Lung transplantation

Libor Fila

Lung transplantation (LuTx)

- Treatment possibility in advanced lung diseases
- Patients on maximum conservative management with predicted survival 12-18 months
- Patients have to be able to undergo this extensive surgical procedure

Historical notes

- Prof. Hardy (University of Mississippi) 1963: first LuTx in man (Mr. John Russel)

- Dr. Stähelin (Sandoz company, now Novartis) 31.1.1972: immunosuppressive effect of cyclosporin A

Historical notes /2

- Prof. Cooper
  (University of Toronto)
  1983: first successful
  LuTx

- Prof. Klepetko (Vienna
  General Hospital):
  1989 LuTx program
  started in Vienna

First succesful LuTx

- 45th LuTx in the world

- Mr. Thomas Hall
- November 7, 1983
- SLTx for IPF

- Survival 8 years

Historical notes /3

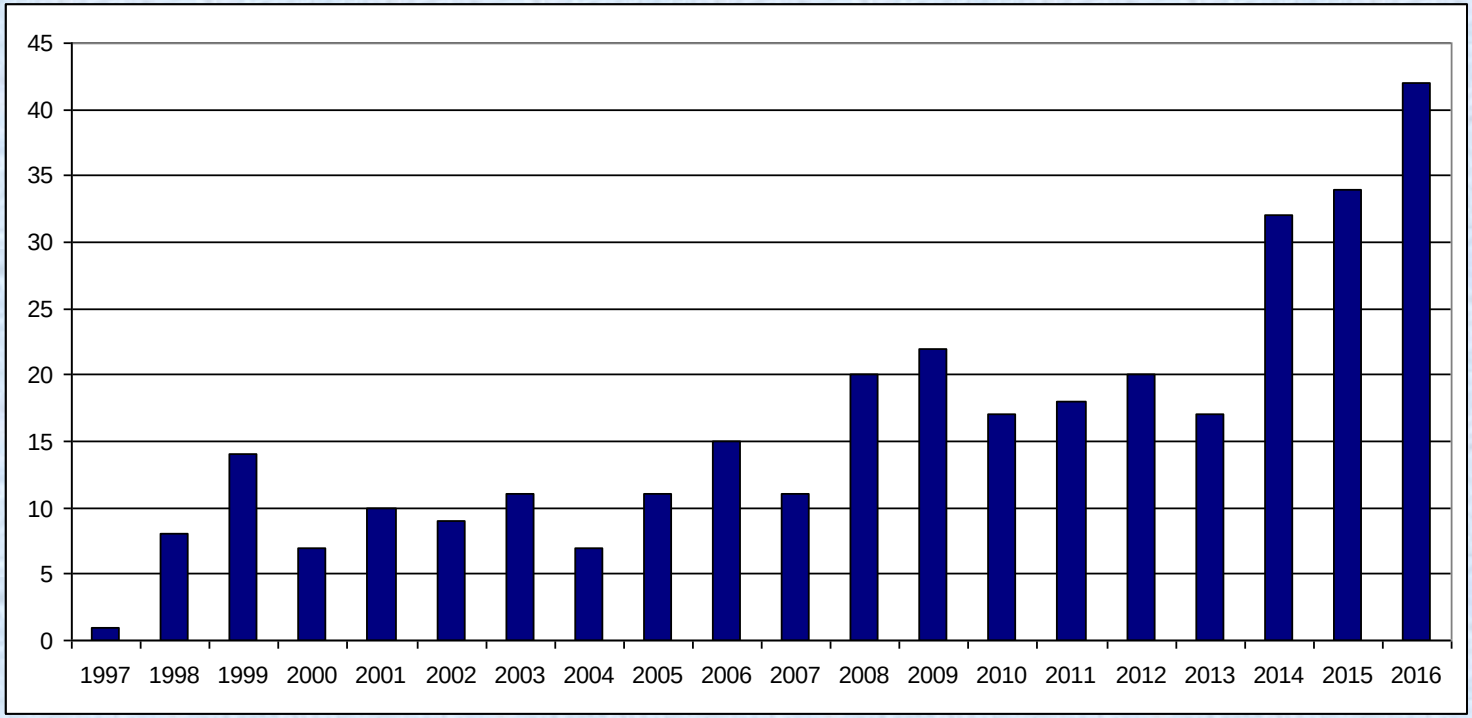
- In 1970 prof. Řehák (3rd Surgical Clinic of General Faculty Hospital, Londýnská street) started with experimental LuTx in cooperation with IKEM

- Since 1994 started cooperation of 3rd Surgical Clinic (prof. Pafko) with Vienna LuTx centre

Historical notes /4

- December 21, 1997: first LuTx in the Czech Republic

Historical notes /5



Prof. Lischke

Number of LuTx at 3rd Surgical Clinic of Faculty Hospital Motol

Guidelines ISHLT

American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

International Guidelines for the Selection of Lung Transplant Candidates

THIS JOINT STATEMENT OF THE AMERICAN SOCIETY FOR TRANSPLANT PHYSICIANS (ASTP)/AMERICAN THORACIC SOCIETY (ATS)/EUROPEAN RESPIRATORY SOCIETY (ERS)/INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION (ISHLT) WAS APPROVED BY THE ATS BOARD OF DIRECTORS FEBRUARY, 1998

International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update—A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation

A consensus document for the selection of lung transplant candidates: 2014—An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation

LuTx indications

- COPD (incl. α_1-antitrypsin deficiency)
- Interstitial lung diseases (eg. UIP-IPF)
- Cystic fibrosis (CF) and bronchiectasis
- Pulmonary vascular diseases (eg. IPAH)

