Evidence tables

Author, Year, Study design	Clinical Trial Design	Study size; population, setting	Intervention group	Control group	Outcome assessed, instruments	Results	Comments (limitations, sources of potential bias)
National emphysema treatment trial (NETT) research group, 2003	Prospective randomized Two arms Intention-to-treat analysis	N=1218 (32.2 % of screened) Patients with severe emphysema underwent pulmonary rehabilitation and were randomized to receive LVRS or continued medical treatment	N=608 (95.4% received surgery; 3.5% refused; 1.2 judged unsuitable post randmz.) Bilateral LVRS. MS: 70%; VATS: 30% Deviation from bilateral protocol: 2% Median time from randmz to surgery: 10 days. 0.7 % of pts. received lung transplants post LVRS	N=610 5.4% received LVRS outside of NETT 2.5% received lung transplants during follow up	**Primary**: survival; maximum exercise capacity (>10watts) 2 yrs. post random. **Secondary**: quality of life (Medical Outcomes Study: SF36; Quality of Well-Being Scale: QWB; St. George's Respiratory Questionnaire: SGRQ) Shortness of breath (UCSD SOBQ); *p*ulmonary function (FEV1) and gas exchange; radiological studies; oxygen requirement; 6-min walk distance; cardiovascular measures; attention and psychomotor functioning: cost-effectiveness. Follow up at baseline, 6, 12, and 24 mos.	99% of surviving pts. in follow-up as of December 2002. Mean f/up: 29.2 mos. **All patients (N=1218):** 90-day mortality rate: LVRS group: 7.9% (CI 5.9 to 10.3%) vs. medical: 1.3 % ($p<0.001$); rate similar for VATS and MS (6.1 vs. 8.6 %, p=0.33) Total mortality rate: 0.11 deaths/persons/year in both groups. No difference in overall mortality between groups (p=0.90). Exercise capacity at 6,12, and 24 mos improved>10 watts in 28, 22, and 15% of LVRS pts vs. 4, 5, and 3% of medical pts. ($p<0.001$ at each time) LVRS pts. showed statistically significant percentage improvement in 6mwd, FEV1, quality of life and dyspnea measures **(See tables 1,2 and 3 for results from high-risk and non-high risk subgroups)**	Group assignment not masked to subjects or investigators

Author, Year	Clinical Trial Design	Study size; population	Intervention group	Control group	Outcome assessed, instruments	Results	Comments (limitations, sources of potential bias)
National emphysema treatment trial (NETT) research group, 2001	Prospective randomized Two arms	N=1033 High-risk group: N=140	N=69	N=70	Same as above	30-day mortality: 16% for LVRS vs. 0 for medical group ($p<0.001$) Overall mortality rate higher in surgical pts: 0.43 vs. 0.11 deaths per person-year; relative risk: 3.9 Surgical survivors had small improvements at 6 mos in exercise capacity, 6mwd, FEV1 but similar health-related quality of life.	Experimental intervention was not masked
Geddes 2000	Prospective randomized Two arms	N=48 (27.6 % of screened) Pts. w/ severe emphysema as shown by CT w/no restriction on disease distribution Age<75; DLco<30% Walk <150m	N=24 Bilateral LVRS Median sternotomy (MS) or thoracoscopic (VATS): numbers NR Stapled resection 6 weeks rehab prior to random..	N=24 6 weeks of rehab prior to random.	Mortality Morbidity SF-36 score Shuttle walking distance Pulmonary function (FEV1, DLco, other)	17 % lost to follow up at 12 months Mortality at 30 days: 12.5 % for LVRS vs. 0 for medical group Mortality at 12 mos: 20.8 % for LVRS vs. 8.4 % for medical	Five of first 15 pts died early in trial; pts had gas transfer values of <30% predicted or walking distance <150 m. Entry criteria modified to exclude these pts. Follow up at baseline, 3, 6, and 12 mos post randomiz.ation
Author,	**Clinical**	**Study size;**	**Intervention**	**Control**	**Outcome assessed,**	**Results**	**Comments**

