Interstitial lung disease

Belfast Pathology
Belfast
Tuesday 20th June 2017

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An approach to the diagnosis of interstitial pneumonias

Interstitial pneumonias (1999)

Too much terminology – Not enough disease
- UIP - Usual interstitial pneumonia
- DIP - Desquamative interstitial pneumonia
- BIP - With bronchiolitis obliterans
- LIP - Lymphocytic interstitial pneumonia
- GIP - Giant cell interstitial pneumonia
- DAD - Diffuse alveolar damage
- AIP - Acute interstitial pneumonia
- Granulomatous interstitial pneumonia
- Hypersensitivity pneumonia
- Hamman-Rich Syndrome
- COP - Cryptogenic organising pneumonia
- BOS - Bronchiolitis obliterans organising pneumonia
- CPI - Chronic pneunomitis of infancy
- CPI - Cellular pneumonitis of infancy
- NSIP - Non-specific interstitial pneumonia
- MIP - Mixed interstitial pneumonia
- IDP - IDIOPATHIC PULMONARY FIBROSIS
- FIP - FIBROSING ALVEOLITIS
- IP - IDIOPATHIC INTERSTITIAL PNEUMONIA

2002 – AREAS OF UNCERTAINTY

COP: Areas of Uncertainty
- What are the incidence and prevalence of the disease?
- What is the role of transbronchial lung biopsy in the diagnosis of COP?
- How frequent are relapses in patients with COP? What impact do recurrences have on long-term outcomes?
- How does the timing of treatment alter the clinical course of patients with COP and the frequency of recurrences?
- Does spontaneous clinical improvement or resolution occur?
- What are the features that distinguish primary COP from secondary COP (that is associated with another process)?
- Why does this fibrotic process resolve, whereas the fibroblastic foot of the UIP lesion lead to progressive end-stage fibrosis?

Many of these areas of uncertainty outlined in 2002 have now been addressed in the literature – so now they are no longer uncertain
However, new areas of uncertainty are being generated

At ten years, it was considered timely to review the 2002 consensus statement.....
**Revised ATS/ERS IIP Classification**
(to be viewed as a supplement to the 2002 document)
*Am J Respir Crit Care Med 2013; 188: 733-748*

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<thead>
<tr>
<th>Clinical Radiologic Pathologic Diagnosis</th>
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<tr>
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<tr>
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**ATS/ERS consensus classification of idiopathic interstitial pneumonias**
*Am J Respir Crit Care Med 2015; 188: 733-748*

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<td>Cryptogenic organising pneumonia</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
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</tbody>
</table>

**Why so little change to the basic structure of the IIP classification?**

1. Global uptake in patient management
c2. Clinical, imaging and histopathology.
3. ATS/ERS classification is reproducible in clinical practice

**Revised ATS/ERS IIP Classification**
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CASE 1

Age: 60, male
Two years of exertional dyspnoea
No obvious steroid effect on disease course
Bilateral basal crackles, not clubbed
Life-long non-smoker
No CTD symptoms
No occupational exposures
BAL: normal differential
Restrictive PFT. FVC 61%, DCO 57%

CASE 1

Usual Interstitial Pneumonia (UIP)

UIP – Patchy involvement of the lung by fibrosis. Intervening lung is normal or nearly normal.
MINOR HISTOPATHOLOGICAL FEATURES IN USUAL INTERSTITIAL PNEUMONIA

**Dense scar**

**Micro Honeycombing**

THIS IS UIP

UIP diagnostic here

**Fibroblast focus**

**Lobule destroyed**

ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management.


Final agreement was better within academic centers (kappa 0.55-0.71) than within community centers (kappa 0.32-0.44).

