Outcomes and Safety of Surgical Lung Biopsy for Interstitial Lung Disease*

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Study objectives: To determine the safety of surgical lung biopsy (SLB) in patients with interstitial lung disease (ILD), and specifically in those with idiopathic pulmonary fibrosis (IPF).

Design: Retrospective cohort.

Setting: Tertiary care university-affiliated military medical center.

Patients: Individuals undergoing SLB for suspected ILD.

Measurements and results: We examined outcomes for subjects with a clinical diagnosis of ILD who had been designated to undergo SLB. Mortality (assessed at 30 and 90 days) following SLB represented the primary end point. Morbidity resulting from complications from SLB served as a secondary end point. The cohort included 83 patients (mean [± SD] age, 57.3 ± 14.2 years; men, 57.8%). IPF was eventually diagnosed in slightly more than half of the subjects. Overall, 30-day and 90-day mortality rates were low (4.8% and 6.0%, respectively). Subjects with IPF did well with SLB (30-day mortality rate, 7.1%) and did not face a higher risk of either death or complications relative to individuals with non-IPF forms of ILD. The only predictors of perioperative mortality were either the need for mechanical ventilation (MV) at the time of SLB or being immunosuppressed prior to undergoing SLB. Excluding persons who met either criterion yielded an overall 90-day post-SLB mortality rate of 1.5% in persons with IPF. Approximately 40% of patients in whom IPF was eventually diagnosed were initially thought to have another form of ILD.

Conclusions: Persons with IPF tolerate SLB well. Requiring MV or being immunosuppressed is associated with an increased risk for death following SLB. Safety concerns should not preclude referral for SLB in patients who are clinically suspected of having IPF.

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Key words: biopsy; idiopathic pulmonary fibrosis; interstitial lung disease; morbidity; mortality; outcomes; safety; surgical lung biopsy

Abbreviations: CI = confidence interval; DLco = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MV = mechanical ventilation; NSIP = nonspecific interstitial pneumonia; SLB = surgical lung biopsy; TBB = transbronchial biopsy; UIP = usual interstitial pneumonia

Interstitial lung diseases (ILDs) comprise a varied group of processes, which range from acute inflammatory disorders to progressive fibrotic conditions.1 Despite significant differences in underlying pathology, most patients with ILD present with similar clinical complaints, such as dyspnea and cough. The results of spirometric testing also tend to be nonspecific. While they may help to narrow the differential diagnosis, these values add little to diagnostic accuracy.2 Imaging studies, on the other hand, provide crucial information in the approach to ILD.

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Certain patterns found either on plain chest radiographs or high-resolution CT (HRCT) scans are

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thought to be diagnostic for particular forms of ILD.\textsuperscript{3} However, the sensitivity and specificity of HRCT scans for the diagnosis of certain ILDs, such as idiopathic pulmonary fibrosis (IPF), vary depending on the population studied and the skill of the individual interpreting the image.\textsuperscript{3,4} For patients with atypical clinical or radiographic presentations, HRCT scans may not prove to be conclusive.\textsuperscript{3,4}

Transbronchial biopsy (TBB) also has a limited role in the evaluation of many forms of ILD.\textsuperscript{5} Although helpful for diagnosing granulomatous diseases, TBB rarely yields sufficient tissue to allow a careful examination of the lung architecture.

Nonspecific findings from physical examinations, radiographs, and spirometry, and the limited utility of TBB complicate noninvasive approaches to the diagnosis of ILD, so clinicians often consider surgical lung biopsy (SLB). SLB almost uniformly results in a precise diagnosis.\textsuperscript{6} With more certainty as to the underlying diagnosis, clinicians can better design treatment regimens and counsel their patients regarding likely outcomes and prognosis. As the classification schemes for ILD become more complex, diagnostic accuracy becomes a more pressing issue. For example, it now appears that IPF has a distinct natural history that may be different from the outcomes seen in nonspecific interstitial pneumonia (NSIP).\textsuperscript{7,8} Similarly, most would agree that therapy with corticosteroids offers little to the patient with IPF except potential toxicity.\textsuperscript{9} In patients with NSIP, there may be a greater role for the use of corticosteroids.\textsuperscript{7,8} Again, although particular clinical and HRCT scan features seem to segregate IPF from NSIP, there remains tremendous overlap.\textsuperscript{10,11}

When deciding whether to pursue SLB, pulmonary physicians must weigh the potential benefits of obtaining a precise diagnosis against the risks of the procedure. The safety of performing SLB in ILD patients remains controversial. For example, Utz and colleagues\textsuperscript{11} noted that SLB when performed in subjects with IPF was associated with a nearly 17\% short-term mortality rate. Kramer et al\textsuperscript{12} also observed a high risk for death following SLB for the diagnosis of ILD. Other investigators have reported that SLB can be performed safely in ILD patients.\textsuperscript{13} Part of the discordance in results in these reports may reflect the clinical characteristics of the patients studied.

