Transbronchial Cryobiopsy in Diffuse Lung Disease

Update for the Pathologist

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Context.—Transbronchial cryobiopsy has recently been proposed as an alternative to surgical biopsy in the diagnosis of diffuse lung disease.

Objective.—To familiarize pathologists with transbronchial cryobiopsy, including what it is, how it is performed, how it compares to other techniques of lung biopsy in diffuse lung disease, what are the technical issues relating to it, what the complications are, how cryobiopsies should be interpreted, and the clinical usefulness of cryobiopsy.

Data Sources.—All the available literature on cryobiopsy in diffuse lung disease through May 2016, primarily in the last 5 years, was reviewed, and some unpublished data known to the authors were included.

Conclusions.—Cryobiopsies are considerably larger than forceps biopsies and allow pattern recognition approaching that of a surgical lung biopsy in many cases. Artifacts associated with cryobiopsy are minimal. In comparison with surgical lung biopsies, the diagnosis rate with cryobiopsies is lower, in the neighborhood of 80%, versus higher than 90% for surgical lung biopsies. Cryobiopsy is proposed as an alternative to surgical lung biopsy and a technique that may appreciably decrease the number of patients who require surgical lung biopsy for diagnosis. This is important because the mortality from cryobiopsy is very small (0.1% to date) compared with surgical lung biopsy (1.7% for elective procedures and considerably higher for nonelective procedures).

WHAT IS A TRANSBRONCHIAL LUNG CRYOBIOPSY?

Put simply, a cryoprobe is inserted into the lung, cooled below freezing, and then retrieved with the lung tissue that has frozen onto it. This tissue is thawed in saline and then transferred to formalin and processed routinely for histologic evaluation.

Background

Cryobiopsies have been used bronchoscopically for more than 40 years, initially for the debulking of endobronchial lesions. Because more tissue can be retrieved than with bronchoscopic forceps biopsies, cryoprobe-retrieved specimens are larger and have also proven more effective than forceps biopsy specimens for retrieving sufficient tissue for histologic diagnosis (and immunohistochemistry as needed) of tumors biopsied endobronchially. In a prospective multicenter trial of nearly 600 patients among 8 centers, cryobiopsy proved superior to forceps biopsy in providing a diagnosis for an endobronchial tumor: 95% versus 85% (268 of 282 patients versus 239 of 281 patients), and the safety profile for cryobiopsy was similar to that of forceps biopsy. Transbronchial cryobiopsy has recently been used in the setting of diffuse lung disease, a setting in which transbronchial forceps biopsies have had only limited usefulness. As stated in the 2009 report by Babiak et al: “transbronchial cryobiopsy is a novel technique, which allows to obtain large biopsy samples of lung parenchyma that exceed the size and quality of forceps biopsy samples.” Since the initial studies, there have been a large number of additional reports from around the world describing this technique in diffuse lung disease, primarily interstitial pneumonias but also in other settings, including lung transplant sampling and airway disease; the safety profile is acceptable and the diagnostic usefulness much greater than forceps biopsies.

HOW IS TRANSBRONCHIAL CRYOBIOPSY PERFORMED?

Transbronchial cryobiopsy is performed with a rigid or flexible bronchoscope, with or without intubation. Usually, under fluoroscopic guidance a cryoprobe (1.9 or 2.4 mm in
(diameter) is inserted through the operating channel of the flexible bronchoscope into the region of interest (typically ~1.0 cm from the pleura), and it is cooled for a short period of time (5–6 seconds), at which point the cryoprobe is withdrawn with tissue stuck/frozen to it; the tissue is thawed and removed from the probe in a saline bath, and then it is transferred to formalin and processed for routine histology. Multiple biopsies can be obtained in the same sitting.

