Surgery for Lung Cancer and Malignant Pleural Mesothelioma

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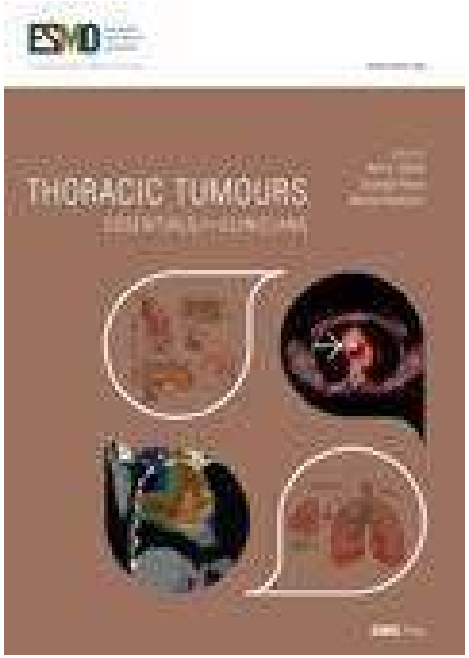
Disclosure

- ☑ I have **no**, real or perceived, direct or indirect conflicts of interest that relate to this presentation.

Summary provided in:

ESMO Thoracic Tumors: Essentials for Clinicians
Chapter 5
Hoda & Klepetko
available at Oncology PRO or by.....



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Surgery for lung cancer

AGENDA

Overview

Surgery for early stage NSCLC

Surgery for locally advanced disease

Surgery for oligometastatic disease

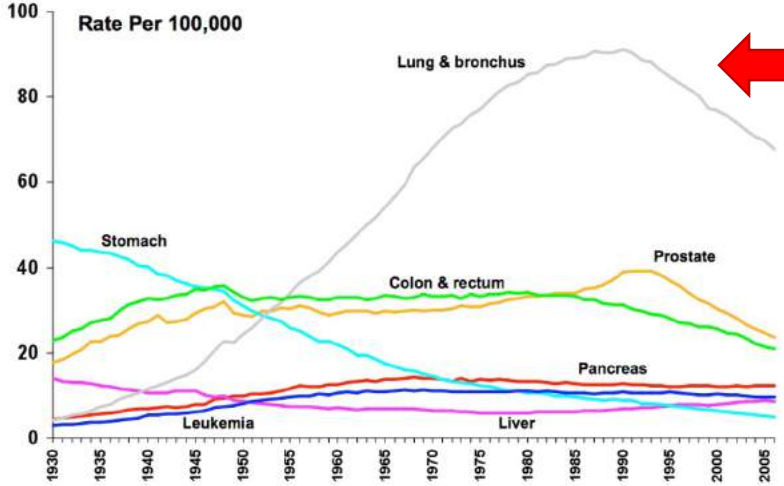
Palliative treatment options

Role of surgery in SCLC

Summary

Male

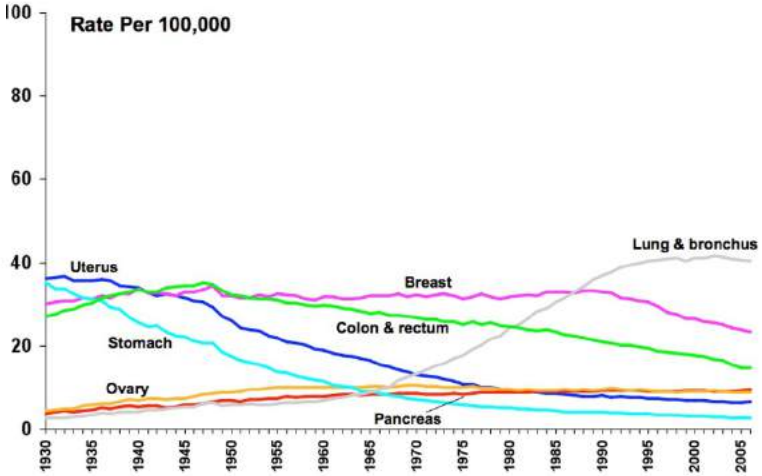
Cancer Death Rates* Among Men, US,1930-2006



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Female

Cancer Death Rates* Among Women, US,1930-2006



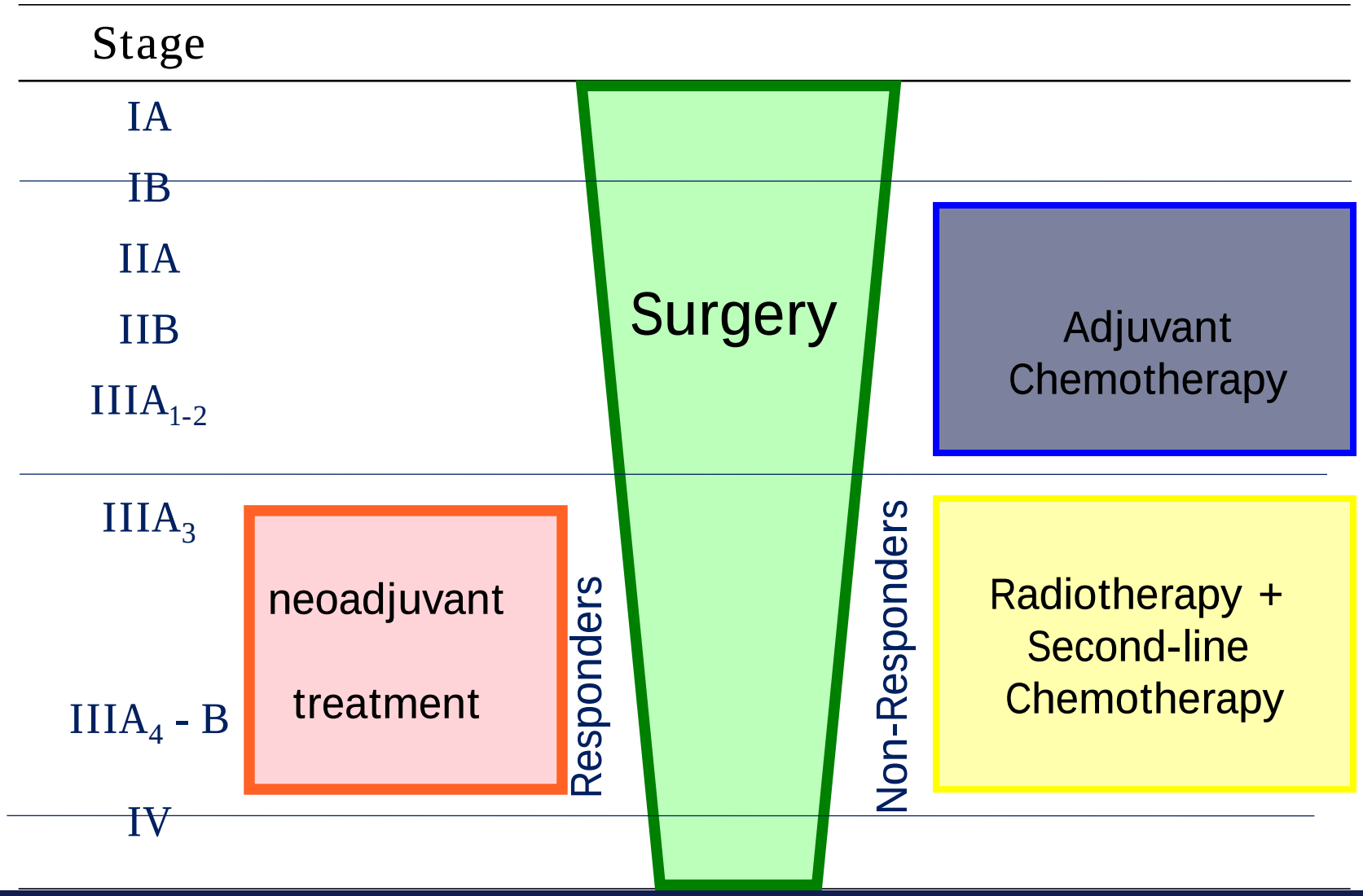
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Lung Cancer Mortality since 1930

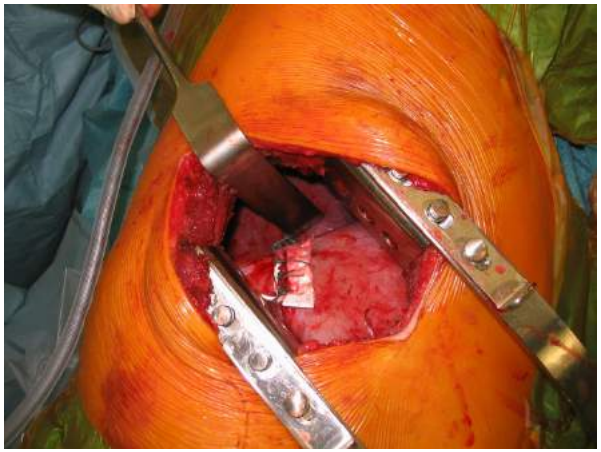
Classical treatment protocol for Lung cancer

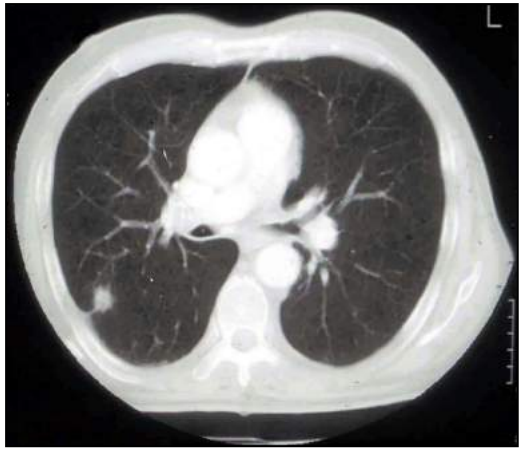
Stage		TNM
IA	Surgery	T1N0M0
IB		T2N0M0
IIA		T1N1M0
IIB		T2N1M0
		T3N0M0
IIIA	Chemo/Radio	T1-3N2M0
		T3N1M0
IIIB		T1-3N3M0
		T4anyNM0

Modern Treatment Algorithm for Lung cancer



Surgery for early stage NSCLC





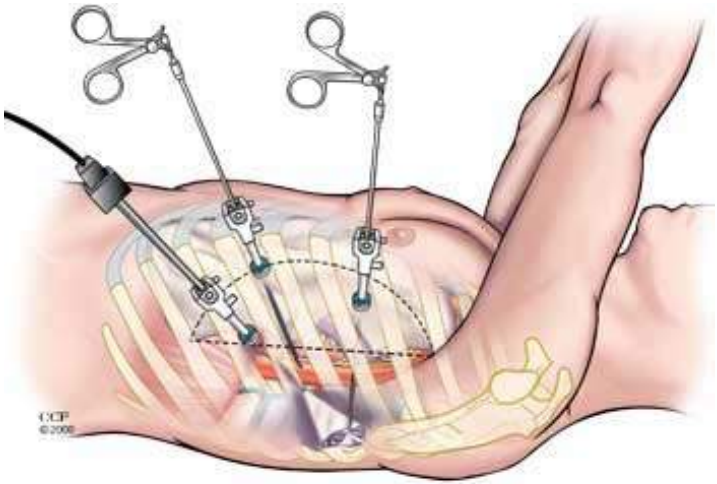
Standard of care:
Lobectomy + mediastinal lymph node dissection (MLND)

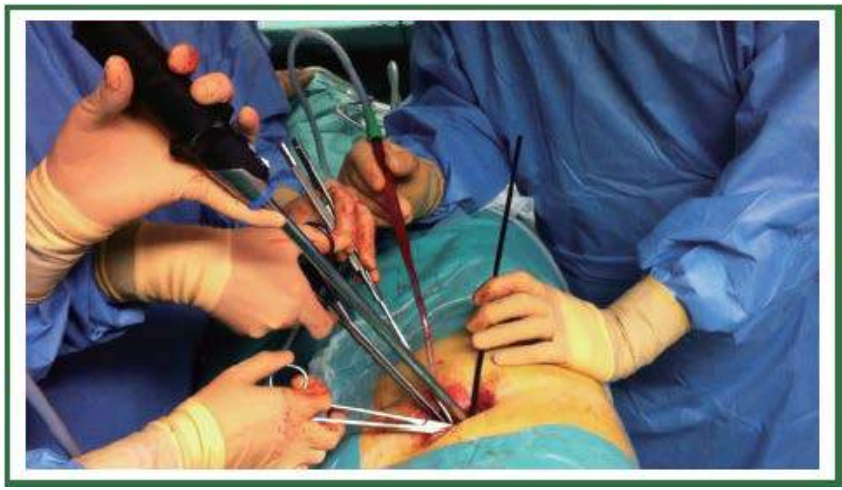
Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg*. 1995;60(3):615–22; discussion 622–623.

Standard of care – new developments

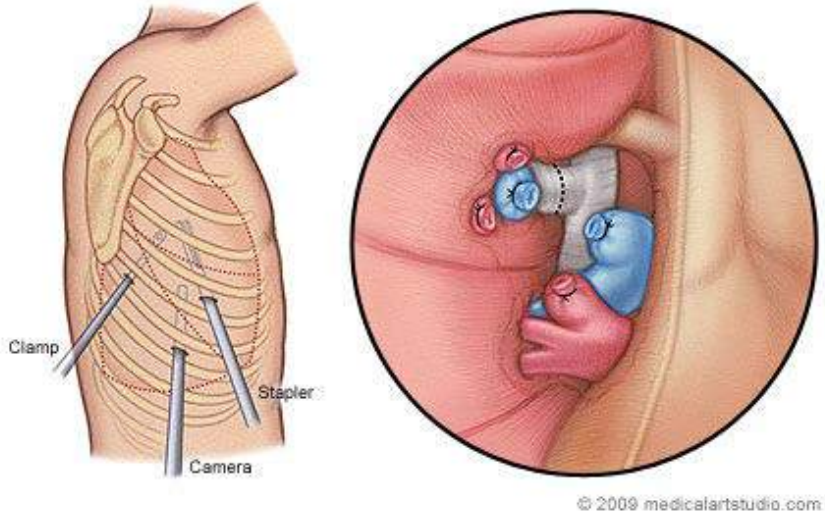
- Minimal invasive resesctions (incl.awake)
- Sublobar resection (limited resections)
- Parenchyma sparing options

Minimal invasive surgery (MIS)





Video assisted thoracic surgery (VATS)



VATS: 3-portal (Hansen et al, 2011)

VATS: uniportal (Gonzalez-Rivas et al, 2013)

Robotic assisted thoracic surgery (RATS)

Awake VATS for SPN

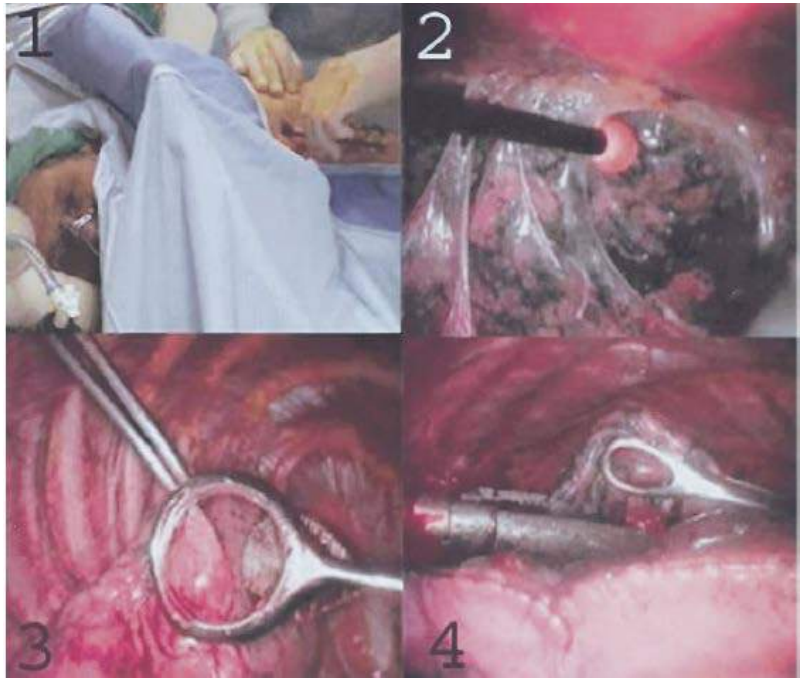
Feasibility and Results of Awake Thoracoscopic Resection of Solitary Pulmonary Nodules

Eugenio Pompeo, MD, Davide Mineo, MD, Paola Rogliani, MD,
Alessandro F. Sabato, MD, and Tommaso C. Mineo, MD

Division of Thoracic Surgery and Multidisciplinary Pulmonary Program, Policlinico Tor Vergata University, Rome, Italy

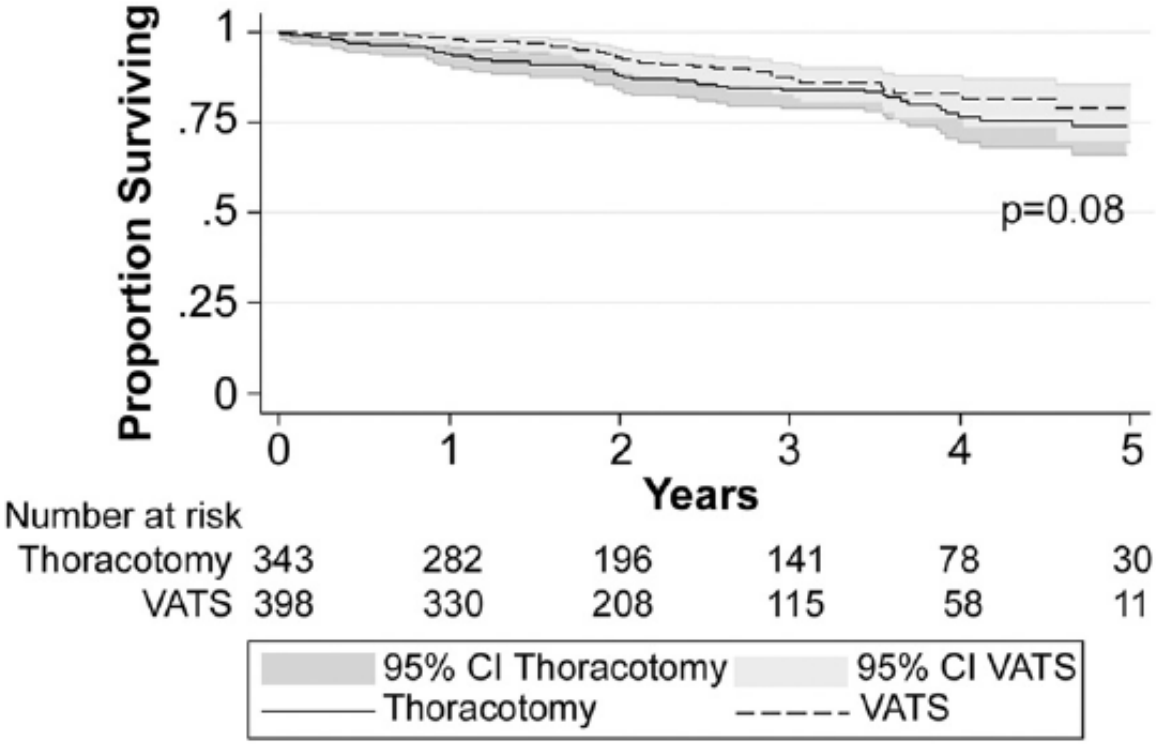
RCT
n=60
Epidural anaesthesia vs GA+DLI

0% mortality



Pompeo et al, ATS 2004

Lobectomy: MIS vs. open surgery



Is VATS Lobectomy Better: Perioperatively, Biologically and Oncologically?

Natasha M. Rueth, MD, and Rafael S. Andrade, MD

Ann Thorac Surg 2010;89:S2107–11

MIS vs. open surgery: morbidity & mortality

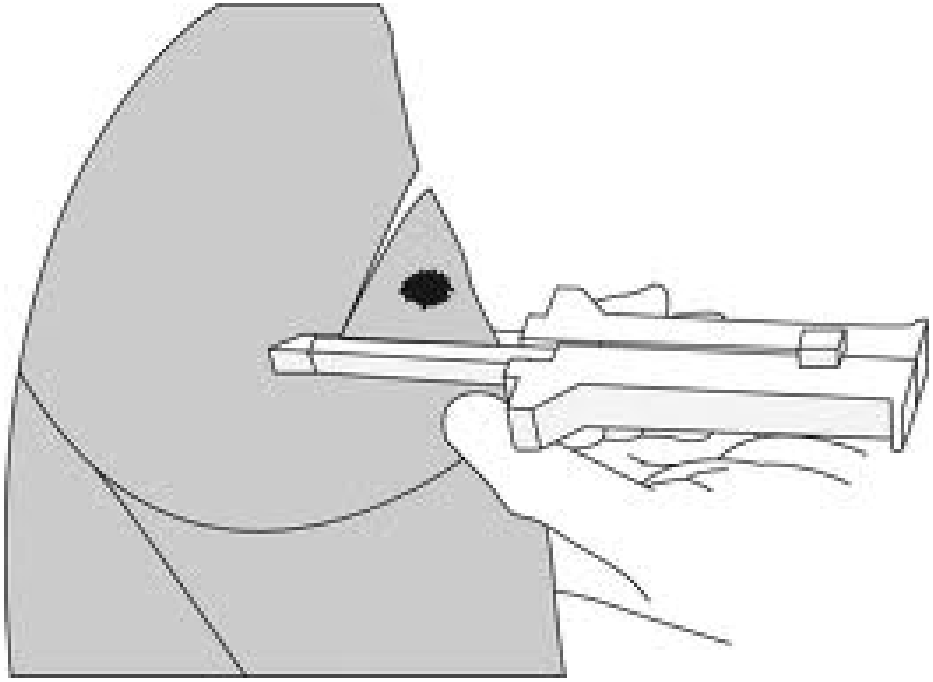
Table 3. Perioperative Outcomes of Lobectomy Comparing Video-Assisted Thoracoscopic Lobectomy With Open

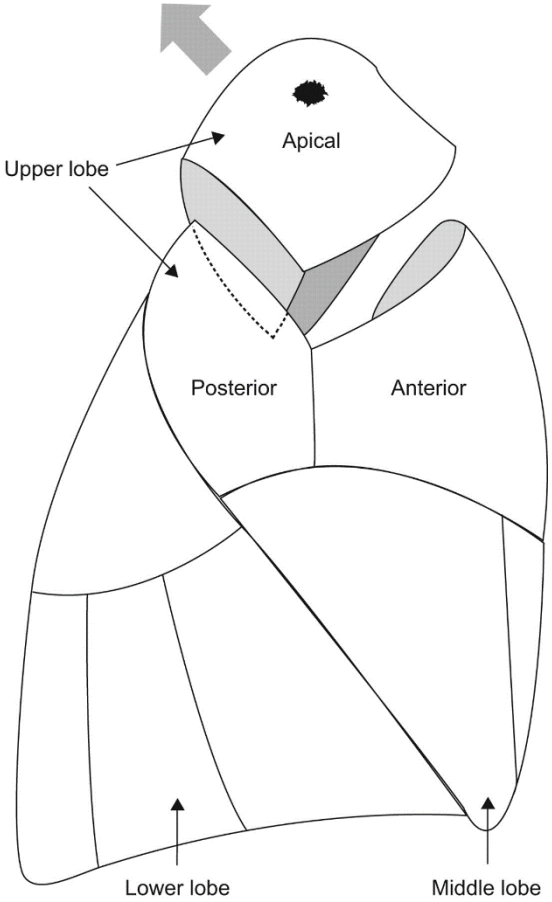
Author, Year	Study Type	Procedure	n	Blood Loss (mL)	Total Complication Rate (%)	Chest Tube Duration (days)[a]	Air Leak (%)[b]	Arrhythmia (%)	Pneumonia (%)	LOS (days)[a]	Mortality (%)
Kirby, 1995 [21]	Prospective	VATS	25	<250 (84%)	24[c]	6.5	12	. . .	. . .	7.1	0
		Open	30	<250 (83%)	53	4.6	27	. . .	. . .	8.3	0
Whitson, 2007 [23]	Retrospective	VATS	59	251	. . .	5	13.6	13.8	3.4[c]	6.4	0
		Open	88	255	. . .	6.1	11.5	10.3	19.3	7.7	0
Whitson, 2008 [24]	Systematic review	VATS	3,114	. . .	16.4[c]	4.2[c]	5	5.2	2.7	8.3[c]	. . .
		Open	3,256	. . .	31.2	5.7	8.8	9	6	13.3	. . .
Handy, 2009 [20]	Retrospective	VATS	49	204[c]	10	>5 (14%)	. . .	6.1[c]	4.1	5.2[c]	4.1
		Open	192	470	22.5	>5 (15%)	. . .	17.3	7.1	6.6	2.6
Villamizar, 2009 [22]	Retrospective	VATS	284[d]	. . .	31[c]	3[c]	12[c]	13[c]	5[c]	4[c]	3
		Open	284[d]	. . .	51	4	19	21	10	5	5
Flores, 2009 [19]	Retrospective	VATS	398[e]	. . .	23[c,f]	. . .	4.2	10.3	. . .	5[c,f]	0.3
		Open	343	. . .	33[f]	. . .	5.2	12.5	. . .	7[f]	0.3

The currently available clinical evidence indicates that VATS lobectomy for early-stage NSCLC is associated with fewer postoperative complications and less negative biologic impact on patients than open lobectomy.
Furthermore, all data to date strongly suggest oncologic equivalence of VATS versus open lobectomy for patients with early-stage NSCLC.

Ann Thorac Surg 2010;89:S2107–11

Sublobar resections





Eur Respir J 2009; 33: 426–435
DOI: 10.1183/09031936.00099808

SERIES "LUNG CANCER"
Edited by C. Brambilla
Number 2 in this Series

Sublobar resections

- Tendency towards less invasive resections for radiological non-invasive tumors
- Tendency towards lung parenchyma sparing resections i.e. segmental (anatomic) resections
- More candidates for surgery (limited lung function e.g.)
- Key question: Are these approaches really oncological radical?

Eur Respir J 2012; 39: 478–486
DOI: 10.1183/09031936.00027511

REVIEW

Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification

P.E. Van Schil*, H. Asamura#, V.W. Rusch¶, T. Mitsudomi+, M. Tsuboi§, E. Brambilla/ and W.D. Travis**

Of special interest to thoracic surgeons are the new categories; adenocarcinoma *in situ* and minimally invasive adenocarcinoma that represent small (≤3 cm), solitary adenocarcinomas consisting purely of lepidic growth without invasion or no greater than a 0.5-cm invasion, respectively. Usually, they correspond to GGO lesions on chest computed tomography.

Adenocarcinoma *in situ* and minimally invasive adenocarcinoma: 100% or near 100% 5-year disease-free survival, respectively, if completely resected.

TABLE 1 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in resection specimens

Pre-invasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma *in situ* (⩽3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma
(⩽3 cm lepidic predominant tumour with ⩽5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC: bronchioloalveolar carcinoma. Reproduced from [1] with permission from the publisher.

Future Prospects

- Lobectomy is still considered the standard surgical treatment for tumours of <2 cm that have a solid appearance on chest CT because such tumours are invasive carcinomas.
- Any change in this standard care awaits the results of two randomised trials (Japan Clinical Oncology Group identifier JCOG 0802/West Japan Oncology Group identifier WJOG3406L in Japan and Cancer and Leukemia Group B identifier CALGB 140503 (www.clinicaltrials.gov identifier NCT00499330) in North America) that randomise such patients in to either lobectomy or sublobar resection.

