High short-term mortality following lung biopsy for usual interstitial pneumonia


ABSTRACT: Usual interstitial pneumonia (UIP) is a specific histological pattern of interstitial pneumonia most often associated with the clinical syndrome of idiopathic pulmonary fibrosis (IPF). There is controversy regarding the use of surgical lung biopsy in the diagnosis of UIP, and the risk of lung biopsy in these patients is largely unknown. This study investigated the 30 day surgical mortality rate in patients undergoing surgical lung biopsy for UIP. Patients undergoing surgical lung biopsy over a 10-yr period from 1986 – 1995 with the ultimate diagnosis of UIP (with or without underlying connective tissue disease) were identified. Pathology, computed tomography, medical records, and survival were assessed.

Ten of sixty patients with usual interstitial pneumonia were found to be dead within 30 days of surgical biopsy. All of these were patients with idiopathic UIP, unassociated with connective tissue disease (clinical condition of IPF).

In conclusion, patients with usual interstitial pneumonia of the idiopathic type, who present with atypical features, may be at higher risk for death following surgical biopsy than patients presenting with more typical features or patients with other interstitial illnesses.

Usual interstitial pneumonia (UIP) is a specific pattern of interstitial pneumonia that typically occurs in patients with the clinical syndrome of idiopathic pulmonary fibrosis (IPF) [1 – 4]. UIP can also occur in association with underlying connective tissue diseases, occupational asbestos exposure (i.e. asbestosis), and with certain drug toxicities [2]. Historically, UIP was considered to be the underlying histology in a subset of patients with IPF; however, current recommendations are that the diagnosis of IPF be restricted to those patients with unexplained UIP (UIP/IPF). The prognosis for patients with UIP/IPF is poor, with a median survival of ~2.8 yrs [5].

In many studies, the diagnosis of UIP has been based upon a combination of characteristic clinical and radiographic features, with histologic confirmation in only selected cases [2, 6 – 10]. Others have advocated wedge biopsies in all patients suspected of having UIP/IPF, especially in those patients <60 yrs of age [1]. High resolution computed tomography (HRCT) of the chest has reduced the proportion of patients undergoing biopsy procedures, such that many patients with a compatible clinical history and physical examination, and an HRCT typical of UIP, are often not subjected to surgical lung biopsy [11]. The relative accuracy of HRCT versus surgical biopsy in the diagnosis of UIP is controversial [2, 12 – 21]. The Mayo Clinic has generally accepted a clinicoradiographic diagnosis of UIP/IPF in patients with typical clinical features and a "classic" appearance on HRCT. The risk of surgical lung biopsy in patients with UIP is largely unknown. This study, therefore, reviewed the 30 day surgical mortality rate in all patients with UIP at the Mayo Clinic, on lung biopsies obtained by either thoracotomy or video-assisted thoracoscopic surgery (VATS) during a 10-yr period (1986 – 1995).

Methods

Patient selection

All pathology reports for lung tissue removed by open thoracotomy or VATS at the Mayo Clinic, Rochester were reviewed for the years 1986 – 1995. Of 3,736 reports, 68 included the diagnosis of UIP. These 68 specimens were jointly reviewed by two of the authors (H.D. Tazelaar and J.L. Myers), without knowledge of the clinical or radiological findings. Only patients with histologically confirmed UIP were retained in the study population.
Pathology review

Criteria for the diagnosis of UIP included a heterogeneous appearance at low magnification resulting from alternating zones of normal lung, patchy interstitial widening due to a combination of inflammation and fibrosis, foci of recent organization with fibroblast proliferation ("fibroblast foci"), and honeycomb changes [2, 3, 5]. The fibrotic changes preferentially affected subpleural and paraseptal parenchyma.

Medical record review

All medical records related to an individual patient at the Mayo Clinic are contained in a single unit record. These records contain all inpatient and outpatient records, laboratory results and correspondence. These records were reviewed and relevant information recorded including age at biopsy, sex, type of biopsy, vital status at last follow-up, preoperative pulmonary function data, clinical-pathological diagnosis, and radiographic imaging dates and results. The reason for biopsy was determined and recorded, as best as it could be in a retrospective fashion. A mailed survey, supplemented by telephone interview of patients or relatives, was utilized to obtain vital status information for all patients not known to be deceased at the time of last contact. Date of death was obtained from death certificates or next of kin. Vital status was determined on all patients reviewed, no patient was lost to follow-up.

