Evaluation of Scadding 'Stage' in Sarcoidosis*

The 'baseline' or presentation CXRs of all 289 patients were *independently* reviewed by two radiologists (a thoracic radiology fellow with two years' and a consultant thoracic radiologist with 25 years' experience) and a chest physician with a specialist interest in pulmonary and cardiac sarcoidosis, blinded to the findings on HRCT studies. All CXRs had been performed in the postero-anterior projection and for clinical purposes in an outpatient setting. Observers were provided with a data collection spreadsheet which included only the random unique identifiers for each case. Observers were required only to assign a Scadding stage for each study as follows:

- 0** *Normal CXR* **OR**
- I** *Intra-thoracic [e.g. symmetrical bilateral hilar $\pm$ right paratracheal/mediastinal] lymph node enlargement but no parenchymal disease* **OR**
- II** *Intra-thoracic nodal enlargement with evidence of parenchymal disease [but no CXR signs of fibrosis]* **OR**
- III** *Parenchymal disease [no fibrosis] alone* **OR**
- IV** *CXR evidence of lung fibrosis*

2.3.3 Preparation of HRCT Studies, Characterisation & Quantification of HRCT Patterns

All HRCT scans were anonymised and downloaded onto a secure drive permanently housed on-site at Royal Brompton Hospital, as stipulated by the study research protocol (Integrated Research Application System Approval No: 276717). Whenever available, volumetric HRCT datasets (n=173) were downloaded in preference to interspaced HRCT (n=116). All studies were then uploaded to ‘PACSbin’ (<http://www.pacsbin.com>), a cloud-based, password-protected DICOM server with an integrated viewer; each study on PACSbin was assigned an individual Uniform Resource Locator (URL). An online data collection website, ‘Radiologist Labs’ (developed in-house to facilitate quantitative imaging research), was used to display the DICOM images via the URL and to permit observers to record observations in the form of user-friendly drop-down boxes (Figure 2.2). On completion, the results for each observer were automatically exported into a spreadsheet for analysis.

The screenshot displays the 'Radiologist Labs' web application. On the left, a CT scan image of the lungs is shown in a DICOM viewer. The image is labeled 'CT 001' and includes technical details at the bottom: 'Scout (Lob: 4.0m)' and 'Z-stack: 1.07'. On the right, a red header bar reads 'Sarcoidosis CT 001'. Below this, a form for recording observations is visible. It includes a 'Your Unique ID' field, a 'Section 1: Scores PER LOBE' header, and two columns for 'Right Upper Lobe (RUL)' and 'Left Upper Lobe (LUL)'. Each column has a dropdown menu for 'Is the parenchyma abnormal?' and a dropdown for 'What % of the lobe is abnormal?'. Below these, there are dropdowns for 'Distribution of abnormal parenchyma' (Peripheral (%), Bronchocentric (%), Random (%)) and a 'Total Distribution Score (must be 100%)' field. At the bottom, there is a section for 'Patterns of abnormal parenchyma' with a dropdown for 'Reticulation (%) (excluding interlobular septal thickening - see below)'.

Figure 2.2 Image capture of the user interface in ‘Radiologist Labs’ — Embedded full (volumetric or interspaced) HRCT datasets are reviewed within the in-built DICOM viewer (*left*) with full scrolling and image manipulation functionality. Observations are recorded (*right*) using ‘drop down’ menus.

All HRCT studies were evaluated independent of CXR review, in random order and blinded to the results of CXR evaluations and clinical/physiological data. A single observer (a consultant radiologist with 25 years’ experience in thoracic imaging) reviewed *all* HRCT studies. However, for the purposes of quantifying observer agreement, the first 63 HRCT studies were also evaluated by five other radiologists (three consultant thoracic radiologists with 4 to 14 years’ experience and two thoracic radiology research fellows (with 2 and 3 years’ experience respectively)).

For each lobe, observers first quantified i) the **extent of abnormal lung** (to the nearest 5%) and, irrespective of individual HRCT patterns, ii) the **proportional distribution of disease** (i.e. bronchocentric versus peripheral versus random; also to the nearest 5% but

totaling 100%). Note that, for the purposes of lobar quantification, the lingula was considered a separate lobe.

Following this, the proportional extent of the following HRCT signs / patterns (Figure 2.3), as defined by the Fleischner Society (315), was quantified in each lobe to the nearest 5% and, again, totaling 100%:

- **Nodular pattern** – including nodules and micronodules, defined as rounded or irregular well- or poorly-defined opacities, measuring up to 3 cm or <3 mm respectively in diameter
- **Reticular pattern** – defined as a collection of innumerable small linear opacities which produce an appearance resembling a net
- **Ground-glass opacification** – defined as a hazy increased opacity with preservation of bronchial and vascular markings
- **Consolidation** – defined as a homogeneous increase in lung density which obscures the margins of vessels and airway walls with or without air bronchograms
- **Decreased attenuation (as part of the mosaic attenuation pattern)** – defined as a patchwork of regions of reduced attenuation in which there is a reduction in the number and/or calibre of pulmonary vessels, likely to reflect obliterative small airways disease (obliterative bronchiolitis) (111, 315)
- **Emphysema** – defined as focal areas or regions of low attenuation, usually without visible walls
- **Fibrocavitary disease**- defined as a gas-filled space and seen as a lucency or low attenuation area within a region of dense reticulation, consolidation or mass
- **Pleuroparenchymal fibroelastosis** – defined and characterised by a combination of upper zone-pleural thickening with associated subpleural reticulation and/or consolidation (342)

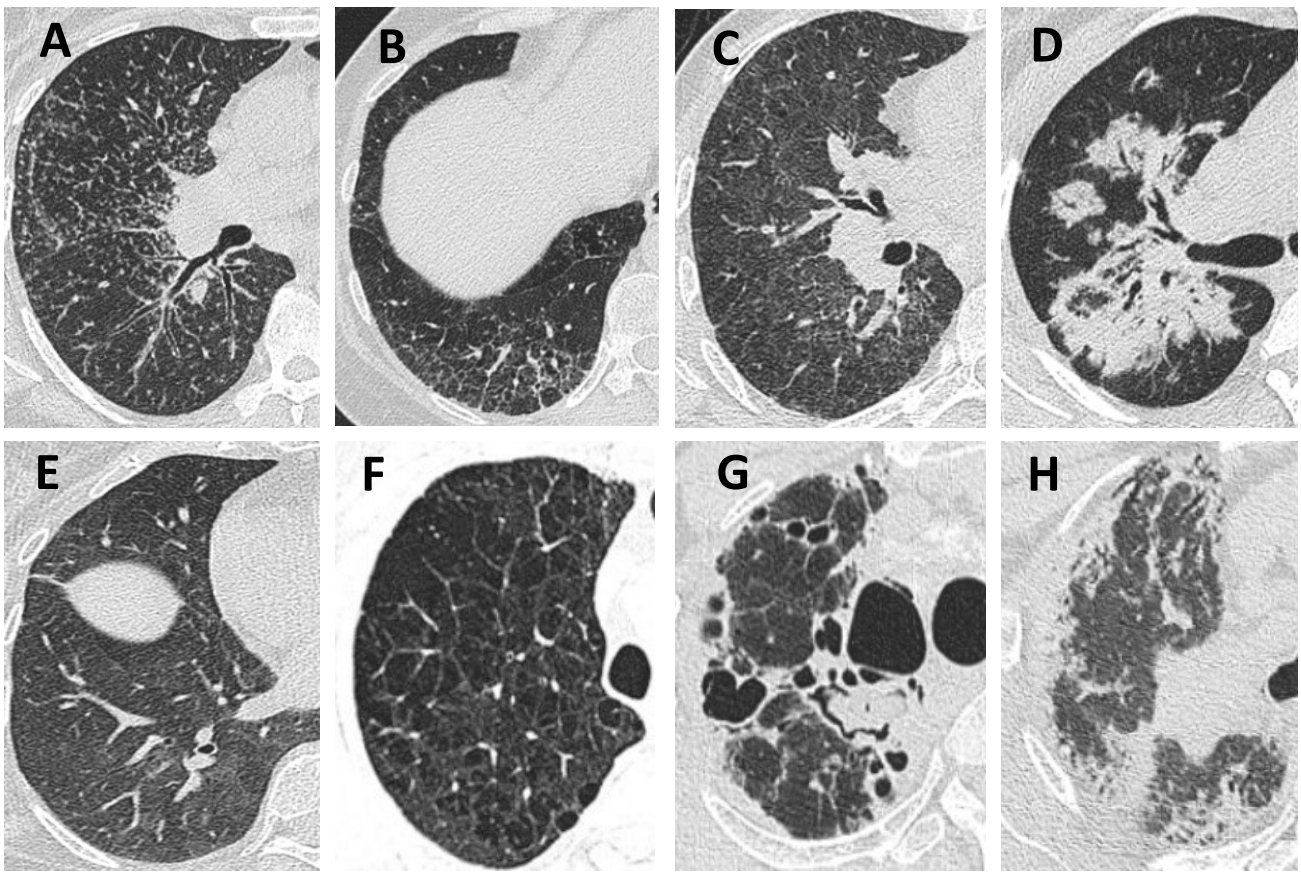


Figure 2.3 Examples of CT patterns scored for extent. A – nodules, B – reticulation, C – groundglass opacity, D – consolidation, E – decreased attenuation (mosaic), F – emphysema, G – fibrocavitary destruction, H – pleuroparenchymal fibroelastosis

When present, the severity of traction bronchiectasis/bronchiolectasis — defined as irregular bronchial or bronchiolar dilatation caused by surrounding retractile fibrosis — was scored semi-quantitatively (0=no traction bronchiectasis/bronchiolectasis present; 1=100-200% diameter compared with the homologous pulmonary artery (PA) branch; 2=200-300% of the PA branch and 3= >300% of the PA branch). Airway varicosity (1=mild; 2=moderate and 3=severe) and the number of bronchopulmonary (BP) segments with traction bronchiectasis/bronchiolectasis (1 BP segment, 2 BP segments and >2BP segments) were quantified. The extent, if present, of interlobular septal thickening in the whole lung (irrespective of lobar distribution) was also quantified (1= <5 visible septa; 2= ≥5 visible

septa but <50% of the pleural surface and 3= >50% of the pleural surface/profuse interlobular septal thickening).

Finally, observers were required to record the presence or absence of the following:

i) 'free-standing' bronchiectasis, ii) honeycombing, iii) a definite/probable UIP pattern, iv) an appearance of progressive massive fibrosis and v) mycetoma.

2.4 PULMONARY FUNCTION TESTING

In all cases, pulmonary function testing had been performed within 90 days of CT scanning; the results are expressed as a percentage of the predicated value based on age, gender and height with adjustment for racial group, using the European Community of Coal and Steel (ECCS) reference equations (343). The lower limit of normal was set at the level of the 5th percentile (or mean - 1.64 SD) of the reference population. The following were recorded: forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁:FVC ratio, total lung capacity (TLC), residual volume (RV), RV:TLC ratio, diffusing capacity of carbon monoxide (DLco) and diffusing capacity of carbon monoxide corrected for alveolar capacity (Kco). Erich Jaeger Masterscreen PFT (Vyair Medical Products Ltd. Basingstoke, RG25 2JR) was used for spirometry and Erich Jaeger Masterscreen Body (Vyair Medical Products Ltd. Basingstoke, RG25 2JR) for plethysmographic static lung volume measurement. DLco was measured by the single breath method Erich Jaeger Masterscreen PFT (Vyair Medical Products Ltd. Basingstoke, RG25 2JR).

2.5 STATISTICAL ANALYSES

The statistical methods employed in this thesis for i) evaluating observer variation and ii) determining relationships between radiological features and pulmonary function indices or outcome are discussed in the sections that follow.

2.5.1 Observer Variation

In studies that depend on *visual* characterisation and/or quantification of CXR or CT abnormalities, it is important to estimate the potential impact of measurement error ‘noise’; put simply, the degree of agreement between observers must be determined in studies of this type. The appropriate method for quantifying observer variation is generally governed by the type of data. For continuous variables, an estimate of the *correlation coefficient* is one simple method for assessing agreement (344). However, correlation must not be considered synonymous with agreement. For instance, if one observer *consistently* over-estimates a particular parameter — say, the extent of fibrosis on CT — as compared with another, correlation *per se* will be good, despite evident disagreement between the observers. Needless to say, the optimal measure of observer variation should consider not only the ‘degree’ of correlation (or association) but also the level of agreement (or proximity) between observations. In this regard, the intraclass correlation coefficient (ICC) is a more reliable measure of agreement between observers (345). The ICC estimates population variance by calculating the variability among a given set of measures. Importantly, there are different forms of ICC depending on the type of variables included (345). McGraw and Wong defined 10 forms of ICC based on the i) model, ii) type and iii) definition of relationship.

With regards to the models themselves, there are three distinct forms, based on the characteristics of the observers and the subjects (346) as follows:

- **One-way random-effects model** – assumes that each subject is rated by a different set of observers. Subjects are representative of a larger group.
- **Two-way random-effects model** – assumes that raters represent a sample of a larger observer group with similar characteristics. Subjects are also representative of a larger subject group.
- **Two-way mixed-effects model** – assumes that observers are not selected from a larger group and this model defines the reliability only between said raters. Subjects are representative of a larger group.

The ‘type’ of model reflects the measurement protocol. A ‘single-rater’ method measures the reliability of a single observer, while a ‘mean of k raters’ uses the mean of the observers as a basis for assessing variation. Finally, the ‘definition of relationship’ is defined as either a ‘consistency’ model, which considers correlations between raters, or an ‘absolute agreement’ model, which considers how close observations are to one another.

When assessing observer variation, the confidence intervals of the ICC (rather than the ICC value itself) are the most important. They are interpreted using the following thresholds (346):

<0.5	Poor reliability
0.5 – 0.75	Moderate reliability
0.75 – 0.90	Good reliability
>0.90	Excellent reliability

Quantifying observer variation for *categorical* data is not straightforward and requires a different approach. At first glance, expressing the agreement as a simple

percentage agreement might seem reasonable. However, this method is unhelpful as it does not account for agreement attributable to chance (347). For example, in the context of a dichotomous variable, a percentage agreement of 80% between two individuals might seem substantial, however 50% of this agreement is expected purely by chance (348). Against this approach, *Cohen's kappa coefficient* (K) is a better method of assessing observer agreement for categorical data (349). The kappa coefficient is the ratio of the observed agreement (in excess of chance) to the maximum possible agreement (in excess of chance), as expressed by the following equation (350):

$$\text{Kappa coefficient (K)} = \frac{P_o - P_e}{1 - P_e}$$

Where P_o = the proportion of observed agreement, P_e = the proportion of expected agreement (by chance)

The K coefficient ranges from 0 (chance agreement alone) to 1 (complete agreement). It is important to appreciate at the outset that, to date, there is no consensus for which level of K constitutes clinically-acceptable observer agreement. Consequently, and out of necessity, the definitions for the level of agreement, based on K, have been defined somewhat arbitrarily as follows (347):

0	Agreement by chance alone
0–0.20	Poor agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Good agreement
0.81–1.00	Very good agreement

The *weighted kappa coefficient* (K_w) is an important modification to Cohen's kappa for data that are ordinal (i.e. 'ranked' as opposed to 'unranked') (348). The K_w is sensitive to the smaller and larger differences between sets of observations. For instance, a one-grade

difference in a set of two readings between two observers would tend to suggest *better* agreement than if the grade difference is greater than one; the Kw accounts for such differences. The Kw can either be calculated using a linear technique or a quadratic technique (348). With linear weighting, the kappa reduces by equal increments for each degree of discrepancy, whereas with quadratic weighting, the reduction in kappa is comparatively small for one or two degrees of discrepancy but falls dramatically if the level of disagreement is greater.

Finally, Fleiss K is yet another modification to Cohen's kappa that is used to measure observer variation when there are multiple raters (348).

2.5.2 *Evaluation of CXR Stage, HRCT Scores and Lung Function Relationships*

The relationship between two independent categorical variables (such as CXR stage and presence/absence of disease on CT) can be assessed using Pearson's Chi squared (χ^2) test (351). Put simply, this test calculates the sum of the differences between the expected values and the observed values for each combination of variables and uses this to determine if there is a statistically significant difference between them. The Chi squared (χ^2) equation is as follows:

$$\chi^2 = \sum \frac{(O-E)^2}{E}$$

Where O is the observed value and E is the expected value

Importantly the Chi squared test becomes unreliable when dealing with small samples sizes (where expected values are less than 5). The Fisher's exact test is an

alternative statistical significance test that can be used with small sample sizes to determine if there is an association between two variables (351).

When comparing categorical data with more than two groups (such as CXR stage) with continuous data (such as disease extent on CT or pulmonary function tests) analysis of variance (ANOVA) can be useful. ANOVA can be used to determine if there is a statistically significant difference between the means of two or more normally distributed groups (352). The Kruskal-Wallis H Test is an alternative test that can be applied for non-normally distributed data. Importantly, while these tests determine if there is a difference between *any* of the groups included, they do not identify *which of the* groups are different. Post-hoc tests are used to determine which groups are statistically significantly different from one another (353).

2.5.3 *Evaluation of Structure-Function Relationships*

The association between a CT pattern and a chosen dependent variable can be evaluated using a univariate method known as linear regression (354). This technique involves applying a 'line of best fit' through a scattergram of datapoints to demonstrate the relationship between the two variables. The straight line is described by the regression equation:

$$y = mx + c$$

Where y is the dependent variable, m is the gradient, x is the independent variable and c is the intercept.

While the regression equation describes the relationship between two variables, it does not account for the strength of the relationship i.e. how close the data points lie to the

line of best fit (354). The correlation coefficient (Pearson's product-moment correlation coefficient for normally-distributed data and Spearman's correlation coefficient for non-normally distributed data) quantifies the strength and direction of relationships and ranges from +1 (complete positive correlation) to -1 (complete negative correlation).

The square of the correlation coefficient (r^2) is a more useful measure of the strength of relationship as it describes the proportion of variation in the dependent variable that is accounted for by a change in the independent variable (354). For example, if the correlation (r) between percentage reticulation (x) and DLco (y) is 0.5, the r^2 value of 0.25 suggests that a quarter of the variation in DLco (y) can be predicted by knowing the percentage reticulation (x).

Multiple regression analysis is a technique that describes the relationship between a single dependent variable and multiple independent variables (354). Independent variables of interest are included in the model and removed in a stepwise fashion if they fail to reach statistical significance (specified as $p < 0.05$ in this thesis). Importantly, variables considered for multivariate analysis are evaluated for multicollinearity and excluded accordingly. The final multivariate model describes the amount of variation that is explained by the statistically significant independent variables. The multiple regression equation is as follows:

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots \beta_n X_n$$

Where y is the dependent variable, β_0 is the intercept, β_1 is the gradient for the first independent variable and X_1 is the first independent variable

2.5.4 *Evaluation of Relationships between CXR Stage, HRCT findings and Survival*

The Cox proportional-hazards model is a regression model that evaluates the association between the survival time of patients and one or more predictor variables (355). This model does not stipulate a specific population distribution but assumes that the effect of the individual variables remain constant and cumulative over time. Univariate analysis, as the name suggests, evaluates the relationship between a single predictor variable and survival, while multivariate analysis describes the effect of multiple independent variables on survival. Importantly, variables considered for multivariate analysis are evaluated for multicollinearity and excluded accordingly. The Cox proportional-hazards model is described by the following equation:

$$h(t) = h_0(t) \times \exp (\beta_1 X_1 + \beta_2 X_2 + \cdots \beta_n X_n)$$

Where $h(t)$ is the hazard at time t , $h_0(t)$ is the baseline hazard ratio (i.e. if all variables were equal to zero), β_1 is the regression coefficient for the first independent variable and X_1 is the first independent variable.

A positive regression coefficient indicates a higher hazard associated with the individual variable. As with multiple linear regression, independent variables of interest are included in the model and removed in a stepwise fashion if they fail to reach statistical significance (specified as $p < 0.05$ in this thesis). The final cox regression model describes how each of the statistically significant predictor variables influences mortality.

Section I | Chapter 3

Observer Agreement for CXR and HRCT Evaluations in Sarcoidosis

3.1 INTRODUCTION & AIMS

In studies that rely on *visual* evaluation of radiological patterns or signs by multiple observers — whether for characterisation or quantification — a certain level of measurement ‘noise’ is only to be expected. Moreover, experience suggests that observer disagreement is likely to be more common and of greater magnitude when evaluating CXR findings. Reasons why this particularly holds true for CXR include the 2-dimensional nature of plain radiography (leading to anatomical superimposition and, so, difficulties in characterisation), poorer contrast resolution compared with CT and lower diagnostic accuracy. For these reasons and before relationships between radiological findings and other clinical parameters (e.g. lung function tests or survival) are explored, observer variation must be quantified. Therefore, the aims of the studies in this chapter are as follows:

- **To determine observer variation in a large patient cohort for CXR ‘staging’ according to the system proposed by Scadding**
- **To quantify observer variation for the characterisation and quantification of HRCT patterns in the same patient cohort**

3.2 PATIENTS & METHODS

The inclusion and exclusion criteria for patients in this study have been outlined in the previous chapter (see section 2.2, page 82). The final study group comprised 289 patients. The criteria for evaluating Scadding stage on CXR and the methodology for characterisation and/or quantification of HRCT patterns in sarcoidosis have also been covered in detail (see sections 2.3.2 and 2.3.3, pages 85 and 86). However, for clarity and in brief, CXRs were reviewed independently by three observers (two radiologists and one chest physicians with a special interest in sarcoidosis); for each CXR, observers were asked to

assign a Scadding 'stage' (0 to IV) blinded to the findings on HRCT and clinical/functional data. For the purposes of quantifying observer disagreement, HRCT studies were reviewed by six radiologists (consultant thoracic radiologists, n=4; research fellows in thoracic radiology, n=2). For each lobe, observers recorded the overall extent of abnormal lung, the predominant distribution of disease (bronchocentric vs. peripheral vs. random) and the proportional extents and/or severity of different HRCT patterns (including nodules, ground-glass opacification, reticulation, consolidation and traction bronchiectasis).

3.3 STATISTICAL METHODS

Overall observer variation for CXR stage was expressed as both weighted and unweighted Kappa (K) coefficients, while observer variation for individual stages was expressed as the Fleiss Kappa (K) coefficient. Kappa statistics were interpreted using the thresholds indicated previously (see section 2.5.1; page 91). Observer variation for CT patterns was calculated as a 'whole lung score': Lobar HRCT patterns were converted into whole lung scores by calculating the mean scores across all lobes. Thus, for instance, the mean percentage extent of reticulation across six lobes was calculated to give a whole lung percentage reticulation score. Inter-observer variation was calculated for mean whole lung scores using a two-way, random effects, mean-rater, absolute agreement intra-class correlation (ICC) methodology. For variables scored for the lungs as a whole (for example, the presence or absence of honeycombing), Fleiss Kappa statistics were used to assess inter-rater agreement.

