SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2013; 30; 3-16

Surgical lung biopsy for the diagnosis of interstitial lung disease: a review of the literature and recommendations for optimizing safety and efficacy

W. Nguyen[1], K.C. Meyer[2]

[1] Department of Anesthesiology, University of Maryland; [2] Department of Medicine University of Wisconsin School of Medicine and Public Health

Abstract. Making an accurate diagnosis of a specific type of interstitial lung disease (ILD) requires a structured and comprehensive approach that includes a complete patient history, careful physical examination, appropriate laboratory testing, and thoracic imaging. If invasive procedures are required, bronchoscopy with bronchoalveolar lavage (BAL) and/or endoscopic lung biopsy (ELB) can frequently establish a confident diagnosis. However, surgical lung biopsy (SLB) may be required to make a confident diagnosis. Because SLB may be associated with a significant risk of morbidity and mortality, we performed a comprehensive literature review of all available literature published in the English language that reported outcomes of surgical lung biopsy performed for the diagnosis of ILD. The overall 30-day mortality for open lung biopsy (OLB) was 4.3% versus 2.1% for video-assisted thorascopic surgery (VATS) biopsy, and non-lethal complications appeared to occur more frequently with OLB (18.1%) vs. VATS (9.6%) procedures. In addition to presenting the results of our comprehensive literature review on SLB for the diagnosis of ILD, we suggest an approach that minimizes risks to patients and optimizes the diagnostic utility of SLB when SLB must be performed to obtain a confident ILD diagnosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 3-16)*

Key words: interstitial lung disease, lung biopsy, diagnosis, diffuse lung disease, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia

Introduction

The term interstitial lung disease (ILD) encompasses a diverse group of diffuse parenchymal lung disorders that vary considerably in their clinical presentation, degree of lung function impairment, thoracic imaging characteristics, and histopathologic changes (1-3). These disorders are usually idiopathic, predominantly subacute or chronic in their clinical course at initial diagnosis, and display a considerable range of inflammation and/or fibrosis on histopathologic examination of lung tissue. Although the etiologies have been identified for some of these disorders, the ultimate cause of most of these disorders remains unknown. Making an accurate diagnosis of a specific form of ILD can present a formidable challenge to the clinician, and invasive testing may be required to make a confident diagnosis.

Making an accurate and confident diagnosis of the specific type of ILD is critical for predicting

Received: 14 December 2011
Accepted after Revision: 3 August 2012
Correspondence: Keith C. Meyer, MD, MS, FACP, FCCP
Department of Medicine
University of Wisconsin School of Medicine
and Public Health
Tel. 608 263-6363
Fax 608 263-3104
E-mail: kcm@medicine.wisc.edu

Support: The George and Julie Mosher Pulmonary Research Fund

prognosis and allows the clinician to recommend the most appropriate therapies and management strategies to the patient. The most commonly encountered type of idiopathic interstitial pneumonia (IIP) is idiopathic pulmonary fibrosis (IPF), and the risk of developing IPF increases considerably with advancing age (4-7). A confident diagnosis of IPF can frequently be made if characteristic findings that predict the presence of usual interstitial pneumonia (UIP) are identified on high-resolution computed tomography (HRCT) of the thorax (5, 8). These findings include reticular abnormalities with a subpleural, basal predominance, honeycomb change with or without traction bronchiectasis, and a lack of features inconsistent with a diagnosis of UIP (extensive ground glass abnormality, upper or mid-lung predominance, peribronchovascular predominance, profuse micronodules, multiple/diffuse discrete cysts, multilobar mosaic attenuation/air-trapping, or significant consolidation (5).

Although confident diagnoses can often be made with adequate clinical data combined with appropriate thoracic imaging (5,8-10), invasive procedures may be required to make a confident diagnosis of specific forms of ILD. Bronchoscopy is quite safe when performed with appropriate safety measures by qualified personnel, and bronchoalveolar lavage (BAL) and/or endoscopic lung biopsy (ELB) may provide adequate diagnostic information for many conditions such as sarcoidosis, hypersensitivity pneumonitis (HP), organizing pneumonia (OP), or eosinophilic pneumonia (EP) (11-14). However, making a confident and accurate diagnosis may require more extensive sampling of tissue that cannot be performed via bronchoscopic procedures. This is particularly true for the IIPs, and when HRCT does not show characteristic diagnostic changes, a surgical lung biopsy (SLB) may be required to make a confident and accurate diagnosis.

Surgical lung biopsy, however, carries some risk of morbidity and mortality (Table 1). The decision to undergo SLB can be difficult, especially if patients have risk factors (advanced age, frailty, significant cardiopulmonary impairment). In order to determine the relative risk and potential complications of SLB when performed on patients with diffuse infiltrates consistent with a potential diagnosis of ILD, we searched PubMed to identify all manuscripts published from 1960 through July, 2011 that reported results of surgical lung biopsies used to evaluate patients with diffuse parenchymal infiltrates. Key search terms included interstitial lung disease, lung biopsy, open lung biopsy, video-assisted thoracic surgery (VATS), and diffuse pulmonary disease. We also examined citations from the references that we retrieved to identify other articles that our initial search did not identify. We combined data from studies that met our criteria and included 30-day mortality in order to calculate overall 30-day mortality rate for open lung biopsy (OLB) and video-assisted thoracic surgery (VATS) procedures.