Absolute contraindications

- Malignancy in last 5 years
- Untreatable advanced dysfunction of another major organ systém; BMI ≥35.0
- Non-curable infection; active TB
- Acute medical instability (sepsis, myocardial infarction, bleeding diathesis)
- Significant chest wall/spinal deformity
- Severely limited functional status and poor rehabilitation potential
- Nonadherence (psychiatric disorders, absence of social support, substance addiction)

Relative contraindications

- Advanced age (>65-75 y, according to biological age and other relative contraindications)
- Critical condition (IMV, ECMO), BMI 30.0-34.9
- Colonization with resistant pathogens (BCC, MAB); serious infections (HIV, HV-B, HV-C)
- Severe osteoporosis or malnutrition (BMI <17.0)
- Previous extensive chest surgery
- Untreated conditions (DM, arterial hypertension, peptic ulcer disease, GER, CAD and others)

Mechanical bridges to LuTx

- <u>ECLS:</u> young age, good potential for rehabilitation, absence of MODS (typically CF, LAM, α_1-antitrypsin deficiency)

- <u>Not recommended:</u>
  - Septic shock, MODS
  - Advanced age, severe atherosclerosis
  - Heparin-induced thrombocytopenia
  - Previous prolonged IMV
  - Obesity

Interstitial lung diseases

Timing of referral:

- Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function.
- Abnormal lung function: forced vital capacity (FVC) $<80\%$ predicted or diffusion capacity of the lung for carbon monoxide (DLCO) $<40\%$ predicted.
- Any dyspnea or functional limitation attributable to lung disease.
- Any oxygen requirement, even if only during exertion.
- For inflammatory interstitial lung disease (ILD), failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.

Timing of listing:

- Decline in FVC $\geq 10\%$ during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing).
- Decline in DLCO $\geq 15\%$ during 6 months of follow-up.
- Desaturation to $<88\%$ or distance <250 m on 6-minute-walk test or >50 m decline in 6-minute-walk distance over a 6-month period.
- Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography.
- Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.

CF and bronchiectasis

Timing of referral:

- FEV_1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV_1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or *B cepacia* complex (see previous comment on *B cenocepacia* and subsequently) and/or with diabetes.
- A 6-minute walk distance <400 m.
- Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or mean PAP >25 mm Hg measured by right heart catheterization).
- Clinical decline characterized by increasing frequency of exacerbations associated with any of the following:
  - An episode of acute respiratory failure requiring non-invasive ventilation.
  - Increasing antibiotic resistance and poor clinical recovery from exacerbations.
  - Worsening nutritional status despite supplementation.
  - Pneumothorax.
  - Life-threatening hemoptysis despite bronchial embolization.

Timing of listing:

- Chronic respiratory failure.
  - With hypoxia alone (partial pressure of oxygen [Pao_2] <8 kPa or <60 mm Hg).
  - With hypercapnia (partial pressure of carbon dioxide [$Paco_2$] >6.6 kPa or >50 mm Hg).
- Long-term non-invasive ventilation therapy.
- Pulmonary hypertension.
- Frequent hospitalization.
- Rapid lung function decline.
- World Health Organization Functional Class IV.

COPD

Timing of referral:

- Disease is progressive, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.
- Patient is not a candidate for endoscopic or surgical LVRS. Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.
- BODE index of 5 to 6.
- $Paco_2$ >50 mm Hg or 6.6 kPa and/or Pao_2 <60 mm Hg or 8 kPa.
- FEV_1 <25% predicted.

Timing of listing (presence of one criterion is sufficient):

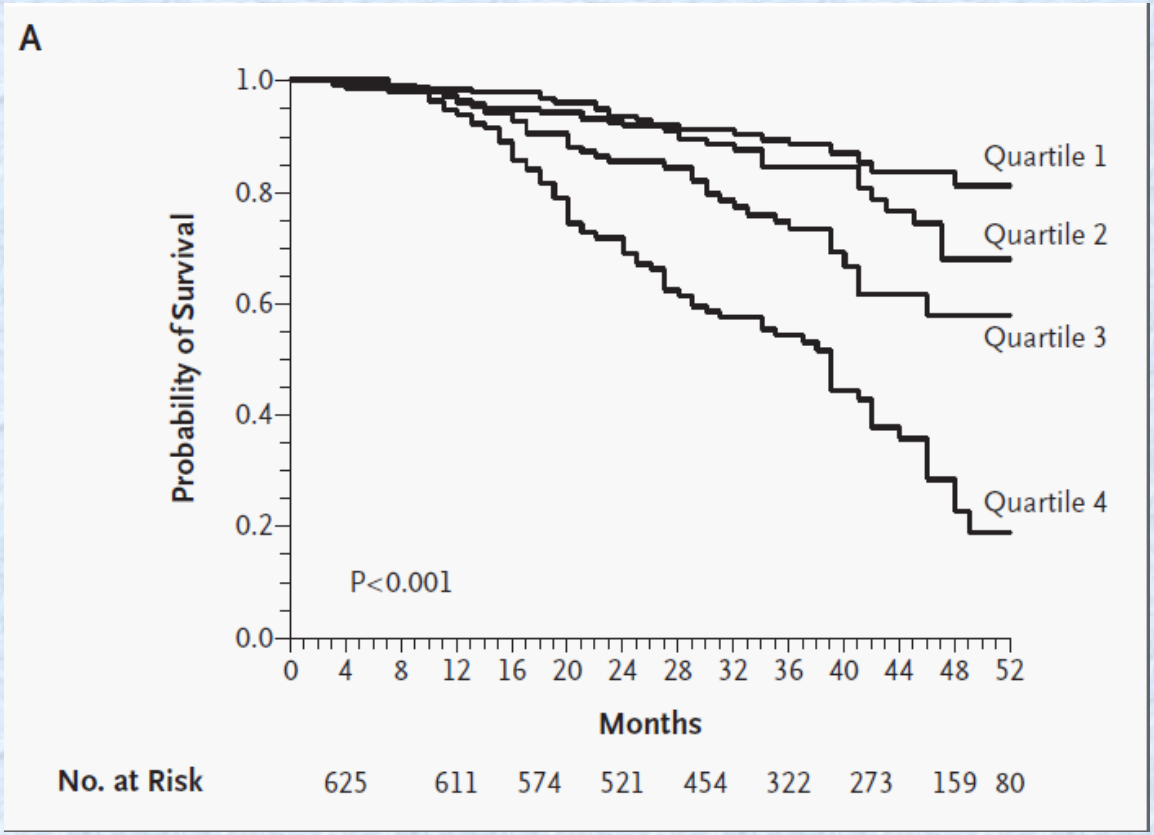
- BODE index ≥7.
- FEV_1 <15% to 20% predicted.
- Three or more severe exacerbations during the preceding year.
- One severe exacerbation with acute hypercapnic respiratory failure.
- Moderate to severe pulmonary hypertension.