3.4 RESULTS

3.4.1 Radiographic Scadding Stages by Observer

In total, 289 CXRs were independently reviewed for Scadding stage. The most frequently recorded CXR stage by all three observers was stage IV [observer 1, 86 (30%), observer 2, 90 (31%) and observer 3, 83 (29%)], Table 3.1). There was disagreement between all observers in 24 cases (8%); the CXRs for these cases were jointly reviewed and a consensus stage assigned. Figure 3.1 provides examples of radiographs with varying degrees of observer agreement. Overall, stage IV was the most prevalent (n=90, 31%), and stage II (n=36, 12%) the least. Across all observers, agreement for CXR staging was ‘moderate’ to ‘good’ for all categories (Fleiss K=0.57, 95% CI 0.54-0.61 [or Kw=0.69, 95% CI 0.63-0.75]). Agreement for individual CXR stages was ‘good’ for Scadding stage IV (Fleiss K = 0.77) but only ‘fair’ (and lowest) for stage III (Fleiss K = 0.40).

CXR Stage	OBSERVER			Fleiss Kappa (K)	Confidence Interval	Final Consensus CXR Stage (%)
	1	2	3			
<i>0</i>	53	78	45	0.61	0.54-0.67	61 (21)
<i>I</i>	34	38	39	0.54	0.47-0.60	36 (12)
<i>II</i>	69	40	78	0.46	0.38-0.52	56 (19)
<i>III</i>	47	43	44	0.40	0.33-0.47	46 (16)
<i>IV</i>	86	90	83	0.77	0.70-0.84	90 (31)
Total	289	289	289			

Table 3.1 Observer variation for CXR stage — Observer agreement, expressed as the Fleiss K, was acceptable for all CXR stages (K=0.40-0.77) but was highest for Stage 4 (K=0.77) and lowest for stage 3 disease (K=0.40). NB *Final consensus stage following joint review; all data (except for K) are numbers of patients with percentages in parentheses*

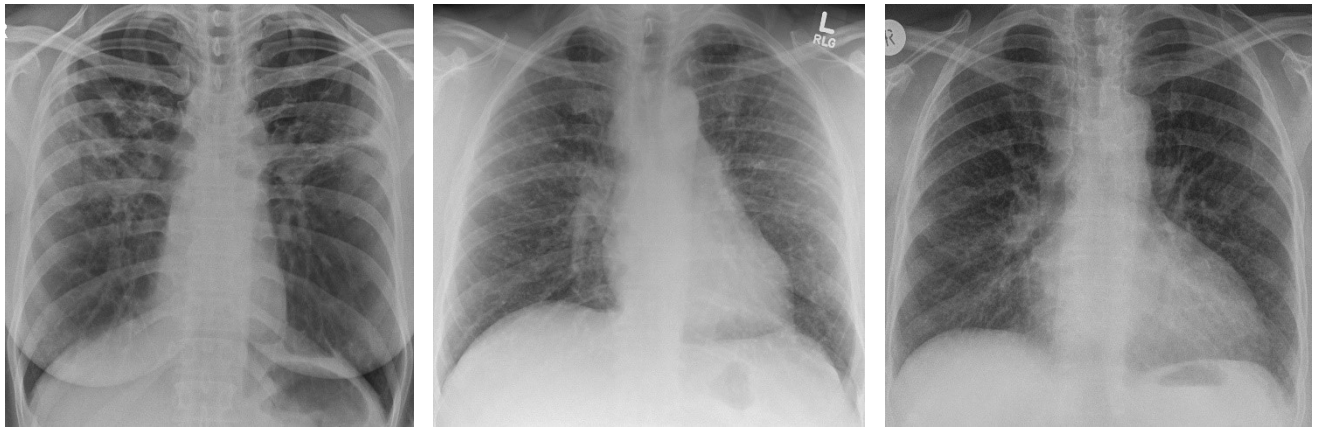


Figure 3.1. Observer agreement for CXR staging in three patients with sarcoidosis. A) *Complete agreement*: 54-year-old female assigned stage IV by all three observers. B) *Partial agreement*: 54-year-old male assigned stage III by two observers and stage II by the third. C) *No agreement*: 53-year-old assigned stages 0, II and III by the three observers — a final consensus of stage III was assigned to this CXR after joint review by the three observers

3.4.2 Observer Agreement for Characterisation/Quantification of HRCT Abnormalities

Observer agreement for the characterisation and quantification of HRCT patterns is shown in Table 3.2. In general, for variables that were quantified on a ‘continuous’ scale to the nearest 5%, observer agreement (calculated using intra-class correlation coefficient [ICC]) was high and higher than for discrete variables. Observer agreement was highest for the proportional CT extent of nodules and consolidation (ICC=0.96; 95% confidence intervals [CI]=0.94-0.97 and ICC=0.94; 95% CI=0.91-0.96 respectively) and lowest for decreased attenuation as part of a mosaic pattern (mean proportional extent=10%; ICC 0.75 [95% CI=0.61-0.85]). There was ‘very good’ agreement for the presence/absence of mycetoma (Fleiss K = 0.85) and ‘good’ agreement for the presence of honeycombing (Fleiss K = 0.66). Agreement for the presence/absence of ‘free-standing’ bronchiectasis and interlobular septal thickening (Fleiss K = 0.11 and 0.23 respectively) was lower than clinically acceptable and excluded from subsequent analysis.

HRCT ABNORMALITY	Mean Severity or Extent	Measure of Agreement	ICC or K	95% CI
Presence/absence of disease	0.74	ICC	0.93	0.89-0.96
Extent of Lobar Abnormality (%)	0.28	ICC	0.92	0.86-0.96
<i>Distribution - Peripheral</i>	0.10	ICC	0.73	0.62-0.82
<i>Distribution - Bronchocentric</i>	0.20	ICC	0.83	0.75-0.89
<i>Distribution - No dominant distribution</i>	0.45	ICC	0.79	0.69-0.86
PROPORTIONAL EXTENTS OF:				
<i>Reticular Pattern</i>	0.07	ICC	0.86	0.80-0.91
<i>Nodular Pattern</i>	0.29	ICC	0.96	0.94-0.97
<i>Decreased Attenuation /Mosaicism</i>	0.10	ICC	0.75	0.61-0.85
<i>Ground-glass Opacification</i>	0.14	ICC	0.89	0.84-0.93
<i>Consolidation</i>	0.12	ICC	0.94	0.91-0.96
<i>Emphysema</i>	0.09	ICC	0.87	0.81-0.91
<i>Fibrocavitary Disease</i>	0.004	ICC	0.93	0.90-0.95
<i>Pleuroparenchymal Fibroelastosis</i>	0.009	ICC	0.89	0.85-0.93
TRACTION BRONCHIECTASIS or BRONCHIOLECTASIS (Per lobe)				
<i>Presence or absence</i>	0.187	ICC	0.91	0.87-0.94
<i>Number of bronchopulmonary segments</i>	0.349	ICC	0.93	0.90-0.95
<i>Severity</i>	0.265	ICC	0.94	0.91-0.96
<i>Varicosity</i>	0.142	ICC	0.90	0.85-0.93
ADDITIONAL HRCT FEATURES (Presence or Absence)				
<i>Free-standing bronchiectasis</i>		Fleiss Kappa	0.11	0.05-0.18
<i>Honeycombing</i>		Fleiss Kappa	0.66	0.59-0.72
<i>UIP</i>		Fleiss Kappa	0.32	0.27-0.38
<i>PMF</i>		Fleiss Kappa	0.49	0.43-0.56
<i>Mycetoma</i>		Fleiss Kappa	0.85	0.79-0.92
<i>Interlobular septal thickening</i>		Fleiss Kappa	0.23	0.19-0.27

Table 3.2 Agreement between six observers for characterisation & quantification of HRCT abnormalities in sarcoidosis. Data are the intra-class correlation coefficient (ICC; calculated using a two-way random-effects multi-rater absolute agreement model) or Fleiss Kappa (K) as appropriate. Variables highlighted in red had clinically-unacceptable observer variation and were accordingly excluded from the analysis. N.B. BP=bronchopulmonary; UIP=usual interstitial pneumonia; PMF=progressive massive fibrosis

3.5 DISCUSSION

The studies in this chapter have explored observer agreement for CXR 'staging' in a reasonably large cohort of patients with sarcoidosis referred to Royal Brompton Hospital. In the same cohort, variation between observers for the characterisation and/or quantification of HRCT abnormalities has also been assessed. The results show that agreement for CXR evaluation was highest for patients judged to have established fibrosis (i.e. Scadding Stage IV) but only low 'moderate' and 'fair' for those with CXR stage II ($K=0.46$) and III ($K=0.40$) disease respectively. Agreement between six observers for HRCT evaluation was surprisingly good with intraclass correlation coefficients (ICC) ranging from 0.73 (CI 0.62-0.82) to 0.96 (CI 0.94-0.97), and this included patterns that were either uncommon or limited in extent (e.g. decreased attenuation as part of the mosaic attenuation pattern or emphysema). Observer variation for detecting the presence/absence of 'free-standing' bronchiectasis (Fleiss $K=0.11$, CI 0.05-0.18) and interlobular septal thickening (Fleiss $K=0.23$, CI 0.19-0.27) was clinically unacceptable.

In previous studies of sarcoidosis, stage I and II disease on CXR have been the most prevalent, with CXR stage IV relatively uncommon (1, 220, 356-358); in four studies from different centres (including the British Thoracic Society registry data), stage II was present in 25-60% of cases, compared with stage IV in just 7-20%. These data conflict with the findings of the present study — in which CXR stage IV disease predominated and accounted for ~30% of cases. Interestingly, a prior study by Zappala et al, also performed at Royal Brompton hospital (albeit in a different cohort), identified a similarly high proportion of stage 4 disease (163/354, 46%) (359). As a tertiary centre for pulmonary sarcoidosis, the Royal Brompton Hospital manages a disproportionately larger number of 'difficult-to-treat'

(and, by implication, fibrotic) cases. Hence, inevitably, a greater proportion of patients with sarcoid-related fibrosis would have been included in the present study. That said, patients with CXR Stage 0 and II each accounted for around one-fifth of cases suggesting that, despite the slight bias towards more complex stage IV sarcoidosis, there was a reasonably good representation of *all* Scadding stages within the cohort for the chapters and studies that follow.

The choice of statistical test for expressing observer variation in CXR evaluation requires brief discussion. In the present study, overall interobserver agreement for Scadding stage has been expressed both as the unweighted (Fleiss $K=0.57$) and weighted ($K_w=0.69$) Kappa coefficient. Of the two measures, it might be argued that the former is most appropriate: earlier studies have expressed variation using the K_w for Scadding stage (263, 280, 359). However, this assumes that there is a predictable progression in CXR 'stages' of sarcoidosis (akin to what is seen in patients with cancer). As discussed previously (see section 1.11.1.4, page 61) the use of the term 'stage' for describing CXR appearances is perhaps misleading: patients with sarcoidosis do not, as a rule, progress from a lower to higher stage. Accordingly, the unweighted Kappa — for *nominal* as opposed to *ordinal* data — would seem the most appropriate. Against this, evidence that outcome (as judged by CXR resolution at 5 years (1), and survival (220), worsens with increasing stage, would tend to favour a weighted Kappa. This notwithstanding, in either case, the findings of the present study indicate more acceptable observer agreement compared with prior research by Baughman and colleagues who reviewed serial CXRs (in treated patients with sarcoidosis) and found suboptimal agreement for baseline radiographic stage ($K_w=0.41$) (280). In a later study by Zappala et al., there was 'very good' observer agreement ($K_w=0.81$) for baseline radiographic stage (359). Importantly, both the above stated studies assessed observer

agreement only among radiologists, in contrast with the present study which has included the observations of a respiratory physician. This has practical significance, particularly in a clinic setting, given that chest physicians may be reviewing and opining on CXRs without recourse to a radiology report.

The current study is the first to quantify reliability of *individual* CXR stages and show that agreement was highest for stage IV (established fibrosis) and lowest for Stage II (nodal disease with parenchymal involvement) and III (parenchymal disease only). In part, our results are in line with the observation of Scadding that stage II and III (and, for that matter, stage III and IV) are not “*sharply demarcated from each other*” (1). The poorer observer agreement for these stages might also be explained by the limited sensitivity of CXR in detecting subtle (non-fibrotic) parenchymal disease (284) and minor hilar nodal enlargement (284, 360). Indeed, in a study of 130 patients, Baughman and colleagues compared radiographic scores assigned by two observers and found discrepancies in the number of cases scored as stage II versus III and also III versus IV, although they did not *quantify* the level of disagreement (280). Observed inconsistencies were attributed to difficulties identifying nodal disease and subtle fibrosis on CXR.

Observer agreement for various HRCT features has been documented in a number of previous studies (Table 3.3). However, from study to study, even a cursory glance shows that there are wide differences not only in the numbers of CT cases reviewed but also, the HRCT features evaluated and the choice of statistical tests for expressing disagreement between readers (109, 114, 221, 284, 311, 314, 332, 336, 361-364). Moreover, barring one study by van den Heuvel (363), the numbers of observers in each has been limited (109, 114, 221, 284, 311, 314, 332, 336, 361, 362, 364). For instance, in a study correlating HRCT

findings with lung function, Drent et al. reported the agreement between only two observers for the extent of bronchovascular bundle thickening, consolidation, nodules, septal and non-septal lines and also the severity of pleural thickening and lymph node enlargement (284). They demonstrated 'near-perfect' agreement for total HRCT score (intraclass correlation coefficient = 0.99), consistent with the findings of the present study. That said, the extent of individual CT patterns was based on semi-quantitative scoring and was only associated with 'fair' to 'good' agreement between observers ($K\omega=0.36-0.78$). Van den Heuvel performed a dedicated study of observer agreement among five observers who were asked to review CT patterns in pulmonary sarcoidosis (363). The extent of individual CT patterns (including nodules, consolidation, groundglass opacity, honeycombing and mosaicism) was quantified semi-quantitatively (with extent scored to the nearest 25%) and found 'fair' to 'good' observer agreement for most CT patterns (363) ($ICC=0.52-0.91$).

The study described in the present chapter — taking into account the observations of six radiologists of varying seniority and experience — is arguably the most comprehensive evaluation of CT findings to date. Not only was the overall extent of abnormal lung recorded but observers were also required to characterise/quantify individual HRCT patterns (as a proportion of abnormal lung), the distribution of disease (i.e. bronchocentric versus peripheral versus no predominant distribution), the extent/severity of traction bronchiectasis and the presence/absence of a number of uncommon but recognised HRCT findings (e.g. usual interstitial pneumonia [UIP] pattern, interlobular septal thickening). Given the potential complexity of the scoring methodology in this study, it was gratifying to note the high levels of agreement for the overwhelming majority of CT features evaluated. CT features traditionally considered to signify 'reversible disease' (i.e. nodules, consolidation and ground-glass opacity) were associated with 'good' to 'excellent' observer agreement, as

were the cardinal features of 'irreversible disease' (i.e. reticulation and traction bronchiectasis) (97). In the study by Drent and colleagues, there was 'good' agreement for nodule scores ($K\omega=0.78$), but only 'moderate' agreement for reticulation ($K\omega=0.57$) (284). Needless to say, when comparing the findings of earlier studies with the present, one of the issues (as highlighted above) is the use of different statistical tests for expressing agreement between readers. That said, the reported observer variation in the study by Sawahata et al was more akin to those in the current chapter: for 'fibrotic CT patterns' in patients with sarcoidosis and chronic respiratory failure, there was near-perfect agreement between two observers for the extent of consolidation, ground-glass opacification and traction bronchiectasis (Spearman's rank correlation = 0.985, 0.996 and 0.998 respectively) (361). However, a key limitation of the study, was the inclusion of only ten patients.

Recording the presence/absence 'free-standing' bronchiectasis and interlobular septal thickening was associated with clinically unacceptable observer disagreement. The reasons for this are not entirely clear but may be linked with the relative infrequency with which these patterns are encountered in sarcoidosis.

Author	Year	HRCT Feature(s) Evaluated	Sample Size	Number of Observers	Observer Agreement
Muller et al. (332)	1989	- Disease extent per lung 'zone'	27	2	ICC $\geq$ 0.84, $P < 0.001$
Bergin et al. (311)	1989	- Individual CT patterns	27	3	K=0.59-0.58
Hansell et al. (114)	1998	- Lobar disease extent	45	2	K ω =0.56-0.76
Abehsera et al. (109)	2000	- Fibrotic phenotypes	80	2	K=0.87
Drent et al. (284)	2003	- Overall disease extent - Individual CT patterns	60	2	Overall: ICC=0.99 Individual patterns: K ω =0.36-0.78
Naccache et al. (362)	2008	- Presence/absence of airway involvement - Dominant pattern - Extent of airway involvement per 'zone'	84	2	K=0.85 and 0.89 ICC = 0.85 for predominant pattern and ICC = 0.81 for overall score
Walsh et al. (221)	2014	- Overall disease extent - Individual CT patterns	251	2	Overall: sdSD=0.9 (0-6.1) Individual patterns: sdSD= 1.6 (0-9.1) to 2.7 (0-14.4)
van den Heuvel et al. (363)	2015	- Extent of HRCT patterns	51	5	ICC=0.11-0.80
Benamore et al. (314)	2016	- CT activity score	85	2	R=0.91; $p < 0.0001$ (Bland Altman)
Duan et al. (336)	2018	- Individual CT patterns - CT activity score	57	2	K=0.85-0.91 [†]
Sawahata et al. (361)	2020	- Presence/absence - Extent of individual CT patterns (quantitative) and other findings	10	2	Presence/absence: K=0.98-1.00 Extent scores: Spearman's Rank correlation coefficient=0.99-1.00
Susam et al. (364)	2021	- Dominant HRCT pattern	145	2	K=0.67, $p=0.035$

Table 3.3 Historical studies documenting observer variation for HRCT evaluation. Considerable variability in sample sizes, numbers of observers, features evaluated and statistical methods for quantifying agreement (i.e. weighted or unweighted Kappa [K or K ω], intra-class correlation coefficient (ICC), single determination standard deviation (sdSD), Bland-Altman analysis or Spearman's rank correlation coefficient)

[†] Uncertainty over which variables were evaluated for observer agreement

KEY POINTS

- Observer agreement for CXR 'staging' in sarcoidosis is influenced by the presence/absence of signs of fibrosis; agreement was highest for stage IV disease and at the lowest threshold for clinical acceptability in patients with stage III sarcoidosis on CXR
- Despite the apparent complexity and multiplicity of radiological signs, agreement for the overall extent of disease, its distribution and the extent/severity of multiple common patterns on HRCT in sarcoidosis is surprisingly good

Section 1 | Chapter 4

Relationships between CXR 'Stage', HRCT Appearances, Physiology & Outcome in Sarcoidosis

4.1 INTRODUCTION & AIMS

The clinical course of sarcoidosis varies from patient to patient; accordingly, predicting outcome — an important aspect of clinical management — becomes a challenge (1, 146, 242, 243). The plain CXR is the most common imaging test requested by chest physicians but, in patients with diffuse lung disease, CXR diagnosis and interpretation are hampered by poor sensitivity and accuracy, when compared with HRCT (365). The system of CXR evaluation proposed by Scadding — frequently (and erroneously) referred to as ‘staging’ — categorises CXR findings into groups according to the presence or absence of intra-thoracic nodal enlargement and parenchymal disease which, broadly-speaking, have a prognostic meaning (1). However, the limitations of this method of CXR evaluation are widely acknowledged (see section 1.11.1.4, page 61) and, in this respect, HRCT is likely to be superior (284, 286). However, no formal comparison of CXR ‘stage’ and HRCT has been undertaken in a large cohort of patients with sarcoidosis. Thus, the specific goals of the investigations in this chapter were as follows:

- **To evaluate relationships between CXR stage and HRCT abnormalities in patients with sarcoidosis**
- **To ascertain and compare the physiological/prognostic impact of CXR stage and HRCT abnormalities in pulmonary sarcoidosis**

4.2 PATIENTS & METHODS

The inclusion and exclusion criteria for patients studied in the present chapter have been outlined previously (see section 2.2, page 82). The final study group comprised 289 patients.

4.2.1 Characterisation & Quantification of HRCT Patterns

HRCT studies were evaluated independent of CXRs, in random order and blinded to clinical/physiological data. The methods for HRCT evaluation have also been described previously (see section 2.3.3, page 86). However, for brief reference, the overall extent of abnormal lung per lobe and the proportional extent of the individual HRCT patterns — including but not restricted to a nodular pattern, reticulation and ground-glass opacification — were quantified to the nearest 5% (totaling 100%). If present, the extent and severity of traction bronchiectasis were quantified semi-quantitatively.

4.2.2 Statistical Methods

The statistical tests employed in this chapter have been discussed previously (see section 2.5, page 91). In brief, lobar HRCT patterns were converted into whole lung scores by calculating the mean scores across all lobes: thus, for instance, the mean percentage extent of reticulation across six lobes was calculated to give a whole lung percentage reticulation score. When examining relationships between CXR Stage and CT patterns, a ‘consensus’ Scadding stage was assigned to all CXRs based on the most frequent score between the three observers; CXRs staged differently by all three observers (n=24) were re-reviewed and assigned a stage by consensus. Chi squared or Fisher’s exact tests (as appropriate) were used to evaluate differences in the presence/absence of CT patterns for each CXR stage. The analysis of variance (ANOVA) or Kruskal-Wallis H test (again, as appropriate) were used to compare mean CT extent scores for each CXR stage depending on the population distribution - relevant *post-hoc* tests were performed if a statistically significant difference was identified between groups. The ANOVA and Kruskal-Wallis H tests were also used to compare CXR stages with lung function tests depending on the population

distribution. When comparing HRCT variables with lung function, linear and multiple linear regression was used. Univariate and multivariate Cox-proportional hazards tests were used to explore relationships between individual HRCT variables and survival. In all cases, a p-value of <0.05 was considered statistically significant.

4.3 RESULTS

4.3.1 Baseline CXR and HRCT Observations

CXR stage IV was the most prevalent stage (90/289 [31%]), followed by stages 0 (61 [21%]), II (56[19%]), III (46 [16%]) and I (36 [12%]). A nodular pattern was the most prevalent finding on CT (153/289 [53%]); consolidation (92/289 [32%]), ground-glass opacification (88/289 [30%]) and reticulation (86/289 [30%]) were less frequent. Emphysema, PPFE, UIP, honeycombing, mycetoma and PMF were each present in $\leq 5\%$ of cases.

4.3.2 Relationships Between CXR Stage and HRCT Features

For the purposes of analysis, stage 0 and I were combined, given the supposed absence of parenchymal involvement in both. There was parenchymal disease on HRCT (irrespective of specific patterns) in the majority of patients (225/289 [78%]), including 40/97 (41%) with CXR stage 0/I (Table 4.1 and Figure 4.1). Conversely, there was no HRCT evidence of parenchymal disease in 2/56 (4%) and 5/46 (11%) of patients with CXR stages II and III respectively. Not surprisingly, there was evidence of parenchymal involvement in the overwhelming majority of patients with stages II (96%), III (89%) and IV (100%) disease.