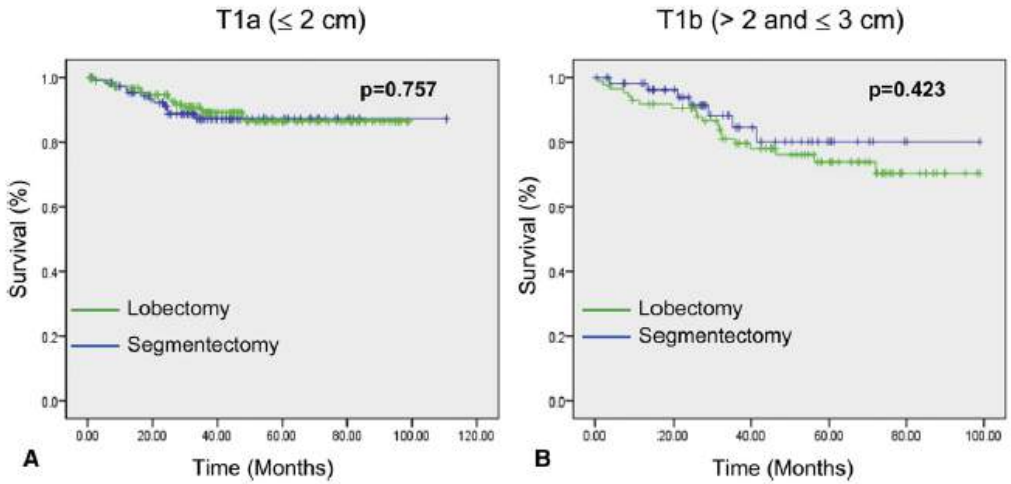
Impact of tumor size on outcomes after anatomic lung resection for stage 1A non–small cell lung cancer based on the current staging system

Shamus R. Carr, MD,[a] Matthew J. Schuchert, MD,[a] Arjun Pennathur, MD,[a] David O. Wilson, MD,[b] Jill M. Siegfried, PhD,[c] James D. Luketich, MD,[a] and Rodney J. Landreneau, MD[a]

TABLE 1. Patient demographics and operative data by T descriptor

	T1a (n = 284)	T1b (n = 145)	*P* value
Age, y			
Mean	67.0	69.4	.009
Range	28–88	43–88	
Gender	123 male, 161 female	75 male, 70 female	.10
Operation			
Segmentectomy	121 (42.6%)	57 (39.3%)	.54
Lobectomy	163 (57.4%)	88 (60.7%)	
Approach			
VATS	142 (50.0%)	62 (42.8%)	.18
Open	142 (50.0%)	83 (57.2%)	

VATS, Video-assisted thoracoscopic surgery.



Carr et al, JCTVS 2012

ORIGINAL ARTICLE

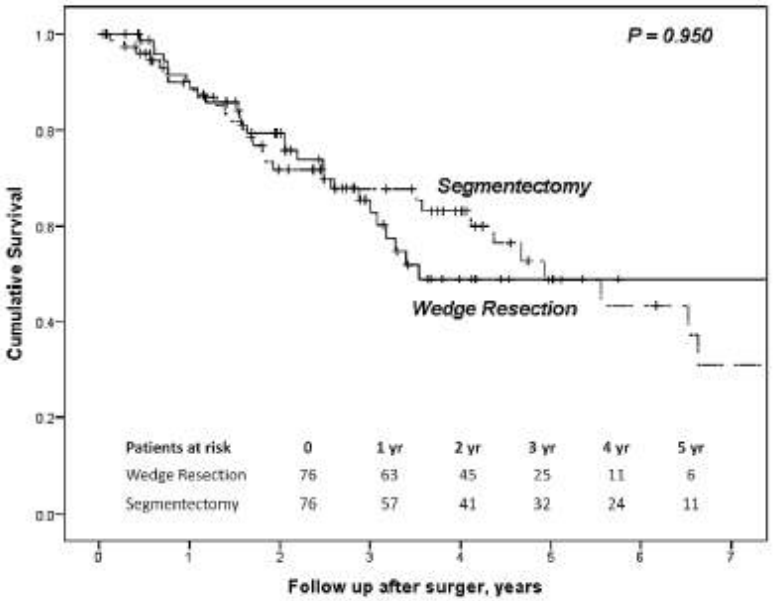
Anatomical Segmentectomy and Wedge Resections Are Associated with Comparable Outcomes for Patients with Small cT1N0 Non-Small Cell Lung Cancer

Nasser K. Altorki, MD,[a,*] Mohamed K. Kamel, MD,[a] Navneet Narula, MD,[b] Galal Ghaly, MD,[a] Abu Nasar, MS,[a] Mohamed Rahouma, MD,[a] Paul C. Lee, MD,[a] Jeffery L. Port, MD,[a] Brendon M. Stiles, MD[a]

[a]*Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York Presbyterian Hospital, Weill Cornell Medical College, New York, New York*
[b]*Department of Pathology, New York Presbyterian Hospital, Weill Cornell Medical College, New York, New York*

retrospective review of a prospective database (2000-2014) for cT1N0 patients
289 patients including WR in 160, and AS in 129

Although AS is associated with a more thorough lymph node dissection, this did not translate to
a survival benefit in this patient population with a low rate of nodal metastases.

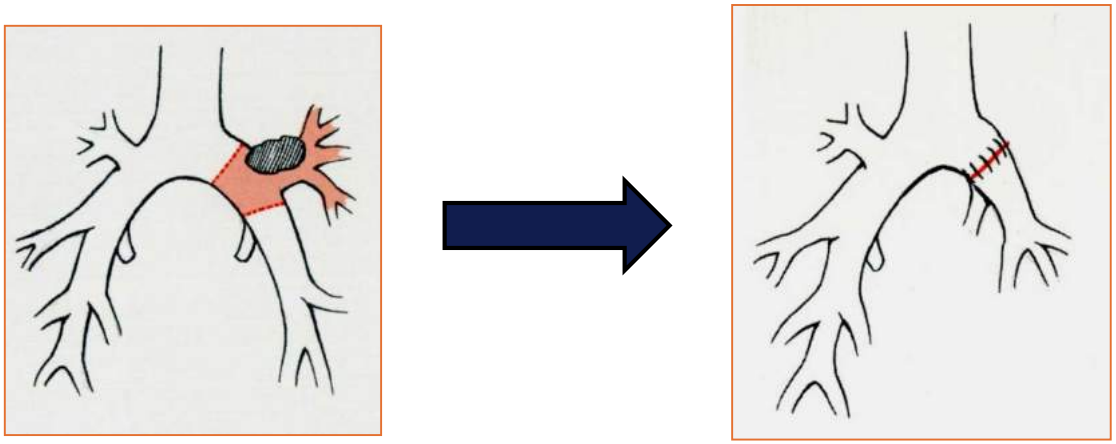


Altorki et al, JTO 2016

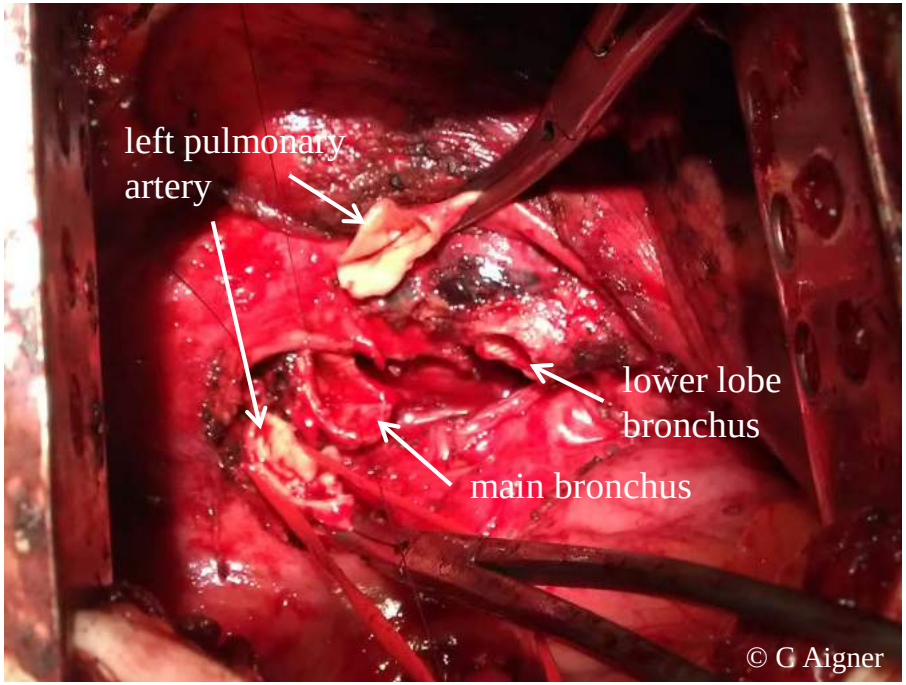
Parenchyma sparing procedures – sleeve lobectomy

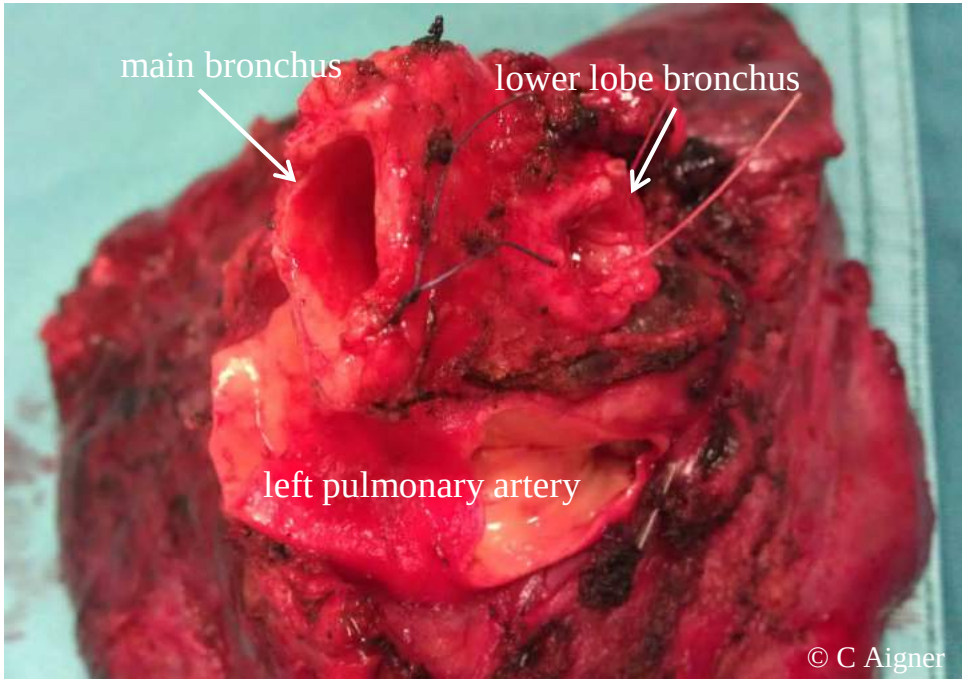
- Bronchoplastic techniques are currently procedures of choice in anatomically suitable patients in order to preserve lung parenchyma

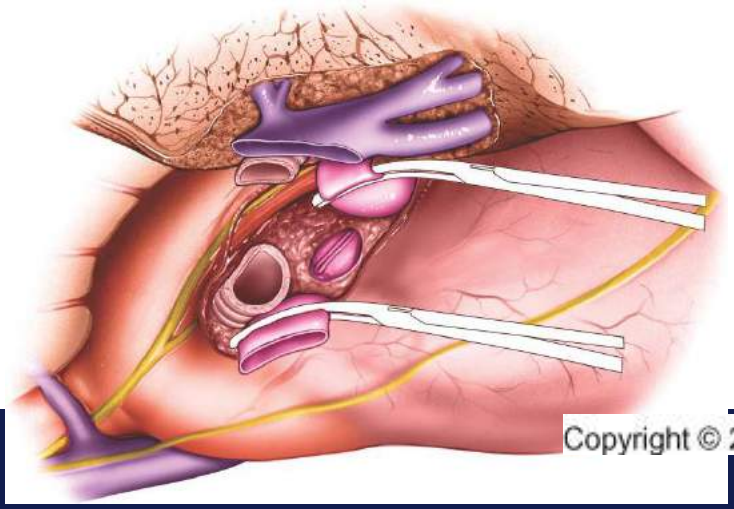
- Bronchoplastic resections are performed in 3 % - 13 % of patients with resectable lung tumors



Bronchoplastic and angioplastic resection of centrally located tumors





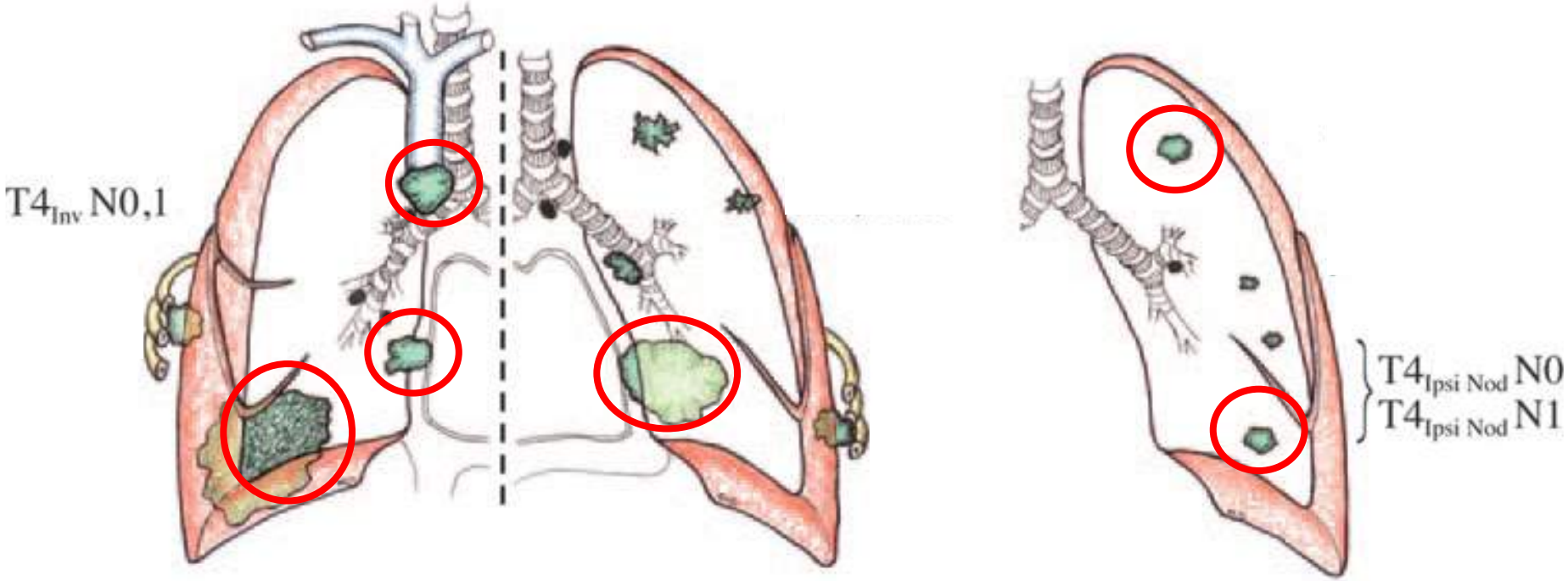


Bronchoplastic resection after neoadjuvant treatment

Author	Journal	Year	Title	n
Milman S.	Ann Thorac Surg	2009	The incidence of perioperative anastomotic complications after sleeve lobectomy is not increased after neoadjuvant chemoradiotherapy	64
Began P.	Ann Thorac Surg	2009	Induction chemotherapy before sleeve lobectomy for lung cancer: Immediate and long-term results	159
Burfeind W.	Ann Thorac Surg	2005	Low morbidity and mortality for bronchoplastic procedures with and without induction therapy	73
Ohta M.	JTCVS	2003	Efficacy and safety of tracheobronchoplasty after induction therapy for locally advanced lung cancer	48
Veronesi G.	Lung Cancer	2002	Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer	55
Rendina E.	JTCVS	1997	Safety and efficacy of bronchovascular reconstruction after induction chemotherapy for lung cancer	68

Surgery for locally advanced NSCLC: T3/T4

T4 Lung cancer



Locally advanced disease: stage IIIA/B – according to T or N

T3/4
N0, N1

1. Surgical approach depending on tumor localisation requiring different surgical approaches

   Pancoast:
   - Paulson (posterior), Hemiclamshell, Dartevelle (anterior)

   Carina:
   - Carinal resection or Sleeve-pneumonectomy

   Invasion of Atrium and greater vessels:
   - Vascular reconstruction, ev. extracorporal circulation (ECMO/HLM)

   Chest wall infiltration:
   - Resection und reconstruction

   Infiltration of the spine:
   - Laminectomy ± Vertebrectomy

1. Inductionchemo- ± radiation

N2

"No surgery" ?

Results of Primary Surgery With T4 Non–Small Cell Lung Cancer During a 25-Year Period in a Single Center: The Benefit is Worth the Risk

Characteristics	Overall (n = 271)	Subgroup of T4 Category			
		Superior Sulcus Tumor (n = 126)	Carinal Invasion (n = 92)	SVC Invasion (n = 39)	Mediastinal (n = 14)
Mean age (y)	56.3	53.6	59.6	58.0	54.5
Range	31–80	31–80	39–80	38–79	36–70
Sex					
Male	221	97	79	34	11
Female	50	29	13	5	3
Type of resections					
Right pneumonectomy	115 (42.4%)	0	81	32	2
Left pneumonectomy	19 (7%)	3	6	0	10
Right upper lobectomy	70 (25.8%)	62	2	5	1
Right upper bilobectomy	1 (0.3%)	1	0	0	0
Left upper lobectomy	37 (13.6%)	36	0	0	1
Wedge resection	26 (9.6%)	24	0	2	0
Carinal reconstruction	3 (1.1%)	0	3	0	0

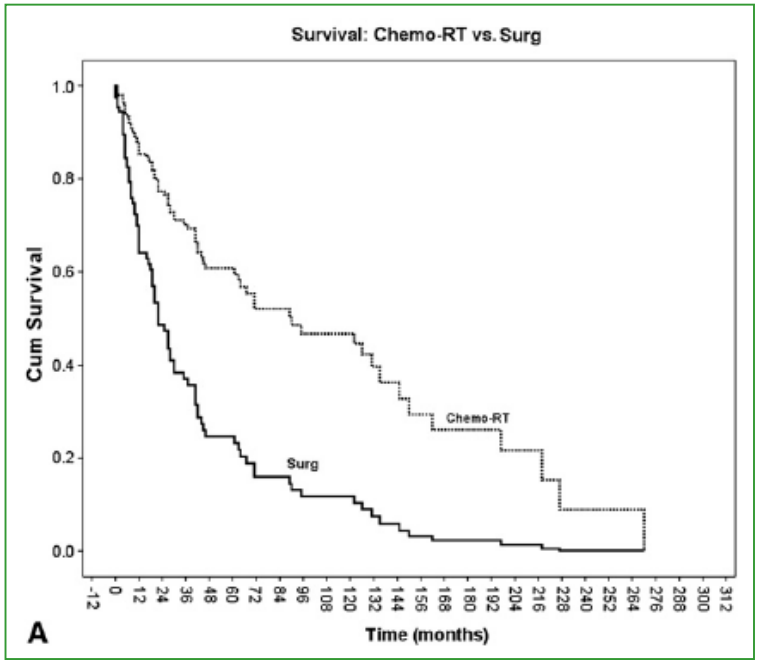
In highly qualified centers, radical surgery of T4 N0/N1 NSCLC can be performed with a 4% MR and may yield a 43% 5-year survival. These results seem to indicate primary surgery as the treatment of choice for T4 non–small cell lung carcinoma, whenever a complete resection is thought to be technically feasible and the patient's condition is compatible with the extent of the planned surgery.

Yıldızeli et al, ATS 2008

Impact of neoadjuvant chemoradiotherapy followed by surgical resection on node-negative T3 and T4 non–small cell lung cancer

110 patients (94 T3N0M0, 16 T4N0M0)
1979-2008

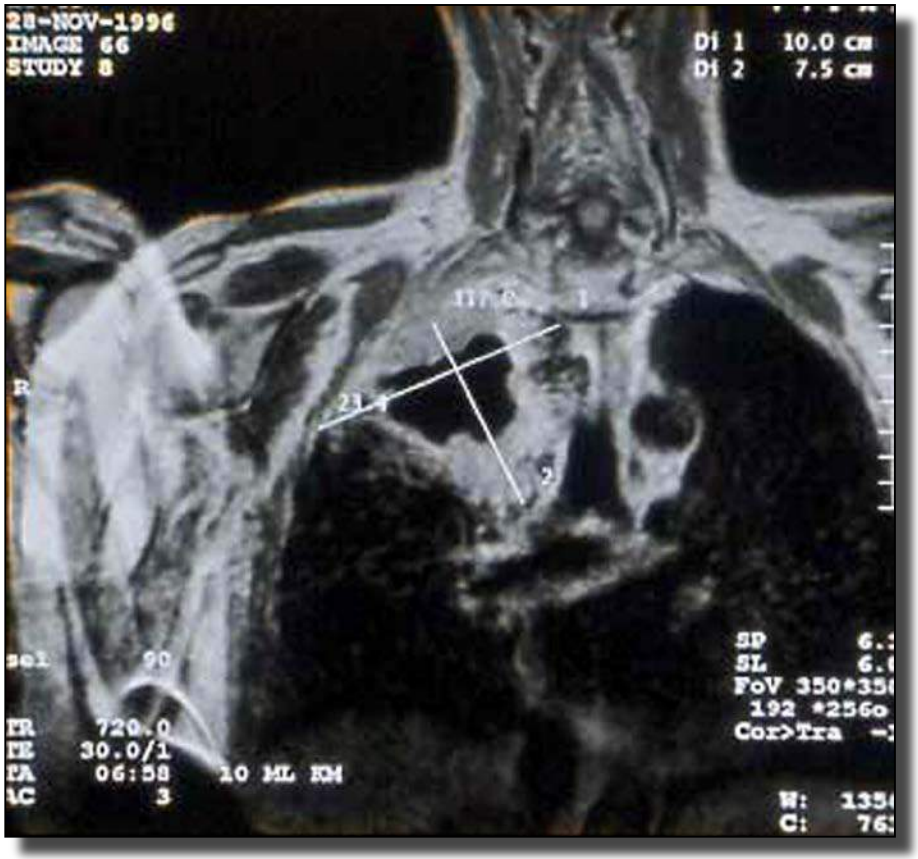
	Induction C/RT	Primary Surgery
5 y survival	61%	22%
10 y surival	50%	14%
Median survival	90 months	22 months



Aggressive treatment of node-negative invasive T3 and T4 NSCLC with induction chemo radiotherapy may significantly prolong survival. This approach should be evaluated in a prospective multicenter national trial.

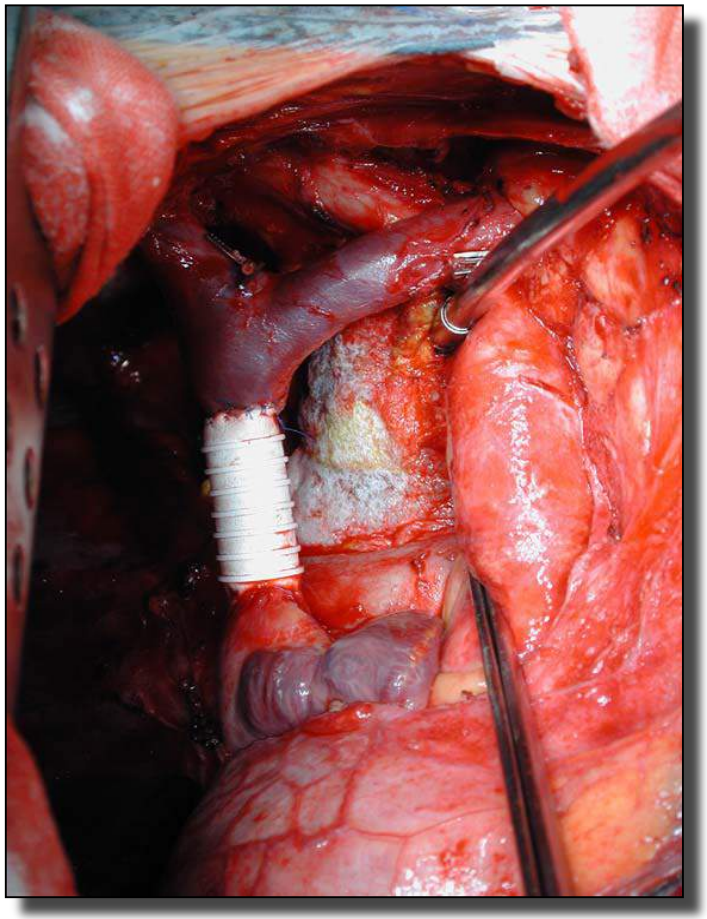
Daly et al, JCTVS 2011

Radical en bloc Resection for Lung Cancer Invading the Spine



Grunenwald et al, JCTVS 2002

Long term follow up of prosthetic replacement of vena cava



- N = 28 patients (1998-2008)
- PTFE grafts
- Perioperative mortality = 3,5% (1 patient)
- Graft thrombosis = 1 patient

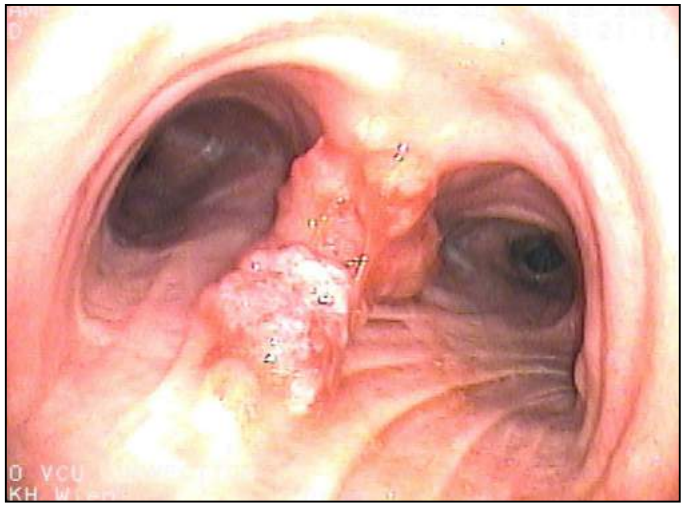
Pastorino et al., EJCTS 2010

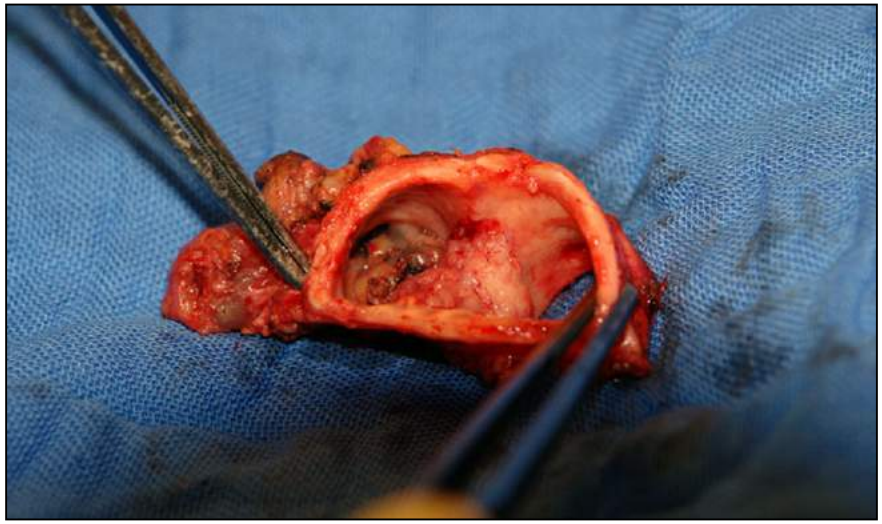
Sleeve Pneumonectomy – Carinal resection