Table 1. Potential complications of surgical lung biopsy

- **Intra-operative**
  - Anesthesia-related complications
  - Lung injury
  - Parenchymal hemorrhage
  - Mediastinal compression
  - Hypotension
  - Equipment malfunction
  - Impaired gas exchange (hypoxemia, hypercarbia)
  - Cardiac dysrhythmia
  - VATS-specific complications
    - CO2 embolism
    - Trocar damage
    - Extrapleural placement
    - Tension pneumothorax
    - Damage to intercostal bundle
- **Post-operative**
  - *Early*
    - Hemorrhage
    - Infection
      - pneumonia
      - empyema
      - soft tissue wound infection
    - Ventilator dependence (>48 hrs)
    - Sustained air leak
    - Persistent atelectasis
    - Persistent pneumothorax
    - Broncho-pleural fistula
    - Excessive/persistent pain
  - *Late/chronic*
    - Persistent pain
    - Persistent atelectasis/trapped lung
    - Broncho-pleural fistula

Current approaches to establishing an accurate ILD diagnosis

The clinical context, tempo of disease progression, and radiologic findings help determine subsequent diagnostic steps. Patients with ILD common-

ly present insidiously with nonspecific complaints including cough, dyspnea, or fatigue. Acute presentations are seen in some ILDs including HP, acute reactions to drugs or inhalational exposures, diffuse alveolar hemorrhage syndromes, cryptogenic organizing pneumonia (COP), acute EP, and acute interstitial pneumonia (AIP) (15, 16). Important clues can be obtained from a carefully taken and comprehensive history, especially past and current occupational and other exposures such as drugs or radiation. Some physical exam findings may help narrow the differential diagnosis. Prominent bibasilar "velcro" crackles are commonly auscultated in patients with IPF and asbestosis, but these are uncommon in many other ILDs such as sarcoidosis or non-IPF IIPs (17, 18). The presence of extrapulmonary symptoms and signs may indicate the presence of a connective tissue disease (CTD), and digital clubbing is common in IPF but relatively unusual in other forms of ILD such as sarcoidosis.

Recommended initial testing includes complete blood count with differential count, screening blood chemistries including liver and kidney function, connective tissue disease (CTD) serologies as indicated, urinalysis, and pulmonary function testing that includes spirometry, lung volumes, diffusing capacity, and oximetry (2, 5, 18, 19). Initial imaging includes routine plain chest radiography, which usually reveals diffuse, bilateral parenchymal infiltrates. Previous chest radiographs and chest CT studies can help establish the time of onset and tempo of the disease. It is important to note that in some patients with ILD, chest radiographs may appear to be normal, while HRCT will usually always reveal parenchymal tissue changes if an ILD is present.

HRCT plays a pivotal role in evaluating patients with ILD of unknown etiology. It is more sensitive and also allows for a more confident and specific interpretation of the parenchyma than chest radiography (8-10, 20). HRCT allows for slices that are 1 to 2 mm thick to be reconstructed with an algorithm that optimizes spatial resolution, and, thus, it allows for detailed visualization and examination of the lung parenchyma. The common pattern found in ILD and especially IPF is a mesh-like pattern of interlacing linear opacities (20, 21), and this mesh-like pattern is often associated with subpleural honeycombing when the diagnosis is IPF. When patients have reached the age of 75 and have an increasing HRCT interstitial score yet lack honeycomb change, Fell et al. (8) found that the likelihood of the presence of UIP/IPF is virtually 100%. However, changes suggestive of ILD are frequently seen in asymptomatic elderly individuals, and such changes may not necessarily indicate the presence of clinically relevant disease (22).

Rendering a specific diagnosis based upon clinical presentation, HRCT findings, and the tempo of disease progression may obviate the need to proceed to SLB. However, making an accurate diagnosis with HRCT can still be challenging, and Aziz et al. (23) reviewed HRCT scans from 131 patients with ILD where the overall agreement of the 11 radiologists was poor. Hunninghake et al. 2001 (24) concluded that "lung biopsy is most helpful when clinical and radiologic data result in an uncertain diagnosis or when patients are thought to have non-IPF ILD."

Transbronchoscopic lung biopsy (TBLB) and BAL may supply critical information that leads to a confident, specific diagnosis of many types of ILD (sarcoidosis, HP, EP, organizing pneumonia, pulmonary Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, pulmonary lymphangioleiomyomatosis, and pulmonary alveolar proteinosis) as well as infections and neoplastic processes when these findings are combined with features of the clinical presentation and HRCT imaging (25). Most of these disorders have distinct histopathologic features that may be discerned in small samples of lung tissue provided by TBLB if adequate tissue sampling has been performed, and characteristic BAL cell profiles may be obtained that strongly support a specific diagnosis (12). However, BAL cell profiles and TBLB specimens are usually not diagnostic of specific types of IIP, and SLB has traditionally been considered the gold standard in the diagnosis in ILD.

Evolution of the SLB technique for the diagnosis of ILD

Traditionally, open lung biopsies (OLB) had been performed to make a secure diagnosis. However, the invasive nature of the procedure and the need for general anesthesia raises concerns of an increased risk of morbidity and mortality, especially in immuncompromised patients (26). The somewhat

less invasive procedure of video-assisted thoracic surgery (VATS) has emerged over the past two decades as an alternative to OLB. However, the risks and benefits of VATS versus OLB have yet to be completely elucidated. The primary objective of our literature review was to determine the comparative safety (morbidity and mortality) of OLB versus VATS when SLB is performed, and we sought to examine the trends in safety and diagnostic accuracy when SLB is used to diagnose suspected ILD.

Mortality

Thirty journal articles met our inclusion criteria and included 30-day mortality data (Table 2) that were specific for the type of procedure (26-55), but the reports that we examined had varied patient inclusion criteria. Over 65% of the data regarding patients who underwent OLB procedures were from papers published before 1995. In contrast, greater than 97% of the data regarding VATS originated from studies from 1993-2009. The data that we used to determine overall 30-day mortality and to identify complications were from manuscripts published from 1955 to 2010. For those studies that specified outcome data specifically for OLB vs. VATS procedures, a total of 2,071 patients underwent OLB, and 1,188 patients underwent VATS. Collectively, 90 (4.3%) patients died within 30 days of undergoing OLB, while 24 (2.1%) patients died within 30 days of undergoing VATS.