Figure 1. Performing cryobiopsies. The cryoprobe is introduced through a rigid bronchoscope by the bronchoscopist (A). The shaded region at the top shows the cryoprobe inserted into the operative channel of the flexible bronchoscope. With fluoroscopic guidance the probe is inserted into the periphery of the lung and cooled (B). Once the specimens are retrieved on the cryoprobe, they are thawed in saline and typically put directly into formalin. Some gross examples of cryobiopsies are shown in C.

Figure 2. Twelve consecutive unselected cryobiopsies from the C.B. Morgagni Hospital in Forli, Italy. It is apparent that most of these are at least 0.5 cm in greatest dimension and that multiple specimens can be taken at one sitting. Specimens that are sufficiently large enough can be divided in two once they are fixed in formalin.

Figure 3. Low-power photomicrograph of a cryobiopsy showing pristine lung tissue without any crush artifact. A small airway cut longitudinally shows some sloughing of epithelium. Such a biopsy would be considered nondiagnostic/normal. Other specimens from this case are shown in Figure 14 (hematoxylin-eosin, approximate original magnification ×60).
As has been emphasized recently, there is a clear need for procedural standardization for this recently introduced technique. Procedural issues include: type and degree of sedation, intubation versus no intubation, types of ventilation (spontaneous breathing or jet ventilation), rigid versus flexible tubes, the size of the cryoprobe used, the number of samples taken, and how many segments or lobes should be sampled. Varying these factors affects both the complication rate and the quality of the samples received, with the best results achieved with intubated and sedated patients.

The instruments required and procedure for transbronchial cryobiopsy are shown in Figure 1.

HOW DOES TRANSBRONCHIAL CRYOBIOPSY IN DIFFUSE LUNG DISEASE COMPARE TO OTHER TECHNIQUES OF LUNG BIOPSY?

The short answers are that transbronchial cryobiopsy far exceeds traditional forceps transbronchial biopsy in providing useful information histologically, and it falls short of that provided by surgical lung biopsy.

When comparing transbronchial cryobiopsy to traditional forceps biopsy and surgical lung biopsy, there are 2 important and interrelated comparisons: the size of the specimens and the diagnostic usefulness of the specimens.

Even the casual observer notices the marked difference in size between cryobiopsies (which often measure 0.5 cm or more in greatest dimension) and lack appreciable crush artifact (see Figure 2) and traditional forceps biopsies, which are in the range of 0.2 to 0.3 cm in diameter, often with appreciable crush artifact.

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Mean Size, mm²</th>
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<tbody>
<tr>
<td>Babiak et al.¹ 2009</td>
<td>41</td>
<td>15.1</td>
</tr>
<tr>
<td>Fruchter et al.,² 2013</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Kropski et al.,³ 2013</td>
<td>25</td>
<td>64.2</td>
</tr>
<tr>
<td>Casoni et al.,² 2014</td>
<td>69</td>
<td>43.1</td>
</tr>
<tr>
<td>Pajares et al.,⁴ 2014</td>
<td>39</td>
<td>14.7</td>
</tr>
<tr>
<td>Griff et al.,³ 2014</td>
<td>52</td>
<td>30.4</td>
</tr>
<tr>
<td>S.T. et al (unpublished observations, March 2016)</td>
<td>310</td>
<td>44.8</td>
</tr>
</tbody>
</table>

Figure 4. Cryobiopsy artifacts. A, A hemorrhage on the left side, which is related to the trauma of the procedure when multiple specimens are being taken. Smoking-related changes are noted on the right side. Some cases show pale eosinophilic intra-alveolar material, also thought to be a procedure-related artifact (B). Depending on the plane of sections and how the tissue is removed from the probe, the hole left in the tissue by the probe may be encountered (C). When the probe remains in proximity to an airway, the airway may become the major portion of the specimen, as shown in D, from a patient with Sjogren syndrome with chronic bronchiolitis well illustrated in the section (hematoxylin-eosin, approximate original magnifications ×40 [A, C, and D] and ×300 [B]).
In the study by Griff et al 24 in 2011, it was shown that cryobiopsies were significantly larger in a morphometric analysis: 4 times larger on average, with approximately 6 times the alveolar tissue. In a number of other studies1,2,5,10,18,25 (including S.T. et al, unpublished data, March 2016) summarized in Table 1, the mean size of cryobiopsy specimens in square millimeters ranged from 10 to 64.2 mm².