	CXR Stage				TOTAL
	0/I	II	III	IV	
Parenchymal disease absent on HRCT	57 (59%)	2 (4%)	5 (11%)	0 (0%)	64 (22%)
Parenchymal disease present on CT	40 (41%)	54 (96%)	41 (89%)	90 (100%)	225 (78%)
TOTAL	97	56	46	90	289

Table 4.1 Relationship between CXR Stage and the presence/absence of lung involvement on HRCT in 289 patients with sarcoidosis. Data indicate the prevalence (i.e. presence or absence [with percentages in parentheses]) of parenchymal disease according to different CXR stages

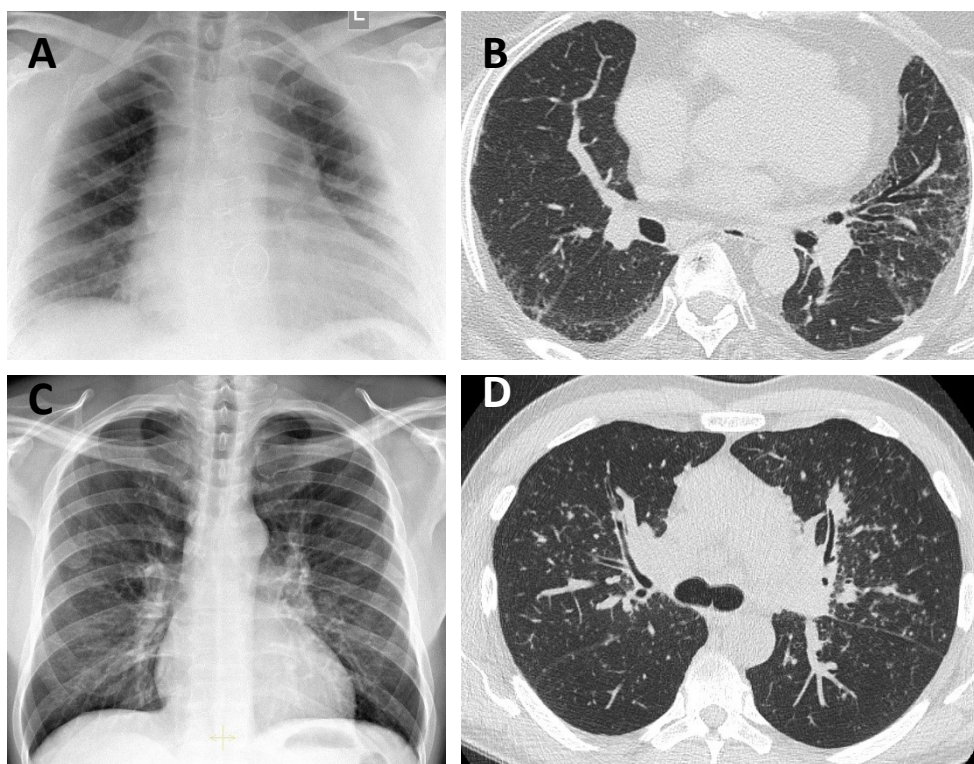


Figure 4.1 CXR stage versus HRCT features in two patients with sarcoidosis.

A) CXR Stage 0 (as graded by all three observers) and **B)** HRCT in the same patient showing parenchymal disease with signs of fibrosis: there is predominant ground-glass opacification, fine reticulation and traction bronchiectasis in the lingula. **C)** CXR Stage I in another patient scored with **D)** contemporaneous HRCT showing innumerable peribronchovascular micronodules on HRCT.

4.3.3 Prevalence, Extent/Severity of Specific HRCT Patterns Stratified by CXR Stage

Table 4.2 details the prevalence of *individual* HRCT patterns according to CXR stage.

Parenchymal nodules on HRCT were most prevalent in patients with CXR stage II (48/56 [86%]). By contrast, reticulation (55/90 [61%]) and traction bronchiectasis (58/90 [64%]) were both most prevalent in CXR stage IV. Decreased attenuation (as part of the mosaic attenuation pattern) was only present in 31/289 (11%) patients but was most often present in those with CXR stage IV disease. Emphysema and signs of PPFE were minor features on CT, present only in 8/289 (3%) and 10/289 (3%) respectively.

	Prevalence within CXR Stage				Prevalence (n=289)	p-value
	Stage 0/I (n=97)	Stage II (n=56)	Stage III (n=46)	Stage IV (n=90)		
<i>Reticulation</i>	8 (8%)	10 (18%)	13 (28%)	55 (61%)	86	<0.001
<i>Nodules</i>	23 (24%)	48 (86%)	28 (61%)	54 (60%)	153	<0.001
<i>Decreased Attenuation</i>	7 (7%)	5 (9%)	1 (2%)	18 (20%)	31	0.005
<i>Ground-glass Opacification</i>	12 (12%)	19 (34%)	15 (33%)	42 (47%)	88	0.001
<i>Consolidation</i>	8 (8%)	22 (39%)	14 (30%)	48 (53%)	92	0.001
<i>Emphysema</i>	1 (1%)	2 (4%)	1 (2%)	4 (4%)	8	0.528
<i>Fibrocavitary disease</i>	0 (0%)	2 (4%)	1 (2%)	19 (21%)	22	0.001
<i>PPFE</i>	2 (2%)	0 (0%)	1 (2%)	7 (7%)	10	0.05
<i>Traction bronchiectasis</i>	1 (1%)	6 (11%)	6 (13%)	58 (64%)	71	0.001
<i>Honeycombing</i>	1 (1%)	1 (2%)	1 (2%)	9 (10%)	12	0.010
<i>UIP</i>	2 (2%)	1 (2%)	4 (9%)	6 (7%)	13	0.160
<i>PMF</i>	0 (0%)	1 (2%)	0 (0%)	14 (16%)	15	<0.001
<i>Mycetoma</i>	0 (0%)	1 (2%)	0 (0%)	13 (14%)	14	<0.001

Table 4.2 Relationship between individual HRCT patterns and/or signs and CXR stage. Each row of data indicates the *prevalence* of specific HRCT patterns/signs in each CXR stage; p-values represent Pearson's chi squared test evaluating differences in prevalence between the CXR stages.

NB PPFE=pleuroparenchymal fibroelastosis; UIP=usual interstitial pneumonia (definite or probable); PMF=progressive massive fibrosis

Between CXR stages, there were significant differences in the overall HRCT extent of disease ($p<0.001$), the extent of reticulation ($p<0.001$), nodules ($p<0.001$), consolidation ($p=0.006$) and fibrocavitary disease ($p=0.004$) (Table 4.3) but there were no significant differences between CXR stages for the extent of ground-glass opacification ($p=0.729$) or decreased attenuation ($p=0.195$)

EXTENT	Prevalence (n=225)	CXR Stage	Mean Extent (SD)	p-Value
<i>Overall HRCT Extent</i>	n/a	I	0.12 (0.19)	<0.001
		II	0.26 (0.26)	
		III	0.24 (0.24)	
		IV	0.36 (0.22)	
<i>Reticulation</i>	86	I	0.08 (0.21)	<0.001
		II	0.04 (0.13)	
		III	0.17 (0.31)	
		IV	0.26 (0.30)	
<i>Nodules</i>	153	I	0.33 (0.38)	<0.001
		II	0.58 (0.39)	
		III	0.52 (0.44)	
		IV	0.27 (0.35)	
<i>Decreased Attenuation</i>	31	I	0.05 (0.17)	NS
		II	0.06 (0.22)	
		III	0.00 (0.01)	
		IV	0.07 (0.20)	
<i>Ground-glass opacification</i>	88	I	0.13 (0.27)	NS
		II	0.15 (0.26)	
		III	0.20 (0.33)	
		IV	0.16 (0.24)	
<i>Consolidation</i>	92	I	0.04 (0.11)	0.006
		II	0.09 (0.19)	
		III	0.05 (0.11)	
		IV	0.14 (0.23)	
<i>Fibrocavitary Disease</i>	22	I	0.00 (0.00)	0.004
		II	0.00 (0.01)	
		III	0.00 (0.00)	
		IV	0.03 (0.10)	

Table 4.3 Differences in HRCT disease extent (overall & individual patterns/signs) between CXR stage. Data presented is the mean extent of individual HRCT patterns for each CXR stage. P values represent analysis of variance (ANOVA) across the CXR stages. NB SD=standard deviation

4.3.4 HRCT Prevalence/Extent of Fibrosis Stratified by CXR Stage

The prevalence of *fibrosis* in different CXR stages was examined by considering HRCT signs most likely to indicate established fibrotic lung disease; this was evaluated in one of two ways:

- I) A '**composite fibrosis score**' based on the presence of any of following HRCT features: i) reticulation, ii) fibrocavitary disease and iii) pleuroparenchymal fibroelastosis.
- II) The **presence of traction bronchiectasis** as the sole marker of established fibrosis.

4.3.4.1 Presence and Extent of Fibrosis vs. CXR Stage

Overall, at least one of the three composite HRCT signs of fibrosis were present in 95/289 (33%) patients (Table 4.4). Fibrosis, based on the composite HRCT signs, was present in 60/90 (67%) with CXR stage IV but also in 14/46 (30%), 11/56 (20%) and 10/97 (10%) with CXR Stages III, II and 0/I respectively. Since the presence/absence of fibrosis is an important distinction between CXR stages III and IV, further analysis was performed and demonstrated a statistically significant difference in the presence of composite fibrosis between these stages ($p < 0.001$) attributable to the presence of reticulation and/or fibrocavitary disease ($p < 0.001$ and $p = 0.002$ respectively) (Table 4.4).

	CXR Stage				Total	p-value
	0/I (n=97)	II (n=56)	III (n=46)	IV (n=90)		
Fibrosis absent	87 (90%)	45 (80%)	32 (70%)	30 (33%)	194	-
Fibrosis present	10 (10%)	11 (20%)	14 (30%)	60 (67%)	95	<0.001†
<i>Reticulation</i>			13	55	68	<0.001†
<i>Fibrocavitary Disease</i>			1	19	20	0.002†
<i>PPFE</i>			1	7	8	NS

Table 4.4 Presence/absence of fibrosis across CXR stages based on ‘composite’ HRCT signs. Data are the prevalence (with percentages in parentheses) of HRCT signs indicating fibrosis based on a composite fibrosis score (overall & sub-categorised by the presence of reticulation, fibrocavitary disease and/or pleuroparenchymal fibroelastosis [PPFE]). NB †comparison between CXR stages III and IV

Mean fibrosis extent scores were calculated for those with evidence of fibrosis on CT (n=95). Despite clear differences in the overall *prevalence* of fibrosis, there was only a statistically significant difference in the *extent* of fibrosis between stages II and IV (p=0.02). Mean fibrosis extent scores were 0.49±0.35 and 0.46±0.29 for stages III and IV respectively. Results for fibrosis extent are provided in Table 4.5.

Scadding Stage	N	Mean Fibrosis Score (SD)	95% Confidence Interval for Mean
0/I	10	0.39 (0.26)	0.23-0.55
II	11	0.20 (0.24)	0.06-0.34
III	14	0.49 (0.35)	0.31-0.67
IV	60	0.46 (0.29)	0.39-0.53
Total	95		

Table 4.5 Mean fibrosis extent scores compared with Scadding stage (n=95). Data are mean extent of fibrosis scores (with standard deviation in parentheses). There was a statistically significant difference between stage II and IV (p=0.02), but no statistically significant difference between the remaining stages.

4.3.4.2 HRCT Traction Bronchiectasis vs. CXR Stage

The presence of traction bronchiectasis was also analysed as a surrogate marker of fibrosis (Table 4.6). There was a significant difference in the presence of traction bronchiectasis between CXR stages ($p < 0.001$), with the highest prevalence in stage IV (58/90, 64%). Importantly, a significant proportion of stage III cases (13%) also demonstrated traction bronchiectasis.

	CXR Stage				Total
	0/I	II	III	IV	
Traction Bronchiectasis Absent	96 (99%)	50 (89%)	40 (87%)	32 (36%)	218
Traction Bronchiectasis Present	1 (1%)	6 (11%)	6 (13%)	58 (64%)	71
Total	97	56	46	90	289

Table 4.6 Presence/absence of fibrosis across CXR stages based on traction bronchiectasis.
Data are the prevalence (with percentages in parentheses) of traction bronchiectasis on HRCT.

4.3.5 HRCT Prevalence/Extent of 'Reversible Disease' Stratified by CXR Stage

As with HRCT signs of fibrosis, two approaches were taken to examine the relationship between the putative signs of 'reversible' disease on HRCT (97, 320, 366) and CXR stage (Table 4.7) as follows: first, a 'composite reversibility score' was generated based on the presence of one or more of the following HRCT features: i) nodules, ii) consolidation and iii) ground-glass opacification (Table 4.7); second, as the most prevalent HRCT pattern ($n=153$), the presence of nodules was then considered as a sole marker of reversible disease (97, 320, 366) [see below]. The analysis was performed in a subgroup of patients with HRCT

evidence of parenchymal abnormality (n=225) in order to evaluate the proportion of disease that may resolve.

Based on the composite score, there was HRCT evidence of reversible disease across all CXR stages with no significant difference in the presence of reversible disease between them (p=0.06).

	CXR Stage				Total
	0/I	II	III	IV	
HRCT features of reversible disease ABSENT	6 (15%)	1 (2%)	3 (7%)	4 (4%)	14
HRCT features of reversible disease PRESENT	34 (85%)	53 (98%)	38 (93%)	86 (96%)	211
Total	40	54	41	90	225

Table 4.7 Presence/absence of HRCT signs of ‘reversibility’ based on a composite score. Data are the prevalence (with percentages in parentheses) of CT signs of *reversible* disease (nodules, consolidation and groundglass opacity) in those with evidence of parenchymal disease on CT.

As the most prevalent CT pattern, and a marker of reversible disease (221, 320, 366), the nodular pattern was scrutinised further. Nodules were present in just over half (153/225, 53%) of the studies with parenchymal disease, and most prevalent in CXR stage II (48/54, 89%) as compared with CXR stages 0/I (23/40 [58%]), III (28/41 [68%]) and IV (54/90 [60%]).

There was no significant difference in the profusion (i.e. extent) of nodules between CXR stage 0/I (mean profusion score, 0.57 ± 0.33 ; 95% confidence interval [CI], 0.43-0.72), stage II (mean profusion score, 0.65 ± 0.35 ; 95% CI, 0.55-0.76) and stage III (mean profusion score, 0.76 ± 0.32 ; 95% CI, 0.63-0.88) (p=0.204-0.789). However, the profusion of nodules on HRCT was significantly lower in CXR stage IV (mean profusion score, 0.44 ± 0.35 ; 95% CI, 0.35-0.54) compared with CXR stages II and III (p=0.017 and p=0.001 respectively).

4.3.6 Functional Impact of CXR Stage

As highlighted previously (see section 2.2, page 82), only patients with pulmonary function tests (PFTs) performed within 90 days of CT (n=207) were included in this aspect of analysis. Furthermore, in contrast with earlier analyses in this chapter, CXR stages 0 and I were considered separately in order to ascertain the possible impact of nodal disease (the distinguishing feature of CXR stage I) on lung function. Mean lung function indices were calculated for each CXR stage (Table 4.8).

There were statistically significant differences in lung function indices between CXR stages on analysis of variance but *post hoc* pairwise analyses demonstrated no significant difference in the FEV₁/FVC ratio comparing CXR stage 0 with both CXR stage I and stage II (p=0.936 and p=0.916 respectively); put simply, there was no demonstrable association between the presence of nodal enlargement on CXR and functional obstruction. However, FEV₁/FVC ratio was significantly lower in CXR stage IV than CXR stage III (p= 0.009), indicating more significant obstruction in the former.

Given the known linkages between the presence of fibrosis and mortality (220, 221, 367), further *post hoc* analyses were performed comparing CXR stage IV with all other stages for differences in lung function. In stage IV, there was a statistically significant reduction in several lung function indices compared with all other stages (FEV₁ pred [p<0.002], FVC pred [p<0.022], DLco pred [p<0.001] and TLC pred [p<0.017]. When evaluating trend between CXR stage and lung function, Spearman's rank correlation indicated that FEV₁ and DLco were the indices correlating most closely with CXR stage (r_s = 0.44 and -0.43 respectively, p<0.001). However, importantly, when excluding CXR stage IV from analysis, RV pred was the only lung function variable that correlated with CXR stage and only weakly so (r_s = -0.27, p=0.001).

Functional Indices	CXR Stage	Mean % (SD)	$r_s^\dagger$
FEV ₁	0	89.21 (19.13)	-0.44
	I	90.12 (17.52)	
	II	77.23 (16.42)	
	III	87.59 (15.55)	
	IV	63.23 (21.60)	
FVC	0	96.16 (18.17)	-0.39
	I	100.53 (13.80)	
	II	86.97 (17.86)	
	III	95.38 (15.45)	
	IV	74.89 (22.45)	
FEV ₁ /FVC	0	74.88 (10.01)	-0.24
	I	72.71 (10.00)	
	II	73.06 (9.79)	
	III	74.49 (8.43)	
	IV	67.51 (12.65)	
DLco	0	74.12 (14.50)	-0.43
	I	83.51 (16.58)	
	II	67.14 (15.89)	
	III	74.47 (17.71)	
	IV	51.15 (19.67)	
TLC	0	92.05 (15.00)	-0.41
	I	96.57 (9.05)	
	II	84.25 (13.62)	
	III	87.69 (14.03)	
	IV	74.66 (17.56)	
RV	0	93.81 (23.43)	-0.28
	I	96.48 (10.78)	
	II	87.72 (17.85)	
	III	82.25 (20.24)	
	IV	82.29 (25.35)	
Kco	0	87.15 (12.35)	-0.18
	I	90.46 (16.54)	
	II	87.05 (15.53)	
	III	90.97 (17.81)	
	IV	79.18 (21.41)	

Table 4.8 Relationships between individual CXR Stage and spirometric / plethysmographic volumes and gas transfer indices. Data are mean ($\pm$ standard deviation [SD]) of lung function variable for each CXR Stage. r_s = Spearman's rank correlation coefficient evaluating association between increasing Scadding stage and lung function indices. † P-value for all Spearman's rank analyses was <0.001. (NB FEV₁=% predicted 1-second forced expiratory volume; FVC=% predicted forced vital capacity; FEV₁/FVC=ratio of FEV₁ and FVC; DLco=% of predicted lung diffusing capacity for carbon monoxide, TLC= % predicted total lung capacity, RV= % predicted residual volume and Kco= DLco/alveolar volume)

4.3.7 Functional Impact of HRCT Abnormalities

Linear regression analysis was used to examine the relationship between HRCT disease extent and PFT variables. Disease extent on HRCT was most strongly linked to a depression of DLco ($r^2=0.28$ [$r=0.53$]; $p<0.001$) (Table 4.9; Figure 4.2). There were weaker associations between disease extent and FEV₁ ($r^2=0.14$; $p<0.001$), FVC ($r^2=0.15$; $p<0.001$), Kco ($r^2=0.14$; $p<0.001$) and TLC ($r^2=0.11$; $p<0.001$).

HRCT Disease Extent		
PFT Variable	R ²	p-Value
FEV ₁	0.14	<0.001
FVC	0.15	<0.001
FEV ₁ /FVC	0.01	0.163
DLco	0.28	<0.001
Kco	0.14	<0.001
TLC	0.11	<0.001
RV	0.001	0.673

Table 4.9 Univariate correlations between HRCT disease and PFT indices. (NB FEV₁=% predicted 1-second forced expiratory volume; FVC=% predicted forced vital capacity; FEV₁/FVC=ratio of FEV₁ and FVC; DLco=% of predicted lung diffusing capacity for carbon monoxide, TLC= % predicted total lung capacity, RV= % predicted residual volume and Kco= DLco/alveolar volume).

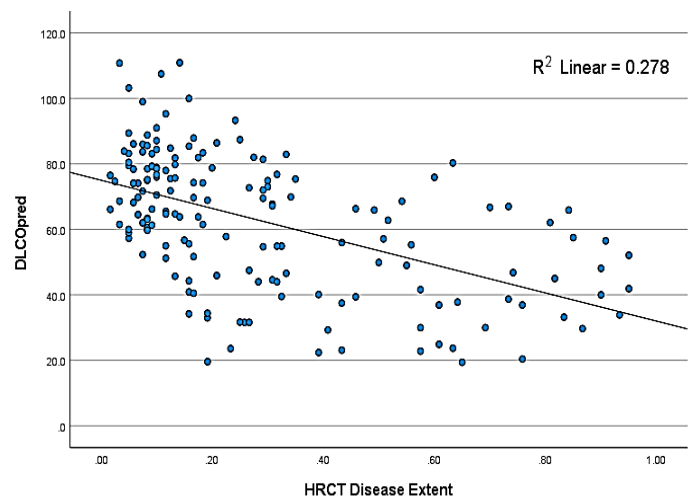


Figure 4.2 Relationship between % predicted DLco and disease extent on HRCT. Data are for 207 patients with pulmonary sarcoidosis.

On multivariate linear regression, the extent of reticulation (regression coefficient, β , = -27.99; $p<0.001$), ground-glass opacification (β = -30.69; $p<0.001$), fibrocavitary disease (β = -94.17; $p<0.001$) and mosaicism (β = -21.16; $p=0.008$) were most strongly and independently linked with percent predicted DLco. Consolidation was only weakly

associated ($\beta = -18.71$, $p=0.017$) and there were no independent linkages between pleuroparenchymal fibrosis or nodules with DLco.

4.3.8 CXR Stage versus Survival

In the whole cohort, there were 50/289 (17%) deaths from all causes; the number of deaths, stratified by CXR stage, were as follows: stage 0, 6/61 (10%); stage I, 3/36 (8%); stage II, 6/56 (11%); stage III, 7/46 (15%) and stage IV 28/90 (31%). On initial evaluation, CXR stage was significantly linked with mortality (hazards ratio [HR] = 1.50; 95% confidence interval [CI] = 1.20-1.88; $p<0.001$) (Figure 4.3), however, further analysis revealed that only CXR stage IV was associated with reduced survival (HR= 3.39; 95% CI: 1.94-5.93, $p<0.001$), and there was no statistically significant difference between the remaining stages ($p=0.675$).