Some studies included patients who underwent SLB under acute conditions and/or immunocompromised patients who were eventually found to have infection (30, 52). Additionally, a number of studies excluded patients receiving mechanical ventilation, patients with oxygen-dependence, and/or patients with acute decompensation, but such patients were included in others. Also, three studies examined SLB performed exclusively in the ambulatory setting (43, 44, 46). Two studies were prospective,(42, 43) while the rest were retrospective in nature (Table 2). Another study (56) provided 30-day mortality data (4 of 83 subjects) but did not specify OLB vs. VATS data. Lee et al. (57) reported 196 cases of diffuse pulmonary disease that underwent SLB from 1995-2003 with a 30-day mortality of 24% (47 of 196) and in-hospital mortality of 34% (66/196). However, only 45 of these patients were ultimately found to have ILD. Sigurdsson et al. (58) reported 73 patients with diffuse lung disease of which 2 patients died within 30 days, but deaths for OLB vs. VATS were not specified. The overall mortality for surgical lung biopsy regardless of whether an OLB vs. VATS procedure was used (excluding Lee et al.) was 3.5% (120 of 3,415 patients) (26-55,56,58).

The 30-day mortalities reported from individual case series for OLB ranged from none to 21%. Six of the 20 studies examining OLB reported 30-day mortality of 1% or less. Studies with the lowest 30-day mortalities included one where OLB was performed on an outpatient basis (44) and another that excluded patients with acute decompensation from undergoing the procedure (42). Nine studies reported 30-day mortalities of 4% or greater for OLB procedures (26, 27, 29, 30, 35, 37, 45, 49, 51). Of these 9 reports, Kramer et al. (26) reported that 21 patients (25%), fifteen of which were immunocompromised, died within 30 days of undergoing OLB.

Park et al. (51) examined SLB outcomes for patients diagnosed as IPF, idiopathic NSIP, or COP and reported 4 deaths (8.0%) within 30 days of undergoing OLB. They also reported that patients with IPF who developed an acute exacerbation had a 28.6% 30-day mortality following SLB compared to a 3.0% 30-day mortality rate in stable patients with IPF. Similarly, Utz et al. (45), who examined patients diagnosed with UIP, reported that 7 (15.9%) OLB patients who subsequently had UIP diagnosed on histopathology died within 30 days, and all deaths occurred in patients diagnosed as IPF but not in patients with CTD-associated UIP. Additionally, Lettieri et al. (56) reported 30-day mortality for patients diagnosed with IPF as 7.1%. These data suggest that patients assigned a diagnosis of IPF may be at somewhat increased risk of 30-day mortality as compared to patients with non-IPF diagnoses. Additionally, Kondoh et al. (59) reported 5 of 236 consecutive patients who underwent SLB experienced an acute exacerbation of IPF following the procedure with 2 patients dying within 30 days of the SLB, and other reports have suggested that SLB may precipitate acute exacerbations of IPF (60, 61).

The 23 studies that examined VATS outcomes reported 30-day mortalities that ranged from none to

Table 2. 30-Day mortality rates for surgical lung biopsy

First Author	Ref #	Year	Study Type	N	Time Span & Cohort Characteristics	Type of Surgery		30-Day Mortality	
						OLB	VATS	OLB	VATS
Ray	27	1976	R	416	1955-1973; Consecutive case series ("clinical and radiologic diagnosis of diffuse pulmonary disease undiagnosed by indirect methods.")	416	0	19	—
Gaensler	28	1980	R	502	1950-1980; Case series; SLB performed for diagnosis of chronic diffuse infiltrative lung disease (a subset of 360 that were seen by group prior to the operation were analyzed)	360	0	1	—
Venn	29	1985	R	101	1979 to 1983; Patients with radiological appearances of "diffuse pulmonary shadowing"	101	0	4	—
Wetstein	30	1986	R	20	1984-1985; Case series of 20 consecutive patients with bilateral diffuse lung disease (17 were acute cases)	20	0	5	—
Shah	31	1992	R	432	Time span=10 years, but dates not given; Patients with diffuse lung disease; 13 post-operative deaths (only one death "procedure related"	432	0	13	—
Bensard	32	1993	R	43	1990-1992; ILD of unknown etiology	21	22	1	0
Ferson	33	1993	R		1987-1992; Patients with diffuse pulmonary infiltrates	28	47	6	3
Bentzon	34	1994	R	9	Time span not specified; Patients with suspected idiopathic interstitial pulmonary fibrosis or allergic alveolitis	0	9	—	1
Molin	35	1994	R	37	1990-1993; patients undergoing elective SLB for suspected ILD	21	16	1	0
Krasna	36	1995	R	26	1990-1993; 26 consecutive patients undergoing thoracoscopic lung resection to diagnose ILD (10 inpatient; 2 MV-dependent)	0	26	—	0
Mouroux	37	1997	R	66	1987-1991 (OLB) & 1991-1994 (VATS); Patients with suspected ILD (3 of 41 VATS procedures converted to mini-thoracotomy	25	41	2	2
Kramer	26	1998	R	103	1980-1994; Patients with diffuse lung disease (including immunocompromised patients)	103	0	21	—
Ravini	38	1998	R	138	1988-1991 (OLB) & 1992-1995 (VATS); Patients with "diffuse lung disease" (5 of 70 initial VATS procedures converted to OLB)	68	65	0	0
Zedgi	39	1998	R	64	1992-1996; Patients with diffuse ILD of unknown cause despite extensive evaluation (10 of 64 converted to OLB)	0	64	—	3
Rena	40	1999	R	58	1993-1999; ILD of unknown etiology after extensive previous investigation	0	58	—	0
Petrakis	41	2000	R	104	1994-2000; SLB for therapeutic purposes or for diffuse and localized lung, pleural, and/or mediastinal disease	0	104	—	0
Ayed	42	2000	P	61	1996-1998; Patients requiring lung biopsy for diagnosis of ILD (patients on ventilators were excluded)	29	32	1	0
Miller	43	2000	P	42	1994-1997; Ambulatory patients with clinical diagnosis of diffuse ILD (exclusion criteria included severe cardiac disease, contraindication to patient-controlled analgesia, or pleural space unsuitable for thoracoscopy)	22	20	0	0
Blewett	44	2001	R	32	1997-1999; Outpatient procedures (all patients ambulatory, non-oxygen dependent, and with pre-procedure clinical diagnosis of diffuse ILD)	32	0	0	—
Utz	45	2001	R	60	1986-1995; patients with UIP (majority biopsied because of atypical clinical or radiographic features or "diagnostic uncertainty")	44	16	7	3