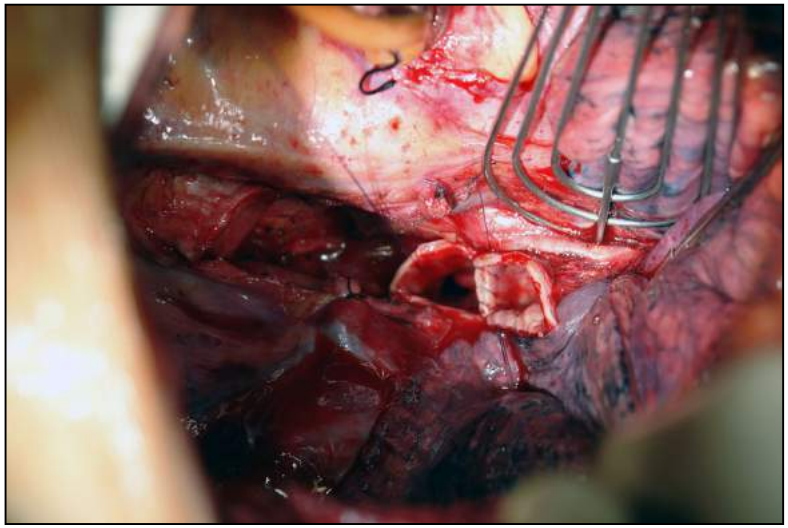
SCC Carina cT4N1

Inductionchemotherapy

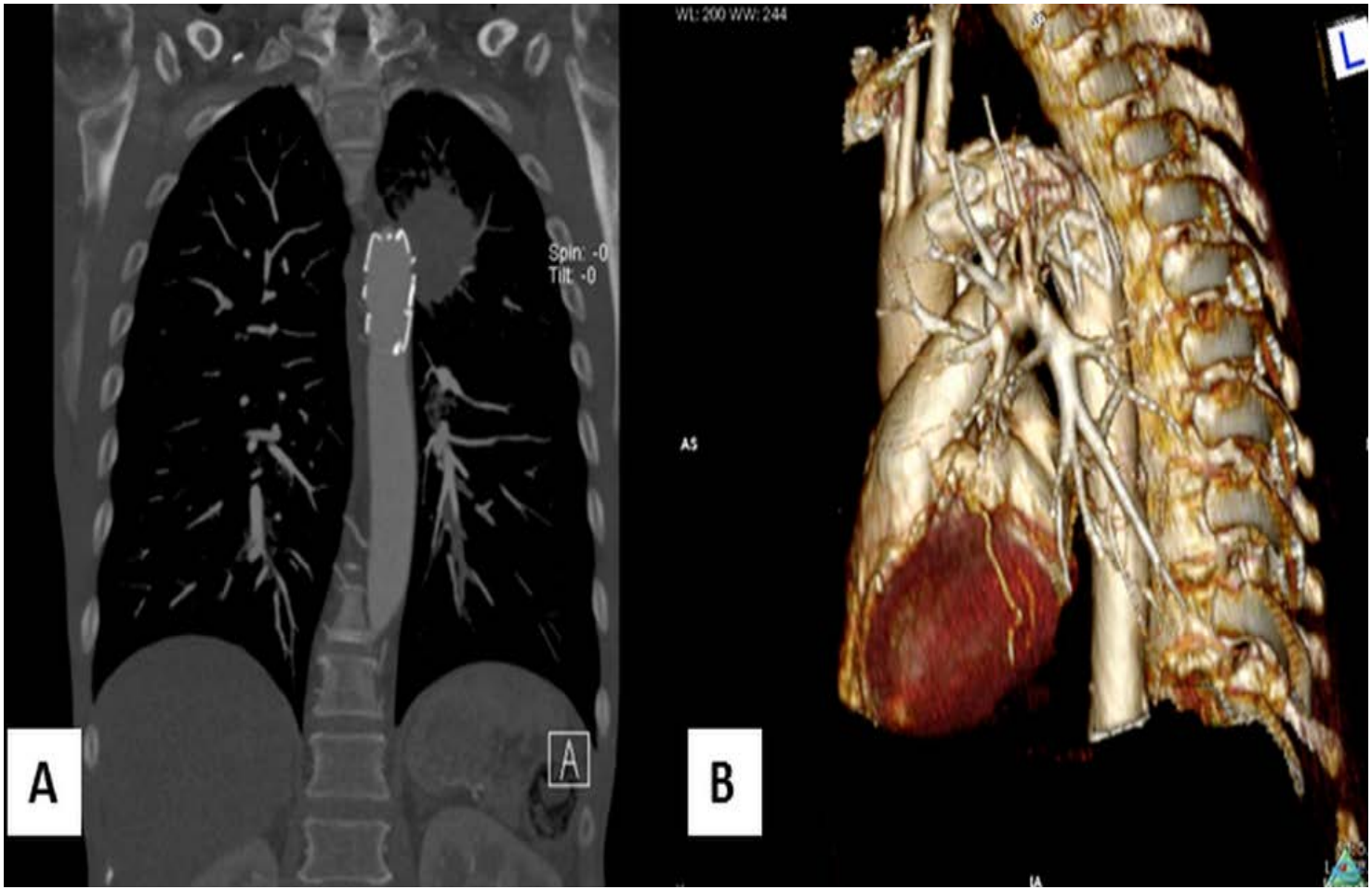
Carinal resection + reconstruction as neocarina on central ECMO



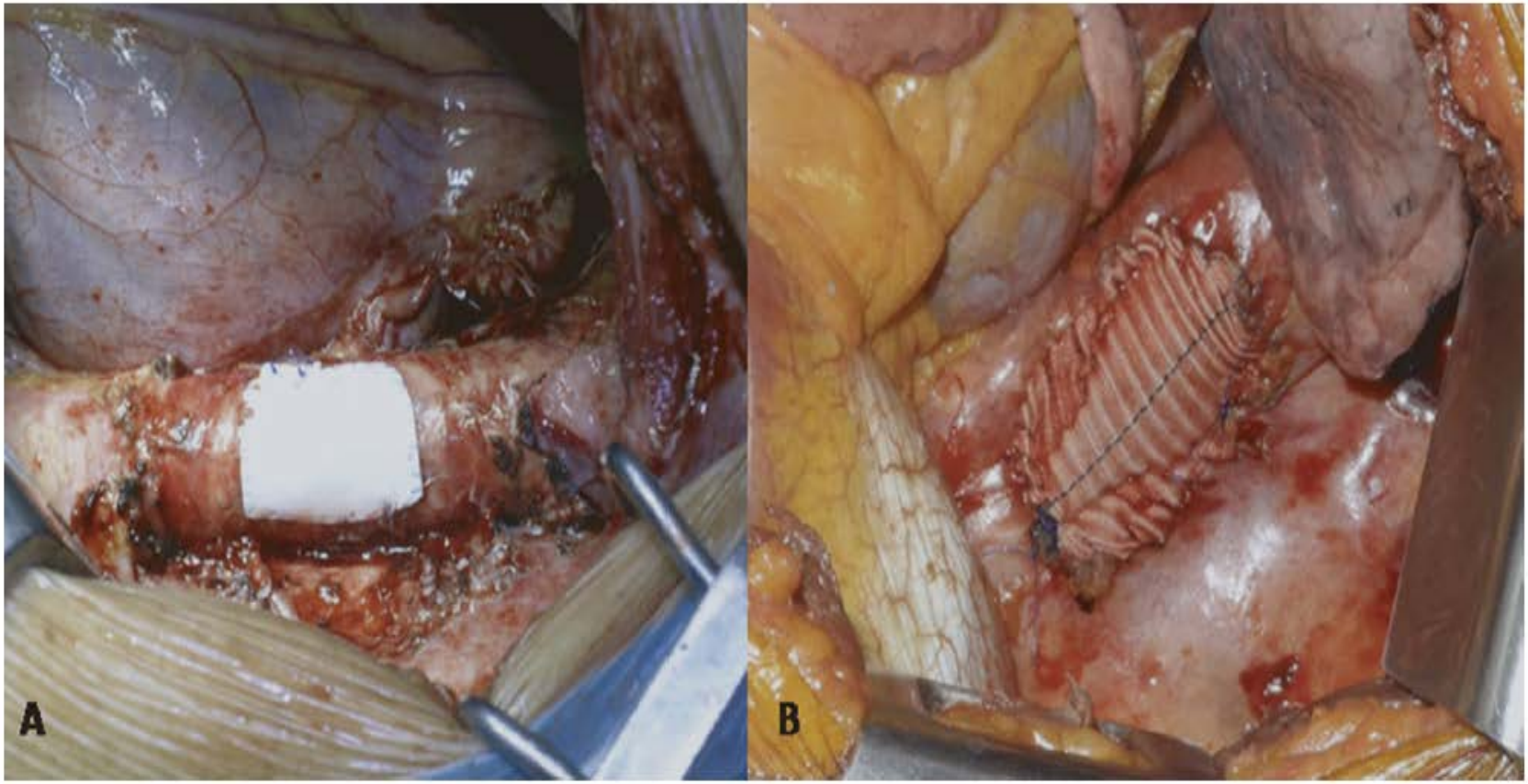




Extended Resections – Invasion der Aorta (T4)



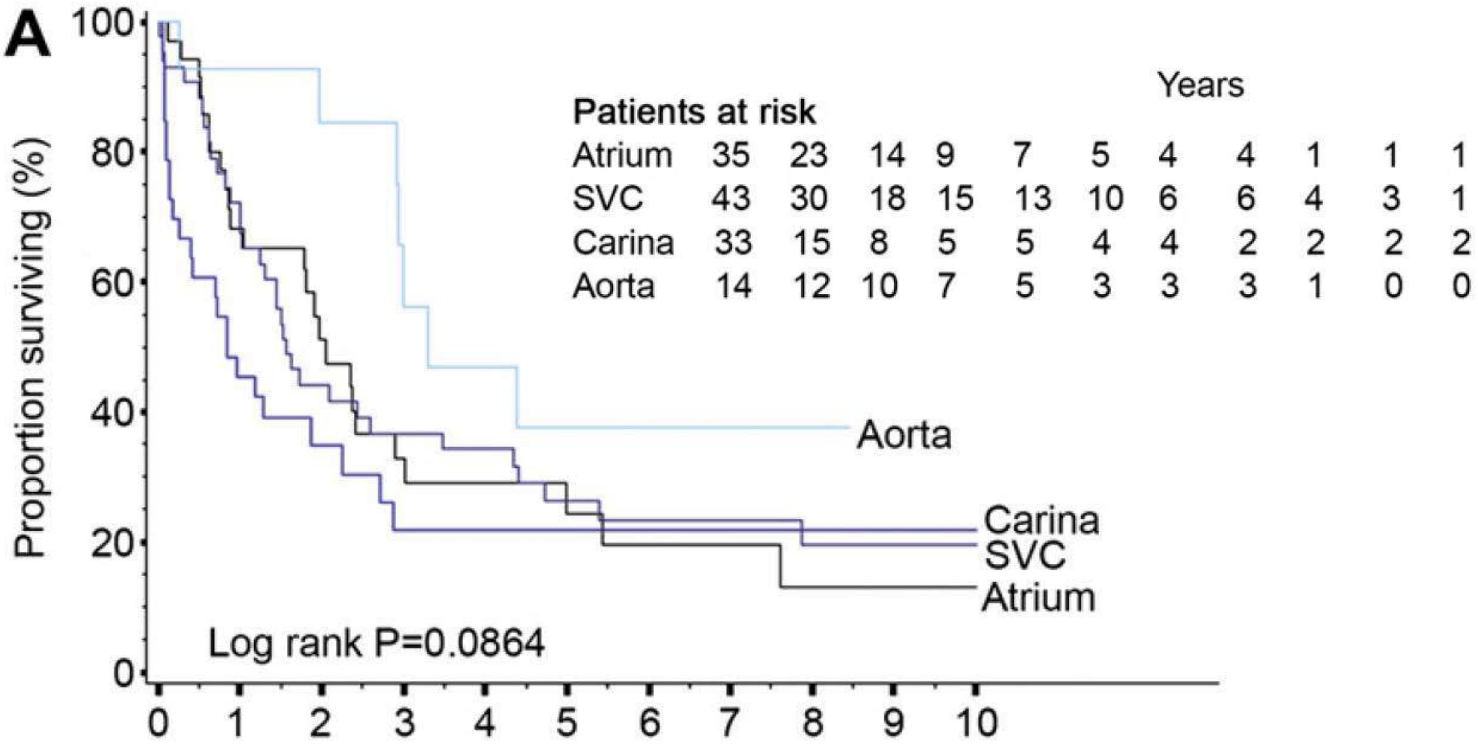
Extended Resections – Invasion der Aorta (T4)



T4 surgery: largest experience in Europe

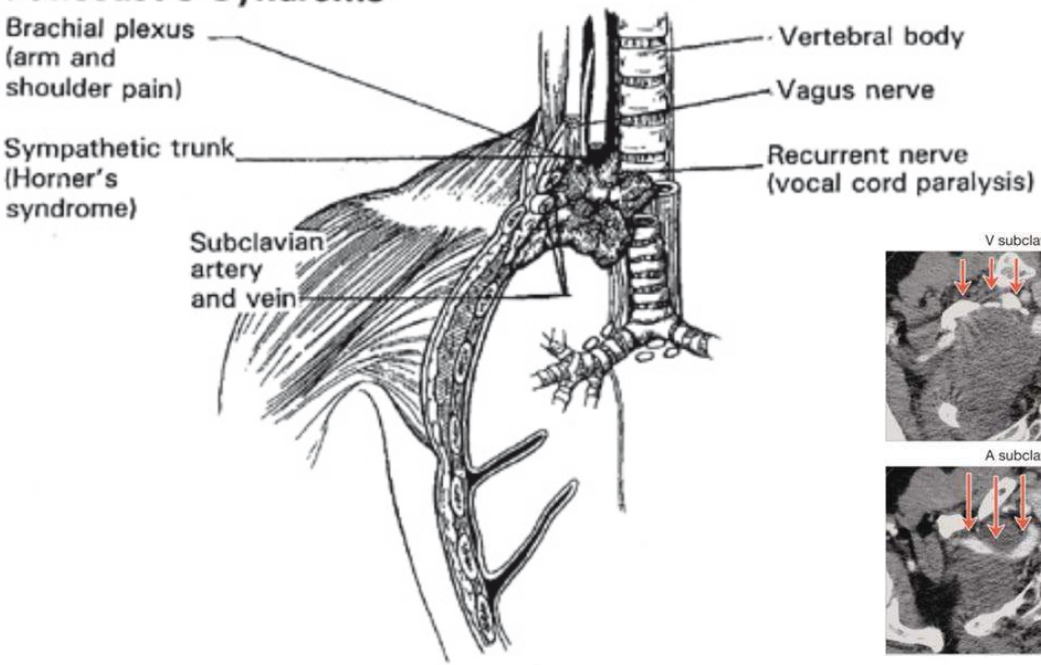
Spaggiari et al, Ann Thorac Surg 2013

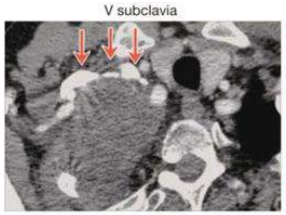
n = 125, extended resections for NSCLC

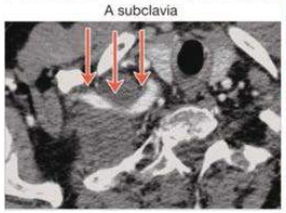


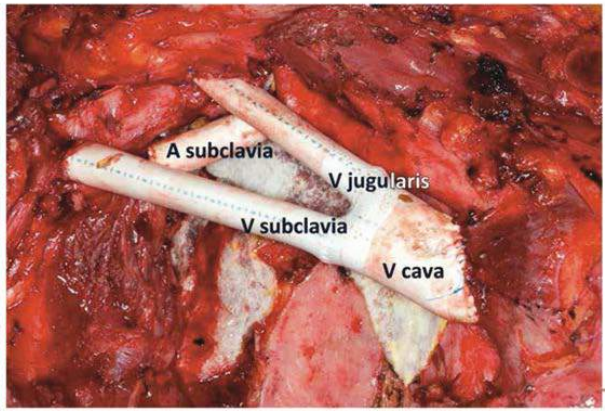
Pancoast/Sulcus superior tumors

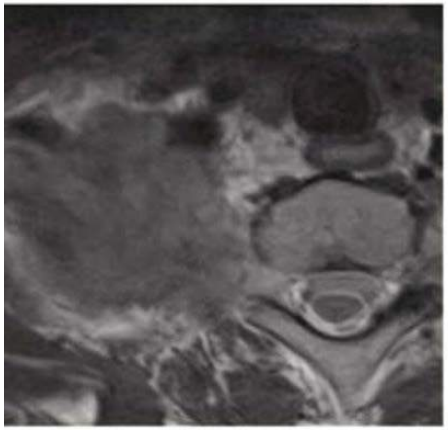
Pancoast's Syndrome

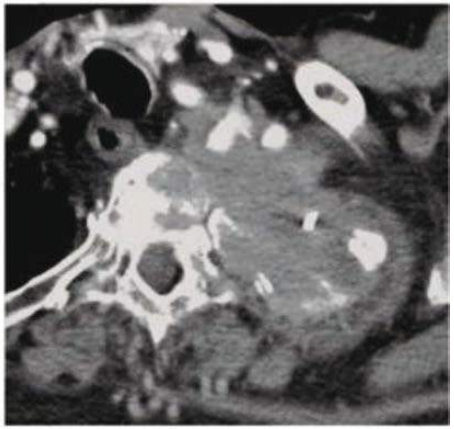


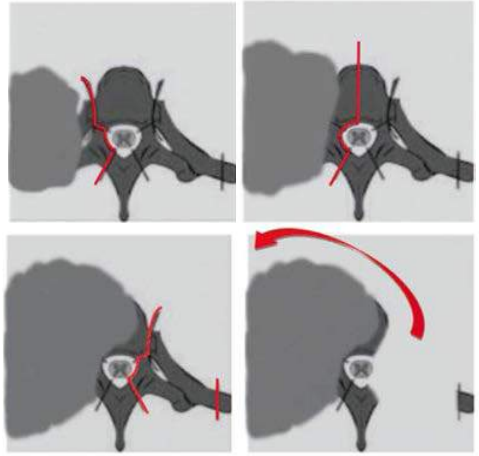


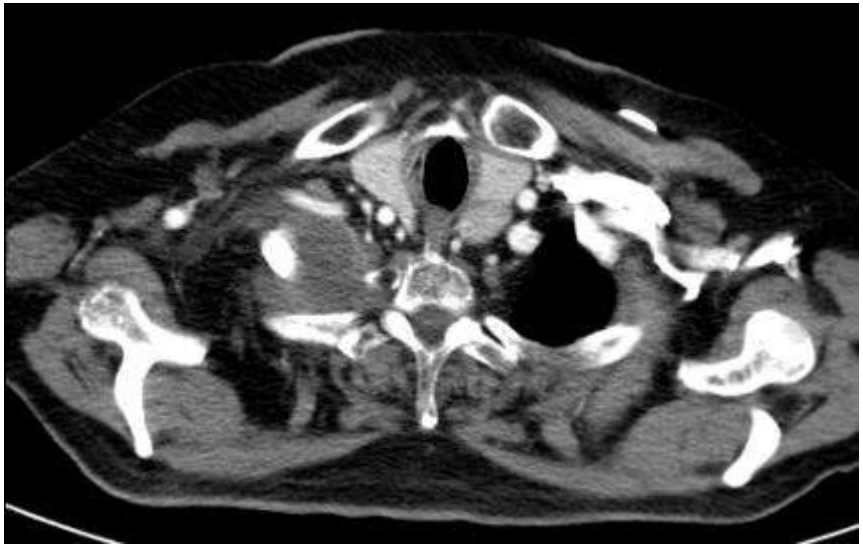


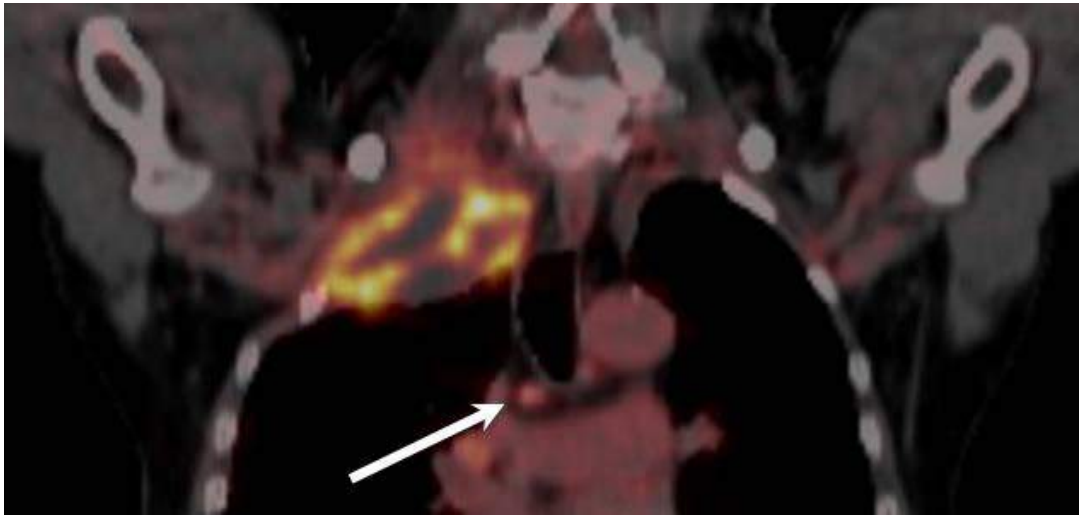






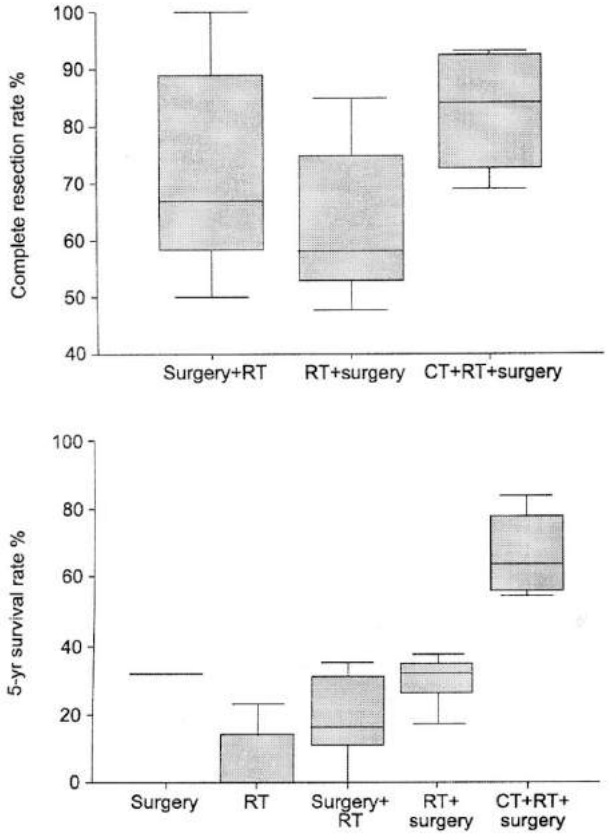






Pancoast-TU
➔
Trimodality
therapy

Pancoast Tumor – Advances in Treatment



- 1930 – 1950
  - Considered inoperable
  - Radiotherapy only
  - Disappointing results
- 1950 -1980
  - Induction radiotherapie (30 Gy) +
  - “en bloc” Resection;
  - R0 only in 60%
- late 1980s – 2000
  - New surgical techniques
  - *(Resection of vertebrae, vessels, …)*
- 2000 -
  - Chemoradiotherapy + Surgery
  - R0 in > 90%

Tamura, Hoda, Klepetko, EJCTS 2011

Trimodality Treatment for Pancoast Tumors

Author	Year of Publication	n	Complete Resection (%)	2 year survival (%)	5 year survival (%)
Martinez-Monge	1994	18	77	NR	56 (4y)
Attar	1998	11	NR	NR	72
Wright	2002	15	93	93	84
Barnes	2002	8	NR	86	NR
Miyoshi	2004	11	NR	73	53
Kwong	2005	36	97	58	50
Rusch	2007	88	76	55	44
Marra	2007	31	94	74	46
Kunitoh	2008	57	68	61 (3y)	56
Pourel	2008	72	98	62	51 (3y)
Kappers	2009	22	100	70	37

DOI: 10.1002/jso.24629

RESEARCH ARTICLE

WILEY Journal of SURGICAL ONCOLOGY

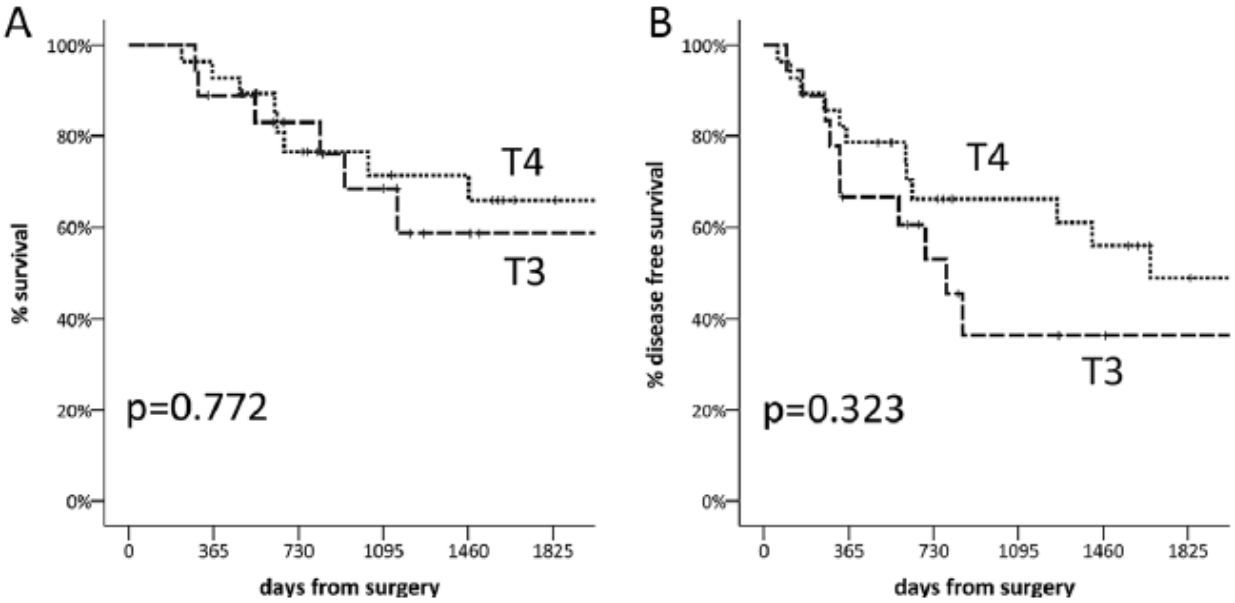
Trimodality therapy for Pancoast tumors: T4 is not a contraindication to radical surgery

Ryuichi Waseda MD, PhD[1,2] | Thomas Klikovits MD[1] | Mir Alireza Hoda MD[1] | Konrad Hoetzenecker MD, PhD[1] | Pietro Bertoglio MD[1] | Karin Dieckmann MD[3] | Sabine Zöchbauer-Müller MD[4] | Robert Pirker MD[4] | Helmut Prosch MD[5] | Balazs Döme MD, PhD[1,6,7] | Walter Klepetko MD[1]

n= 46 (28 T4)

- 30-day mortality was 0%
- major surgical complications in 9 (19.6%) patients

- OS at 5-years was 63%.
- DFS at 5-years was 45%.