BODE index

Number of points	0	1	2	3
FEV_1 (% pred.)	≥65	50-64	36-49	≤35
6MWD (m)	≥350	250-349	150-249	≤149
Dyspnea (MMRC)	0-1	2	3	4
BMI (kg/m^2)	>21	≤21		

MMRC Dyspnea Scale	
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Survival according to BODE index



- Quartile 1: 0-2 pt.
- Quartile 2: 3-4 pt.
- Quartile 3: 5-6 pt.
- Quartile 4: 7-10 pt.

Pulmonary vascular diseases

Timing of referral:

- NYHA Functional Class III or IV symptoms during escalating therapy.
- Rapidly progressive disease (assuming weight and rehabilitation concerns not present).
- Use of parenteral targeted pulmonary arterial hypertension (PAH) therapy regardless of symptoms or NYHA Functional Class.
- Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

Timing of transplant listing:

- NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
- Cardiac index of <2 liters/min/m^2.
- Mean right atrial pressure of >15 mm Hg.
- 6-minute walk test of <350 m.
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).[1,61,62]

LuTx: evaluation of candidates

- Standardized protocol !

- Complete evaluation (clinical, laboratory, cardiopulmonary function, endoscopic,..)
- Lung size: chest X-ray in 1 m distance
- Imunology: ABO system, HLA sensitization
- Quantitative lung perfusion scintigraphy
- Right heart catheterization: PAH
- Psychological examination !

Example of protocol

Protokol vyšetření před TX plic 1.strana - náběry štítek

datum	náběry
	HLA typizace, Luminex *(termín objednat v IKEM tel. 261 362 353)* Cytotoxické protilátky (CDC)
	Hematologie: Krevní skupina, KO+diff., Quick, APTT
	Biochemie: Na, K, Cl, Ca, P, Fe, Mg, kys. močová, cholesterol, TAG, HDL, LDL, glukóza, glykovaný hemoglobin, CRP, ALT, AST, ALP, GMT, AMS, LD, CK, Celk. bílkovina, albumin, transferin, prealbumin, cholinesteráza, elfo bílkovin, bilirubin alfa-1-antitrypsin panel hepatitid onkomarkery - CEA všem, u žen CA 15-3, u mužů PSA 25-OH D vitamin, TSH
	Moč: bioch. + sediment moč K+C **kotinin**
	Moč za 24 hod. Clearance kreatininu/24h Proteinurie/24h Elfo bílkovin moče Mikroalbuminurie/24h Odpady minerálů/24h (Na, K, Ca, Cl, P) Frakční exkrece minerálů Na, K, Cl
	Moč za 3 hod. Hamburger sediment
	Imunologie: IgA, M,G, IgE, C3, C4, CIK-PEG, ANA, ANCA, ACLA, RF, ds DNA
	Serologie: BWR, Toxoplasma, Aspergillus, Candida
	Virologie: HSV, VZV, EBV, CMV, CMV-PCR
	HIV
	Mikrobiologie: - kultivace na BK - MGIT statim 3x*(posílá se jako na BK)*, Quantiferon, MTXII - kultivace sputa nespec fl. 2x - sputum na mykózy U CF **sputum PCR na Burkholderia cepacia** - *posílat na mikrobiol.FN Motol*
	MTX II + prosim zapsat výsledek sem
	Quantiferon
	Stolice na OK - 1.odběr - 2.odběr - 3.odběr

