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Research Article

Evaluating the Role of a Surgical Biopsy in Patients Suspected with Interstitial Lung Disease

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Abstract

Rationale: Interstitial lung disease (ILD) are a heterogeneous group of lung diseases affecting the interstitium. Diagnosis is determined on specific clinical, radiological and histopathological features. A surgical lung biopsy (SLB) is frequently offered to find a diagnosis and aid with pharmacological management.

Objectives: To investigate whether a timely surgical lung biopsy influences the management of patients with interstitial lung disease.

Methods A retrospective data collection on patients referred to University Hospital Southampton with interstitial lung disease and had undergone surgery between 2008 to 2018.

Measurements: Surgical pathway, subsequent treatment, functional and clinical outcomes were primarily investigated. Pulmonary function tests and treatment were compared before and after surgery.

Results: Data was collected from 64 patients, including 41 males and 23 females with a mean age of 63 years. The average Forced Expiratory Volume in one second (FEV1) pre-surgery ranged between 0.77L to 3.9L, whilst the transfer coefficient extended from 33% to 84%. In terms of performance status, 45% of the patient's symptoms were stable after commencing their treatment. 44% of patients were diagnosed with idiopathic pulmonary fibrosis. 17% were treated with Nintedanib, 13% on Pirfenidone and 45% received immunosuppressants. Mortality rates remained at 23.4% compared to 45.3% for those diagnosed via a high-resolution computed tomography (HRCT). Operative mortality remained at zero.

Conclusion: The study displayed differences in the management of patients before and after a surgical biopsy, with more patients given a definitive diagnosis. This enabled a more tailored approach with the most suitable medication for improving the patient's prognosis.

Keywords: *Surgical Lung Biopsy; Interstitial Lung Disease; High-Resolution Computed Tomography*

Abbreviations

ILD: Interstitial Lung Disease; IPF: Idiopathic Pulmonary Fibrosis; HRCT: High-Resolution Computed Tomography; HP: Hypersensitivity Pneumonitis; CTD-ILD: Connective Tissue Disease-Related ILD; MDT: Multi-Disciplinary Meeting; DPLD: Diffuse Parenchymal Lung Disease; UIP: Usual Interstitial Pneumonia; NSIP: Nonspecific Interstitial Pneumonia; DOB: Date of Birth; MRC: Medical Research Council; WHO: World Health Organization

Introduction

Interstitial lung disease (ILD) or diffuse parenchymal lung disease (DPLD) are a heterogeneous group of lung diseases affecting the region between the alveolar epithelial and capillary endothelial basement membranes, the interstitium. These disorders manifest as a result of destruction to the composition of the lung parenchyma by various aetiologies. Damage is not exclusively limited to the interstitium and can spread to supportive structures including blood vessels, air spaces, and peripheral airways [1].

The cause of a plethora of ILDs remains idiopathic**.** Although, they are frequently associated with connective tissue diseases (CTD-ILD), autoimmune diseases, and drug side effects. The most common form of ILD is idiopathic pulmonary fibrosis (IPF), with a median survival of 3 - 4 years [2].

Diagnosis is often achieved through an MDT meeting, following a certain criterion to is to confirm 'the presence of interstitial lung disease' [3], finalise a diagnosis, stage the disease and consider potential treatment options. This is achieved through a combination of history, physical examination, CT scans, spirometry test, and additional laboratory tests. Routinely, the diagnosis of ILD patients is centralised on the findings of their HRCT results. Although the conclusive diagnosis cannot always be achieved, and these patients will possibly be offered further sampling through a surgical lung biopsy which will assist the diagnosis through histological confirmation [3]. A diagnostic surgical lung biopsy is routinely obtained with video-assisted thoracoscopic surgery (VATS). A pathological diagnosis enables physicians to offer a more tailored approach in comparison to customary management [4].