Waseda et al, JSO 2017

Perioperative issues

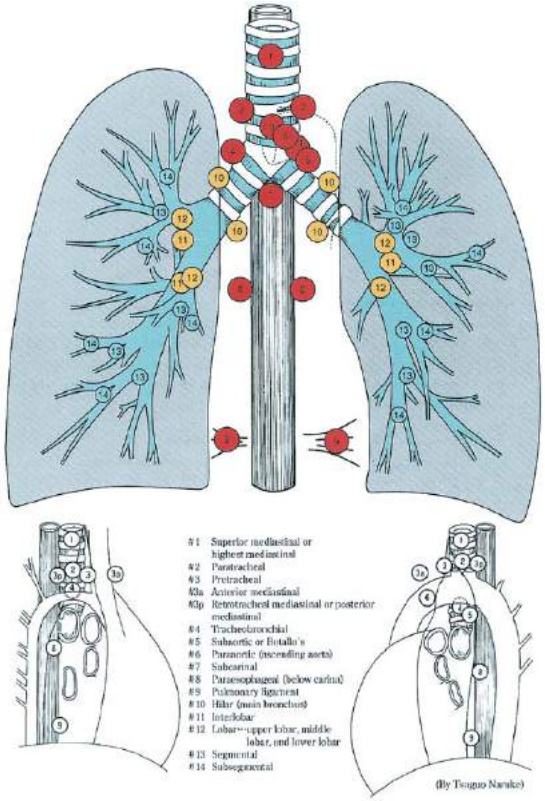
Symptom	Etiology	Therapy
Lung atelectasis	Thoracic wall resection ± Resection of the phrenic nerve	BSK Intensified Physiotherapy
Local pain	Extended resection Neural injuring	i.v. pain medication (pain pump)
Headache	Neural fluid loss	Fluids Conservative medication
Unilateral venous congestion	Graft occlusion	Adequate anticoagulation
Hoarseness	Resection of the recurrent nerve	Logopedic treatment Late vocal cord plastic (implants)
Impaired mobility of shoulder	Osteo-muscular resection	Special individualized physiotherapy

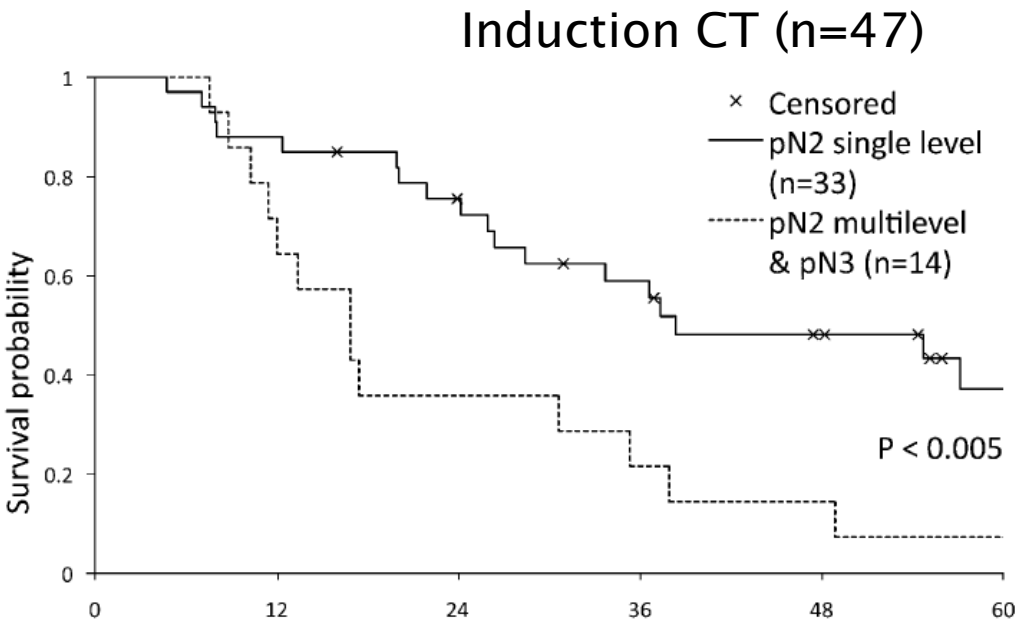
Surgery for locally advanced NSCLC: N2

N2 disease is a very heterogenous entity !

Stage IIIA (N2)

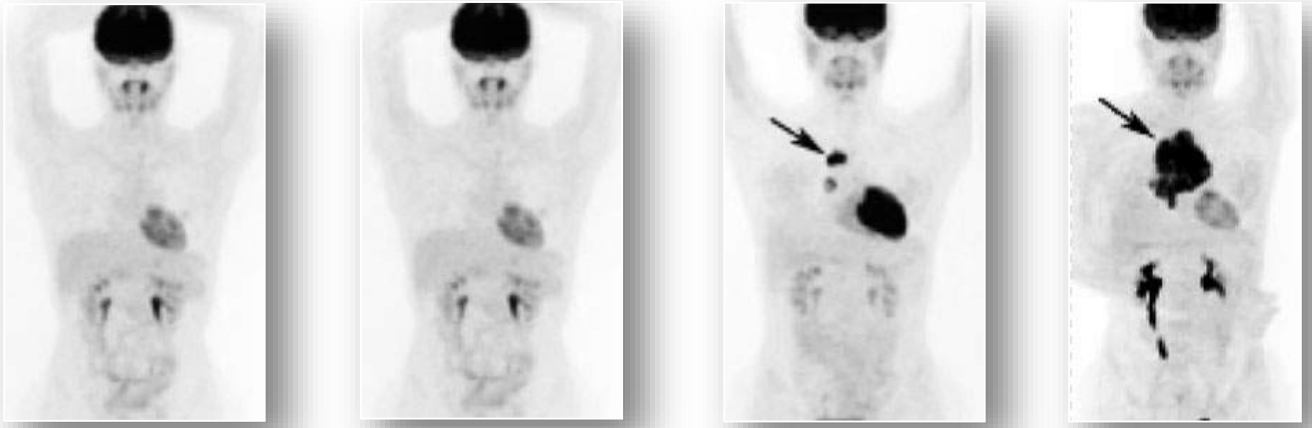
- involvement of single/ multiple stations
- +/- microscopic / full thickness / transcapsular





Decaluwe et al. EJCTS 2009

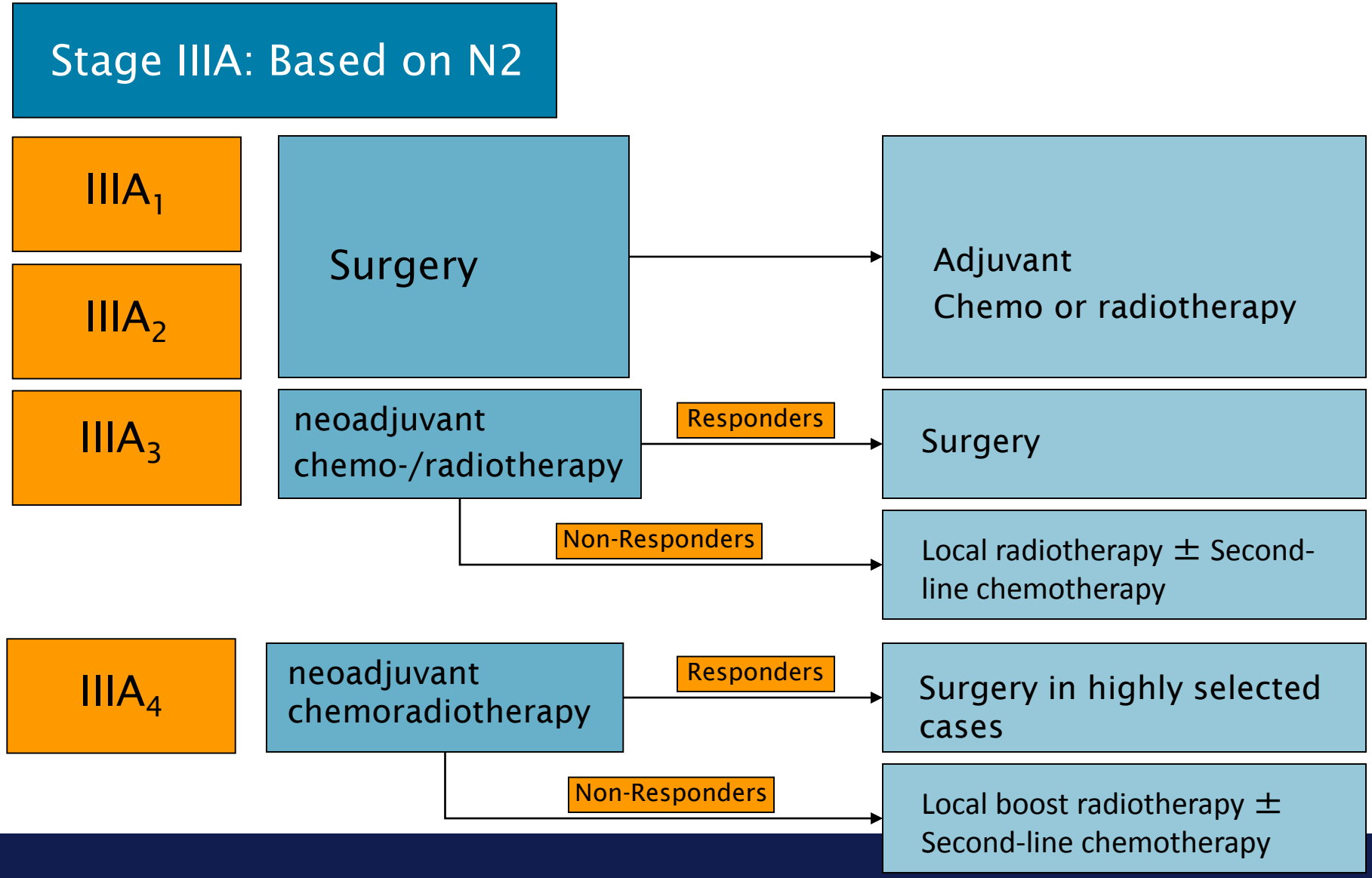
Subsets of Stage IIIA (N2)



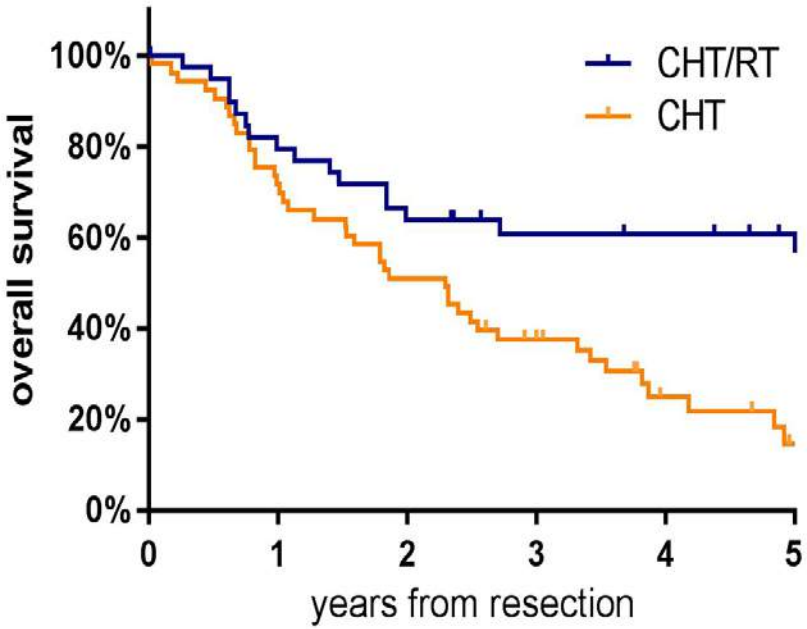
$IIIA_1$	Incidental nodal metastases found on final pathologic examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

Robinson LA, et al *Chest 2003*

Surgery for N2 positive NSCLC

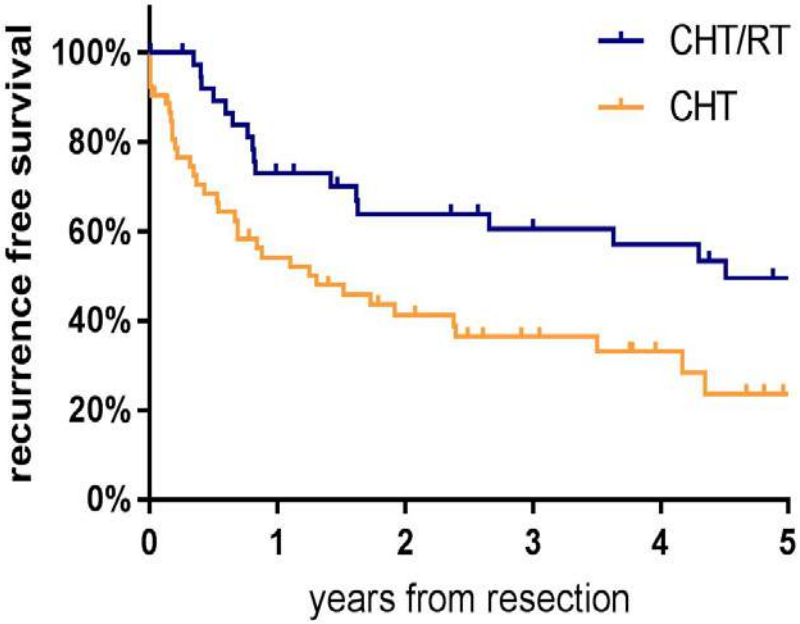


Results – MUV



Median OS
82.0 vs 29.0 months

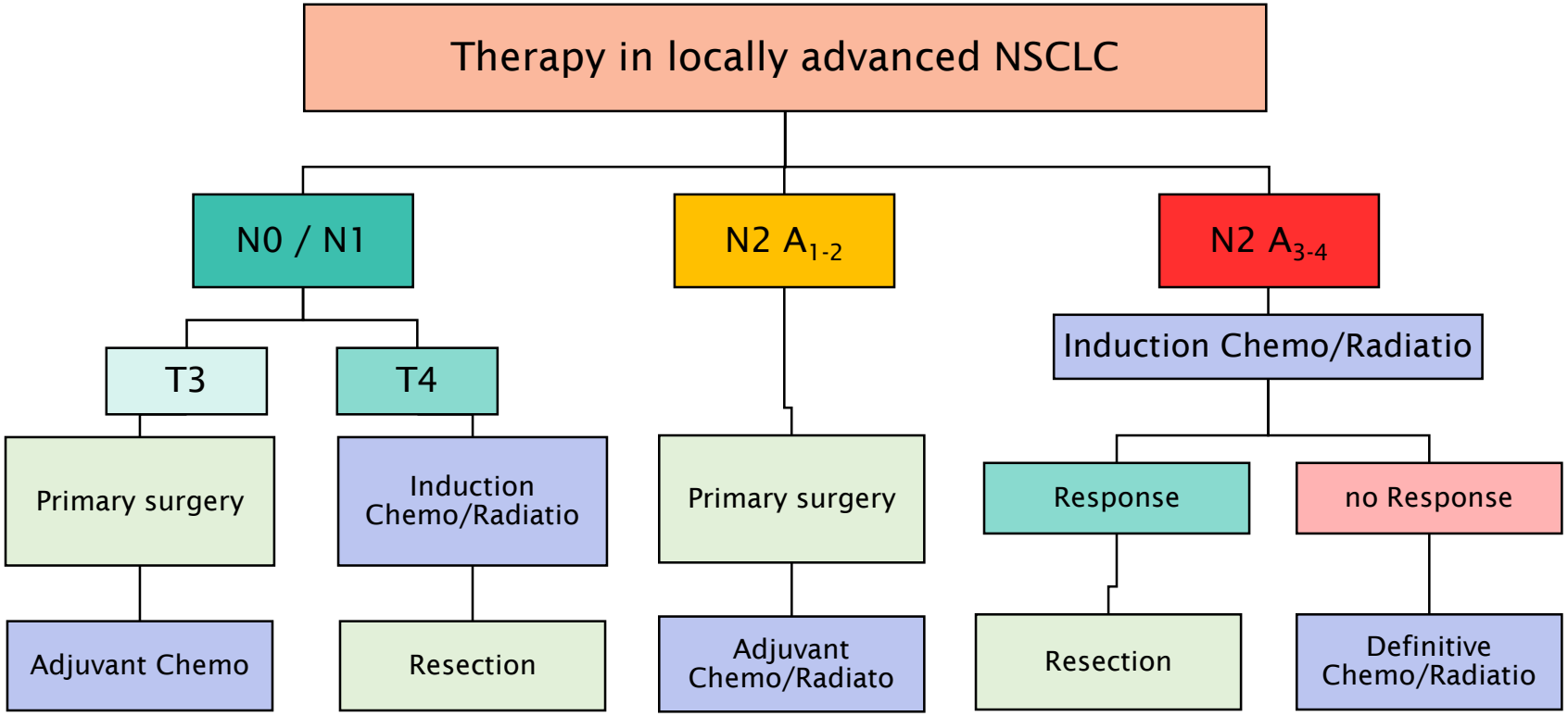
p=0.003



Median RFS
54.8 vs 15.3 months

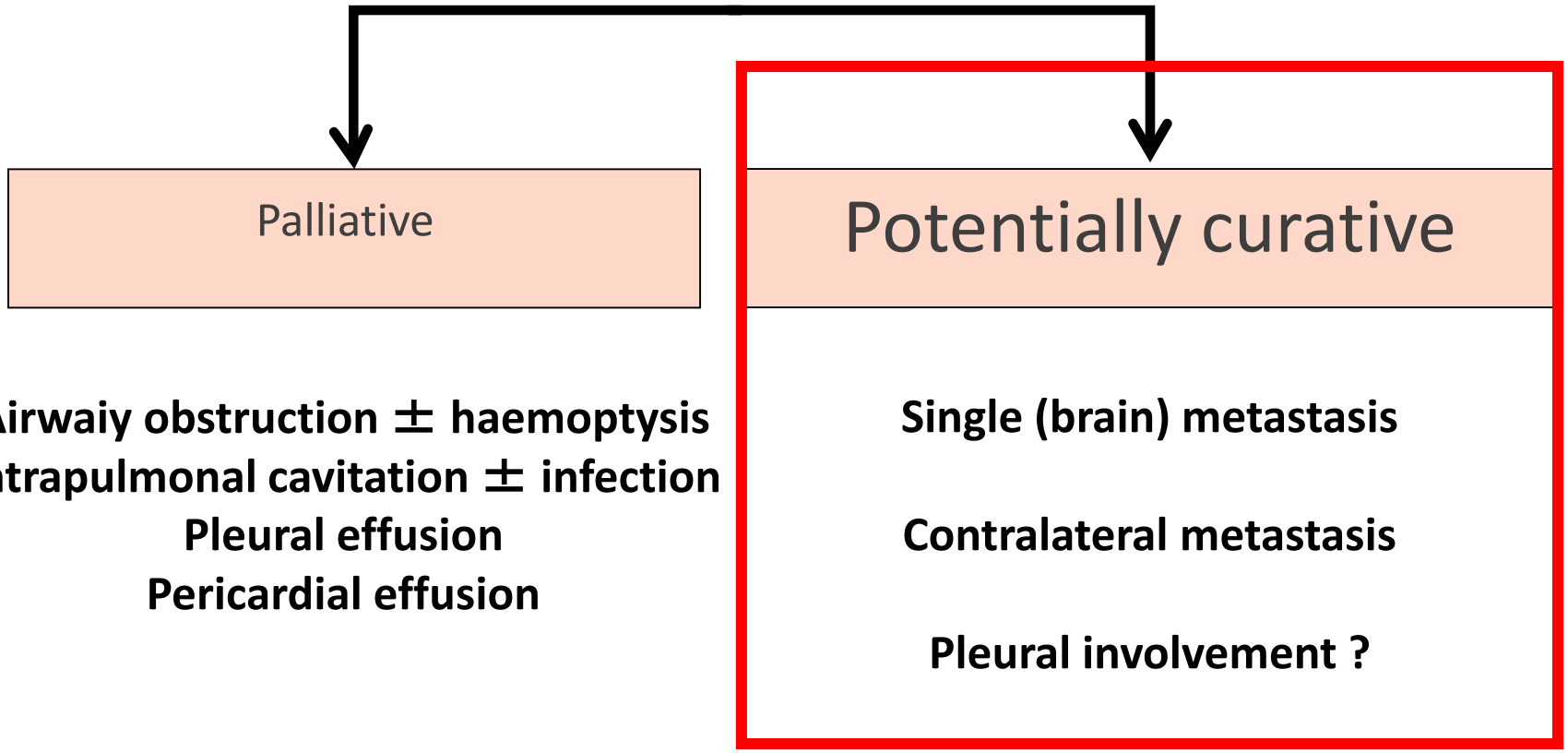
p= 0.019

Proposed algorithm – Vienna protocol



Surgery for oligometastatic disease & palliative surgical options

Surgery Stage IV NSCLC



Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

G. D'Addario[1], M. Früh[2], M. Reck[3], P. Baumann[4], W. Klepetko[5] & E. Felip[6]
On behalf of the ESMO Guidelines Working Group*

Annals of Oncology 21 (Supplement 5): v116–v119, 2010

isolated adrenal metastasis

Systemic chemotherapy is recommended. In selected fit patients adrenalectomy can be considered, if lung disease is resectable as well.

lung

Solitary lesions in the contralateral lung should be considered as secondary primary and treated with curative intention if both tumours are potentially curable.

solitary brain metastasis

- Resection or stereotactic radiosurgery (SRS) are the primary alternatives.
- If the primary tumour is resectable (i.e. T1–3 N0–1): surgery with or without chemotherapy is an option in highly selected, fit patients. Alternatively, radiotherapy or chemoradiation is an option in selected patients with localized thoracic disease. In other patients chemotherapy is recommended [III, C].

NSCLC with Single brain metastasis: Metaanalysis

153 relevant papers 1035 patients

- ✓ **Curative intent group** median survival 23,12 ±3,3 mo.

  1y and 5y survival 63,9 ±5,6% and 18 ±5,7%

- ✓ **Palliative group** median survival 10,3 +/- 2.9 mo.
  1y and 5y survival 35,3 +/- 3,8 % and 0 %

A. Modi, HA Vohra, DF Weeden. Does surgery for primary NSCLC and cerebral metastasis have any impact on survival? ICVTS 2009; 8:467-73.

NSCLC with Single brain metastasis: Metaanalysis

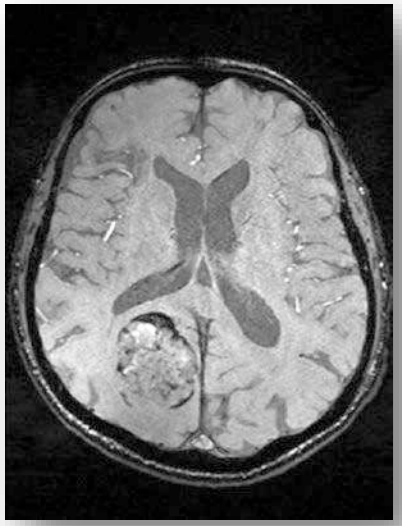
In absence of mediastinal LN involvement combined surgical resection improved prognosis.

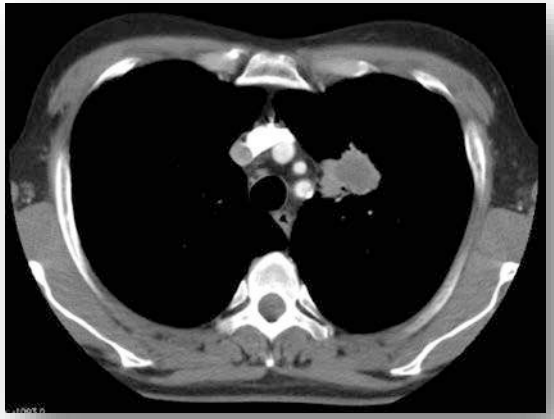
Parameters for good prognosis:

* Adenocarcinoma
- low CEA levels at presentation
- high Karnofsky performance score
- response to induction CR

A. Modi, HA Vohra, DF Weeden. Does surgery for primary NSCLC and cerebral metastasis have any impact on survival? ICVTS 2009; 8:467-73.