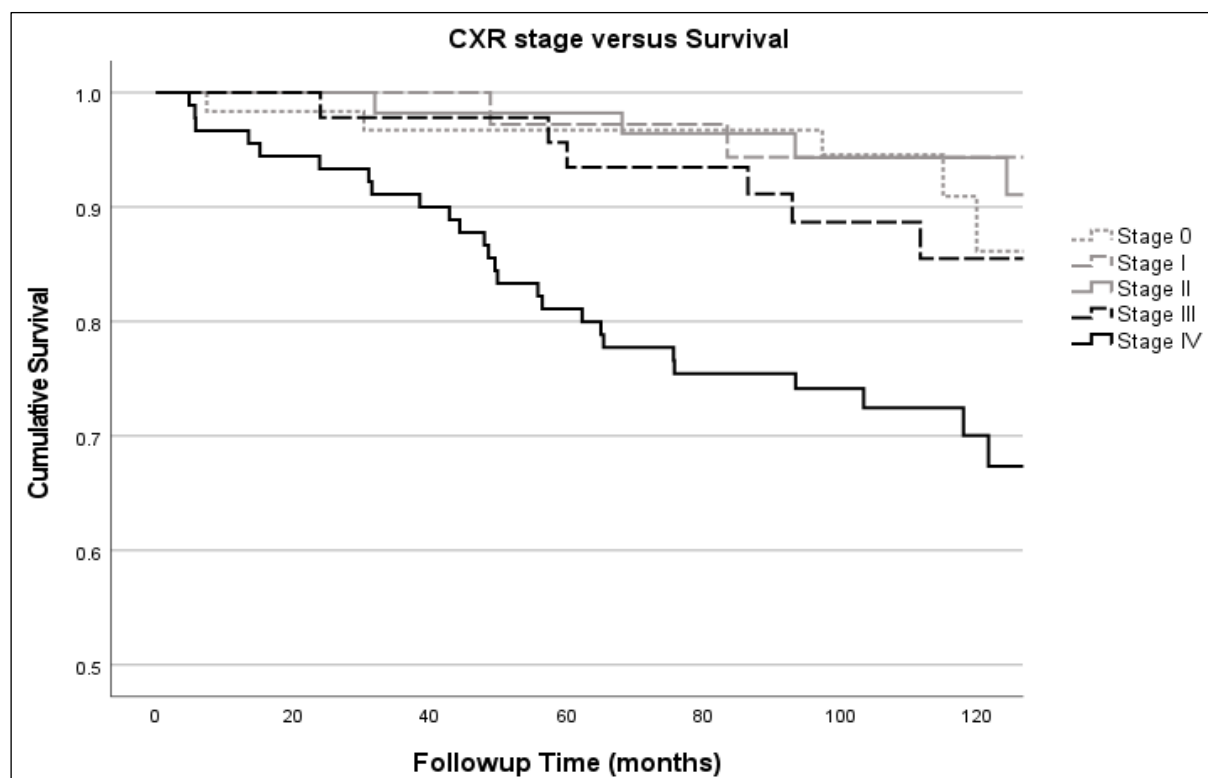


Figure 4.3 Kaplan-Meier survival for individual CXR stages. Significant difference in all-cause mortality for patients with CXR stage IV pulmonary sarcoidosis compared with other CXR Stages (HR 3.39, 95% CI 1.94-5.93, $p<0.001$). No difference in survival between the remaining CXR stages ($p=0.675$).

4.3.8 HRCT Variables versus Survival

Cox proportional hazards modelling was used to identify associations between individual HRCT variables and all-cause mortality (Table 4.10). Disease extent (HR=1.02; 95% CI: 1.01-1.03, $p<0.001$), plus the extents of reticulation (HR=1.02; 95% CI: 1.02-1.03, $p<0.001$), ground-glass opacification (HR=1.02; 95% CI: 1.01-1.02, $p<0.001$), emphysema (HR=1.08; 95% CI: 1.03-1.12, $p<0.001$) and fibrocavitary disease (HR=1.05; 95% CI: 1.02-1.08, $p<0.001$) were predictive of mortality while decreased attenuation (as part of the mosaic attenuation pattern), consolidation and PPFE had no impact on survival ($p=0.198$, 0.409 and 0.524 respectively). The presence/absence of traction bronchiectasis (HR=12.73; 95% CI: 6.12-26.48, $p<0.001$), honeycombing (HR=9.87; 95% CI: 4.73-20.58, $p<0.001$), a UIP pattern (HR=6.35; 95% CI: 2.96-13.65, $p<0.001$) and modified composite fibrosis (devised earlier in this chapter and comprising reticulation and fibrocavitary disease [see Section 4.3.4, page 118]) (HR=5.73; 95% CI: 3.17-10.35, $p<0.001$) were most strongly linked with mortality.

	Hazards Ratio	95% Confidence Intervals	P value
Disease Extent	1.02	1.01-1.03	<0.001
Reticulation	1.02	1.02-1.03	<0.001
Nodules	0.98	0.97-0.99	0.001
Decreased Attenuation	1.01	1.00-1.02	NS
Ground-Glass Opacification	1.02	1.01-1.02	<0.001
Consolidation	0.99	0.97-1.01	NS
Emphysema	1.08	1.03-1.12	<0.001
Fibrocavitary Disease	1.05	1.03-1.08	<0.001
PPFE	1.01	0.98-1.05	NS
Composite Fibrosis†	5.73	3.17-10.35	<0.001
Traction bronchiectasis††	12.73	6.12-26.48	<0.001
Honeycombing†	9.87	4.73-20.58	<0.001
UIP†	6.35	2.96-13.65	<0.001
PMF†	0.635	0.15-2.62	0.529
Mycetoma†	2.99	1.27-7.04	<0.001
CXR Stage IV	3.39	1.94-5.93	<0.001

Table 4.10 Cox proportional hazards for individual HRCT variables. Univariate analysis for individual HRCT variables against survival. **NOTE:** In bivariate analysis CXR stage IV (HR=1.38; 95% CI, 0.64-2.96; p=0.41) failed to reach statistical significance against traction bronchiectasis (HR=9.45; 95% CI, 3.47-26.01; p<0.001). PPFE=pleuroparenchymal fibroelastosis; UIP=usual interstitial pneumonia; PMF=progressive massive fibrosis. †HRCT variables scored as 'presence/absence' for *lungs as a whole*; †† Scored as presence/absence *per lobe* and analysed as mean score for whole lung. All remaining HRCT variables scored as continuous variables.

Multivariate analysis was conducted to identify the relationship between HRCT signs plus demographic variables (age and sex) and survival. Reticulation, nodules, ground-glass opacification, traction bronchiectasis and consolidation scores were analysed as continuous variables, while composite fibrosis, decreased attenuation, fibrocavitary disease, PPFE, free-standing bronchiectasis, honeycombing, UIP, mycetoma and CXR stage IV were analysed as discrete variables.

Ground-glass opacification, traction bronchiectasis, honeycombing and age were the only independent predictors of mortality in the multivariate hazards model (Table 4.11), with traction bronchiectasis (scored as present/absent per lobe) and honeycombing the strongest predictors of mortality (HR=9.06; 95% CI: 3.87-21.23, $p<0.001$ and HR=3.08; 95% CI: 1.38-6.88, $p=0.006$). Importantly, when evaluated against CT variables, once again, CXR stage IV did not reach statistical significance.

	HR	95% Confidence Intervals	p-Value
Ground-glass Opacification	2.87	1.12-7.40	0.029
Traction Bronchiectasis	9.06	3.87-21.23	<0.001
Honeycombing	3.08	1.38-6.88	0.006
Age	1.09	1.06-1.12	<0.001

Table 4.11 Multivariate Cox regression analysis of HRCT features against survival. Data are hazards ratios (HR) with 95% confidence intervals

4.4 DISCUSSION

The plain CXR is probably the most frequently requested *imaging* test and findings on CXR contribute to management/treatment decisions in sarcoidosis. The studies in this chapter explored two key areas: firstly, the relationships between the so-called ‘Scadding CXR stage’ and findings on HRCT and, secondly, a comparison of the functional/prognostic impact of CXR and HRCT abnormalities in patients with pulmonary sarcoidosis.

The observations herein cast some light on the true ‘meaning’ of CXR findings: not unexpectedly, the majority of patients with CXR stages II, III and IV had evidence of lung involvement as judged by CT findings. However, it was noteworthy that a significant minority (~40%) of patients with CXR stages 0/I also had signs of parenchymal disease on

HRCT, with 10% harbouring signs of fibrosis. Additionally, one fifth and nearly one third of patients with (non-fibrotic) CXR stages II and III disease respectively, also had signs indicative of fibrosis on HRCT. These findings confirm not only that CXR is insensitive but also that plain radiographs may be 'blind' to (prognostically-important) fibrosis, even in patients with 'lower' CXR stages. With regards to HRCT findings, nodules (53%), consolidation (32%), ground-glass opacification (30%) and reticulation (30%) were the common patterns. Indeed, it was noteworthy that nodules — the most prevalent HRCT abnormality — and, particularly, signs of 'reversible' disease were present across *all* CXR stages. Not surprisingly, functional impairment correlated more closely with disease extent on HRCT than CXR stage, and DLco was the best *single* marker of overall disease extent. Finally, while CXR stage IV was linked with mortality, the more forensic exploration of HRCT patterns has shown that *individual* CT signs of fibrosis predict outcome in sarcoidosis and traction bronchiectasis strikingly so.

The notion that CXR may 'mask' signs of parenchymal disease is hardly new. Drent et al. evaluated HRCT patterns in sarcoidosis stratified by CXR stage and, as in the present study, found disease in CXR stages 0 and I (284). In a separate study, total disease extent on HRCT was compared with CXR stages and, again, there was 'occult' disease in the lower CXR stages (241). The data in these earlier studies were restricted to the *presence* and *overall extent* of disease across the stages without the more detailed analysis of individual HRCT patterns in this study. Somewhat akin to the current study, Aleksoniene et al., evaluated CXR and HRCTs in 80 consecutive patients, and reported limited 'linear opacities' across CXR stages I to III (262). However, patients with CXR stage IV were excluded and so, drawing comparisons between the extent of linear opacities in the lower CXR stages and a CXR Stage IV (in which fibrosis is expected) becomes impossible. Admittedly, Drent and co-workers

identified a high prevalence of ‘septal and non-septal’ lines in lower CXR stages but, once again, other CT features of fibrosis were not evaluated (284).

The identification of radiological signs that might indicate ‘reversible’ disease (irrespective of the underlying disorder) is likely to be of interest to clinicians. In sarcoidosis, Benamore and colleagues evaluated markers of disease activity on HRCT (314). They devised a ‘CT activity score’ (CTAS), comprising the extent of nodules, consolidation, interlobular septal thickening and ground-glass opacity and found that these features of reversible disease correlated with markers of disease activity and response to treatment. In *this* chapter, the presence and extent of reversible disease on CT was evaluated across CXR stages and indicated that CXR stage *per se*, does not reliably identify patients with potentially reversible disease. Interestingly, in Scadding’s original work, based on a review of serial radiographs in 136 patients, baseline CXR stage was linked with the probability of radiographic resolution at 5 years (1). However, Scadding simply evaluated the proportion of patients with normal versus abnormal radiographs after 5 years and therefore did not evaluate the prevalence of *partial* improvement between the stages. Thus, Scadding’s study undoubtedly underestimated the amount of reversible disease in those with evidence of fibrosis on CXR.

In nature, structure and function are inextricably linked. Accordingly, a study of functional-morphological relationships has the potential to provide valuable insights. Structure versus function relationships have been explored in numerous studies, including (but not confined to) sarcoidosis (262, 280, 284, 311, 332, 369-375). The present study has shown that disease extent on HRCT correlates much more closely with lung function decline than CXR stage. Drent and co-workers also found HRCT disease extent to be a stronger

marker of lung function decline than CXR (284), however by comparison, Ors et al found some lung function indices were more strongly related to CXR stage (241). This finding can be explained by the more detailed analysis undertaken in this chapter, which has shown that when excluding CXR stage IV, previously significant trends become statistically insignificant in most cases, highlighting that while there is a dichotomy between stage IV and non-stage IV on CXR with respect to lung function, there is no convincing trend from stage 0 to III. Interestingly, in a small study comprising 54 patients, evidence of functional impairment was also limited to those with CXR stage IV but, unlike the current study, functional trends across CXR stages were not explored (370).

A reasonably consistent finding in different diffuse fibrotic lung diseases has been the strong association between the percent predicted DLco and overall disease extent on HRCT (373, 374, 376-380). In IPF, DLco has been shown to be the most sensitive marker of parenchymal disease (381) and correlates closely with disease extent on CT (379, 380). In systemic sclerosis, DLco has been shown to be the best functional biomarker of total disease extent, extent of alveolitis and extent of fibrosis as judged by CT (377) and similarly, in rheumatoid ILD, it has been shown to be the only lung function variable to correlate reasonably with profusion of parenchymal disease on CT (382). The observations in this chapter confirm that a similar relationship exists in patients with parenchymal sarcoidosis. This contrasts with prior studies which have found FEV₁ and FVC to be more closely linked to disease extent on CT (241, 284, 311). However, comparing results with these previous studies is difficult. Firstly, in prior studies, the sample sizes were considerably smaller and more importantly, they all utilised broad semi-quantitative scores of disease extent unlike the quantitative scoring method used in the present study. That said, other studies that have adopted semi-quantitative scoring have found comparable results to the present (319,

332, 337). Jeong et al (337) used a scoring method that is perhaps closest to the present study and found DLco as the strongest marker of overall HRCT disease extent (correlating closest with reticular abnormalities and ground-glass opacity as individual markers). Indeed these findings are supported by evidence that DLco is a more sensitive marker of parenchymal disease in sarcoidosis than other lung function indices, particularly in lower radiographic stages (262).

The relationships between CXR stage, HRCT abnormalities and survival were also explored in this chapter. With regard to CXR, perhaps not surprisingly, the highest proportion of all-cause deaths occurred in patients with stage IV disease with no statistically significant difference in survival between other CXR stages. This highlights an important ‘failing’ of CXRs given the key observation in this chapter that fibrosis — of variable extent — is present on HRCT across all CXR stages. Few studies have examined the relationship between CXR stage and outcome over the last five decades (220, 263, 383). Viskum et al., as in the present study, reported that mortality risk was confined to the highest radiographic stage (383). However, details on the choice of CXR classification system in that study were, at best, sparse. A subsequent epidemiological review of 142 patients with CXR stage IV sarcoidosis also found that fibrotic disease on CXR was associated with a significantly reduced survival with a mortality risk comparable to that seen in the current study (263). More recently, Kirkil and colleagues evaluated outcomes in 452 patients and found that mortality increased sequentially from stage I to IV; a finding that may be explained by the ‘hidden’ fibrosis in lower CXR stages identified in this chapter (220). Importantly, however, pairwise analyses were not provided by the investigators to evaluate whether differences between *individual* stages were statistically significant. It is also of interest that the authors

reported a considerably lower mortality rate than our study, probably explained by their use of sarcoid-specific deaths as opposed to all-cause mortality.

Individual HRCT patterns in fibrosing lung disease are known to have prognostic meaning. For instance, in idiopathic pulmonary fibrosis, CT fibrosis score (comprising reticulation and honeycombing) has been consistently shown to be predictive of mortality (373, 384-387). Honeycombing, as a marker of more severe fibrosis, has also been shown to be an *independent* predictor of mortality in IPF and other fibrosing interstitial lung diseases (388-391). More recently, traction bronchiectasis has emerged as a marker of mortality in IPF (387), CHP (392), CTD-ILD (393) and fibrotic idiopathic interstitial pneumonias in general (394). By comparison there is very little research on HRCT biomarkers of survival in sarcoidosis. Prior studies have identified ‘extent’ of fibrosis (defined as reticulation with or without honeycombing/ground-glass opacity/other features) as a predictor of mortality on CT (220, 221, 229, 367). Walsh et al showed that using a threshold of 20% fibrosis extent in patients stratified by physiological indices, was more useful for predicting survival than the extent of fibrosis alone (221). Kirkil et al and Jeny et al later showed that >20% fibrosis on HRCT was a robust independent predictor of survival (even without composite physiological data) (220). The investigations in this chapter, in a large subset of patients with sarcoidosis, support the findings of these earlier investigations: the mere presence of lung fibrosis — as judged by reticulation and/or fibrocavitary disease — is an indicator of poor survival. However, among individual HRCT signs, traction bronchiectasis appears to be by far the strongest independent predictor of mortality. This finding is novel in sarcoidosis and is interesting from a historical perspective: the view among most radiologists has been that traction bronchiectasis is, at best, a ‘by-product’ or epiphenomenon of fibrosis. Multiple studies of the idiopathic interstitial pneumonias, including the present, now challenge this

perception. Indeed, in IPF, increasingly severe traction bronchiectasis was shown to be independently linked with reductions in DLco, FVC and pO₂ (395). Similar findings in some of the studies alluded to above, have strengthened the impression that traction bronchiectasis is an important prognostic 'signal' across many fibrotic lung diseases. The presence of mycetoma as a complication of fibrocavitary sarcoidosis is also worthy of discussion due its association with massive haemorrhage and potentially increased mortality (324). In this study, the prevalence of mycetoma was comparable to the literature (1-2%) (228) and its presence was not predictive of mortality when modelled against other CT variables. This complements a previous study which found no difference in survival between patients with sarcoid-associated chronic pulmonary aspergillosis and healthy controls (229), supporting the theory that mortality in these patients is probably explained by the underlying fibrocavitary disease, rather than the mycetoma itself.

Key Points

- CXR 'staging' of sarcoidosis frequently under-represents the presence of parenchymal disease; HRCT not only reveals signs of fibrosis but also features of potentially reversible/treatable disease across *all* CXR stages.
- Lung fibrosis in sarcoidosis portends poorer survival.
- Of individual HRCT signs, traction bronchiectasis on HRCT is the strongest predictor of mortality, superseding previously described prognostic markers in pulmonary sarcoidosis.

Section 2 | Chapter 5

Identifying HRCT Phenotypes in Sarcoidosis – A Delphi Study

5.1 INTRODUCTION & AIMS

It is broadly true that the outlook for patients with sarcoidosis is better than in patients with other fibrotic interstitial lung disease and, this is perhaps particularly true when comparing survival between sarcoidosis and idiopathic pulmonary fibrosis (220, 396, 397). However, against this, it must be remembered that sarcoidosis is more common. Furthermore, there is a major sub-group of patients with sarcoidosis for whom the outlook is more bleak (220, 221). As discussed previously (see section 1.12, page 79), there are good reasons for suggesting that the diagnostic label of sarcoidosis might simply be a convenient ‘catch-all’ for what are, in fact, multiple separate entities. Indeed, the imaging literature itself is a testament to the highly varied morphological appearances in sarcoidosis. However, until now, no effort has been made to formalise the separation of these morphological phenotypes (109, 114, 123, 311). Moreover, it is not known whether the recognisable HRCT phenotypes are predictive of outcome (114). In this chapter, the specific aims were as follows:

- ***To recruit a large panel of international experts — comprising radiologists and chest physicians — with recognised experience in sarcoidosis***
- ***To develop a Delphi questionnaire with the main aim of identifying, by consensus, the principal HRCT phenotypes in sarcoidosis***

5.2 THE DELPHI METHODOLOGY

5.2.1 History & Key Principles

The Delphi method, for reaching consensus among recognised experts, was first introduced in the 1950s by Dalkey and Helmer (398). The term ‘Delphi’ refers to the Greek

'Oracle of Delphi', the priestess renowned for prophecies about the future. In the absence of any specific methodology for calculating likelihood, the original concept was established as a means of assessing the potential impact of technology based on the probability, frequency, and intensity of future enemy attacks in wartime (398); as might be imagined, predicting the outcome of conflict is challenging and, in its place, the Delphi method exploited the experience of industry experts to guide military decisions (398). The Delphi technique has since been used in a variety of quite different settings, including education research (399), economics (400) and healthcare (401-403).

The methodology is relatively straightforward: broadly speaking, experts select their level of agreement with a series of statements that are devised by the study investigators. Responses to the statements are analysed and statements not reaching consensus are presented to the experts in subsequent iterations along with feedback from previous rounds. Three fundamental principles underpin all Delphi-based studies (404):

- i) **Anonymity** – to reduce the impact of *dominant* personalities in the survey exercise
- ii) **'Controlled' feedback** – the provision of clearly summarised results from earlier rounds provided to facilitate a convergence of opinion AND
- iii) **Statistical representation** – of the group response

The key advantages of the Delphi method are firstly, by garnering the experience of experts in the field, the ability to shed light on topics where there is a paucity of published data and, secondly, the relative speed with which consensus may be achieved. Against this are the need for continued participation of a potentially large pool of invitees through study

rounds, criticisms of reliability (405) and the variety of methodologies that have been used in different studies to date (406).

5.2.2 *The Sarcoidosis Delphi ‘Study Management Committee’*

As a first step, a central Delphi Study Management Committee was formed, comprising four members: two radiologists (the Chief investigator [NS] and the lead project supervisor [SRD]), a chest physician based at Royal Brompton Hospital (project co-supervisor [AUW]) and a second chest physician (KJ) based in the Department of Medicine University of Calgary, with specific expertise in conducting Delphi studies. The study was structured according to the proposed methodological criteria for Delphi studies (406).

5.2.3 *Creating Delphi Statements – The Sarcoidosis Delphi Study ‘Core Panel’: Preliminary Qualitative Study*

From a proposed ‘*core panel*’ of 13 international experts from seven countries, 11 (85%) agreed to participate in the preliminary qualitative study (Figure 5.1). Core panel members were chosen based on i) an affiliation and established practice in an international teaching institution and ii) verifiable research contributions in sarcoidosis and/or interstitial lung diseases. The core panel comprised a roughly equal mix of physicians and radiologists with the aim of addressing not only questions of imaging morphology but also clinical implications. Virtual meetings using Zoom (Zoom Video Communications, Inc., San Jose, California) were held with individual core panel members to explore five general themes in sarcoidosis (Table 5.1). The meetings were conducted using open-ended questions designed to encourage experts to provide their own opinions on the broad discussion themes.

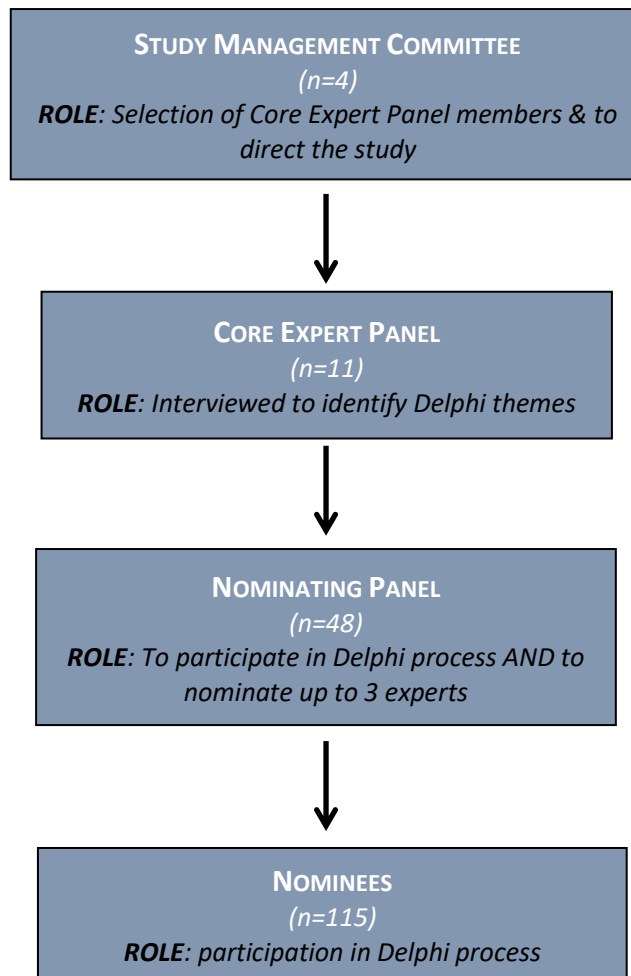


Figure 5.1 Composition and formation of the international sarcoidosis Delphi panels and participants. The Study Management Committee convened the Core Expert Panel, conducted preliminary themed interviews and oversaw the Delphi process. The nominating panel (i.e. members of *The Fleischner Society* & *The World Association of Sarcoidosis and Other Granulomatous Disease* [WASOG]) participated in the Delphi process and nominated up to 3 experts in the field.

Virtual meetings were recorded and transcribed using a commercial transcription service (Rev, Austin, Texas). All meeting transcripts were reviewed at a later stage and condensed into key concepts using a ‘content analysis’ approach (407). Statements for the first round of the Delphi were created based on the principal themes arising from the core panel interviews.