Radiographic review

All available Mayo and outside computed tomographic (CT) scans of the chest were reviewed jointly by two readers (T.E. Hartman and J.P. Utz) in the absence of any clinical information. Patients in whom HRCT images were available for review were classified as (1) diagnostic for UIP, (2) possibly UIP, or (3) not consistent with UIP. HRCT criteria for a confident diagnosis of UIP included symmetric, lower lung predominant, bilateral irregular linear opacities occurring in a subpleural distribution with associated honeycombing. Traction bronchiectasis and areas of ground glass attenuation could be present, but were not required for diagnosis. CT studies were classified as "possible UIP" if the irregular linear opacities lacked a lower lung predominance or subpleural distribution, or if the irregular linear opacities were asymmetric or if honeycombing was not present. CT scans interpreted as "not consistent with UIP" demonstrated findings other than those noted above.

Statistical analysis

Cumulative survival probabilities were estimated using the Kaplan-Meier method [22]. Patients that died within 30 days following biopsy were compared to those that survived beyond 30 days, using the rank sum test for continuous variables and Fisher’s exact test for categorical variables. In all cases, two-tailed p-values ≤0.05 were considered statistically significant.

Results

Pathological review confirmed the diagnosis of UIP in 60 of 68 cases. Eight patients were excluded from further analysis because their biopsies showed non-specific interstitial pneumonia (4 patients), sarcoidosis (1), nonspecific scarring with adenocarcinoma (1), nonspecific scarring with emphysema (1), and a nonclassifiable interstitial pneumonia (1). Among the 60 patients with UIP, there were 41 males and 19 females. The age at time of biopsy was 63.4 ± 10.5 yrs (mean ± sd). Forty-four (73%) biopsies were obtained by open thoracotomy, and 16 (27%) were obtained by VATS. Baseline pulmonary function testing at time of biopsy is shown in table 1. Clinicopathological diagnoses included UIP/IPF in 46 patients (76.7%) and UIP associated with connective tissue disease (UIP/CTD) in 14 patients (23.3%). The associated connective tissue diseases included primary systemic sclerosis (4 patients), dermatomyositis/polymyositis (4), rheumatoid arthritis (2), mixed connective tissue disease (1), suspected connective tissue disease with nonspecific features (2), and uncharacterized vasculitis (1). Five of the 60 patients had evidence of diffuse alveolar damage (DAD) superimposed on underlying UIP. Of these 5 patients, 4 had UIP/IPF and 1 had UIP/CTD.

The majority of patients were biopsied because of atypical clinical or radiographic features, or because of "diagnostic uncertainty". Seven patients were primarily biopsied in order to rule out a secondary process (i.e. infection) based upon an accelerated decline in function or a change in the character of radiographic infiltrates. Aside from DAD, no secondary process was identified in any patient. Some patients were biopsied to obtain a "definitive diagnosis" or to "define activity" of disease, generally prior to considering a prolonged course of corticosteroids. Five patients had lung biopsies coincident with other thoracic surgery. These indications included cardiac surgery in two patients (mitral valve replacement and mitral valve replacement with coronary artery bypass grafting), lung cancer surgery, pleurodesis for pneumothorax, and take-down of a failed Nissen fundoplastication, in a single patient each.

Twenty-eight patients (46.7%) had a preoperative HRCT, eight had only a conventional CT scan (13.3%), and 24 (40.0%) had no preoperative CT scan. Cases in which only conventional CT images were available were intrinsically unable to achieve a label of "consistent with UIP" since these criteria are based on HRCT features. Of the 28 patients with HRCT scans prior to lung biopsy, 25 were available for review. Three (12%) were considered diagnostic of UIP, 17 (68%) were possibly UIP, and 5 (20%) were not consistent with UIP.