NSCLC with single brain metastasis





Limited surgical resection + CX

Gamma Knife
Stereotactic Rx
Surgical removal

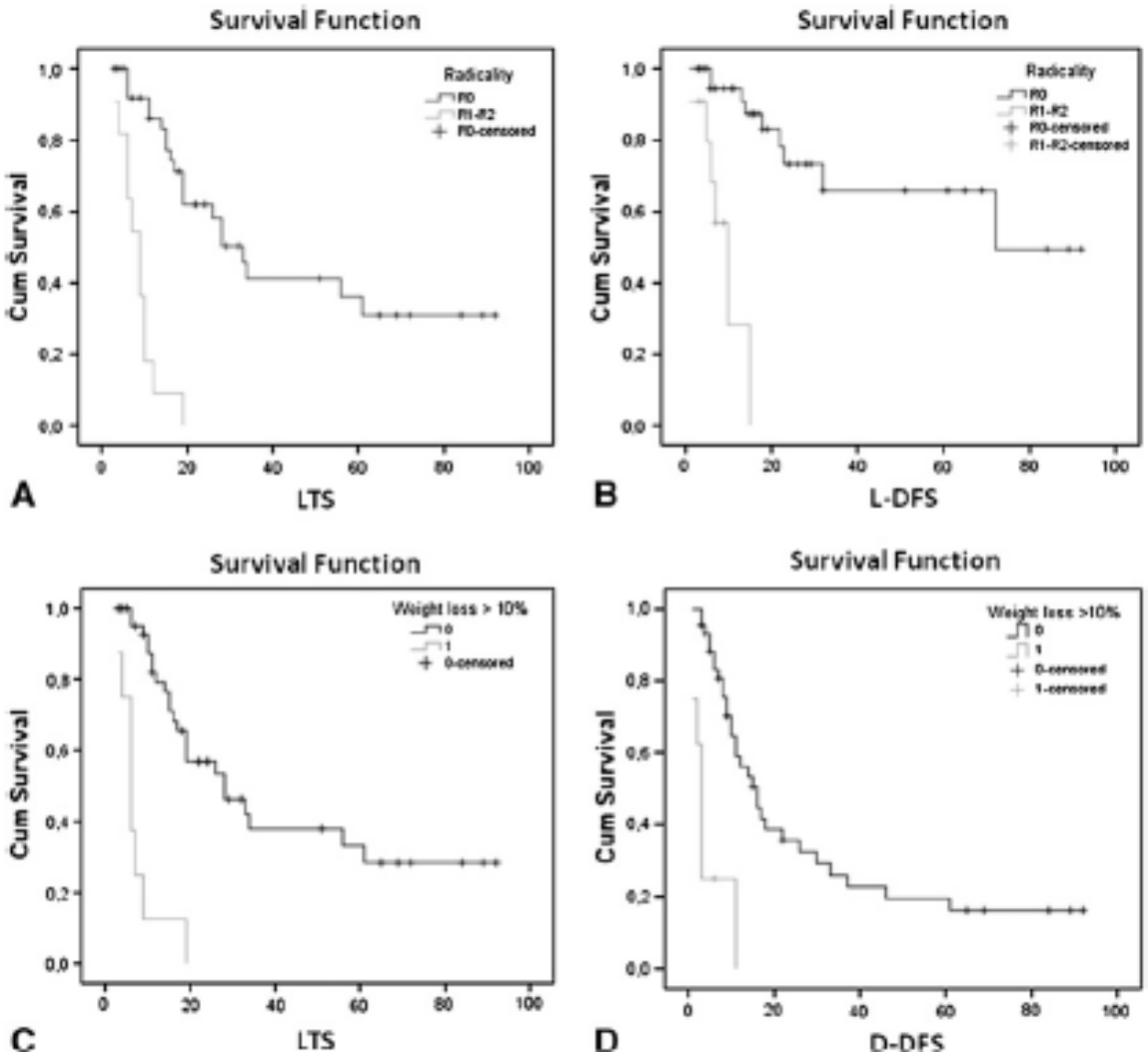
Definitive CX or CX/Rx

Surgery for ologometastatic NSCLC: long-term results from a single center experience

N=53
1997-2010
Majority: brain, adrenal (n=47)
feasible and safe

In combination with multimodality protocols

Good survival:
-Complete resection of primary
-Radical control of distant met
-Weight loss – prognostic factor

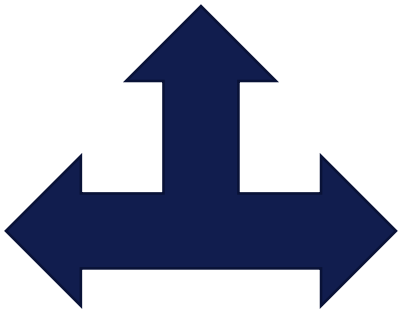


Congedo , JTCVS 2012

NSCLC with contralateral lesion

Contralateral metastasis

Multifocal tumor



Secondary tumor with different histology

1. Histological proof mandatory
2. Genetic analysis
3. Extent of surgical resection?

Synchronous bilateral lung cancer

Retrospective study 1990 – 2007

57 pat with bilat lesion identified
15 unilateral resection only
6 benign disease unilaterally
36 with bilat NSCLC resected same histology 18
different histology 18

- ✓ **Postoperative mortality**
  2,8%
- ✓ **Median survival** **25,4 mo**
- ✓ **5 y survival** **38%**
- ✓ **No significant difference between different vs. same histology**

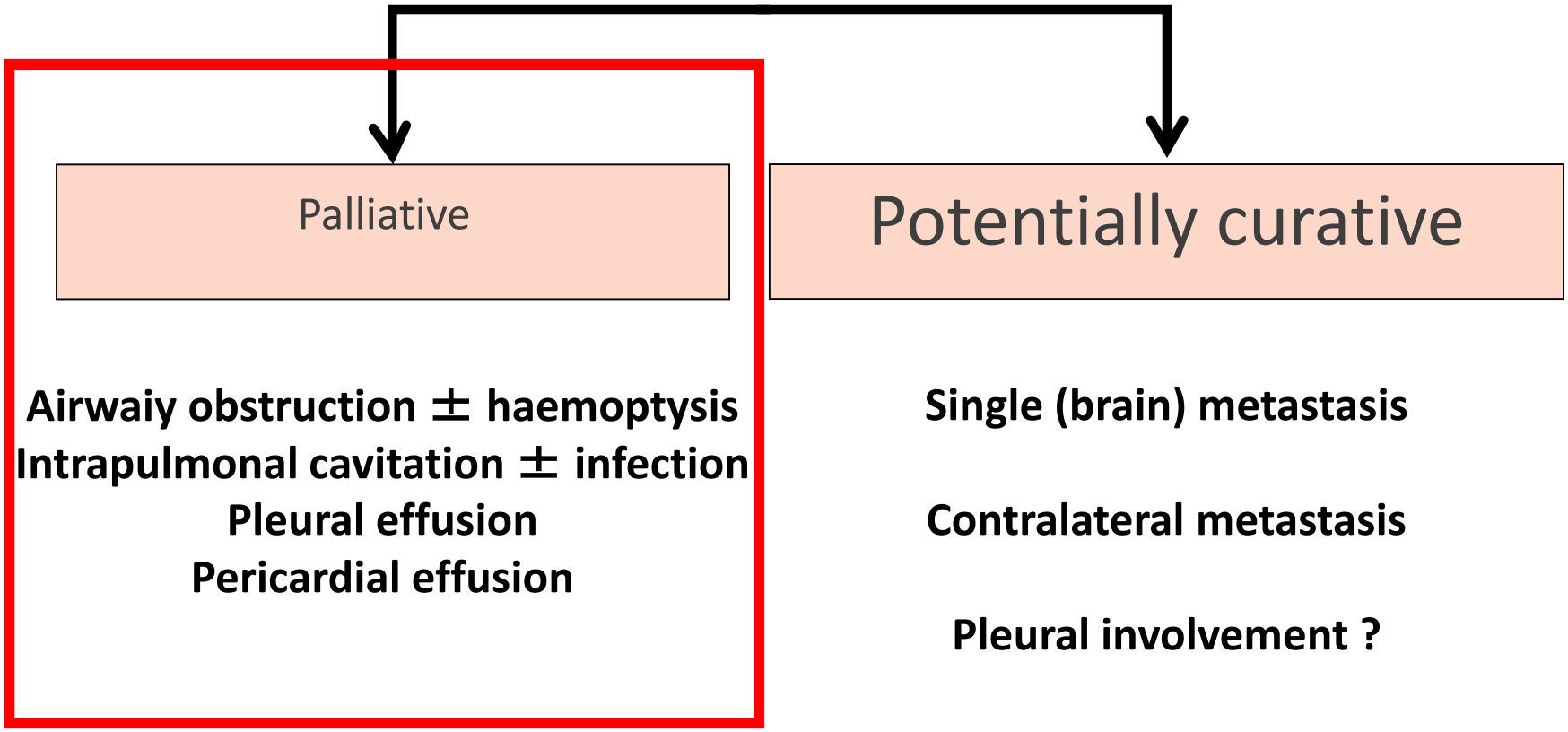
P De Leyn, Tony Lerut. Survival after resection of synchronous bilateral lung cancer. EJCTS 2008 34:1215-22.

Synchronous bilateral lung cancer

- ✓ **Selected patients with bilateral lung cancer benefit from an aggresive approach**
- ✓ **patients with a single contralateral lesion should not be treated as disseminated disease – Stage IV**
- ✓ **Bilateral resection should be considered in otherwise fit patients**

P de Leyn, Tony Lerut. Survival after resection of synchronous bilateral lung cancer. EJCTS 2008 34:1215-22.

Surgery Stage IV NSCLC



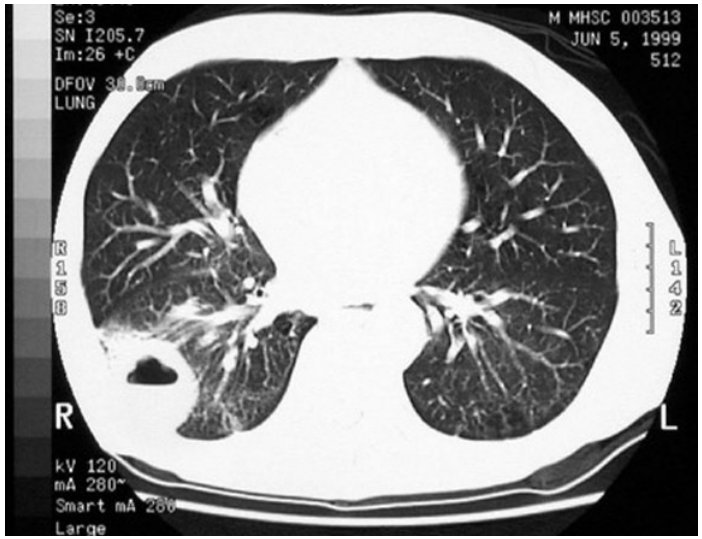
Palliative Lung resections

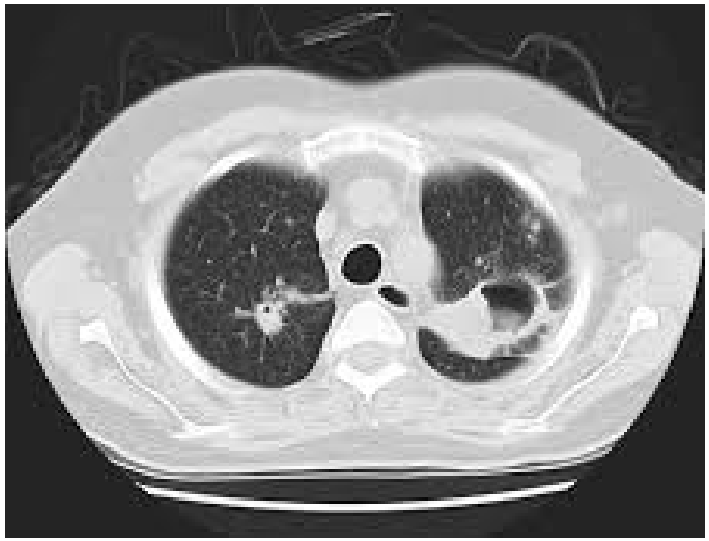
- Patients with advanced-stage lung cancer (metastatic or locally-advanced) under normal circumstances not being considered for surgery
  - massive haemoptysis
  - large cavitated or infected tumour
  - no other treatment option after chemo and/or radiotherapy
  - tumors compressing: vertrebral body, treachea, great vessels
  - tumors with chest wall infiltration causing pain

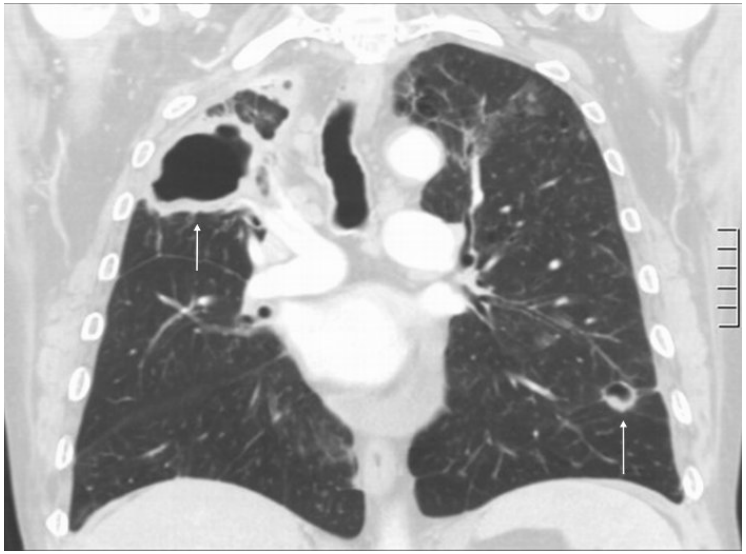
precluding safe administration of palliative chemotherapy due to the risk of sepsis or tumor perforation

<u>surgical intervention seems justified if patient has a life expectancy of >3 months</u>

Typical scenarios







Malignant pleural effusion

- Malignant pleural effusion is staged M1a in the new TNM classification.

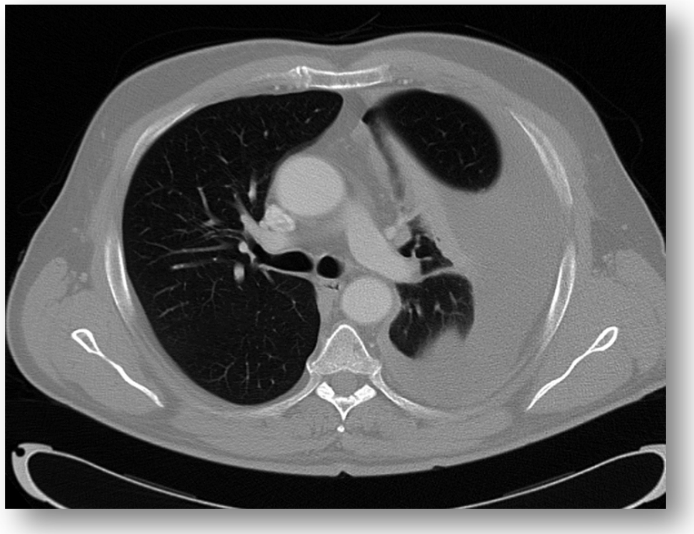
- very common problem in thoracic surgical practice and third common cause of dyspnea in lung cancer patients

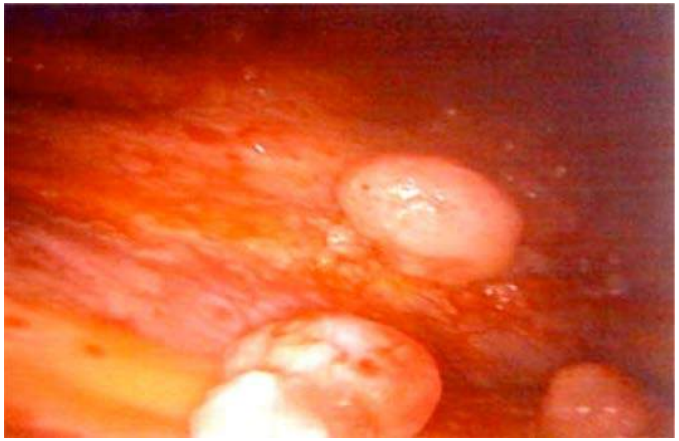
- Surgical pleurodesis slighly more successful than application of talc slurry with 75-100% success rate

- In patients fit for a surgical procedure, a videothoracoscopy under general anaesthesia, can be offered to drain the effusion, obtain multiple pleural biopsies for histopathology and mutational analysis and to perform pleurodesis

Kvale PA e tal. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition) Chest. 2007 Sep;132(3 Suppl):368S-403S.

Examples



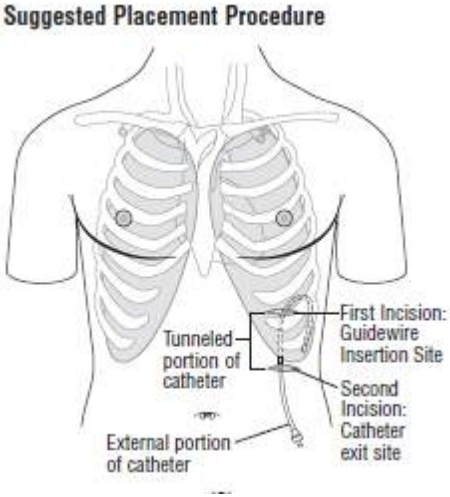


Other options than VATS

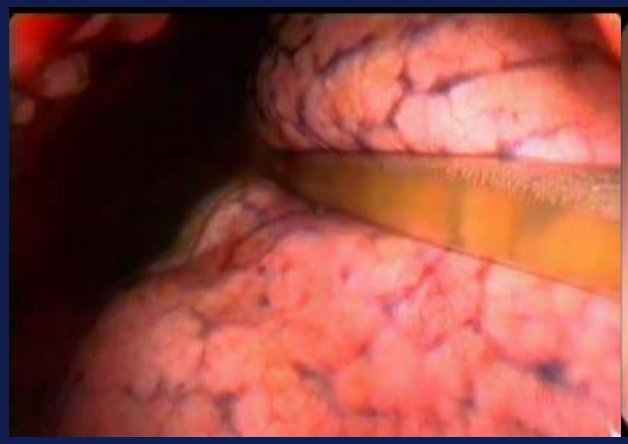
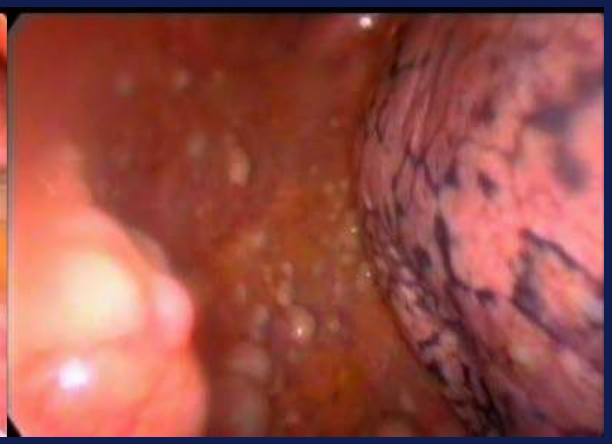
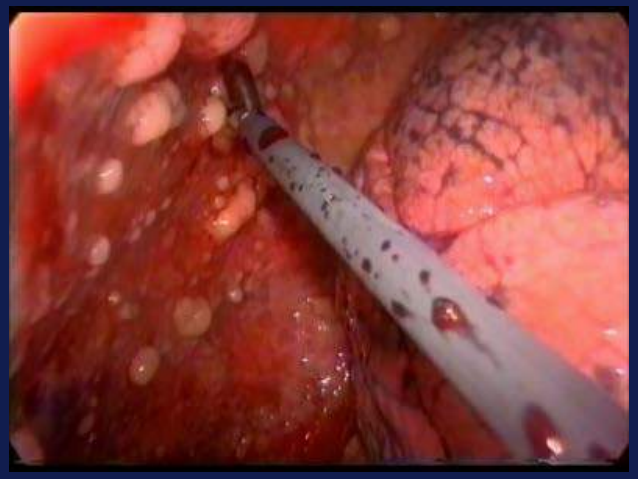
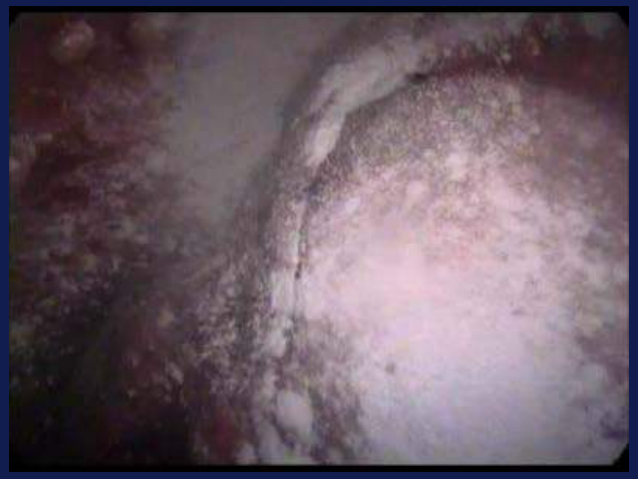
Thoracoscopic Talc Versus Tunneled Pleural Catheters for Palliation of Malignant Pleural Effusions

Ben M. Hunt, MD, Alexander S. Farivar, MD, Eric Vallières, MD, Brian E. Louie, MD, Ralph W. Aye, MD, Eva E. Flores, LPN, and Jed A. Gorden, MD

Division of Thoracic Surgery and Interventional Pulmonology, Center for Pleural Diseases, Swedish Cancer Institute, Swedish Medical Center, Seattle, Washington

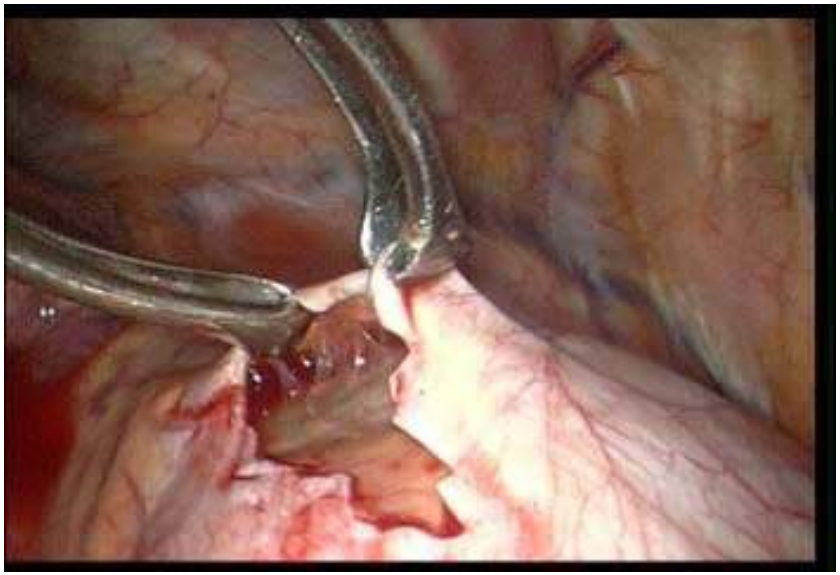


VATS : biopsy and talc pleurodesis

Obtains diagnosis in combination with VATS biopsy (histology, Staging)
Therapeutic / palliative for persisting pleural effusion

Pericardial window



Moores D et al. Subxiphoid pericardial drainage for pericardial tamponade. J Thorac Cardiovasc Surg. 1995 Mar;109(3):546-51; discussion 551-2.
http://www.ctsnet.org/sections/clinicalresources/thoracic/expert_tech-32

Surgery for small cell lung cancer

The Role of Surgery in the Treatment of Limited Disease Small Cell Lung Cancer

Time to Reevaluate

Eric Lim, FRCS (C-Th), Elizabeth Belcher, FRCS,
Yoon Khoong Yap, MRCS, Andrew G. Nicholson, FRCPath, and Peter Goldstraw, FRCS

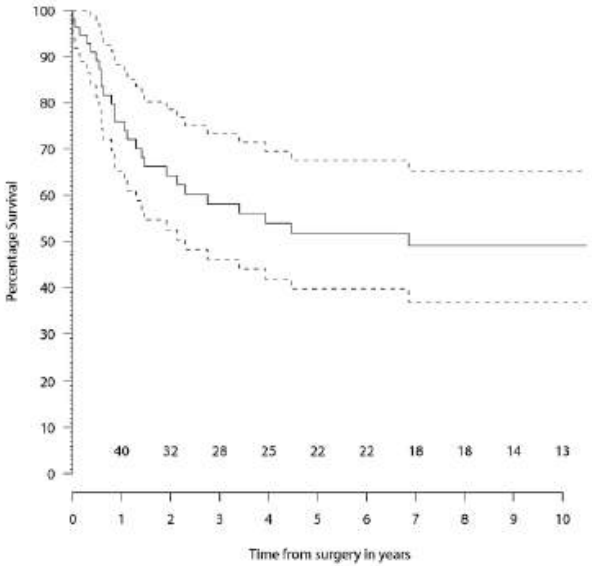


FIGURE 1. Overall survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

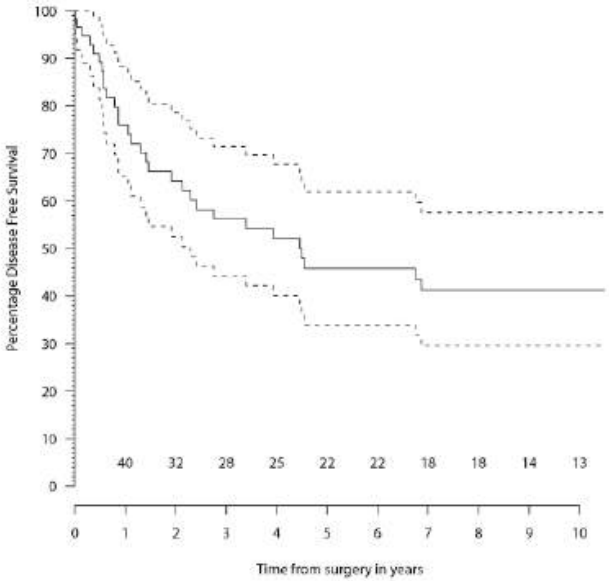


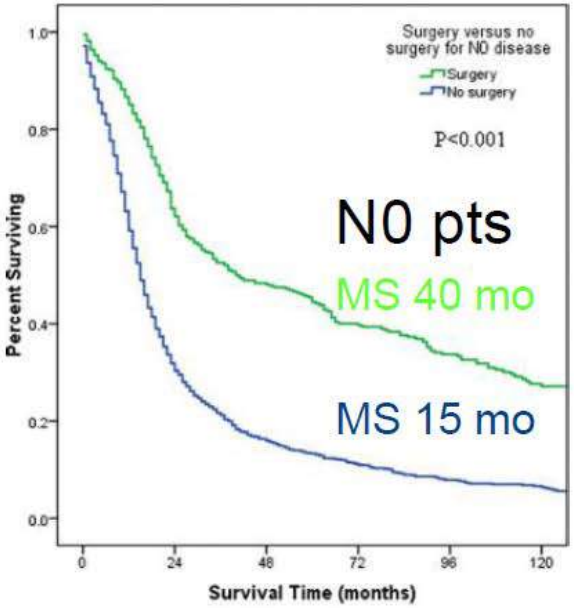
FIGURE 2. Disease free survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

n = 59
Stage IA – IIIB
1y surv: 76%
5y surv: 52%

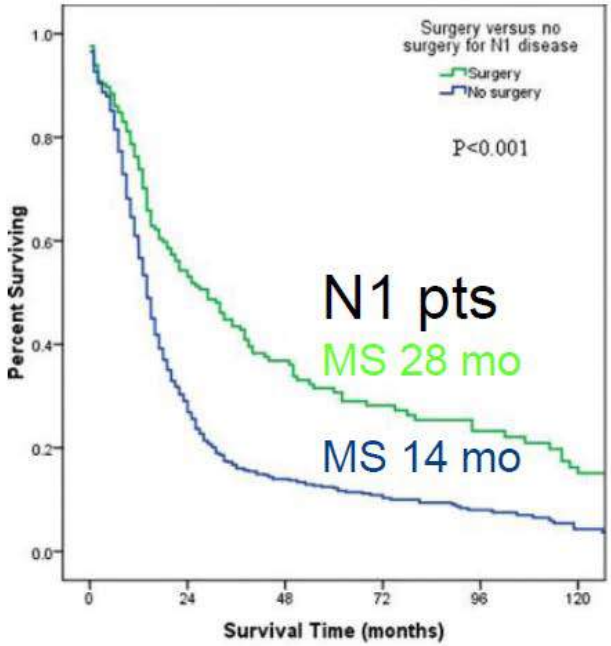
1y DFS: 76%
5y DFS: 46%

JTO 2008

Surgery vs. no surgery



Number at Risk	0	2	4	6	10years
Surgery	435	275	173	122	54
No Surgery	1816	577	214	102	34



Number at Risk	0	2	4	6	10years
Surgery	164	89	50	32	14
No Surgery	638	184	70	39	7

Schreiber et al. Survival outcomes with the use of surgery in LD SCLC: should its role be re-evaluated? Cancer 2010.

