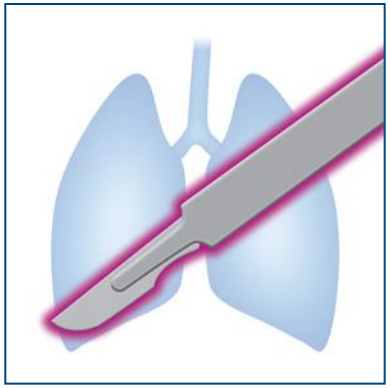
Pneumo Update Europe 2017

9-10 June, Vienna

Thoracic Surgery & Lung Transplantation



Gilbert Massard, France

Methodology

- Review of the thoracic surgical literature
- Selection of papers which might be of interest for pulmonary physicians
- Preference to reviews, registry studies and meta-analyses

Thoracic surgery

VATS lobectomy: Striving towards evidence ?

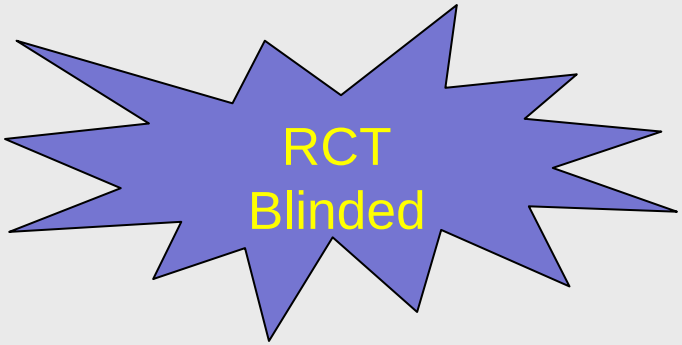
State of the Art

VATS lobectomy is credited as the gold standard because of reduced complication rate and hospital stay, while long term results remain comparable to open lobectomy

However:

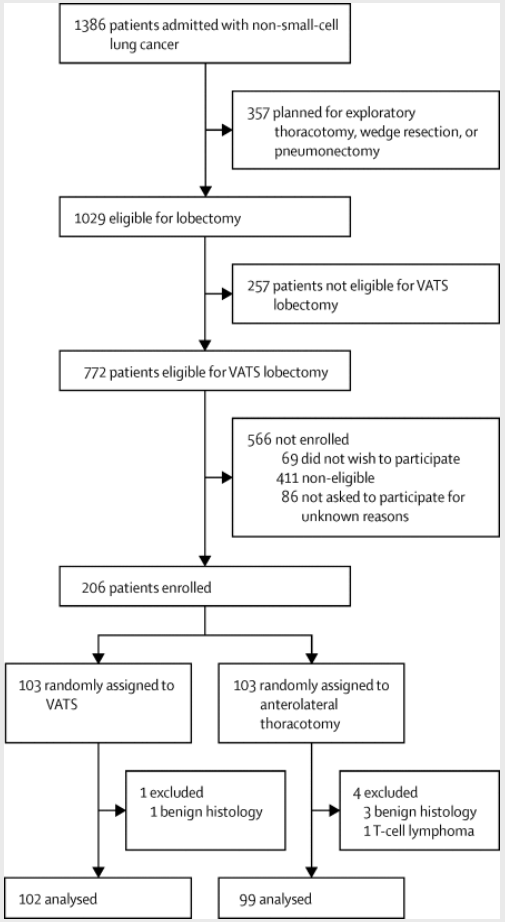
- Evidence is based on registry studies, systematic reviews and meta-analyses only
- Commercial pressure and opinions disseminated though social media bypass evidence based surgery !!
- Quality of oncologic surgery in terms of extent of lymph node dissection is questioned

Postoperative pain and quality of life after lobectomy via VATS or anterolateral thoracotomy for early stage lung cancer



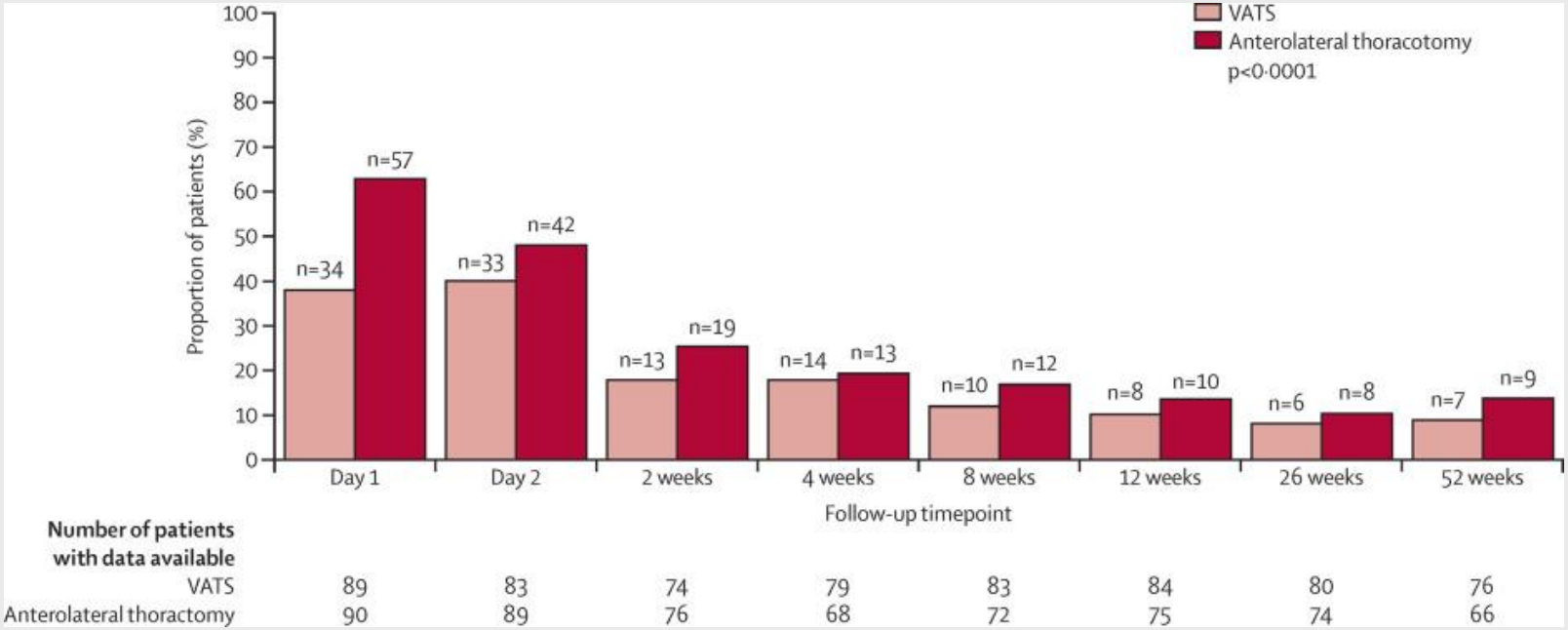
Endpoints

- Post-operative pain
- Quality of life



Bendixen M et al, Lancet Oncol 2016;17:836-44

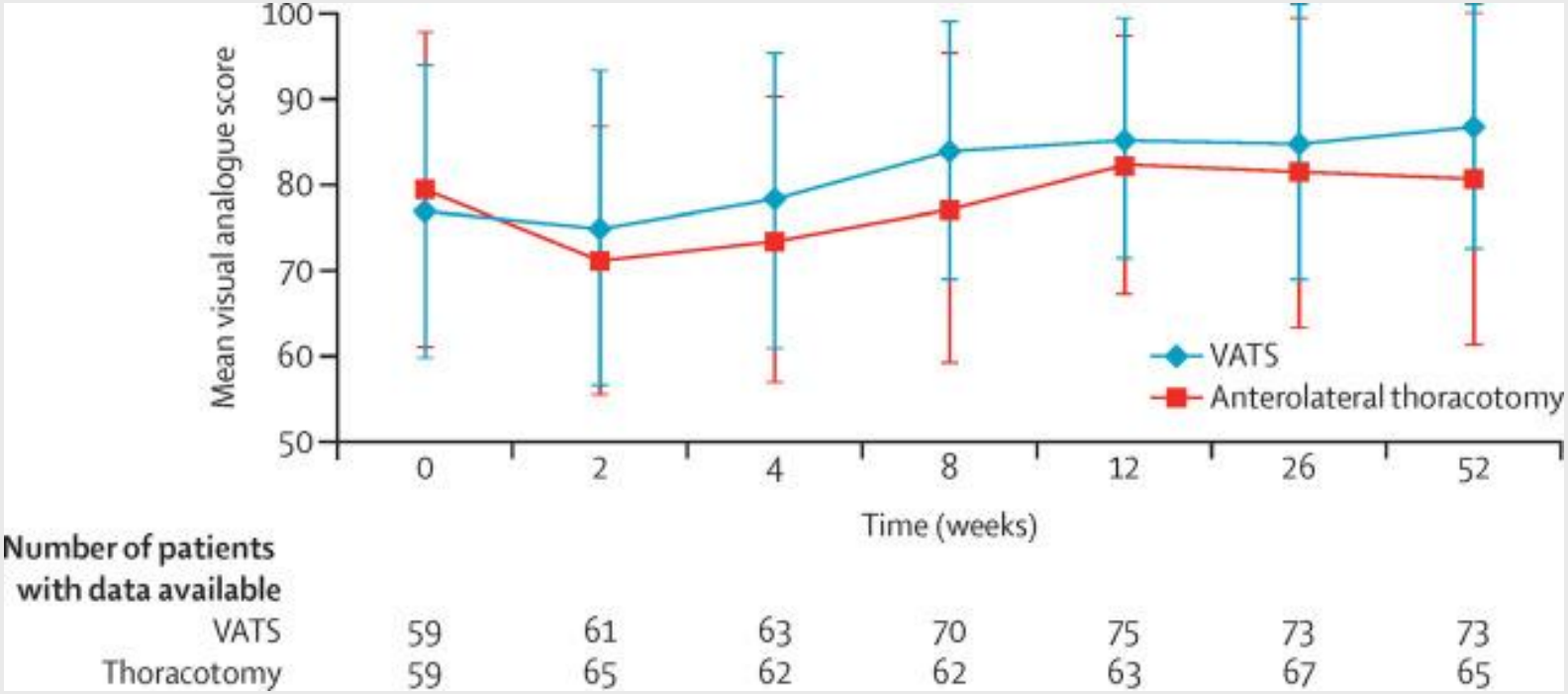
Postoperative pain and quality of life after lobectomy via VATS or anterolateral thoracotomy for early stage lung cancer



Proportion of patients with moderate-to-severe postoperative pain during 52 weeks of follow-up
Moderate-to-severe pain was defined as pain that scored at least 3 on the numeric rating scale.
p value is for a between-group comparison of the proportions...

Bendixen M et al, Lancet Oncol 2016;17:836-44

Postoperative pain and quality of life after lobectomy via VATS or anterolateral thoracotomy for early stage lung cancer

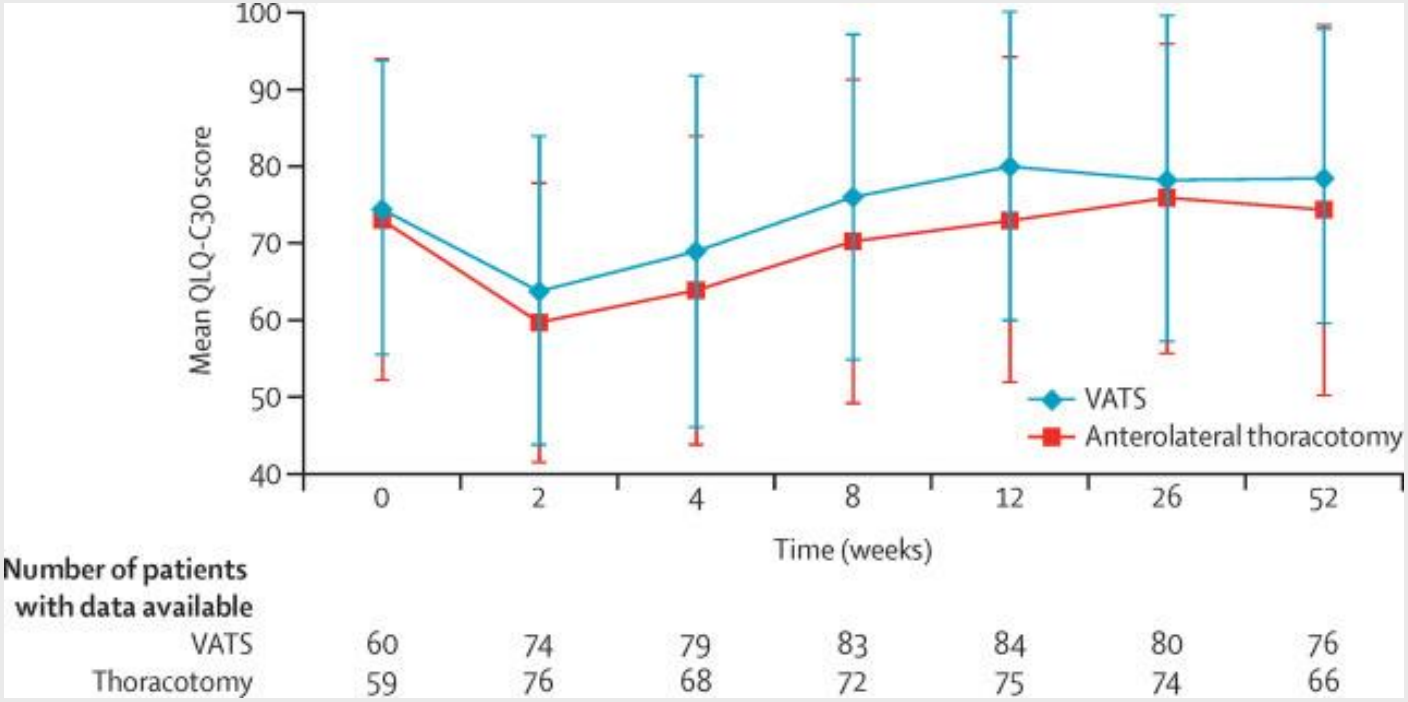


Number of patients with data available							
VATS	59	61	63	70	75	73	73
Thoracotomy	59	65	62	62	63	67	65

Self-reported quality of life by the EQ5D questionnaire
Error bars show SD..
EQ5D=EuroQol 5 Dimensions.

Bendixen M et al, Lancet Oncol 2016;17:836-44

Postoperative pain and quality of life after lobectomy via VATS or anterolateral thoracotomy for early stage lung cancer

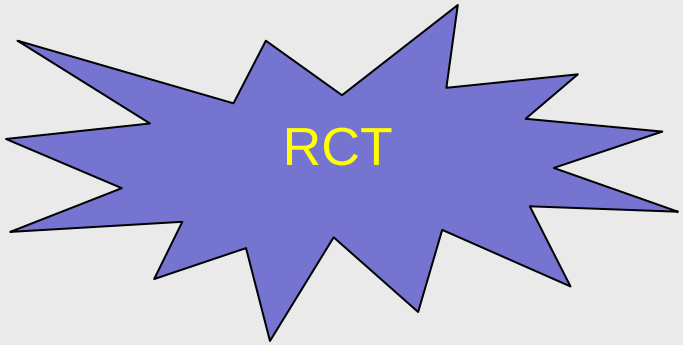


Number of patients with data available							
VATS	60	74	79	83	84	80	76
Thoracotomy	59	76	68	72	75	74	66

Quality of life by the EORTC QLQ-C30 questionnaire
Error bars show SD.
EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer 30 item Quality of Life Questionnaire.