**Fibroblastic foci in UIP...**


A The frequency of fibroblastic foci in usual interstitial pneumonia and their relationship to disease progression. Nicholson AG et al. AJRCCM 2002; 166: 173-177

Aetiology and treatment of UIP/CFA

- N-acetyl cysteine
- Nintedanib
- Pirfenidone
- Steroids and cyclophosphamide

IPF response to therapy

- Valeyre D et al. Am J Respir Crit Care Med 2010;181:A6026

CASE 2

- 57 year old female never smoker.
- Increasing shortness of breath
- History of “Farmer’s Lung” 20 years previously treated with steroids.
- Arthritis for 10 years (Autoimmune screen negative).
- On Omeprazole and Fesoterodine.

Case presentation

- CT showed patchy ground-glass opacifications in mid and upper zones.
- BAL
  - Eosinophilia (17%) and mild neutrophilia (6%). No lymphocytosis (8%).
- Lung function tests:
  - Moderate restrictive defect
  - Reduction in lung volumes and impairment of gas transfer.
  - Resting hypoxaemia on blood gas testing.
  - These changes are in keeping with the known interstitial lung disease.
Case presentation

Cryobiopsy undertaken.

Case 2

The features favour fibrotic non-specific interstitial pneumonia (NSIP), possibly secondary to progression of organising pneumonia.

MDT REVIEW: Most likely to be F-NSIP. No serological evidence of connective tissue disease but could be associated given 10 year history of arthritis. Possibility of a drug reaction also considered.

F-NSIP - ? idiopathic, ? secondary to CTD or drug reaction
Treated with immunosuppression and stable at 3 months.

ATS/ERS subdivision of NSIP

Cellular

Fibrotic

ATS/ERS workshop. AJRCCM 2008;177:1338-47
Sixty-seven cases (out of 305)
Mean age was 52 years, 67% were women, 69% were never smokers.
Dyspnea (96%) and cough (87%); 69% had restriction.
HRCT - lower lung predominant, reticular pattern (87%) with traction bronchiectasis (82%) and volume loss (77%).
Five year survival was 82.3%.

Distinct clinical entity that occurs mostly in middle-aged women who are never smokers. The prognosis of NSIP is very good.

CT-Path of NSIP
OP and cellular NSIP

NSIP versus DIP
Smoking-related interstitial lung disease

Histopathology: F-NSIP

- MDT review:
  - HRCT favours chr HP
  - History of bird exposure
- Levels cut on blocké

> FINAL DIAGNOSIS:
  > CHR HP

ATS/ERS workshop: ‘Relatively few at the centre of the circle’
A SOME PATIENTS WITH IDIOPATHIC NSIP SUBSEQUENTLY DEVELOP COLLAGEN VASCULAR DISEASES


17% developed CVD during the follow-up period (5.5 ± 5.0 years);
DM = 3, DM/SSc = 1, RA = 1

A SUBDIVISION OF PATIENTS WITH A BIPOLAR SHOWING NSIP PROVIDES PROGNOSTIC INFORMATION


Bronchoscopic biopsy has lower complication rates and mortality rates compared to SLB (7)

A BRONCHOSPINAL SYNDROME IN NSIP


DIP showed greater extents of eosinophilic, follicular hyperplasia and fibrosis
No difference histologically between smokers and non-smokers with DIP
Some cases of DIP are truly idiopathic.

A Best kept as separate histologic patterns

A PROS OF CRYOBIOPSY


Survival was better for UCTD than for idiopathic NSIP

A INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES (IPAF) - A NEW ENTITY


A a morphologic domain consisting of specific chest imaging, histopathological features
A designation of IPAF should be used to identify individuals with IP and features suggestive of, but not definitive for, a CTD.

A CONS OF CRYOBIOPSY

Ravaglia et al. Interstitial pneumonia subdivision into pathological subgroups is clinically relevant

Some cases of DIP are truly idiopathic

A Should we combine RB-ILD and DIP into SR-IP?


Nearly all cases of RB were in smokers but only 60% of DIP were smokers (probably nearer 60%)
DIP showed greater extents of eosinophilic, follicular hyperplasia and fibrosis
No difference histologically between smokers and non-smokers with DIP
Some cases of DIP are truly idiopathic.

A Best kept as separate histologic patterns

A Should we use the term SR-IP?