The quality of cryobiopsies is operator dependent, and a poor cryobiopsy may be no larger than 0.2 or 0.3 cm in greatest dimension and provide no more information than a traditional transbronchial forceps biopsy in terms of diagnostic usefulness.

Although transbronchial cryobiopsies are significantly larger than transbronchial forceps biopsies (ideally, cryobiopsies are 0.5 cm in greatest dimension or more; Figure 2), they are still significantly smaller than surgical lung biopsies (SLBx; herein including traditional open lung biopsy and video-assisted surgical/video-assisted thoracoscopic surgical biopsies). In a study from the Mayo Clinic that included both video-assisted surgical/video-assisted thoracoscopic surgical biopsies and traditional open lung biopsies, the mean single largest dimensions of the specimens were 4.1 and 4.2 cm, respectively.26

This translates into surgical lung biopsies providing in the neighborhood of 32 times more surface area than a single cryobiopsy (assuming an SLBx biopsy of 4 × 2 cm and a single cryobiopsy 0.5 in diameter). Although this is a large difference in size, there is enough tissue in many cryobiopsy specimens (especially when multiple samples are taken) to identify patterns not easily recognizable on forceps biopsies. In actual practice, a suboptimal SLBx that measures less than 1 cm in greatest dimension, approaching the size of a cryobiopsy, is not uncommonly encountered.

In terms of diagnostic usefulness, that of transbronchial cryobiopsy biopsy clearly exceeds that of traditional transbronchial forceps biopsy. In a review by Churg,27 it was estimated that approximately one-third of transbronchial biopsies in diffuse lung disease provided significant diagnostic usefulness. In the early study by Babiak et al,1 transbronchial cryobiopsy was compared to forceps biopsy in the diagnosis of 41 consecutive cases of patients with diffuse lung disease. The diagnoses in this series included idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, pulmonary lymphangioleiomyomatosis, hypersensitivity pneumonitis, sarcoidosis, and drug reaction. In 14 of 41 patients (34%), a diagnosis was reached on the basis of history, lung function, and radiologic studies. In 24 of 41 patients (59%), a diagnosis was reached when the findings on forceps biopsy were added. With the addition of findings on cryobiopsy, a diagnosis was reached in 39 of 41 patients (95%). In the cryobiopsies, crush artifact was not

Figure 5. Cryobiopsy artifacts. As the cryoprobe is pushed through the airway wall, it may carry nests of bronchiolar epithelium into the alveolar parenchyma, seen as small, bluish nodules at scanning power microscopy (A) but readily recognizable as bronchial epithelium at high power (B), with cilia apparent (5 o’clock just off-center) (hematoxylin-eosin, approximate original magnifications ×40 [A] and ×600 [B]).

Figure 6. Visceral pleura in a cryobiopsy. An appreciable percentage of cryobiopsies include visceral pleura. In A, visceral pleural and subpleural tissue are apparent in the upper right-hand corner of the field. The mesothelial lining is readily apparent at high-power microscopy (B) (hematoxylin-eosin, approximate original magnifications ×40 [A] and ×300 [B]).
found to be a problem, and the cellular detail was as well preserved as in usual microscopic sections.