In order to clarify the safety of performing SLB in ILD patients and to explore the impact of various patient characteristics as potential predictors of short-term mortality, we conducted a retrospective analysis of SLB at our institution. We hypothesized that SLB would be associated with little risk for mortality, and that the procedure would be safe to perform in patients who eventually were diagnosed both with IPF and other forms of ILD.

### Materials and Methods

**Subjects**

We retrospectively reviewed the records and radiographs of all patients who underwent SLB for suspected ILD at our institution between January 1996 and December 2002. We excluded from analysis all subjects < 18 years of age and those who had a history of biopsy-proven ILD. As defined by the American Thoracic Society statement on interstitial pneumonias, patients with suspected ILDs showed diffuse parenchymal infiltrates of varying degrees of inflammation or fibrosis that were not attributable to an acute and defined process (eg, acute infectious pneumonia).\textsuperscript{1} From each record, we abstracted data regarding demographics, factors known to increase perioperative mortality (eg, medical history and use of tobacco), and pulmonary function. In addition to routine spirometry, we noted whether the individual required supplemental oxygen at time of SLB and whether they were in the ICU receiving mechanical ventilation (MV) when the SLB was performed. We defined immunocompromised persons as meeting any of the following criteria: treatment with noncorticosteroid immunosuppressive medications; active therapy for malignancy; or the presence of HIV infection. We also recorded the procedural technique (ie, open vs video-assisted SLB). Referral for SLB was not protocolized in our clinic during this time, so that the decision to send the patient for SLB reflected the decision of the individual physician. The study protocol was approved by our Department of Clinical Investigations.

**End Points**

Mortality in the first 30 and 90 days following SLB represented the primary end point. Secondary end points included perioperative morbidity and complications up to 90 days after SLB. Morbidity was defined as follows: prolonged initial hospitalization (> 7 days); hospital readmission for surgical complication after hospital discharge; development of a nosocomial infection; extended need for MV (ie, > 72 h); prolonged air leak from the thoracostomy tube (ie, > 96 h); or other commonly accepted postoperative complication (eg, myocardial infarction).

In order to explore the impact of the underlying disease on outcomes, we compared patients in whom IPF was eventually diagnosed to those who were found to have other forms of ILD. The final diagnosis of IPF was made in accordance with the guidelines of the American Thoracic Society and required the appearance of usual interstitial pneumonia (UIP) on biopsy specimens.\textsuperscript{8} We also compared those patients who had died in the 90 days after undergoing SLB to patients surviving to identify potential factors associated with an increased risk in SLB.

To gauge the relationship between the preoperative diagnosis and the final histopathologic diagnosis, we determined how often patients with a clinical diagnosis of IPF demonstrated UIP histopathologically. Conversely, we recorded the frequency with which patients in whom IPF eventually was diagnosed based on the presence of a UIP pattern on SLB tissue specimens were thought by their primary pulmonologist to have an alternative condition.

**Statistical Analysis**

Categoric variables (eg, morbidity and mortality) were reported as frequency distributions and were compared using the Fisher
As shown in Table 1, the mean age of the cohort was 57.3 years, and slightly more than half were men. At the time of SLB, 45.8% of the subjects were receiving supplemental oxygen therapy, and nearly one in five patients were immunocompromised. Slightly more than one quarter of SLBs (27.7%) were performed as open procedures. Individuals with a final diagnosis of IPF were older and had a lower diffusing capacity of the lung for carbon monoxide (DLCO) than patients with other conditions (Table 1).

SLB yielded a definitive diagnosis for all patients. Among the 83 individuals, 84 conditions were identified. IPF was most frequently noted (50.6%), followed by NSIP (13.3%), sarcoidosis (12.0%), and cryptogenic organizing pneumonia (6.0%).

The overall 30-day mortality rate was low in our population, with only four deaths (4.8%) occurring. The cumulative 90-day mortality rate was also low (5 of 83 subjects; 6.0%). Among patients with IPF, death following SLB was rare at either time point and, as shown in Figure 1, did not differ statistically from the mortality observed in patients with non-IPF ILD. Specifically, at 30 and 90 days after SLB the cumulative mortality rates of those patients with IPF were 7.1% (3 of 42 subjects) and 9.5% (4 of 42 subjects), respectively, compared to 2.4% (1 of 41 subjects) and 2.4% (1 of 41 subjects) in non-IPF subjects (difference was nonsignificant for all comparisons).

