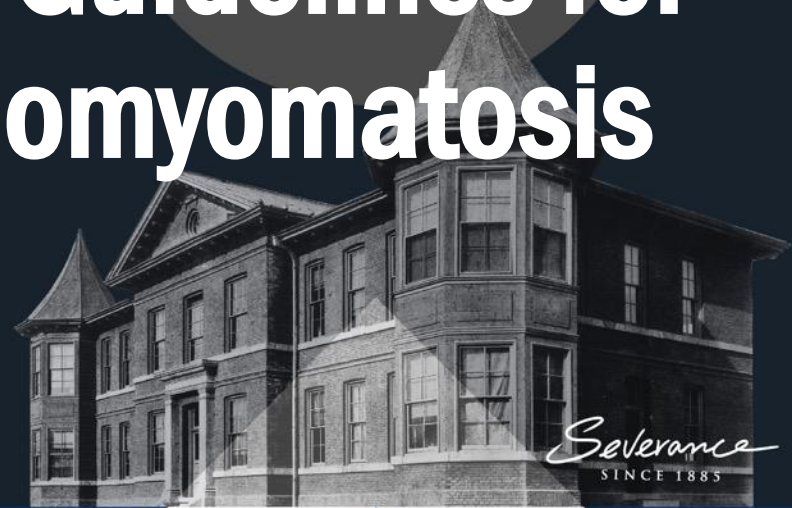


2021-06-05



YONSEI  
UNIVERSITY

# Updates of Practice Guidelines for ILD : lymphangiomyomatosis



*Severance*  
SINCE 1885

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# European Respiratory Society guidelines for the diagnosis and management of lymphangioliomyomatosis

S.R. Johnson\*, J.F. Cordier\*, R. Lazor, V. Cottin, U. Costabel, S. Harari,

## AMERICAN THORACIC SOCIETY DOCUMENTS

### Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioliomyomatosis Diagnosis and Management

Francis X. McCormack, Nishant Gupta, Geraldine R. Finlay, Lisa R. Young, Angelo M. Taveira-DaSilva, Connie G. Glasgow, Wendy K. Steagall, Simon R. Johnson, Steven A. Sahn, Jay H. Ryu, Charlie Strange, Kuniaki Seyama, Eugene J. Sullivan, Robert M. Kotloff, Gregory P. Downey, Jeffrey T. Chapman, MeiLan K. Han.

## AMERICAN THORACIC SOCIETY DOCUMENTS

### Lymphangioliomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management

An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline

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THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY OCTOBER 2017 AND BY THE JAPANESE RESPIRATORY SOCIETY AUGUST 2017

*Eur Respir J* 2010; 35: 14–26

*Am J Respir Crit Care Med* . 2016 ; 15;194(6):748-61

*Am J Respir Crit Care Med* 2017; 196:1337–1348

## Strong Recommendation

Most individuals in this situation would want the recommended course of action, and only a small proportion would not.

Patients

Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.

Clinicians

The recommendation can be adopted as policy in most situations.

Policy makers

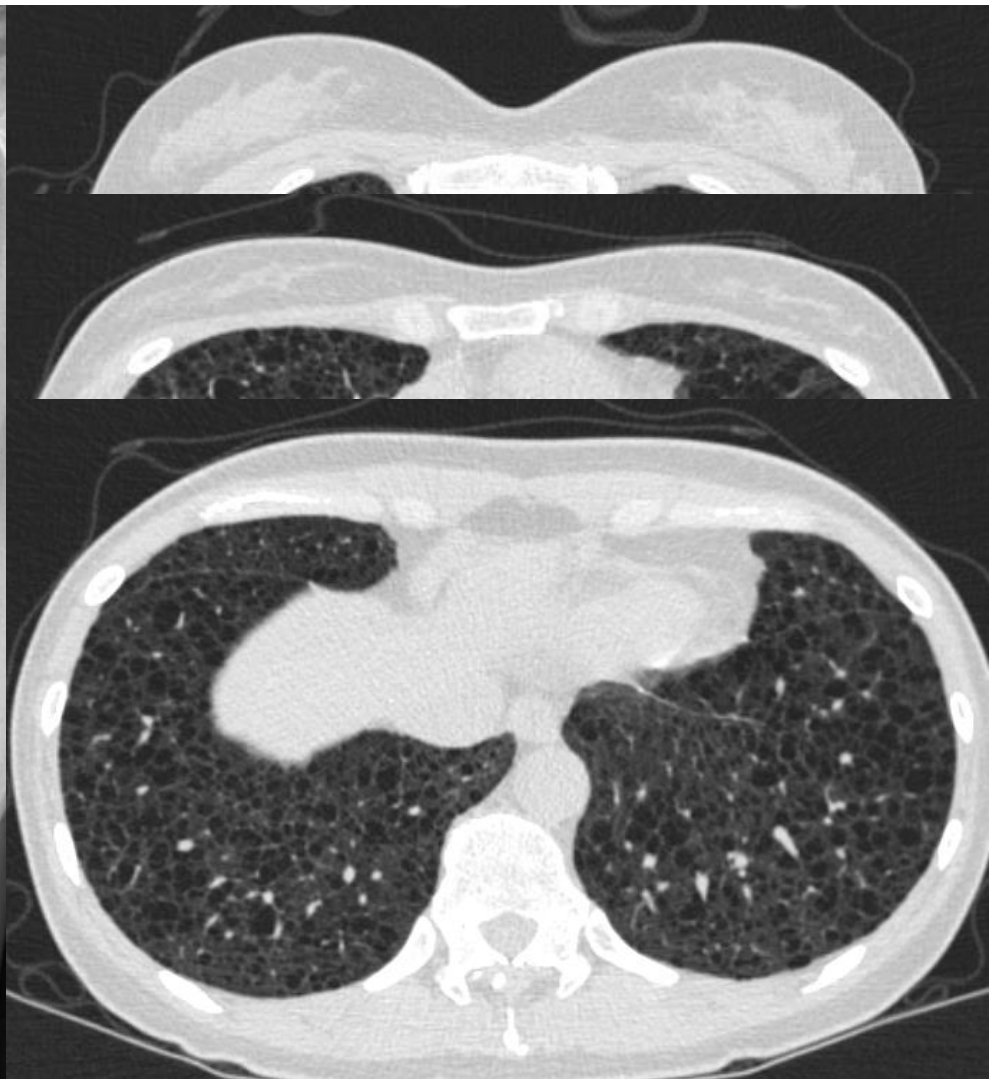
## Conditional Recommendation

The majority of individuals in this situation would want the suggested course of action, but many would not.

Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.

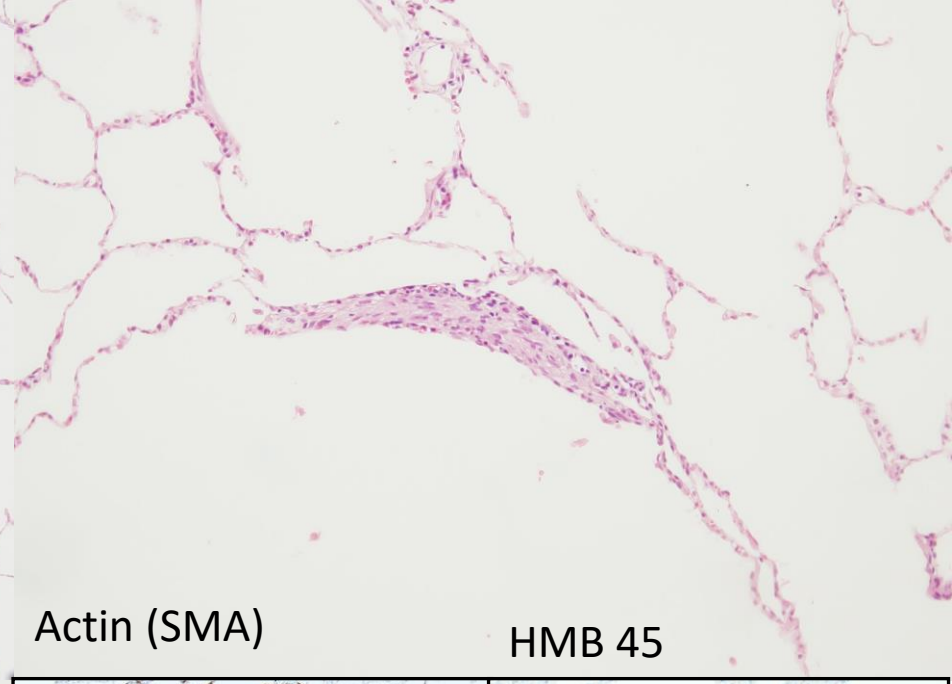
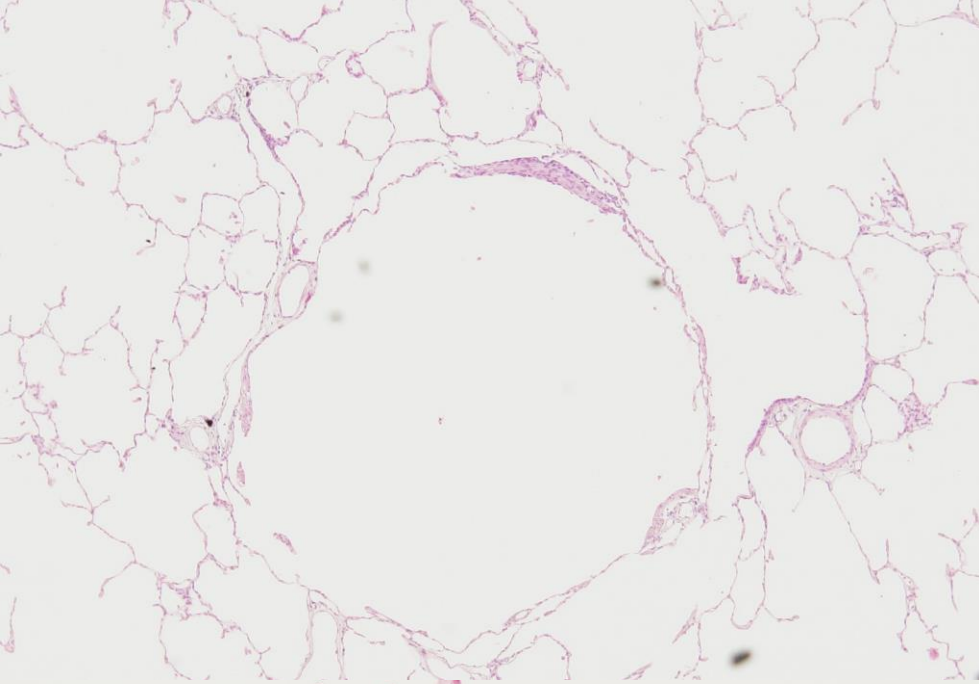
Policy making will require substantial debate and involvement of various stakeholders.