Delphi Core Expert Panel Principal Interview Themes
• Recognition of distinct HRCT appearances in sarcoidosis from own clinical practice
• Defining and categorising principal HRCT phenotypes
• Clinical / prognostic implications of HRCT phenotypes (e.g. response to treatment & survival)
• Possible relationships between HRCT phenotypes and lung function
• Potential relationships between HRCT phenotypes and bronchoalveolar lavage profiles
Table 5.1 Exploratory interview themes. In developing the Delphi questionnaire, all interviews followed a general theme with ‘open-ended’ questions posed to core panel interviewees

5.2.4 Selection of ‘Nominators’ & ‘Nominees’ for the Sarcoidosis Delphi Study

Following the thematic interviews described above, a system was devised to facilitate the recruitment of international experts to the Delphi exercise. The system comprised ‘nominators’ and ‘nominees’. Nominators were members of two major international organisations, The Fleischner Society or World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) with a proven expertise and track-record of peer-reviewed publications in sarcoidosis and/or interstitial lung disease. Nominators were invited not only to participate in the Delphi process but also to nominate three nominees (physicians or radiologists), also with experience in sarcoidosis but paying due attention to geographical and gender representation. The final list of Delphi participants comprised members of i) the core panel, ii) nominating panel and iii) nominees.

5.2.5 The Delphi Survey

Delphi statements were presented to participants using the commercial survey software 'Qualtrics' (Qualtrics XM, Seattle, Washington), a web-based survey tool that provides a user-interface for data collection (Figure 5.2; Appendix A 'Delphi Round 1 Questionnaire', page 216). For each Delphi statement, observers were required to indicate a level of agreement, using a 5-point Likert scale as follows:

- **Strongly agree**
- **Agree**
- **Neutral / unsure**
- **Disagree**
- **Strongly disagree**

Participants were encouraged to add free-text comments for each statement, including any proposed changes and new questions for subsequent rounds. For the overwhelming majority of Delphi statements, anonymised volumetric 'sample' CT datasets were also provided as visual examples. All participants were sent individualised links to the survey by email via the Qualtrics platform, with the suggestion that participants aim to complete the survey in ~ 4 weeks; weekly reminders were sent by the study management committee.

The nodular phenotype includes the following distinct subset:

a) **Multiple peri-bronchovascular, peri-fissural / subpleural micronodules** predominantly in the mid/upper zones

WITH OR WITHOUT:

- A minority component of other CT abnormalities
- Additional features: larger nodules and surrounding micronodules (the 'galaxy sign'), architectural distortion, upper lobe volume loss

[Example 1](#)
[Example 2](#)
[Example 3](#)
[Example 4](#)

☐ Strongly agree
 ☐ Agree
 ☐ Neutral/unsure
 ☐ Disagree
 ☐ Strongly disagree
 ☐ Comments (if any, including suggested changes to the question)

Figure 5.2 Image capture of a single Delphi statement on Qualtrics. Study participants were required to provide a level of agreement for each statement and were given the option to specify issues or suggest modifications (or additions) to Delphi statements for subsequent rounds. NB Interactive, anonymised examples of different proposed sarcoid phenotypes were provided to study participants

5.3 STATISTICAL METHODS – ‘CONSENSUS OPINION’ IN DELPHI STUDIES

5.3.1 General Principles

Historically, the definition of what constitutes *consensus* in a Delphi survey has varied (408): a systematic review of 100 previous Delphi studies conducted over a 10-year period, revealed 11 different definitions! That said, a ‘threshold percentage agreement’ appears to be the most commonly used with a median threshold for determining consensus of 75% (range=50-97%) agreement (408). Importantly, only 72% of studies stated their definition of consensus when presenting results and only 64% did so *a priori*. The optimal threshold for determining consensus is debated. For instance, a study of critical care guideline development methods compared guidelines created using a Delphi methodology with evidence-based methods (409). Interestingly, the study investigators showed that

guidelines developed using a 70% consensus Delphi threshold were almost identical to those created from a full evidence-based systematic review. In the same study, a sensitivity analysis using a 50% expert agreement threshold generated guidelines that were only 89.6% concordant with the evidence-based method, but perhaps more importantly, raising the threshold to 80% only served to reduce the number of recommendations that could be made in spite of high levels of concordance.

For the purposes of the current study an *a priori* threshold of $\geq 70\%$ agreement was used to define 'consensus'. Specifically, statements with 70% of participants agreeing or strongly agreeing were deemed to have reached consensus. A threshold of $\geq 70\%$ was justified on the basis that a large number of participants were to be included in the present study which would result in an inherently lower standard deviation of responses compared with most Delphi studies performed historically. Thus, 70% agreement in the present study, undoubtedly represents a majority opinion. Statements with $\leq 30\%$ agreement were defined as '*unlikely to reach consensus*' and were excluded from the subsequent round.

5.3.2 'Stopping Criteria'

Outlining the criteria for termination of a Delphi study is an important study quality indicator (406). Accordingly, from the outset, we determined a defined number of rounds as the most appropriate stopping criteria for the proposed Delphi study. A two-round methodology was chosen and composed as follows:

- **ROUND 1:**
 - Consideration of all initial Delphi statements
- **ROUND 2:**
 - Clarification of issues / questions raised in Round 1 (with provision of results from Round 1 where relevant)
 - Refining questions based on participant comments
 - Addition of further Delphi statements, where relevant

A 'two-round' method was judged ideal to allow initial statements to be refined based on results and participant feedback. Additional rounds were considered unlikely to yield greater consensus and risked increasing participant attrition (410) and furthermore, the clinical utility of any established phenotypes in any case would require validation with formal research rather than expert opinion.

5.4 RESULTS

5.4.1 Core Panel Interviews

Eleven out of 13 (84.6%) invited core panelists agreed to participate in the interview stage; from the interview process, 22 individual concepts or themes were identified (Table 5.2) which included possible phenotypes, clinical manifestations of specific HRCT features and prognostication. Importantly, core panel members unanimously agreed that there are distinct HRCT phenotypes, however there were diverse views on what the individual phenotypes were. For example, most identified the peri-lymphatic nodular pattern as a distinct phenotype, however other suggested phenotypes, such as the 'UIP look-alike' pattern, were only recognised by a few.

Delphi statements for Round 1 (n=34) were created using concepts/themes raised at interview and the clinical experience of the study management committee. For example, the theme 'PMF phenotype, even with airway distortion, can respond dramatically to treatment' gave rise to the following Delphi statement: '*A HRCT pattern comprising large mid/upper zone-predominant bronchocentric masses (i.e. progressive massive fibrosis [PMF] look-alike) can regress with treatment*'. The full list of Delphi statements is provided in the appendix (see Appendix A 'Delphi Round 1 Questionnaire', page 216).

Concepts/themes described by >90%

- The CT appearances of sarcoidosis *can* be grouped into ‘imaging phenotypes’
- A perilymphatic nodular pattern is the most frequently observed manifestation of parenchymal sarcoidosis, predicts a good prognosis and is generally responsive to treatment while fibrotic patterns confer a worse outcome.
- CT phenotypes in sarcoidosis can be considered ‘*fibrotic*’ or ‘*non-fibrotic*’; alternatively, CT phenotypes may be ‘*typical*’ or ‘*atypical*’
- Perihilar fibrosis with posterior retraction of the hila is a distinct fibrotic phenotype (NB described by one expert as ‘pathognomonic’)
- Perihilar reticulation is a distinct imaging feature of sarcoidosis
- Upper lobe fibrocavitary destruction +/- honeycombing is a recognised fibrotic phenotype
- Predominant ground-glass opacification (with or without nodules) indicates a non-fibrotic phenotype
- A CT pattern of pleuroparenchymal fibroelastosis is *not* associated with sarcoidosis
- A UIP pattern is a rare finding in patients with sarcoidosis (NB divided opinion over whether UIP pattern is truly a manifestation of sarcoidosis or, simply, indicative of co-existent disease)
- No linkage between CT phenotypes and findings in bronchoalveolar lavage fluid

Concepts described by 50-90%

- A ‘PMF-like’ appearance — comprising mid-to-upper zone mass-like consolidation — is a recognised imaging phenotype
- Fibrocavitary destruction with mycetoma confers a particularly poor prognosis

Concepts described by 10-50%

- The PMF phenotype, even with airway distortion, can respond dramatically to treatment (n=3)
- An obstructive lung function profile is more related to bronchocentric disease than any other form of disease (n=5)
- A reticular pattern is related to an obstructive lung function profile (n=2).
- A mosaic pattern can present in isolation and therefore may form a distinct, albeit rare, phenotype (n=2)
- Discrete cavitating nodules are a rare presentation of sarcoidosis (n=2)

Concepts raised by <10%

- 'Soft' mediastinal nodal calcification is typical of sarcoidosis; calcified granulomas in the liver and spleen favours histoplasmosis (common in USA) over sarcoidosis
- Diffuse interlobular septal thickening is a rare presentation of sarcoidosis (n=1)
- Even in advanced disease, prognosis is good and imaging appearances often remain unchanged for years (n=1)
- Lung volume may be an important prognostic marker: marked volume loss (esp. upper lobes) anecdotally fares worse (n=1)
- A lymphocytic BAL profile is most frequently seen in patients with a nodular pattern due to active disease (n=1)

Table 5.2 Key concepts raised by core expert panel members based on 'thematic' interviews. The themes and concepts elucidated from interviews formed the basis of Round 1 Delphi statements

5.4.2 Delphi Participant Demographics & Characteristics

Of invited participants, 146/174 (84%; radiologists, n=48 and physicians, n=98; mean duration in practice, 21±10 years; M:F, 82:62) completed Delphi Round 1 (Table 5.3). There was a wide geographical representation, but with most participants practicing in USA (25%) and UK/mainland Europe (France [10%]; Italy [9%]; UK [8%]; Netherlands [7%] and Germany [5%]) (Table 5.4). At registration, virtually all participants (145/146 [99%]) declared an interest in interstitial lung disease with ~90% also indicating a specialist interest in sarcoidosis. The majority of radiologists (44/48 [92%]) indicated that >50% of reporting time was spent reviewing thoracic imaging studies. The annual number of patients assessed by chest physicians was evenly distributed between all categories (<50 patients through to >250 patients).

Participant Characteristics (n=146)	
Specialty	
<i>Pulmonology</i>	98 (67.1)
<i>Radiology</i>	48 (32.9)
Age	53 ± 10 years
Sex (M:F)	82:62†
Years in senior practice	21 ± 10 years
Special interest in ILD/ sarcoidosis	145 (99.3)/130 (89)
RADIOLOGISTS: Proportionate time devoted to thoracic imaging	
<25%	1 (2.1)
25-50%	3 (6.3)
51-75%	14 (29.2)
>75%	30 (62.5)
CHEST PHYSICIANS: Approximate numbers of sarcoid patients evaluated/year	
<50	23 (23.5)
50-100	24 (24.5)
101-250	27 (27.6)
>250	24 (24.5)

Table 5.3 Demographic and other characteristics of participants in the Delphi study. Data are numbers with percentages in parenthesis. † 'Prefer not to say' (n=2)

COUNTRY	No (%)	COUNTRY	No (%)	COUNTRY	No (%)	COUNTRY	No (%)
Argentina	4 (2.7)	Denmark	1 (0.7)	Mexico	1 (0.7)	South Africa	2 (1.4)
Australia	2 (1.4)	France	14 (9.6)	Netherlands	10 (6.8)	South Korea	8 (5.5)
Austria	1 (0.7)	Germany	7 (4.8)	New Zealand	2 (1.4)	Spain	5 (3.4)
Belgium	2 (1.4)	Greece	1 (0.7)	Portugal	2 (1.4)	Switzerland	1 (0.7)
Brazil	2 (1.4)	India	4 (2.7)	Romania	1 (0.7)	Turkey	2 (1.4)
Canada	2 (1.4)	Italy	13 (8.9)	Russia	4 (2.7)	UK	11 (7.5)
Chile	1 (0.7)	Japan	6 (4.1)	Serbia	1 (0.7)	USA	36 (24.7)

Table 5.4 Geographical distribution of participants in the Delphi study. The table shows the numbers of participants by country with percentages in parentheses. The highest proportion of participants (highlighted in red font) were practicing in USA or UK/major mainland European countries

5.4.3 Delphi Survey Results

5.4.3.1 — Agreement vs. Disagreement on Delphi Statements in Round 1 & Clarifications/Amendments for Round 2

In Round 1, 34 individual statements were reviewed by participants. A detailed summary of the responses for all round 1 statements is provided in Table 5.5. At the completion of Round 1, 13/34 (38%) statements reached the agreement threshold of 70%, with no statements meeting the criteria for consensus disagreement. Three statements demonstrated <30% agreement thereby meeting the criteria for '*unlikely to reach consensus*' (see section 5.3.1, page 143) and were removed for the purposes of Round 2. A single statement not meeting either of these criteria ('soft' intra-thoracic nodal calcification with hepatic and splenic calcified granulomas favours histoplasmosis over sarcoidosis') was removed following a review by the core management committee as it was felt to be outside the scope of the present study.

In addition to responses to specific Delphi statements, participants also submitted 619 free-text comments; all comments were reviewed by the study management committee to identify areas of uncertainty requiring clarification in Round 2. Two key areas of uncertainty emerging from Round 1 free-text comments were as follows:

- 1) There was a perception among some participants that Delphi statements were referring to the **diagnostic** utility of specified patterns/phenotypes on HRCT. For instance, one free-text response stated '*neutral/unsure – would send for a biopsy*'
- 2) There was misinterpretation among some participants that the purpose of the study was to comment on whether the provided volumetric sample CT datasets (See Section 5.2.5 The Delphi Survey, page 142) were representative of specific Delphi statements. For example, one free-text response stated '*Disagree – example 1 is sarcoidosis because of adenopathy; 2 not very sure*'

Issues raised in free-text comments were resolved prior to the commencement of Round 2. With specific regard to the uncertainty about the *diagnostic utility* of HRCT, each relevant statement in Round 2 was clarified accordingly: for instance, the Round 1 statement '*Consolidation as the predominant or sole abnormality is a distinct HRCT pattern in sarcoidosis*', was amended to "***In patients with a confirmed diagnosis of sarcoidosis, consolidation as the predominant or sole abnormality is a distinct HRCT pattern.***" Other areas of uncertainty highlighted by free-text comments were clarified by email and/or in the instructions provided for Round 2 (see Appendix B 'Delphi Round 2 Questionnaire', page 222). Finally, a single new statement '*HRCT findings strongly indicative of fibrotic disease is associated with BAL neutrophilia*', was added as a variant of an existing statement to address a topic that the Core Management Committee felt important to explore. Thus, in Round 2, participants were presented with 18 statements, evaluated in the same manner as in Round 1; the full list of Round 2 statements is provided in the Appendix (see Appendix B 'Delphi Round 2 Questionnaire', page 222). Importantly, participants were also provided with feedback for all statements that had been modified after Round 1.

At the completion of Round 2, there was consensus agreement on a further 9 statements. There were no statements meeting criteria for consensus disagreement or '*unlikely to reach consensus*'; a detailed summary of responses for all Round 2 statements is provided in Table 5.6.

5.4.3.2 —Agreement vs. Disagreement on Delphi Statements Regarding the Role of HRCT & the Occurrence / Pathological 'Meaning' of HRCT Patterns in Sarcoidosis

On completion of Round 2, 22 out of 35 individual statements (63%) presented over both rounds reached consensus agreement (Tables 5.5 and 5.6). There was a high level of agreement among participants for the statement that '*HRCT should be performed at*

baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement' and that *'There are distinct HRCT phenotypes in sarcoidosis'* (95% and 97% agreement respectively).

The following Delphi statements regarding the possible pathological 'meaning' of HRCT patterns also achieved consensus agreement: i) *'HRCT features can be categorised as fibrotic and non-fibrotic'* (83% agreement), ii) *'Nodules alone or a predominance of nodules are almost always non-fibrotic'* (82% agreement), iii) *'Reticulation on HRCT almost always represents fibrosis (80%)*, and, after clarification/feedback in Round 2, iv) *Large bronchocentric masses with or without cystic/bullous destruction almost always represents fibrosis (83% agreement)*, v) *'(In patients with a confirmed diagnosis of sarcoidosis) a predominant ground-glass opacification pattern is almost always non-fibrotic in the absence of ancillary CT features of fibrosis'* (80% agreement). By contrast, the following Delphi statements did not reach consensus agreement:

- In patients with a confirmed diagnosis of sarcoidosis a predominant **consolidation** pattern is almost always non-fibrotic (33% agreement)
- In patients with a confirmed diagnosis of sarcoidosis a **mosaic attenuation pattern** is almost always non-fibrotic (56% agreement)

Table 5.5 – Round 1 Delphi Responses

Delphi Statement Number	Delphi Statement	Strongly Agree	Agree	Neutral/ Unsure	Disagree	Strongly Disagree	Total Agree (%)	Total Disagree (%)
1	HRCT should be performed at baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement	107	31	4	4	0	138 (94.5)	4 (2.7)
2	There are distinct HRCT phenotypes in sarcoidosis	84	58	4	0	0	142 (97.3)	0 (0)
3	HRCT features can be categorised as ‘fibrotic’ and ‘non-fibrotic’	29	92	16	8	1	121 (82.9)	9 (6.2)
4	Nodules alone or a predominance of nodules are almost always non-fibrotic	44	75	16	10	1	119 (81.5)	11 (7.5)
5	A predominant ground-glass opacification pattern is almost always non-fibrotic	22	57	38	28	1	79 (54.1)	29 (19.9)
6	A predominant consolidation pattern is almost always non-fibrotic	8	42	38	50	8	50 (34.2)	58 (39.7)
7	A predominant mosaic attenuation pattern is almost always non-fibrotic	17	44	38	44	3	61 (41.8)	47 (32.2)
8	Nodules as the predominant or sole abnormality a distinct HRCT pattern in sarcoidosis	53	67	13	13	0	120 (82.2)	13 (8.9)
9	Multiple peri-bronchovascular, peri-fissural / subpleural micronodules is a distinct pattern	105	37	1	2	1	142 (97.3)	3 (2.1)
10	Multiple <i>randomly</i> distributed micronodules is a distinct pattern	16	67	31	28	4	83 (56.8)	32 (21.9)
11	Multiple larger peri-bronchovascular nodules is a distinct pattern	33	81	19	10	3	114 (78.1)	13 (8.9)
12	Scattered larger nodules is a distinct pattern	11	57	35	39	4	68 (46.6)	43 (29.5)
13	Scattered larger <u>cavitating</u> nodules is a distinct pattern	3	24	30	65	24	27 (18.5)	89 (61)
14	Ground-glass opacification as the predominant or sole abnormality is a distinct pattern	12	54	22	47	11	66 (45.2)	58 (39.7)
15	Consolidation as the predominant or sole abnormality is a distinct pattern	18	73	25	27	3	91 (62.3)	30 (20.5)
16	Mosaic attenuation as the predominant or sole abnormality is a distinct pattern	8	34	32	56	16	42 (28.8)	72 (49.3)
17	Reticulation on HRCT almost always represents fibrosis	20	66	28	28	4	86 (58.9)	32 (21.9)
18	Interlobular septal thickening on HRCT represents fibrosis	7	26	37	60	16	33 (22.6)	76 (52.1)
19	Large bronchocentric masses with or without cystic / bullous ‘destruction’ on CT in sarcoid almost always represents fibrosis	23	67	23	32	1	90 (61.6)	33 (22.6)
20	Bronchocentric reticulation +/- dense parenchymal opacification <u>WITHOUT</u> cavitation is a distinct pattern	49	69	22	6	0	118 (80.8)	6 (4.1)
21	Bronchocentric reticulation and dense parenchymal opacification <u>WITH</u> cavitation is a distinct pattern	38	76	19	12	1	114 (78.1)	13 (8.9)

22	Large bronchocentric masses (i.e. progressive massive fibrosis [PMF] look-alike) is a distinct pattern	43	73	21	8	1	116 (79.5)	9 (6.2)
23	Predominant interlobular septal thickening is a distinct pattern	9	54	35	48	0	63 (43.2)	48 (32.9)
24	Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike) is a distinct pattern	14	43	22	45	22	57 (39)	67 (45.9)
25	PPFE look-alike is a distinct pattern	12	55	44	30	5	67 (45.9)	35 (24)
26	'Soft' intra-thoracic (mediastinal / hilar) nodal calcification occurs in sarcoidosis	70	70	5	1	0	140 (95.9)	1 (0.7)
27	'Soft' intra-thoracic nodal calcification with hepatic and splenic calcified granulomas favours histoplasmosis over sarcoidosis†	18	47	58	21	2	65 (44.5)	23 (15.8)
28	Specific HRCT appearances correspond to specific lung function profiles	16	72	35	19	4	88 (60.3)	23 (15.8)
29	A predominant reticular pattern on HRCT is associated with a restrictive lung function defect	14	89	28	15	0	103 (70.5)	15 (10.3)
30	A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect	11	68	45	22	0	79 (54.1)	22 (15.1)
31	A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis	17	71	46	12	0	88 (60.3)	12 (8.2)
32	Bronchocentric reticulation +/- dense parenchymal opacification WITH cavitation predicts a poor response to treatment	40	80	19	6	1	120 (82.2)	7 (4.8)
33	A PMF look-alike pattern can regress with treatment	8	70	28	36	4	78 (53.4)	40 (27.4)
34	Lobar volume loss (particularly the upper lobes) is associated with a poor outcome in sarcoidosis	7	71	53	14	1	78 (53.4)	15 (10.3)

Table 5.5. Responses to Round 1 Delphi statements. Colour-coding indicates statements reaching consensus threshold agreement ($\geq 70\%$ agreement; *in dark green*), statements with indeterminate agreement in Round 1 (≥ 30 to $< 70\%$ agreement; *in light green*) and statements unlikely to reach consensus ($< 30\%$ agreement; *in red*).