More review articles than investigative papers

Kawabata Y et al Histopathology 2002;38:707. Smoking-related changes in lung resections
Kawabata et al Human Pathology 2010;41:216-25. Clinically apparent emphysema

Vassallo RJ Chest 2003; 123: 859-865. The overlap between respiratory bronchiolitis and nonspecific interstitial pneumonia prevents reliance on histologic high-resolution CT. Anatomic and functional correlations

A ATIS/ERS ILD workshop ...

Appropriate clinical categorisation for cases with a histological patterns of RB or DIP in the correct clin-radiopath context

Histopathologists should describe patterns present

A USAGE OF CRYOBIOPSIES

Hernández Aguado et al. Validation of bronchoscopic cryobiopsy for Interstitial Lung Disease Diagnosis: A Perspective From Members of the Pulmonary Pathology Society Arch Pathol Lab Med. 2016;140:1193-9

Ravaglia et al. Transbronchial cryobiopsy has a meaningful impact on diagnostic confidence in NSIP. Il Clinico. 2016;50:20-6

Cryobiopsy has lower diagnostic yield than surgical lung biopsy in the diagnostic algorithm of interstitial lung disease.

In 75% of cases, SLB showed no additional benefits

Nearly all cases of RB were in smokers but only 60% of DIP were smokers (probably nearer 60%)
DIP showed greater extents of eosinophilic, follicular hyperplasia and fibrosis
No difference histologically between smokers and non-smokers with DIP
Some cases of DIP are truly idiopathic.

A Best kept as separate histologic patterns
**Acute exacerbation of UIP/IPF**

**Definition:**
An acute, clinically-significant deterioration in lung function of undiagnosable cause in a patient with underlying IPF.

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**CT-Path of OP**

**Noise analysis (2 observers per differential diagnosis)**

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<th>Condition</th>
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<th>OP</th>
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**Progression to interstitial fibrosis**
Needs HRCT/chin correlation and sometimes longitudinal behaviour

Presence of interstitial fibrosis is an adverse prognostic indicator

**CASE 3**

50 year old female with ? ILD

Revised ATS/ERS IIP Classification
(to be viewed as a supplement to the 2002 document)

*Am J Respir Crit Care Med* 2013; 188: 733-748

### Clinical Radiologic Pathologic Diagnosis

- Idiopathic Pulmonary Fibrosis
- Idiopathic Nonspecific Interstitial Pneumonia
- Respiratory Bronchiolitis Interstitial Lung Disease
- Desquamative Interstitial Pneumonia
- Cryptogenic Organizing Pneumonia
- Acute Interstitial Pneumonia

### Rare IIP

- Idiopathic LIP
- Idiopathic pleuroparenchymal fibroelastosis

### Rare Histologic Patterns

- Acute fibrinous & organizing pneumonia
- Bronchiocentric patterns of IP

### Unclassifiable IIP

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**CASE 3**

Pleuroparenchymal fibroelastosis (PPFE)
Pleuroparenchymal Fibroelastosis

- Idiopathic setting
- Sufficient evidence for PPFE to be recognised as a distinct idiopathic clin-radiopath entity
- Wider spectrum of appearances than in published series
- Distant parenchymal fibrosis frequent
- Non-idiopathic cases as causes and associations emerge
- Not as rare as initially thought (n=40 since 2012)

Clinical data of cases in Japanese literature

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<th>Year</th>
<th>Reporter</th>
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<th>PM/PT</th>
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Total: 22 cases

Pleuroparenchymal fibroelastosis

- Sufficient evidence for PPFE to be recognised as a distinct idiopathic clin-radiopath entity
- Wider spectrum of appearances than in published series
- Not as rare as initially thought (n=40 since 2012)

Acute fibrinous and organizing pneumonia (AFOP)
Beasley M et al. Arch Path Lab Med 2002 (AFIP)

Acute fibrinous organising pneumonia
Critical review....
Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease

2004;28:62-8

IDIOPATHIC BRONCHIOLOCENTRIC INTERSTITIAL PNEUMONIA (BrIP)