# F/38 DOE (mMRC 1) for 1yr



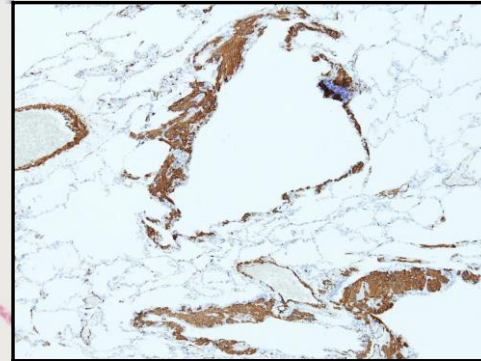
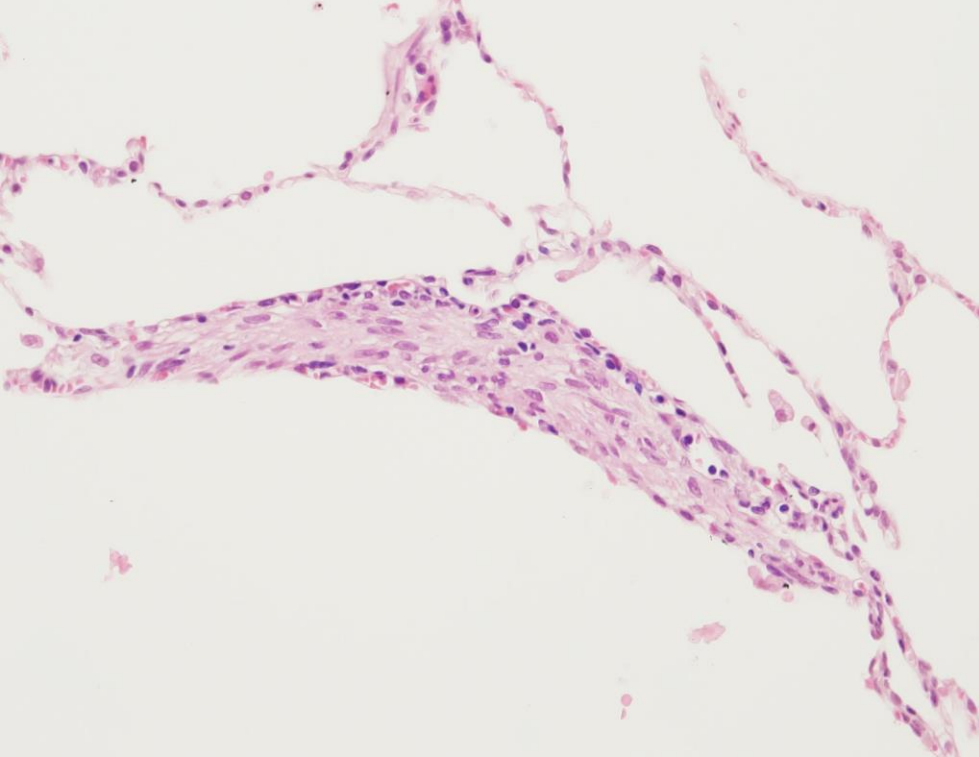
		Ref	Pre	% Ref	Post	% Ref	%Chg
<b>Spirometry</b>							
FVC	Liters	3.51	2.92	83	3.06	87	5
FEV1	Liters	2.75	1.62	59	1.84	67	14
FEV1/FVC	%	78	55		60		
FEV3	Liters		2.38		2.56		7
FEV6	Liters		2.75		2.90		5
FEF25-75%	L/sec	3.22	0.75	23	0.87	27	16
IsoFEF25-75	L/sec	3.22	0.75	23	1.08	34	44
FEF50%	L/sec	3.81	0.98	26	1.13	30	15
PEF	L/sec	6.18	4.50	73	5.75	93	28
FET100%	Sec		9.30		10.37		12
FIF50%	L/sec		1.43		3.37		136
<b>Diffusing Capacity</b>							
DLCO	mL/mmHg/min	19.2	7.7	40			
DL Adj	mL/mmHg/min	19.2	7.7	40			
DLCO/VA	mL/mHg/min/L	4.44	2.20	49			
DL/VA Adj	mL/mHg/min/L		2.20				
VA	Liters		3.53				
IVC	Liters		2.54				

- VATS assisted RML, RLL Bx

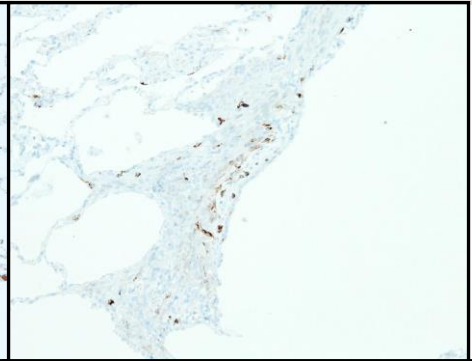


Actin (SMA)