(continued)

Table 2. 30-Day mortality rates for surgical lung biopsy

First Author	Ref #	Year	Study Type	N	Time Span & Cohort Characteristics	Type of Surgery		30-Day Mortality	
						OLB	VATS	OLB	VATS
Chang	46	2002	R	37	2000-2001; Adult ambulatory patients with clinical diagnosis of DILD or indeterminate focal pulmonary nodules	0	37	—	0
Qureshi	47	2002	R	100	1995-1999; Patients with thoracic imaging showing suspected ILD (patients with focal changes excluded)	30	70	0	0
Yamaguchi	48	2004	R	30	1994-2002; Stable ILD patients for definitive histopathologic diagnosis (none were immuno-compromised or receiving mechanical ventilation)	0	30	—	0
Tiitto	49	2005	R	76	1973- 2002; Retrospective identification of patients with histopathological confirmation of UIP	42	34	4	0
Ooi	50	2005	R	70	1998-2003; Patients with diffuse lung disease	15	55	0	1
Park	51	2007	R	200	1990-2003; Patients diagnosed as IPF, idiopathic NSIP or COP by SLB	50	150	2	6
Kreider	52	2007	R	68	1998-2004; Outpatients for diagnosis of suspected ILD (8 required mechanical ventilation for respiratory failure immediately before biopsy)	0	68	—	2
Ishie	53	2009	R	48	1999-2007: Patients with diffuse infiltrates (patients requiring MV in the ICU or oxygen-dependent excluded)	0	48	—	0
Guerra	54	2009	R	53	1998-2007; Patients with suspected ILD (VATS vs. minithoracotomy)	16	37	0	1
Zhang	55	2010	R	418	1999-2009; Patient with ILD who underwent surgical lung biopsy	196	139	3	2
						Total: 2071	**Total: 1133**	**Total: 90 (4.3% Mortality Rate)**	**Total: 24 (2.1% Mortality Rate)**

Abbreviations: COP=cryptogenic organizing pneumonia; CT=computed tomography; DILD=diffuse interstitial lung disease; ICU=intensive care unit; ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; LUL=left upper lobe; LLL=left lower lobe; MV-mechanical ventilator; N=number of subjects; NSIP-non-specific interstitial pneumonia; OLB=open lung biopsy; P=prospective study; PFT=pulmonary function testing; R=retrospective study; SLB=surgical lung biopsy; UIP=usual interstitial pneumonia; VATS=video-assisted thorascopic lung biopsy; VTLB=video-assisted lung biopsy

18.8%. Thirteen of the 23 studies reported no deaths within 30 days. Five studies reported 30-day mortalities of 4.0% or more. Utz et al. (45) reported a VATS 30-day mortality of 18.8%, which is slightly higher than their OLB 30-day mortality of 15.9%. As mentioned above, Utz et al. (45) reported that all of the deaths, regardless of the type of procedure, occurred in patients with UIP/IPF. Park et al. (51) reported 4.0% 30-day mortality in VATS patients with a diagnosis of IPF, idiopathic NSIP or cryptogenic OP. Benzton et al. (34) reported 1 patient (11.1%) death within 30 days, but their study reported outcomes for a cohort of only 9 patients. Of the 13 studies that compared OLB and VATS mortality outcomes, none, including the two prospective studies, reported any differences as statistically significant.

When these reports were grouped by approximate time period during which SLB was performed, SLB performed prior to 1990 (exclusively OLB) had a cumulative 30-day mortality of 3.2% (42 of 1329 procedures) (27-31). Those case series for which procedures were predominantly performed during the 1990-1998 time period had a cumulative 30-day mortality of 9.9% (39 of 393 procedures for OLB (although cumulative mortality was 6.2% [18 of 290 procedures] if the report by Kramer et al. was excluded) and 2.3% (12 of 520 procedures) for VATS (26,32-45). The 30-day mortality for procedures predominantly performed from 1998 to present was 2.9% (9 of 307 procedures for OLB and 2.4% (12 of 495) for VATS.

Morbidity

Thirty studies reported morbidity data from SLB (26-44, 46-55, 57). For this portion of the review, we identified 2,101 patients that underwent OLB and 1,294 patients that underwent VATS. A total of 381 patients (18.1%) who underwent OLB experienced one or more complications (significant, non-lethal complications), while 114 patients (9.6%) who underwent VATS experienced one or more complications (Table 3). The most common complications included pleural effusion (EFF), pneumothorax (PTX), persistent air leak (PAL) and hemothorax (HTX).