(Yousem and Dacic in Mod Pathol
2002; 15:1148-1153)

PERIBRONCHIOLAR METAPLASIA AND FIBROSIS

(Fukuoka et al. in AJSP 2005;29:948-954)

Bronchiolocentric interstitial pneumonias...
...adapted from Colby synopsis (USCAP 2008) and critical review

- Female predilection and most patients in their 50s and 60s
- Mortality between series is variable (0% - 45%). No statistical differences in follow-up between series

LITERATURE EVIDENCE
- Sufficient for recognition as a histological pattern
- Not sufficient for a clinical entity - more evidence required.

Important differential diagnostic considerations

- Coexisting patterns
- Hypersensitivity pneumonitis
- Collagen-vascular disease-associated IPs
- Familial interstitial pneumonias

Unclassifiable pneumonias

Molecular aspects of IIPs

25% of cases rejected as not UIP by reference pathologists
50% F-NSIP
23% EAA (8% in total)

Chronic HP versus UIP/IPF....

BUILD 1 drug trial

Patient subsets

All patients
Placebo
Bosentan

Diagnosis of UIP/IPF by local pathologist
At time reviewed by the central pathology panel
Cases confirmed as UIP/IPF by central pathology panel

20 or 20
60 or 60
60 or 60
60 or 60

CASE 4

54 year old female. SLE. Bilateral cystic lung disease with nodule in left lung

Buté

Robert Miller’s dog Christie

Inter-relationship of histologic patterns

- OP → F-NSIP
- DIP → F-NSIP
- DAD → OP → F-NSIP
- RB → DIP
- C-NSIP → LIP
- DIP does not progress to UIP

Pathologic patterns and survival in chronic HP

Churg et al. AJSP 2009;33:1765

50% F-NSIP
23% EAA (8% in total)
54 year old female. SLE. Bilateral cystic lung disease with nodule in left lung

DIFFUSE LYMPHOID HYPERPLASIA AND AMYLOIDOSIS WITH DEVELOPMENT OF MALT LYMPHOMA IN LEFT LUNG

Table 1: 2013 Revised ATS/ERS IIP Classification

- Rare idiopathic interstitial pneumonias
  - Idiopathic lymphoid interstitial pneumonia
  - Idiopathic pleuroparenchymal fibroelastosis

- Unclassifiable IIP

- Rare Histologic Patterns
  - (data insufficient for recognition clinically as IIP)
    - Acute fibrinous & organizing pneumonia
    - Bronchiocentric patterns of IP
The prevalence of interstitial pneumonias in patients with connective tissue diseases

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The same spectrum of patterns exists in CTDs as for idiopathic disease
- The prevalence differs overall (NSIP common)
- The prevalence of IP patterns differs for each CTD
- Treatment and prognosis differ from idiopathic disease

When to biopsy (will a biopsy add something...)

- "Unexpected" longitudinal behaviour
- Multiple anatomic compartments
- Risk of malignancy

- Drug reaction or CTD-related disease
- Prognostication
- Rare diseases

Clinicopathological correlation - LIP pattern

- Exclude lymphoma (light chain restriction/PCR).
- Exclude other diseases such as EAA. Look for clinical association.
- Infection (especially Pneumocystis carinii, hepatitis B, Epstein-Barr virus, HIV, CMV).
- Connective tissue disease, especially Sjögren’s syndrome, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, microscopic polyangiitis, chronic active hepatitis, primary biliary cirrhosis, Drug induced toxicity exposure.
- Other immunologic disorders: Autoimmune thyroiditis, myasthenia gravis, pernicious anemia, Hashimoto’s thyroiditis, chronic active hepatitis, primary biliary cirrhosis.

Is LIP a vanishing disease?

- Polychromatophilia: 3 of 15 in one series (Cha SI et al. ERJ 2006;28:364-9).