Demographic factors, type of surgical procedure (ie, open vs video-assisted), or measures of pulmonary function were not associated with postoperative death. For example, the mean FVC was 70.1 ± 15.4% predicted among 90-day survivors compared to 64.0 ± 6.2% predicted among nonsurvivors (difference not significant) [Table 2]. The need for supplemental oxygen therapy also failed to correlate with mortality.

Only two factors seemed to differentiate survivors from nonsurvivors. Specifically, 60.0% of those who died within 90 days were receiving MV at the time they underwent SLB as opposed to 6.4% of survivors (p = 0.006). Those requiring MV were 21.9 times more likely to die (95% CI, 3.0 to 162.7). Immunosuppressed persons also faced a heightened risk of death (odds ratio, 30.7; 95% CI, 3.1 to 305.5). Excluding those who were either receiving MV or had been immunosuppressed prior to the procedure, there was only one death (mortality rate, 1.5%) among these persons. This single patient died on postoperative day 10 of a myocardial infarction. He was not receiving MV and was not immunosuppressed. Surgery had been performed on an outpatient basis, and ultimately he received a diagnosis of IPF. As a screening test to predict the cumulative 90-day mortality rate, the need for MV or immunosuppression was associated with a sensitivity of 80.0% and a specificity of 82.1%. The positive and negative predictive values of these factors in terms of death were 77.8% and 98.5%, respectively.

Exploring morbidity, seven patients (8.4%) experienced complications, which included acute myocardial infarction (n = 2), nosocomial pneumonia (n = 2), stroke (n = 1), pancreatitis (n = 1), and prolonged MV therapy (n = 1). Patients with non-IPF conditions were more likely to experience postoperative complications (12.2%), while only two complications (4.8%) occurred in patients in whom IPF had been diagnosed. This difference, however, was not statistically significant.

In those subjects who were clinically suspected of having IPF, 85.7% were noted to have UIP hist-

### Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 83)</th>
<th>IPF (n = 42)</th>
<th>Non-IPF (n = 41)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57.3 ± 14.2</td>
<td>63.5 ± 9.2</td>
<td>52.3 ± 7.3</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>69.8 ± 15.1</td>
<td>72.9 ± 9.7</td>
<td>66.7 ± 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>67.9 ± 15.9</td>
<td>73.3 ± 7.9</td>
<td>62.7 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>42.7 ± 14.8</td>
<td>39.4 ± 5.4</td>
<td>46.2 ± 7.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Male, %</td>
<td>57.8</td>
<td>71.4</td>
<td>43.9</td>
<td>0.015</td>
</tr>
<tr>
<td>Tobacco use, %</td>
<td>53.0</td>
<td>61.9</td>
<td>43.9</td>
<td>NS</td>
</tr>
<tr>
<td>Supplemental oxygen, %</td>
<td>45.8</td>
<td>52.4</td>
<td>39.0</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressed,%</td>
<td>16.9</td>
<td>14.3</td>
<td>19.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanically ventilated, %</td>
<td>9.6</td>
<td>7.1</td>
<td>12.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated. NS = not significant.
that mortality was more likely to be related to the acute illness and not to either SLB or the underlying ILD.

Several other investigators have examined the risks associated with SLB in IPF patients. In a similarly designed retrospective study covering over a decade, Utz and colleagues\(^\text{11}\) reported that 10 of 60 subjects with IPF died shortly following SLB. Mouroux et al\(^\text{13}\) also reviewed their experience with SLB in patients with suspected ILD. They reported a perioperative mortality rate of 7.6% among 66 subjects and found that the operative approach used (i.e., open procedure vs video-assisted) did not affect outcomes. Our point estimate of the 30-day perioperative mortality rate at 4.8% is substantially lower. Dissimilarities in the populations studied likely explain these observed differences. For example, Utz et al\(^\text{11}\) restricted their analysis to patients with UIP, while we included all patients who had been referred for SLB. Nonetheless, even when limiting our investigation to persons with UIP/IPF, we still found SLB to be safe to perform. Moreover, variability in disease severity between the two cohorts, as measured by pulmonary function tests, fails to explain the discordance. Both populations were similar with respect to the mean FVC, FEV\(_1\), and DLCO values.\(^\text{11}\) Rather, 6 of the 10 deaths described by Utz and coworkers\(^\text{11}\) occurred in patients who were experiencing an accelerated decline in pulmonary function, while one death followed an SLB that had been performed as a secondary procedure during a complicated cardiovascular operation. Our report, therefore, helps to clarify and put in context the observations made by Utz et al.\(^\text{11}\) Hence, it seems that in stable patients with UIP, mortality related to SLB is rare.