Protokol vyšetření před TX plic 2.strana – vyšetření štítek

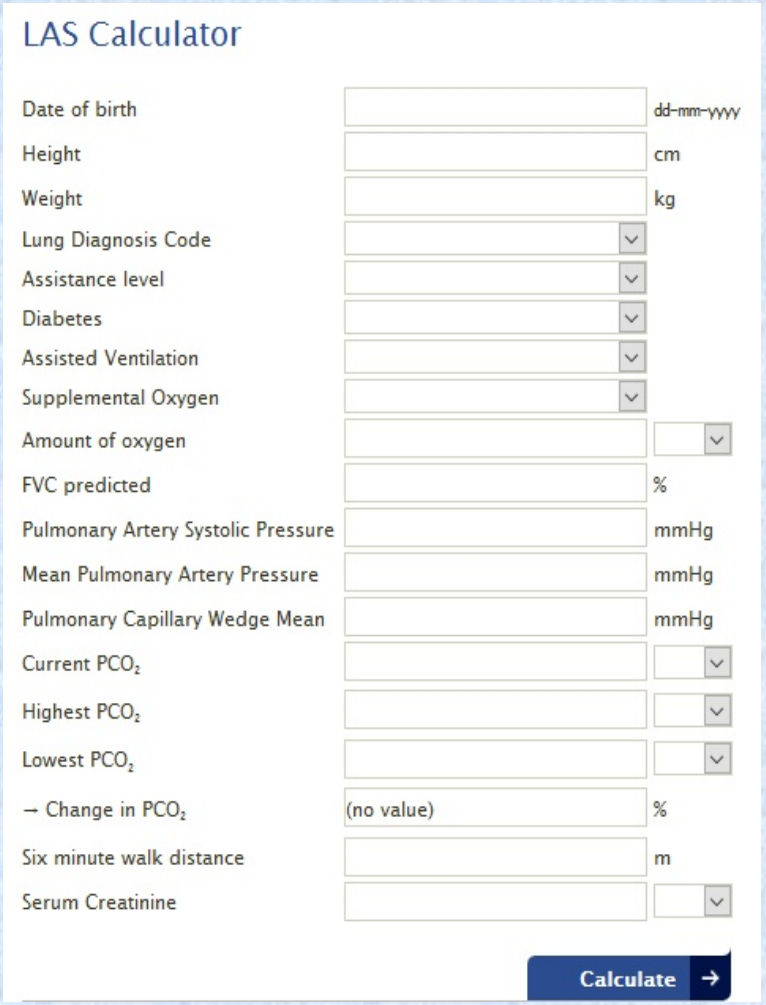
výsledek v systému	žádanka vypsána / datum vyšetření	vyšetření
		Perfusní scintigrafie plic *(l.4626)*
		Katetrizace pravostranná + Koronarografie *(l.4914, 4967)*
		ECHO *(l.4966)*
		Sono karotid, sono tepen dolních končetin po třísla *(elektronicky lékař, event. l. 8129)*
		Denzitometrie + vyš. v osteocentru *(obj. v ÚVN, tel. 973 202 878, či v místě bydliště)*
		O2 test *(l. 6694)*
		Bronchoskopie *(l. 6685)*
		Body test, DLCO *(l.6669, 6675)*
		6MWT
		Psychologické vyšetření (elektronicky lékař, *Mgr. Hodková tel. 721 100 359)*
		RTG z 1.m
		Sono břicha + UZ ledvin s popisem rozměrů ledvin a parenchymu ledvin *(elektronicky lékař)*
		HRCT+CT s kontrastem- popis pulmonálních tepen *(elektronicky lékař)*
		CT VDN u CF *(elektronicky lékař)*
		Zubní vyšetření *(lze u oš. zubaře)*
		24 hodinové pH/impedanční monitorování + high resolution manometrie jícnu *(obj. tel. 4021 - FNM, příp. kontaktní osoba MUDr. Štoviček. lze dovyš. až po zařazení na WL)* - objednávat obojí najednou – pHmetrie+manometrie jícnu!!!
		ženy: gynekologie mammografie (event. sono prsů)
		muži: urologie
		konzilia
		Nefrologické konzilium s výsledky - prof. Matoušovic
		Infekční konzilium s výsledky *(odesílá lékař elektronicky)*
		Konzilium fyzioterapeuta – edukace respirační fyzioterapie
X		Při význ. plicní hypertenzi kontaktovat Centrum pro plicní hypertenzi II. Interní kliniky VFN, Dr. Jansa

Waiting list (WL)

- Suitable candidates are listed
- Visits every 3 months, re-evaluation every 6-12 months (depends on disease stability)
- 50 new LuTx candidates every year in CZ
- Median WL time: 150 days
- WL mortality: Eurotransplant 10-15%

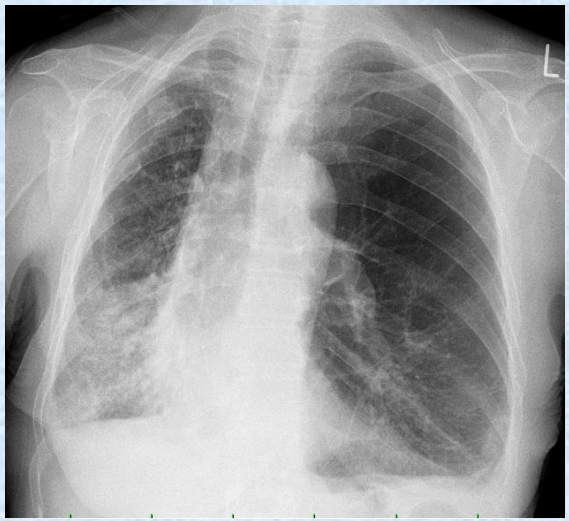
Lung allocation score (LAS)

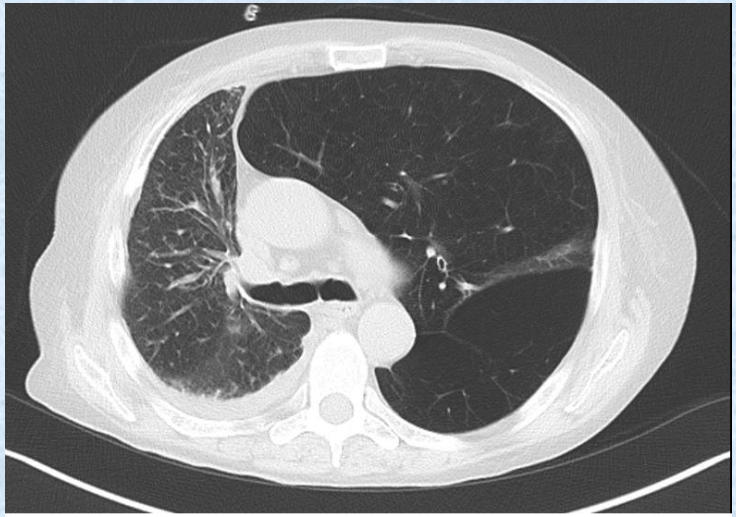
- Evaluates urgency of LuTx
- Introduced in 2005 in the U.S.A.
- Eurotransplant: 2011
- Czech Republic: 2014
- Calculated every 3 months and when disease progresses
- Urgent patients: LAS >40-50 pts.