HMB 45



PR

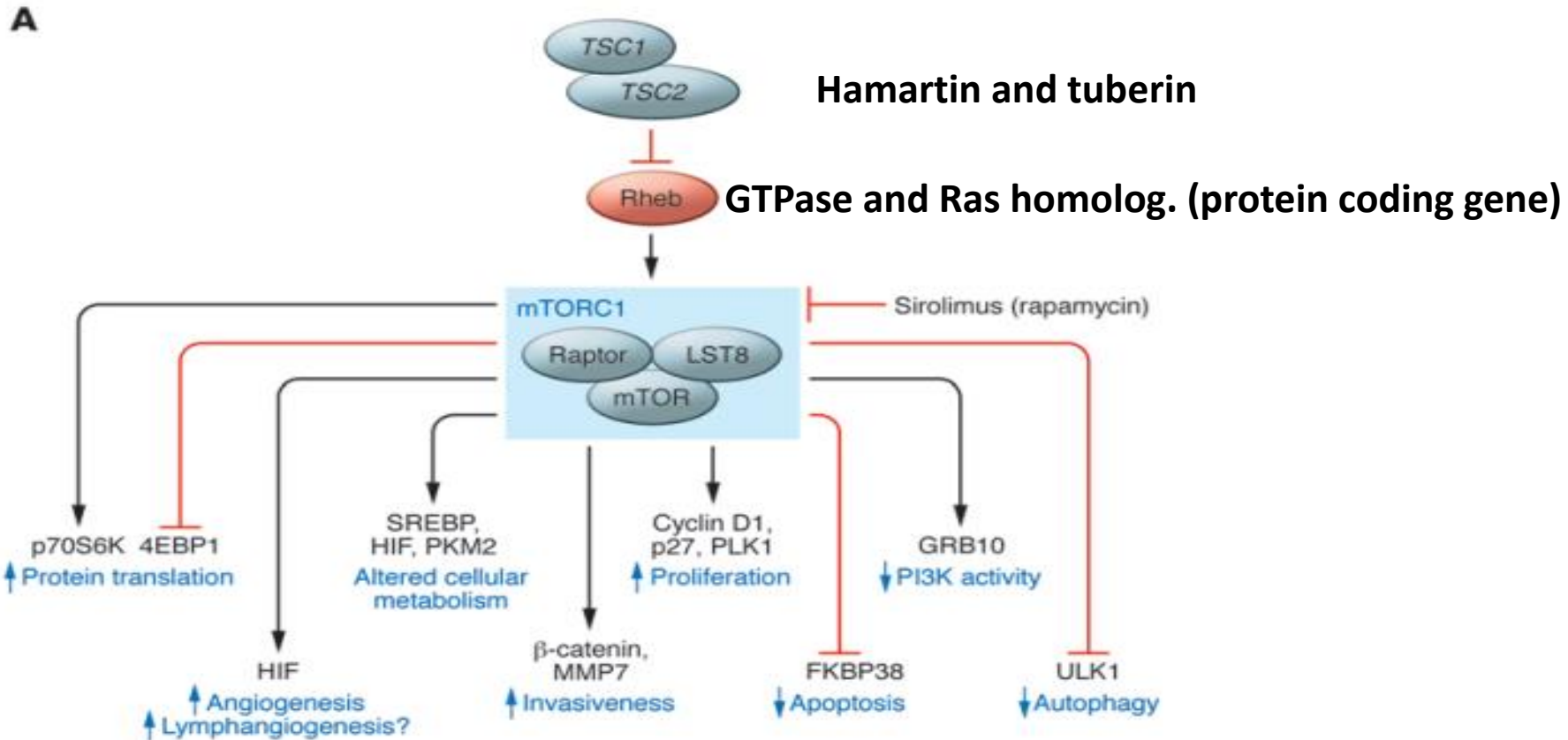


Melan A

# Lymphangiomyomatosis

- Rare , exclusive female occurrence
- Systemic neoplastic diseases
  - Cystic lung destruction
  - Chylous fluid accumulations
  - Abdominal tumors: angiomyoipoma, lymphangiomyomas
- Prevalence : about 5 / 1,000,000
- Average age is about 35 yrs
- **Sporadically** or **tuberous sclerosis** complex (TSC) related
- LAM cells spreads via the lymphatics and targets primarily the lung, resulting in cystic remodeling

# Pathogenesis



**Cell Growth & proliferation**

- **TSC related**

- TSC1 or TSC 2( TSC1 < TSC 2) mutation
  - Loss of function of TSC1 or TSC 2 protein
- 2/3 : Familiy Hx X → de novo germline heterozygous mutation
- Autosomal dominant disorder

- **Sporadic**

- May be caused by somatic mutation or postembryonic somatic mutation in TSC2

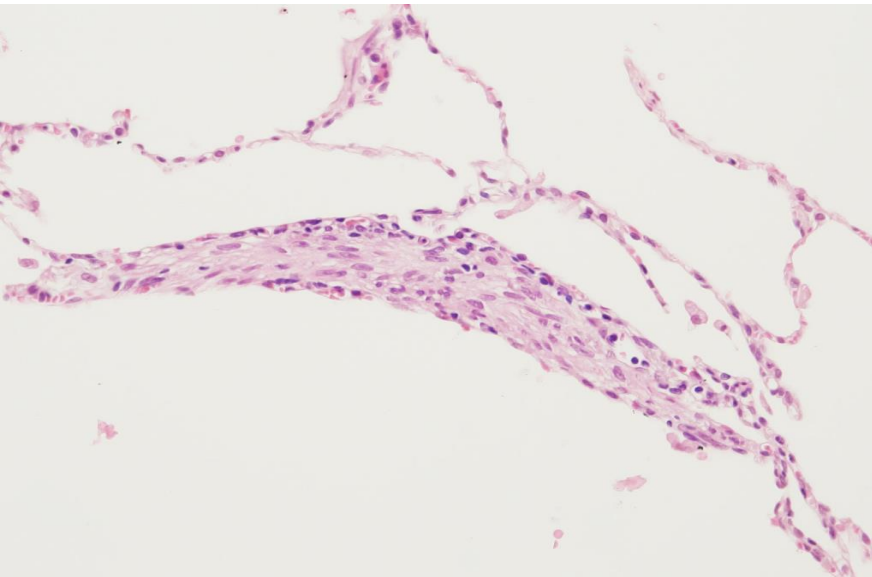
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	<b>TSC-LAM</b>	<b>S-LAM</b>
Lung cysts	Often mild	Often profuse
Elevated serum VEGF-D	100%	70%
Chylous pleural effusion	10%	30%
Pneumocyte hyperplasia	12%	0%–1%
Abdominal lymphangioliomyoma	9%	29%
Renal angiomyolipoma	93%	32%
Single	0%	46%
Bilateral	92%	19%
Uterine PEComas	100%	70%

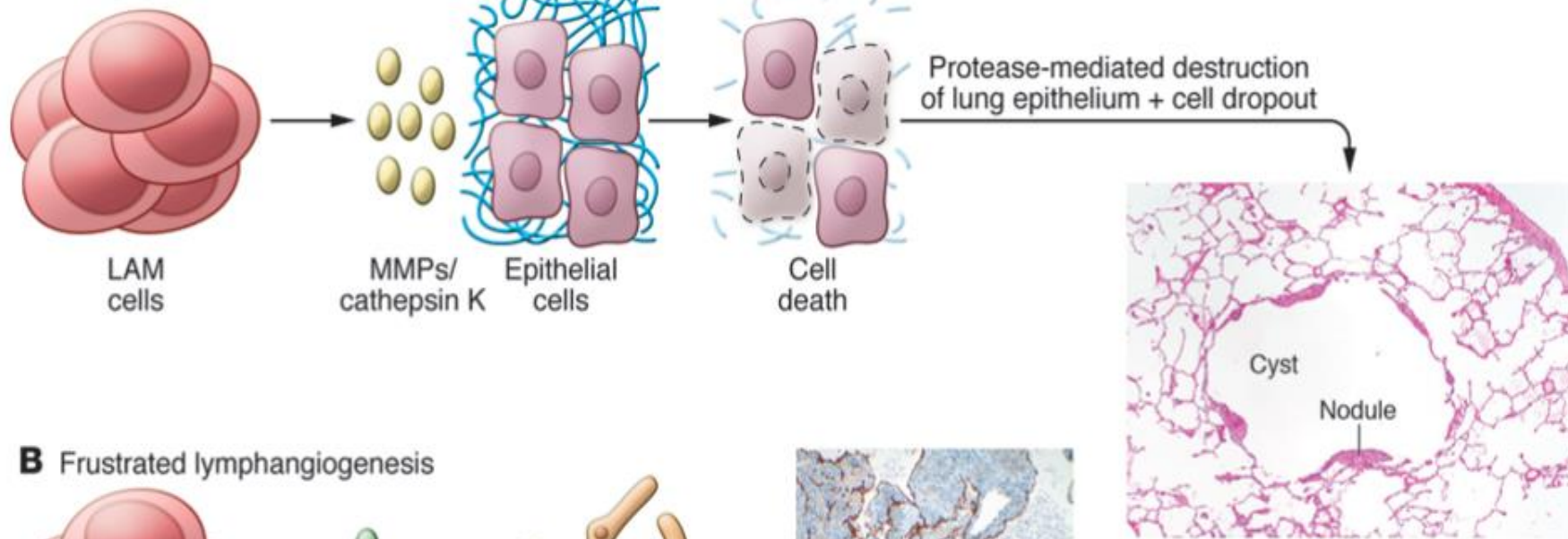
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# Histopathology

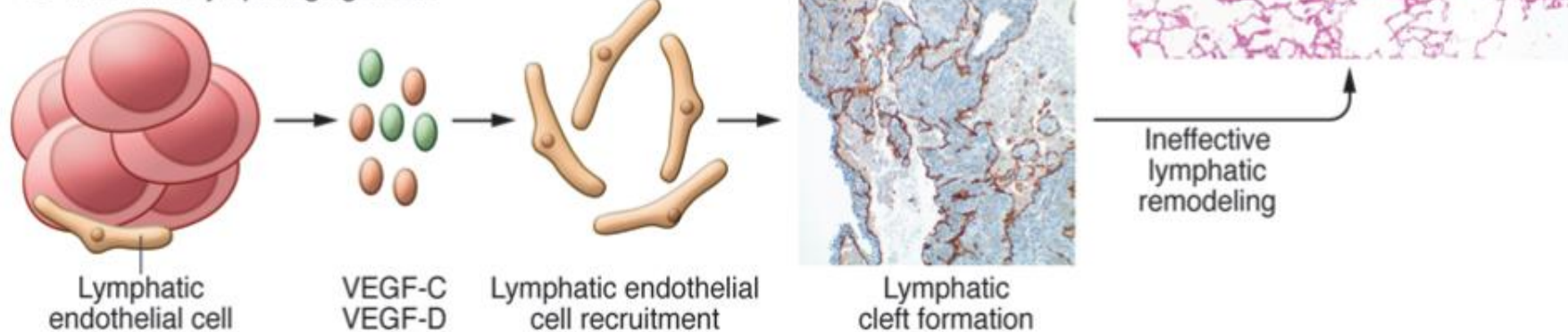
- LAM cells
  - Small, spindle –shaped cells that express smooth muscle protein such as **alph-actin, vimentin, desmin**, proliferating cell nuclear antigen (PCNA)
  - Large, epithelioid cells that display a high degree of immunoreactivity with **HMB 45 Ab**, with **Estrogen , progesterone receptor**