Year	Trial Design	population	group	group	instruments		(limitations, sources of potential bias)
Pompeo et al 2000	Prospective randomized Two arms	N=60 (25.3 % of screened) Diffuse bullous and non-bullous severe emphysema w/ heterogeneous distribution by CT FEV1 <40% DLco >20 % 4 mo smoking abstinence Age 75 or less No comorbidity	N=30 Unilateral (N=13) and bilateral (N=17) VATS Stapled resection No pre-randomiz. rehab	N=30 6 wks rehab after randomiz.	Mortality Morbidity Dyspnea index Six-minute walk test Pulmonary function measures (FEV1, others) F/up at baseline, 3 and 6 mos post-randomization	Mortality at 6 mos: 6.7 % for LVRS vs. 3.3 % for medical 3 % of pts lost to f/up at 6 mos.	
Criner et al 1999	Prospective randomized Two arms	N=37 (18.5 % of screened) NY Heart Association Class III-IV (?) Evidence of airflow obstruction (FEV1<30%) Diffuse bullous emphysema by HRCT No significant comorbidity	N=19 Bilateral MS Stapled resection 8 wks of pre-randomiz. rehab	N=18 8 wks of pre-randomiz. Rehab Further 3 mos post-randomiz. rehab	Mortality Morbidity Sickness impact profile SF-36 Six-minute walk test Symptom limited incremental treadmill test Pulmonary function measures (FEV1, DLco, others) F/up at baseline (post-rehab), 3 mos	13 % of pts lost to f/up at 3 mos Mortality at 30 days: NR Mortality at 3 mos: 16.7 % for LVRS vs. 0 % for medical	Five of first 15 pts (3 surgical, 2 medical) died early in the trial. All had DLco<30% or walking distances <150m; entry criteria modified to exclude these pts. Protocol allowed crossover of pts from medical to surgical arm after completion of 3-mo evaluation; 13/18 pts did this
Author, Year	**Clinical Trial**	**Study size; population**	**Intervention group**	**Control group**	**Outcome assessed, instruments**	**Results**	**Comments (limitations, sources**

	Design						**of potential bias)**
Wilkens et al 2000	Prospective Non-randomized Two arms, formed based on pt preference	N=57 (63.3 % of screened) MRC Dyspnea score: = or >3 Smoking cessation >3mo TLC >120 of predicted	N=29 Bilateral MS (23/29) Anterolateral thoracotomy (6/29) Stapled resection 6 wks rehab pre-treatment	N= 28 Pts agreed to postpone LVRS for one year 6 wks rehab pre-treatment	MRC dyspnea score Six –minute walk test Pulmonary function measures (FEV1, DLco, others)	29%, 40%, 54% of pts lost to f/up at 6, 12, 18 mos.	After 18 mos, 5 pts underwent LVRS (data not included in results)

Table 1a. 90-day mortality rate. (a)

	LVRS Deaths/N (%)	**Medical Deaths/N (%)**	**P-value** (b)
All Patients	48/608 (7.9)	8/610 (1.3)	<0.001
High-risk patients (c)	20/70 (28.6)	0/70 (0)	<0.001
Other Patients	28/538 (5.2)	8/540 (1.5)	0.001
Subgroups			
Upper lobe			
Low exercise (d)	4/139 (2.9)	5/151 (3.3)	1.00
High exercise	6/206 (2.9)	2/213 (0.9)	0.17
Non-upper lobe			
Low exercise	7/84 (8.3)	0/65 (0)	0.02
High exercise	11/109 (10.1)	1/111 (0.9)	0.003

(a) Mortality was measured from the date of randomization in both treatment groups.
(b) P-value comparing proportions dead in the LVRS and medical groups (Fisher's exact test).
(c) High-risk patients have FEV1 <or = 20% predicted and either heterogeneous emphysema on CT or DLco < or = 20% predicted
(d) Low (high) baseline exercise capacity is defined as post-rehabilitation baseline maximum work > or = the gender specific 40th percentile for post-rehabilitation baseline maximum work (25 watts for females, 40 watts for males).

Table 1b. Overall mortality rates (a)

	LVRS Deaths/N (rate/patient/year)	**Medical Deaths/N (rate/PY)**	**Risk-ratio LVRS : medical (P-value)** (b)
All Patients	157/608 (0.11)	160/610 (0.11)	1.01 (0.90)
High-risk patients (c)	42/70 (0.33)	30/70 (0.18)	1.82 (0.06)
Other Patients	115/538 (0.09)	130/540 (0.10)	0.89 (0.31)
Subgroups			
Upper lobe			
Low exercise (d)	26/139 (0.07)	51/151 (0.15)	0.47 (0.005)
High exercise	34/206 (0.07)	39/213 (0.07)	0.98 (0.70)
Non-upper lobe			
Low exercise	28/84 (0.15)	26/65 (0.18)	0.81 (0.49)
High exercise	27/109 (0.10)	14/111 (0.05)	2.06 (0.02)

a) Total mortality rates are based on a mean follow-up of 29.2 months.
b) P-value comparing proportions dead in the LVRS and medical groups (Fisher's exact test).
c) High-risk patients have FEV1 <or = 20% predicted and either heterogeneous emphysema on CT or DLco < or = 20% predicted
d) Low (high) baseline exercise capacity is defined as post-rehabilitation baseline maximum work > or = the gender specific 40th percentile for post-rehabilitation baseline maximum work (25 watts for females, 40 watts for males).

Table 1c. Overall mortality: percent of total by group defined by individual risk factor [a]

Distribution of emphysema

Upper lobe	LVRS	Medical	Total	Non upper lobe	LVRS	Medical	Total
Alive	285	274	559	Alive	138	136	274
Dead	60	90	150	Dead	55	40	95
Total	345	364	709	Total	193	176	369
Mortality %	17.4%	24.7%	21.2%	Mortality %	28.5%	22.7%	25.7%
	CHI	p =	0.017		CHI	p =	0.275
	Fisher		0.021		Fisher		0.234

Exercise capacity at baseline

High Exercise	LVRS	Medical	Total	Low Exercise	LVRS	Medical	Total
Alive	254.0	271.0	525	Alive	169	139	308
Dead	61.0	53.0	114	Dead	54	77	131
Total	315.0	324.0	639.0	Total	223	216	439
Mortality %	19.4%	16.4%	17.8%	Mortality %	24.2%	35.6%	29.8%
	CHI	p =	0.321		CHI	p =	0.028
	Fisher		0.352		Fisher		0.009

[a] Based on a mean follow-up of 29.2 months.

Table 2a. Improvement in exercise capacity (maximum work). (a)

	LVRS Improved/N (%)	**Medical Improved/N (%)**	**Odds-ratio LVRS : medical (P-value)** (b)
All Patients	54/371 (15)	10/378 (3)	6.27 (p<0.001)
High-risk patients (c)	4/58 (7)	1/48 (2)	3.48 (0.37)
Other Patients	50/313 (16)	9/330 (3)	6.78 (p<0.001)
Subgroups			
Upper lobe			
Low exercise (d)	25/84 (30)	0/92 (0)	∞ (<0.001)
High exercise	17/115 (15)	4/138 (3)	5.81 (0.001)
Non-upper lobe			
Low exercise	6/49 (12)	3/41 (7)	1.77 (0.5)
High exercise	2/65 (3)	2/59 (3)	0.90 (1.0)

(a) 24 mos after randomization. Improvement in exercise capacity is defined as an increase in maximum work more than 10 watts above the patient's post-rehabilitation baseline; patients who died or who missed the 24 months assessment were considered not improved.
(b) P-value from Fisher's exact test comparing proportions improved in the LVRS and Medical groups.
(c) High-risk patients have FEV1 < or = 20% predicted and either heterogeneous emphysema on CT or DLco < or = 20% predicted
(d) Low (high) baseline exercise capacity is defined as post-rehabilitation baseline maximum work below or at (above) the gender specific 40th percentile for post-rehabilitation baseline maximum work (25 watts for females, 40 watts for males).

Table 2b. Improvement in quality of life (SGRQ). (a)

	LVRS Improved/N (%)	**Medical Improved/N (%)**	**Odds-ratio LVRS : medical (P-value)**
All Patients	121/371 (33)	34/378 (9)	4.90 (<0.001)
High-risk patients	6/58 (10)	0/48 (0)	∞ (0.03)
Other Patients	115/313 (37)	34/330 (10)	5.06 (<0.001)
Subgroups			
Upper lobe			
Low exercise	40/84 (48)	9/92 (10)	8.38 (<0.001)
High exercise	47/115 (41)	15/138 (11)	5.67 (<0.001)
Non-upper lobe			
Low exercise	18/49 (37)	3/41 (7)	7.35 (0.001)
High exercise	10/65 (15)	7/59 (12)	1.35 (0.61)

(a) 24 mos after randomization. Improvement in quality of life defined as a decrease in the St. George's Respiratory Questionnaire score of more than 8 units below the patient's post-rehabilitation baseline; patients who died or who missed the 24 month assessment were considered not improved.

Table 3a. Inclusion Criteria*

Assessment	Criteria
History and physical examination	Consistent with emphysema
	BMI, ≤ 31.1 kg/m^2 (men) or ≤ 32.3 kg/m^2 (women)
	Stable with ≤20 mg prednisone (or equivalent) qd
Radiographic	HRCT scan evidence of bilateral emphysema
Pulmonary function (prerehabilitation)	FEV_1, ≤ 45% predicted (≥ 15% predicted if age ≥70 years)
	TLC, ≥100% predicted post-bronchodilator
	RV, ≥150% predicted post bronchodilator
Arterial blood gas level (prerehabilitation)	P_{CO_2}, ≤ 60 mm Hg (P_{CO_2}, ≤ 55 mm Hg if one mile above sea level)
	P_{O_2}, ≥ 45 mm Hg on room air (P_{O_2}, ≥ 30 mm Hg if one mile above sea level)
Cardiac assessment	Approval for surgery prior to randomization by cardiologist if any of the following are present: unstable angina; LVEF cannot be estimated from the echocardiogram; LVEF < 45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (> 5 PVCs per minute; cardiac rhythm other than sinus; PACs on EKG at rest)
Surgical assessment	Approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation
Exercise	Post-rehabilitation 6-min walk of ≥140 m; able to complete 3 min unloaded pedaling in exercise tolerance test (pre- and post-rehabilitation)
Consent	Signed consents for screening, and rehabilitation.
Smoking	Plasma cotinine level ≤ 13.7 ng/mL (or arterial carboxyhemoglobin ≤ 2.5% if using nicotine products)
	Nonsmoking for 4 mo prior to initial interview and throughout screening
Rehabilitation/ adherence	Must complete pre- rehabilitation assessments, rehabilitation program, and all post-rehabilitation assessments

* Patients must meet all criteria to be eligible for the procedure. BMI = body mass index; HRCT = high-resolution computed tomography; LVEF = left ventricular ejection fraction; PAC = premature atrial contraction; PVC = premature ventricular contraction; RV = residual volume; TLC = total lung capacity.

Table 3b. Exclusion Criteria*

Assessment	Criteria
Previous surgery	Lung transplant
	LVRS
	Sternotomy or lobectomy
Cardiovascular	Dysrhythmia that might pose a risk during exercise or training
	Resting bradycardia (< 50 beats/min); frequent multifocal PVCs; complex ventricular arrhythmia; sustained SVT
	History of exercise-related syncope
	MI within 6 mo and LVEF < 45%
	Congestive heart failure within 6 mo and LVEF < 45%
	Uncontrolled hypertension (systolic, > 200 mm; diastolic, > 110 mm)
Pulmonary	History of recurrent infections with clinically significant sputum production
	Pleural or interstitial disease that precludes surgery
	Clinically significant bronchiectasis
	Pulmonary nodule requiring surgery
	Giant bulla (> 1/3 volume of lung)
	Pulmonary hypertension: peak systolic PPA, ≥ 45 mm Hg (Denver criterion: ≥ 50 mm Hg) or mean PPA, ≥ 35 mm Hg (Denver criterion: ≥ 38 mm Hg). (Right heart catheter is required to rule out pulmonary hypertension if peak systolic PPA on echocardiogram is ≥ 45 mm Hg)
	Requirement for > 6 L O_2 to keep saturation ≥ 90% with exercise
Radiographic	CT evidence of diffuse emphysema judged unsuitable for LVRS
General	Unplanned weight loss of > 10% usual weight in 90 d prior to enrollment
	Evidence of systemic disease or neoplasia expected to compromise survival during 5-yr period
	6-min walk distance ≤140 m after rehabilitation
	Any disease or condition that interferes with completion of initial
	Unwillingness or inability to complete screening or baseline data collection procedures

* The presence of any one criterion makes the patient ineligible for the procedure; MI = myocardial infarction; PPA = pulmonary artery pressure; SVT = supraventricular tachycardia. For other abbreviations, see Table 3a.