Ten of 60 patients with UIP were dead within 30 days of biopsy (16.7%, 95% exact confidence interval 8.3–28.5%). These included three of 16 patients subjected to VATS biopsy (18.8%) and seven of 44 (15.9%) patients subjected to thoracotomy and biopsy. All of the patients that died within 30 days following biopsy were in the UIP/IPF group (10/46, 21.7%, versus
0/10 for the UIP/CTD group, p ~ 0.098). Four of the five patients with DAD on UIP were in the IPF group, and two of the four died within 30 days, while the remaining two died within four months of biopsy. The fifth patient with DAD on UIP had primary systemic sclerosis (PSS) and was alive at 87 months after biopsy. A lower diffusing capacity for carbon monoxide (DLCO) was predictive of death within 30 days with a mean DLCO of 52.1% predicted in the 30 days survivors versus 34.7% predicted in the patients dead within 30 days (p = 0.028). Cause of death in all 10 patients dead within 30 days of biopsy was attributed to a respiratory cause, most often adult respiratory distress syndrome (table 2).

Table 2. – Patients dead within 30 days

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Preoperative diagnosis</th>
<th>Reason for biopsy</th>
<th>Biopsy result</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>61/M</td>
<td>IPF</td>
<td>AD R/O secondary mass</td>
<td>UIP</td>
<td>Increase in infiltrate, bleeding, unresponsive one day after TOCP</td>
</tr>
<tr>
<td>71/M</td>
<td>IPF</td>
<td>AD R/O secondary process</td>
<td>DAD on UIP</td>
<td>Respiratory failure, never extubated*</td>
</tr>
<tr>
<td>69/M</td>
<td>IPF</td>
<td>AD R/O secondary process</td>
<td>UIP</td>
<td>Respiratory failure, probable ARDS*</td>
</tr>
<tr>
<td>68/M</td>
<td>IPF</td>
<td>AD R/O secondary process</td>
<td>UIP</td>
<td>ARDS</td>
</tr>
<tr>
<td>67/F</td>
<td>BOOP/DAD?</td>
<td>DU Subacute course</td>
<td>DAD on UIP</td>
<td>ARDS</td>
</tr>
<tr>
<td>64/M</td>
<td>UIP</td>
<td>AD (but myocardial infarction, flail mitral leaflet)</td>
<td>UIP</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>64/F</td>
<td>AIP?</td>
<td>DU Subacute course, alveolar infiltrates</td>
<td>UIP*</td>
<td>ARDS</td>
</tr>
<tr>
<td>58/M</td>
<td>UIP/eosinophilic granuloma?</td>
<td>DU Atypical CT distribution</td>
<td>UIP*</td>
<td>Acute pulmonary oedema or severe UIP</td>
</tr>
<tr>
<td>40/M</td>
<td>IPF?</td>
<td>DU Atypical young age</td>
<td>UIP*</td>
<td>ARDS</td>
</tr>
<tr>
<td>58/M</td>
<td>UIP/eosinophilic granuloma/Sarcoidosis</td>
<td>DU Upper lobe predominant infiltrates</td>
<td>UIP</td>
<td>Pneumothorax/ Empyema/sudden death</td>
</tr>
</tbody>
</table>