Determining the diagnostic yield of cryobiopsy is difficult and varies somewhat with the study and the methods, but a figure of ~80% (for both histologic diagnosis and multidisciplinary discussion [MDD] diagnosis) was found in a review of 15 series that included more than 780 patients. This is clearly better than the ~33% diagnostic rate of transbronchial forceps biopsy, but it falls short of that of surgical lung biopsy. In a large series of consecutive cases that included 297 patients with cryobiopsy and 150 with surgical lung biopsies, more than 98% (148 of 150 patients) of the surgical lung biopsies were considered diagnostic in comparison with more than 82% (246 of 297 patients) of the cryobiopsies. The figure of 98% for the diagnostic utility of surgical lung biopsy exceeds those of older series in the literature: 97%, 95%, and 91%.

**WHAT IS AN ADEQUATE TRANSBRONCHIAL CRYOBIOPSY?**

The adequacy of any medical test can be assessed in terms of an absolute value or a relative value. One can apply absolute criteria of adequacy to a cryobiopsy in terms of minimum size, presence of or minimum number of alveoli, etc. Alternatively, one can apply a relative value of adequacy if a biopsy is considered sufficient for diagnosis, or at least sufficient for MDD, diagnosis, and reasonable patient management. Both assessments have usefulness. In a large cryobiopsy study comprising 297 patients, the specimens from 51 patients (17.2%) were considered nondiagnostic inadequate because of the presence of normal tissue or tissue showing minimal pathologic changes, such as microfocus of inflammatory infiltrate, minimal focal fibrosis, etc.

### Table 2. Events That May Complicate Lung Biopsies for Interstitial Lung Diseases

<table>
<thead>
<tr>
<th>Cryobiopsy</th>
<th>Complications</th>
<th>Surgical Lung Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Pneumothorax</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Prolonged air leak</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Postprocedure chest pain</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Bleeding</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Transient respiratory failure</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Fever</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Pneumonia/empyema</td>
<td>X</td>
</tr>
<tr>
<td>X</td>
<td>Acute exacerbation/death</td>
<td>X</td>
</tr>
</tbody>
</table>

### Table 3. Complications From the Forli Study

<table>
<thead>
<tr>
<th>Cryo, % (No.) of Patients</th>
<th>Complications</th>
<th>VATS, % (No.) of Patients</th>
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</thead>
<tbody>
<tr>
<td>20 (60)</td>
<td>Pneumothorax</td>
<td>100</td>
</tr>
<tr>
<td>0.3 (1)</td>
<td>Prolonged air leak</td>
<td>3.3 (5)</td>
</tr>
<tr>
<td>0.7 (2)</td>
<td>Transient respiratory failure</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>Fever</td>
<td>4.7 (7)</td>
</tr>
<tr>
<td>0</td>
<td>Pneumonia/empyema</td>
<td>2 (3)</td>
</tr>
<tr>
<td>0.3 (1)</td>
<td>Acute exacerbation/death</td>
<td>3.3 (5)</td>
</tr>
</tbody>
</table>

**Abbreviations:** cryo, cryobiopsy; VATS, video-assisted surgical/video-assisted thoracoscopic surgical.

* Data derived from Ravaglia et al. Cryo, n = 297; VATS, n = 150.
WHAT ARE THE ARTIFACTS, TECHNICAL ISSUES, AND NONPULMONARY TISSUES THAT MAY BE ENCOUNTERED WITH TRANSBRONCHIAL CRYOBIOPSY?

Compared with traditional cryostat frozen sections, transbronchial cryobiopsies show little if any “frozen artifact.” Very slight lack of crispness of nuclear and cytoplasmic features and of connective tissue can sometimes be found in cryobiopsies, but there is no significant effect on histologic interpretation (Figure 3). When multiple transbronchial cryobiopsies are taken, the trauma of the procedure itself, in the form of intra-alveolar hemorrhage and/or proteinaceous fluid, may be encountered (Figure 4). Similarly, as the cryoprobe is thrust through the bronchial wall, bronchial epithelium may be implanted in the alveolar tissue (Figure 5). Ideally, transbronchial cryobiopsies sample the middle third of the lung tissue between the large airways and the pleura ~1.0 cm from the visceral pleura. In practice, more peripheral lung tissue, including visceral pleura itself, is not infrequently encountered (Figures 6 and 7). In the large study reported by Ravaglia et al, approximately 30% of the cases showed the presence of visceral pleura. In addition, one may rarely encounter parietal pleura and/or even chest wall skeletal muscle in a transbronchial cryobiopsy. As with other biopsy techniques, including forceps biopsy, the presence of medium-sized vessels may correlate with clinical evidence of hemorrhage at the time of the procedure.

WHAT ARE THE COMPLICATIONS FOR PATIENTS FROM TRANSBRONCHIAL CRYOBIOPSY PROCEDURES?

The overall list of complications of lung biopsies and their relative significance in transbronchial cryobiopsy and surgical lung biopsy are shown in Table 2. Events at the top of Table 2 tend to be the most frequent, whereas those toward the bottom are the most serious.
Given the relative frequency of visceral pleural tissues in transbronchial cryobiopsies, it is not surprising that the rate of pneumothorax is relatively high; 10% in a large literature review of almost 1000 patients and 20% (60 of 297 patients) in the large series from Forli, Italy. The figure of 20% is notable because it is significantly lower than the 30% of cases (92 of 310; S.T., unpublished observations, June 2016) in which visceral pleura was identified histologically from the same institution during nearly the same period.

Death following SLBX is significant. In a recent study by Hutchinson et al., during an 11-year period there were 9491 deaths following surgical lung biopsy. Death occurred in 1.7% of patients following elective procedures and in 16% following non-elective procedures (ie, a "sicker" population of patients). The results to date for cryobiopsy are much more favorable: death following the procedure occurred in 0.1% (1 of 994 patients).

If one takes the findings from the large Forli study and looks at the frequency of complications listed in Table 2, the results are shown in Table 3. Although not captured by the literature, mild bleeding is frequently observed with cryobiopsy. With the preventive use of Fogarty we observed moderate bleeding, defined as bleeding that required a prolonged use of Fogarty (3–20 minutes) or the instillation of saline water and/or antihemorrhagic drugs, in 5.5% (13 of 297) of patients (S.T., unpublished observations, June 2016).

In the published meta-analysis, moderate bleeding was reported in 7 of 12 studies, with a pooled estimate of 12%. Severe bleeding (requiring blood transfusion or intensive care unit admission) to date has never been reported. Even if unlikely, severe bleeding is a serious and potentially lethal complication, and we strongly recommend the use of a prophylactic bronchial blocker in all cases.

Comparing all adverse events, excluding pneumothorax, cryobiopsy was significantly better than SLBX. This difference would remain significant even when one considers that a minority of patients who have nondiagnostic cryobiopsies may ultimately need an SLBX to achieve a diagnosis. In addition, patients who received cryobiopsy in the large Forli study had a shorter hospital stay than those who received SLBX (P < .001).

**HOW SHOULD TRANSBRONCHIAL CRYOBIOPSIES BE INTERPRETED?**

In the absence of specific guidelines, we would recommend interpreting transbronchial cryobiopsies by the same criteria that one applies to surgical lung biopsies. Simplistically, they should be thought of as a small SLBX rather than a large forceps transbronchial biopsy (TBBx) to help overcome subjective bias in...
assuming that forceps TBBx is often nondiagnostic and therefore should be approached with caution. With cryobiopsy, one should expect a somewhat lower diagnostic yield than with surgical lung biopsies, but it will be appreciably higher than transbronchial forceps biopsies.

Our approach to cryobiopsies involves assigning a “low” or “high” confidence to our diagnostic impressions, acknowledging that cryobiopsies are smaller than video-assisted surgical/video-assisted thoracoscopic surgical biopsies and thus may convey less histologic information. This approach also provides information to the multidisciplinary team for MDD. Knowing that cases will go through MDD reminds the pathologist that the histologic impressions can be supported (or refuted) from other information presented in the MDD.

Interobserver agreement between pathologists looking at cryobiopsy is relatively good. The weighted $\kappa$ coefficient comparing 3 pathologists’ first choice diagnosis from the large Forli study was 0.63 (S.T., unpublished observations, March 2016), a figure that compares favorably with similar studies in the setting of interstitial lung disease. The studies are just beginning to come out on the clinical utility of cryobiopsy in the setting of multidisciplinary discussion for diffuse lung disease. In the study by Casoni et al, 69 cases of fibrosing diffuse parenchymal lung disease with nondiagnostic high-resolution computed tomography were studied. Six cases were considered inadequate or nondiagnostic. Of the remaining 63, a pathologic diagnosis of usual interstitial pneumonia (UIP) was favored in 47 (36 with high confidence and 11 with low confidence) and other diagnoses favored in 16, most being nonspecific interstitial pneumonia. Of the 36 cases with high histologic confidence, 17 were regarded as idiopathic pulmonary fibrosis (IPF) and 19 as possible IPF. Of the 11 cases of UIP with low confidence, the final MDD diagnosis was IPF in 3 and unclassifiable in 8. Thus, the findings of this study confirm that cryobiopsy adds significant value, but it is short of that of surgical lung biopsy. From a practical point of view one could consider these data as supporting cryobiopsy as an initial diagnostic procedure and reserving surgical lung biopsy for a minority of cases in which MDD diagnosis could not be made.

Hagmeyer et al came to the same conclusion: that the findings from transbronchial cryobiopsy could dispense with the need for surgical lung biopsy in a proportion of cases.

Probably the most compelling study confirming the diagnostic usefulness of cryobiopsy is that by Tomassetti et al, in which 117 patients with fibrotic interstitial lung disease without a UIP pattern on high-resolution computed tomography were evaluated. A total of 58 patients underwent cryobiopsy, and 59 underwent surgical lung biopsy. The cases were studied in a format similar to that used by Flaherty et al, in which clinicians’ diagnoses were tracked as information was added in a stepwise fashion up to the point that the cases were discussed in a multidisciplinary session. In this format, an individual’s confidence of diagnosis was tracked as information was added, including clinical history, high-resolution computed tomography

CLINICAL USEFULNESS OF CRYOBIOPSY

Cryobiopsies are here to stay and, like it or not, we will be getting them to interpret.

The studies are just beginning to come out on the clinical utility of cryobiopsy in the setting of multidisciplinary discussion for diffuse lung disease. In the study by Casoni et al, 69 cases of fibrosing diffuse parenchymal lung disease with nondiagnostic high-resolution computed tomography were studied. Six cases were considered inadequate or nondiagnostic. Of the remaining 63, a pathologic diagnosis of usual interstitial pneumonia (UIP) was favored in 47 (36 with high confidence and 11 with low confidence) and other diagnoses favored in 16, most being nonspecific interstitial pneumonia. Of the 36 cases with high histologic confidence, 17 were regarded as idiopathic pulmonary fibrosis (IPF) and 19 as possible IPF. Of the 11 cases of UIP with low confidence, the final MDD diagnosis was IPF in 3 and unclassifiable in 8. Thus, the findings of this study confirm that cryobiopsy adds significant value, but it is short of that of surgical lung biopsy. From a practical point of view one could consider these data as supporting cryobiopsy as an initial diagnostic procedure and reserving surgical lung biopsy for a minority of cases in which MDD diagnosis could not be made.