Other cases still exist.
The prevalence of interstitial pneumonias in patients with connective tissue diseases:

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++ = frequent, + = not infrequent, +/− = rare; ? = prevalence currently uncertain; * = Probable incidental to pulmonary symptoms.

Polymyositis-dermatomyositis-associated interstitial lung disease.

- 70 patients with ILD and either PM or DM.
- Jo 1 antibody present in 38%.
- Synchronous associated malignancy in 5.7%.
- NSIP in 18 of 22 patients (82%).
- DAD in 9%, OP in 4.5%, UIP in 4.5%.
- Survival was significantly better than idiopathic UIP.
- More consistent with survival in idiopathic NSIP.

Interstitial pneumonia in RA

- Pulmonary fibrosis seen in about <5% of patients.
- NSIP and follicular bronchiolitis are commonest histologic patterns, often superimposed in Brompton experience.
- Early studies suggest survival similar to idiopathic NSIP.

RA – NSIP, fibrotic + FB

Airway and pleura (no interstitial pneumonia)
Other anatomic compartments...

54 year old with rheumatoid arthritis and obstructive LFTs

Coexistent pathologies in same anatomic compartment:

Differential diagnoses in cystic lung disease....

Sjogren’s and lung cysts (1997 case)

Amyloidosis and lymphoid hyperplasia, Sjogren’s

Clinicopathologic approach to pulmonary amyloidosis

Ensure the amyloid subtype (AL)

COMPLETE SCREENING

SAP scan

CT

Echocardiography

Bone marrow investigation

Serum and urine studies

Immunohistochemical analysis of biopsy samples

More accurate prognostic data

In 2016 - Lymphocytosis on BAL and appropriate clinical/HRCT enough for confident diagnosis unless unexpected behaviour
Amyloidosis OR Light chain deposition disease (LCDD)
MZ NHL OR LIP (+ Sjogren’s syndrome)
Solid AND/OR cystic, localised OR multifocal

CASE 5
17 male, chronic autoimmune osteomyelitis, working as a tree surgeon

CASE 5
17 year old tree surgeon with pulmonary nodules and consolidation, ? ILD

FUNGAL INFECTION (ADIASPIROMYCOSIS)

Infections

- Viral infections
- Acute bacterial infections
- Chronic bacterial infections
- Fungal infections
- Parasitic infections

Histopathology is a useful adjunct to microbiology in identifying certain organisms. Histologic diagnosis is not always specific!

Communicate clinical suspicions (history of travel, contacts, immunosuppression) prior to sending specimens.

Discuss with pathologist/microbiologist to ensure correct specimens for investigation are undertaken.
Fungal infections - Identification

- Identification of fungi in tissue may be first point of recognition of diagnosis (patterns of fungal disease may mimic other entities, e.g. tumours).
- Most are opportunistic. Only a few are directly pathogenic to humans (e.g. C. Immitis). Consider immune compromise, especially in children.
- Varying patterns of disease (e.g. Aspergillus).
- Consider in differential of granulomatous inflammation.
- History of travel to endemic areas.
- Combination of microbiology and histology to obtain diagnosis (e.g. Mucormycosis).

CASE 5

FUNGAL INFECTION (ADIASPIROMYCOSIS) DUE TO CHRONIC GRANULOMATOUS DISEASE OF CHILDHOOD

Interstitial lung disease in children

- Same definitions for histologic patterns can be applied to biopsies but ..
- Frequency of patterns differs from adults, especially for interstitial pneumonias
  - UIP is very rare
  - Commonest patterns are LIP and NSIP
  - Some additional patterns are unique to children
- Clinical correlates and prognoses differ from adults
  - Different differential diagnoses to consider - mimics of ILD
  - Consider congenital disorders

Chronic pneumonitis of infancy

- Uniform marked alveolar septal wall thickening by plump spindle cells
- No significant collagen deposition and minimal interstitial inflammation
- Florid type 2 cell hyperplasia
- Infants and very young children
- Possibly reflecting resolving/recurrent pneumonia, possibly lung immaturity
  - ? Surf B abnormality.

Desquamative interstitial pneumonia in children.