†Statement 27 was considered outside the scope of the study and accordingly excluded from Round 2. HRCT=high-resolution CT; PMF=progressive massive fibrosis; UIP=usual interstitial pneumonia; NSIP=non-specific interstitial pneumonia; PPFE=pleuroparenchymal fibroelastosis; BAL=bronchoalveolar lavage

Table 5.6 – Round 2 Delphi Responses								
Statement Number (Round 1)	Delphi Statement	Strongly Agree	Agree	Neutral/ Unsure	Disagree	Strongly Disagree	Total Agree (%)	Total Disagree (%)
	IN PATIENTS WITH A CONFIRMED DIAGNOSIS OF SARCOIDOSIS...*							
5	A predominant ground-glass opacification pattern is almost always non-fibrotic (<i>in the absence of ancillary HRCT features of fibrosis</i>)	32	83	17	11	1	115 (79.9)	12 (8.3)
6	A predominant consolidation pattern is almost always non-fibrotic	9	38	29	61	7	47 (32.6)	68 (47.2)
7	A predominant mosaic attenuation pattern is almost always non-fibrotic	18	62	25	38	1	80 (55.6)	39 (27.1)
10	Multiple randomly distributed micronodules is a distinct nodular phenotype	31	64	17	26	6	95 (66.0)	32 (22.2)
12	Scattered larger nodules is a distinct nodular phenotype	23	82	20	14	4	105 (72.9)	18 (12.5)
14	Ground-glass opacification as the predominant or sole abnormality is a distinct pattern	22	64	12	41	5	86 (59.7)	46 (31.9)
15	Consolidation as the predominant or sole abnormality is a distinct pattern in sarcoidosis	45	88	4	6	1	133 (92.3)	7 (4.9)
17	Reticulation on CT almost always represents fibrosis	33	82	9	19	1	115 (79.9)	20 (13.9)
19	Large bronchocentric masses with or without cystic / bullous destruction almost always represents fibrosis	50	70	11	13	0	120 (83.3)	13 (9)
23	Predominant interlobular septal thickening is a distinct pattern	17	83	18	21	5	100 (69.4)	26 (18.1)
24	Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike) is a distinct pattern	6	51	18	52	17	57 (39.6)	69 (47.9)
25	PPFE look-alike is a distinct pattern	24	76	22	19	3	100 (69.4)	22 (15.3)
28	Specific HRCT appearances correspond to specific lung function profiles	27	88	14	13	2	115 (79.9)	15 (10.4)
30	A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect	24	79	28	13	0	103 (71.5)	13 (9)
31	A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis	27	73	41	3	0	100 (69.4)	3 (2)

	HRCT findings strongly indicative of fibrotic disease is associated with BAL neutrophilia†	8	41	66	24	5	49 (34.0)	29 (20.1)
33	<i>A minority of patients with sarcoidosis and a PMF look-alike pattern on HRCT will demonstrate partial or complete regression with treatment</i>	16	88	21	17	2	104 (72.2)	19 (13.2)
34	Lobar volume loss (particularly the upper lobes) is associated with a poor outcome	18	84	35	6	1	102 (70.8)	7 (4.9)

Table 5.6. Responses to Round 2 Delphi statements. Following Round 1, note that *all* statements in Round 2 were preceded with the sentence ‘In patients with a confirmed diagnosis of sarcoidosis...’. Modifications made for clarity to statements in Round 1 are *underlined and italicised*.

† New statement added in Round 2 to explore a clinically important question not addressed in Round 1.

5.4.3.3 — Agreement vs. Disagreements on Delphi Statements Regarding Distinct (Recognisable) HRCT Phenotypes in Sarcoidosis

On completion of Round 2, there was consensus agreement on **seven** HRCT phenotypes (Table 5.7, Figures 5.3 and 5.4) broadly divided into the ‘non-fibrotic’ and ‘fibrotic’ subtypes. Of the agreed seven phenotypes, five reached consensus in Round 1 (consensus agreement, 78-97%). Of the non-fibrotic HRCT phenotypes, a pattern of ‘Multiple peri-bronchovascular, peri-fissural / subpleural micronodules’ had the highest level of expert agreement (97%). Only two phenotypes met the criteria for ‘*unlikely to reach consensus*’ (Table 5.5).

HRCT Phenotypes	
1	† Multiple peri-bronchovascular, peri-fissural / subpleural micronodules (Consensus agreement=97%; Fig 5.3A)
2	† Multiple larger peri-bronchovascular nodules (Consensus agreement=78%; Fig 5.3B)
3	†† Scattered larger nodules (Consensus agreement=73%; Fig 5.3C)
4	†† Predominant consolidation pattern (Consensus agreement=92%; Fig 5.3D)
5	† Bronchocentric reticulation +/- dense parenchymal opacification <i>WITHOUT</i> cavitation (Consensus agreement=81%; Fig 5.4A/B)
6	† Bronchocentric reticulation +/- dense parenchymal opacification <i>WITH</i> cavitation (Consensus agreement=78%; Fig 5.4C)
7	† Large bronchocentric masses (PMF-look-alike) (Consensus agreement=79%; Fig 5.4D)

Table 5.7 HRCT phenotypes reaching consensus following Delphi Rounds 1 & 2. The 7 principal phenotypes broadly broken down into ‘non-fibrotic’ (*light blue background*) and ‘fibrotic’ (*darker blue background*) sub-types. NB †Delphi Statements achieving consensus in Round 1; ††Delphi Statements achieving consensus in Round 2, after clarifications/feedback.

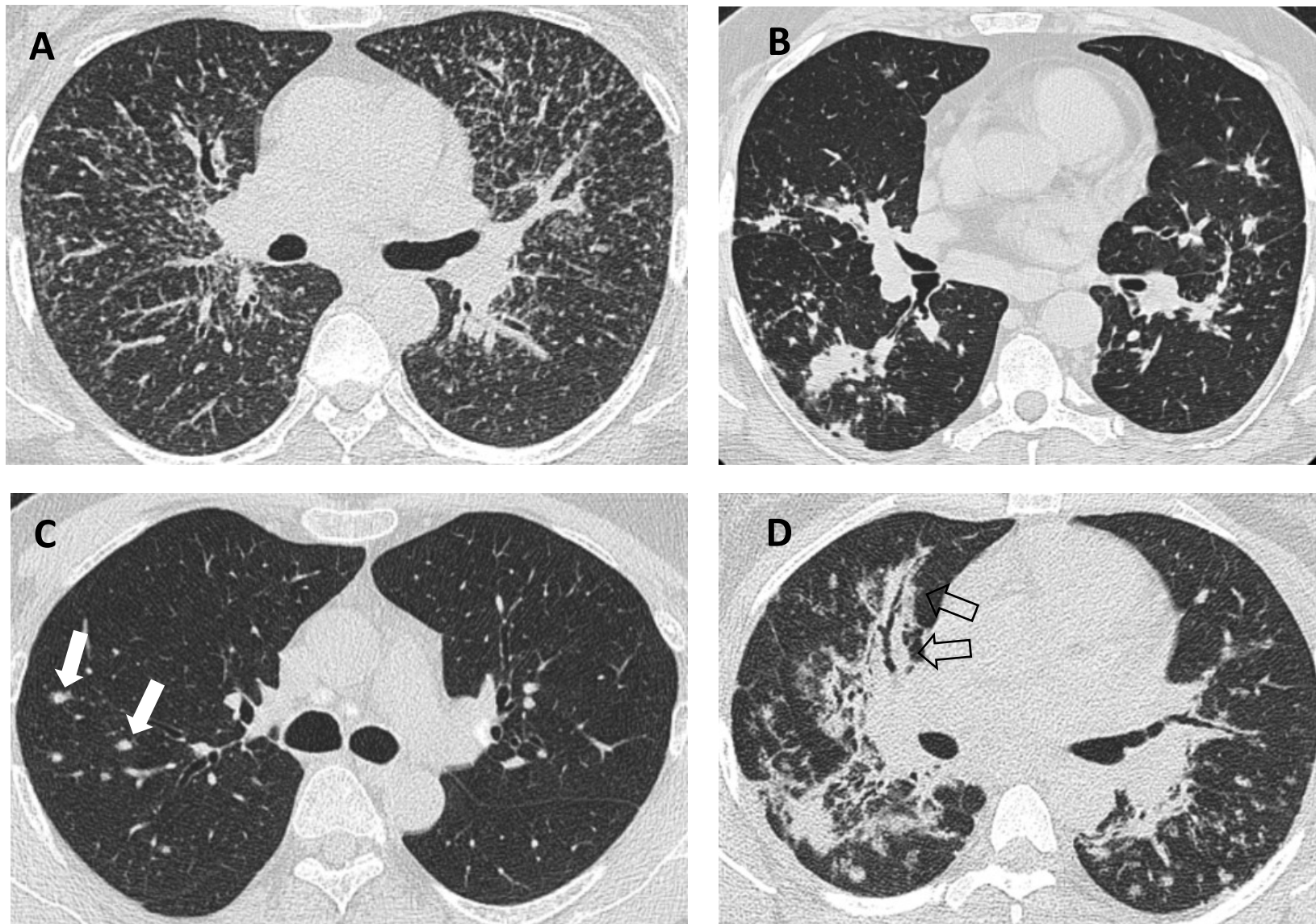


Figure 5.3: HRCT images showing four phenotypes — considered *non-fibrotic* — reaching Delphi consensus. **A)** HRCT image just below the carina showing innumerable peri-bronchovascular, peri-fissural and sub-pleural micronodules; **B)** Image in another patient with multiple larger peri-bronchovascular nodules; some of the larger nodules have smaller surrounding micronodules (the 'galaxy sign'); **C)** HRCT image at the level of the carina showing scattered larger nodules (*arrows*) which appear unrelated to bronchovascular structures and **D)** a pattern of predominant consolidation which, in the anterior segment of the right upper lobe, also appears to be strikingly bronchocentric (*open black arrows*)

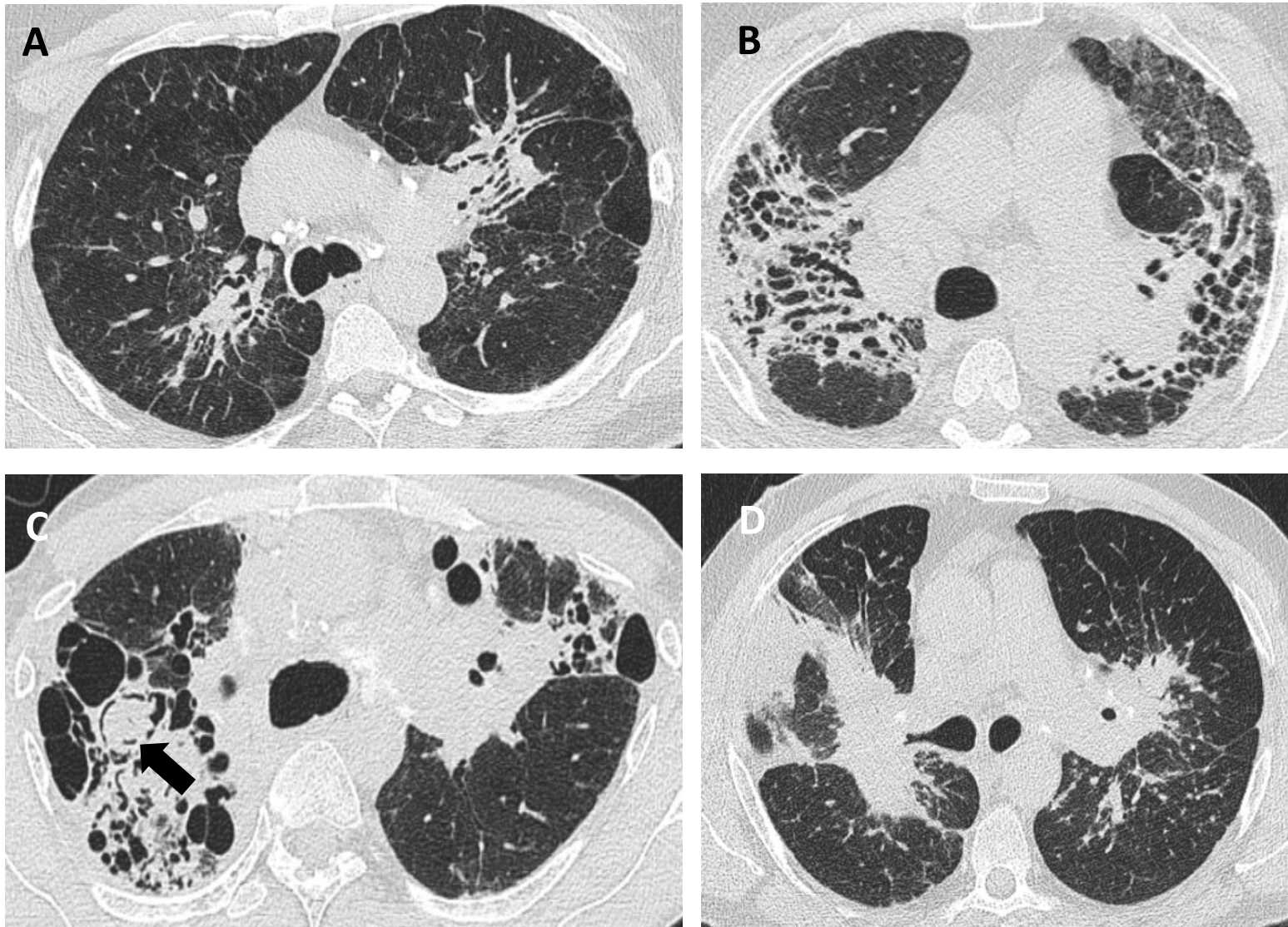


Figure 5.4: HRCT images showing three phenotypes — considered *fibrotic* — reaching Delphi consensus. A) HRCT image just at the carina with bilateral bronchocentric reticulation; there is also a pattern of 'loose' reticulation in both lungs; **B)** HRCT through the upper lobes, in another patient, showing more extensive, symmetrical bronchocentric reticulation; **C)** Image just above the carina demonstrating upper lobe fibrocavitary disease. NB There is a mycetoma in one of the right upper lobe cavities (*arrow*) and **D)** dense, bilateral bronchocentric 'masses' giving an appearance of progressive massive fibrosis. There are a few scattered micronodule in the left lung but this is not the dominant abnormality

5.4.3.4 —Agreement vs. Disagreement on Delphi Statement Regarding the Relationships Between HRCT Phenotypes & Lung Function / Outcome

There was agreement that ‘specific’ HRCT appearances correspond to specific lung functional profiles: in particular, 71% agreed that a predominant reticular pattern on HRCT is associated with a restrictive lung function defect and 72% agreed that a bronchocentric pattern of fibrosis is associated with an obstructive lung function defect. In terms of relationship to outcome, most experts (72%) agreed that a minority of patients with a ‘progressive massive fibrosis’ pattern on HRCT partially or completely regress with treatment. Finally, lobar volume loss was considered, by consensus, a marker of poor outcome.

5.5. Discussion

The investigations in this chapter have used Delphi methodology to interrogate the experience/opinions of multiple experts — physicians and radiologists — currently working in the field of interstitial lung disease and sarcoidosis. This is the first study to explore the expertise of a large *international* body anchored to morphological (HRCT) appearances as opposed to findings on histopathological examination. The approach differs from what has occurred historically in sarcoidosis whereby, because of the reliance on histological diagnosis (namely the presence of non-caseating granulomata), a multitude of HRCT patterns/features in pulmonary sarcoidosis have — perhaps for sake of convenience — been ‘lumped’ under the single diagnostic label of sarcoidosis. This runs counter to the approach in many other lung diseases where every effort has been made to ‘split’ the disorders based not just on pathological features, but also HRCT appearances, functional impairment and disease ‘behaviour’ or outcome.

Before discussing the key morphological aspects of the Delphi exercise, an important clinical message to emerge was that the overwhelming majority of experts agreed that HRCT should be performed *at baseline* in sarcoidosis in patients with evidence of pulmonary involvement (*Delphi Statement 1; consensus agreement, 94%*). This result came as something of a surprise: while there is little doubt that HRCT is more sensitive than plain CXR in sarcoidosis (284, 286) there is, to date, no consensus or guidance on the role of HRCT in *routine* assessment. In the original 1999 American Thoracic Society / European Respiratory Society / World Association of Sarcoidosis and Other Granulomatous Disease Consensus Statement on Sarcoidosis, CXR is regarded the mainstay of radiological diagnosis, with CT reserved for ‘atypical’ findings on CXR, the detection of complications and/or the assessment of radiographically-occult disease (155). The more recent BTS sarcoidosis clinical statement suggests that ‘*all patients...should have a chest X-ray*’ and ‘*if they have typical findings...a CT scan may not be necessary*’ (240). However, the results of chapter 4 have shown clearly that ‘typical’ findings on CXR (and specifically in CXR stage 0/I or CXR stage II disease) cannot be relied on to exclude significant parenchymal disease in sarcoidosis. The body of expert opinion consulted in the current Delphi exercise clearly supports this view which, should perhaps, be borne in mind for future guideline development in sarcoidosis.

Establishing the presence and nature of HRCT phenotypes in sarcoidosis was a key aim in this chapter. In this respect, not only did participants agree that there are recognisable HRCT phenotypes in sarcoidosis (*Delphi Statement 2; consensus agreement, 97%*) but also that HRCT abnormalities may broadly be categorised as being fibrotic or non-fibrotic (*Delphi Statement 3; consensus agreement, 83%*). Among the HRCT phenotypic subtypes recognised by Delphi participants, there was widespread agreement about nodular

patterns — in particular, micronodular forms; hence, in the first Delphi round, 97% of participants either agreed or strongly agreed that multiple bronchocentric, peri-fissural or subpleural micronodules comprised a distinct HRCT pattern in sarcoidosis (*Delphi Statement 9*). However, this is not surprising since variants of a nodular pattern have long been regarded as ‘classical’ on HRCT in sarcoidosis (241, 262, 304, 312, 314, 322, 338). The distinction between nodular patterns, based on size, is interesting (262, 312, 411) with macronodules supposedly signifying more ‘extensive’ disease, presumably related to the coalescence of granulomata (312). The view that individual HRCT patterns might be linked to particular patterns of functional impairment is now supported by an international consensus as shown in this chapter. The results in this chapter have shown that the Delphi statements, ‘*Specific HRCT appearance correspond to specific lung function profiles*’ (Statement 28), ‘*A predominant reticular pattern on HRCT is associated with a restrictive lung function defect*’ (Statement 29) and ‘*A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect*’ (Statement 30) all achieved consensus agreement (80%, 70% and 71% respectively).

Three other HRCT phenotypes which, broadly speaking, might be considered predominantly fibrotic, were identified by consensus through the Delphi exercise: these were ‘*Bronchocentric reticulation +/- dense parenchymal opacification without cavitation*’ (Delphi Statement 20), ‘*Bronchocentric reticulation +/- dense parenchymal opacification with cavitation*’ (Delphi Statement 21) and ‘*Large bronchocentric masses (i.e. a progressive massive fibrosis-look alike)*’ (Delphi Statement 22). In a previous small study comprising 80 consecutive patients with CXR stage IV disease, Abehsera et al., attempted to phenotype the different forms of fibrosis in sarcoidosis (109). In just under half of all cases (38/80, 47%),

there was predominant ‘central bronchial distortion’ — a review of the provided images in this published study suggests that this pattern essentially corresponds to the pattern of bronchocentric reticulation without cavitation (Delphi Statement 20). However, on further reading, it can be argued, fairly convincingly, that another of their reported fibrotic HRCT variants, termed the so-called ‘linear pattern’ (seen in 19/80, 24%), also broadly corresponds to the *same* pattern of abnormalities described in Delphi Statement 20 (see also Figures 5.4A and 5.4B above). Interestingly, it is noteworthy that there was disagreement between two observers for distinguishing between the bronchial distortion and linear patterns in one of the provided images. A final, but important, critique of the earlier paper would be regarding the pattern of peripheral honeycombing in sarcoidosis. A pattern mimicking UIP has been reported in sarcoidosis (300, 412, 413). Indeed, in the paper by Abehsera et al., this pattern of fibrosis was reported in nearly one third of patients (109). However, against this and even after clarification in the second round of the Delphi, the international consensus view was that UIP could *not* be considered a distinct HRCT phenotype in patients with a confirmed diagnosis of sarcoidosis (Delphi Statement 24; Round 1, 39% agreement and Round 2, 40% agreement).

A number of morphological phenotypes ‘rejected’ in Round 1 achieved consensus only after clarification. For instance, Delphi Statement 12 and 15 — regarding scattered larger nodules and consolidation as distinct sarcoid phenotypes — reached consensus agreement after clarification (Round 1 versus Round 2 agreement, 47% and 62% respectively versus 73% and 92% agreement respectively). This is a strength of the Delphi process allowing for clarifications between rounds. Indeed, the pattern of consolidation in

patients with proven sarcoidosis eventually emerged as one of the final seven recognised HRCT sarcoid phenotypes.

A number of proposed HRCT phenotypes did not achieve consensus agreement. Indeed, the presence of scattered large cavitating nodules (*Delphi Statement 13; consensus agreement, 18%*), a mosaic attenuation pattern (*Delphi Statement 16, consensus agreement, 29%*) and interlobular septal thickening (*Delphi Statement 18, consensus agreement, 23%*) all fell below the *a priori* threshold for consensus agreement in Delphi Round 1. There is a traditional view, particularly among radiologists, that the HRCT manifestations of sarcoidosis are varied and legion. Even so, cavitating nodules (NB to be differentiated from the fibro-cavitary disease apparent in some patients) must be considered among the rare, if not rarest, of HRCT manifestations. The international consensus view in this chapter, is in line with this. By contrast with cavitating nodules, the finding that a mosaic attenuation pattern (reflecting obstructive small airways disease) did not reach consensus was a little more surprising. Involvement of airways in sarcoidosis is well recognised (105, 111, 112, 114, 335) (see section 1.4.2, page 33). In line with this, Gleeson and colleagues demonstrated evidence of air trapping on expiratory HRCT in three patients with sarcoidosis (111). In a separate larger study, Hansell et al. found that areas of decreased attenuation at end-expiration were present in 40/45 (89%) cases and more prevalent than any other HRCT pattern (114). Moreover, the extent of decreased attenuation was independently linked with airflow limitation. The reasons why this pattern of abnormality on CT (and, for that matter, interlobular septal thickening) did not reach consensus are not entirely clear. One explanation might be that such patterns are often seen in combination with other signs of sarcoidosis (e.g. nodules, reticulation) and, so, may not be seen as ‘typical’ of sarcoidosis.

The Delphi exercise reported in this chapter also took the opportunity to explore views on possible relationships between HRCT appearances and i) their pathological meaning, ii) patterns of functional impairment, iii) treatment implications and iv) prognosis. With regard to the first, there was agreement that two HRCT patterns were generally indicative of established fibrosis namely, a reticular pattern (*Delphi Statement 17; consensus agreement, 80% [after Round 2]*) and large bronchocentric masses (*Delphi Statement 19; consensus agreement, 83% [also after Round 2]*). There seems little that is controversial or unexpected with this finding. Similarly, there was also consensus on the statements that specific HRCT appearances correspond with specific lung function profiles (*Delphi Statement 28; consensus agreement, 80% [after Round 2]*), that predominant reticulation is linked with restrictive lung function indices (*Delphi Statement 29; consensus agreement, 71%*) but that bronchocentric fibrosis predicts obstructive lung function (*Delphi Statement 30; consensus agreement, 71%*). A final interesting point to make is regarding a statement about CT abnormalities and treatment implications: after clarification, there was agreement or strong agreement (*Delphi Statement 32; consensus agreement, 72%*) on the statement that in a *minority* of patients, a progressive massive fibrosis (PMF)-look-alike pattern may partially or completely regress on treatment. This view is seemingly counter-intuitive and difficult to explain. Historically, this pattern of fibrosis has, most often, been linked to occupational exposures and, more often than not, signifies 'end-stage' disease (414-417). However, the Delphi exercise has disclosed not only that there is a recognisable PMF-look-alike on HRCT in sarcoidosis but that, in the view of an international expert panel, this may be treatable, albeit in a minority of patients. Clearly this presents an avenue for future research in sarcoidosis.