*: autopsy declined; #: bronchiolitis obliterans organizing pneumonia/diffuse alveolar damage; ?: open lung biopsy 4 years prior; ~: indicates video assisted thoracoscopic biopsy, all others open surgical biopsy; IPF: idiopathic pulmonary fibrosis; UIP: usual interstitial pneumonia; DAD: diffuse alveolar damage; ARDS: adult respiratory distress syndrome; BOOP: bronchiolitis obliterans organizing pneumonia; AIP: acute interstitial pneumonia; AD: accelerated decline; DU: diagnostic uncertainty; TOCP: transtracheal oxygen catheter placement; ?: uncertain diagnosis.
The fact that 40% of biopsied patients did not have preoperative CT may reflect the atypical presentation of these patients, the perceived urgency to biopsy, or the time frame studied (1986 – 1995). A more recent analysis of 487 patients with UIP seen at our institution from 1994 – 1996 indicated that 94.7% of patients underwent surgical biopsy [26]. Interestingly, 9% of patients underwent VATS biopsy occurred in those with diffuse lung infiltrates, though all of these patients had preoperative respiratory failure. In that study, of the 224 patients who underwent VATS wedge resection for a pulmonary nodule (no conversion to an open procedure), there were no surgical deaths. All deaths (n = 15) occurred in patients undergoing VATS wedge biopsy for diffuse pulmonary infiltrates (types not specified). Wedge specimens (147) were collected from patients with diffuse infiltrates, though some patients may have had more than one specimen (the precise number of patients with diffuse infiltrates was not specified). Therefore, the mortality rate in these patients with diffuse infiltrates was at least 10% (15/147), if one assumes only one wedge specimen per patient. If any patients had more than one specimen, the number of patients represented by 147 specimens drops, thereby increasing the calculated mortality. Recent 30-day surgical mortality rates at the Mayo Clinic were 0.4% after lobectomy, 2.7% following wedge resection, and 5.4% after pneumonectomy (personal communication, M.S. Allen, Division of General Thoracic Surgery, Mayo Clinic, Rochester, MN, USA).

All short-term mortality in this study occurred in patients with UIP/IPF rather than UIP/CTD. Indeed, the 30-day mortality rate for patients with UIP/IPF was 21.7% (10/46). Explanations for the high surgical mortality rate in this population of patients are largely speculative. There did not appear to be any differences in surgical technique, anaesthesia, or postoperative care between patients who died within 30 days of biopsy and the survivors. The authors are unaware of any variance in the thoracotomy or VATS technique in this group of patients versus others subjected to thoracotomy or VATS procedures with other conditions. It is possible that the high 30-day surgical mortality rate reflects more severe lung disease in patients undergoing a surgical biopsy compared to those not subjected to biopsy. Lower DLCO (% predicted) was the only preoperative parameter that showed a significant correlation with the risk of postoperative death in biopsied patients (p = 0.028). Other pulmonary function parameters were not statistically different. Seven patients were biopsied because of accelerated disease progression, suggesting that this subset of patients may be at higher risk of early postoperative death. The presence of DAD and UIP in open lung biopsies has been described in patients with accelerated deterioration or acute exacerbation of IPF [28, 29]. In the present study this combination of findings did not necessarily correlate with either a clinical history of accelerated disease, or early postoperative death, although all but one had died within 4 months of biopsy.

Although it is difficult to be certain, given the selection bias inherent in a retrospective analysis of this sort, the present findings suggest that patients with UIP presenting with atypical features may be at higher risk for death following open thoracotomy or VATS biopsy than those presenting with typical features or patients with other illnesses. Two other reports offer additional evidence that the risk of surgical biopsy in these patients may be higher than currently appreciated. Salazar-Flores and Salas-Hernandez [30] reported in abstract form the causes of death in 110 patients with "pulmonary fibrosis". While details of this series are not known, 13.6% of deaths in these 110 patients were attributed to complications of biopsy. Tazelaar et al. [31] described three histologic subtypes of patients with polymyositis and dermatomyositis, including bronchiolitis obliterans-organizing pneumonia, DAD, and UIP. Of the patients with UIP on surgical biopsy, 60% (3/5) were dead within 30 days of biopsy, indicating that patients with UIP/CTD may also be at increased risk, despite the absence of early postoperative deaths in the present study's reported patients with UIP/CTD.

It is difficult to formulate specific recommendations in the absence of large prospective studies evaluating the risk of lung biopsy in patients with suspected usual interstitial pneumonia. The authors would urge others to report their own experience with wedge lung biopsy in their own patients to further discern whether patients with usual interstitial pneumonia may be subject to a previously unappreciated high risk following surgical biopsy. This may be particularly crucial since, in current practice, surgical biopsy is often done in a minority of patients and recommendations suggest surgical biopsy in patients with presentations atypical for usual interstitial pneumonia [8, 24, 32 – 34]. The present findings indicate that this subset of patients may be at higher risk for surgical biopsy than previously recognized.

References

4. Katzenstein AA. Idiopathic interstitial pneumonia: