Transbronchial Cryobiopsy in Diffuse Lung Disease

*Overview and Update*

Thomas V. Colby MD
Sara Tomassetti MD

**Disclosure**

Dr. Colby has nothing to disclose

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**Historic Background of Cryobiopsy**

- A correct diagnosis of IIPs and particularly Fibrosing Interstitial Lung Diseases (f-ILDs) requires a multidisciplinary approach and, when appropriate, integration of CR data with histological findings.

- Surgical lung biopsy is still considered the gold standard to provide lung samples large enough for identification of complex patterns such as usual interstitial pneumonitis (UIP) and other f-ILDs.

- However, this procedure has significant morbidity and mortality and is performed in minority of patients.
From surgery to less invasive biopsy methods.

- Surgical Lung Biopsy
- Transbronchial Lung Biopsy
- Bronchoscopic Lung Cryobiopsy

UIP-pattern can be identified in a minority of TBBx with a very high specificity (92-100%) and positive pred value (86-100%)

Why is TBBx not used in fibrotic ILD diagnosis

- Very Low Sensitivity (30%)

- Low negative predictive value (46%-55%): the presence of TBB findings consistent with alternative diagnosis (ie. DIP, NSIP, ALI) does not rule out UIP.

- Complications: pneumothorax 8% (5/64), requiring chest tube 1/5 (20%). One pneumomediastinum (2%).
Cryobiopsy: the technique.

Cryobiopsy: The equipment

Different sizes of Cryoprobes

2.4 mm  1.9 mm

The gas at the tip expands due to the sudden difference in pressure (Joule-Thomson effect), resulting in a drop in temperature at the tip of the probe.
Standardization is needed ...

Deep sedation/Conscious sedation?

Rigid/Flexible?

How many samples? How many segments? Different lobes?

Standardization is needed ... ongoing international protocol

Deep sedation/Conscious sedation?

Rigid/Flexible?

How many samples? How many segments? Different lobes?
2 in each lobe, at least two lobes (min 4 max 6)

Hetzel, Poletti, Wells, Costabel et al, European Multicenter Study

The endoscopy room

The anesthesiologist 1 bronchoscopist 2 endoscopy nurses

Fogarty positioning through the rigid bronchoscope
The cryoprobe is inserted through the operative channel of the fibrobronchoscope.

Transbronchial Cryobiopsy

2. Pathologic Specimens

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Cryobiopsy: the specimens

Cryobiopsy: Size of specimens

<table>
<thead>
<tr>
<th>STUDY</th>
<th># Patients</th>
<th>Mean Size (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babiak 2009</td>
<td>41</td>
<td>15.1</td>
</tr>
<tr>
<td>Fruchter 2013 (Lung Tx)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Kropski 2013</td>
<td>25</td>
<td>64.2</td>
</tr>
<tr>
<td>Casoni 2014</td>
<td>69</td>
<td>43.1</td>
</tr>
<tr>
<td>Pajares 2014</td>
<td>39</td>
<td>14.7</td>
</tr>
<tr>
<td>Griff 2014</td>
<td>52</td>
<td>30.4</td>
</tr>
<tr>
<td>Forli Study (in prep)</td>
<td>310</td>
<td>44.8</td>
</tr>
</tbody>
</table>

BUT....Not all cryobiopsies are created equal. A bad cryobiopsy is no better than a bad TBBx.
Artifact: “Implanted” Bronchiolar Epith.

Other Tissues found in Cryobx’s

Transbronchial Cryobiopsy

3. Complications

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Events complicating lung biopsy for ILDs

Most Frequent
- Pneumothorax
- Prolonged air leak
- Post procedure chest pain
- Bleeding
- Transient Resp. Failure NOS
- Fever
- Pneumonia/Empyema
- Acute Ex / Death

Most Serious
Events complicating lung biopsy for ILDs

- Pneumothorax
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- Acute Ex / Death

PNX is the most frequent procedure related event

CRYO, N=297
- Pneumothorax, 20% (N=60)
- Prolonged air leak >5 days post procedure
- Chest drainage 15% (46/297), 76% (46/60)

VATS, N=150
- Pneumothorax is part of the procedure,
  -> 100% chest drainage

Ravaglia C et al, Respiration 2016

Prolonged air leak (>5 days post procedure)

Cryo 0.3% (1§/297)
VATS 3.3% (5*/150)
P 0.035

§ 1 Prolonged chest tube
* 3 Prolonged chest tube; 1 emopatch; 1 surgical revision

Ravaglia C et al, Respiration 2016

Cryo: less frequent complications

Bleeding (not severe)* 13 (5.5%)
Resp failure NOS 2§ (0.7%)
Seizures 2§ (0.7%)

* prolonged Fogarty (3 to 20min); saline+antihaemorr drug.