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**Figure 12.** Eosinophilic pneumonia in a transbronchial cryobiopsy. The scanning power shows well-preserved lung tissue without any crush artifact and with diffuse airspace filling by cells and scattered lymphoid follicles (A). Slightly higher-power microscopy shows similar features with some associated alveolar septal widening and type 2 cell metaplasia (B). At high power (C), nests of eosinophils are easily seen (right upper), and there are scattered intra-alveolar giant cells, an occasional finding in eosinophilic pneumonia. The histologic and cytologic features in this case are virtually identical to those that would be encountered in a surgical lung biopsy (hematoxylin-eosin, original magnifications ×40 [A], ×60 [B], and ×300 [C]).
findings, pathologic findings, and finally full multidisciplinary discussion. The findings of histopathology, including either cryobiopsy or surgical biopsy, comprised part of the MDD discussion, and the results of the discussion and MDD determination for the cryobiopsy cases were compared to those of SLBx cases. The results for IPF MDD diagnosis were not statistically significantly different from the histopathologic findings of both cryobiopsy and surgical lung biopsy, providing added value.12

UIP/IPF is the most common fibrosing idiopathic interstitial pneumonia, and that diagnosis comprises the emphasis of most studies. The number of non-UIP/IPF cases is limited, but anecdotal observations on relatively small numbers suggest that cryobiopsy is also potentially useful in these settings as well.

The ultimate proof of the value of cryobiopsy in the setting of interstitial lung disease will be showing that it can stratify patients prognostically. Preliminary observations from the large Forli study have shown that cryobiopsy can do just that in cases confirmed as IPF by MDD in comparison with non-IPF patients, with a statistical significance of \( P = .01 \) (S.T. et al, unpublished observations, June 2016). Further studies will, of course, need to confirm these findings.

**CRYOBIOPSY: FINAL CONSIDERATIONS**

Any new test is controversial, and cryobiopsy is no exception: it is considered by some to be a step forward,8 and by others to be a step backward.24 Concerns primarily revolve around safety and diagnostic usefulness that fall short of SLBx. The discussion is one of risk versus benefits.
that will play out for some time. With this in mind, there are some points that we would like to emphasize:

- Properly performed cryobiopsy procedures should provide specimens at least 0.5 cm in diameter.
- SLBx is not without appreciable risk, and readers are reminded of the study by Hutchinson et al. There were more than 9400 deaths in the United States from surgical lung biopsies in the period from 2000 to 2011, with an in-hospital mortality of 1.7% for elective procedures and 16% for nonelective procedures. This compares to a mortality of 0.1% to date for cryobiopsy. 
- If one models risk or mortality in scenarios where cryobiopsy is done first and then followed by SLBx if the cryobiopsy is nondiagnostic, the final mortality is still lower than with SLBx as the sole diagnostic procedure.

Although surgical lung biopsy is a relatively common procedure at many institutions in North America, in many practice settings it is often not an option, and cryobiopsy might be an acceptable alternative in those settings.

Inherent in the discussion of SLBx versus cryobiopsy is that SLBx represents the gold standard to which cryobiopsy should be compared. But was SLBx ever proven against a gold standard? Early studies supporting the acceptance of SLBx primarily showed that it was more likely to give a “diagnosis” in comparison with other biopsy techniques available at the time. The “diagnosis” was made by expert pathologists or taken from pathology reports. Currently, one could use lung explants to validate SLBx, but there are relatively few such studies. In the study by Katzenstein et al of 20 total cases, there were 19 UIP cases—all showed an explant diagnosis of UIP, whereas the cryobiopsy primarily showed that it was more likely to give a “straightforward UIP.” In the study by Rabeyrin et al, which included 22 cases, there were 10 cases that showed a definite UIP pattern in the explant, and 5 of these had a prior biopsy, and in none of those was a definite diagnosis of UIP made. These are small studies and there are obviously issues of the time between biopsy and explant, but they do point out that surgical lung biopsies have their own risk of sampling error compared with a much larger specimen.

Finally, we are reminded that surgical lung biopsies themselves are actually relatively small pieces of 2 very large organs, and a good-sized surgical lung biopsy still represents less than 0.5% of the lung volume (based on the assumption that normal lung volume is 6000 mL [6000 cm³], and a good-sized surgical lung biopsy is ~25 cm³ [4 × 3 × 2 cm³]).

References