Key Points

- Experts overwhelmingly recommend HRCT as a baseline investigation in patients with pulmonary sarcoidosis who have evidence of parenchymal disease
- There is agreement that HRCT phenotypes exist in sarcoidosis and that these are broadly divided into 'fibrotic' and 'non-fibrotic' sub-groups (comprising nodular patterns or consolidation)
- There is agreement that distinct phenotypes may be associated with distinct outcomes and lung function profiles

Section 2 | Chapter 6

Variation Between Observers for Identifying CT Phenotypes

6.1 INTRODUCTION & AIMS

In sarcoidosis the general tendency is that all cases are ‘lumped’ under a single diagnostic label. However, it is abundantly clear from the literature and the findings of the previous chapter that pulmonary sarcoidosis has a number of guises. That said, to date, attempts to classify sarcoidosis based on morphological (HRCT) phenotypes have been few and far between (109, 114, 123, 311). The large international Delphi study, presented in chapter 5, proposed that there may be seven recognisable HRCT phenotypes in pulmonary sarcoidosis. These HRCT phenotypes may form the basis of a new classification system. However, the utility of any proposed classification system in clinical practice, must be based on two key aspects: ‘reproducibility’ and ‘clinical utility’. Accordingly, the specific aims of the investigations in this chapter were as follows:

- ***To assess the utility of identifying HRCT phenotypes by i) assessing the ‘ease’ with which observers are able to identify a predominant or single phenotype in sarcoidosis and ii) quantifying the average time taken to review each HRCT study***
- ***To determine variability between observers for identifying HRCT phenotypes in patients with sarcoidosis***

6.2 METHODS

The inclusion / exclusion criteria for patients in this study have been outlined previously (see section 2.2; page 82): in brief, consecutive patients with sarcoidosis and evidence of parenchymal disease on HRCT were included. HRCT studies were presented to observers on the in-house-developed ‘RadiologistLabs’ online data collection tool: full volumetric HRCT datasets were reviewed for each case and observations regarding phenotypes recorded using easy-to-use ‘drop-down’ responses. In addition to cases for review, observers were provided a link to sample images of all relevant HRCT phenotypes

(together with written descriptions). Observers evaluated HRCT scans for the presence of a *primary* (or dominant) phenotype, defined as an HRCT pattern accounting for greater than 50% of the parenchymal abnormality. Where mixed patterns were present, observers had the facility to record a *secondary* phenotype (i.e. accounting for <50% of the parenchymal abnormality). In cases where a secondary phenotype was assigned, participants were required to specify the percentage attributed to each pattern (for instance, 60% primary: 40% secondary). Based on results of the Delphi study in chapter 5, HRCT phenotypes were divided into ‘nodular’, ‘fibrotic’ and ‘other’ subtypes (see section 5.4.3.3, page 158); note that, for the purposes of the current study, in addition to the seven HRCT phenotypes agreed by final consensus, observers had the facility to assign other phenotypes (as originally presented in two Delphi rounds). Furthermore, where no definite HRCT phenotype was discernible, observers had the facility to record ‘*No classifiable phenotype*’. The following primary/secondary HRCT phenotypes were recorded:

NODULAR HRCT PHENOTYPES

- ***Micronodular: bronchovascular, peri-fissural/subpleural distribution with or without: larger nodules +/- surrounding micronodules (‘galaxy sign’); architectural distortion; volume loss***
- ***Micronodular: random distribution with or without: larger nodules +/- surrounding micronodules (‘galaxy sign’); architectural distortion; volume loss***
- ***Nodular (>3 mm but < 3cm): bronchovascular, peri-fissural/subpleural distribution with or without: larger nodules +/- surrounding micronodules (‘galaxy sign’); architectural distortion; volume loss***
- ***Nodular (>3 mm but < 3cm): random distribution***
- ***Nodular cavitating (>3 mm but < 3cm): random distribution***

FIBROTIC HRCT PHENOTYPES

- ***Reticular: bronchocentric +/- dense parenchymal opacification; NO cavitation or fibro-bullous destruction with or without: delicate bands of ‘loose’ reticulation;***

enlarged peripheral pulmonary arteries, central pulmonary artery enlargement; mosaic attenuation pattern

- **Reticular: bronchocentric +/- dense parenchymal opacification; WITH cavitation or fibro-bullous destruction with or without: delicate bands of 'loose' reticulation;** *enlarged peripheral pulmonary arteries, central pulmonary artery enlargement; mosaic attenuation pattern*
- **Masses: large bronchocentric ('PMF-look alike') with or without: delicate bands of 'loose' reticulation;** *enlarged peripheral pulmonary arteries, central pulmonary artery enlargement; mosaic attenuation pattern*
Reticular: mid/lower zone predominant, sub-pleural +/- honeycombing ('UIP-' or 'NSIP look-alike')
- **Upper zone pleural thickening, subpleural reticulation and consolidation ('PPFE look-alike')**

OTHER PHENOTYPES

- **Ground-glass opacification** *as the dominant or sole abnormality*
- **Consolidation** *as the dominant or sole pattern*
- **Decreased attenuation** *as part of the mosaic attenuation pattern) as the dominant or sole abnormality*
- **Interlobular septal thickening** *as the dominant or sole pattern*

NO CLASSIFIABLE PHENOTYPE

Observers were requested to record the time taken to complete the HRCT phenotyping exercise. This was then used to calculate the average 'time per case' as one measure of 'user-friendliness' in CT phenotyping.

6.3 STATISTICAL METHODS

Observer agreement for identifying primary and secondary phenotypes was quantified using Fleiss Kappa and interpreted using the thresholds indicated previously (see section 2.5.1; page 91). A rough estimate of the 'prevalence' of specific HRCT phenotypes

was derived by the number of cases where a particular HRCT phenotype was selected as the dominant pattern.

6.4 RESULTS

6.4.1 Baseline Findings & 'Prevalence' of Single HRCT Phenotypes

Two hundred and twenty one HRCT studies, in patients with established parenchymal disease caused by sarcoidosis, were evaluated by 13 observers (thoracic radiologists, n=7; chest physicians, n=6; M:F, 8:5) The mean duration of observer experience was 16.7±8.5 years. Eleven out of 13 (85%) observers recorded the time taken to review all cases. The average time taken per case was 60±34 secs. The number of cases for which an observer assigned only a *single* (i.e. primary) phenotype is shown in Table 6.1. With the exception of two observers, 11/13 were able to assign a single primary HRCT phenotype in a majority of cases (i.e. >50%).

OBSERVER	N	%	OBSERVER	N	%
<i>Radiologist 1</i>	129	58	<i>Physician 1</i>	88	39
<i>Radiologist 2</i>	91	41	<i>Physician 2</i>	129	58
<i>Radiologist 3</i>	131	59	<i>Physician 3</i>	153	69
<i>Radiologist 4</i>	141	64	<i>Physician 4</i>	114	52
<i>Radiologist 5</i>	126	57	<i>Physician 5</i>	120	54
<i>Radiologist 6</i>	130	59	<i>Physician 6</i>	134	60
<i>Radiologist 7</i>	143	65			

Table 6.1 Assignment of *single* HRCT phenotypes by radiologists and physicians. Data are the number of HRCT cases (out of 221), with percentages, for which each observer recorded a *single*, primary phenotype

Across all cases and observers (i.e. 13x221=2873 individual case observations), a primary phenotype *alone* was assigned in 1629/2873 (57%) (Table 6.2). Among specific HRCT phenotypes, a bronchocentric, peri-fissural/subpleural micronodular pattern, (recorded in 336/2873 [12%]) and a bronchocentric reticular pattern without cavitation (266/2873 [9%]) were the most common (Figure 6.1). In 186/2873 (6%) observations, no definable HRCT phenotype could be ascribed (Figure 6.2).

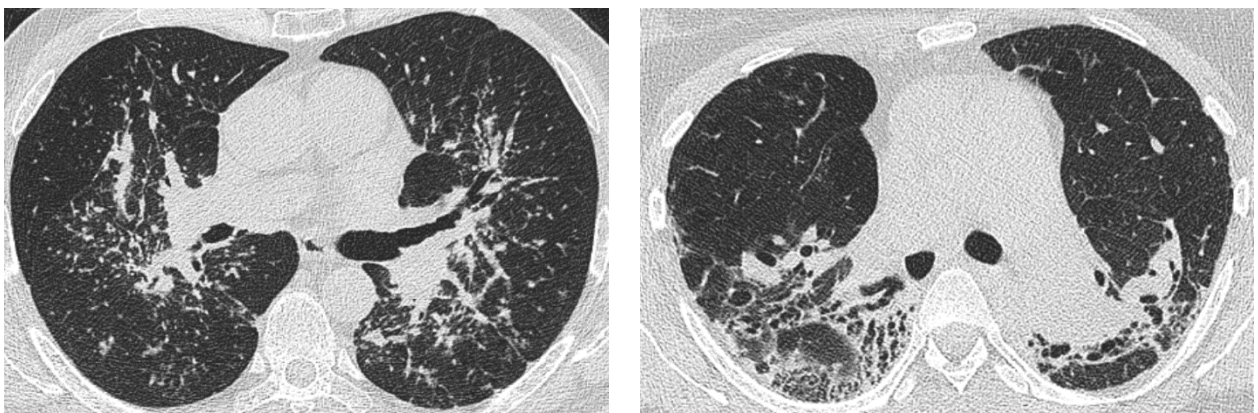


Figure 6.1: HRCT examples of the two most commonly identified phenotypes. A) image just below the carina showing a bronchocentric, peri-fissural/subpleural micronodular pattern. B) HRCT image in another patient showing a bronchocentric reticular pattern without cavitation.

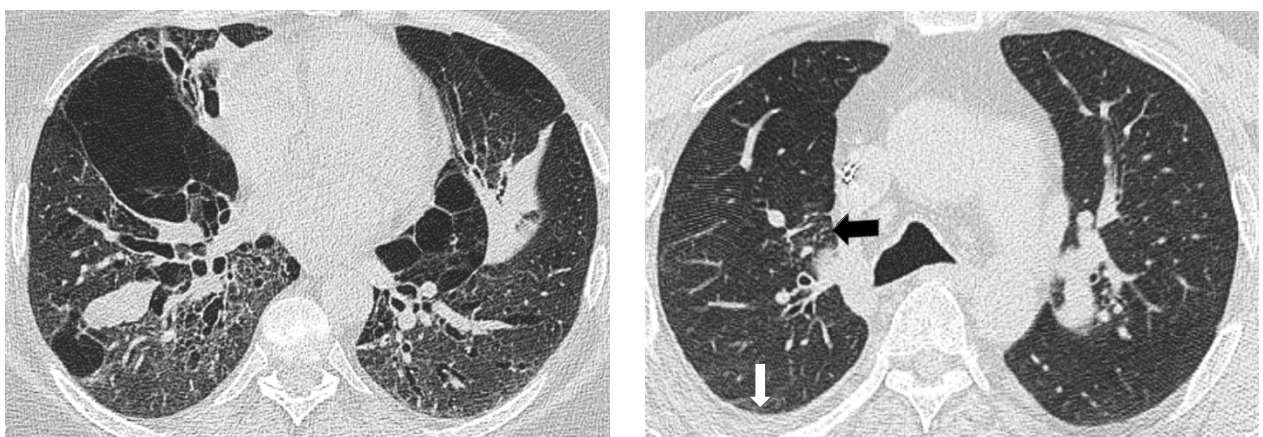


Figure 6.2: HRCT examples scored as ‘no classifiable phenotype’. A) Image through the lower lobes of a patient demonstrating a combination of bullous emphysema, groundglass opacification and central traction bronchiectasis. B) Another example of ‘no classifiable phenotype’ – this study demonstrates a minor micronodular component (black arrow) and mild right sided pleural thickening (white arrow).

HRCT PHENOTYPE	N	'Relative prevalence' (%)
NODULAR		
<i>Micronodular - bronchovascular, perifissural/subpleural distribution†</i>	336	12
<i>Micronodular – Random distribution</i>	113	4
<i>Nodular – larger (>3 mm) bronchovascular, perifissural/subpleural distribution†</i>	211	7
<i>Nodular – Random distribution†</i>	69	2
<i>Nodular - Cavitating</i>	3	0.1
FIBROTIC		
<i>Reticular - bronchocentric without cavitation†</i>	266	9
<i>Reticular - bronchocentric with cavitation†</i>	118	4
<i>Masses – bronchocentric (PMF look-alike)†</i>	72	3
<i>UIP/NSIP look-alike</i>	188	6
<i>PPFE</i>	22	0.8
OTHER		
<i>Ground-glass opacification</i>	105	4
<i>Consolidation†</i>	48	2
<i>Decreased attenuation</i>	49	2
<i>Interlobular septal thickening</i>	29	1
NO CLASSIFIABLE PHENOTYPE	186	6

Table 6.2 'Prevalence' of HRCT phenotypes based on all observations. Data are the number of instances, N, across all cases & observers (NB total observations, n=2873) and the 'relative prevalence' of each phenotype (i.e. the number of times that a specific phenotype was chosen as the *sole* phenotype, expressed as a percentage of the total number of observations). UIP=usual interstitial pneumonia; NSIP=non-specific interstitial pneumonia; PPFE=pleuroparenchymal fibroelastosis. † HRCT phenotypes identified in Delphi.

6.4.2 Observer Agreement for HRCT Phenotypes

Data on observer agreement, expressed as the Fleiss Kappa coefficient (K) for the identification of HRCT phenotypes are shown in Table 6.3. Agreement across all observers for *all* nodular phenotypes was 'moderate' (K=0.56) and 'good' among thoracic radiologists (K=0.61). However, agreement for *individual* nodular phenotypes was below clinically acceptable limits (K <0.40 for all). Observer agreement improved when the two

micronodular HRCT phenotypes were combined (i.e. disregarding the distribution of micronodules, $K=0.42$ for all observers and $K=0.40$ for thoracic radiologists).

There was moderate observer agreement for the fibrotic HRCT phenotype category for all observers, radiologists alone and chest physicians ($K=0.57$, $K=0.59$ and $K=0.57$ respectively). Among radiologists, there was moderate to good agreement for bronchocentric reticulation with cavitation, bronchocentric reticulation without cavitation and UIP/NSIP look-alike (Fleiss K 0.67, 0.44 and 0.67).

There was moderate agreement between all observers and between radiologists for the 'other' phenotype category (Fleiss K 0.41-0.43). Agreement was highest for the ground-glass opacity phenotype (Fleiss K 0.43-0.46) and lowest for the consolidation phenotype (Fleiss K 0.27 – 0.29). Combining consolidation and PMF look-alike into a single phenotype improved observer variation to Fleiss K 0.46 for all observers and for radiologists alone.

HRCT PHENOTYPE	Fleiss K <i>Primary phenotype All Observers†</i>	Fleiss K <i>Primary phenotype Radiologists†</i>	Fleiss K <i>Primary phenotype Physicians†</i>
NODULAR	0.56	0.61	0.53
<i>Micronodular - bronchovascular, peri-fissural/subpleural distribution†</i>	0.34	0.34	0.31
<i>Micronodular – Random distribution</i>	0.22	0.17	0.27
<i>Nodular – larger (>3 mm) bronchovascular, peri-fissural/subpleural distribution†</i>	0.28	0.30	0.25
<i>Nodular – Random distribution†</i>	0.20	0.33	0.13
<i>Nodular - Cavitating</i>	n/a	n/a	n/a
FIBROTIC	0.57	0.59	0.57
<i>Reticular - bronchocentric without cavitation†</i>	0.40	0.44	0.37
<i>Reticular - bronchocentric with cavitation†</i>	0.65	0.67	0.66
<i>Masses – bronchocentric (PMF look-alike)†</i>	0.41	0.38	0.42
<i>UIP/NSIP look-alike</i>	0.63	0.67	0.62
<i>PPFE</i>	n/a	n/a	n/a
OTHER	0.41	0.43	0.38
<i>Ground-glass opacification</i>	0.43	0.46	0.39
<i>Consolidation†</i>	0.29	0.27	0.28
<i>Decreased attenuation</i>	0.45	0.58	0.33
<i>Interlobular septal thickening</i>	0.29	0.33	0.24
NONE	0.26	0.33	0.23

Table 6.3 Agreement between observers for HRCT phenotype. Data are the Fleiss Kappa statistic for observer agreement on the dominant phenotype or the presence of a phenotype (irrespective of dominance) between *all* participants (n=13) or radiologists (n=7) as indicated. N.B. *PMF=progressive massive fibrosis*; *UIP=usual interstitial pneumonia*; *NSIP=non-specific interstitial pneumonia*, *PPFE=pleuroparenchymal fibroelastosis*. † HRCT phenotypes identified in Delphi.

6.5 DISCUSSION

The Delphi study reported in Chapter 5 identified seven morphological phenotypes on HRCT in sarcoidosis. However, before such data can be used to propose a new morphological/HRCT classification it is important to know whether observers can reliably identify and distinguish between HRCT subtypes. The Delphi process, at its core, is a *descriptive* process and, while ‘sample’ HRCT were provided to observers in this study, it could not be assumed that the HRCT descriptors would necessarily translate into a ready recognition of HRCT patterns which, in essence, is a *visual* exercise. Accordingly, in this chapter, the principal aim was to evaluate agreement between observers for recognising different morphological subtypes on HRCT in a large cohort of patients with parenchymal sarcoidosis. The utility or ‘user-friendliness’ of a potentially new morphological classification was also tested by i) including thoracic physicians in the evaluation of HRCT studies and ii) estimating the average time taken to review each study.

The results in this chapter show that participants are able to assign a *single* primary phenotype in a majority of instances: with the exception of two observers — one thoracic radiologist and one chest physician — a single primary phenotype had been assigned in 52-69% of cases. This is an important finding suggesting that distinct HRCT phenotypes not only can be recognised by a majority of observers but also that, in many cases (but, admittedly, not all [see below]), HRCT phenotypes were being linked with the written descriptors generated by the Delphi. Three patterns were most frequently selected as the sole phenotypes: i) micronodules in a bronchovascular, peri-fissural/sub-pleural distribution, ii) bronchocentric reticulation without cavitation and, iii) large bronchovascular, peri-fissural/sub-pleural nodules. All other HRCT sub-types were less commonly recorded by participants. For example, observers only considered randomly distributed micronodules as

a distinct single phenotype in 113/2873 (4%) observations. Similarly, whilst there were cases in which predominant ground-glass opacification (4%), consolidation (2%) and interlobular septal thickening (1%) were the primary phenotype, these were significantly in the minority. The analyses also showed that for 6% of observations, there was no classifiable phenotype recorded. The exact reasons for the latter were not formally explored but it might be reasonably concluded that those with no classifiable phenotype comprised cases with a more complex admixture of patterns (for instance, groundglass opacification, emphysema and traction bronchiectasis) and also those with relatively limited disease [see also Figure 6.2].

The data presented in this chapter provide a crude but useful estimate of the *relative* prevalence of different HRCT phenotypes in sarcoidosis (262, 284, 301, 319, 364). In this regard, an unexpected finding was the somewhat high 'prevalence' of a HRCT pattern resembling UIP/NSIP in this cohort. Indeed, the 'UIP/NSIP look-alike' pattern was more commonly selected as a sole phenotype than other HRCT appearances that might, on first thought, be considered more common in sarcoidosis, for example, bronchocentric fibrosis with cavitation/fibro-bullous destruction. In part, this may simply reflect a selection bias given the tertiary/quaternary nature of the sarcoidosis practice at Royal Brompton Hospital. That said, a UIP pattern, though uncommon, has been reported but whether this signifies a unique manifestation of sarcoidosis or co-existent idiopathic pulmonary fibrosis is open to question (300, 333, 412, 413). On this note, it is telling that the extant data on a UIP pattern in sarcoidosis is limited to case reports and small case series (333, 412, 413).

A nodular HRCT pattern is rightly considered one of the more common manifestations of pulmonary sarcoidosis (241, 262, 314). The data in the present chapter indicate that there is good overall agreement between observers for the recognition of a

nodular pattern *per se* (radiologists [Fleiss Kappa, 0.61] and physicians [Fleiss Kappa, 0.53]). However, the same was not true for the different forms of a nodular pattern: for instance, observers were less inclined to agree on — and, by implication, less able to differentiate between — the presence of bronchovascular, peri-fissural/sub-pleural micronodules and randomly distributed micronodules. At first glance these results seem a little surprising and especially so given that in Chapter 5 there was overwhelming consensus (>97%) among Delphi participants that a bronchovascular, peri-fissural/sub-pleural micronodular pattern constitutes a distinct CT phenotype (Table 5.5, page 154). However, against this it will have been noted that, even after two Delphi rounds, a randomly distributed micronodular pattern did not achieve consensus as a discrete HRCT phenotype (Round 1, 57% agreement; Round 2, 66% agreement). That said, it might be argued that the intricate separation of nodular patterns into different HRCT sub-types, examined in the present chapter, is of little practical value. After all, among the common CT manifestations of sarcoidosis, nodules are believed to reflect reversible or treatable disease (320, 364, 366). In this regard, it perhaps makes sense to group the various nodular patterns into a *single* nodular HRCT phenotype.

As a whole, fibrotic HRCT phenotypes were also associated with moderate observer agreement (radiologists [Fleiss Kappa, 0.59] and physicians [Fleiss Kappa, 0.57]). However, in contrast with nodular subtypes, observer agreement for individual fibrotic HRCT phenotypes was generally better: variation was lowest for bronchocentric reticulation with cavitation (thoracic radiologists [Fleiss Kappa, 0.67]; physicians [Fleiss Kappa, 0.66]) and for scans with a ‘UIP/NSIP look-alike’ pattern (thoracic radiologists [Fleiss Kappa, 0.67]; physicians [Fleiss Kappa, 0.62]), the latter being broadly in line with the published literature (418-421). Accordingly, in contrast to nodular HRCT patterns, the data herein suggest that fibrotic HRCT phenotypes might readily be further sub-divided in any new classification system.

It will have been noted from the Methods section (see section 6.2, page 170) that the ‘choice’ of primary and secondary HRCT phenotypes were *not* restricted to the seven phenotypes identified in the Delphi exercise. In this respect, an interesting finding was that for ~18% of observations, a single primary phenotype was selected from the list that were *not* one of the seven HRCT phenotypes identified in the Delphi (namely, randomly distributed micronodules [4%]; cavitating nodules [0.1%]; UIP/NSIP look-alike [6%]; pleuroparenchymal fibroelastosis [0.8%]; ground-glass opacification [4%]; decreased attenuation [2%] and interlobular septal thickening [1%]). Of these ‘non-Delphi’ subtypes, one (i.e. decreased attenuation as part of the mosaic attenuation pattern) is worthy of brief discussion. In sarcoidosis, regions of decreased attenuation — indicating obstructive small airways disease — are well recognised and surprisingly common (111, 114, 422-424). In the study by Hansell and co-workers, regions of decreased attenuation on CT were the most prevalent finding, seen in 40/45 (89%) (425). Admittedly, decreased attenuation on CT may be subtle and difficult to detect particularly when coupled with other features of parenchymal disease or in the absence of expiratory scans (111, 426, 427). This might, in part, explain the difference in observer agreement between thoracic radiologists (Fleiss Kappa, 0.58) and chest physicians (Fleiss Kappa, 0.33). A final surprising observation in this chapter was the poor agreement for both radiologists (Fleiss Kappa, 0.27) and physicians (Fleiss Kappa, 0.28) for the predominant consolidation pattern, despite consolidation being a common finding in radiology, irrespective of cause. Once again, the precise reason for this finding was not formally explored but one possibility is that the distinction of ‘true’ consolidation from a pattern of dense bronchocentric reticulation or, even, progressive massive fibrosis can be considered subjective. Indeed, this is supported by the finding of

increased observer agreement when combining consolidation and PMF look-alike into a single phenotype.