Tumor stages

NSCLC						
„limited disease“					„advanced disease“	
N0	N0	N1	N1	N2	N3	Any
IA	IB	IIA	IIB	IIIA	IIIB	IV
Surgery					No surgery	

SCLC						
„limited disease“				„advanced disease“		
N0	N0	N1	N1	N2	N3	Any
IA	IB	IIA	IIB	IIIA	IIIB	IV
Surgery				No surgery		

Conclusions Surgery in SCLC

- R0 resection essential
- Surgery only recommended for T1-2, N0-N1 (limited disease)
- Evidence is limited
- Gold standard of treatment not yet defined
- Further prospective trials needed

Proposed classification

Incidental SCLC	SCLC incidentally found during surgery	**-> Primary resection**
Verified SCLC Limitied disease (N0)	Single nodule stage I (N0) SCLC	**-> Primary resection, adjuvant treatment**
Verified SCLC Limited disease (N1)	Stage IIA – IIB (N1) SCLC Complete response after induction	**-> Resection after induction CHT/RT**
Verified SCLC Advanced disease (N2/3)	SCLC with proven N2/N3 disease	**-> CHT/RT**

Summary: Surgery for lung cancer

Early stages	Lobectomy (VATS), sublobar resections, parenchyma sparing options
Local advanced stages	Multimodality treatment including surgery in selected cases
Oligometastatic disease	Combined Surgery and multimodality treatment reasonable in selected cases
Palliation and control of symptoms	Talc –Pleurodesis, PleurX Cath. Impl., Salvage resection
SCLC	Good long term results for radically resected early SCLC

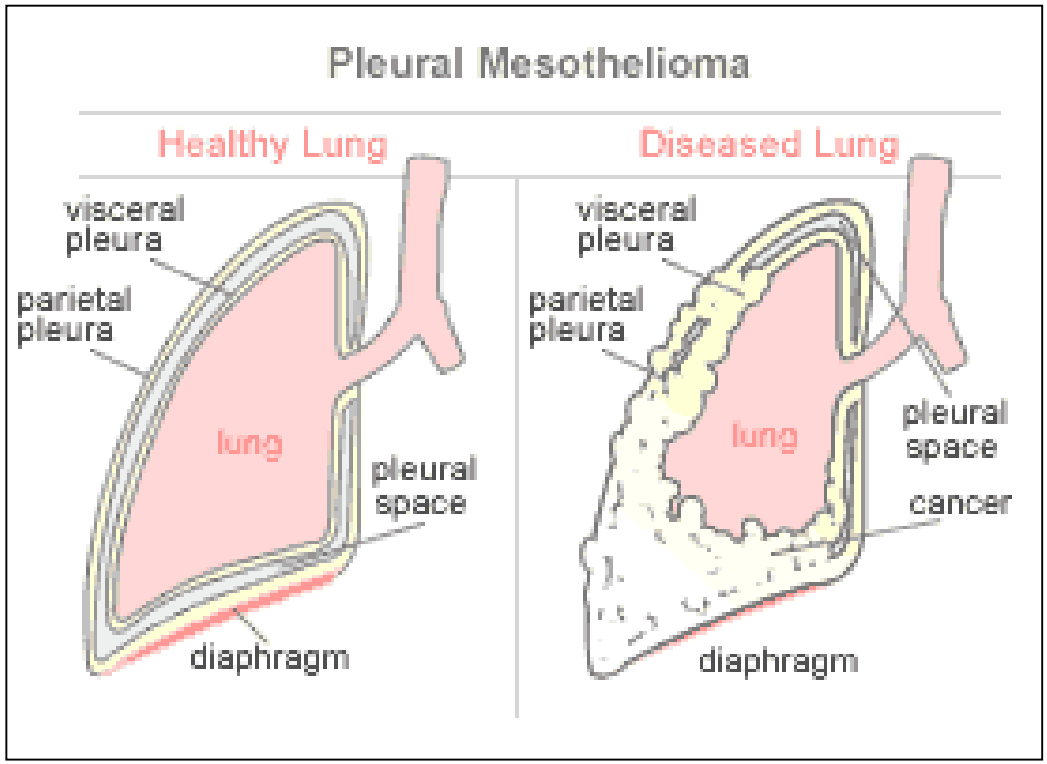
Surgery for malignant pleural mesothelioma

Outline

- Overview
- Diagnosis and Staging
- Surgical procedures
- Multimodality treatment
- Intracavitary treatment options
- New approaches
- Summary

Malignant Pleural Mesothelioma

- Etiology: 50-70% pos. anamnesis of asbestos exposure
- Latency periode between exposure and diagnosis: approx. 20-35 y.
- In early stage, MPM forms multiple small nodules mostly in parietal pleura
- In advanced stage, MPM is characterized by thick tumor gross surrounding the whole lung
- Mean survival without therapy: 6-7 Mo
- Trimodality treatment: 11-22 Mo.
- 5 year survival rate: 5%



Source: http://mesoblog.org/mesothelioma/pleural-mesothelioma.php

Epidemiology

Country or Region	Incidence *cases/million population*	Predicted Peak Years	Predicted No. of Deaths in Next 40 Yr†	Predicted Cost‡ *billions of U.S. dollars*
United States	15	2004	72,000	200
Europe	18 §	2015–2020	250,000	80
Japan	7	2025	103,000	—
Australia	40	2015	30,000	5–10

Bruce W.S. Robinson and Richard A. Lake, *N Engl J Med 2005; 353: 1591-603*

Histological characteristics

- First description of MPM in 1767

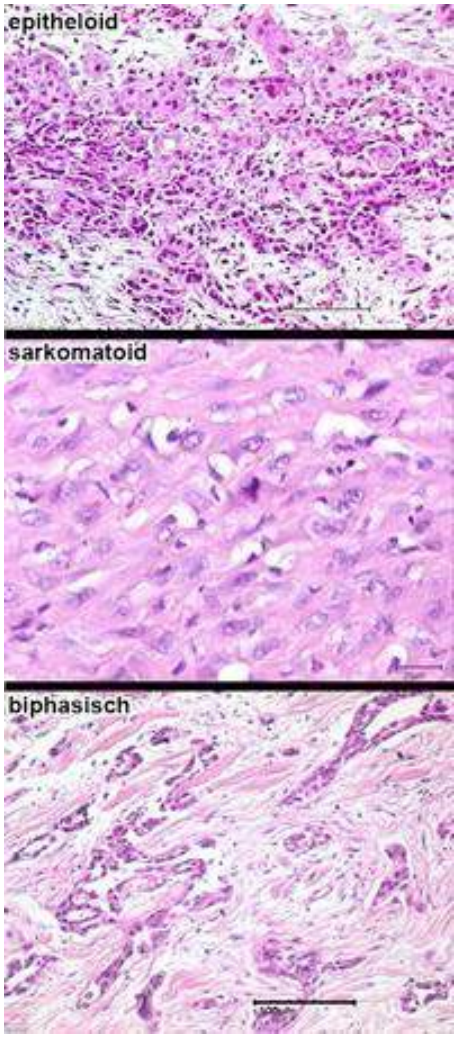
- First subclassification in 1931

- Immunohistochemical examination as a gold standard in differentiating MPM from metastatic disease of another primary cancer

- Established markers:
Calretinin (positive), MOC31 (negative), BerEP4 (negative), D2-40 (positiv), TTF-1 (negativ),
Cytokeratine (positive) und WT-1 (positive)

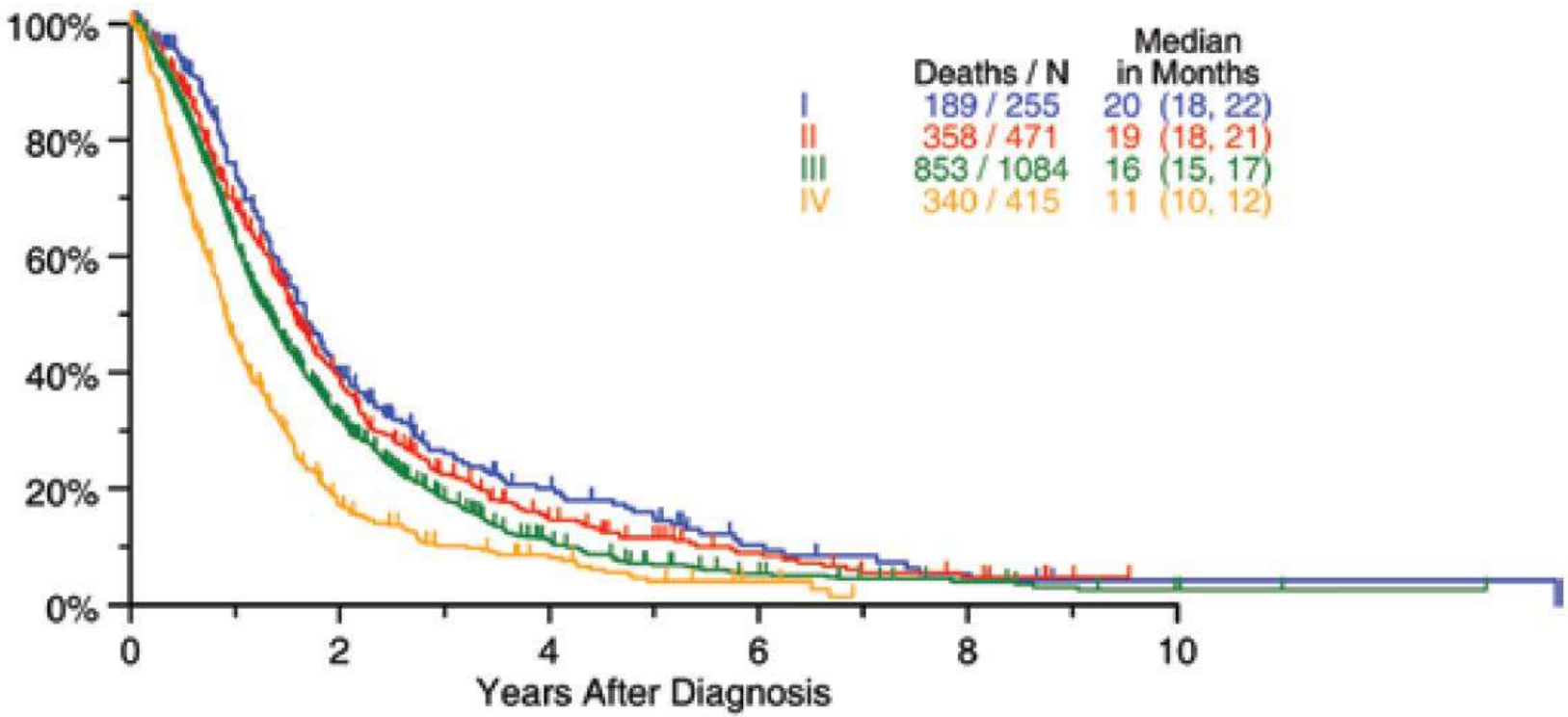
- Histological subtypes:

  Epitheliod: ~ 50%
  Sarcomatoid: ~ 25%
  Biphasic: ~ 25%



Feldman et al JCO 2003

Expected Survival for MPM



Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012 (n=3101)

Therapy for MPM

- Survival 9-12 months
- Therapy: **nihilism** to **multimodality therapy**
- Chemotherapy Pemetrexed & Cisplatin
- ***Trimodality therapy***
  - Induction chemotherapy
  - Cytoreductive surgery (EPP vs. P/D)
  - Adjuvant Radiotherapy
- Outcome after treatment strongly varies
- Only around 50% are able to complete trimodality therapy
- Benefit of multimodality therapy recently was questioned (**M.A.R.S.-Trial**)

Robinson B et al, Lancet 2005 , M de Perrot, et al JCO 2009, NJ Vogelzang et al JCO 2003, Treasure T et al Lancet 2011

Prognostic factors

TABLE 7. Final Model of Clinical, Pathologic, and Laboratory Variables (n = 550)

	Variable	Hazard Ratio	*p* Value
Stage	Pathologic stage II vs. I	1.48	0.0802
	Pathologic stage III vs. I	2.2	0.0002
	Pathologic stage IV vs. I	2.49	0.0001
Histology	Other histology vs. epithelial	1.8	<0.0001
Sex	Male vs. female	1.7	0.0006
Age	Age ≥50 vs. younger	1.61	0.012
Treatment	Palliative vs. curative intent	1.67	0.0008
Adjuvant treatment	No vs. yes	1.7	0.0002
Platelets	≥400 vs. <400	1.5	0.0004
WBC	≥15.5 vs. <15.5	2.39	0.0007

WBC, white blood cell count.

Prognostic Variables for Pleural Mesothelioma: A Report from the IASLC Staging Committee

JTO 2014

Diagnostic algorithm

Patient: asbestos exposure, pleural effusion, pain, …

↓

CT scan

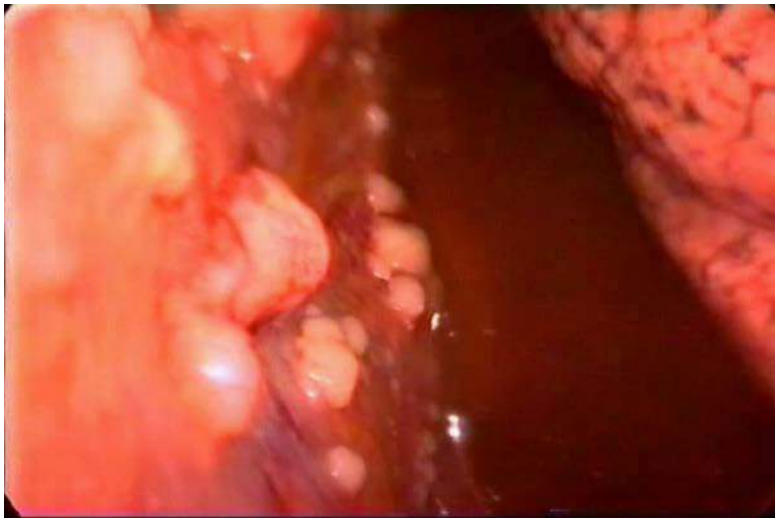
↓

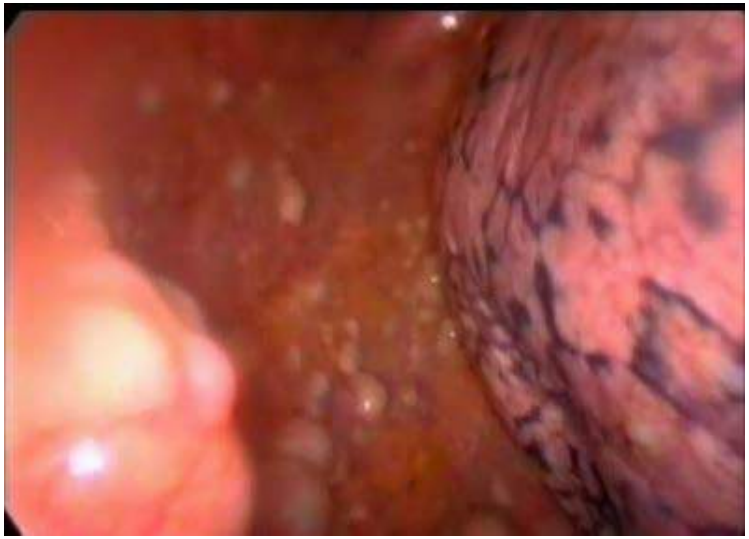
Cytology and/or biopsy negative

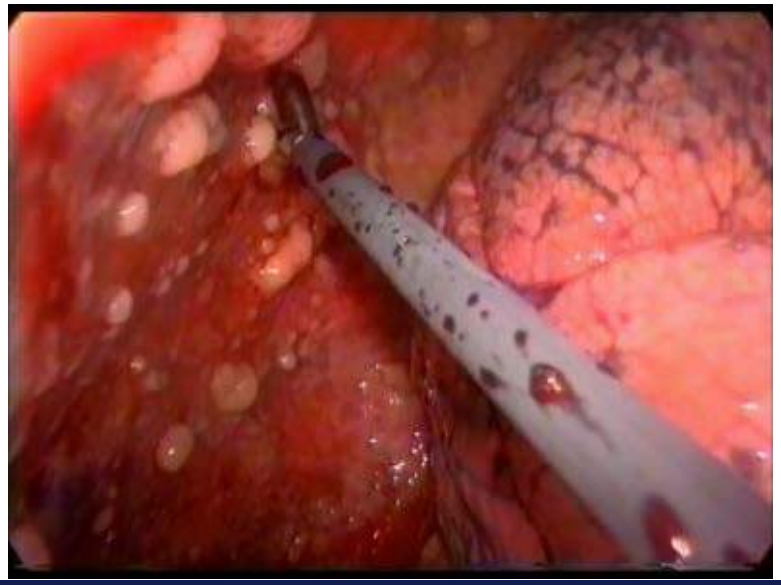
↓

VATS

VATS biopsy







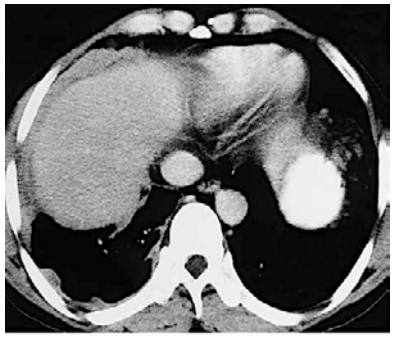
Malignant Pleural Mesothelioma

Heterogenous disease

Classification by staging?

Staging modalities

- **Non-invasive**: imaging modalities (CT, PET-CT, MRI)



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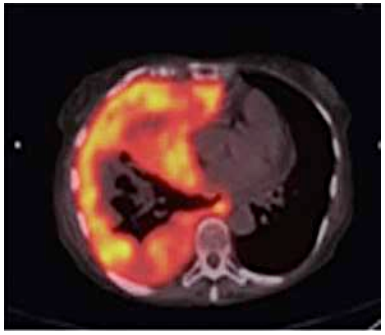
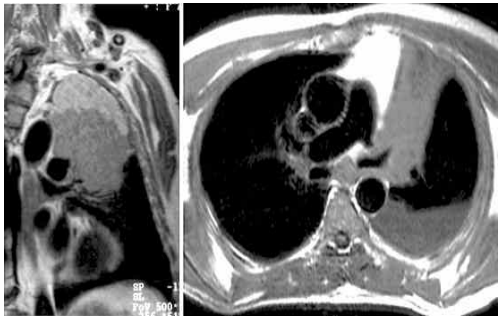
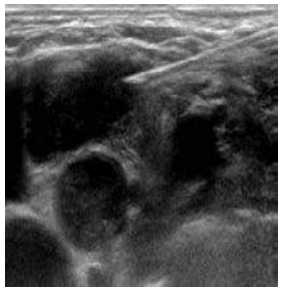
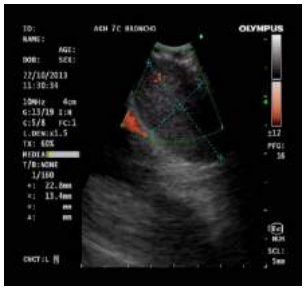
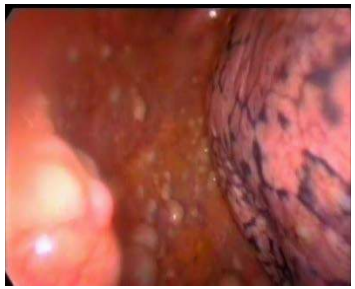




- **Invasive**: ultrasound-guided biopsy, EBUS-TBNA, mediastinoscopy, VATS, laparoscopy







TNM (7th edition) – T descriptors

T1a

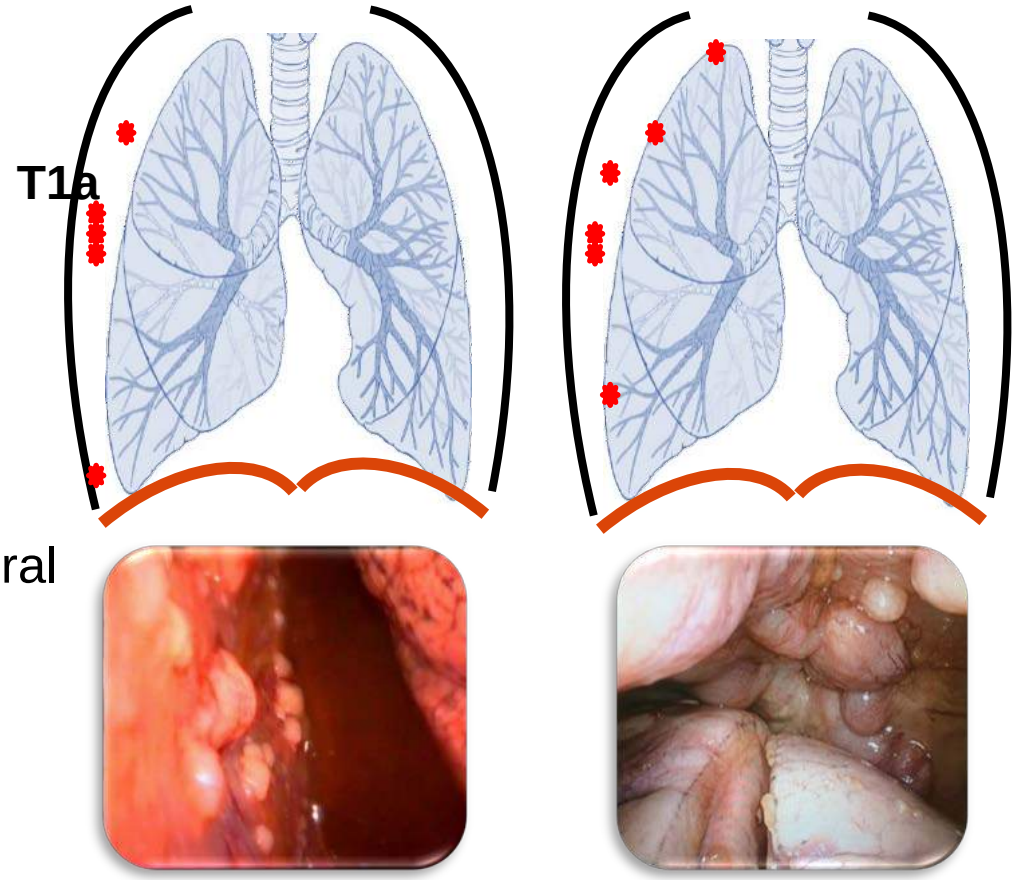
potentially resectable

- only parietal pleura
- no viszeral or mediastinal pleural involvement

T1b

potentially resectable

- parietal pleura and
- scattered foci of visceral pleural involvement



Rusch V et al, Chest 1995

TNM (7th edition) – T descriptors

T2

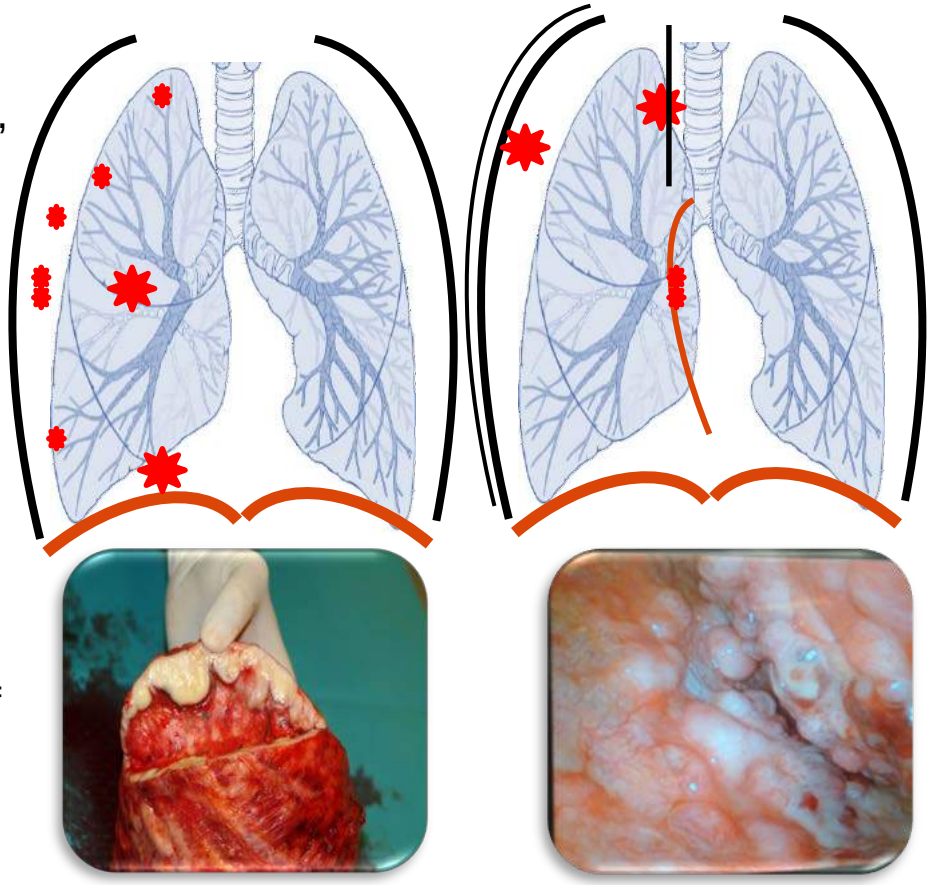
potentially resectable

- parietal and visceral pleural involvement, and / or
- pulmonary parenchymal involvement and/or
- diaphragmatic muscle involvement

T3

potentially resectable

- localised tumour extension into endothoracic fascia and / or
- localised non-transmural involvement of pericardium and / or
- localised extension into mediastinal fat, soft tissue chest wall



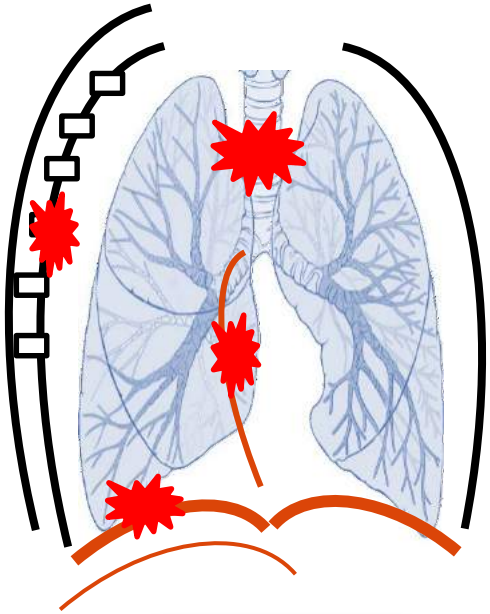
Rusch V et al, Chest 1995

TNM (7th edition) – T descriptors

T4

unresectable

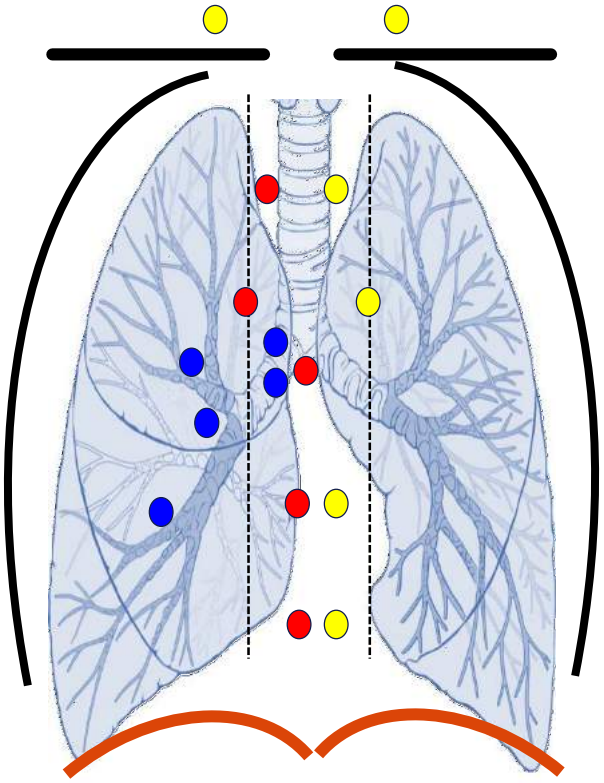
– multiple foci of extension into chest wall +/-
rib destruction and/or
– extension through diaphragm into peritoneum
and / or
– extension into contralateral pleura and / or
– extension into mediastinal organs and / or
– extension through pericardium +/- direct extension into heart



Rusch V et al, Chest 1995

TNM (7th edition) – N descriptors

N0: no evidence of nodal involvement
N1: ipsilateral bronchopulmonary or hilar nodal involvement
N2: subcarinal or ipsilateral mediastinal / internal mammary or peridiaphragm or pericardial or intercostal nodes
N3: contralateral mediastinal / internal mammary nodes,or ipsilateral / contralateral supraclavicular nodes



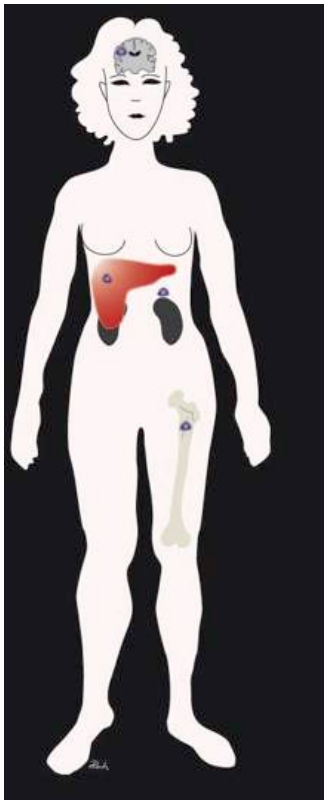
Rusch V et al, Chest 1995

TNM (7th edition) – M descriptors and stage grouping

M0: no evidence of distant metastasis

M1: distant metastasis

(contralateral lung (pleura), brain, liver, spleen, thyroid, Bone, extrathoracic LN (other than supraclav.))