Twenty-one studies reported morbidities ranging from none to 50% for patients who underwent OLB (26-33, 35, 37, 38, 42-44, 47, 49-51, 54, 55). Six of the twenty studies reported morbidity percentages less than 10%, while an additional six studies reported morbidity rates ranging from 10.1% to 20.0%. Ray et al. (27) reported a 50% complication rate in patients who underwent OLB including 106 with post-operative pleural effusions and 97 with pneumothorax.

Twenty-three studies (32-43, 46-55, 57) could be identified that reported morbidity (significant, non-lethal complications) data for VATS, and morbidity ranged from 0.02% to 33.3%. In the mid 1990s, two retrospective studies (32, 33) suggested that VATS may be superior to OLB in terms of morbidity and other measures that included operative time, reduction in analgesic use, and pleural drainage duration. Bensard et al. (32) reported that VATS "was a safe and effective alternative to OLB." They also reported that VATS was associated with significant reduction in time necessary for pleural drainage when compared to OLB, and length of hospital stay was significantly shortened. Similarly, Ayed et al. (42) performed a prospective study and reported no significant difference in morbidity, but patients who underwent VATS had a significantly shortened operative time, less analgesia administered, and shortened hospital stay. Another prospective study from Miller et al. (43) also found no significant differences in morbidity for VATS versus OLB, However, in contrast to Ayed et al (42), they found no differences in operative time, analgesia administered, or duration of chest tube drainage for VATS vs. OLB). Ferson et al. (33) found that OLB patients experienced a more significant number of complications

Table 3. Complications of surgical lung biopsy

Author	Ref #	Year	Number of patients		Associated Morbidity N (%)		Types of Complications	
			OLB	VATS	OLB	VATS	OLB	VATS
Ray	27	1976	416	0	208(50.0)	—	EFF: 106, PTX: 97 (only 24 requiring chest tubes), HTX: 2, WI: 3	—
Gaensler	28	1980	360	0	14(3.9)	—	EMP: 1, RI: 2, MI: 1, PED: 1, LH: 1, WI: 1, EFF: 2, TP: 2, MA: 1, SS: 2	—
Venn	29	1985	101	0	18(17.8)	—	RTI:6, WI:8, HTX:1, PAL: 3	—
Wetstein	30	1986	20	0	6(30.0)	—	PTX: 3, HTX: 1 WI: 2	—
Shah	31	1992	432	0	22(5.1)	—	WI: 11, PTX: 9, HTX: 1, PAL:2	—
Bensard	32	1993	21	22	5 (19.0)	2(9)	BPF: 1, P: 1, PE: 1,HEM: 1.	PTX:1; HEM:1.
Ferson	33	1993	28	47	14(50)	9(19)	Progressive RI: 2 AT: 3, PAL: 4, sepsis: 3, pancreatitis: 1, RF: 2, bleeding: 2, PE:1	Progressive RI: 1, AT:3, PAL 2, sepsis:1, pancreatitis: 1.

(continued)

Table 3. Complications of surgical lung biopsy

Author	Ref #	Year	Number of patients		Associated Morbidity N (%)		Types of Complications	
			OLB	VATS	OLB	VATS	OLB	VATS
Benzton	34	1994	0	9	—	3(33)		PTX: 3
Molin	35	1994	21	16	1(4.8)	4(25)	chest tube breakage on removal: 1	BFP: 1, prolonged intubation: 1, P: 1, ARDS: 1
Krasna	36	1995	0	26	—	2(7.7)	—	P: 1, prolonged MV: 1
Mouroux	37	1997	25	41	3(12)	4(9.8)	PAL: 2, HEM: 1	AR: 1, P:1, PAL: 1, PTX: 1.
Kramer	26	1998	103*	0	26(25.2)	—	MV: 8, Infection: 7, AT: 2, PTX: 7, PM: 1, HTX: 3, Re-exploration: 1 Uncontrolled bleeding: 1	—
Ravini	38	1998	68	65	8(11.8)	7(10.8)	PAL:2, WD: 6	Lymph Effusion: 1; PAL: 3, PLC: 2, RF: 1.
Zedgi	39	1998	0	64	—	7(10.9)	—	PTX: 5 , HTX: 1, PAL: 1
Rena	40	1999	0	58	—	2(3.4)	—	PAL: 2
Petrakis	41	2000	0	104	—	7(6.7)	—	PAL: 4, EFF: 3
Ayed	42	2000	29	32	6(20.7)	3(9.4)	PAL: 1, RF: 2, PE:1, AT: 2	PAL :3
Miller	43	2000	22	20	4(19)	4(20)	AR: 1, PAL: 1, stapler injury to lung: 1 WI: 1	2 trocar injuries of pericardium, P: 1, PTX: 1
Blewett	44	2001	32	0	0	—	0	—
Chang	46	2002	0	37	—		—	0
Qureshi	47	2002	30	70	6(20.0)	7(10)	WI: 4, AT: 2	AT: 3, RF: 1,WI: 3
Yamaguchi	48	2004	0	30	—	3(10)	—	RF: 2 PAL: 1
Lee	57	2005	74	122	7(9.5)	4(3.3)	PAL:7	PAL: 4. Unclassified: 1 HTX, 1 acute MI.
Ooi	50	2005	15	55	0	4(7.2)	None.	PTX: 1, HTX: 1 UR: 2
Tiitto*	49	2005	42	34	6(14.3)	1(2.94)	PTX: 2, HTX: 2, P & HTX:1 P: 1	PTX: 1
Park	51	2007	50	150	8(16.0)	22(14.7)	Details not given	Details not given
Kreider	52	2007	0	68	—	17(25)	—	PTX: 4, HTM: 1; PAL: 3; P: 2; PHS: 3; MV: 4
Ishie	53	2009	0	48	—	1(0.02)	—	PTX: 1
Guerra	54	2009	16	37	3	2	PAL=2; PTX=1	PAL=1; HEM=1
Zhang	55	2010	196	139	16(8.2)	8(5.8)	Details not given	Details not given
Overall:			**2101**	**1294**	**Total: 381 Morbidity Rate: 18.1%**	**Total: 123 Morbidity Rate: 9.6%**		