Lack of diagnosis can cause difficulty in pharmacological management and can have severe implications for patients. Experimenting with different drugs can also have a negative effect on the prognosis of IPF as it is a relatively progressive disease [5]. A prompt and precise diagnosis is crucial as it will enable the introduction of treatment during the primary phases of the disease which could possibly have the greatest influence on lowering its advancement [6].

Aim of the Study

The aim of this study is to investigate the effectiveness of a surgical lung biopsy, in relation to the outcome of patients with ILD. To examine any substantial difference between both management and diagnostic accuracy of VATS compared to HRCT.

Materials and Methods

Data was collected on patients who had been referred with ILD and reviewed in multidisciplinary team meetings. Sixty-four patients who had undergone a surgical lung biopsy, between 8th April 2008 to the 14th February 2018, for diagnostic purposes were highlighted. The exclusion criteria removed patients; operated before 2007 and if pulmonary function results were not accessible. Patient information was collected, from the hospital database, regarding their subsequent treatment, functional and clinical outcomes for comparative analysis with those that had treatment without the need for a biopsy. Two separate databases were created, for patients who had reached a diagnosis with a surgical biopsy versus HRCT. This included essential records such as date of birth, gender, age at MDT. Lung function and current medication were recorded, prior to surgery. CT diagnosis, surgical diagnosis, and surgical patterns were also retrieved. The latest pulmonary function and medication at the time of the study was noted. Due to the severity of breathlessness and cough in some patients, it was not possible to record all the responses.

Presenting symptoms were noted and grouped into five categories. Patient case notes were reviewed and assigned values based on their clinical assessment by physicians. Performance status was ranked using 3 different scales: Medical Research Council (MRC), World Health Organization (WHO) and Karnofsky. Overall patient outcome was graded from one, being an improvement in prognosis, to four, resulting in death.

Data was analysed after all required information was collected using Microsoft Excel and GraphPad Prism. The analysis included descriptive statistics and t paired test. Results with $P < 0.05$ were considered statistically significant.

Results

Data was collected from sixty-four patients including forty-one males (64%) and twenty- three females (36%). The median age was 63 years with a range between 35 to 82 years. Sixty-four patients diagnosed via HRCT were included in this study. The median age was 73 years ranging between 53 to 86 years. This consisted of forty-two males (66%) and twenty-two females (34%).

A pathological sample was attained by a lung biopsy in all 64 (100%) patients. 60 (94%) patients received a definite surgical diagnosis, contrary to only 54 (84%) patients with HRCT.

The most common diagnosis was IPF, with a usual interstitial pneumonia pattern, which was present in 28 (44%) patients. Nineteen (30%) patients were diagnosed with Hypersensitivity pneumonitis, four (6%) patients with pulmonary fibrosis and 3 (5%) patients with CTD-ILD. 2 (3%) patients were confirmed to have Respiratory bronchiolitis-associated interstitial lung disease (RBILD). Four (6%) patients diagnosis remained unknown and 1 patient was detected with Squamous Cell Carcinoma. The remaining diagnoses included Sarcoidosis, Langerhans cell histiocytosis, and Anti-synthetase syndrome.

In relation to patients diagnosed via HRCT, thirty-seven patients (58%), five (8%) with hypersensitivity pneumonitis. 3% of (2) patients were discovered with Sarcoidosis, asbestosis, fibrotic non-specific interstitial pneumonia, and pulmonary fibrosis respectively. 10 (15.6%) patients were not given a conclusive diagnosis and grouped in the unclassified category. Other diagnoses accounted for 6.25% (4 patients) of the total, which included Nitrofurantoin-related ILD, Rheumatoid associated ILD, acute alveolitis and CTD-ILD.