Ravaglia C et al, Respiration 2016
Complications not found with Cryo compared to VATS

<table>
<thead>
<tr>
<th></th>
<th>Cryo (297)</th>
<th>VATS (150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever</td>
<td>0</td>
<td>7 (4.37%)</td>
</tr>
<tr>
<td>Pneumonia/empyema</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Chest wall paresthesia</td>
<td>0</td>
<td>52%§</td>
</tr>
</tbody>
</table>


Cryo has significantly less complications and shorter hospitalization compared to VATS

All adverse events, excluding PNX:
- Cryo 6/297 0.2%  
- VATS 20/150 13%  

\[ P<0.0001 \]

Median time of Hospitalization, days:
- Cryo 2.6 (0-17)  
- VATS 6.1 (3-48)  

\[ P<0.0001 \]

Mortality following SLB for ILD in the USA: 2000-2011

- 9,700 deaths (95% CI 9,209-10,192)
- overall in-hospital mortality of 6.4% (95% CI 6.1%-6.7%)

\[ \text{Hutchinson JP et al, AJRCCM 2015} \]
Mortality following SLB for ILD in the USA: 2000-2011

Hutchinson JP et al, AJRCCM 2015

Mortality following lung Bx for ILD at our center: 2003-2015

Ravaglia C et al, Respiration 2016

Mortality following CryoBx for ILD
Review of literature (Medline & Embase)

from 406 ARTICLES to
15 STUDIES FOR SAFETY ANALYSIS,
INCLUDING 994 PATIENTS: only one death reported

Mortality for cryobiopsy 0.1%

Ravaglia C et al, Respiration 2016

Cryo+/-VATS appears to be lower than VATS only

The mortality of a combined diagnostic algorithm
Cryo+/VATS appears to be lower than VATS only

Cryo

VATS

20% SUBSEQUENT VATS

Mortality 0.1%

Mortality 0.34%

Mortality 1.7%

Mortality 0.44%
Transbronchial Cryobiopsy

4. Pathologic Diagnosis

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BOTTOM LINE – IT WORKS!!
Hypersensitivity pneumonitis

UIP

Smoking Related ILD

Questions You Should Have

How easy are they to interpret?
Comparison to TTBx?
Comparison to Surgical Lung Biopsy?
  Diagnostic accuracy
  Confidence of diagnosis
TB Cryobiopsy vs. Forceps TBBx

Randomized trial published in 2014*
77 pts randomized

<table>
<thead>
<tr>
<th>Technique</th>
<th>Specimen Size mm²</th>
<th>Histologic Dx</th>
<th>MMD Dx</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forceps TBBx</td>
<td>3.3 +/- 4.1</td>
<td>74%</td>
<td>51%</td>
<td>1. Bleeding &gt; in Cryobx (NS)</td>
</tr>
<tr>
<td>TB Cryobiopsy</td>
<td>14.7 +/- 11</td>
<td>34%</td>
<td>29%</td>
<td>2. PTX similar</td>
</tr>
</tbody>
</table>

Cryobiopsy clearly superior to traditional Forceps TBBx

(* Pajares et.al. Respirology 2014; 19: 900-906)

Ideally Cryo should be proven against SLBx

But was SLBx ever proven as sueful against a gold standard ? NO

Cryobiopsies

(Forli Study 3/11 – 1/15)

524 cryobiopsies in 310 patients with ILD and non-diagnostic clinical-radiologic findings
1-6 Bx’s per patient
Biopsies inadequate in 33 pts (10.6%)
(Normal tissue or minimal changes)
“Adequate” in 277 pts (89.4%)

Here is what we were dealing with: photo of 21 consecutive specimens.

Forli Study: Slide Review

Two reviewers: T Colby, A Cavazza
Blinded to clinical and other pathologist
Histologic criteria: As for a SLBx*
First, second, third choice diagnoses
Confidence (Hi vs Lo) of primary diagnosis

* Some SLBx’s are no larger than a cryobiopsy
AC Diagnoses after MDD

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Diagnosis after MDD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP Hi Conf</td>
<td>58 IPF</td>
<td>6 other diagnoses</td>
</tr>
<tr>
<td>UIP Lo Conf</td>
<td>27 IPF</td>
<td>19 other diagnoses</td>
</tr>
<tr>
<td>NSIP/OP Lo Conf</td>
<td>14 NSIP/OP</td>
<td>22 other diagnoses</td>
</tr>
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</table>