Problems in COPD

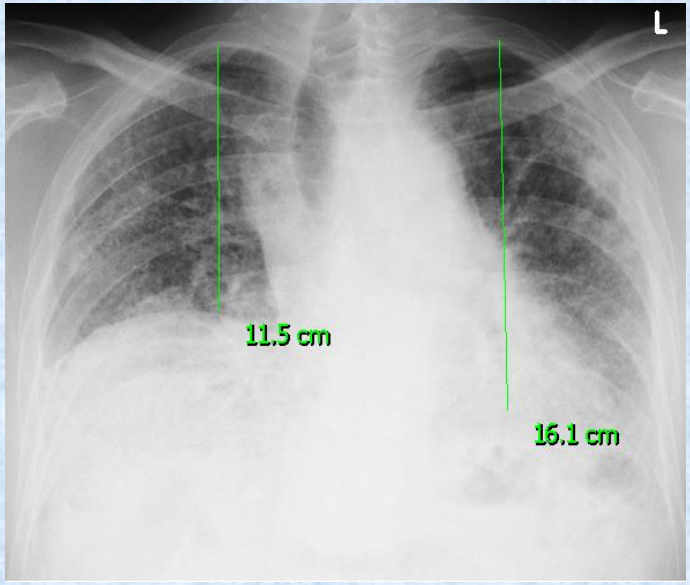
- Higher age: more comorbidities
- Smokers are not suitable for LuTx
- SLTx in emphysema: risk of hyperinflation of native lung with graft dysfunction

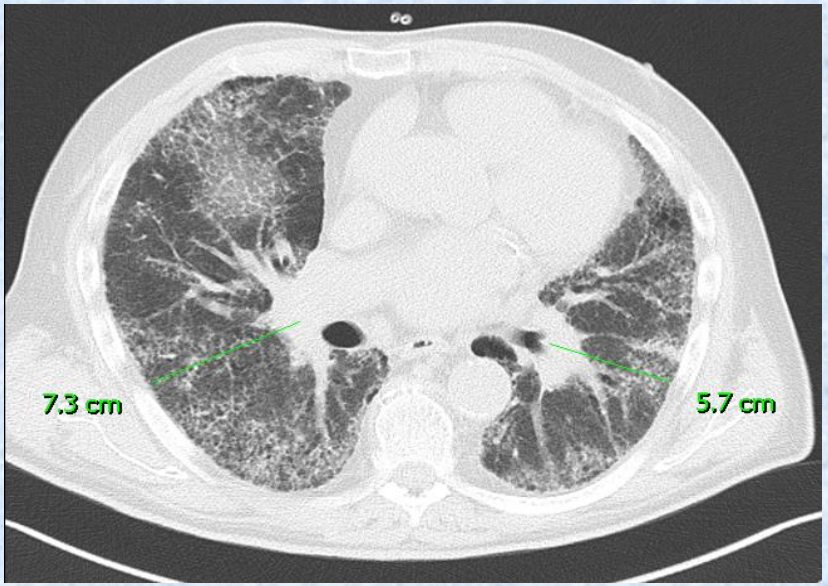




Problems in ILD

- Worse results of LuTx
- Small pleural cavities
- Frequent PAH: SLTx is not appropriate
- Patients on steroids: obesity and osteoporosis