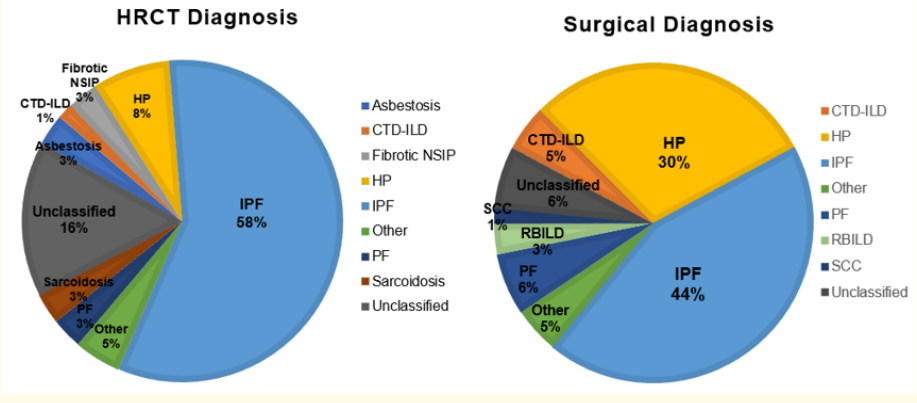

Figure 1: *Pie charts representing the percentage of different pathological diagnoses with SLB and HRCT.*

Forty-two (65.6%) patients undergone SLB presented with a cough on initial examination, whilst fifty-five (85.9%) experienced shortness of breath. Sixteen (25%) patients complained of reduced exercise tolerance, eleven (17.1%) individuals encountered chest pain whilst nine (14%) patients recorded some degree of weight loss.

Pre-surgery PFT was performed on all sixty-four patients and included Forced Expiratory Volume (FEV1), forced vital capacity (FVC), FEV1: FVC ratio, transfer factor for carbon monoxide (TLCO) and transfer Coefficient (KCO) measurements. FEV1 pre-surgery ranged between 0.77L to 3.9L with an average value of 2.33L (SD =0.72). A decrease in mean is noted across all four groups. The largest difference postoperatively appears in TLCO (5.74) highlighting the decline in pulmonary gas exchange. There is a statistical significance before and after an SLB in all characteristics, expect KO, p= 0.0684. Overall, there is no improvement in lung function after the procedure.

	Pre-SLB	Post-SLB	T value	P value
FEV1	2.332 ± 0.7244	2.139 ± 0.7864	2.934	0.0048
FEV1: FVC	79.48 ± 10.34	82.91 ± 12.23	2.078	0.0421
TLCO	56.18 ± 15.11	50.44 ± 21.52	2.455	0.0178
KCO	79.82 ± 17.69	76.46 ± 20.44	1.864	0.0684

Table 1: *Pulmonary function test before and after SLB.*

A negative trend can be sighted in the performance status before and after surgery. The mean score of the MRC scale is 1.5, whilst the majority of patients are classified as number 1 on with the WHO scale pre-surgery and increases to 1.5 after surgery. The mean Karnofsky score alters from 80% to 70%, presenting a decline in quality of life.

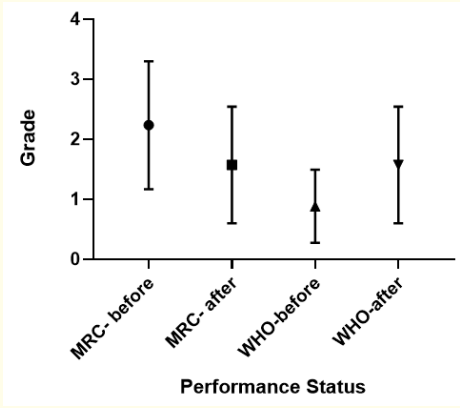

Figure 2: *Graphs representing the mean difference in dyspnoea and performance status before and after surgery.*

Concerning the overall outcome of surgical patients, 3 (4.7%) patients displayed an improvement in condition, 29 (45.3%) patients scored 2 presenting stabilisation of disease and 17 (26.6%) patients score, highlighting disease progression.

Comparatively with HRCT patients, 1(1.6%) patient scored 1 indicating a positive outcome, 26 (40.6%) patients remained stable and 8 (12.5%) patients conditioned worsened.