**A** Indiscriminate protease expression



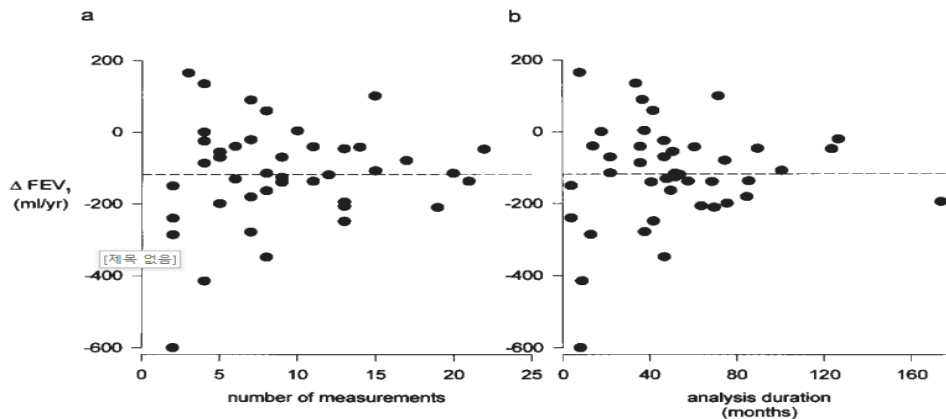
**B** Frustrated lymphangiogenesis



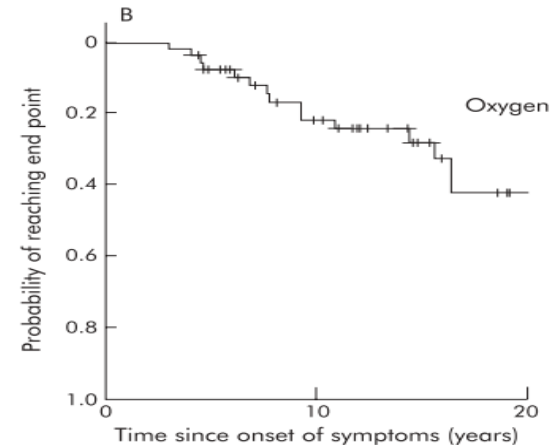
Mechanisms of airspace enlargement in LAM. Two models of airspace enlargement in LAM are presented; these may not be mutually exclusive. **(A)** LAM cells secrete proteases including MMPs and cathepsin K, which degrade the extracellular matrix and induce apoptosis of alveolar epithelial cells. **(B)** LAM cells express lymphangiogenic growth factors, VEGF-C and VEGF-D, recruit lymphatic endothelial cells, drive the formation of lymphatic vascular channels and distort the lung architecture. Original magnification,  $\times 200$ .

- **Lung : most involvement**

- Pneumothorax (1/3) , dyspnea (1/3)
- Chylous effusion
- Decline of lung function (2 -4 times or more)



- Dyspnea with daily activities
- UK 2004 reports
  - Hypoxia requiring O<sub>2</sub>: 10yrs from sx
  - Median survival : 12.6 yr (2.3-37)
  - 10yr survival from sx : 91%



- Lymphangioliomyoma
- Angiomyolipoma
- Meningioma

---

	<b>TSC-LAM</b>	<b>S-LAM</b>
Lung cysts	Often mild	Often profuse
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Renal angiomyolipoma	93%	32%
Single	0%	46%
Bilateral	92%	19%
Uterine PEComas	100%	70%

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## 2010 ERS proposed definitions : Diagnostic criteria

<b>Definite</b>	<b>1) Characteristic or compatible lung HRCT + Lung biopsy fitting the pathological criteria for LAM</b> <b>OR</b> <b>2) Characteristic lung HRCT + any of the followings</b> <ul style="list-style-type: none"><li>• <b>Angiomyolipoma (kidney)</b></li><li>• <b>Thoracic or abdominal chylous effusion</b></li><li>• <b>Lymphangiomyoma</b></li><li>• <b>LN involved by LAM</b></li><li>• <b>Definite or probable TSC</b></li></ul>
<b>Probable</b>	<b>1) Characteristic HRCT + compatible Hx</b> <b>OR</b> <b>2) Compatible HRCT + any of the followings</b> <ul style="list-style-type: none"><li>• <b>Angiomyolipoma (kidney)</b></li><li>• <b>Thoracic or abdominal chylous effusion</b></li></ul>
<b>Possible</b>	<b>Characteristic or compatible lung HRCT</b>

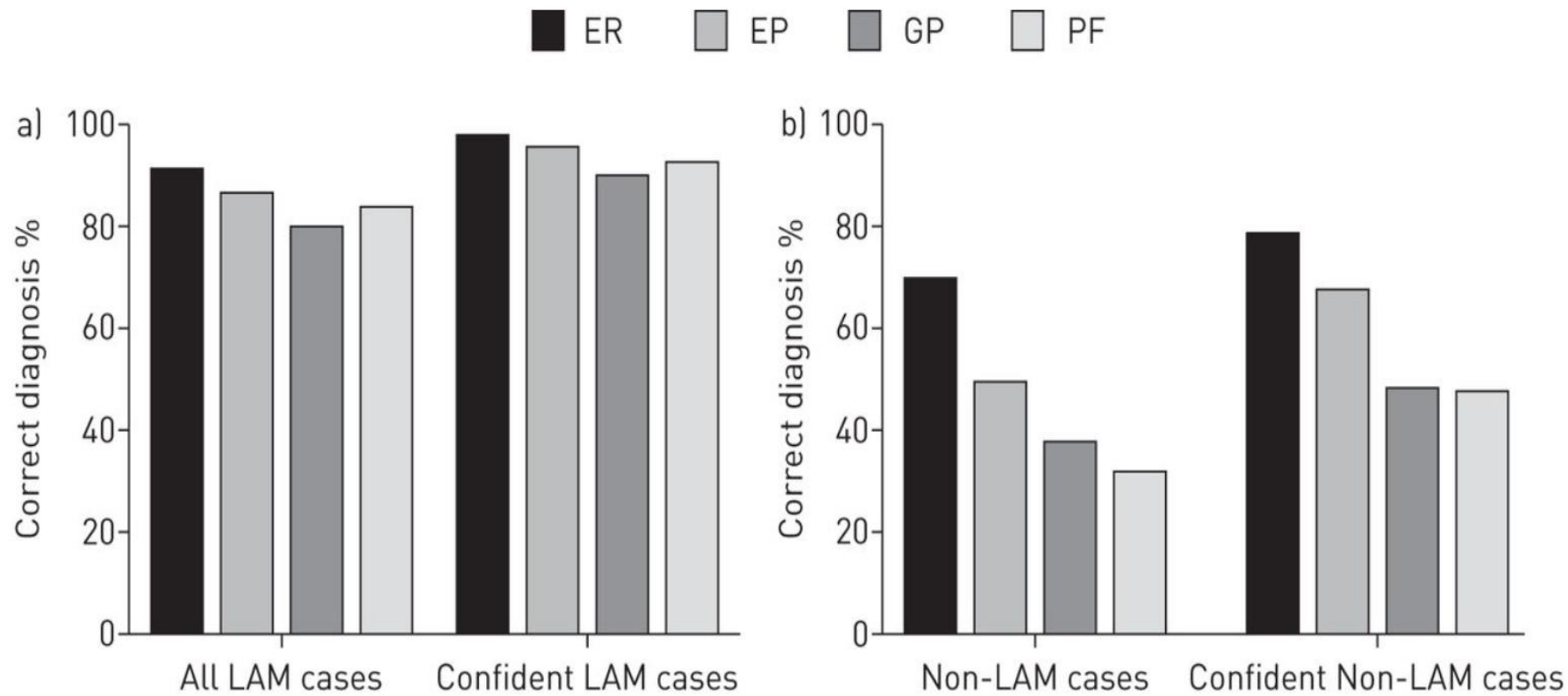
## Questions

Should patients be clinically diagnosed with LAM on the basis of their **HRCT findings alone** if they have cystic changes in the lung parenchyma that are characteristics of LAM but have no additional confirmatory characteristics of LAM (i.e. clinical, radiologic, or serologic)?

Should patients undergo **transbronchial lung biopsy** for the diagnosis of LAM if they have cystic changes that are characteristic of LAM on HRCT of the chest but have no additional confirmatory characteristics of LAM (i.e. clinical, radiologic, or serologic)?

Should **VEGF-D** be used to confirm the diagnosis of LAM in women with compatible cystic change on HRCT ?