Stage	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1,T2	N1	M0
	T1,T2	N2	M0
	T3	N0-2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Rusch et al, Chest 1995

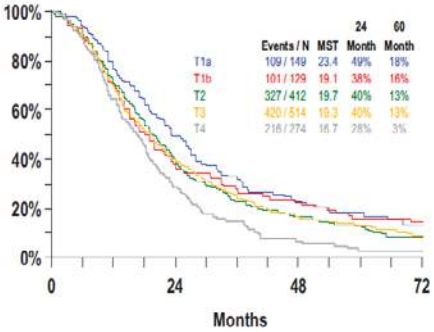
Miller et al, Ann Am Thorac Soc.2014
Finn et al, Chest 2012

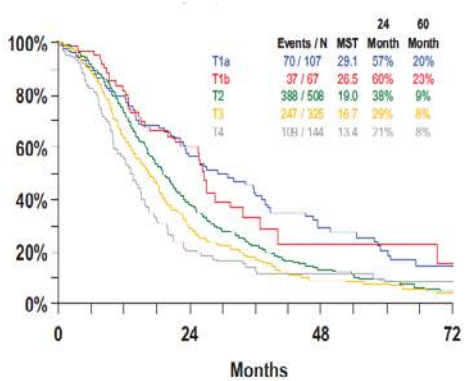
Changes in TNM (8th edition)

Changes T-descriptors

- **Collapse of T1a and T1b into a single T category (Tumor limited to ipsilateral parietal+/- visceral +/-mediastinal +/- diaphragmatic pleura)**

- Measurement of pleural tumor thickness (prognostic variable)





- Classification of pleural involvement pattern in minimal, nodular and rind-like (prognostic impact)

- cT better prognosis than pT

Nowak et al, JTO 2016

A Multicenter Study of Volumetric Computed Tomography for Staging Malignant Pleural Mesothelioma

Valerie W. Rusch, MD, Ritu Gill, MD, Alan Mitchell, MS, David Naidich, MD, David C. Rice, MB, BCh, Harvey I. Pass, MD, Hedy L. Kindler, MD, Marc De Perrot, MD, MS, and Joseph Friedberg, MD, on behalf of the Malignant Mesothelioma Volumetric CT Study Group*

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York; Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts; Cancer Research and Biostatistics, Seattle, Washington; Department of Radiology, New York University School of Medicine, New York, New York; Department of Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Surgery, New York University School of Medicine and Comprehensive Cancer Center, New York, New York; Department of Medicine, The University of Chicago, Chicago, Illinois; Department of Surgery, Toronto General Hospital and Princess Margaret Hospital, Toronto, Ontario, Canada; and Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

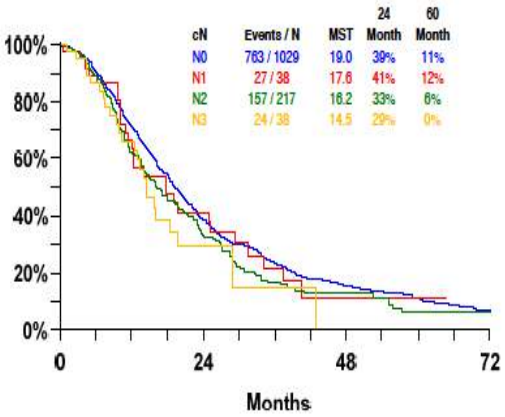
Rusch et al, ATS 2016

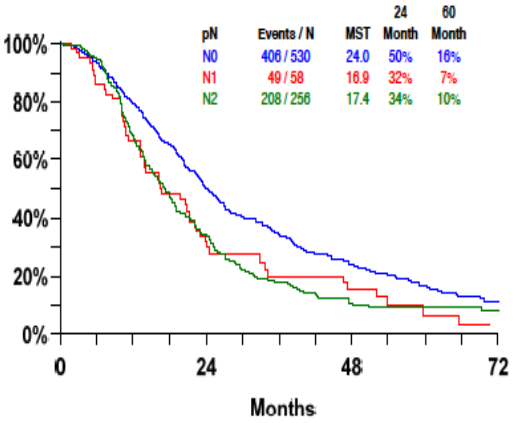
Changes in TNM (8th edition)

Changes N-descriptors

- **Collapse of both clinical and pathological N1 and N2 into a single N category (ipsilateral, intrathoracic) = N1**
- **Previously N3 reclassified as N2**

- Tumor thickness predicts risk of nodal metastasis
- No difference between single vs. multiple stations





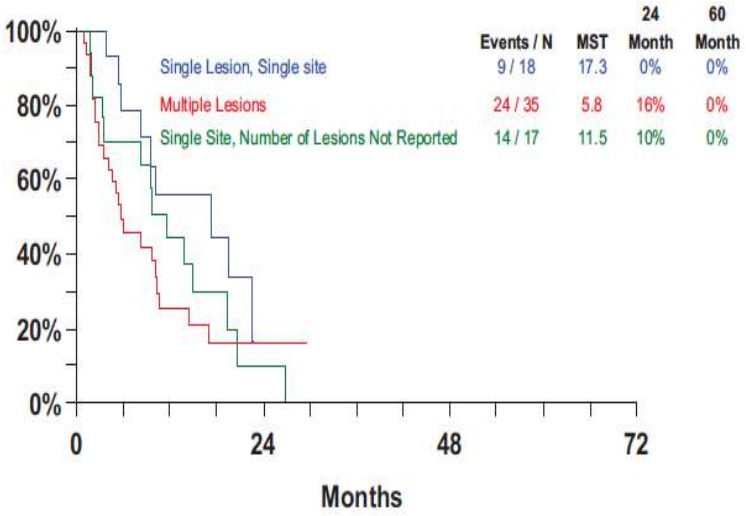
Rice et al, JTO 2016

Changes in TNM (8th edition)

Changes M-descriptors

- **No changes in M-descriptors**

- Better prognosis in patients with only a single metastasis



Changes in stage groups

- **Stage III changed to stage IIIA (T3N1M0) and stage IIIB (T1-3N2M0 and T4anyNM0)**

	N0		N1/N2	N1	N3	N2
	v7	v8	v7	v8	v7	v8
T1	I (A,B)	IA	III	II	IV	IIIB
T2	II	IB	III	II	IV	IIIB
T3	II	IB	III	IIIA	IV	IIIB
T4	IV	IIIB	IV	IIIB	IV	IIIB
M1	IV	IV	IV	IV	IV	IV

Rusch et al, JTO 2016

Surgical procedures for MPM

Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma

A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group

David Rice, MB, BCh, Valerie Rusch, MD,† Harvey Pass, MD,‡ Hisao Asamura, MD,§ Takashi Nakano, MD,‖ John Edwards, MB, ChB, PhD,¶ Dorothy J. Giroux, MS,# Seiki Hasegawa, MD,** Kemp H. Kernstine, MD, PhD,†† David Waller, MD,‡‡ and Ramon Rami-Porta, MD§§, on behalf of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group*

- Online survey of surgeons experienced in MPM
- 62 answers, 39 centers, 14 nations

Definitions

- **EPP:** En bloc resection of the lung incl. parietal and visceral pleurae and pericardium/diaphragm

- **Extended P/D:** Parietal and visceral pleurectomy with resection of pericardium and diaphragm

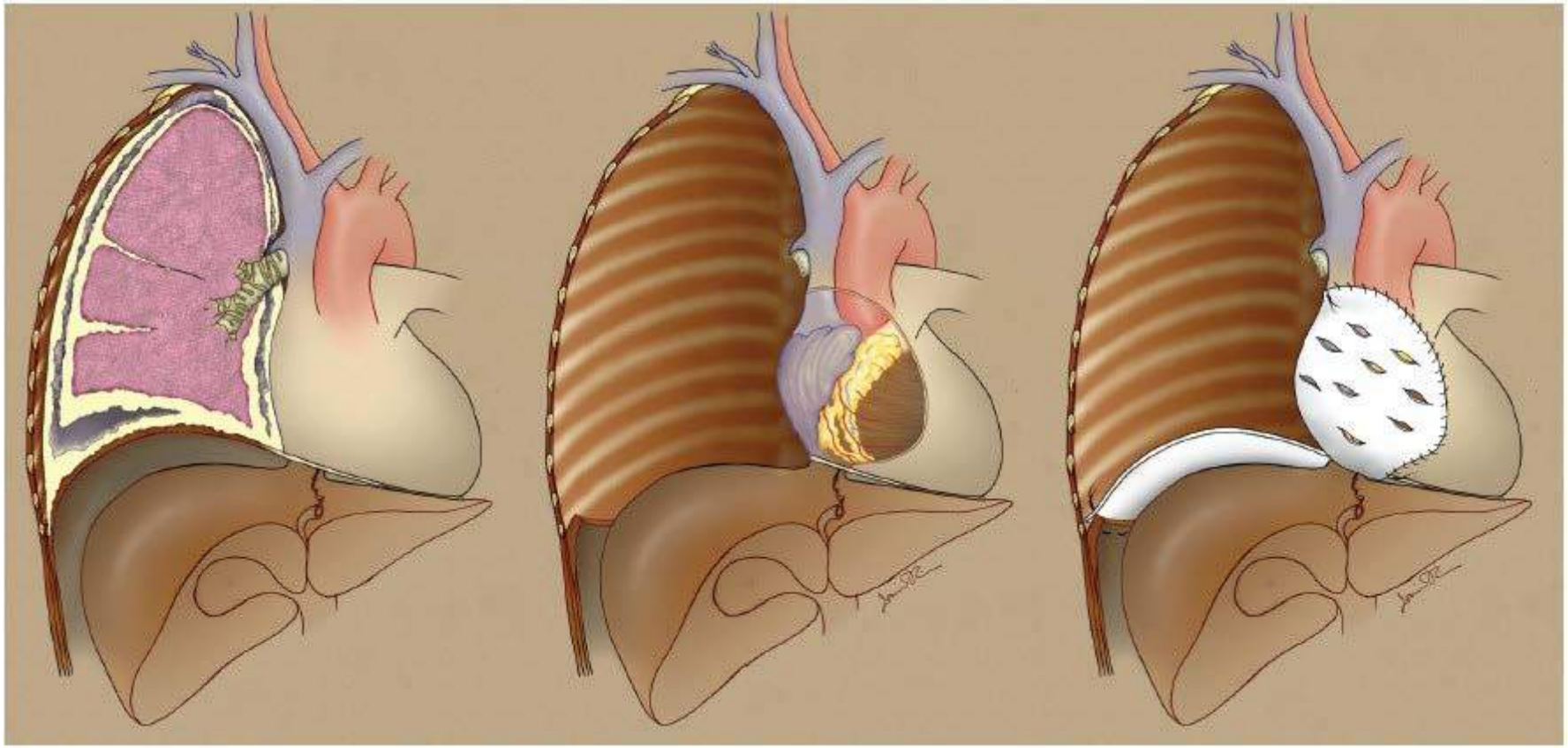
- **P/D:** Parietal and visceral pleurectomy without resection of pericardium and diaphragm

- **Partial pleurectomy:** Resection of parts of parietal and/or visceral pleura for diagnostic or palliative purposis, no macroscopic complete resection

Surgery for MPM

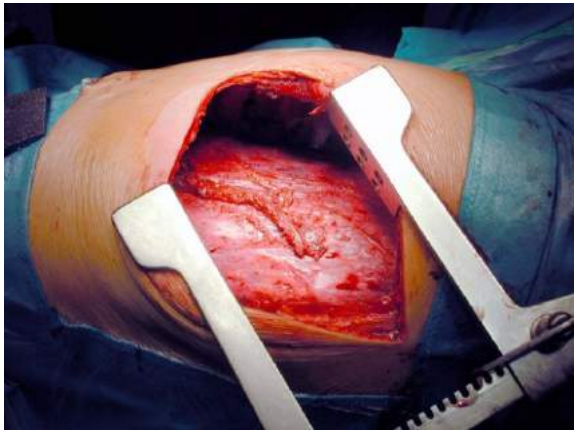
Surgical cytoreduction is indicated when macroscopic complete resection is deemed achievable

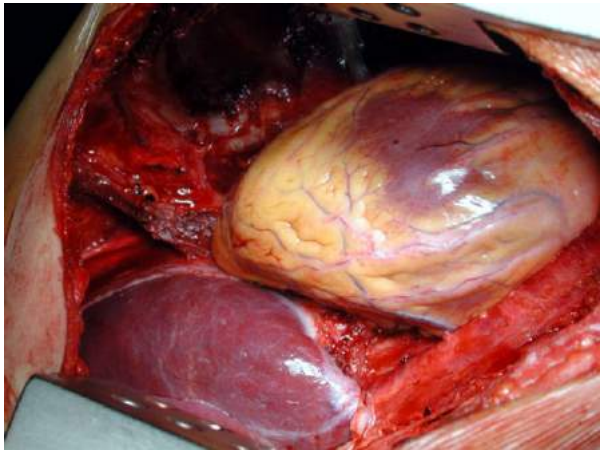
EPP

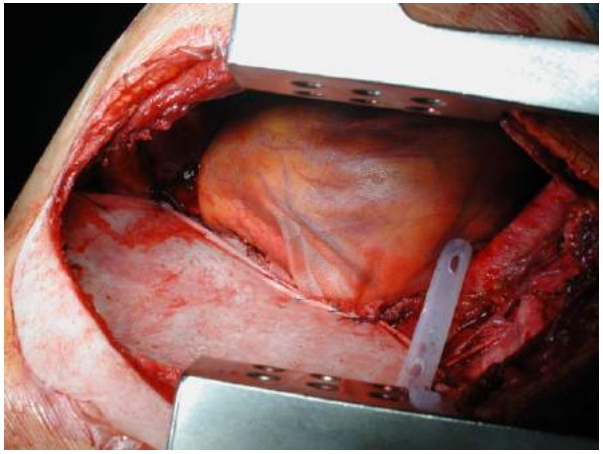


Rice D. Standardizing surgical treatment in malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1(4):497-501.

EPP







EPP: Indications

- Epithelial subtype and intrapleural localized disease with chance of a R0-Resection, regardless of LNN status (except N3)
- Sarcomatoid and mixed subtypes only in N0 or N1
- Only in combination with a multimodality treatment approach
- Good performence status (Karnofsky > 80%)
- Predicted postoperative FEV1 > 1 L

Ann Surg Oncol (2011) 18:2973–2979
DOI 10.1245/s10434-011-1728-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Summary of Prognostic Factors and Patient Selection for Extrapleural Pneumonectomy in the Treatment of Malignant Pleural Mesothelioma

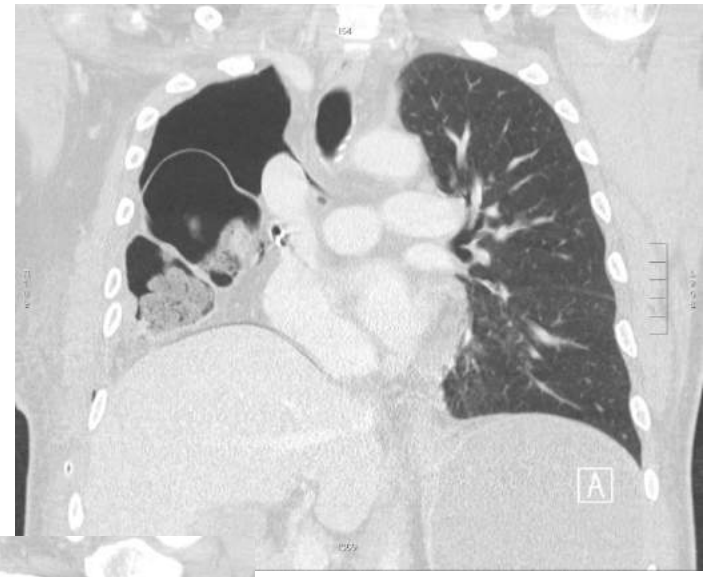
- 17 studies
- 13 centers

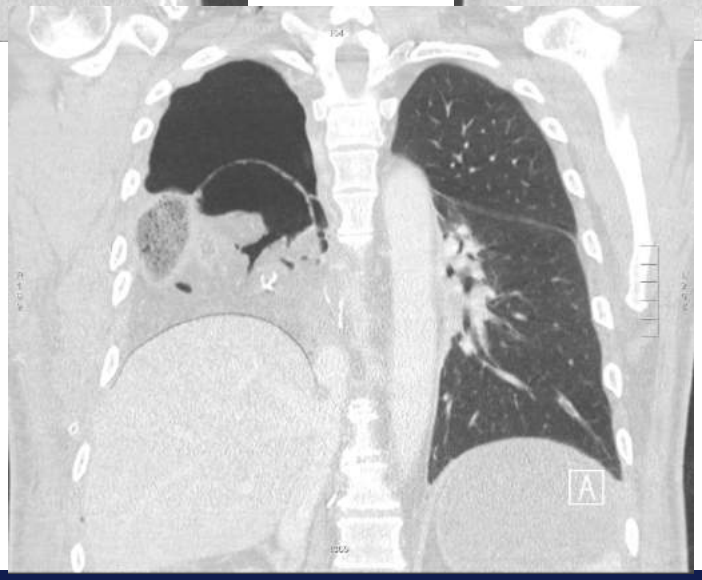
Christopher Cao, BSc (Med), MBBS, Tristan D. Yan, BSc (Med), MBBS, PhD, Paul G. Bannon, MBBS, PhD, FRACS, and Brian C. McCaughan, MBBS, FRACS

TABLE 2 Summary of significant and nonsignificant prognostic factors on survival from referenced studies on extrapleural pneumonectomy for patients with malignant pleural mesothelioma

Variables	Significant	Nonsignificant
Quantitative factors		
Staging system	7, 8, 9, 10, 11, 18, 22	6, 13, 16, 21
T stage	7, 17*, 20	14, 16, 18, 21
Nodal involvement	7, 10, 11*, 12*, 13*, 14*, 16*, 18, 19*, 21*, 22	6, 17, 20
Laterality		8, 9, 11, 18, 19, 21
Histopathology	8, 9, 10, 11*, 12, 13*, 14, 17*, 18, 21*, 22	6, 7, 15, 16, 19, 20
Clinical factors		
Age	8 (E), 21*	8 (N), 9, 11, 14, 16, 18, 19, 20
Gender	8 (E), 11, 13*, 17*	6, 8 (N), 9, 14, 16, 18, 19, 20, 21
Smoking history		11, 18
Asbestos exposure	19*	11, 18, 20
Performance status	12	
Serological markers	8, 12*, 13*, 17*	
Treatment related factors		
Completeness of resection	11*, 16, 18	10, 19
Adjuvant chemotherapy	12*, 14, 19*, 20*, 22	21
Adjuvant radiotherapy	7, 19*, 21	
Interval to surgery	8 (E)	8 (N)
Surgical access site	12	

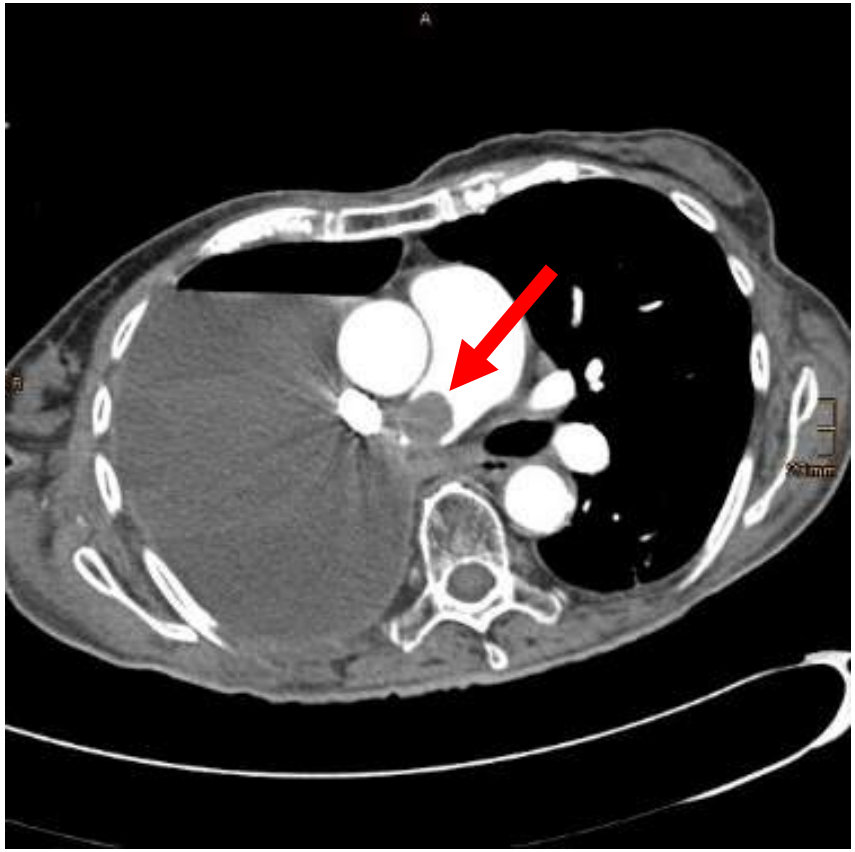
EPP: Morbidity

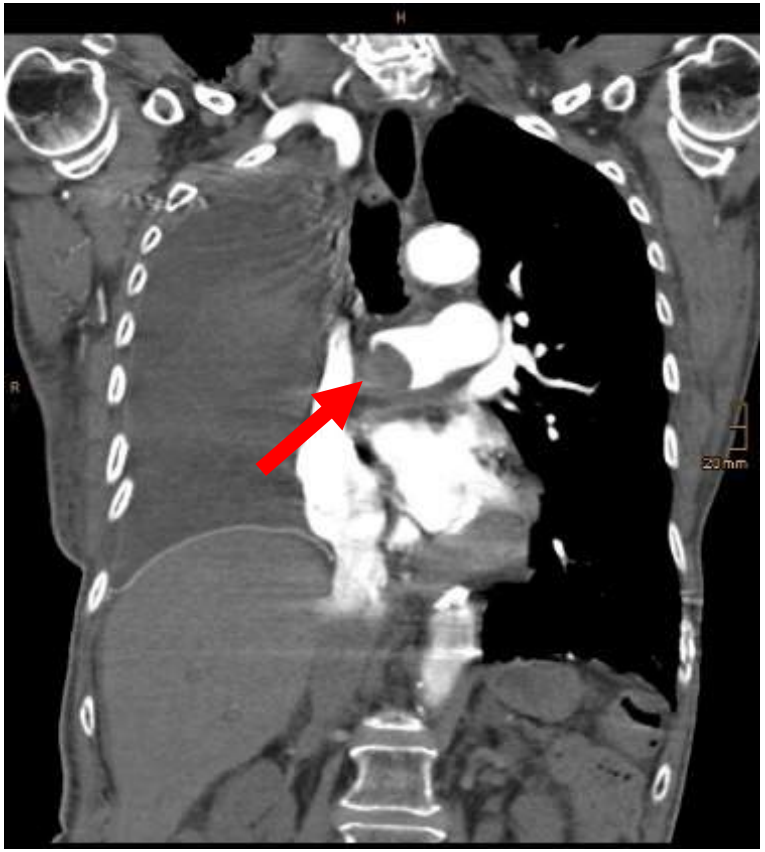




Pulmonary embolism

- 5% of cases





1,5 monts after EPP

EPP outcome & morbidity

- Median overall survival: 9.4 – 27.5 months
- 1-year survival: 36 – 83%
- 3-year survival: 0 – 41%
- 5-year survival: 0 – 24%
- Median disease free survival: 7 – 19 months
- Perioperative mortality: 0 – 11.8%
- Major morbidity: 12.5 – 48%

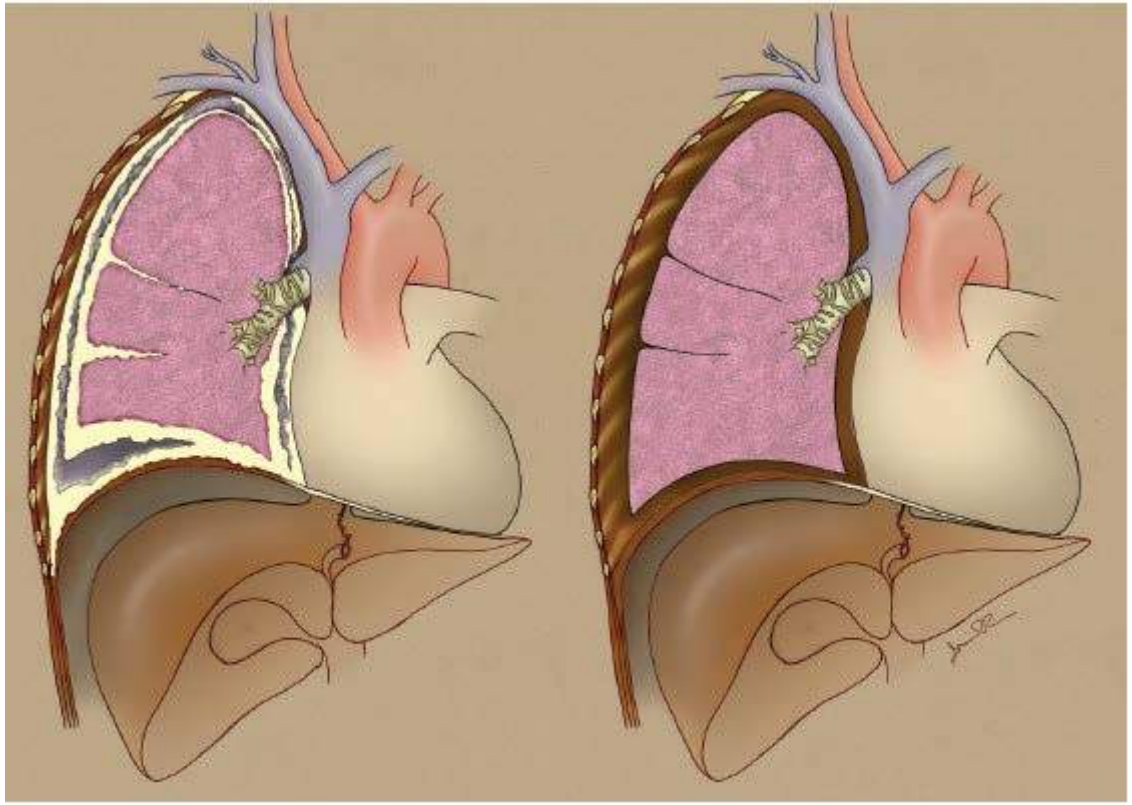
EPP: Morbidity

- Morbidity overall (minor + major) about 50%
- Diaphragmatic patch dehiscence
- Mediastinal shift - Pleural effusion
- Chylothorax
- Hemothorax
- Vocal cord paralysis
- Subclavian vein thrombosis
- New onset AF
- Cardiac arrest – Luxation?
- PE
- Stroke
- Pneumonia
- Infection – intracavitary, chest wall, wound
- Bronchopleural Fistula