Problems in CF

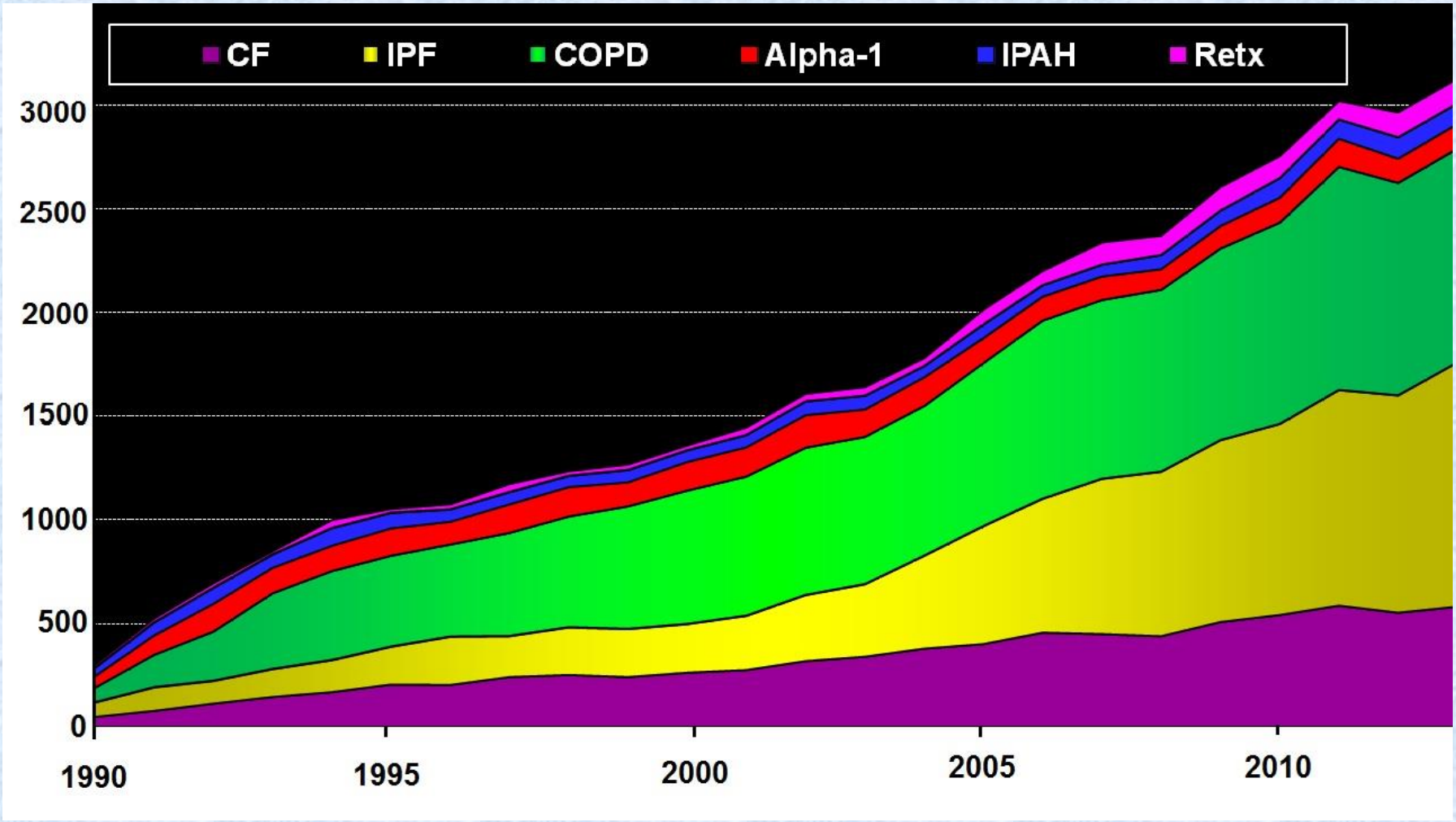
- Infection with resistant Gram-negative bacteria
  - *B. cepacia* complex, *A. xylosoxidans*, MDR *P. aeruginosa*
- Infection with nontuberculous mycobacteria
  - *M. abscessus*

Ex vivo lung perfusion and reconditioning

- Allows evaluation of graft function in *ex vivo* conditions
- prof. Steen: in 2007 first LuTx after *ex vivo* reconditioning (initially not accepted organ)
- XVIVO system (Toronto 2011, prof. Keshavjee)

Number of LuTx in adults

Number of LuTx by diagnoses



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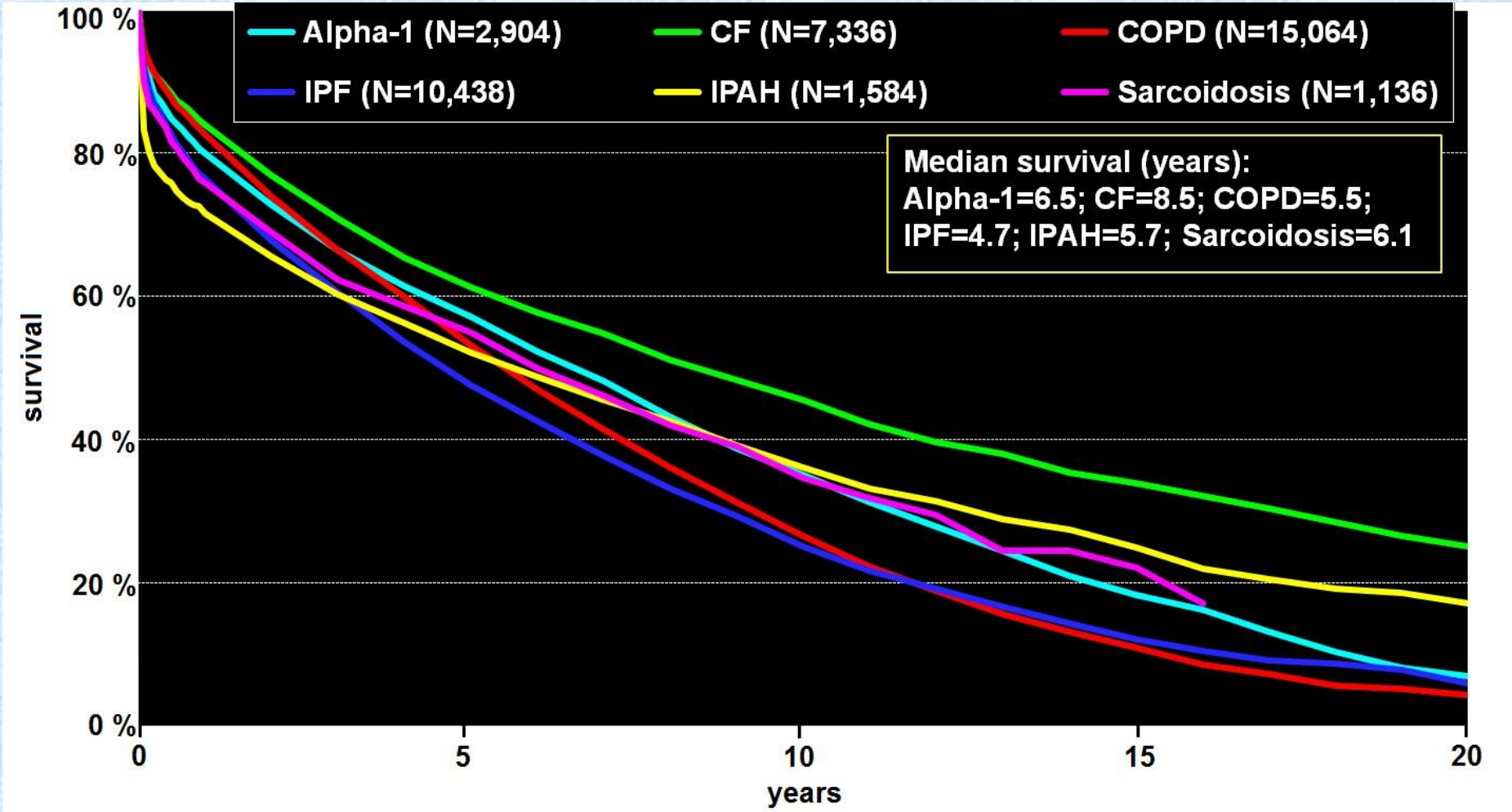
Survival after LuTx in adults