# Diagnosis-HRCT alone



Pooled data -ER : Sensitivity 87.5%, Specificity 97.5%

*Eur respir J 2015;46:1196-1199*

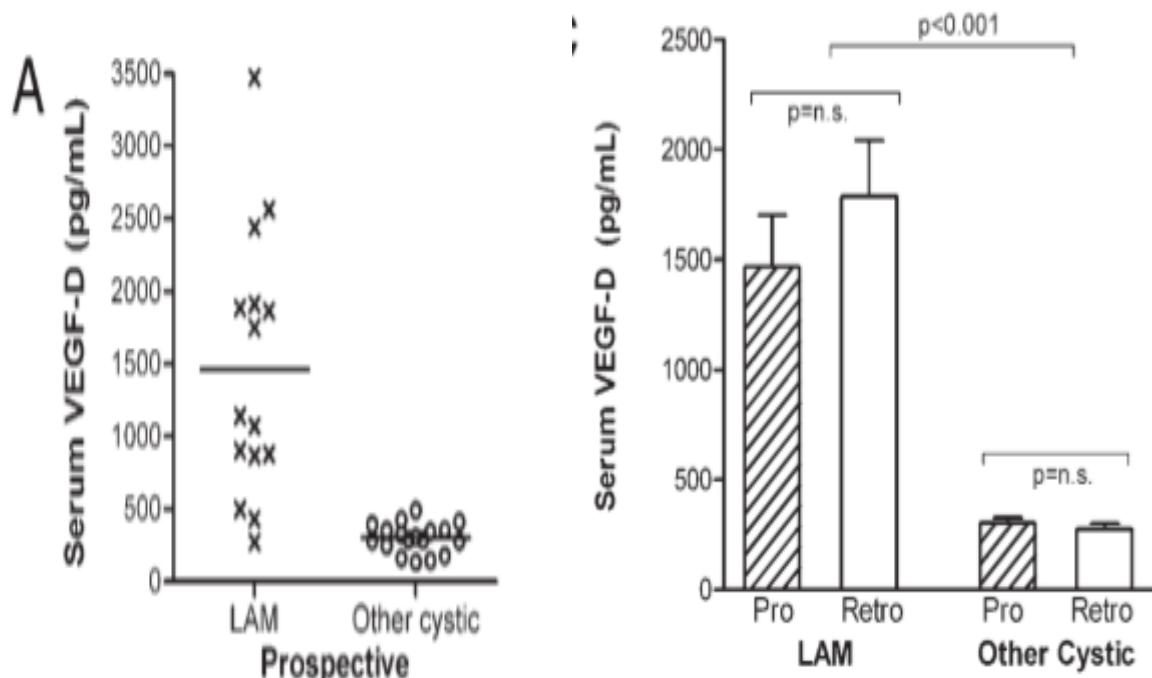
**We suggest NOT using the HRCT features in isolation to make a clinical diagnosis of LAM**  
*(Conditional recommendation, low confidence in estimated effects)*

- 5 case series
- Pooled data
  - 48 out of 81 patients (60%) TBLB → confirmed LAM
  - Complications not high
    - 14% (pneumothorax 6%, bleeding 2%..)
- Mild , asymptomatic patients → close monitoring
- Low burden of cysts : surgical biopsy > TBLB
- Previous op : re-review of pathology

When a **definitive diagnosis** is required in patients who have parenchymal cysts on HRCT that are characteristic of LAM, but no additional confirmatory features of LAM, we suggest a diagnostic approach that includes **TBLB before a surgical lung bx .**

*(Conditional recommendation, very low confidence in estimated effects)*

# Diagnosis-VEGF-D



1. 195 cystic lung dz
2. VEGF-D : **800pg/mL**

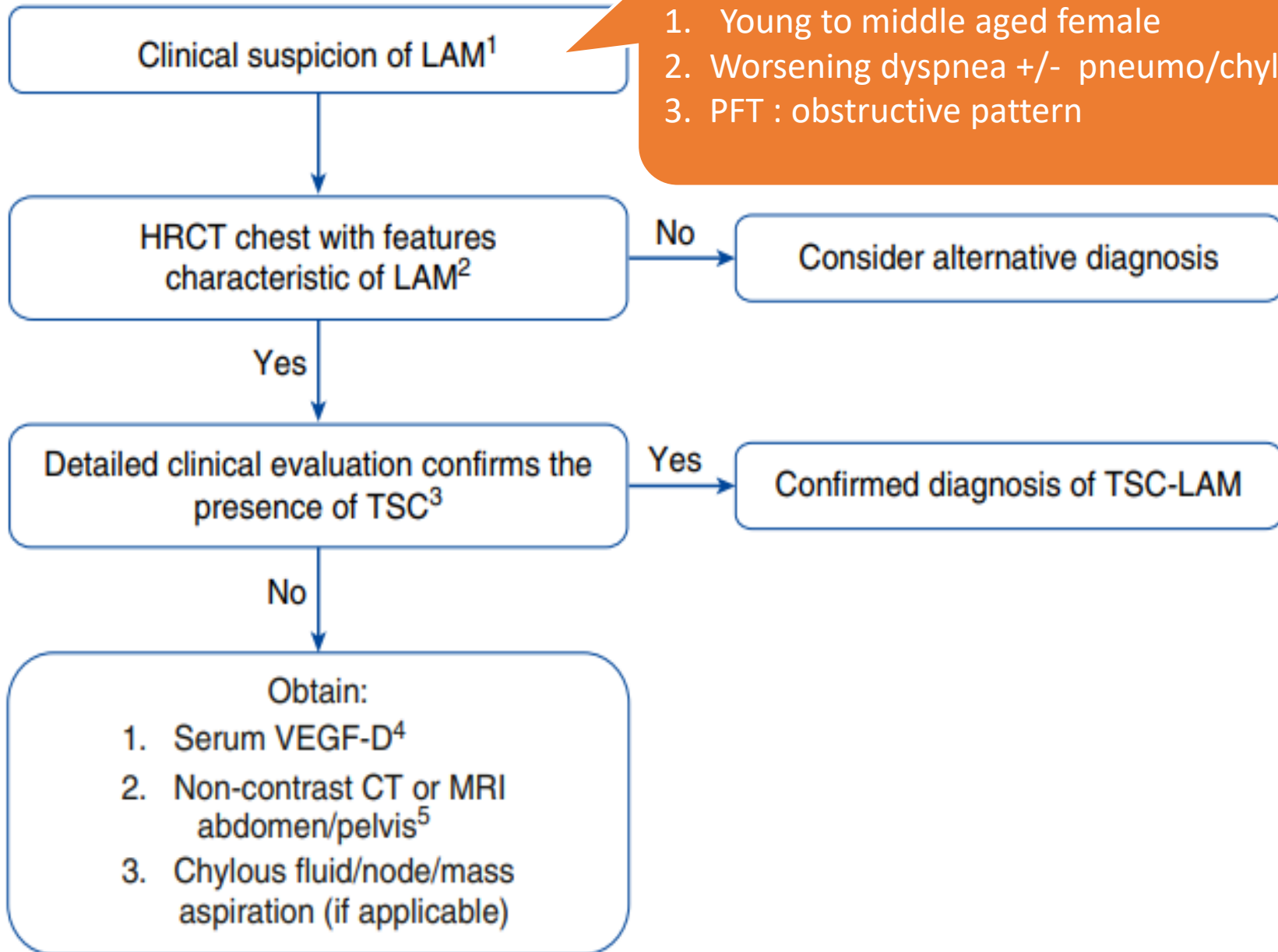
**Sensitivity: 60%**  
**Specificity; 100%**