AC vs TVC Diagnoses

<table>
<thead>
<tr>
<th>AC Diagnoses</th>
<th>TVC Diagnoses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP Hi - 64</td>
<td>UIP Hi and Lo – 57</td>
<td>7 other Dx's</td>
</tr>
<tr>
<td>UIP Lo - 46</td>
<td>UIP Hi and Lo – 35</td>
<td>11 other Dx's</td>
</tr>
</tbody>
</table>

TVC and AC Agreement for UIP vs non-UIP
Kappa = 0.72

Pathologist #1 (AC)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>Hi Conf (%)</th>
<th>Lo Conf (%)</th>
<th>TOTAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>23</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>NSIP/OP</td>
<td>0</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>HP</td>
<td>4</td>
<td>7.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Rb/DIP</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>PLCH</td>
<td>1.5</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>5.5</td>
<td>2 (grans NOS)</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Transbronchial Cryobiopsy

5. Clinical management implications

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The utility of lung Bx for ILDs

Lung Bx is not always indicated: histopathology is required only when the clinical radiological picture does not allow a confident diagnosis of ILD (e.g. a half of IPF cases).

Histopathology alone is insufficient to diagnose ILDs: histopathology is no longer the diagnostic gold standard.

MDD is currently the diagnostic gold standard, and the role of pathology is to provide useful information to the MDT.

What supports the use of SLB in ILD

Diagnostic accuracy (sens, spec, ppv and npv) of SLB has never been measured ... what would be the gold standard to test SLB, the whole lung ??

The use of SLB is supported by:
- Historical and cultural heritage
- Studies showing that:
  1. SLB provides useful informations in the MD diagnosis of ILDs
  2. SLB can predict prognosis of ILDs

What supports the use of Cryo in ILD:

- 1. diagnostic accuracy
- 2. Impact in the MDD
- 3. Prognostic significance

Does Cryo impact the multidisciplinary diagnosis of IPF?

AIM to evaluate the impact of Cryo on:
1. MDT diagnostic impression
2. inter-observer agreement
3. Observers’ self reported confidence levels

and to COMPARE CRYO TO SLB

Outcome measures
Measure the change of variables 1, 2 and 3 change after addition of histopathology informations.

Methodology adopted from Flaherty KR et al, AJRCCM 2004

C= Wells AU, Costabel U
R= Sverzellati N, Carloni A
P= Colby TV, Cavazza A, Rossi G

<table>
<thead>
<tr>
<th>STEP</th>
<th>DATA</th>
<th>PARTICIPANTS</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>C + II</td>
<td>Individual</td>
</tr>
<tr>
<td>2</td>
<td>Clinical/Radiological data</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>C + R + P</td>
<td>Individual</td>
</tr>
<tr>
<td>4</td>
<td>BAL</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>C + R + P</td>
<td>Individual</td>
</tr>
<tr>
<td>8</td>
<td>FOLLOW-UP data</td>
<td>Group</td>
<td></td>
</tr>
</tbody>
</table>

17% of cases in the BLC group and 19% of cases in the SLB group were reclassified as IPF.
2. Kappa coefficient of agreement

![Graph showing Kappa coefficient of agreement](image)

**Tomassetti S et al, Am J Respir Crit Care Med, 2016**

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![Graph showing Kappa coefficient of agreement](image)

**Tomassetti S et al, Am J Respir Crit Care Med, 2016**

3. Observers’ self reported confidence levels

![Graph showing confidence levels](image)

**Tomassetti S et al, Am J Respir Crit Care Med, 2016**

Cryo has a meaningful impact on MDT diagnosis of ILDs
What supports the use of Cryo in ILD:

- diagnostic accuracy
- **prognostic significance**
- Impact in the MDD

Patients who underwent Bronchoscopic Lung Cryobiopsy between 2011 and 2014

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRANULOMATOSIS</td>
<td>20</td>
<td>6%</td>
</tr>
<tr>
<td>MALIGNANCIES</td>
<td>13</td>
<td>4%</td>
</tr>
<tr>
<td>OTHER</td>
<td>29</td>
<td>10%</td>
</tr>
</tbody>
</table>