Survival after LuTx by diagnoses



LuTx: donor selection

- Age <55 y, similar lung size and AB0 system
- Normal CXR lung appearance
- P_aO_2 >300 mm Hg (FiO_2 1,0 and PEEP 5)
- Without purulent secretions in the lower airways
- Negative sputum microscopy (Gram staining)
- No chest trauma, aspiration and sepsis
- No lung diseases and cardiopulmonary surgery
- Smokers <20 pack-years

Evaluation of potential donor

- Hight and weight
- Chest shape, lung size (1 m CXR)
- AB0 system
- Bronchoscopy
- IMV with FiO_2 <0,4
- Preventive measures against lung edema

- Only approx. 15% of donors are suitable for LuTx !

LuTx: choice of procedure

- SLTx: diseases with low compliance (fibroses) and COPD without predominant emphysema
- DLTx: diseases with high compliance (emphysema), septic diseases (CF) and IPAH
- HLTx: Eisenmenger's syndrome and conditions with left heart failure
- „split-lung Tx“ and lobar Tx from living donors: children and adults of short stature

LuTx: surgical aspects

- Organ harvesting after evaluation of donor lung (also macroscopic appearance)
- Donor lung is stored in Perfadex solution on 4°C temperature
- Maximal cold ischemia time is 6-8 hours
- LuTx recipient: in DLTx two sequential anterolater thoracotomies or „clamshell“ incision
- Sometimes is ECMO used

Early after LuTx

- ICU stay
- Risk of reperfusion edema, early rejection and infection
- Ideally: extubation in few hours
- Further care: immunosuppression, antibiotics, analgesics, nutritional therapy, chest physiotherapy

Immunosuppression

- Early high doses of methylprednisolone and antithymocyte globulin
- Chronic immunosuppression: prednisone + tacrolimus (substituted cyclosporine A) + mycophenolate mophetil
- Monitoring of drug levels (tacrolimus and cyclosporine A: nephrotoxicity)
- Post-transplant lymphoproliferative disorder

Infection management

- CMV: hyperimmune globulin and ganciclovir early after LuTx
- *Pneumocytis jiroveci*: lifelong preventive administration of cotrimoxazole
- During bronchial anastomoses healing: gentamicin and amphotericine B
- Further ATB based on previous cultures (eg. in CF patients)

Further care after LuTx

- Protocol-based !
- Lenght of hospital stay 3-4 weeks
- Visits every 4-8 weeks, stable patients every 3 months
- Lung function tests, chest X-ray, bronchoscopy with TBBx (chronic rejection)
- In-patient treatments for any intercurrent diseases are performed usually in Tx centre

Limitations of LuTx

- Selection of candidates: contraindications
- Organs accessibility: donors shortage
- Primary graft dysfunction: low predictability of graft function
- Survival after LuTx: infections and CLAD (chronic lung allograft dysfunction)

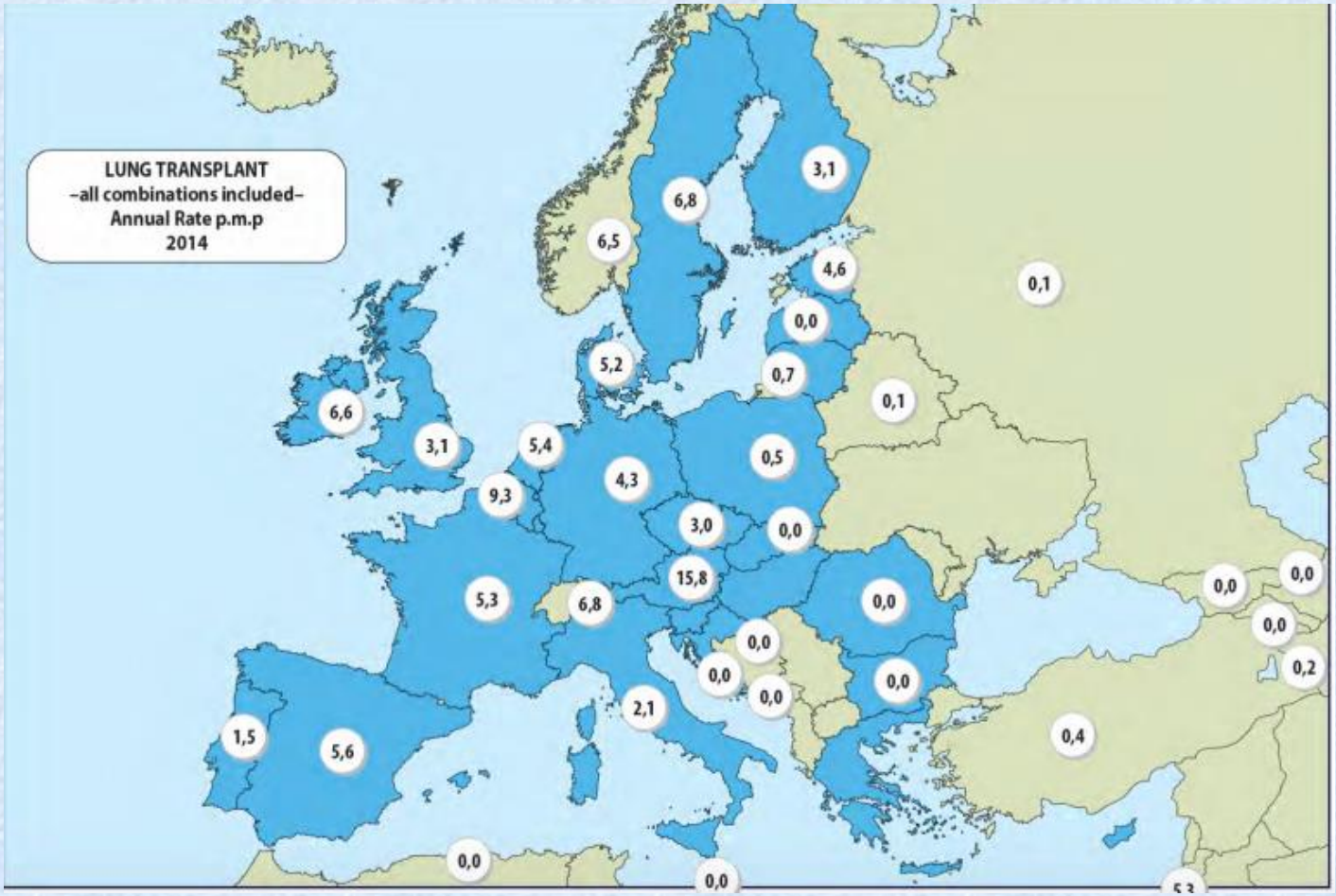
  - BOS (bronchiolitis obliterans syndrome)
  - RAS (restrictive allograft syndrome)
  - CLAD from other causes than rejection