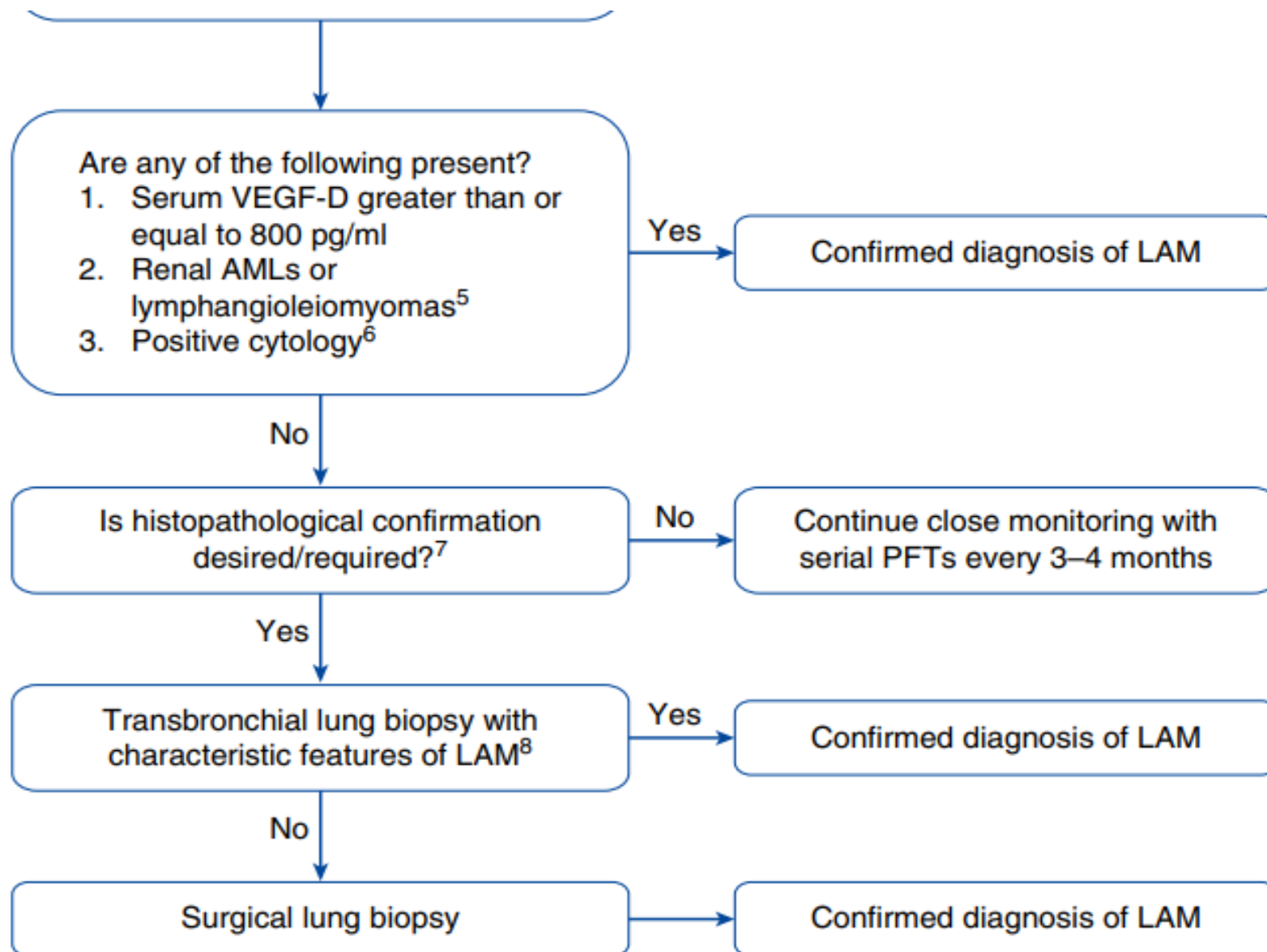
*CHEST 2010; 138(3):674-681*

For patients whose CT shows cystic abnormalities characteristic of LAM but have no confirmatory clinical or extrapulmonary radiologic features of LAM, we recommend **VEGF-D** testing **before** consideration fo proceeding to diagnostic lung **biopsy** .

*(Strong recommendation, moderate confidence in estimated effects)*

1. Young to middle aged female
2. Worsening dyspnea +/- pneumo/chylothorax
3. PFT : obstructive pattern





## Definite LAM

Definite diagnosis of LAM can be established if a patient with compatible clinical history\* and characteristic HRCT of the chest<sup>†</sup> has **one or more** of the following features:

1. Presence of TSC<sup>‡</sup>
2. Renal angiomyolipoma(s)<sup>§</sup>
3. Elevated serum VEGF-D  $\geq 800$  pg/ml
4. Chylous effusion (pleural or ascites) confirmed by tap and biochemical analysis of the fluid
5. Lymphangiomyomas (lymphangiomyomas)<sup>§</sup>
6. Demonstration of LAM cells or LAM cell clusters on cytological examination of effusions or lymph nodes<sup>||</sup>
7. Histopathological confirmation of LAM by lung biopsy or biopsy of retroperitoneal or pelvic masses

**Compatible Hx:** young to middle-aged female patients presenting with worsening dyspnea and/or pneumothorax/chylothorax and the absence of features suggestive of other cystic lung diseases, most obstructive lung function

**Characteristic of HRCT :** multiple, bilateral, uniform, round, thin-walled cysts in a diffuse distribution

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## Questions

Should patients with LAM be treated with **sirolimus**?

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Should patients with LAM be treated with **doxycycline**?

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Should patients with LAM be treated with **hormone** therapy?

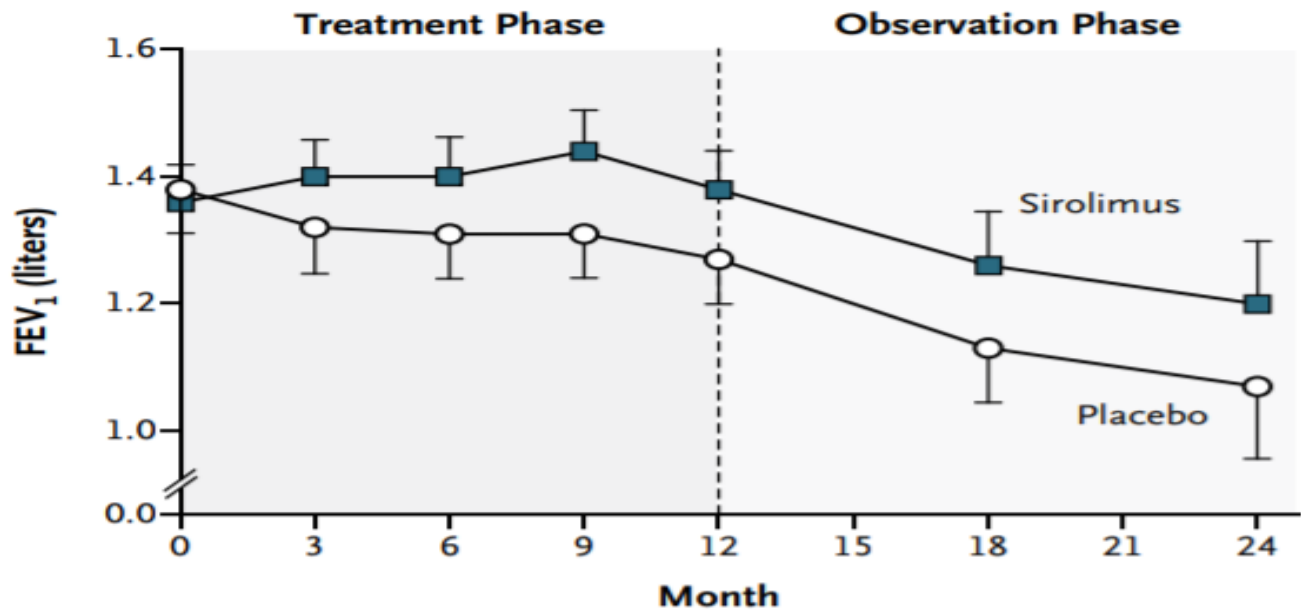
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Should patients with LAM undergo ipsilateral **pleurodesis** after an initial pneumothorax or wait for a recurrence before intervening with a pleural symphysis procedure?

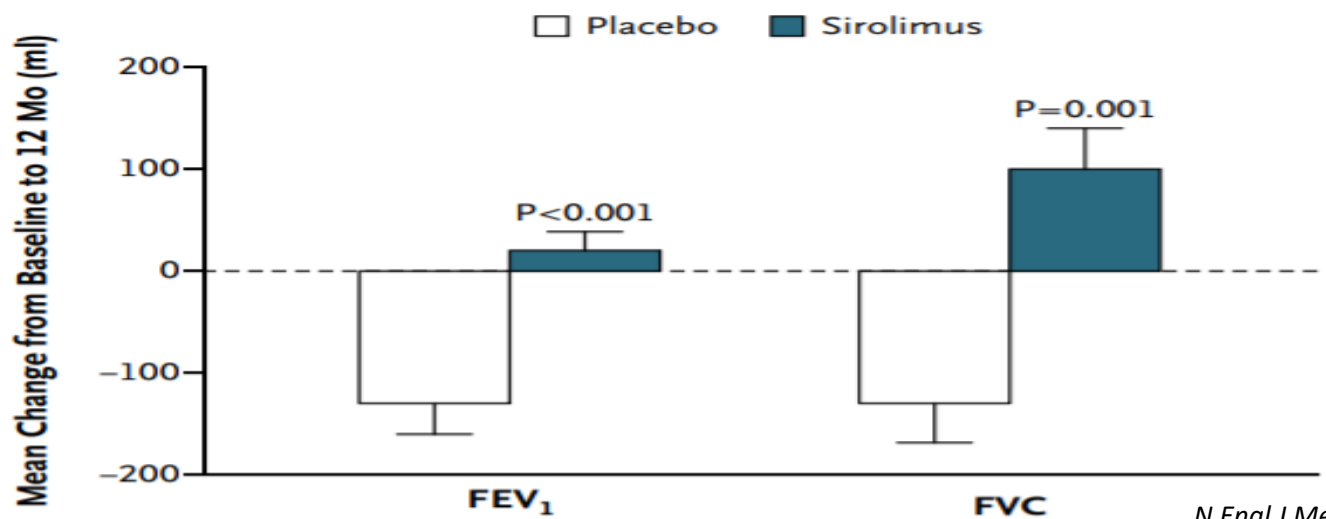
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- **Sirolimus (mTOR inhibitor)**