Abbreviations: AR=arrhythmia; ARDS=acute respiratory distress syndrome; AT=atelectasis; BPF=bronchopleural fistula; EMP=empyema; EFF=pleural effusion; HEM=hemorrhage; HR=hospital readmission; HTX=hemothorax; HTM: Hematoma ICH=intracerebral hemorrhage; LH=herniated lung; MA=muscle adhesions; MI=myocardial infarction; MV=prolonged mechanical ventilation; P=Pneumonia PAL=persistent air leak; PE=pulmonary embolism; PED=pulmonary edema; PHS=prolonged hospital stay; PLC=partial lung collapse; PM=pneumomediastinum; PTX=pneumothorax; RI=respiratory insufficiency; RF=renal failure; RTI=respiratory tract infection; SS=subcutaneous sinus tract; TP=transient pneumonitis; UR=urinary retention; WD=wound dehiscence; WI=wound infection;
*39 subjects significantly immunocompromised at time of biopsy

(14 of 28) than VATS patients (9 of 47). In contrast, Mouroux et al. (37) reported that morbidity rates were comparable in both groups (VATS vs. OLB).

Diagnostic Efficacy

Sixteen of 20 studies that reported diagnostic efficacy data specifically for VATS stated that a confident diagnosis was attained in more than 90% of cases (Table 4), and eight manuscripts reported a confident diagnosis for 100% of their study subjects. Similarly, the efficacy for OLB in reaching a confident diagnosis was greater than 90% for 16 of 17 studies that reported data specifically for OLB. In one case series that included a substantial number of immunocompromised patients who underwent OLB, the percentage with a confident diagnosis was

Table 4. Diagnostic utility of surgical lung biopsy

Author	Ref #	Year	Number of Patients		Confident Diagnosis (%)		Comments
			OLB	VATS	OLB	VATS	
Ray	27	1976	416	—	100%	—	Dx: 29% "non-specific pulmonary disease"
Gaensler	28	1980	360	0	94.4%	—	Dx: IP-130(25.9%); UIP-64
Venn	29	1985	101	0	91%	—	Dx: CFA-51
Wetstein	30	1986	20	0	100%	—	Biopsy of lingual compared to other area
Shah	31	1992	432	0	94.9%	—	Dx: CFA-173; malignancy-55
Bensard	32	1993	21	22	100%	95%	
Ferson	33	1993	28	47	100%	100%	
Bentzon	34	1994	0	9	—	100%	
Molin	35	1994	21	16	95%	94%	UIP most common
Krasna	36	1995	—	26	—	100%	UIP; location of biopsy.
Mouroux	37	1997	25	41	100%	97.3%	
Kramer	26	1998	103	0	87%	—	39 subjects were ICH; CIT: 46%
Ravini	38	1998	68	65	92.6%	86.2%	Final diagnosis predominantly sarcoidosis (VATS 47, OLB 55)
Zedgi	39	1998	0	64	—	92.2%	Dx: 19 IPF
Rena	40	1999	0	58	—	86%	DX: 14 IPF, 10 sarcoidosis
Petrakis	41	2000	0	104	—	98.5%	Dx: 6 interstitial fibrosis, 6 BOOP
Ayed	42	2000	29	32	93.1%	97%	
Miller	43	2000	22	20	100%	100%	DX:UIP
Blewett	44	2001	32	0	100%	—	Dx: 26 UIP
Chang	46	2002	0	37	—	96.3%	
Qureshi	47	2002	30	70	42% Overall		Of those patients given a specific diagnosis, 59.5% had therapy altered
Yamaguchi	48	2004	0	30	—	100%	Dx: IPF 12, NSIP: 7
Lee	57	2005	74	122	100%	100%	Dx: 30% infection, 13.3% neoplasm
Lettieri	56	2005	23	60	100%	100%	Approximately 40% with IPF mis-diagnosed prior to SLB
Ooi	50	2005	15	55	100%	100%	37.1% had UIP
Kreider	52	2007	0	68	—	75%	23 (34%) had UIP; 23.5% non-classifiable
Ishie	53	2009	0	48	—	98.0%	Dx: 14 UIP; Non-specific honeycombing 1
Sigurdsson	58	2009	45	28	81% Overall		Clinical diagnosis changed for 73%; Change in therapy for 53%; 19% (non-specific inflammation or non-specific interstitial fibrosis)
Guerra	54	2009	16	37	94.3% Overall		
Zhang	55	2010	200	129	92%;	89.1%	

Abbreviations: BOOP=bronchiolitis obliterans organizing pneumonia; Dx=diagnosis; CFA=cryptogenic fibrosing alveolitis; CIT=change in treatment; ICH=immunocompromised host; IP=interstitial pneumonia; IPF=idiopathic pulmonary fibrosis; OLB=open lung biopsy; SLB=surgical lung biopsy; UIP=usual interstitial pneumonia; VATS=video-assisted thorascopic surgery

85% (26). In the eleven retrospective studies that had data for both VATS and OLB, there did not appear to be a significant difference in the percentage of patients who received a confident histopathologic diagnosis for one procedure versus the other. Similarly, the two prospective studies that were identified (42, 43) indicated that there were no significant differences for VATS compared to OLB in the percentage of patients for which biopsy provided a confident diagnosis.