Bendixen M et al, Lancet Oncol 2016;17:836-44

Uniportal VATS lobectomy versus other VATS lobectomy techniques



Randomization

- Uniportal VATS: 51
- Multiportal VATS: 54

Endpoints

- Post-op pain (VAS)
- Morphine requirements
- Drainage time
- Hospital stay

Perna V et al, Eur J Cardiothorac Surg 2016;50:411-5

Uniportal VATS lobectomy versus other VATS lobectomy techniques

	Uniport	Multiport	p-value
N patients	51	55	
Median VAS day 1	3	3	0.58
Median VAS day 2	2	2	0.64
Median VAS day 3	1	1	0.85
Median morphine use (mg) day 2	8	7	0.81
Median morphine use (mg) day 3	2	2	0.64

	Uniport	Multiport	p-value
Median duration of drainage (days)	1	1	0.65
Median hospital stay (days)	3	3	0.62

Perna V et al, Eur J Cardiothorac Surg 2016;50:411-5

Subcarinal lymph nodes should be dissected in all lobectomies for NSCLC, regardless of primary tumor location

Set-up

- Danish Lung Cancer Registry
- 2004-2011
- 5577 patients

Endpoints

- Screening for unsuspected N2

Eckhardt J et al, Ann Thorac Surg 2017;103:1121-5

Subcarinal lymph nodes should be dissected in all lobectomies for NSCLC, regardless of primary tumor location

Location of primary tumour and incidence of unsuspected N2

T location	N patients	All N2 (%)	N2 station 7(%)	N2 station 7 / all N2
Right upper lobe	1669	146 (8.7)	30 (1.8)	20.5 %
Left upper lobe	1366	139 (10.2)	17 (1.2)	12.2 %
Right lower lobe	911	93 (10.2)	62 (6.8)	66.6 %
Left lower lobe	770	72 (9.4)	37 (4.8)	51.4 %
Middle lobe	256	18 (7.0)	13 (5.1)	72.2 %

Eckhardt J et al, Ann Thorac Surg 2017;103:1121-5

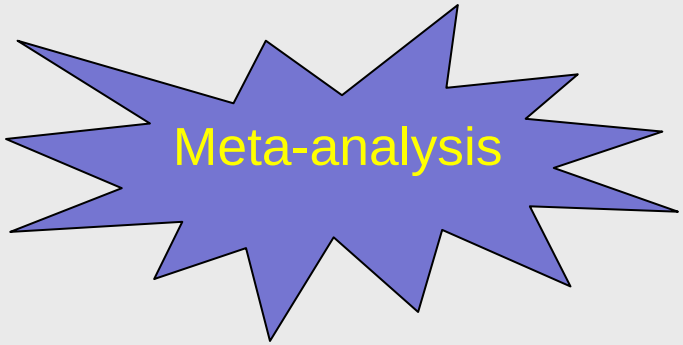
Subcarinal lymph nodes should be dissected in all lobectomies for NSCLC, regardless of primary tumor location

Unsuspected N2 after negative mediastinal investigation

Procedure	N patients	All N2 (%)	N2 station 7(%)	N2 station 7 / all N2
PET-CT	3892	347 (8.9)	117 (3.0)	33.7 %
Mediastinoscopy	1865	272 (14.6)	107 (5.7)	39.3 %
EBUS-TBNA	2526	232 (9.2)	78 (3.1)	33.6 %

Eckhardt J et al, Ann Thorac Surg 2017;103:1121-5

VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer

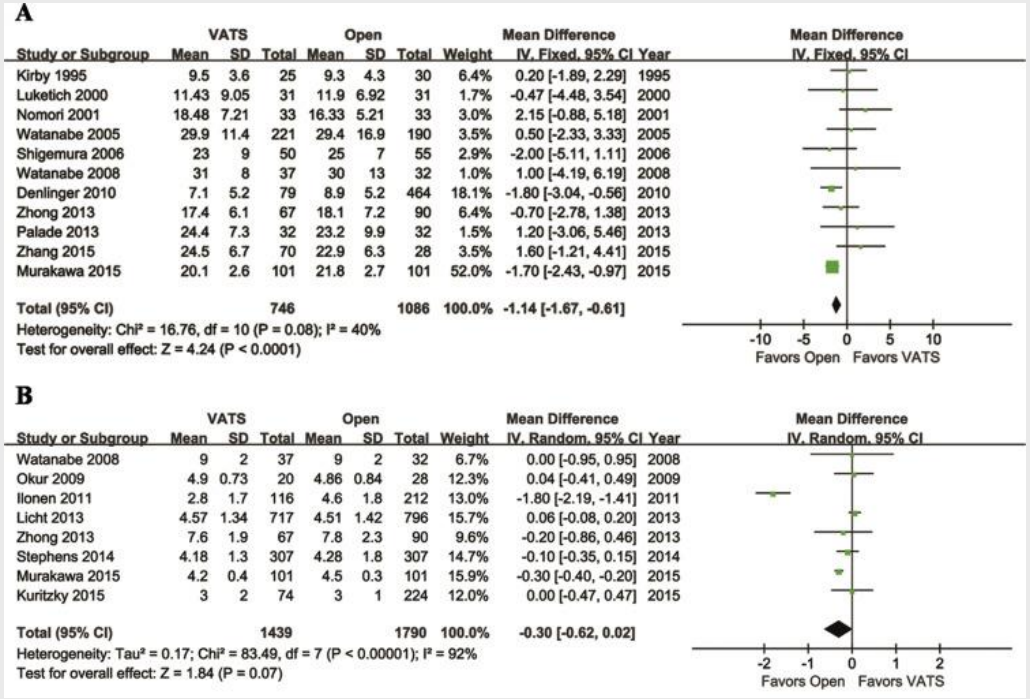


Ongoing debate on value of node dissection during VATS

- VATS preferred approach for stage I
- Opponents to VATS argument that node dissection is more extensive during thoracotomy

Zhang et al, Ann Thorac Surg 2016;101:2417-24

VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer



A. Number of nodes

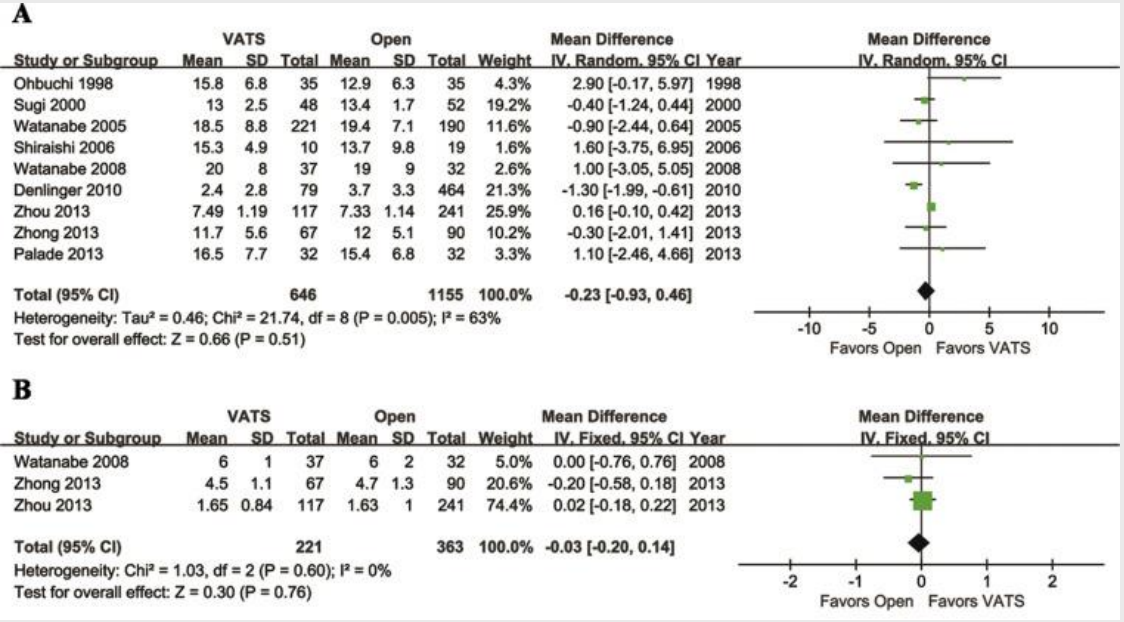
Favours thoracotomy

B. Number of node stations

No difference

Zhang et al, Ann Thorac Surg 2016;101:2417-24

VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer



A

Study or Subgroup	VATS Mean	VATS SD	VATS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ohbuchi 1998	15.8	6.8	35	12.9	6.3	35	4.3%	2.90 [-0.17, 5.97]	1998
Sugi 2000	13	2.5	48	13.4	1.7	52	19.2%	-0.40 [-1.24, 0.44]	2000
Watanabe 2005	18.5	8.8	221	19.4	7.1	190	11.6%	-0.90 [-2.44, 0.64]	2005
Shiraishi 2006	15.3	4.9	10	13.7	9.8	19	1.6%	1.60 [-3.75, 6.95]	2006
Watanabe 2008	20	8	37	19	9	32	2.6%	1.00 [-3.05, 5.05]	2008
Denlinger 2010	2.4	2.8	79	3.7	3.3	464	21.3%	-1.30 [-1.99, -0.61]	2010
Zhou 2013	7.49	1.19	117	7.33	1.14	241	25.9%	0.16 [-0.10, 0.42]	2013
Zhong 2013	11.7	5.6	67	12	5.1	90	10.2%	-0.30 [-2.01, 1.41]	2013
Palade 2013	16.5	7.7	32	15.4	6.8	32	3.3%	1.10 [-2.46, 4.66]	2013
Total (95% CI)			**646**			**1155**	**100.0%**	**-0.23 [-0.93, 0.46]**	

Heterogeneity: Tau² = 0.46; Chi² = 21.74, df = 8 (P = 0.005); I² = 63%
Test for overall effect: Z = 0.66 (P = 0.51)

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10
Favors Open Favors VATS

B

Study or Subgroup	VATS Mean	VATS SD	VATS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Watanabe 2008	6	1	37	6	2	32	5.0%	0.00 [-0.76, 0.76]	2008
Zhong 2013	4.5	1.1	67	4.7	1.3	90	20.6%	-0.20 [-0.58, 0.18]	2013
Zhou 2013	1.65	0.84	117	1.63	1	241	74.4%	0.02 [-0.18, 0.22]	2013
Total (95% CI)			**221**			**363**	**100.0%**	**-0.03 [-0.20, 0.14]**	

Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)

Mean Difference IV, Fixed, 95% CI

-2 -1 0 1 2
Favors Open Favors VATS

A. Number of N2 nodes

No difference

B. Number of N2 node stations

No difference

Zhang et al, Ann Thorac Surg 2016;101:2417-24

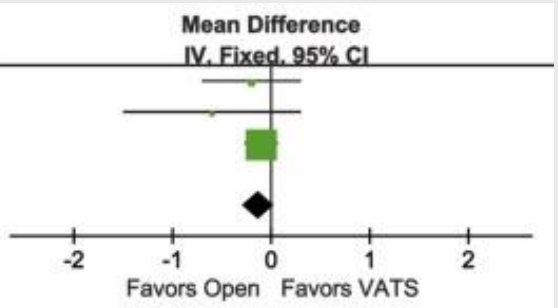
VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer

A. Number of N1 nodes

No difference

Study or Subgroup	VATS Mean	VATS SD	VATS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Sugi 2000	8.2	1.5	48	8.4	1	52	9.5%	-0.20 [-0.70, 0.30]	2000
Denlinger 2010	4.8	3.8	79	5.4	3.6	464	3.0%	-0.60 [-1.50, 0.30]	2010
Zhou 2013	5.04	0.67	117	5.14	0.9	241	87.5%	-0.10 [-0.27, 0.07]	2013
Total (95% CI)			**244**			**757**	**100.0%**	**-0.12 [-0.28, 0.03]**	

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.57 (P = 0.12)

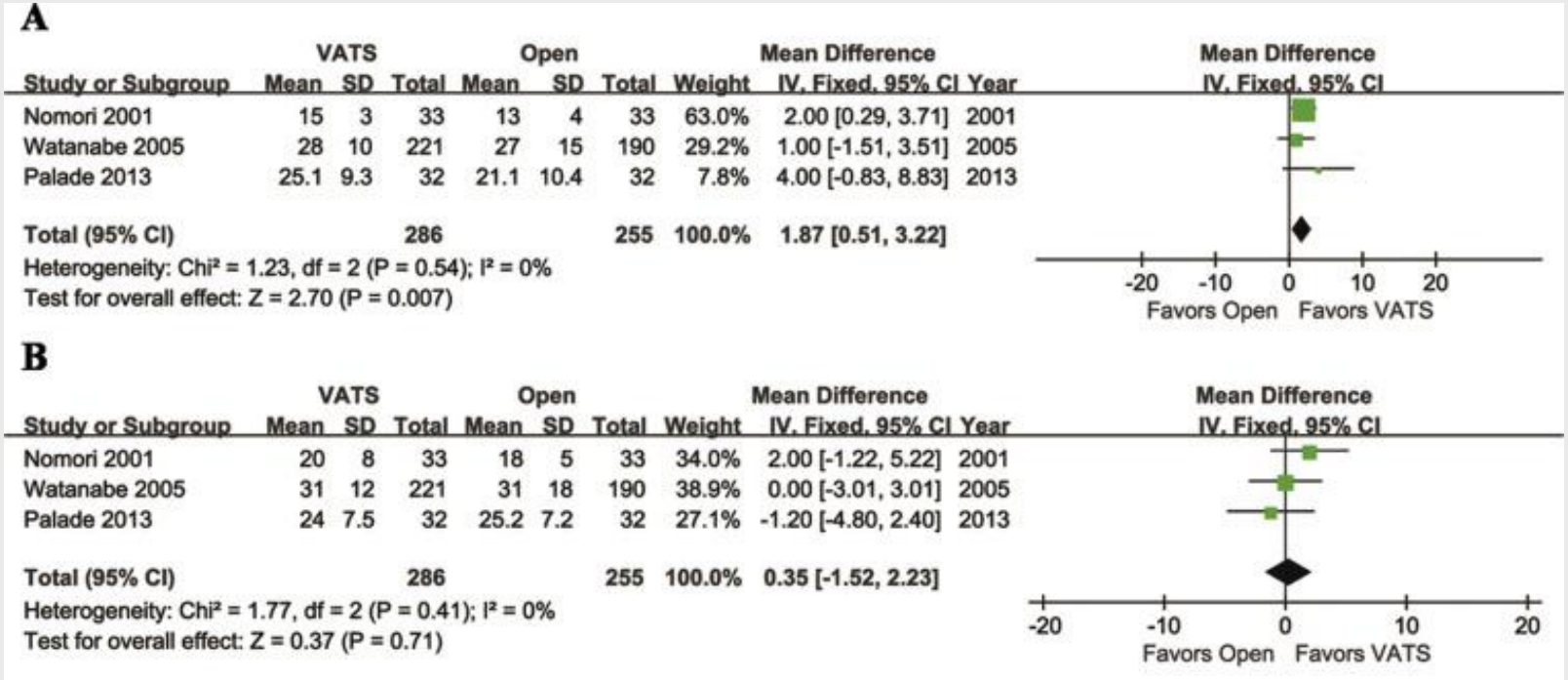


Zhang et al, Ann Thorac Surg 2016;101:2417-24

VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer

A. Number of nodes / left side — Favours VATS

B. Number of nodes / right side — No difference



A

Study or Subgroup	VATS Mean	VATS SD	VATS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Nomori 2001	15	3	33	13	4	33	63.0%	2.00 [0.29, 3.71]	2001
Watanabe 2005	28	10	221	27	15	190	29.2%	1.00 [-1.51, 3.51]	2005
Palade 2013	25.1	9.3	32	21.1	10.4	32	7.8%	4.00 [-0.83, 8.83]	2013
Total (95% CI)			286			255	100.0%	1.87 [0.51, 3.22]	

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favors Open Favors VATS

B

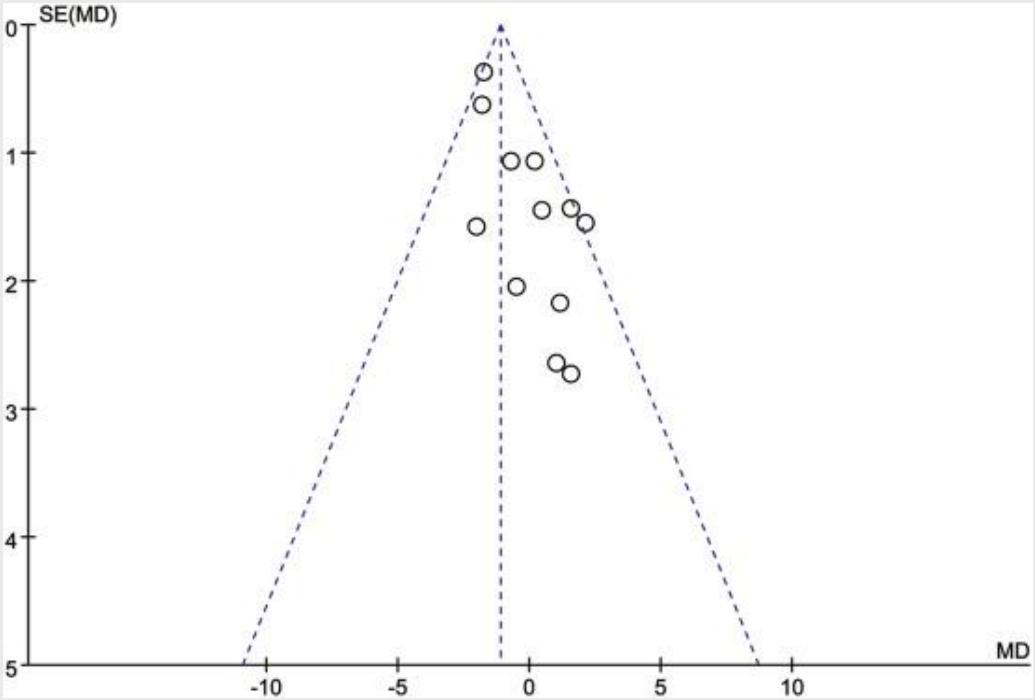
Study or Subgroup	VATS Mean	VATS SD	VATS Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Nomori 2001	20	8	33	18	5	33	34.0%	2.00 [-1.22, 5.22]	2001
Watanabe 2005	31	12	221	31	18	190	38.9%	0.00 [-3.01, 3.01]	2005
Palade 2013	24	7.5	32	25.2	7.2	32	27.1%	-1.20 [-4.80, 2.40]	2013
Total (95% CI)			286			255	100.0%	0.35 [-1.52, 2.23]	

Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Favors Open Favors VATS

Zhang et al, Ann Thorac Surg 2016;101:2417-24

VATS versus thoracotomy lymph node dissection in clinical stage I lung cancer



Funnel plot:

Marked symmetry

No publication bias

Zhang et al, Ann Thorac Surg 2016;101:2417-24

Survival implications of variation in the thoroughness of pathologic lymph node examination in ACOZOG Z0030

Background:

- Lymph node dissection is well standardized
- Thoroughness of pathologic examination remains questionable

Design:

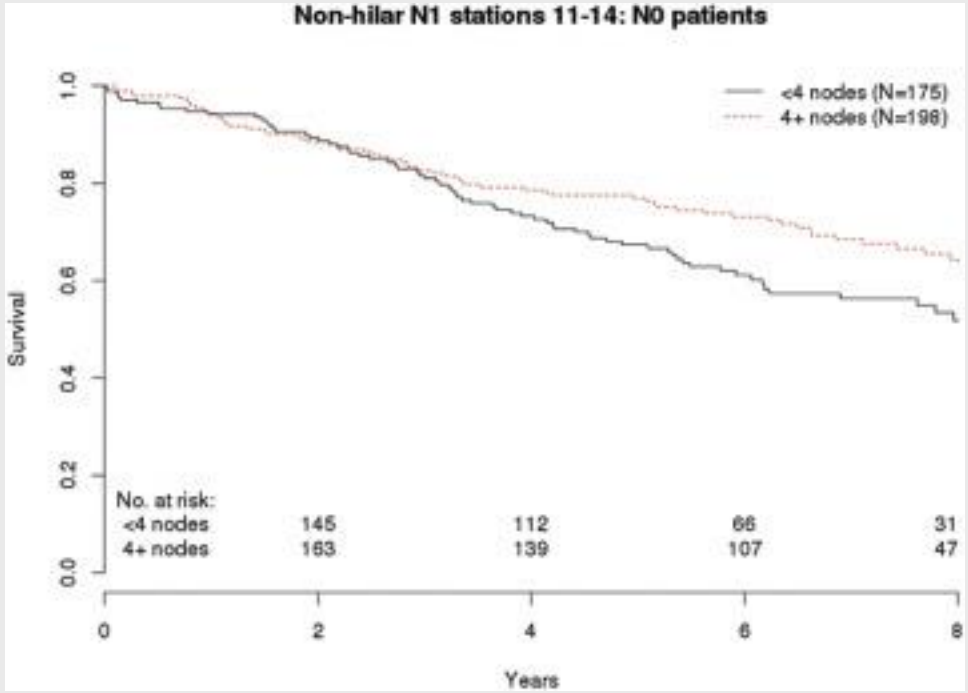
- Review of mediastinal dissection arm of ACOZOG Z0030
- 513 patients

	pN0 435	pN1 60	pN2 17
Mean number of mediastinal nodes	13.5	13.1	17.1
Mean number station 10	2.4	2.7	2.6
Mean number stations 11-14	4.6	6.1	6.7
Mean total number of nodes	19.7	21.3	25.3

Osarogiagbon et al, Ann Thorac Surg 2016;102:363-29

Survival implications of variation in the thoroughness of pathologic lymph node examination in ACOZOG Z0030

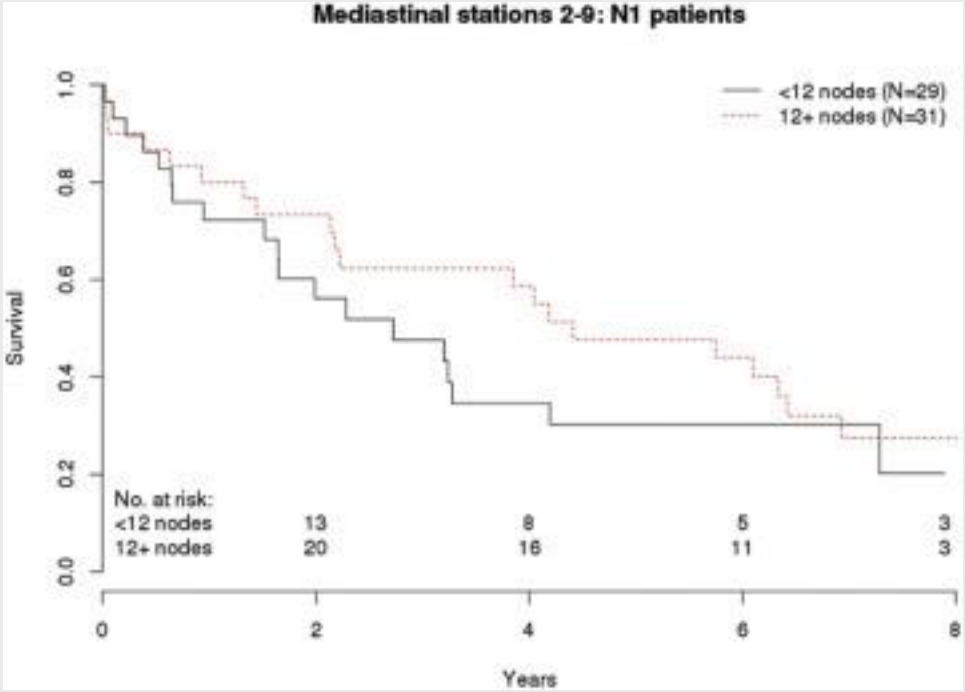
Improved survival for N0 when > 4 N1 nodes were examined



Osarogiagbon et al, Ann Thorac Surg 2016;102:363-29

Survival implications of variation in the thoroughness of pathologic lymph node examination in ACOZOG Z0030

Improved survival for N1 when > 12 mediastinal nodes were examined

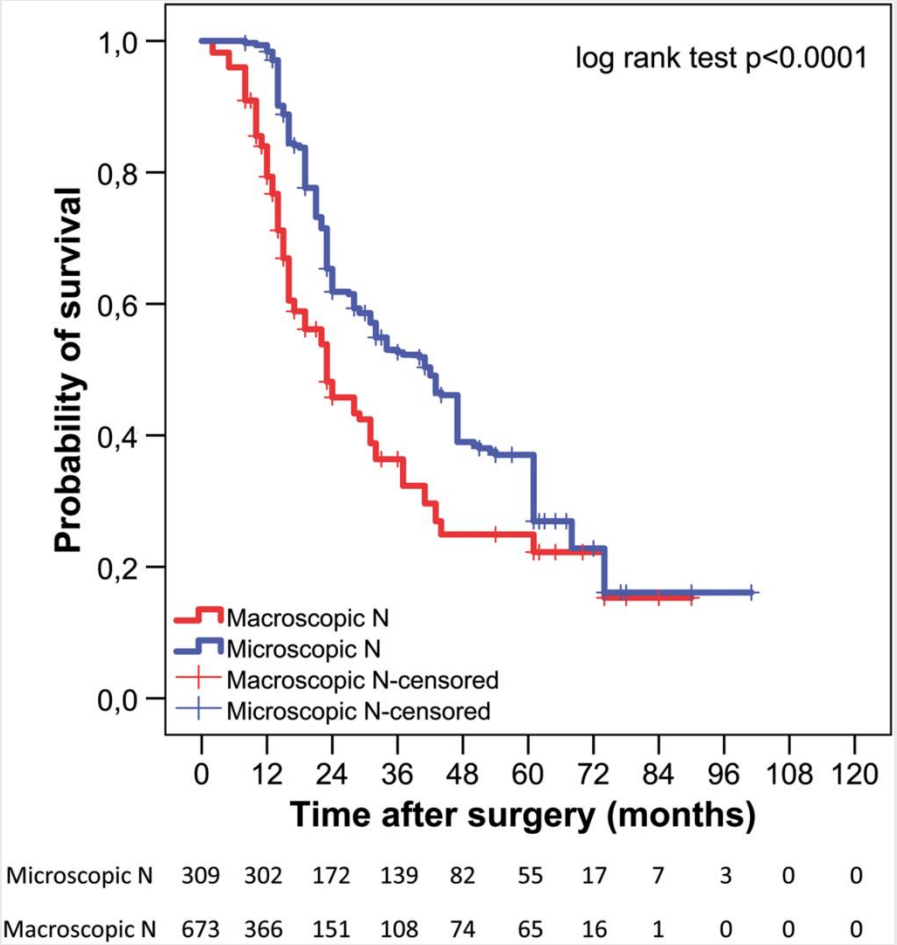


Osarogiagbon et al, Ann Thorac Surg 2016;102:363-29

Microscopic N2 exhibits a better prognosis in resected non-small cell lung cancer

- single centre study
- 982 pN2 patients

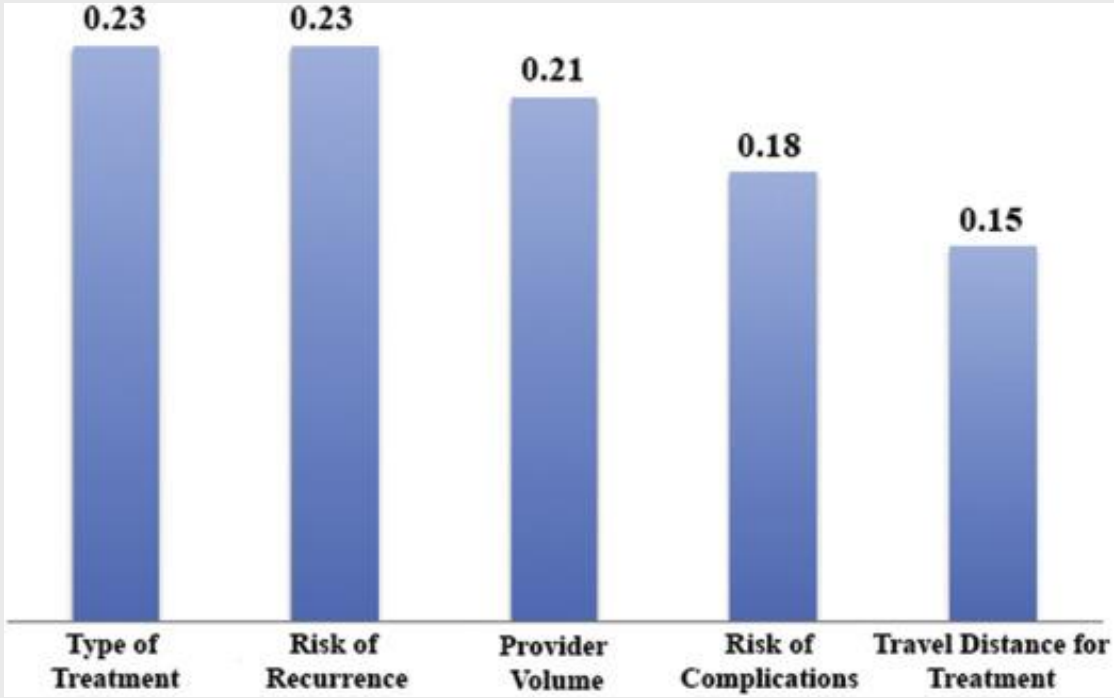
- microN2 309 patients (31.5%)
- HR 0.681



Garelli et al, Eur J Cardiothorac Surg 2016;50:322-8

Patient preferences in treatment choices for early-stage lung cancer

- 225 healthy volunteers
- Questionnaire oriented on treatment modalities, outcomes, distance to care provider
- Conjoint analysis



Tong BC et al, Ann Thorac Surg 2016;102:1837-44

Take-Home Message

Some EBM statements about VATS

- VATS is less painful than thoracotomy (level 1)
- Number of ports is not an issue (level 1)
- Routine complete dissection is recommended (level 2)
- Accurate node dissection by VATS is feasible (level 1)
- All nodes should be examined by the pathologist (level 2)
- Prognosis of microscopic N2 is acceptable (level 2)
- Patients prefer minimally invasive surgery and oncologic safety (level 3)

List of References

1. *Bendixen M et al, Lancet Oncol 2016;17:836-44*
2. *Perna V et al, Eur J Cardiothorac Surg 2016;50:411-5*
3. *Eckhardt J et al, Ann Thorac Surg 2017;103:1121-5*
4. *Zhang et al, Ann Thorac Surg 2016;101:2417-24*
5. *Osarogiagbon et al, Ann Thorac Surg 2016;102:363-29*
6. *Garelli et al, Eur J Cardiothorac Surg 2016;50:322-8*
7. *Tong BC et al, Ann Thorac Surg 2016;102:1837-44*

Thoracic surgery

SBRT:
End of lobectomy for cT1N0?

State of the Art

Alternative options for cT1N0 NSCLC ?

- Surgeons still consider lobectomy as gold standard, with increased oncologic safety compared to sublobar resections
- VATS made lobectomy more patient-friendly
- SBRT has been introduced as alternative to surgery for cT1N0 lung cancer

SBRT new standard for c-stage I ?

Stereotactic ablative radiotherapy versus lobectomy for operable stage I NSCLC: a pooledanalysis of 2 randomised trials

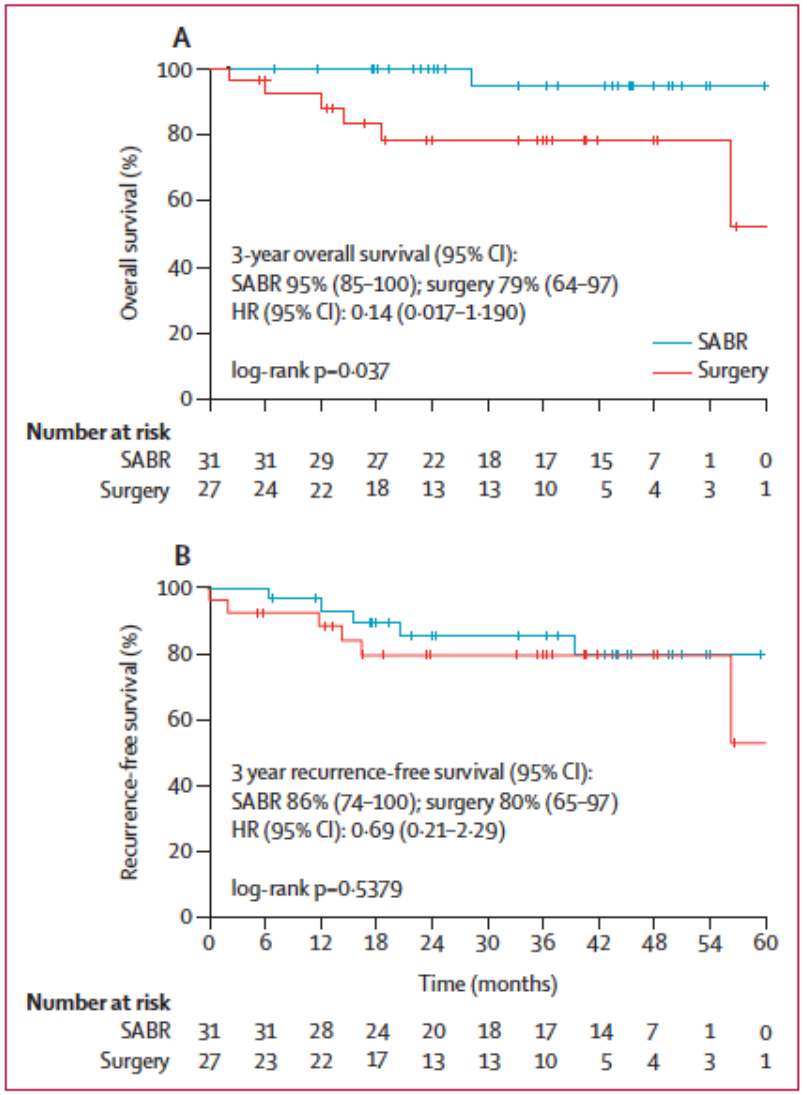


***Figure 2*: Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

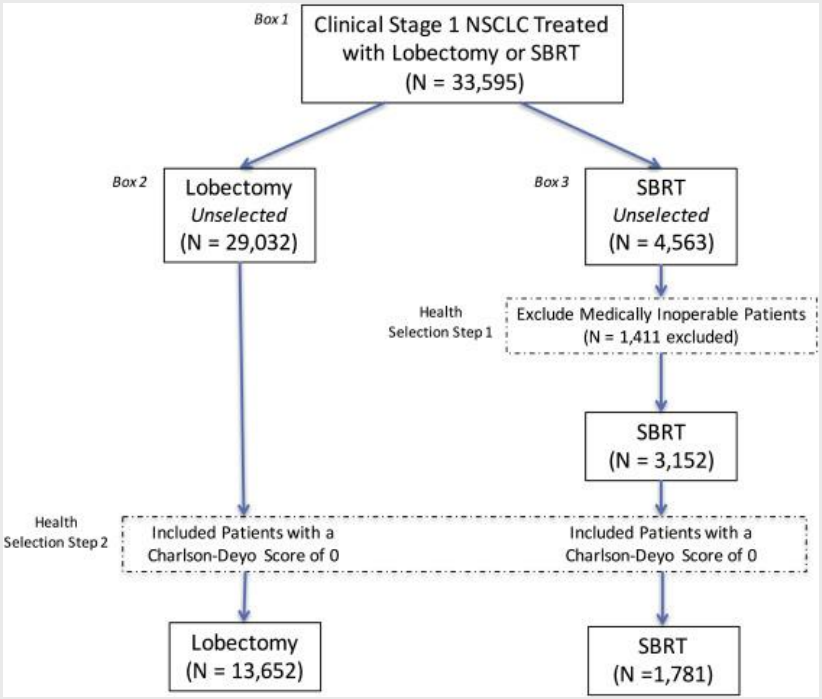
Chang JY, Lancet Oncol 2015;16:630-7

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials.

- Both trials closed for lack of accrual
  - STARS trial : 28 sites - 36 patients
  - ROSEL study: 10 sites - 22 patients
- Overmortality of open lobectomy (3.7%)
- Undermortality of SBRT
- Lack of follow-up : median survival not joined
- Tissue diagnosis in SBRT 27% (ROSEL)
- Local recurrence
  - SBRT 16.1 %
  - Lobectomy: 4.1 %

Opitz I et al. Lancet Oncol 2015;16: 672–3

Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer

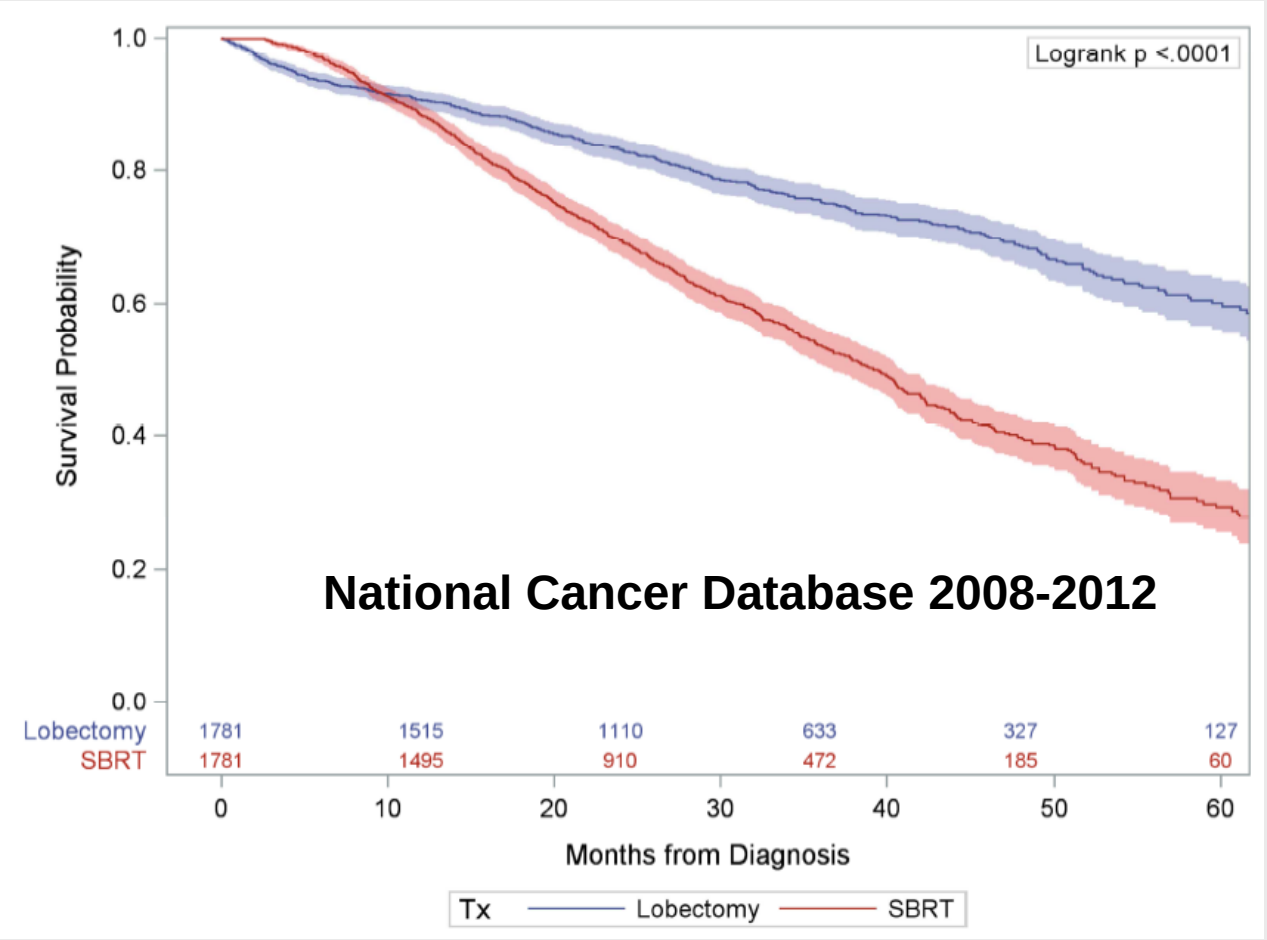


Registry study

- National Cancer Data Base
- 13662 lobectomies
- 1781 SBRT

Rosen JE et al, J Thorac Cardiovasc Surg 2016;152:44-54

Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer



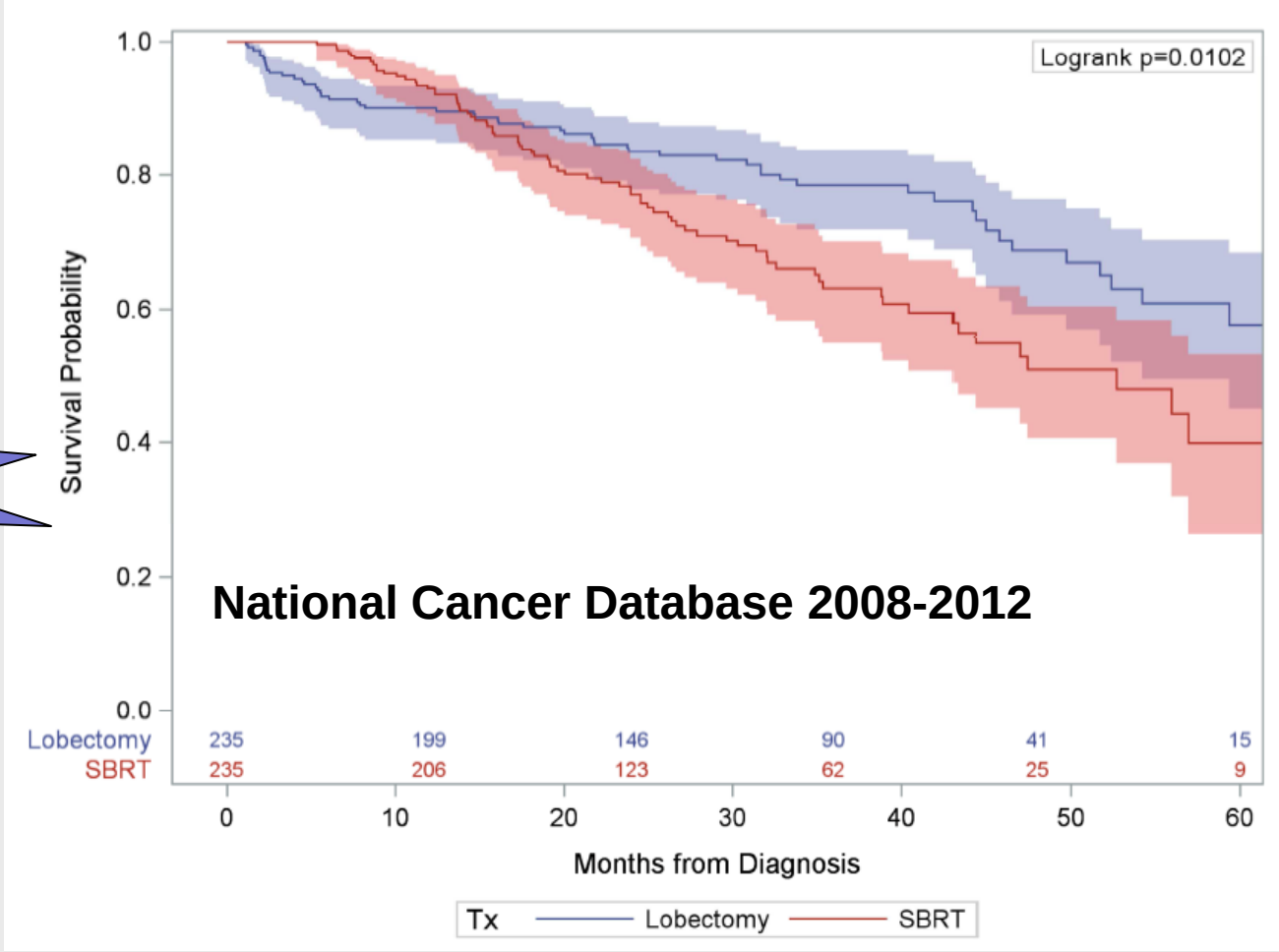
Registry study

1781 propensity-matched "healthy" lobectomy and SBRT patients pairs

Rosen JE et al, J Thorac Cardiovasc Surg 2016;152:44-54

Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer

Registry study



235 Propensity matched lobectomy patients and SBRT patients pairs who were recommended to have surgery, but refused.

Rosen JE et al, J Thorac Cardiovasc Surg 2016;152:44-54

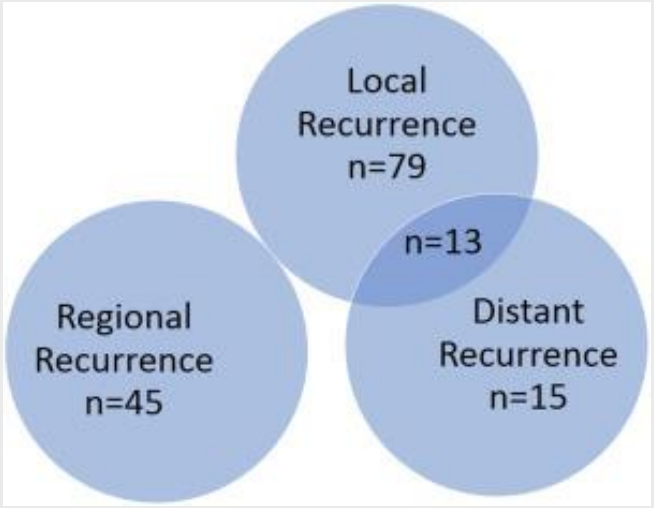
Detection of recurrence patterns after wedge resection for early stage lung cancer: rationale for radiologic follow-up

- Single centre study
- 2000-2012
- 446 patients
- Wedge for clinical stage I
- Routine follow-up for all

- 283 survivors – 163 died
- Median follow-up 44.6 months
- Median survival 82.6 months
- Oncologic events:
    - 36 new primaries
    - 156 recurrences (35%)
        - 79 local
        - 45 regional
        - 28 distant

Billè A et al, Ann Thorac Surg 2016;102:1067-73

Detection of recurrence patterns after wedge resection for early stage lung cancer: rationale for radiologic follow-up

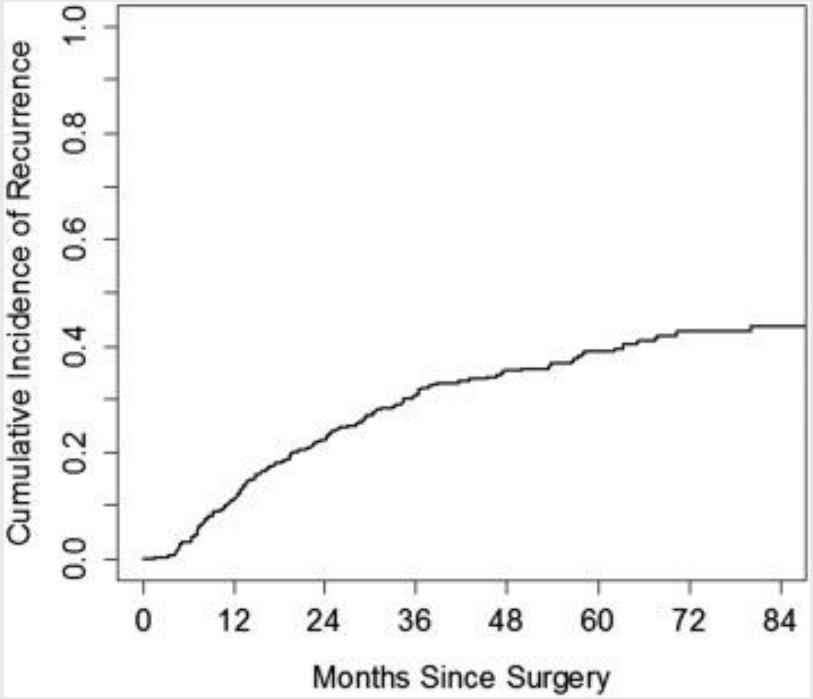


Delay	Cumulative index for recurrence		
	Local	Regional	Distant
1 year	5.2	3.7	2.3
2 years	11.1	6.6	4.7
3 years	14.9	9.5	6.4

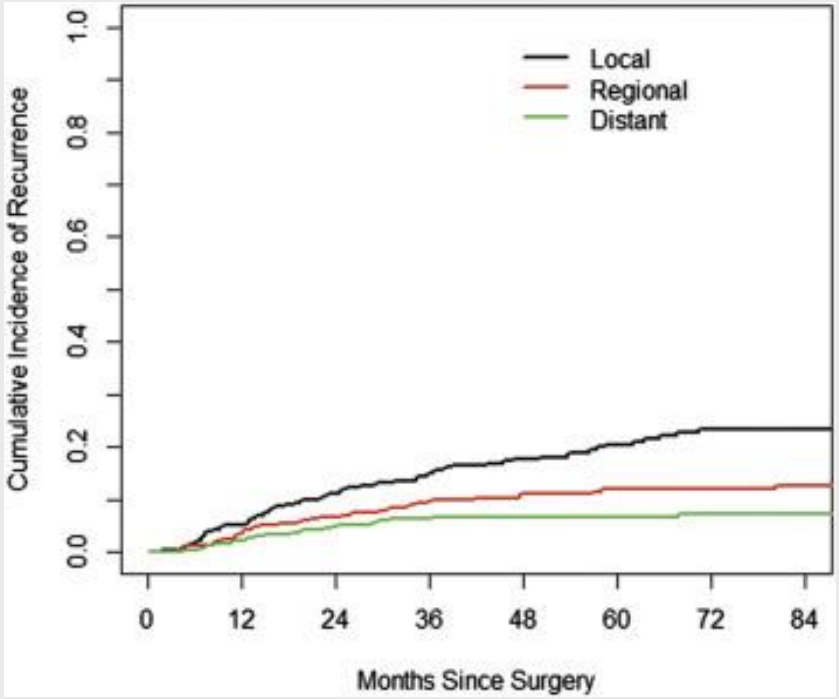
Billè A et al, Ann Thorac Surg 2016;102:1067-73

Detection of recurrence patterns after wedge resection for early stage lung cancer: rationale for radiologic follow-up

Cumulative index of recurrence



All events



By sub-type

Billè A et al, Ann Thorac Surg 2016;102:1067-73

Take-Home Message

- Lobectomy is still the gold standard for cT1N0 NSCLC in operable patients. Survival is significantly increased when compared to ourcomes after SBRT.

- Wedge excision of cT1N0 lung cancer exposes, similar to SBRT, to a relatively high recurrence rate.

Thoracic surgery

Miscellaneous
Prognosis of operated NSCLC

State of the Art

- Timing of perioperative chemotherapy for stage II – N1 non-small cell lung cancer remains controversial.
- Molecular markers indicating sensitivity to targeted treatments are increasingly utilized for prognosis, but should we forget about KRAS mutations ?
- When interpreting clinical trials, we have learned to be aware of different biases (lead-time, selection bias, etc). Might there be an intercontinental practice bias ?

Induction chemotherapy is not superior to a surgery-first strategy for clinical N1 NSCLC

Value of induction therapy still debated !

- National Cancer Database
- 2006-2011
- 5364 patients
  - 565 received induction chemo (10.5 %)
  - 4799 were operated upfront
    - Accurate N1 staging in 68.6%
    - Overstaging in 16.3% (N 0)
    - Understaging in 10.7% (N2-3)

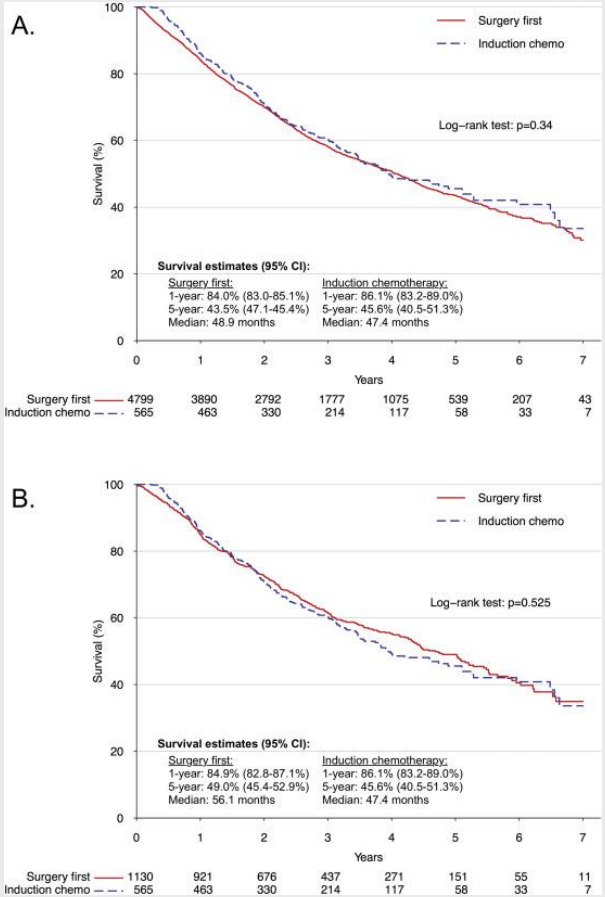
Survival analysis

- **Unadjusted**
- **Propensity matched**

Speicher PJ et al, Ann Thorac Surg 2016;102:884-94

Induction chemotherapy is not superior to a surgery-first strategy for clinical N1 NSCLC

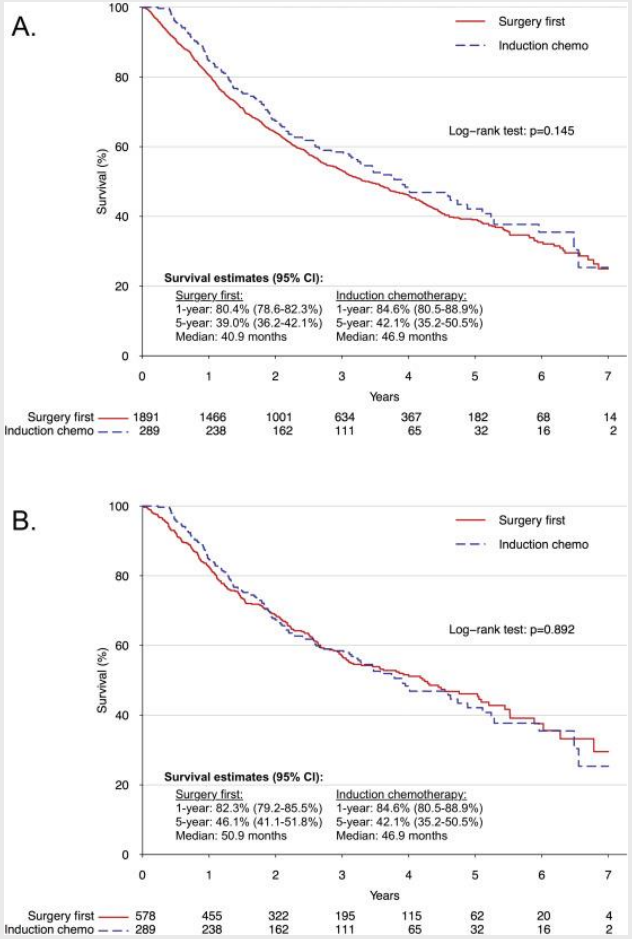
No difference for T1-3 N1



Speicher PJ et al, Ann Thorac Surg 2016;102:884-94

Induction chemotherapy is not superior to a surgery-first strategy for clinical N1 NSCLC

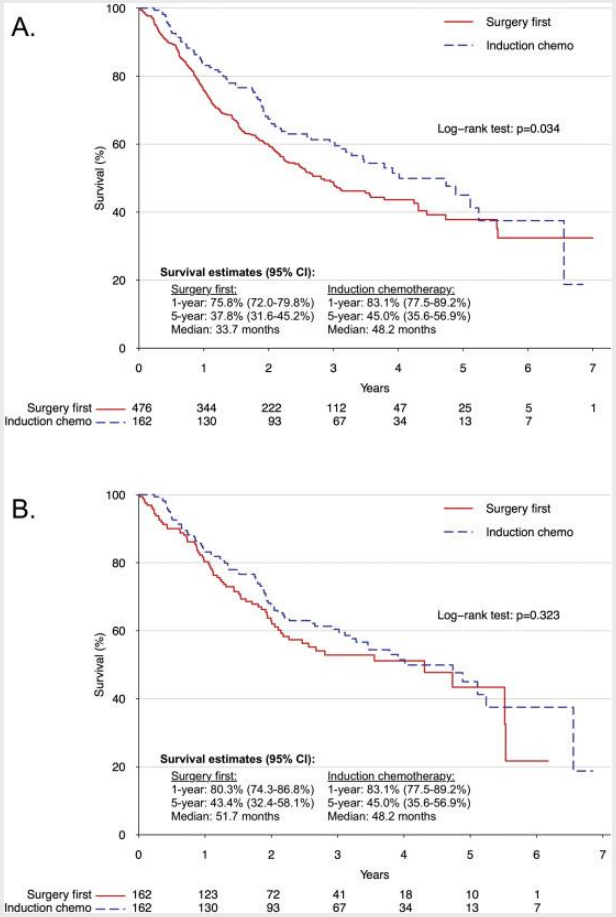
No difference for T>4cm, N1



Speicher PJ et al, Ann Thorac Surg 2016;102:884-94

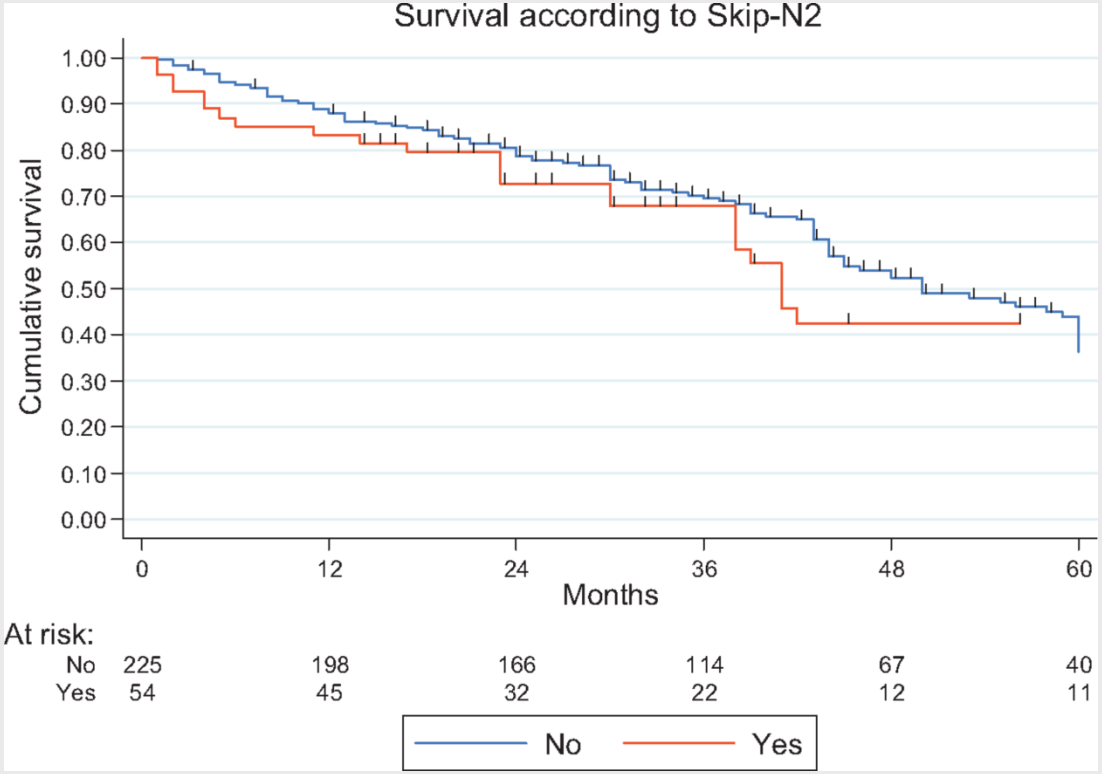
Induction chemotherapy is not superior to a surgery-first strategy for clinical N1 NSCLC

No difference for T3 N1



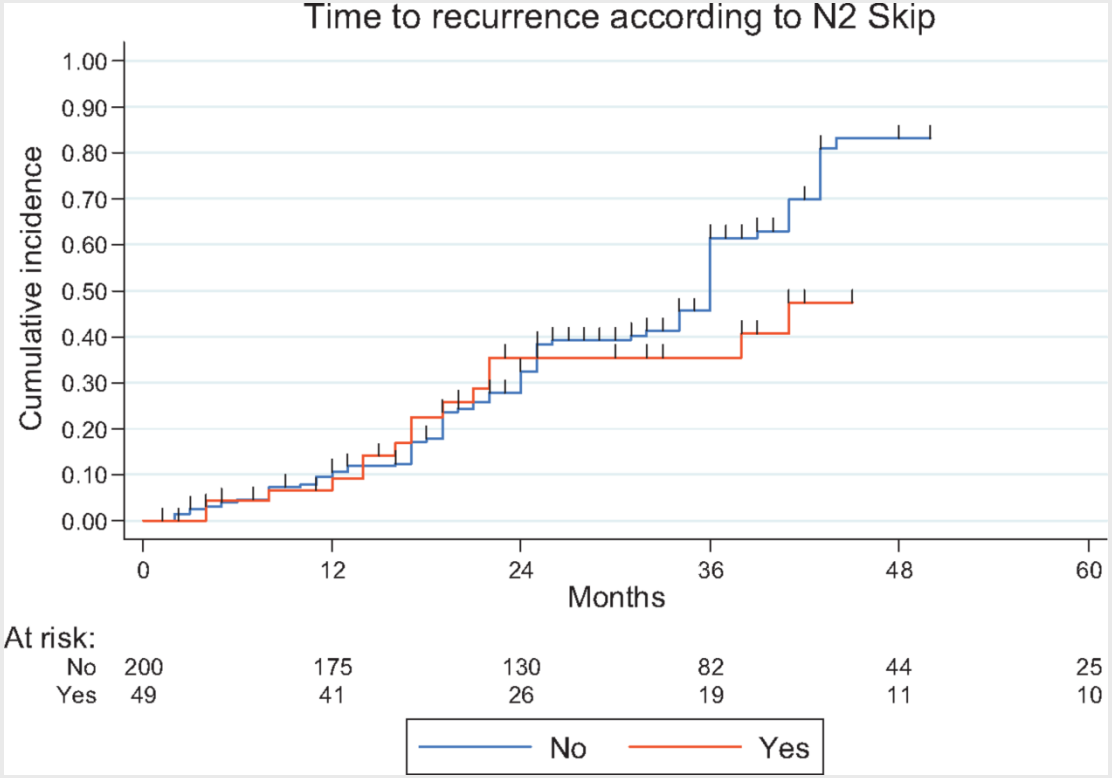
Speicher PJ et al, Ann Thorac Surg 2016;102:884-94

Epidermal growth factor receptor mutations are linked to skip N2 lymph node metastasis in resected non-small-cell lung cancer adenocarcinomas



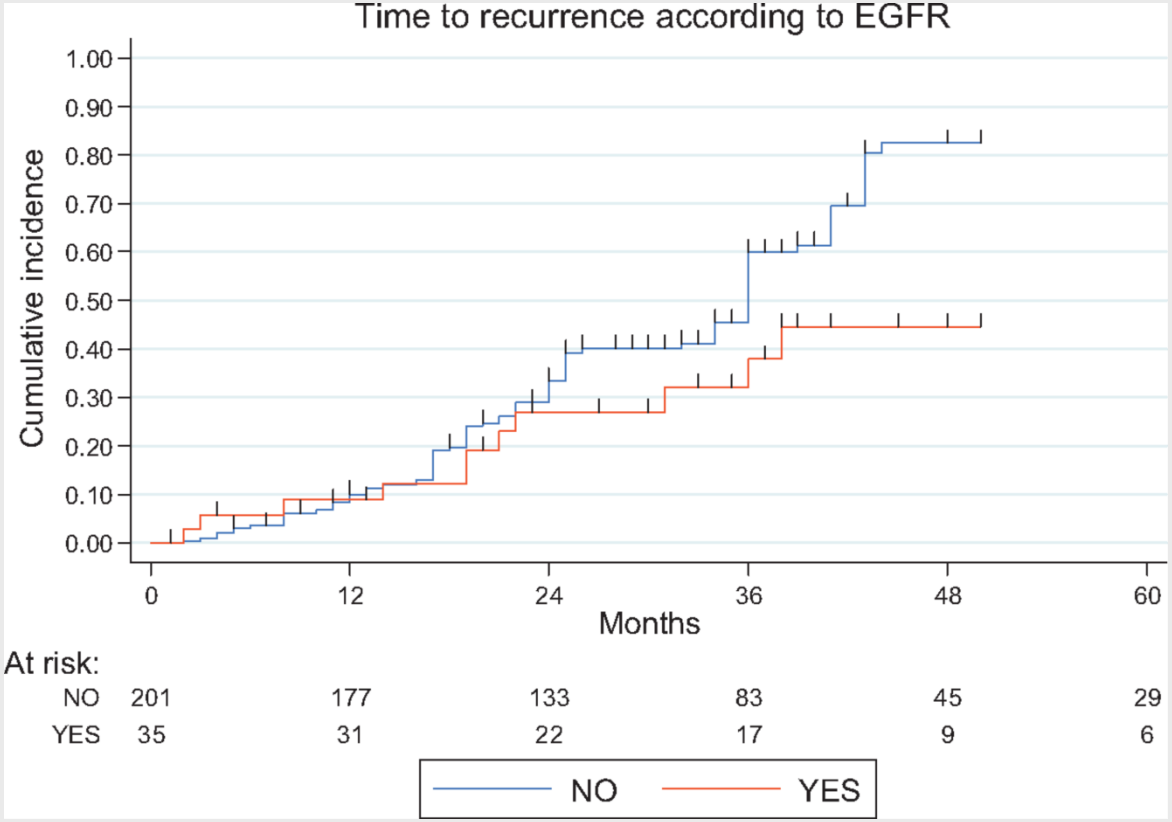
Guerrera et al, Eur J Cardiothorac Surg. 2016;51(4):680-688

Epidermal growth factor receptor mutations are linked to skip N2 lymph node metastasis in resected non-small-cell lung cancer adenocarcinomas



Guerrera et al, Eur J Cardiothorac Surg. 2016;51(4):680-688

Epidermal growth factor receptor mutations are linked to skip N2 lymph node metastasis in resected non-small-cell lung cancer adenocarcinomas



Guerrera et al, Eur J Cardiothorac Surg. 2016;51(4):680-688

KRAS mutations: new insights

- G12V related to catastrophic outcome
- Type of mutation related to natural history
  - Wild type: brain and liver metastases
  - G12C: bone metastases
  - G12V: pleural & pericardial metastases
    resistance to radiation therapy

Renaud et al, Br J Cancer 2015;113:1206-15
Renaud et al, Br J Cancer 2016;115:346-53

Variation in pulmonary resection practices between the STS and ESTS general thoracic databases

Type of resection	STS N=47539	ESTS N=30673	p-value
VATS wedge resection	15557 (32.5)	3493 (11.3)	< 0.05
VATS lobectomy	**13147 (27.5)**	**2557 (8.3)**	**< 0.05**
VATS segmentectomy	923 (1.9)	605 (2)	< 0.05
VATS bilobectomy	180 (0.4)	47 (0.1)	< 0.05
VATS pneumonectomy	72 (0.2)	27 (0.1)	< 0.05
Open wedge resection	3301 (6.9)	3836 (12.4)	< 0.05
Open segmentectomy	954 (2)	1657 (5.4)	< 0.05
Open lobectomy	**10735 (22.5)**	**14175 (46)**	**< 0.05**
Open sleeve lobectomy	515 (1.1)	638 (2.1)	< 0.05
Open bilobectomy	**889 (1.9)**	**1407 (4.6)**	**< 0.05**
Open pneumonectomy	**1266 (2.6)**	**2249 (7.3)**	**< 0.05**

Seder CW et al, Ann Thorac Surg 2016;101:2077-84

Take-Home Message

- The outcomes of operated cN1 lung cancer are similar regardless of the timing of perioperative chemotherapy. Upfront surgery may simplify patient management and correct staging errors
- Skip N2 metastases have an improved prognosis compared to non-skip N2. Prevalence of EGFR mutations is higher in patients with skip-N2
- Subtypes of KRAS mutations herald different outcomes and are associated with specific oncologic events
- There are considerable differences in surgical practice between Europe and North-America. This may flaw conclusions from registry studies.

List of References

1. *Chang JY, Lancet Oncol 2015;16:630-7*
2. *Opitz I et al. Lancet Oncol 2015;16: 672–3*
3. *Rosen JE et al, J Thorac Cardiovasc Surg 2016;152:44-54*
4. *Speicher PJ et al, Ann Thorac Surg 2016;102:884-94*
5. *Guerrera et al, Eur J Cardiothorac Surg. 2016;51(4):680-688*
6. *Renaud et al, Br J Cancer 2015;113:1206-15*
7. *Renaud et al, Br J Cancer 2016;115:346-53*
8. *Seder CW et al, Ann Thorac Surg 2016;101:2077-84*
9. *Billè A et al, Ann Thorac Surg 2016;102:1067-73*

Lung Transplantation

Airway complications

State of the Art: Airway complications

Bronchial healing = the Achilles heel of lung transplantation.

- Interruption of bronchial vascular supply
- Antiproliferative effect of immunosuppressive drugs
- Primary graft failure
- Surgical technique

Over the past 2 decades, fatal outcome due to bronchial complications has decreased.

However, bronchial complications still exist and negatively impact onto hospital stay, quality of life and cost of treatment

Shennib H & Massard G, Ann Thorac Surg 1994;57:506-11
Massard G et al, Eur Respir Mon 2009;45:177-93

Bronchial complications after lung TX are associated with primary lung graft dysfunction and surgical technique

- Single centre study
- Considered all bronchial events causing symtoms and/or requiring treatment

270 patients

- 11 post-op deaths without bronchial complications (4.5%)
- 259 patients included (213 bilateral – 46 unilateral)
- 52 bronchial complications (20 %)
- 12 deaths with bronchial complications

Olland A et al, J Heart Lung Transplant 2017;36(2):157-65

Bronchial complications after lung TX are associated with primary lung graft dysfunction and surgical technique

Results of multivariate analysis: OR / bronchial complications

Variable	Odds Ratio	p
PGD / 72 hours	2.55	0.08
Surgical technique	0.47	0.037

subgroup analysis

- COPD
- Pyogenic or aspergillus infection

Olland A et al, J Heart Lung Transplant 2017;36(2):157-65

Airway complications after lung TX: Contemporary survival and outcomes

- UNOS database 2000-2012
- 16156 lung TX
- 223 developed air way complications (1.4 %)

Multivariate analysis of risk factors

Variable	Odds ratio	p
Recipient age	1.02	0.01
Male recipient	1.61	0.001
Bilateral TX	1.97	< 0.001
Non-ICU hospit.	1.73	0.02
ICU hospit.	2.13	0.001

Hayanga JW et al, J Heart Lung Transplant 2016;35(10):1206-11

Airway complications after lung TX: Contemporary survival and outcomes

Multivariate analysis of risk factors for 1-year mortality

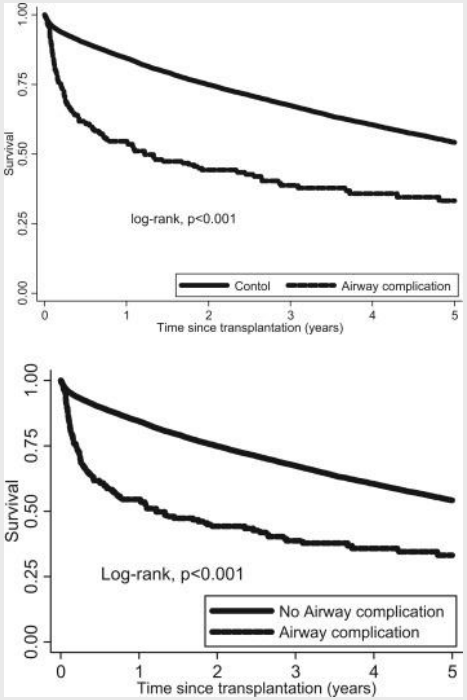
Variable	Odds ratio	p
Airway complication	3.38	< 0.0001
Age by year	1.01	< 0.001
Non-ICU hospit.	1.32	< 0.001
ICU hospit.	2.54	< 0.001
Bilateral TX	0.86	< 0.001

Hayanga JW et al, J Heart Lung Transplant 2016;35(10):1206-11

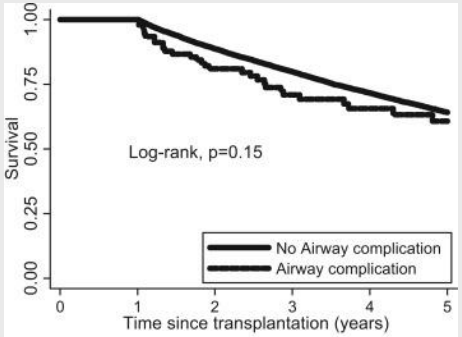
Airway complications after lung TX: Contemporary survival and outcomes

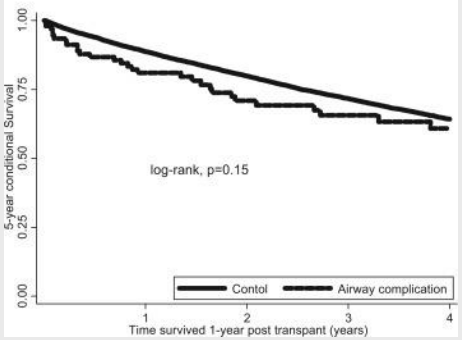
Impact of airway complications on survival

All



1-year survivors





Hayanga JW et al, J Heart Lung Transplant 2016;35(10):1206-11

Take-Home Message

Airway complications

- Still occur in 10-20% of recipients
- Adversely impact long-term survival
- Favoured by PGD
- Rate decreased by surgical technique keeping a short donor bronchus

Lung Transplantation

Cardiac comorbidity

State of the Art: Cardiac comorbidity

- Impact of Atrial fibrillation on survival after lung TX remains controversial

- Ischemic heart disease has been considered as a contra-indication.
- Impact of cardiac revascularisation has not been assessed

Gleva MJ & Huddleston CB, J Thorac Cardiovasc Surg 2016;152(3):910-11

Early and late atrial arrhytmias after lung TX

- Single Centre Study
- 271 lung TX
- Early post-TX atrial arrythmia 33%
- Late post-TX atrial arrythmia 8.8%
- ***No impact on survival !!***

Predictors of early atrial arrythmia

Variable	Odds ratio	p
Recipient age	2.353	0.004
COPD	2.126	0.021

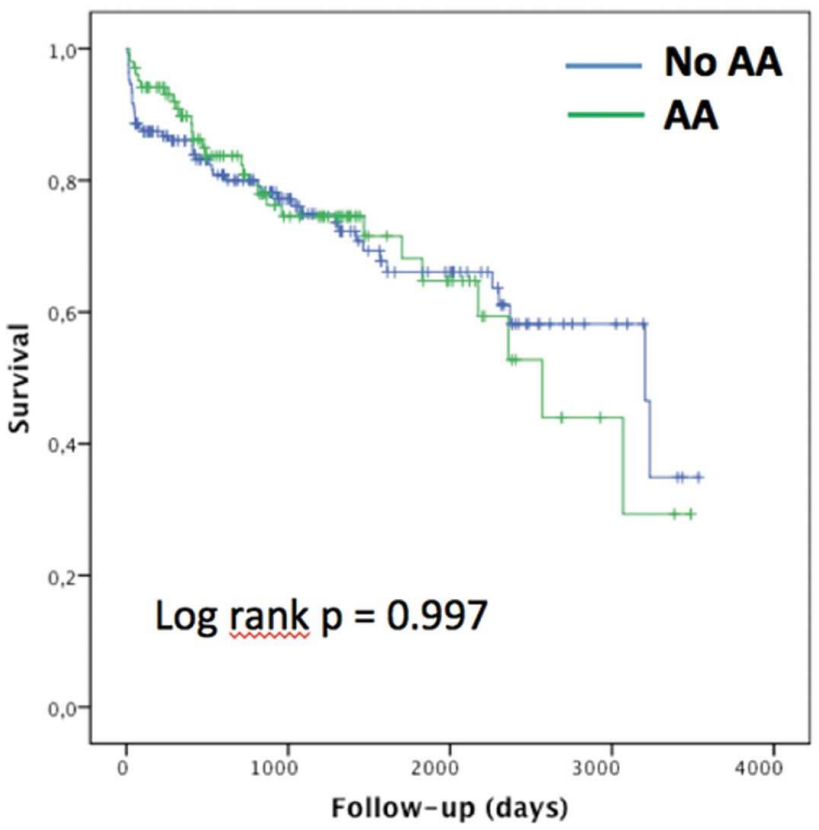
Predictors of late atrial arrythmia

Variable	Odds ratio	p
sPAP TTE	1.028	0.041

Jesel L et al, Circ J 2017;81:660-7

Early and late atrial arrhytmias after lung TX

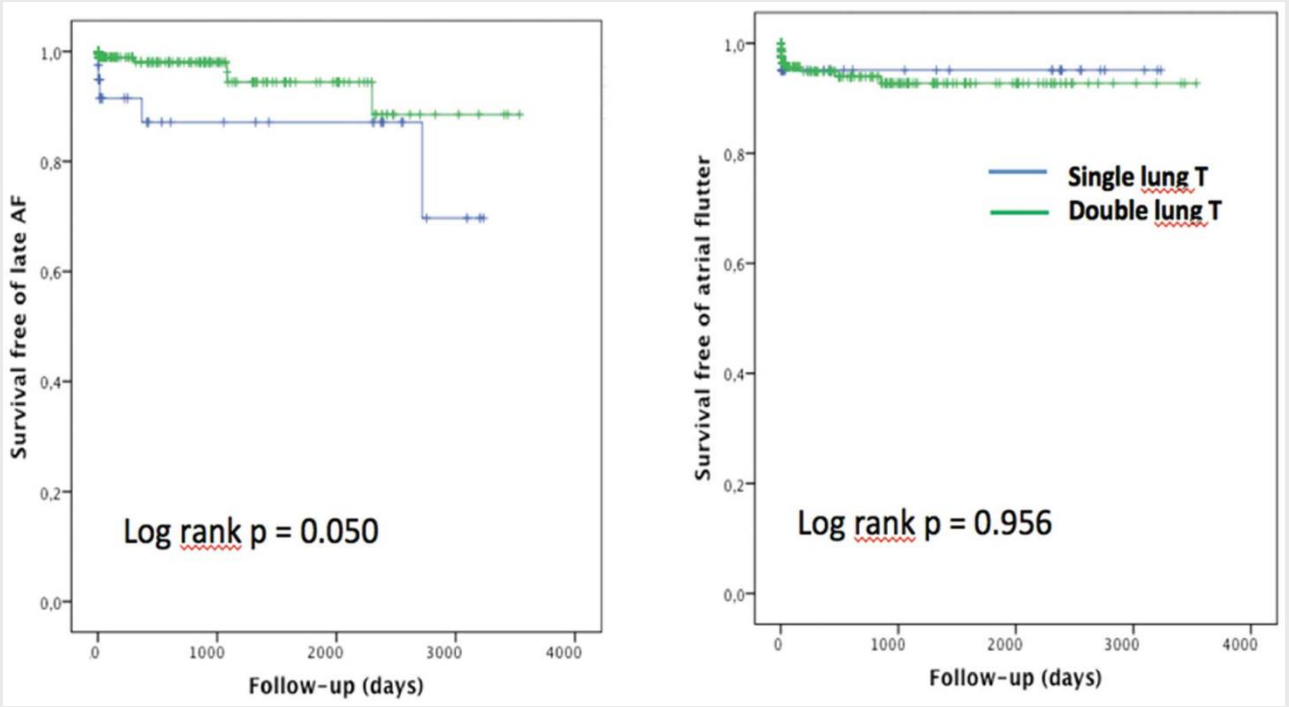
Atrial arythmia does not impact onto survival !!



Jesel L et al, Circ J 2017;81:660-7

Early and late atrial arrhytmias after lung TX

Late atrial arythmia / type of transplantation



Jesel L et al, Circ J 2017;81:660-7

Atrial arrhytmias after lung TX: Incidence and risk factors in 652 lung TX recipients

- 652 patients received lung TX
- 198 developed atrial arythmia (30.4 %)

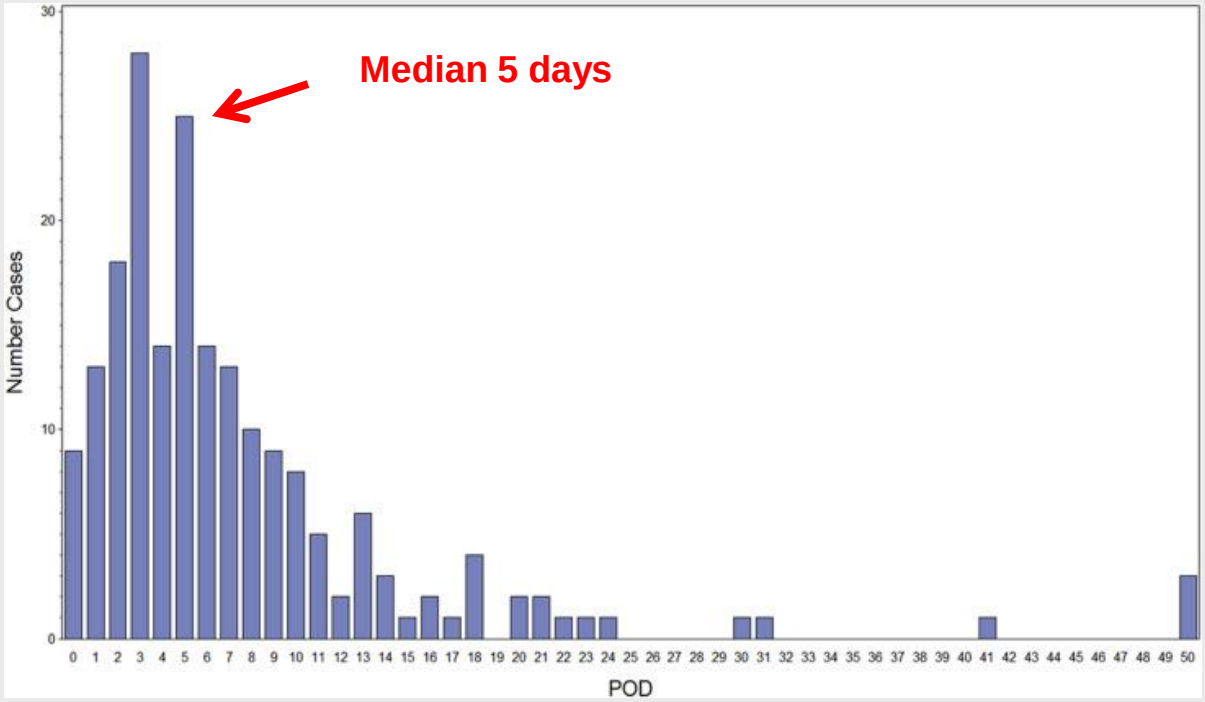


Figure 1. Incidence of AA per POD (within first 50 POD; n = 198): AA events occurred most frequently within the first postoperative week, with the greatest number of events occurring on day 3. (Patients at risk). POD, Postoperative day.

D'Angelo AM et al. J Thorac Cardiovasc Surg 2016;152:901-9

Atrial arrhytmias after lung TX: Incidence and risk factors in 652 lung TX recipients

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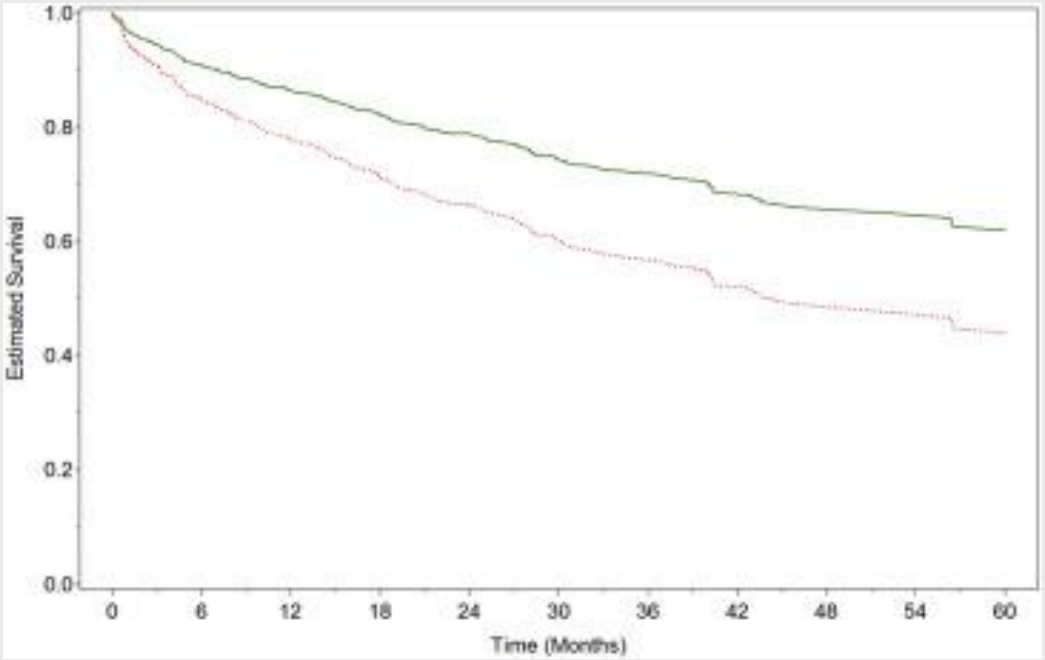


Figure 2. Competing risk survival analysis in patients who develop AA after LTx: estimated survival among patients who developed AA postoperatively versus those who did not (P = .02).

D'Angelo AM et al. J Thorac Cardiovasc Surg 2016;152:901-9

Atrial arrhytmias after lung TX: Incidence and risk factors in 652 lung TX recipients

Risk factor analysis

Risk factor	Adjusted HR	P value
Age at TX per year	1.03	<0.001
Previous CABG	2.77	0.002
Previous arrythmia	***0.28***	***<0.001***

D'Angelo AM et al. J Thorac Cardiovasc Surg 2016;152:901-9

Lung TX following coronary artery bypass surgery – improved outcomes following single-lung TX

- UNOS registry 2004-2013
- 14791 patients
- 292 previously underwent CABG (2%)
  - Single left 68
  - Single right 181
  - Bilateral 43

Time point	HR	p-value
30 days	1.97	<0.01
1 year	1.54	<0.01
3 years	1.38	<0.01
5 years	1.38	<0.01

McKellar SH, J Heart Lung Transplant 2016;35:1289-1294

Lung TX following coronary artery bypass surgery – improved outcomes following single-lung TX

Compared survival at 30 days, 1 year, 3 years and 5 years

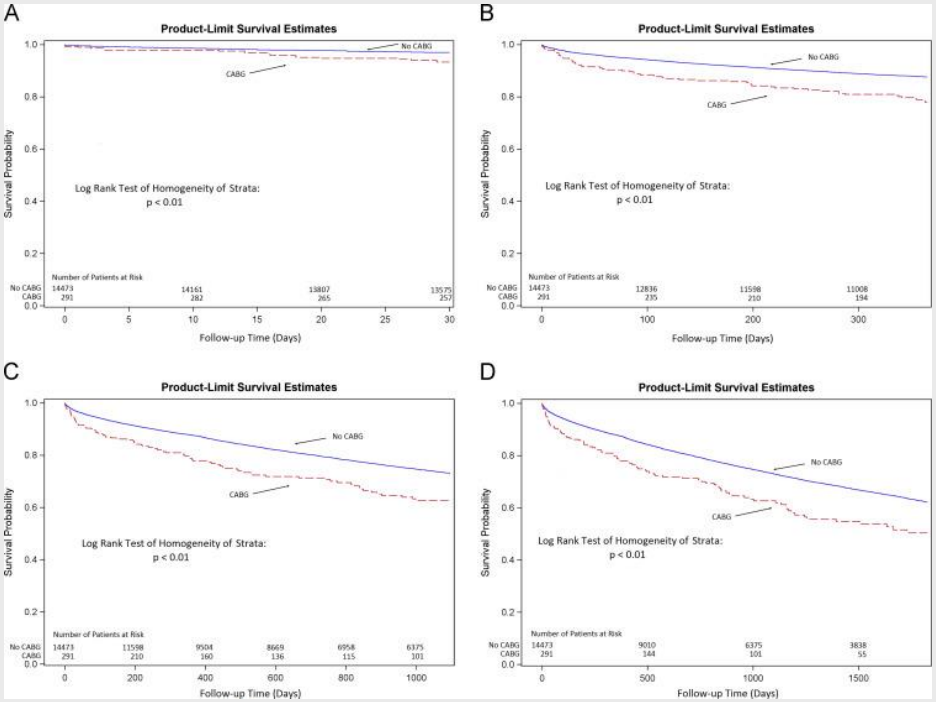


Figure 1. Kaplan-Meier plots of patient survival comparing patients who had CABG performed before LTx (red dashed line) and patients in whom CABG was not performed (blue solid line) at (A) 30 days, (B) 1 year, (C) 3 years, and (D) 5 years.

McKellar SH, J Heart Lung Transplant 2016;35:1289-1294

Lung TX following coronary artery bypass surgery – improved outcomes following single-lung TX

Comparison single/double TX at 30 days, 1 year, 3 years and 5 years

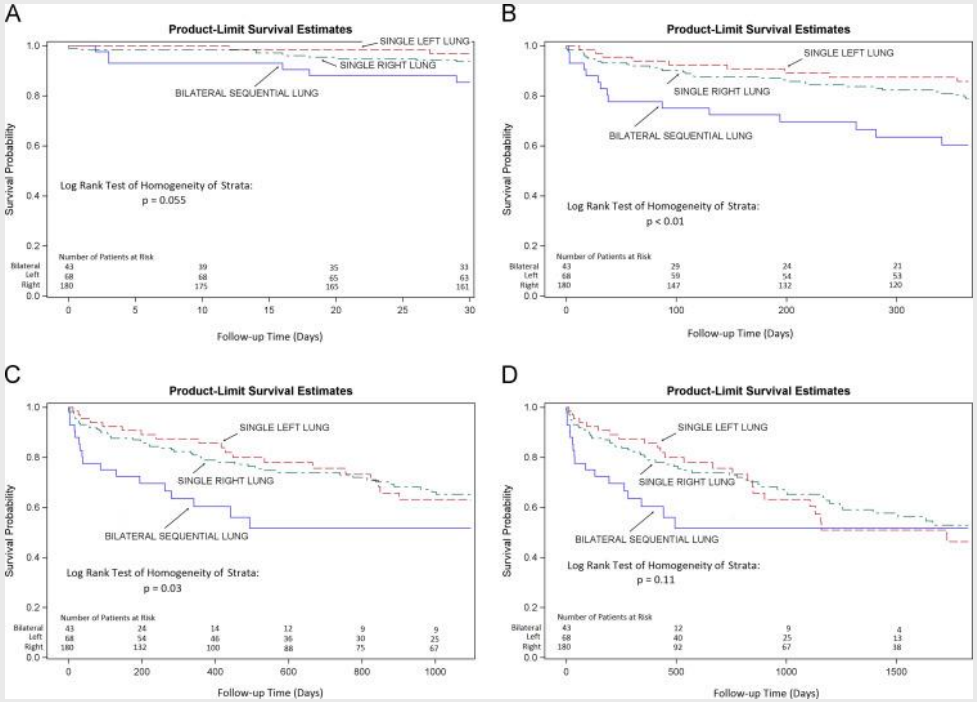


Figure 2. Kaplan-Meier plots of patient survival for patients with history of CABG stratified by type of LTx at (A) 30 days, (B) 1 year, (C) 3 years, and (D) 5 years. Blue solid line refers to bilateral LTx; red dashed line refers to single left LTx; green das...

McKellar SH, J Heart Lung Transplant 2016;35:1289-1294

Take-Home Message

Atrial arythmia

- Frequent problem: 30% of recipients
- Impact on survival still questionable
- Favoured by advanced age

TX after CABG

- CABG negatively influences survival
- Single lung TX seems to be better tolerated

List of References

1. *Shennib H & Massard G, Ann Thorac Surg 1994;57:506-11*
2. *Massard G et al, Eur Respir Mon 2009;45:177-93*
3. *Olland A et al, J Heart Lung Transplant 2017;36(2):157-65*
4. *Hayanga JW et al, J Heart Lung Transplant 2016;35(10):1206-11*
5. *Gleva MJ et al, J Thorac Cardiovasc Surg 2016;152(3):910-11*
6. *Jesel L et al, Circ J 2017;81:660-7*
7. *D'Angelo AM et al. J Thorac Cardiovasc Surg 2016;152:901-9*
8. *McKellar SH, J Heart Lung Transplant 2016;35:1289-1294*

Lung Transplantation

Chronic Lung Allograft Dysfunction

State of the Art

- Humoral rejection is recognized as a main factor for chronic lung allograft dysfunction; detection of Donor Specific Antibodies is an argument for diagnosis.

- Chronic lung allograft dysfunction is the most reasonable indication for retransplantation

- Retransplantation is a contradictory issue: prognosis is similar to primary TX in Europe, and less favorable in the US

- Ambulatory patients are credited the favorable outcome after retransplantation

Lung intragraft donor-specific antibodies as a risk factor for graft loss

- Single Centre Study
- 53 lung TX recipients
- Identification of immunoglobulin G DAS in sera and biopsy specimens

Graft loss at 1 year

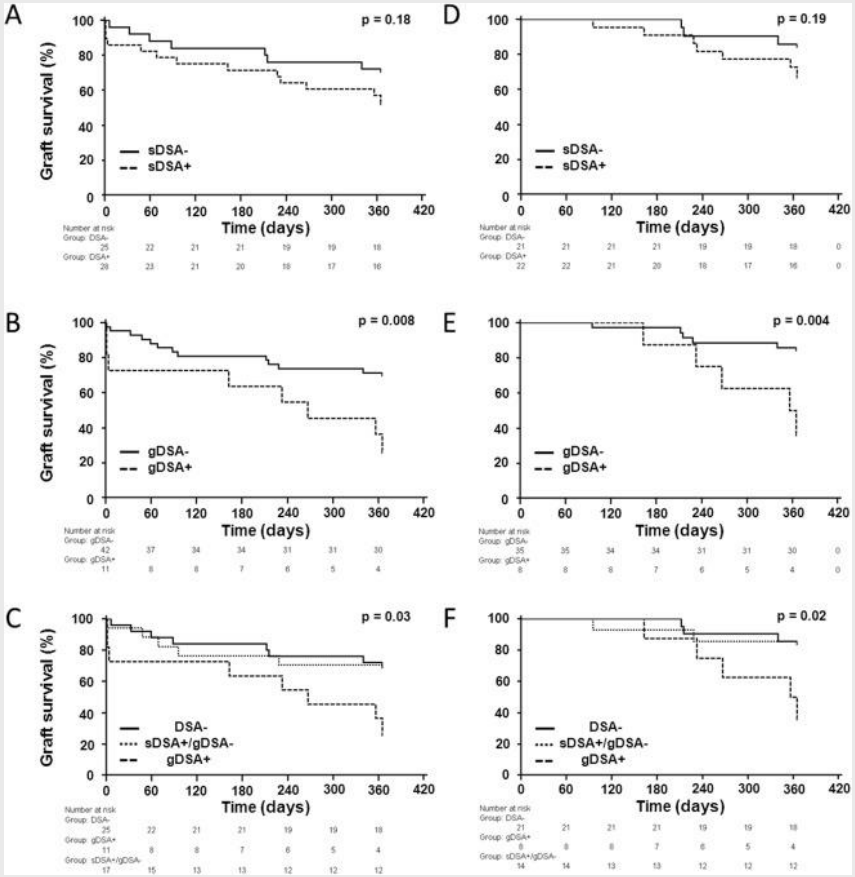
variable	O.R.	p-value
Infection	5.65	0.03
Graft DSA	5.85	0.03

Graft loss overall

variable	O.R.	p-value
Infection	3.67	0.006
Graft DSA	4.51	0.001

Visentin J et al, J Heart Lung Transplant 2016;35:1418-26

Lung intragraft donor-specific antibodies as a risk factor for graft loss

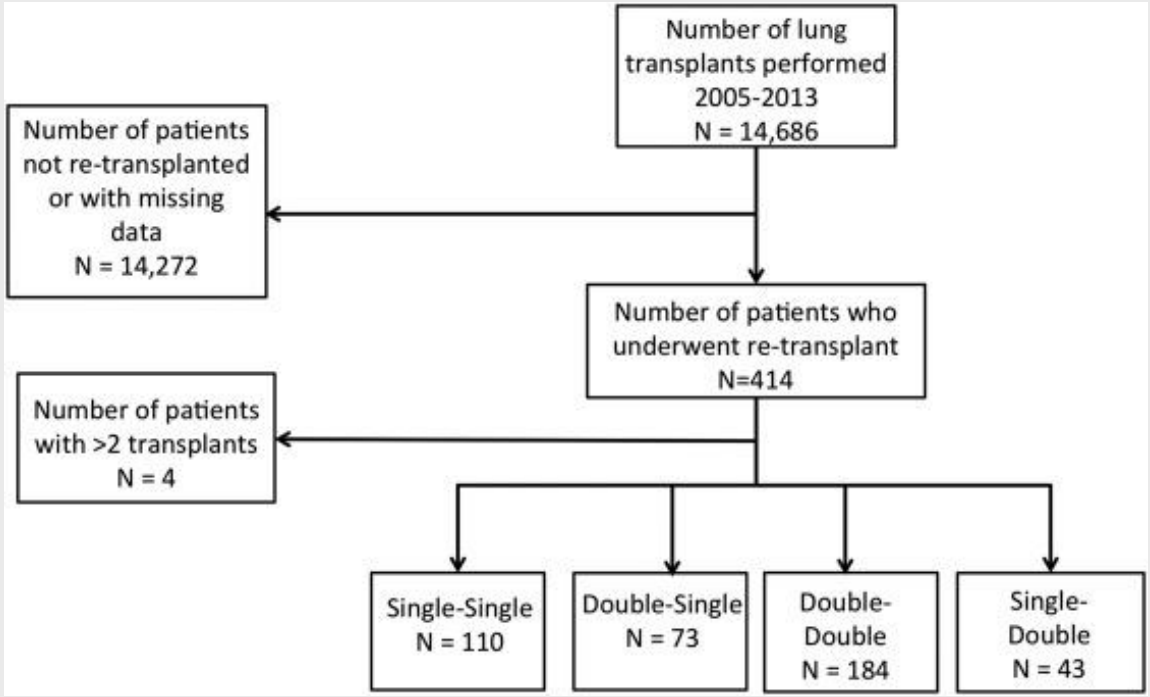


Visentin J et al, J Heart Lung Transplant 2016;35:1418-26

Single versus double lung retransplantation does not affect survival based on previous transplant type

- UNOS registry 2005-2013
- 414 redo TX recipients

Registry study



Schumer EM et al, Ann Thorac Surg 2017;103:236-40

Single versus double lung retransplantation does not affect survival based on previous transplant type

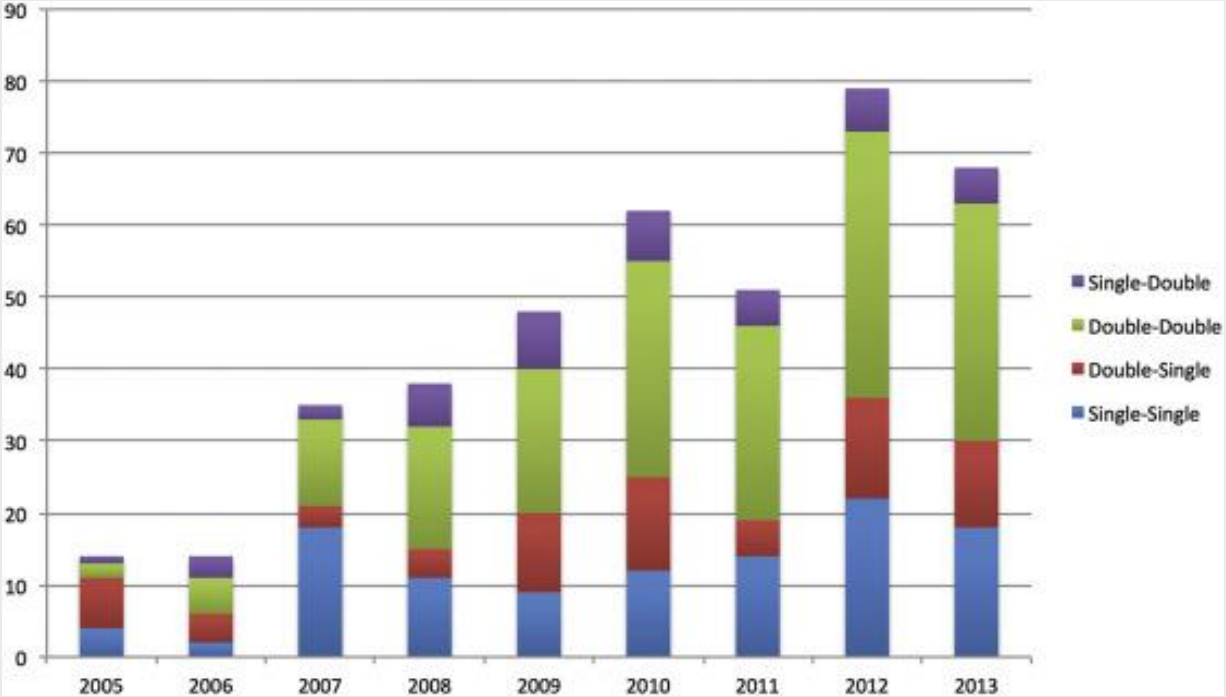


Fig 2. Annual number of patients who underwent repeat lung transplantation from 2005 to 2013. The groups were stratified by single followed by single, double followed by single, double followed by double, and single followed by double lung transplantation.

Schumer EM et al, Ann Thorac Surg 2017;103:236-40

Single versus double lung retransplantation does not affect survival based on previous transplant type

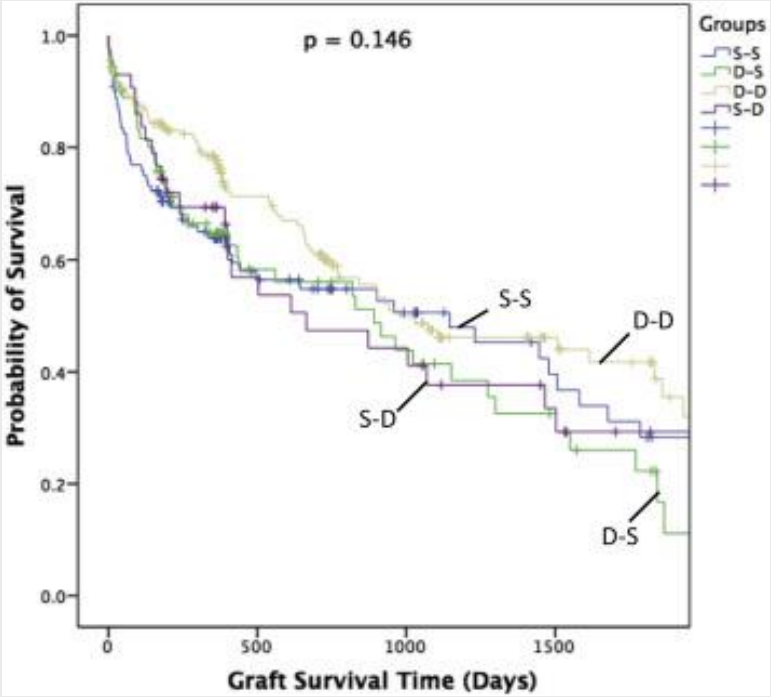


Fig 3. Comparison of graft survival following retransplant for single followed by single (S-S), double followed by single (D-S), double followed by double (D-D), and single followed by double (S-D) lung transplantation. There was no difference in overall survi...

Schumer EM et al, Ann Thorac Surg 2017;103:236-40

Single versus double lung retransplantation does not affect survival based on previous transplant type

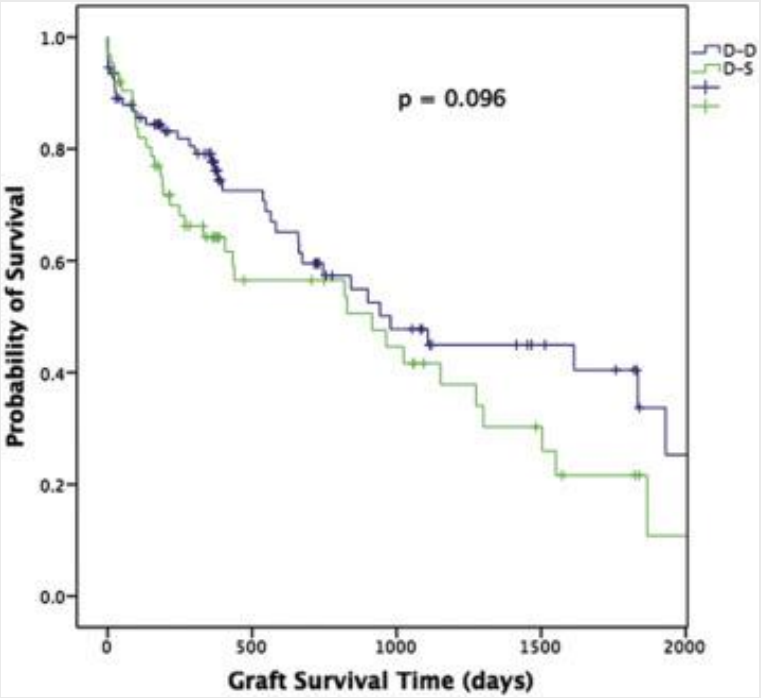


Fig 4. Comparison of graft survival following retransplant for double followed by single and double followed by double lung transplantation after propensity matching. There was no difference in overall survival between the 2 groups (p = 0.096).

Schumer EM et al, Ann Thorac Surg 2017;103:236-40

Single versus double lung retransplantation does not affect survival based on previous transplant type

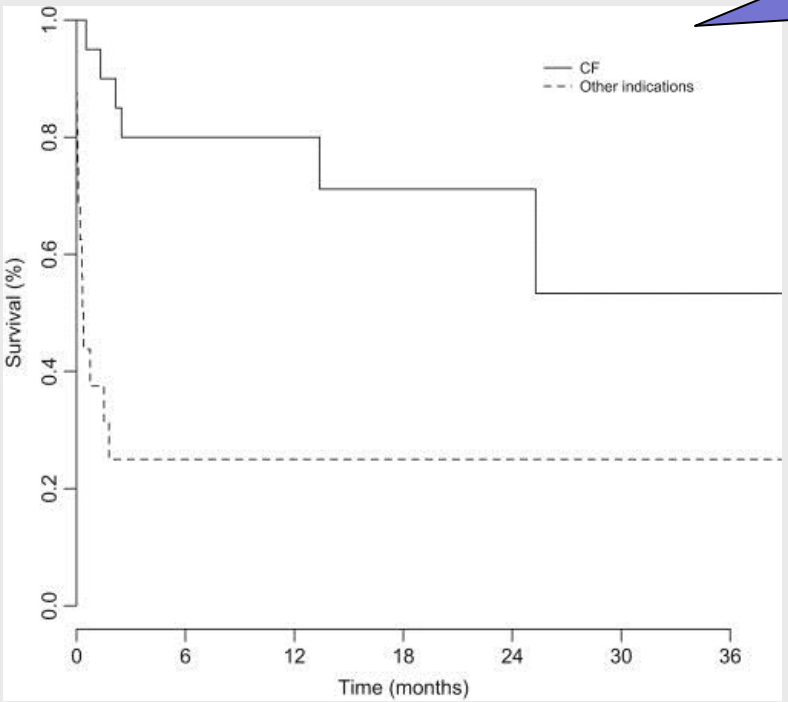
"When retransplantation is performed, single lung retransplantation shhould be considered, regardless of previous transplant type, in an effort to maximize organ resources"

Schumer EM et al, Ann Thorac Surg 2017;103:236-40

Transplantation after bridging ECMO

Poor prognosis in non-CF

Registry study

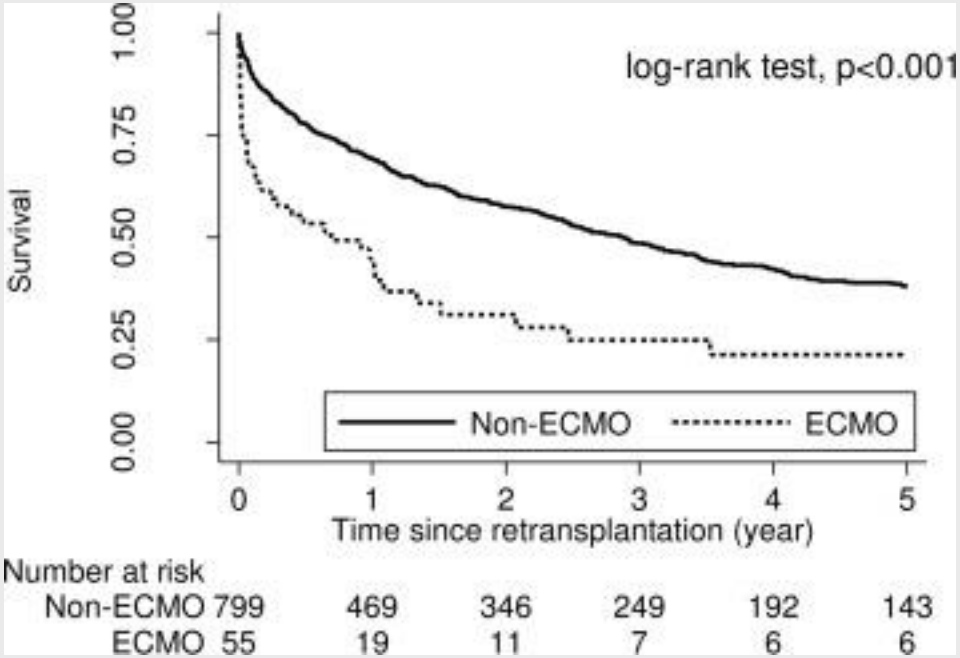


Data from the French National Registry run by the « Agence de Biomédecine **»**

Lafarge M et al. J Heart Lung Transplant 2013;32:905-13

ECMO as a bridge to lung retransplantation: is there a role ?

- UNOS registry
- 854 retransplants
- 55 bridge-ECMO (6.8%)



Registry study

Hayanga JW et al. J Heart Lung Transplant 2016;35:901-905

Take-Home Message

- DSA detected on graft biopsy might be the most sensitive predictor of CLAD
- It seems reasonable to use single lung TX for retransplantation, because outcome is similar to double lung TX
- Retransplantation in patients on ECMO offers a dismal prognosis

Lung Transplantation

Primary lung graft dysfunction

State of the Art

- Primary lung graft dysfunction is the main cause of early mortality after lung TX.
- Mechanisms leading to primary lung graft dysfunction are multifactorial.
- Ischemia-reperfusion injury is considered as the main cause.
- Recipient related factors are mainly pulmonary hypertension and indication for interstitial pulmonary fibrosis.
- Donor related factors are unclear.

Massive donor transfusion potentially increases recipient mortality after lung transplantation

- UNOS database 1996-2014
- 86398 potential donors
- 16255 TX
- Analysis of all cause mortality at 30 days, 90 days and 1 year

- 54% of donors received at least 1 transfusion
- 6% received massive transfusion (> 10 units)

Broders CF et al. J Thorac Cardiovasc Surg 2017;153:1197-203

Massive donor transfusion potentially increases recipient mortality after lung transplantation

- UNOS database 1996-2014
- 16255 TX
- Analysis of all cause mortality at 30 days, 90 days and 1 year
- 54% of donors received at least 1 transfusion
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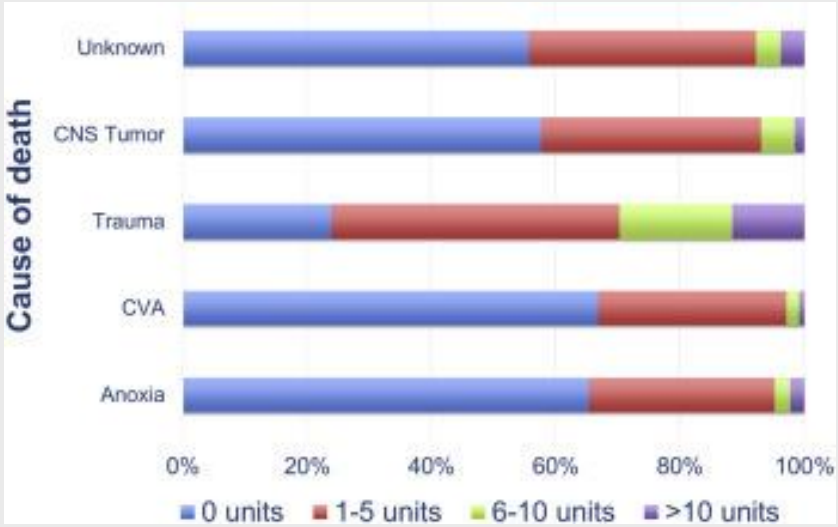
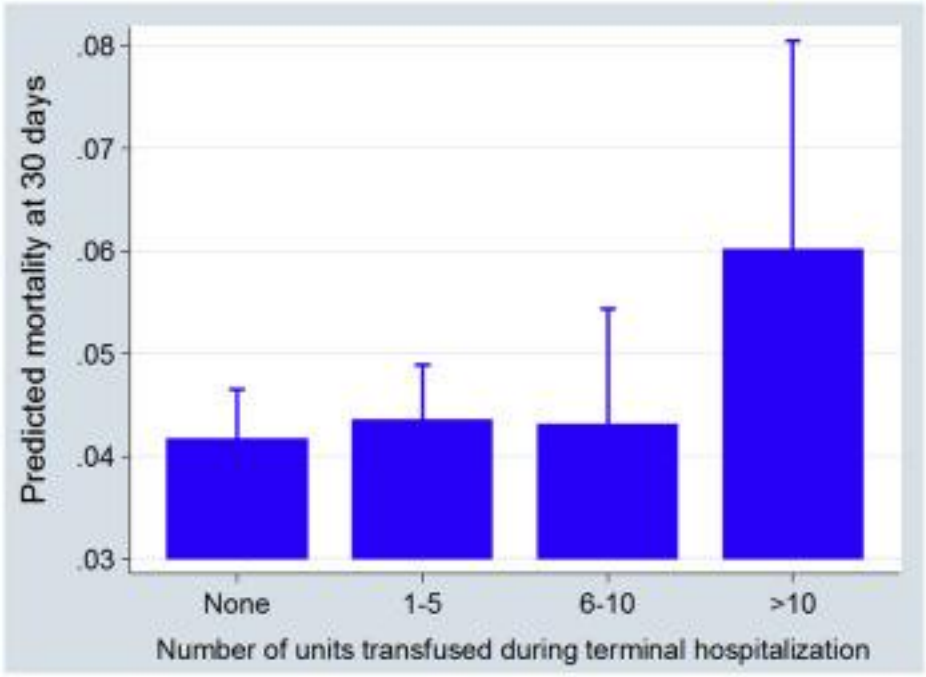


Broders CF et al. J Thorac Cardiovasc Surg 2017;153:1197-203

Massive donor transfusion potentially increases recipient mortality after lung transplantation



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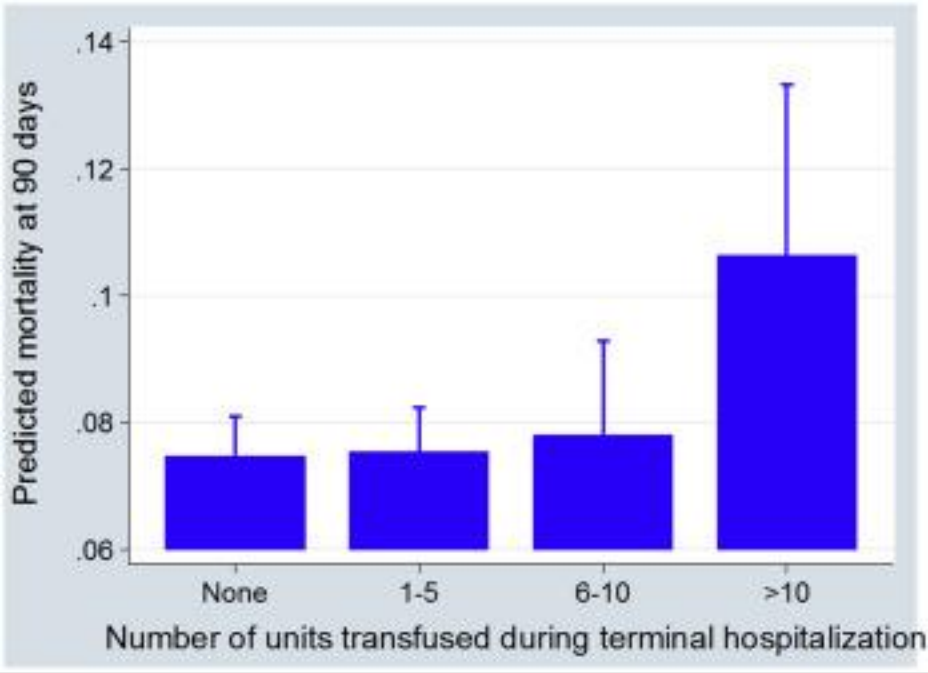

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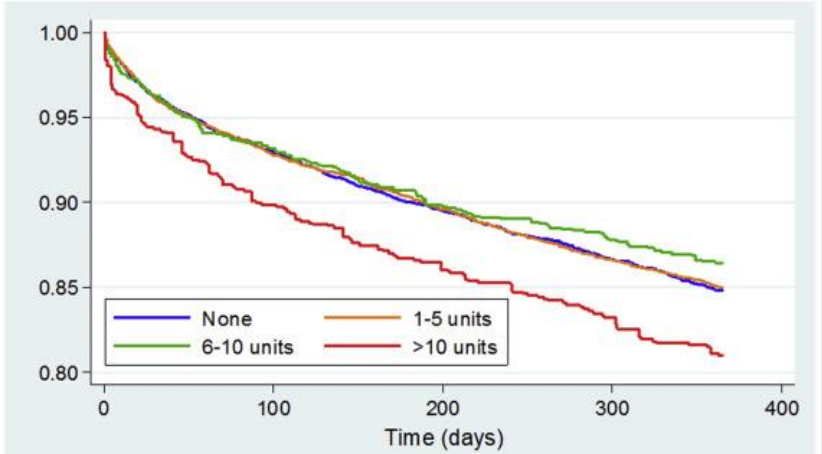


Transfusion	30-days	90-days	1-year
None	0.96 [0.96, 0.97]	0.93 [0.92, 0.94]	0.84 [0.83, 0.85]
1-5 units	0.96 [0.95, 0.97]	0.93 [0.92, 0.94]	0.85 [0.84, 0.86]
6-10 units	0.96 [0.95, 0.97]	0.93 [0.92, 0.95]	0.86 [0.84, 0.88]
>10 units	0.94 [0.92, 0.96]	0.90 [0.87, 0.93]	0.81 [0.77, 0.84]

Number at Risk	0-days	30-days	90-days	1-year
None	7420	6931	6583	5203
1-5 units	6197	5800	5507	4465
6-10 units	1622	1519	1447	1185
>10 units	1016	934	890	702

Broders CF et al. J Thorac Cardiovasc Surg 2017;153:1197-203

Take-Home Message

- Massive blood transfusion may lead to an increase of early mortality (30 days and 90 days)
- Massive transfusion is obviously related to polytrauma and younger age of donor

Lung Transplantation

Paediatric TX for cystic fibrosis

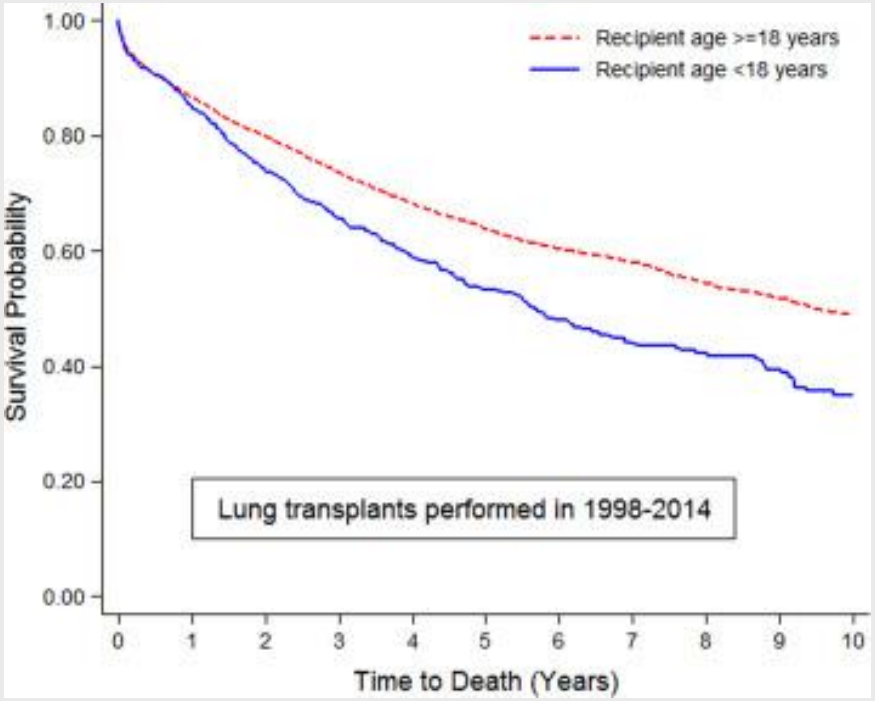
State of the Art

- Cystic fibrosis is the leading indication for paediatric lung TX.
- Medium and long term outcomes of lung TX seem to be lower in children than in adults.

Age related survival disparity associated with lung TX in CF

Registry study

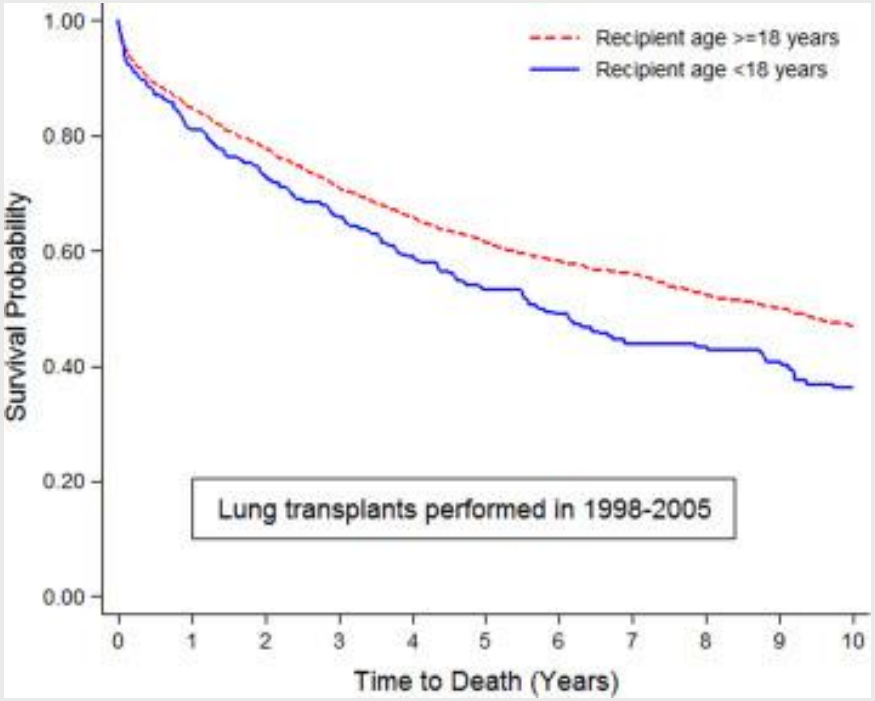
- ISHLT registry
- 7245 TX for CF
- 12% < 18 years

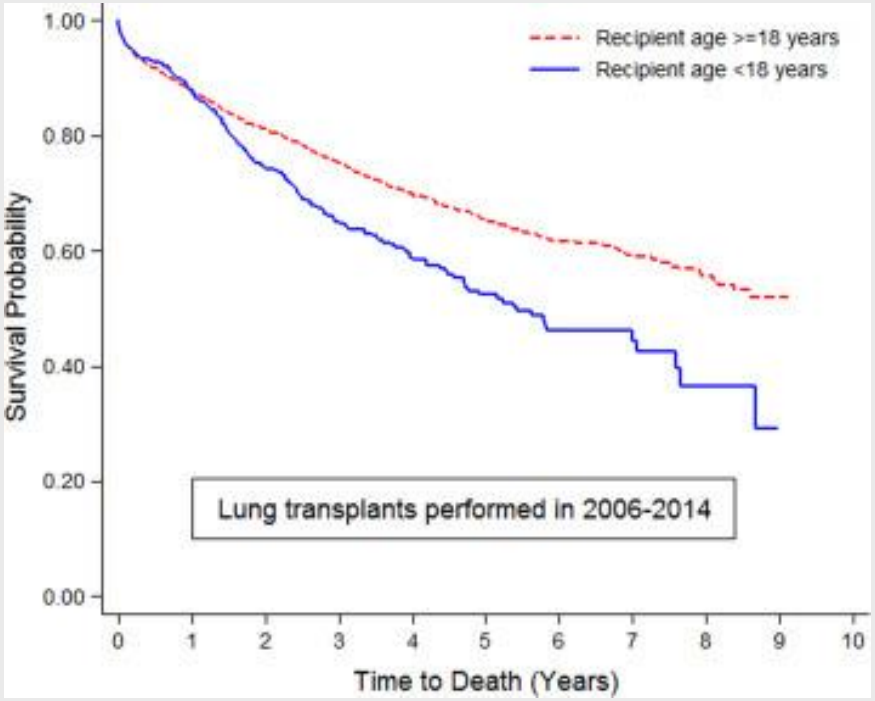


Significant risk factors
- Age < 18
- TX on ventilator

Hayes D et al. J Heart Lung Transplant 2016;35:1108-15

Age related survival disparity associated with lung TX in CF





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Take-Home Message

- Survival after lung TX in children is lower compared to adults in the UNOS experience
- TX on ventilator is an additional and independant adverse prognostic factor

List of References

1. *Visentin J et al, J Heart Lung Transplant 2016;35:1418-26*
2. *Hayes D et al. J Heart Lung Transplant 2016;35:1108-15*
3. *Lafarge M et al. J Heart Lung Transplant 2013;32:905-13*

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1. *Schumer EM et al, Ann Thorac Surg 2017;103:236-40*
2. *Broders CF et al. J Thorac Cardiovasc Surg 2017;153:1197-203*
3. *Visentin J et al, J Heart Lung Transplant 2016;35:1418-26*
4. *Hayes D et al. J Heart Lung Transplant 2016;35:1108-15*
5. *Lafarge M et al. J Heart Lung Transplant 2013;32:905-13*
6. …
7. …

List of Abbreviations

- CABG: coronary artery bypass grafting
- CF: cystic fibrosis
- COPD: chronic obstructive lung disease
- DSA: donor specific antibodies
- ECMO: extra-corporal membrane oxygenation
- NSCLC: non-small cell lung cancer
- SBRT: Stereotactic beam radiation therapy
- sPAP: systolic pulmonary artery pressure
- TX: transplantation
- UNOS: United Network for Organ Sharing
- VAS: visual analogic score
- VATS: video-assisted thoracoscopic surgery