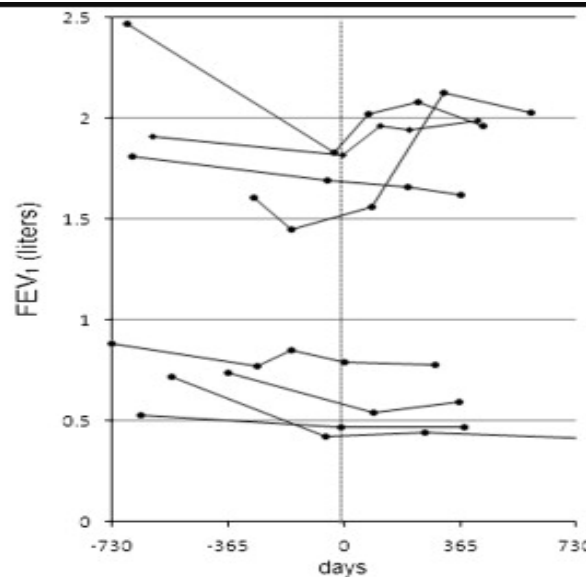
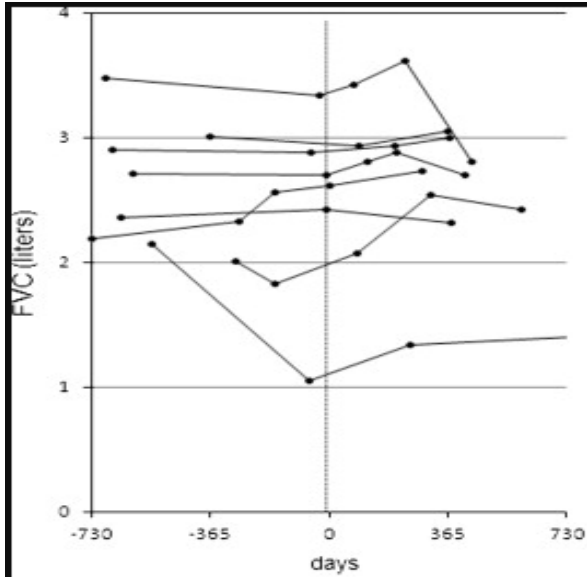
- The MILES (Multicenter International LAM Efficacy of Sirolimus) Trial
  - 89 LAM patients, (FEV1 <70% after BD)
  - 12 mon randomized, double blind , placebo controlled
  - Followed by a 12-month observation period
  - Sirolimus , level 5-15 ng/mL
  - Primary outcome: rate of change in FEV1 /months

**A****No. at Risk**

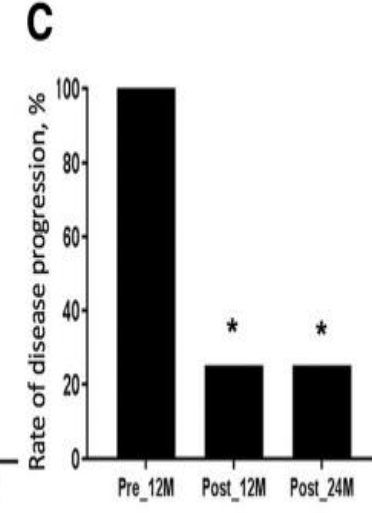
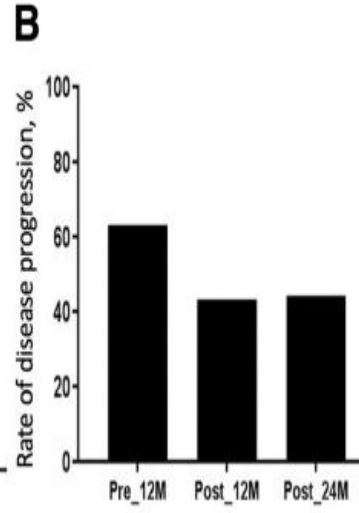
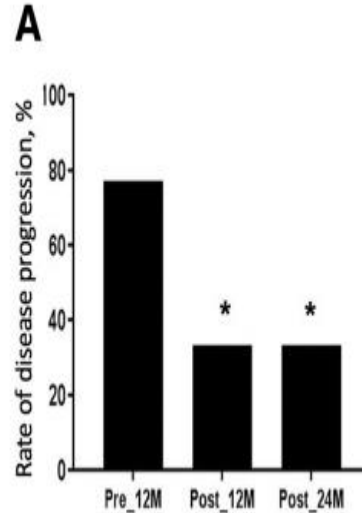
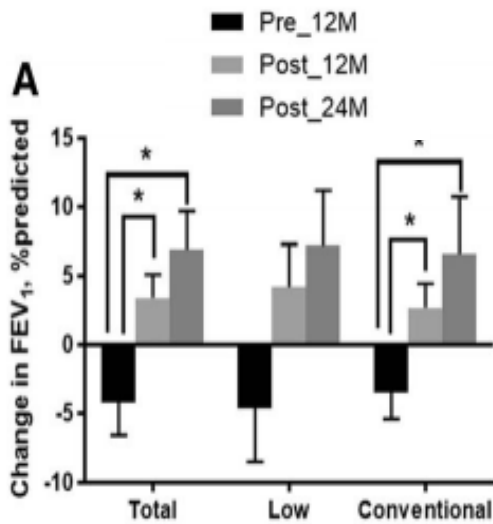
Sirolimus	46	43	41	38	41	21	14
Placebo	43	40	42	39	34	22	13

**B**

Category	Total Adverse Events				Serious Adverse Events			
	Treatment Period		Observation Period		Treatment Period		Observation Period	
	Placebo	Sirolimus	Placebo	Sirolimus	Placebo	Sirolimus	Placebo	Sirolimus
	<i>number of events</i>							
Allergy or immunologic event	13	11	1	1				
Auditory or ear-related event	2	4	0	1				
Blood or bone-marrow event	4	12	1	0	0	1	0	0
Cardiac arrhythmia	0	2	0	2				
Cardiac event, general	12	15	3	2	0	5	0	0
Constitutional symptom	35	46	7	7				
Death not related to an event	0	0	1	0	0	0	1	0
Dermatologic event	41	106	8	11				
Endocrinologic event	3	2	2	0	0	0	1	0
Gastrointestinal event	181	275	12	20	1	3	0	0
Hemorrhage or bleeding event	14	17	3	1	0	0	1†	0
Hepatobiliary or pancreatic event	1	0	1	0	0	0	1	0
Infection	74	78	20	24	3	2	1	0
Lymphatic event	8	15	6	0				
Metabolic event or abnormal laboratory result	26	56	1	6	0	1	0	0
Musculoskeletal or soft-tissue event	21	35	2	4	0	1	0	1
Neurologic event	27	33	4	7				
Ocular or visual problem	3	8	1	2				
Pain	115	130	9	13	1	7	0	0
Pulmonary or upper respiratory event	121	97	17	32	13	2	0	0
Renal or genitourinary event	8	11	0	2				
Sexual or reproductive problem	8	5	0	0				
Vascular event	1	1	0	0	0	1	0	0
Total adverse events	718	959	99	135				



- 15 LAM pts
- >6month
- Sirolimus
- Level < 5ng/mL



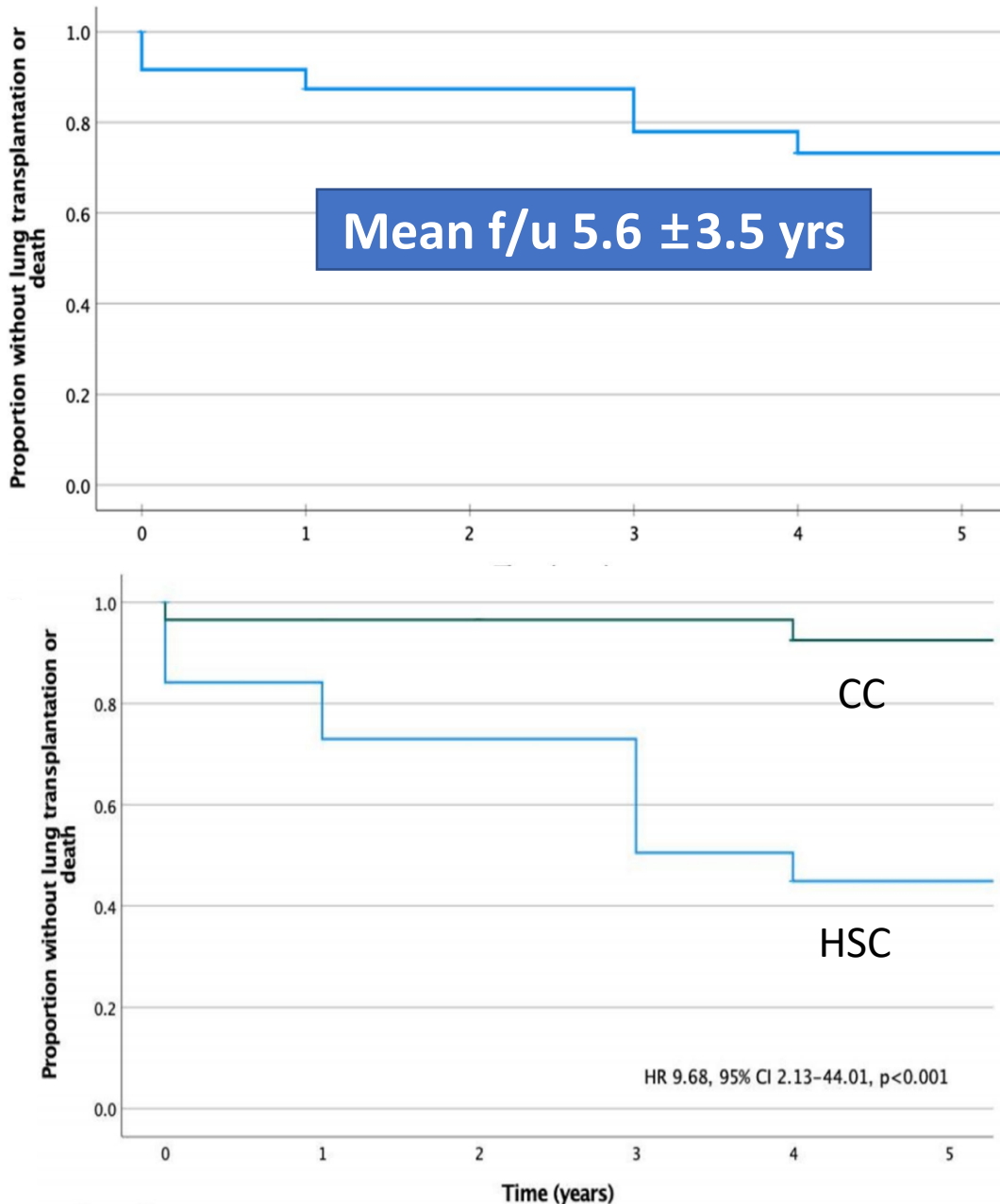
- 39 LAM pts , 2011-2017
- Low dose (20) vs. Conventional dose (19)