In summary, the investigations in this chapter have evaluated observer agreement among thoracic radiologists and chest physicians for specific HRCT phenotypes in sarcoidosis. The results show that, in general, there is acceptable observer variation among both groups for the identification of nodular and fibrotic phenotypes. Indeed, observers appear relatively adept at identifying fibrotic subtypes. By contrast the subdivision of nodular HRCT patterns into more precise subtypes — for instance, bronchocentric micronodular versus randomly-distributed micronodules — appears to increase observer disagreement, perhaps reflecting a ‘disconnect’ between the *written* descriptions of HRCT patterns and *visual* interpretation of HRCT scans. Needless to say, it remains to be seen whether the identification of the subtleties in different nodular patterns has clinical/prognostic meaning.

Key points

- Observer agreement for nodular and fibrotic phenotypes as a whole is 'moderate' to 'good', however subclassifying the nodular patterns by distribution and nodule size unacceptably increases observer variation
- There is acceptable observer agreement for several CT phenotypes that reached consensus during the Delphi exercise; these can be reasonably considered for a CT-based classification system for sarcoidosis
- Future studies are required to evaluate the prevalence, functional significance and prognostic implications of the proposed CT phenotypes

Chapter 7

Conclusion

7 CONCLUSION

Since its earliest description, sarcoidosis has been an enigma. Diagnosis relies on a combination of compatible clinical-radiological signs and, where available, pathological evidence of non-necrotising granulomas plus the exclusion of alternative causes of granulomatous inflammation. Yet, securing a high-confidence diagnosis remains a clinical challenge for many. The clinical course of sarcoidosis varies greatly from patient to patient: and so, while complete resolution is the norm for a majority, inexorable progression to end-stage lung disease is seen in a not insignificant minority. The interpretation of lung function poses a challenge, with restrictive, obstructive and mixed profiles regularly encountered in patients. The morphological manifestations (particularly on HRCT) of sarcoidosis are many and varied. Indeed, this prompts the question as to how the myriad HRCT appearances in sarcoidosis have come to be ‘lumped’ under a single diagnostic label, in contrast to what has happened with other diffuse interstitial lung diseases where the tendency has been to ‘split’ based on histopathologic findings, defined triggers and outcome. One issue in sarcoidosis has perhaps been the absolute or sole reliance on histological appearance (i.e. the non-caseating granuloma), not only for diagnosis but also when aiming to understand prognostic differences. Indeed, it might be argued that had the grouping (or classification) of sarcoidosis been based on CT features, this might have provided more precise phenotypic separation when related to outcome. By concentrating most on radiological appearances, the investigations in this thesis have sought to answer some of the issues highlighted above.

The general methodologies employed in this work are summarised in **Chapter 2** and the key studies are covered in two sections: in Section I (**Chapters 3 & 4**), CXR appearances

— in particular, so-called CXR ‘staging’ — and HRCT features were first compared and contrasted; potential linkages between radiological abnormalities, lung function tests and outcome were then tested. In Section II, **Chapter 5** the principal aim was to define and gain agreement on recognisable HRCT ‘morphological phenotypes’ in sarcoidosis, by consensus of an international body of expert thoracic radiologists and chest physicians. Having then identified a set of HRCT phenotypes, **Chapter 6** asks whether observers can reliably distinguish between ‘groups’ of HRCT appearances in a large cohort of patients with sarcoidosis.

In Chapter 3, observer agreement for CXR stage and for the detection, characterisation and quantification of HRCT patterns was evaluated. Not surprisingly, given the absence of anatomical superimposition and the better contrast resolution, observer agreement was better on HRCT than when reviewing CXR. That said, ***agreement overall for CXR stage was in the clinically-acceptable range but varied between the individual CXR stages***: put simply, in the absence of radiographic signs of fibrosis (i.e. CXR stage IV), there was greater observer disagreement. This was particularly true for CXR stages II and III, an observation that was to be expected (given the lower sensitivity of CXR for more subtle parenchymal disease) and convincingly revealed in Chapter 4. Indeed, the concurrent comparison with HRCT also showed that ~40% of patients with so-called CXR stage 0/I disease had signs of parenchymal involvement. Another key finding in Chapter 4, previously not emphasised in the literature, was ***the presence (and progressively high proportion) of lung fibrosis in patients with ‘lower’ CXR stages***: there were HRCT signs of fibrosis in each of CXR stages 0/I (10%), II (20%) and III (30%). Given the prognostic importance of fibrosis

shown later in Chapter 4 (and discussed further below) this is an important finding of the thesis. Put another way, the results suggest that ***clinicians cannot rely on CXR stage per se when making prognostic statements in sarcoidosis.***

Chapter 4 also explored the inter-relationships between CXR features, HRCT abnormalities, lung function indices and, crucially, outcome. With regard to CXR, ***only stage IV disease was linked to reductions in functional parameters.*** On HRCT, overall disease extent was most closely correlated to DLco, a finding that is consistent with the results of structure-versus-function studies in other fibrosing lung diseases. Additionally, HRCT allowed a more detailed analysis of the impact of *individual* HRCT patterns, over and above the extent of abnormal lung and confirmed that ***four HRCT signs — reticulation, ground-glass opacification, fibrocavitation and a mosaic attenuation pattern — were independently predictive of DLco.*** Finally, in Chapter 4, there was a broader exploration of the relationships between imaging findings and survival. Not unexpectedly, there was a clear separation between CXR stage IV and ‘lower’ radiographic stage. However, among other individual CXR stages (say, CXR stage 0/1 versus CXR stage III) there were no clear differences. Yet again, the greater scrutiny afforded by HRCT provided insights into the prognostic meaning of specific morphological abnormalities. Of these, perhaps the most important was the striking prognostic impact of traction bronchiectasis, a sign which, at one time, was simply regarded an epiphenomenon in fibrotic lung. The findings in this thesis reinforce the notion that, all other factors being equal (and irrespective of cause), ***the presence of traction bronchiectasis in fibrotic lung is the harbinger of a poor outcome.***

In Section II, the aim was to identify, by consensus, the principal HRCT phenotypes in sarcoidosis. This was as a prelude to developing and proposing a new morphological classification in sarcoidosis: 146 respiratory physicians and radiologists from around the globe participated in the Delphi process, an exercise which has not previously been attempted. Before considering the radiological findings, it is important to highlight an important — and somewhat unexpected — clinical statement which emerged at the outset: there was broad consensus that ***HRCT should be requested as a baseline investigation in patients with pulmonary sarcoidosis who have evidence of interstitial involvement***. To date, such a statement has not been made in published guidelines for sarcoidosis. Accordingly, there has been a historical and undue reliance on plain radiography in assessment. The view that HRCT should have a central role at baseline from an international body is important and likely to influence future guideline development.

It has long been known that the morphological manifestations of sarcoidosis vary considerably and perhaps more than any other disease. The Delphi process was designed to identify the existence of distinct or ‘recognisable’ HRCT subtypes. Accordingly, another key finding of the Delphi study was the agreement on ***seven HRCT phenotypes (comprising ‘clusters’ of HRCT patterns or abnormalities) broadly classified as ‘fibrotic’ or ‘non-fibrotic’***. Among the phenotypes reaching consensus, the former group comprised three nodular patterns plus a pattern of predominant consolidation with the second group made up of different forms of fibrotic sarcoidosis.

The above findings might be seen as an important first step in developing a *morphological* (HRCT) classification of sarcoidosis. However, there are additional elements that are required before any new classification is proposed. One of these (not evaluated in

this body of work) is to understand the ‘real-world’ prevalence of such HRCT phenotypes and the second would be to establish observer agreement for their recognition on HRCT.

Observer variation overall for the recognition of nodular and fibrotic subtypes was clinically acceptable and the mean time taken to characterise morphology on each scan was of the order of one minute. The latter is an important practical message. Interestingly, agreement for recognising the different *forms* of nodular pattern (e.g. bronchocentric versus random micronodules) was poor. The exact reasons for this are unclear at present but may relate to some difficulty in relating a written descriptor with the visual appearance on HRCT. This will undoubtedly warrant future evaluation and fine-tuning.

The limitations of the studies in this thesis need to be presented. First, the Royal Brompton Hospital sarcoidosis clinic is a regional and national referral centre. This invariably means that many patients present with ‘difficult-to-manage’ or ‘end-stage’ disease resulting in higher levels of fibrosis than in the general population. The obvious implication is that the present research is skewed towards those on the fibrotic end of the sarcoidosis spectrum. Against this, it is known that the small proportion of patients with higher CXR stage disease generally account for the greatest morbidity/mortality burden. Second, it may be argued that quantitative analysis of HRCT, which is undoubtedly more time-consuming than CXR evaluation, is not practicable and of little value, particularly in those with limited disease. However, while further work is certainly needed, the HRCT phenotypes identified in this thesis may well prove to be physiologically and prognostically important.

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APPENDIX

APPENDIX A: Delphi Round 1 Questionnaire

Demographics

1. Are you a **Pulmonologist** or **Radiologist**?
2. How many years has it been since you completed your (pulmonology/radiology) training?
3. What is your age?
4. What is your gender? (Male/Female/Prefer not to say)
5. Which country do you practice in?
6. What is the name of your institution?
7. Do you have a special interest in interstitial lung disease?
8. Do you have a special interest in sarcoidosis?
9. What proportion of your reporting time is dedicated to thoracic radiology? (<25%, 25-50%, 50-75%, >75)
10. On average, approximately how many sarcoid patients do you evaluate per year? (<50, 50-100, 101-250, >250)

Morphological Patterns

HRCT in Pulmonary Sarcoidosis

1. HRCT should be performed at baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement (on CXR/pulmonary lung functions tests/symptoms).

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

2. There are distinct CT phenotypes/patterns in pulmonary sarcoidosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

3. In a clear majority of cases, the HRCT features of sarcoidosis can be categorized as 'fibrotic' and 'non-fibrotic'.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Non-fibrotic CT Patterns in Sarcoidosis

4. An HRCT pattern comprising nodules alone or a predominance of nodules in sarcoidosis is almost always non-fibrotic.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

5. An HRCT pattern comprising a predominance of ground-glass opacification in sarcoidosis is almost always non-fibrotic.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

6. An HRCT pattern comprising predominant consolidation in sarcoidosis is almost always non-fibrotic.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

7. A mosaic attenuation pattern as the predominant abnormality in sarcoidosis is almost always non-fibrotic.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

Specific Morphologic CT Subtypes – Nodular Patterns

8. Nodules as the predominant or sole abnormality is a distinct HRCT pattern in sarcoidosis.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

9. The nodular phenotype includes the following distinct subset:

Multiple peri-bronchovascular, peri-fissural / subpleural micronodules predominantly in the mid/upper zones.

- WITH OR WITHOUT: A minority component of other CT abnormalities.
- Additional features: larger nodules and surrounding micronodules (the 'galaxy sign'), architectural distortion, upper lobe volume loss

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

10. The nodular phenotype includes the following distinct subset:

Multiple randomly distributed micronodules.

- WITH OR WITHOUT: A minority component of other CT abnormalities.
- Additional features: larger nodules and surrounding micronodules (the 'galaxy sign'), architectural distortion, upper lobe volume loss

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

11. The nodular phenotype includes the following distinct subset:

Multiple larger peri-bronchovascular nodules (>3 mm but < 3 cm diameter)

- WITH OR WITHOUT: A minority component of other CT abnormalities
- Additional features: larger nodules and surrounding micronodules (the 'galaxy sign'), architectural distortion, upper lobe volume loss

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

12. The nodular phenotype includes the following distinct subset: **scattered larger nodules** up to 3 cm in diameter with no obvious peri-bronchovascular/fissural/subpleural or zonal predilection.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

13. The nodular phenotype includes the following distinct subset: **scattered larger cavitating nodules**, up to 3 cm in diameter

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

Specific Morphologic CT Subtypes - OTHER PATTERNS

14. **Ground-glass opacification** as the **predominant or sole** abnormality is a distinct HRCT pattern in sarcoidosis.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

15. **Consolidation** as the **predominant or sole** abnormality is a distinct HRCT pattern in sarcoidosis.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

16. **A mosaic attenuation pattern** as the **predominant or sole** abnormality is a distinct HRCT pattern in sarcoidosis.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

Fibrotic CT patterns in sarcoidosis

17. **Reticulation** on CT in sarcoid almost always represents fibrosis.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

18. **Interlobular septal thickening** on CT in sarcoid almost always represents fibrosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

19. **Large bronchocentric masses with or without cystic / bullous ‘destruction’** on CT in sarcoid almost always represents fibrosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Specific HRCT Morphologic Subtypes - RETICULATION, MASSES, SEPTAL THICKENING

20. The following is a distinct HRCT pattern in sarcoidosis: **Bronchocentric reticulation +/- dense parenchymal opacification WITHOUT cavitation / fibrobullous destruction**

- WITH OR WITHOUT: A minority component of other CT abnormalities
- Additional features: delicate bands of (‘loose’) reticulation, enlarged peripheral pulmonary arteries (the ‘reverse signet ring’ sign), central pulmonary artery enlargement, a mosaic attenuation pattern

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

21. The following is a distinct HRCT pattern in sarcoidosis: **Bronchocentric reticulation and dense parenchymal opacification WITH cavitation / fibrobullous destruction**

- WITH OR WITHOUT: A minority component of other CT abnormalities
- Additional features: delicate bands of (‘loose’) reticulation, enlarged peripheral pulmonary arteries (the ‘reverse signet ring’ sign), central pulmonary artery enlargement, a mosaic attenuation pattern, signs of a mycetoma

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

22. The following is a distinct HRCT pattern in sarcoidosis: **Large bronchocentric masses** (i.e. progressive massive fibrosis [PMF] look-alike)

- WITH OR WITHOUT ancillary features (e.g. nodules, cavitation etc)

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

23. The following is a distinct HRCT pattern in sarcoidosis: **Predominant interlobular septal thickening**

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

24. The following is a distinct HRCT pattern in sarcoidosis: **Mid/lower zone-predominant subpleural reticulation with or without honeycombing** (i.e. UIP / NSIP look-alike).

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

25. The following is a distinct HRCT pattern in sarcoidosis: **Upper zone pleural thickening, with sub-pleural consolidation and reticulation +/- upper zone volume loss** (i.e. pleuroparenchymal fibroelastosis look-alike)

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

Miscellaneous HRCT Subtypes

26. 'Soft' intra-thoracic (mediastinal / hilar) nodal calcification occurs in sarcoidosis.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

27. 'Soft' intra-thoracic (mediastinal / hilar) nodal calcification **accompanied by hepatic and splenic calcified granulomas**, favours a diagnosis of histoplasmosis over sarcoidosis.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

Possible Linkages Between HRCT Subtypes and PFTs, BAL, Outcome etc.

28. Specific HRCT appearances correspond to specific lung function profiles (e.g. isolated reduction in gas transfer or restrictive/obstructive/mixed ventilatory defects).

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

29. A predominant reticular pattern on HRCT is associated with a restrictive lung function defect.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

30. A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

31. A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

32. **Bronchocentric reticulation +/- dense parenchymal opacification WITH cavitation / fibrobullous destruction WITH OR WITHOUT mycetoma predicts a poor response to treatment**

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐ ☐ ☐ ☐ ☐

33. An HRCT pattern comprising **large bronchocentric masses** (i.e. progressive massive fibrosis [PMF] look-alike) can **regress with treatment**.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

34. **Lobar volume loss** (particularly the upper lobes) is associated with a **poor outcome** in sarcoidosis.

Strongly Agree

☐

Agree

☐

Neutral/unsure

☐

Disagree

☐

Strongly disagree

☐

APPENDIX B: Delphi Round 2 Questionnaire

Dear Delphi Study Participant,

Thank you for completing Round 1 of our Delphi study. Round 2 seeks to *a)* clarify areas of ‘uncertainty’ and, where applicable, *b)* pose additional questions generated by Round 1 feedback.

Notes for Round 2 —

- As per Delphi protocol, questions from round 1 already meeting consensus and questions that are *unlikely* to reach consensus **are not repeated**. The remaining questions have either been modified, based on the comments received in the previous round, or have been repeated unchanged. Please note, changes to previous questions will be highlighted in bold.
- Where relevant, results from the previous round will be provided.
- A key confusion in some of the responses in Round 1 centred on the issue of ‘*diagnosis*’. For Round 2, we would like to stress that the study is **not** looking to establish the diagnostic CT features of sarcoidosis **nor** the appearances on CT that differentiate sarcoidosis from other diagnoses. Put simply, when responding you should assume that each Delphi statement refers to patients **WITH** a confirmed diagnosis of sarcoidosis.
- An additional source of confusion, arising from comments in Round 1, appears to be related to the CT examples provided. We would like to stress that the ‘sample’ CT studies merely serve as **examples** to illustrate the Delphi statements. We are **not** looking for agreement on whether the Delphi statement agrees or disagrees with provided examples. However, you should note that **all** examples provided are in patients referred to or followed at our institution with confirmed sarcoidosis.
- As in Round 1, you are required to respond to all Delphi statements using the 5-point scale (from ‘*strongly agree*’ to ‘*strongly disagree*’). Also, where relevant, we strongly again encourage free text comments.

Morphological Patterns

Non-fibrotic CT Patterns in Sarcoidosis

35. **In patients with a confirmed diagnosis of sarcoidosis**, an HRCT pattern comprising a predominance of ground-glass opacification is almost always non-fibrotic (**in the absence of ancillary CT features of fibrosis**).

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: An HRCT pattern comprising a predominance of ground-glass opacification in sarcoidosis is almost always non-fibrotic. **54% strongly agree or agree, 26% neutral/unsure, 20% disagree or strongly disagree.**

36. **In patients with a confirmed diagnosis of sarcoidosis**, an HRCT pattern comprising predominant consolidation is almost always non-fibrotic.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: An HRCT pattern comprising predominant consolidation in sarcoidosis is almost always non-fibrotic. **34% strongly agree or agree, 26% neutral/unsure, 40% disagree or strongly disagree**

37. **In patients with a confirmed diagnosis of sarcoidosis**, a mosaic attenuation pattern as the predominant abnormality is almost always non-fibrotic.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: A mosaic attenuation pattern as the predominant abnormality in sarcoidosis is almost always non-fibrotic. **42% strongly agree or agree, 26% neutral/unsure, 32% disagree or strongly disagree.**

Specific Morphologic CT Subtypes – Nodular Patterns

38. **In patients with a confirmed diagnosis of sarcoidosis**, the nodular phenotype includes the following distinct subset: multiple *randomly* distributed micronodules.

- WITH OR WITHOUT: A minority component of other CT abnormalities
- Additional features: larger nodules and surrounding micronodules (the 'galaxy sign'), architectural distortion, upper lobe volume loss

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: the nodular phenotype includes the following distinct subset: multiple *randomly* distributed micronodules. **34% strongly agree or agree, 26% neutral/unsure, 40% disagree or strongly disagree.**

39. **In patients with a confirmed diagnosis of sarcoidosis,** the nodular phenotype includes the following distinct subset: scattered larger nodules up to 3 cm in diameter with no obvious peri-bronchovascular/fissural/subpleural or zonal predilection.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: The nodular phenotype includes the following distinct subset: scattered larger nodules up to 3 cm in diameter with no obvious peri-bronchovascular/fissural/subpleural or zonal predilection. **47% strongly agree or agree, 24% neutral/unsure, 29% disagree or strongly disagree.**

Specific Morphologic CT Subtypes - OTHER PATTERNS

40. **In patients with a confirmed diagnosis of sarcoidosis,** ground-glass opacification as the predominant or sole abnormality is a distinct HRCT pattern.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: Ground-glass opacification as the predominant or sole abnormality is a distinct HRCT pattern in sarcoidosis. **45% strongly agree or agree, 15% neutral/unsure, 40% disagree or strongly disagree**

41. **In patients with a confirmed diagnosis of sarcoidosis,** consolidation as the predominant or sole abnormality is a distinct HRCT pattern.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: Consolidation as the predominant or sole abnormality is a distinct HRCT pattern in sarcoidosis. **62% strongly agree or agree, 17% neutral/unsure, 21% disagree or strongly disagree.**

Fibrotic CT patterns in sarcoidosis

42. **In patients with a confirmed diagnosis of sarcoidosis,** reticulation on CT almost always represents fibrosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: Reticulation on CT in sarcoid almost always represents fibrosis. **59% strongly agree or agree, 19% neutral/unsure, 22% disagree or strongly disagree.**

43. **In patients with a confirmed diagnosis of sarcoidosis**, large bronchocentric masses with or without cystic / bullous ‘destruction’ on CT almost always represents fibrosis.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

Round 1 Results: Large bronchocentric masses with or without cystic / bullous ‘destruction’ on CT in sarcoid almost always represents fibrosis. **62% strongly agree or agree, 15% neutral/unsure, 23% disagree or strongly disagree.**

44. **In patients with a confirmed diagnosis of sarcoidosis**, the following is a distinct HRCT pattern: predominant interlobular septal thickening.

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

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☐

Round 1 Results: The following is a distinct HRCT pattern in sarcoidosis: predominant interlobular septal thickening. **43% strongly agree or agree, 24% neutral/unsure, 33% disagree or strongly disagree**

45. **In patients with a confirmed diagnosis of sarcoidosis**, the following is a distinct HRCT: Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike).

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐
☐
☐
☐
☐

Round 1 Results: The following is a distinct HRCT pattern in sarcoidosis: Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike). **39% strongly agree or agree, 15% neutral/unsure, 46% disagree or strongly disagree.**

46. **In patients with a confirmed diagnosis of sarcoidosis**, the following is a distinct HRCT pattern: Upper zone pleural thickening, with sub-pleural consolidation and reticulation +/- upper zone volume loss (i.e. pleuroparenchymal fibroelastosis look-alike)

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐
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Round 1 Results: The following is a distinct HRCT pattern in sarcoidosis: Upper zone pleural thickening, with sub-pleural consolidation and reticulation +/- upper zone volume loss (i.e. pleuroparenchymal fibroelastosis look-alike). **46% strongly agree or agree, 30% neutral/unsure, 24% disagree or strongly disagree.**

Possible Linkages Between HRCT Subtypes and PFTs, BAL, Outcome etc.

47. Specific HRCT appearances correspond to specific lung function profiles (e.g. isolated reduction in gas transfer or restrictive/obstructive/mixed ventilatory defects).

Strongly Agree Agree Neutral/unsure Disagree Strongly disagree

☐
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☐

Round 1 results: **60% strongly agree or agree, 24% neutral/unsure, 16% disagree or strongly disagree**

48. A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 results: **54% strongly agree or agree, 31% neutral/unsure, 15% disagree or strongly disagree**

49. A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 results: **60% strongly agree or agree, 32% neutral/unsure, 8% disagree or strongly disagree**

50. HRCT findings strongly indicative of fibrotic disease is associated with BAL neutrophilia.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

51. A minority of patients with sarcoidosis and a PMF pattern on HRCT will demonstrate partial or complete regression with treatment.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: An HRCT pattern comprising large bronchocentric masses (i.e. progressive massive fibrosis [PMF] look-alike) can regress with treatment. **53% strongly agree or agree, 20% neutral/unsure, 27% disagree or strongly disagree**

52. Lobar volume loss (particularly the upper lobes) is associated with a poor outcome in sarcoidosis.

Strongly Agree	Agree	Neutral/unsure	Disagree	Strongly disagree
☐	☐	☐	☐	☐

Round 1 Results: **53% strongly agree or agree, 37% neutral/unsure, 10% disagree or strongly disagree**