- Desquamative interstitial pneumonia in children
  - Stillwell PC et al. Chest 1980;77:165-71
  - Report of 28 cases.
  - 61% survival - higher incidence of death than adults.

  - 4 infants: 2 sibs in each of 2 separate families. All 4 infants died despite intensive care and immunosuppressive therapy.
  - ? Familial cases carries a worse prognosis than that reported in sporadic cases.
  - ? Inborn errors of metabolism

- c.218T>C in the SFTPC gene

2 year old female

Increasing shortness of breath, ILD

Fibrotic NSIP

2016
- Some are related to surfactant protein disorders
- Other inborn errors of metabolism
Diffuse lung disease in infancy and childhood: expanding the chILD classification (0-2 years/2-18 years/mimics of ILD).


Deutsch G et al. AJRCCM 2007:176:1120-8

Diffuse Lung Disease in Biopsied Children 2 to 18 Years of Age. Application of the chILD Classification Scheme.


Histologic patterns specific to children

Pulmonary Interstitial Glycogenosis (PIG)

Canakis AM et al ARJCCM 2002:165:1557-65

Neuroendocrine cell Hyperplasia of infancy (NEHI)


Persistent Tachypnea of Infancy. Usual and Aberrant.

Rauch D et al. AJRCCM 2016:193:438-47

Includes both PIG and NEHI

Usual – does not usually require biopsy as typical clinical and CT presentation

Aberrant – additional localized CT findings

GROUP A: HISTOLOGICAL PATTERNS MORE PREVALENT IN CHILDREN <2 YEARS

Diffuse developmental and growth disorders

Alveolar-vascular dysplasia

Acute hyalinizing alveolar disease

Other

Specific conditions of undefined aetiology

Bronchiolitis obliterans organizing pneumonia

Surfactant protein disorder-associated histological patterns

Chronic peri-vascular disease

Pulmonaryeosinophilic interstitial disease

Non-specific interstitial pneumonia (fibrotic and acute)

GROUP B: HISTOLOGICAL PATTERNS MORE PREVALENT IN CHILDREN OF 2-18 YEARS

Interstitial pneumonias (idiopathic, or with known cause/association other than SPD)

Organising pneumonia

Acute fibrinous organising pneumonia

Diffuse alveolar damage

Usual interstitial pneumonia

Desquamative interstitial pneumonia

Non-specific interstitial pneumonia (cellular and fibrotic)

Other

GROUP C: DISORDERS MIMICKING DIFFUSE LUNG DISEASE

Small airways disease

Acute, subacute, chronic bronchiolitis

Obstructive bronchiolitis

Exuberant bronchiolitis

Other

Vascular disorders (primary and secondary pulmonary involvement)

Primary pulmonary hypertension

Pulmonary capillaritis

Lymphangioleiomyomatosis

Lymphangitis carcinomatosa

Thromboembolic disease

Lymphangectasia (primary and secondary)

Secondary vasculopathies (e.g., due to cardiac disease)

Primary and secondary pulmonary vasculitis

Other

Infections (Viral, Bacterial, Fungal, Parasitic)

Neoplasias (Tumours)

*more than one pattern of disease may be present, especially in group A

17 male, chronic autoimmune osteomyelitis, working as a tree surgeon

Chronic granulomatous disease of childhood

Granulomatous-lymphocytic interstitial lung disease (GL-ILD) as a presentation of CVD
12 month old female
Born three weeks prematurely (birth weight 3.5kg) with severe hyaline membrane disease that required ventilation for 10 days. Has since had recurrent respiratory tract infections.

Non-specific interstitial pneumonia in children

2003
2013

Pre-operative targeting
Size: <2.0 cm i suboptimal/inadequate
>3.0 cm (and deep) i optimal
Number: 2 or more sites recommended

By following this protocol, no cases were considered “inadequate” or “end-stage” whilst this was 11% in those not following protocol.

SLBx: Discuss with surgeon pre-operatively

Gentle inflation fixation with a small bore needle