Other complications

- Stenoses of bronchial anastomoses
- Infections (aspergillus, pseudomonas, pneumocystis, CMV), nephrotoxicity (calcineurin inhibitors), osteoporosis and diabetes (CS)
- Lymphoproliferation and lymphomas (IS), malignancies (BCA in COPD or IPF in SLTx)
- Recurrence of primary disease (sarcoidosis)

Number of LuTx in Europe

LuTx per 1.000.000 population



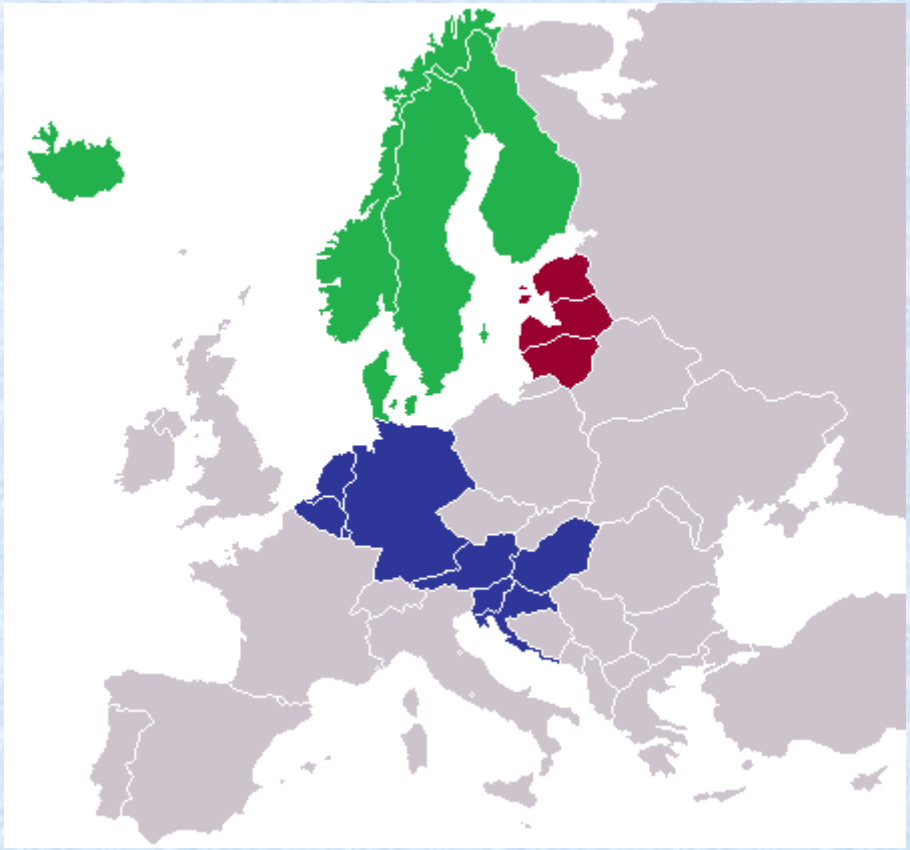
Numbers of LuTx and pacients on WL

- Eurotransplant:
- 135 000 000 population
- WL: approx. 760 patients (eg. 5.6/1 000 000)
- LuTx: approx. 650 yearly (eg. 4.8/1 000 000)

- The Czech Republic:
- 10 000 000 population
- WL: approx. 55-60 patients
- LuTx: approx. 45-50 yearly

International cooperation in Europe

- Scandiatransplant
- Balttransplant
- Eurotransplant



Conclusions

- LuTx is established treatment method in advanced lung diseases
- Evaluation of LuTx candidates and patients management after LuTx is protocol-based
- Approx. 75% of evaluated candidates are listed for LuTx and approx. 75% of listed patients undergo LuTx
- 5-year survival after LuTx is approx. 50 %
- Shortage of donors is continuing problem