Poletti V et al, unpublished

Weighted Kappa coefficient for first choice diagnosis

<table>
<thead>
<tr>
<th>Histologic pattern</th>
<th>AC-TC (95 CI 0.53-0.67)</th>
<th>TC-GR (95 CI 0.66-0.80)</th>
<th>GR-AC (95 CI 0.55-0.71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>0.67 (0.58-0.75)</td>
<td>0.74 (0.66-0.80)</td>
<td>0.64 (0.55-0.71)</td>
</tr>
<tr>
<td>NSIP</td>
<td>0.39 (0.28-0.52)</td>
<td>0.25 (0.16-0.38)</td>
<td>0.24 (0.14-0.38)</td>
</tr>
<tr>
<td>HP</td>
<td>0.26 (0.13-0.45)</td>
<td>0.30 (0.13-0.54)</td>
<td>0.31 (0.17-0.48)</td>
</tr>
<tr>
<td>SR-ILD</td>
<td>0.72 (0.50-0.87)</td>
<td>0.42 (0.29-0.58)</td>
<td>0.41 (0.27-0.56)</td>
</tr>
<tr>
<td>GRANULOMATOSIS</td>
<td>0.90 (0.68-0.98)</td>
<td>0.78 (0.56-0.92)</td>
<td>0.87 (0.65-0.97)</td>
</tr>
<tr>
<td>MALIGNANCIES</td>
<td>0.93 (0.64-1.00)</td>
<td>0.86 (0.56-0.97)</td>
<td>0.80 (0.51-0.95)</td>
</tr>
<tr>
<td>OTHER</td>
<td>0.62 (0.38-0.65)</td>
<td>0.39 (0.27-0.51)</td>
<td>0.40 (0.27-0.54)</td>
</tr>
<tr>
<td>NON DIAGNOSTIC</td>
<td>0.45 (0.29-0.61)</td>
<td>0.08 (0.01-0.28)</td>
<td>0.06 (0.01-0.23)</td>
</tr>
</tbody>
</table>

Cryo’s prognostic significance: histopathology alone

Poletti V et al, unpublished
Cryo's prognostic significance: histopathology alone

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**The MDT diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>INSIP</th>
<th>HP</th>
<th>CVD-ILD</th>
<th>SR-ILD</th>
<th>DRUG-REL</th>
<th>OTHER</th>
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<tbody>
<tr>
<td>UIP</td>
<td>116</td>
<td>95</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NSIP</td>
<td>34</td>
<td>2</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>HP</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>SR-ILD</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

TOTAL 191

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Cryo has prognostic significance

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Cryo: survival analysis by subgroups

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Median survival
IPF 50.5mo (47-53)
NOT IPF 56.6mo (55-57)
Cryo’s prognostic impact for ILD

Pathologists recognize on Cryo histologic patterns that carry prognostic significance, as for SLB, the multidisciplinary approach is helpful to improve prognostication and to correctly manage those patients.

What supports the use of Cryo in ILD:

- diagnostic accuracy
- prognostic significance
- impact in the MDD

Cryo and MD Diagnosis of f-ILDs

key questions

Does Cryo impact the multidisciplinary diagnosis of IPF?

and

How do Cryo and SLB compare in the scenario of the dynamic interactions between clinicians, radiologists and pathologists?

Tomassetti S et al, AJRCCM 2015
Does Cryo impact the multidisciplinary diagnosis of IPF?

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Tomassetti S et al, Am J Respir Crit Care Med, 2016

1. MDT diagnostic impression

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<tr>
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<th>DISCUSSION</th>
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<tbody>
<tr>
<td>1</td>
<td>C + R</td>
<td>Individual</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>C + R</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C + R</td>
<td>Individual</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C + R</td>
<td>Individual</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>C + R</td>
<td>Group</td>
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<tr>
<td>6</td>
<td>C + R</td>
<td>Individual</td>
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<tr>
<td>7</td>
<td>C + R</td>
<td>Group</td>
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</tr>
<tr>
<td>8</td>
<td>C + R</td>
<td>Group</td>
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2. Kappa coefficient of agreement

Tomassetti S et al, Am J Respir Crit Care Med, 2016
2. Kappa coefficient of agreement

<table>
<thead>
<tr>
<th>Step</th>
<th>Diagnosis</th>
<th>BLC</th>
<th>SLB</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.94</td>
<td>0.84</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>2</td>
<td>0.80</td>
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<td>0.74</td>
<td>0.74</td>
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<tr>
<td>3</td>
<td>0.86</td>
<td>0.74</td>
<td>0.74</td>
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<tr>
<td>4</td>
<td>0.89</td>
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<tr>
<td>5</td>
<td>0.91</td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
</tr>
</tbody>
</table>

3. Observers’ self reported confidence levels

Tomassetti S et al, Am J Respir Crit Care Med, 2016

Conclusion

Cryobiopsy in ILDs is:
- Feasible (diagnostic yield, approx 80%)
- Safe (mortality, approx 0.1%)
- and has a meaningful impact in the scenario of dynamic interactions of the MDT, comparable to that of SLB.

Future guidelines should implement Cryo in the diagnostic algorithm of ILDs diagnosis.

References