Discussion

A major problem with analyzing case series that span a number of decades is that surgical techniques have changed somewhat over time, which could significantly affect mortality and morbidity rates. However, instances of death within 30 days have still been reported for patient cohorts that underwent SLB from 1998 onward (50-52, 54, 55). In comparing mortality rates for case series for the period of 1990-1998 vs. 1998 onward, the mortality rate declined to 2.9% for OLB while the mortality rate for VATS remained essentially unchanged (2.3 vs. 2.4%). The overall 30-day mortality and morbidity data suggest that VATS is safer than OLB. However, the majority of the published reports were retrospective, which may confer significant reporting bias. Also, a large portion of the OLB data was published from 1955-1993.

The literature shows an evolution of the preferred SLB technique such that the procedure of choice has shifted from OLB to VATS procedures, and the data suggest an associated overall decrease in mortality and morbidity in more recent years for all SLB. Studies that included more "high-risk" patients included those with acute respiratory failure, an immunocompromised state, and oxygen-dependency that likely contributed to a proportionate increase in the number of patients who died within 30 days of the procedure and/or experienced serious complications (26, 57). Interestingly, the results of at least two studies (45, 51) suggest that patients who are ultimately diagnosed with IPF subsequently experience worse post-procedure outcomes when compared to patients diagnosed with other forms of ILD. These data suggest that in patients suspected of having IPF, the benefits and potential complications of undergoing SLB to confirm a diagnosis must be weighed carefully against the risk of complications that are potentially life-threatening, such as triggering an acute exacerbation of IPF.

The majority of the published case series of SLB were performed prior to the advent of improved thoracic imaging capability (HRCT), the revision of the definition of IPF (IPF = idiopathic UIP), and the recognition and classification of the IIPs as distinct entities. HRCT is now recognized as being capable of providing a confident diagnosis of a UIP pattern (5) for a substantial number of patients and can also provide reasonably confident identification of many other ILD patterns, thereby decreasing the need to proceed to invasive procedures. Additionally, the combination of clinical data, HRCT imaging, and less invasive procedures (bronchoscopy with BAL and/or endoscopic lung biopsy) can establish a confident ILD diagnosis for many forms of ILD (62, 63). However, this is usually not the case for the IIPs including early UIP with non-diagnostic HRCT imaging, and SLB may be required to make a confident, specific diagnosis.

Flaherty et al. (64) found that surgical lung biopsies obtained from different lung regions in a given patient with a clinical diagnosis of IIP often showed discordant histopathology. A substantial number of patients had UIP histopathology in one regional biopsy but had changes consistent with NSIP in another region when two or more biopsies were performed in different region. Additionally, survival was observed to be better for patients with concordant NSIP/NSIP and worst for those with concordant UIP/UIP. Patients with discordant UIP/NSIP biopsies had a survival curve that was similar to that for patients with concordant UIP/UIP. Additionally, Katzenstein et al. (65) examined lung explants from patients with a pre-transplant diagnosis of IPF who underwent lung transplantation and found that such explants are highly likely to show areas consistent with changes of NSIP as well as some areas that suggest a desquamative interstitial pneumonia (DIP) type of histopathologic change.

The recently updated ATS/ERS/JRS/ALAT statement on IPF (5) revised the previous suggested approach (66) to the diagnosis of IPF. Bronchoscopy with BAL and/or ELBx is no longer recommended for the majority of patients undergoing diagnostic testing, but SLB is recommended for all

Table 5. Suggested approach to surgical lung biopsy

Indications
- HRCT features are not diagnostic for UIP or other ILD
- Unable to make a confident diagnosis via less invasive measures (especially if patient age is <50 yrs)

Suggested Technique
- Use VATS approach (lesser risk of complications with VATS versus OLB)
- Obtain adequate sampling in ≥2 separate geographic areas
- Avoid sampling areas of honeycomb change
- Use HRCT as a guide to identify and select areas to be biopsied

Seek consensus in interpretation of the biopsy (clinician, pathologist, radiologist)

Avoid in situations with increased risk of untoward outcome
- Advanced age
- Severely impaired lung function
- Significant medical comorbidities
- Unstable condition
- Mechanical ventilation

patients for whom a confident diagnosis cannot be made from thoracic imaging with HRCT. Additionally, it was suggested that HRCT should be used pre-operatively to target appropriate biopsy sites that avoid areas of extensive honeycomb change that are unlikely to provide tissue specimens that show diagnostic changes consistent with UIP. A suggested approach to the use of SLB is provided in Table 5, and we suggest that for patients with risk factors such as substantial physiologic impairment or the presence of significant co-morbid conditions that predict an increased likelihood of an untoward outcome if SLB is performed, such risks may outweigh the benefit of establishing a secure diagnosis of UIP/IPF or other ILD types. The decision to proceed with SLB for such patients must consider the clinical situation for each individual patient, and we suggest an approach that uses non-SLB modalities (HRCT and bronchoscopic findings combined with clinical features) to attempt to establish a confident diagnosis before proceeding to a SLB and avoiding SLB, if possible, especially if clinical factors indicate an increased likelihood of significant complications (Figure 1).

Our literature review suggests that VATS biopsy is associated with lower morbidity and mortality than OLB, and some studies have also suggested that length of stay is shorter with VATS (32, 33, 43, 67). However, the choice of procedure should include consideration of individual patient characteristics and available surgical expertise. If SLB biopsy is performed, sampling of adequate amounts of tissue in more than one lung region is recommended to make an accurate diagnosis of IPF as the lungs of patients with IPF may have extensive areas that show changes consistent with NSIP or DIP, while other areas have the characteristic histopathologic changes of UIP (64, 65). Additionally, various studies (68, 69) suggest that a multi-disciplinary approach that includes a discussion among clinicians, radiologists, and pathologists will increase the likelihood of attaining an accurate, ultimate diagnosis when agreement is reached via communication among experienced clinical experts who consider the combination of clinical characteristics, HRCT imaging, and histopathologic changes (when a SLB is included in the diagnostic approach).