	Before Sirolimus Began	After Sirolimus Began
Mean time, yr	-7.2 ± 5.1	3.4 ± 2.0
Change in % predicted FVC	-0.4 ± 0.1	0.8 ± 0.2*
Change in FVC, ml	-35 ± 4	23 ± 10 <sup>†</sup>
Change in % predicted FEV <sub>1</sub>	-2.2 ± 0.1	1.0 ± 0.3 <sup>†</sup>
Change in FEV <sub>1</sub> , ml	-79 ± 3	25 ± 8 <sup>†</sup>
Change in % predicted DL <sub>CO</sub>	-2.6 ± 0.1	0.9 ± 0.2 <sup>†</sup>
Change in DL <sub>CO</sub> , ml/min/mm Hg	-0.61 ± 0.02	0.22 ± 0.05 <sup>†</sup>

- 38 LAM pts
- Duration : **3.4 ± 2.0 years**

- Adverse events: manageable
  - Hypertriglyceridemia (34.2%) /Diarrhea (55.3%), Stomatitis (57.9%)
  - Acne (50%), Rash (26.3%), Delayed wound healing (26.3%)
  - Thrombocytopenia (21.1%),Leukopenia/ Neutropenia (39.5%)
  - Arthralgia (23.7%) /Headache (39.5%)
  - Proteinuria (21.1%)/ Upper respiratory infection (65.8%)
  - Peripheral edema (52.4%), HTN (34.2%)
  - Pain (other) (39.5%)

# Sirolimus : Long term use +When?



- 48 LAM pts
- Sirolimus tx
- 1990-2020
- Sirolimus available after 2007
- **HSC** : before 2007  
(baseline FEV1 59% (30-81))
- **CC** : after 2007  
(baseline FEV1 77% (62-94))

# Chylous effusion

- Sirolimus
  - 19 LAM patients with chylous effusion
  - 11 – pleural effusion / 7 ascites
  - 9 pleural effusion patients : complete resolution
    - Complete resolution of effusions after  $410 \pm 111$  days
    - 6 patients, effusions resolved after  $131 \pm 61$  days
- Conservative care
  - Fat free diet with supplementation with mid-chain TG
  - Intervention ; severity , recurrence, symptom..

For patients with LAM with **abnormal/declining** lung function, we recommend treatment with **sirolimus** rather than observation .

*(strong recommendation based on moderate quality evidence).*

For patients with LAM with **symptomatic chylous fluid accumulations**, we suggest treatment with **sirolimus** before invasive management.

*(conditional recommendation based on very low-quality evidence)*



- Doxycycline : inhibit the production of several MMPs

We suggest **NOT using doxycycline** as treatment for LAM . *(conditional recommendation based on low-quality evidence)*

- Hormonal therapy : some observational studies
  - Progestin, GnRH agonist, SERM like tamoxifen, oophorectomy..
  - Estrogen agonist, SERM → discontinue

We suggest **NOT using hormonal** therapy as treatment for LAM. *(conditional recommendation based on very low-quality evidence)*

- Pneumothorax in LAM
  - 7 case series, 2 observational studies
  - Pneumothorax ; 902 out of 1,591 (57%)
  - Recur ; 29-81% (most estimates 70%)
    - 65% recur in conservative management group
    - 18-32% recur in pleurodesis group

We suggest that patients with LAM be offered ipsilateral **pleurodesis after their initial pneumothorax** rather than waiting for a recurrent pneumothorax before intervening with a pleural symphysis procedure.

*(conditional recommendation very low confident in the estimated effects.)*

- Lung transplantation (LTx)
  - NYHA III or IV , advanced LAM
  - Prior pleurodesis, surgical procedure: high risk , but not contraindication
  - LAM can be recur after LTx

- Patients advice
  - Pneumothorax risk
  - Pregnancy
    - Risk of pneumothorax , chylothorax ↑
    - Lung function decline ↑ / Angiomyolipoma bleeding risk ↑
    - Pregnancy is patients' decision , but information should be offered / It may be appropriate to discourage patients in severe status
  - Avoid estrogen including contraceptive pill and HRT
  - Air travel
    - Minimal sx, mild → ok except in cases of new respiratory symptom
    - Severe → need for oxygen, some patients should consider alternatives to air travel
    - Untreated pneumothorax or recent pneumothorax → X
- Pulmonary rehabilitation
- Vaccination: influenza, pneumococcal
- Inhaled bronchodilators

# Prognosis

- Lung function
  - FEV1 decline : 40-120mL/yr
- Mortality
  - 8-10 yrs from diagnosis – early reports
  - 29 yrs from symptom and 23 yrs from diagnosis: U.S.A data
  - 10 yr survival : 91%, 20yr survival : 20% : U.K data
- Prognostic factors
  - Premenopausal status
  - Presentation with dyspnea
  - Poor baseline lung function
  - High level of serum VEGF-D

*Lancet Respir Med 2013; 1:445.*

*N Engl J Med 2011; 364:1595.*

*Medicine (Baltimore) 1999; 78:321.*

*Medicine (Baltimore) 1999; 78:321.*

*N Engl J Med 1990; 323:1254.*

*Chest 2004; 126:1867. Am J Respir Crit Care Med 1995; 151:527.*

*Lung 2013; 191:35.*

*Respir Investig 2016; 54:193.*

*Thorax 2004; 59:800.*

# Case progress

- Sirolimus : 3yr 6mon 유지중
- PFT

		Ref	Pre	% Ref	Post	% Ref	%Chg
<b>Spirometry</b>							
FVC	Liters	3.51	2.92	83	3.06	87	5
FEV1	Liters	2.75	1.62	59	1.84	67	14
FEV1/FVC	%	78	55		60		
FEV3	Liters		2.38		2.56		7
FEV6	Liters		2.75		2.90		5
FEF25-75%	L/sec	3.22	0.75	23	0.87	27	16
IsoFEF25-75	L/sec	3.22	0.75	23	1.08	34	44
FEF50%	L/sec	3.81	0.98	26	1.13	30	15
PEF	L/sec	6.18	4.50	73	5.75	93	28
FET100%	Sec		9.30		10.37		12
FIF50%	L/sec		1.43		3.37		136

		Ref	Pre	% Ref
<b>Diffusing Capacity</b>				
DLCO	mL/mmHg/min	19.2	7.7	40
DL Adj	mL/mmHg/min	19.2	7.7	40
DLCOVA	mL/mHg/min/L	4.44	2.20	49
DLVA Adj	mL/mHg/min/L		2.20	
VA	Liters		3.53	
IVC	Liters		2.54	

		Ref	Pre	% Ref	Post	% Ref	%Chg
<b>Spirometry</b>							
FVC	Liters	3.45	2.90	84	2.93	85	1
FEV1	Liters	2.96	1.46	49	1.57	53	8
FEV1/FVC	%	84	50		54		
FEV3	Liters		2.27		2.39		5
FEV6	Liters		2.74		2.83		3
FEF25-75%	L/sec	3.10	0.62	20	0.71	23	15
IsoFEF25-75	L/sec	3.10	0.62	20	0.84	27	35
FEF50%	L/sec	3.71	0.71	19	0.84	23	19
PEF	L/sec	6.08	4.74	78	5.25	86	11
FET100%	Sec		9.78		9.47		-3
FIF50%	L/sec		4.11		3.99		-3

		Ref	Pre	% Ref
<b>Diffusing Capacity</b>				
DLCO	mL/mmHg/min	21.9	7.3	33
DL Adj	mL/mmHg/min	21.9	7.3	33
DLCOVA	mL/mHg/min/L	4.77	2.03	43
DLVA Adj	mL/mHg/min/L		2.03	
VA	Liters		3.62	
IVC	Liters		2.72	

# Summary

- LAM is rare and a type of neoplastic disease.
- LAM cells can spread via the lymphatics and targets primarily the lung, resulting in cystic remodeling.
- LAM can be diagnosed with typical history and CT findings and other clinical features.
- Sirolimus in progressive LAM and lung transplantation in advanced LAM can be considered.

Thank you