Score	Definition
1	Improved
2	Stable
3	Deteriorated
4	Death

Table 2: *Score tables used to measure the overall outcome of patients' conditions after diagnosis using information extracted from follow-up appointments.*

The mortality rate of surgical patients remained at 23.4% (15 patients), compared to 45.3% (29 patients) with CT. Operative mortality rates remained at zero.

All sixty-four patients had undergone CT scan pre-operatively and 26 (40.6%) patients received no clear diagnosis. Postoperatively, 24 (92.3%) of these patients were given a definitive and conclusive diagnosis, whilst 2 (7.7%) patients remained without a diagnosis. From the 38 patients receiving a CT diagnosis, 65.8% (n = 25) of their tissue diagnosis was discordant with their CT result, whilst 34.2% (n=13) remained concordant.

75% (21) of patients with IPF had not received any treatment prior to the surgery. 11 (52.3%) patients were treated with Nintedanib and 9 (42.9%) required oxygen therapy. Seven (33.3%) patients were prescribed Pirfenidone, 8 (38%) on steroids and 6 (28.6%) with N-acetylcysteine. The remaining 7 (25%) patients with prior treatment, all had a change in their pharmacological management after surgery.

Four (21%) patients diagnosed with HP, were commenced on steroids after surgery, whilst three (15.8%) patient's prescriptive dosage was altered and/or reduced. Five (26.3%) patients were treated with oxygen therapy,3(15.8%) with Cyclophosphamide and 1 (5.6%) with N-acetylcysteine. Five (26.3%) did not have any change to their treatment after surgery.

Eleven (64.7%) of the remaining seventeen patient's pharmacological management was modified post-operation. Six (35.2%) patients did not receive any change to their treatment.

Discussion and Conclusion

The diagnosis of ILD is commonly accomplished with the aid of HRCT, clinical examinations and in some case with the assistance of tissue diagnosis. Although the diagnosis is possible without surgery, 65.8% of patients received a correct diagnosis compared to 34.2% precisely diagnosed with HRCT in this study. More definite and accurate results were produced with a biopsy, with 60 out of 64 patients given a conclusive diagnosis. This enabled physicians to offer the best treatment options for each case [7]. Majority of patient's treatment plan were altered and/or commenced after surgery highlighting the fundamental relationship between the two factors. Nevertheless, adjustment to pharmacological management does not always imply or result in a better outcome [8]. For example, many patients discontinued their Nintedanib treatment due to severe side effects of vomiting, diarrhoea and photosensitive rashes.

In the past, SLB has been associated with a significant rate of mortality and morbidity due to the invasiveness of open lung thoracotomy [9]. Presently, majority of lung biopsy are achieved by using VATS, which have lower morbidities, is less painful and require a shorter hospital stay [10]. Mortality rates for patients not possessing any additional risk varies from 0% to 11% [11]. From this study, mortality rates remained at zero.

Early referral for diagnostic biopsy is crucial for many reasons. Firstly, it will enable patients to be in a fitter state for anaesthesia and surgery. Additionally, it aids the commencement of the most suitable treatment as soon as possible. This is crucial in the management and reducing the effect of irreversible damage with progressive diseases [12].

Whilst diagnosis results are greater with an SLB, four patients in this study did not receive a definitive diagnosis. With a biopsy that could be operator dependant whether sampling unrepresentative area of lung or lack of expertise in examining the samples. However, this should become less with referral to superregional centres with better expertise in pathology, better targeting based on MDT review of CT Images and more advancement of molecular and biomarkers testing of samples on top of the classical histology.

In summary, it can be concluded that surgical biopsy is often the best option for a definitive diagnosis when HRCT results are inconclusive. The operative procedure frequently provides concise answers which are beneficial for the patient's long-term. A definite and accurate diagnosis can often resolve previous uncertainties in pharmacological management. Patients trialed on different treatments when no diagnosis is reached may suffer negatively, resulting in a poor prognosis. Early diagnosis coupled with the correct treatment can influence prognosis and reduce the rate of dependence which can be obtained from a lung biopsy.

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