Summary and Conclusions

A thorough clinical evaluation and HRCT imaging may prove diagnostic when performed on patients with suspected ILD. If a confident diagnosis cannot be reached after a HRCT has been obtained, a less invasive approach using bronchoscopy with BAL and/or ELB can be diagnostic and may obviate the need for proceeding to SLB. Surgical lung biopsies are associated with a relatively low but not negligible risk of mortality and are also associated with potential significant morbidity. Patients diagnosed with IPF may be at somewhat greater risk of serious complications including death when subjected to SLB, and some reports suggest that SLB may trigger an acute exacerbation of the disease. The mortality risk appears to be lower with VATS versus

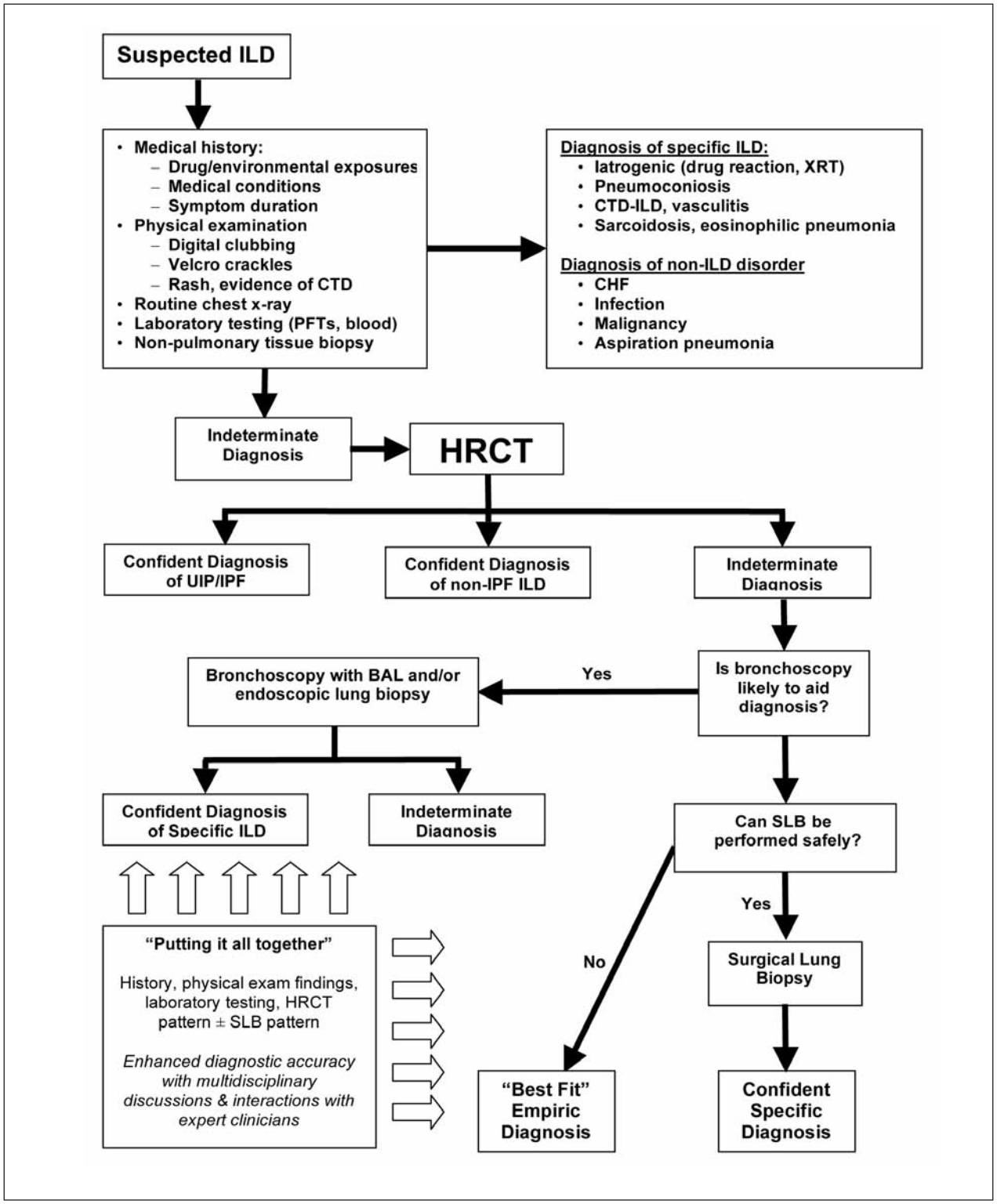

Fig. 1. Suggested Algorithm for the Diagnosis of ILD.
Abbreviations: BAL=bronchoalveolar lavage; CHF=congestive heart failure; CTD=connective tissue disease; HRCT=high-resolution computed tomography of the thorax; PFT=pulmonary function testing; SLB=surgical lung biopsy; XRT=radiotherapy

OLB procedures, although improved surgical techniques in general may account for a trend suggesting decreased risk of significant complications over the past decade for both OLB and VATS procedures. If a confident diagnosis cannot be made without proceeding to SLB, an individual patient's risk of suffering serious complications as a consequence of SLB should be assessed before the decision to perform a SLB is performed, and the patient should clearly understand the risks and benefits of undergoing SLB.

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