Only one prospective study has described outcomes for SLB in suspected IPF. Hunninghake et

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### Table 2—Correlates of 90-Day Postoperative Mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n = 78)</th>
<th>Nonsurvivors (n = 5)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57.7 ± 14.3</td>
<td>62.6 ± 12.8</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>70.1 ± 15.4</td>
<td>64.0 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>FEV(_1), % predicted</td>
<td>66.8 ± 16.3</td>
<td>68.0 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>42.8 ± 15.4</td>
<td>41.8 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>57.7</td>
<td>60.0</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco use, %</td>
<td>59.0</td>
<td>60.0</td>
<td>NS</td>
</tr>
<tr>
<td>Supplemental oxygen, %</td>
<td>44.9</td>
<td>60.0</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressed, %</td>
<td>11.5</td>
<td>80.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Mechanically ventilated, %</td>
<td>6.4</td>
<td>60.0</td>
<td>0.006</td>
</tr>
<tr>
<td>IPF, %</td>
<td>48.7</td>
<td>80.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values given as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviation not used in the text.

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**FIGURE 1.** Postoperative mortality.
plans. Although Hunninghake et al. reported that the findings from SLB can affect therapeutic ease processes. This observation indirectly suggests that IPF was diagnosed in nearly one patient. Hunninghake et al. prospectively evaluated 91 individuals with ILD in order to determine the ability of clinical criteria to successfully identify patients with IPF. In this trial, all individuals underwent SLB and > 90% did well with the procedure. Only one patient died as a complication of SLB (1.1%). Our observed 1.5% mortality rate in patients with IPF who were neither receiving MV nor immunosuppressed is consistent with the results of Hunninghake et al.

Our report also builds on each of these earlier investigations by providing a more detailed analysis of confounding factors that might contribute to perioperative mortality as a result of SLB for the diagnosis of ILD. Specifically, commonly used predictors of adverse operative outcomes, such as age and the need for supplemental oxygen, failed to identify individuals who were at an increased risk for death. As such, clinicians should not reflexively deny SLB to their patients because they are either elderly or they require supplemental oxygen.

Safety, however, is only one consideration when determining whether to refer a patient for SLB. Pulmonologists weigh the risks associated with any procedure against its likely yield. In the case of SLB, this crucial issue requires a balancing of any risk in the context of how the results of SLB might alter patient management. In our subjects, we found that those suspected clinically of having IPF were, in fact, likely to show UIP on histopathology. On the other hand, many patients in whom IPF was eventually diagnosed were initially thought to have other disease processes. This observation indirectly suggests that the findings from SLB can affect therapeutic plans. Although Hunninghake et al. reported that a clinical diagnosis of IPF made by physicians with expertise in ILD has a high sensitivity and specificity, they cautioned that lung biopsy will be most helpful when the clinical picture is unclear or when patients are thought to have conditions other than IPF. Correspondingly, Raghu and colleagues determined that clinical assessment combined with HRCT scanning has a specificity of > 90% for the diagnosis of IPF. However, the sensitivity of clinical and radiographic evaluations was lower, suggesting that relying solely on clinical criteria without SLB findings would result in a significant potential for missing the diagnosis of IPF. In fact, without SLB, Raghu et al. would have missed diagnosing IPF in nearly one third of patients. Our approximately 40% rate of clinical misdiagnoses is consistent with that observation. In addition, NSIP, particularly fibrotic NSIP, may mimic both the clinical and radiographic findings associated with IPF, further warranting the performance of SLB.

Our study has several limitations. First, our analysis was retrospective, and, therefore, potentially confounded by recall and coding bias. Our primary end point, however, was death. As such, the ascertainment of vital status is not prone to misclassification. Second, our population size was limited. This necessarily constrains the strength of our conclusions. However, our sample was as large as those of most earlier reports. More importantly, our findings are in agreement with those of the only prospective trial performed on this topic. Third, our results represent the experience of only one center. Our institution is not an IPF referral center. Our findings may therefore, not apply to other centers with differing degrees of experience in the care of patients with ILD. The low event rates for both death and morbidity limit our ability to perform a multivariate analysis to more precisely identify the correlates of poor outcome. However, with the data available, only the need for MV or the presence of immunocompromised states was associated with an increased risk of death following SLB. Additionally, the majority of deaths occurred in those subjects in whom IPF was diagnosed, and our conclusions may not apply to those with other conditions. Finally, referral for SLB was not protocolized. The possibility of selection bias implies that some very ill patients were never considered to be candidates for SLB by their primary pulmonologists. This, in turn, suggests that we may have overestimated the safety of SLB.

In summary, we conclude that SLB can be safely performed in patients with ILD. SLB also may uncover cases of IPF that otherwise would have been misdiagnosed. The decision about whether or not to refer a patient for SLB must be individualized, and neither fear of poor outcome nor the need for absolute diagnostic certainty should solely drive this clinical decision. In patients receiving MV or in those who are immunosuppressed, clinicians must carefully weigh how the results from SLB will affect patient care since such individuals are at high risk for death following this procedure.

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