P/D: Indications

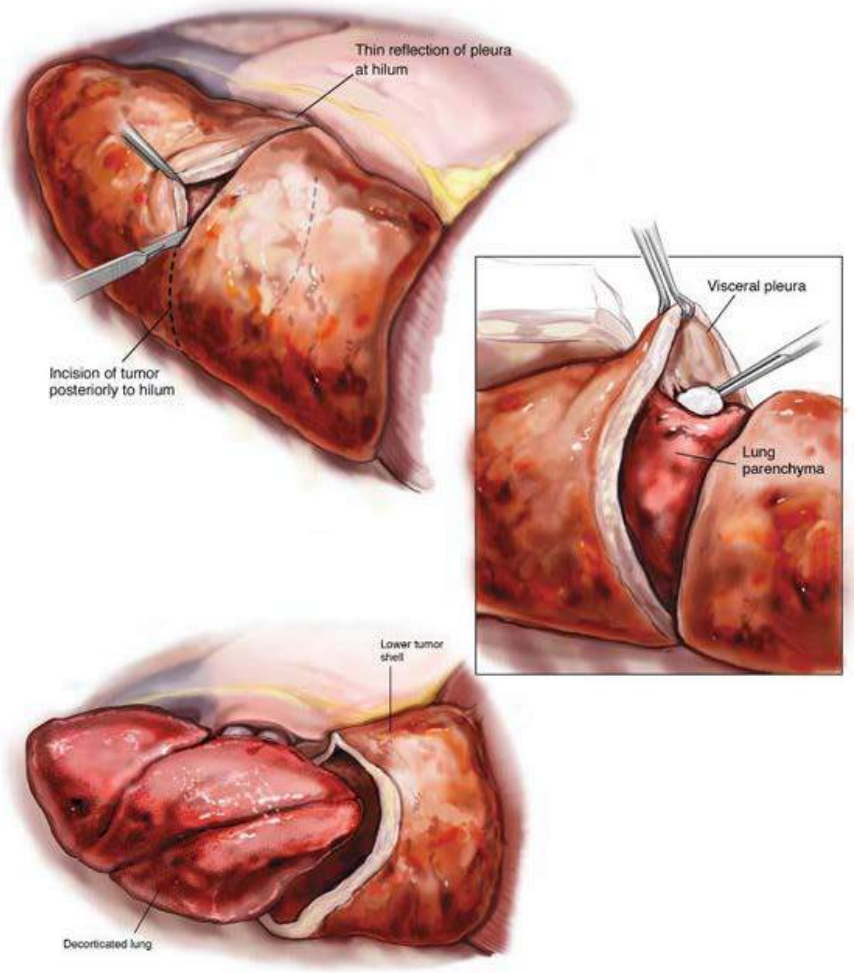
- Offered to patients who do not have the cardiopulmonary reserve to tolerate pneumonectomy
- Early-stage disease (confined to parietal pleura without lung infiltration) – lung sparing to decrease morbidity and mortality risk
- In combination with neoadjuvant or adjuvant treatment modalities
- Cytoreductive procedure (no R0 resection)

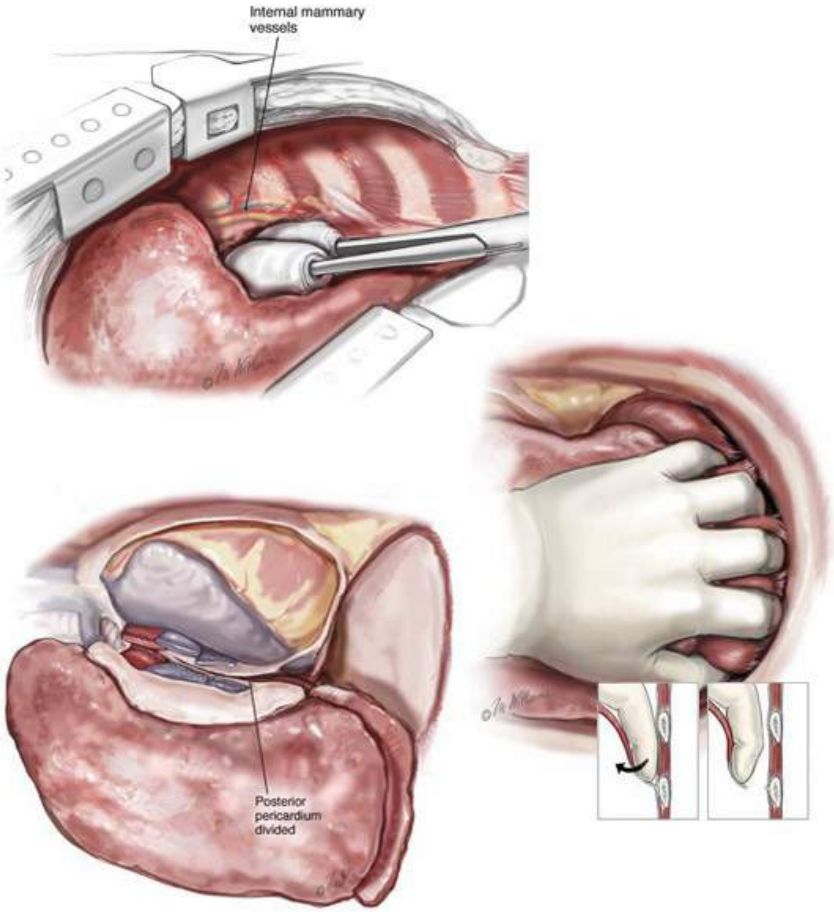
P/D



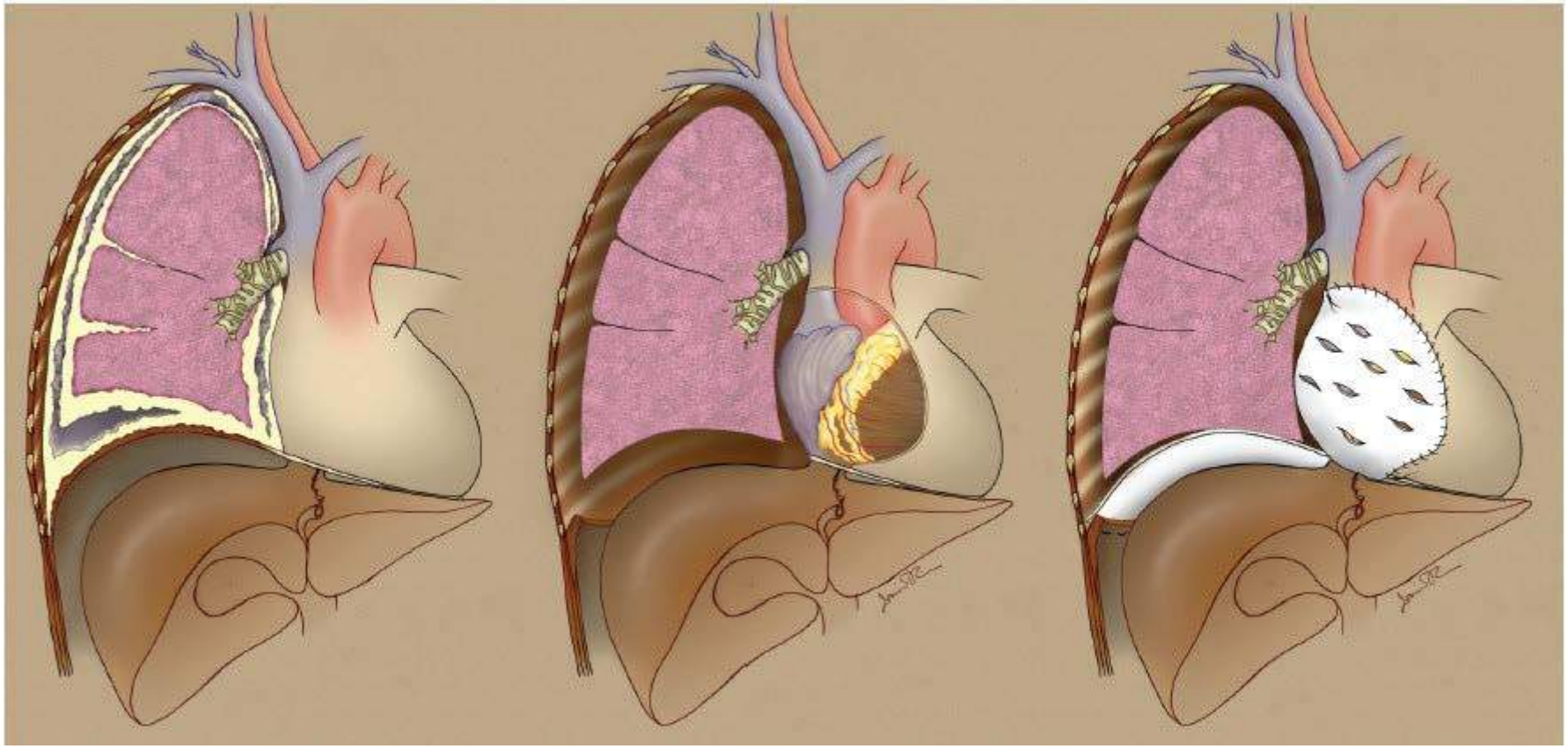
Rice D. Standardizing surgical treatment in malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1(4):497-501.

P/D



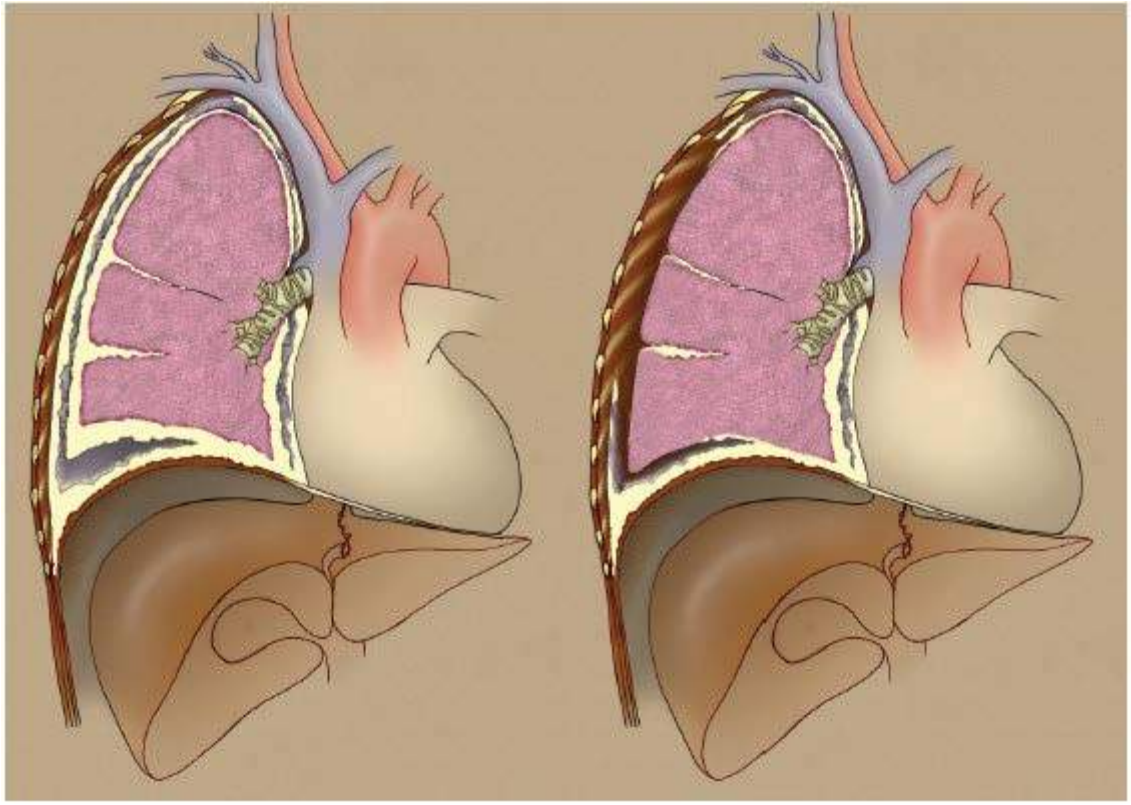


Extended P/D



Rice D. Standardizing surgical treatment in malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1(4):497-501.

Partial Pleurectomy



Partial pleurectomy: partial removal of parietal and/ or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind

A systematic review of lung-sparing extirpative surgery for pleural mesothelioma

Elaine Teh[1] • Francesca Fiorentino[2] • Carol Tan[3] • Tom Treasure[2]

Author	Start year	End year	n	Op mort (%)	1 year survival (%)	2 year survival (%)	3 year survival (%)	4 year survival (%)	5 year survival (%)	Median (months)
Achatzy[32]	1969	1985	120						2	10.1
Alberts[40]	1965	1985	26							10.9
Allen[27]	1958	1993	56	5	30	9			5	9.0
Aziz[21]	1989	1999	47	0	50	0	0		0	14.0
Ball[30]	1981	1985	13		55	20	18		8	17.0
Brancatisano[28]	1984	1989	45	2	58	21				16.0
Branscheid[29]	1978	1989	82	2	35	20	17			10.5
Ceresoli[23]	1986	1999	54		50					12.5
Clarke[14]	1989	1999	100	2						14.6
Colaut[15]	1985	2002	40			28	17			
Colleoni[24]	1990	1994	20		44	32	0		0	11.5
de Vries[17]	1976	2001	29	4	14	10	8		5	9.0
Flores[5]	1990	2006	278	4	62	30	20		15	16.0
Harvey[31]	1965	1988	9		43	0	0		0	12.0
Law[33]	1971	1980	28		82	32		11		20.0
Lee J[25]	1986	1993	15		37	15	7	0	0	11.5
Lee T[22]	1995	2000	26		64	32	18		12	18.1
Lucchi[12]	1999	2004	49	0		60			23	26.0
Matzi[16]	1993	2003	34							
Monneuse[18]	1990	2000	16	6	69	50	42		8	41.3
Nakas (Radical)[7]			51	6	53	41	25	13		15.3
Nakas (Non-radical)[7]			51	10	32	10	2	0	0	7.1
Okada[13]	1986	2006	34	0	60	40	24	19	10	17.0
Phillips[19]	1989	1999	15		54	40	33	28	28	14.0
Sauter[26]	1988	1992	20		50	25				12.0
Schipper SP[11]			31	3	30	15	4	4	0	8.1
Schipper TP[11]			10	0	80	35	35	35	35	17.2
Yom[20]	2000	2001	8	25	13					6.5
Weighted average				4	51	26	16	11	9	

Mean survival all studies (26 papers):

1-year surv: 51%

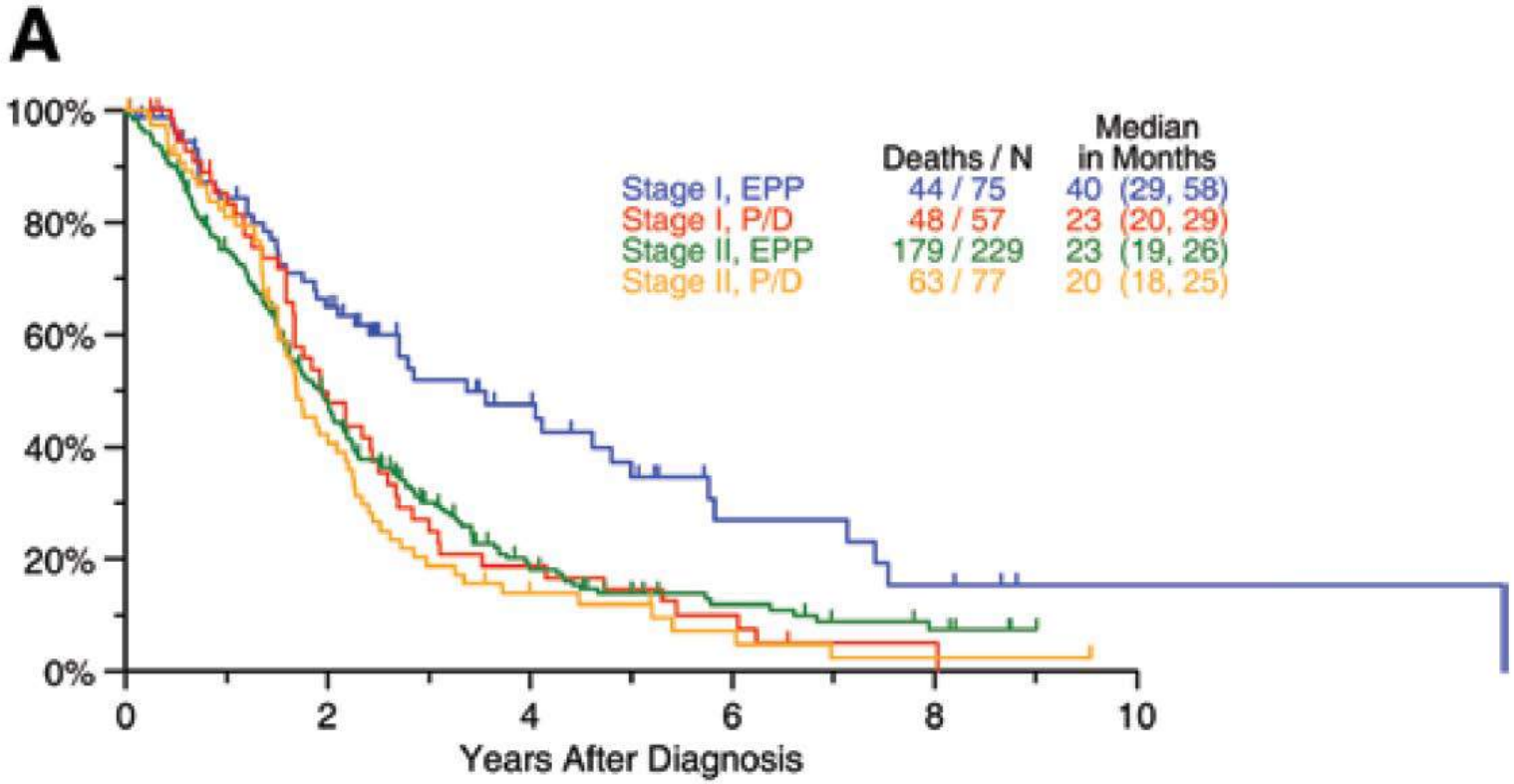
2-year surv: 26%

3-year surv: 16%

4-year surv: 11%

5-year surv: 9%

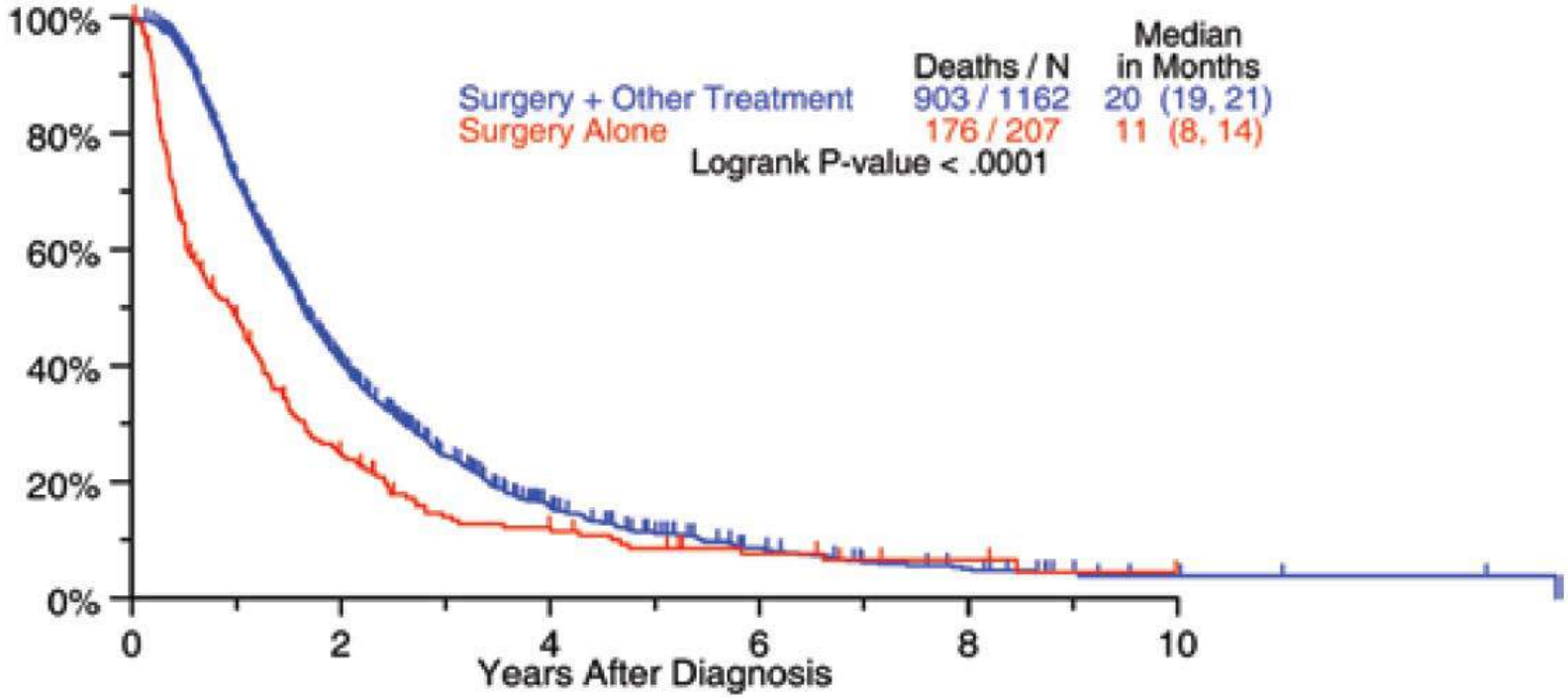
P/D vs. EPP



Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012

Multimodality approaches

(Tri)Multimodale Therapie



Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012 (n=3101)

(Tri)Multimodale Therapie

	Hazard ratio	Confidence interval	*P* value
Age	1.0	(1.01–1.02)	$P < .001$
Female gender	1.3	(1.05–1.64)	$P = .02$
EPP	1.4	(1.18–1.69)	$P < .001$
Non-epithelioid	1.3	(1.11–1.60)	$P < .001$
Stage III/IV	1.4	(1.28–1.55)	$P < .001$
Multimodality therapy	.45	(0.38–0.54)	$P < .001$

EPP, Extrapleural pneumonectomy.

Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. JTCVS 2008

Multimodality approaches

Surgery (PD) | Postop. Chemo

Induc

Surge

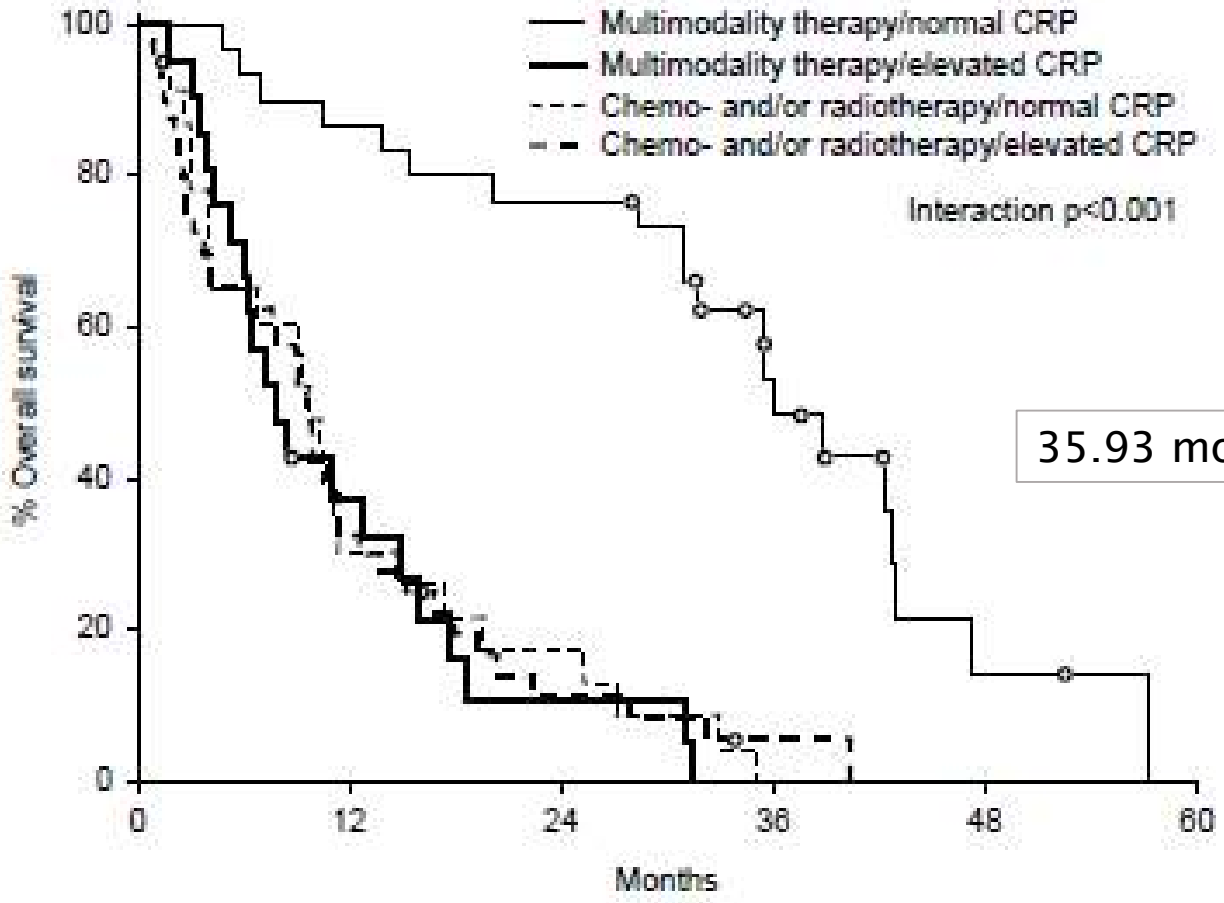
What´s the best stategy?

Who should be selected?

Induction Chemo | Surgery (PD / EPP) | Intraop. therapy | Postop. Chemo

Induction IMRT | Surgery (PD / EPP) | Postop. Chemo

CRP is a simple predictive biomarker



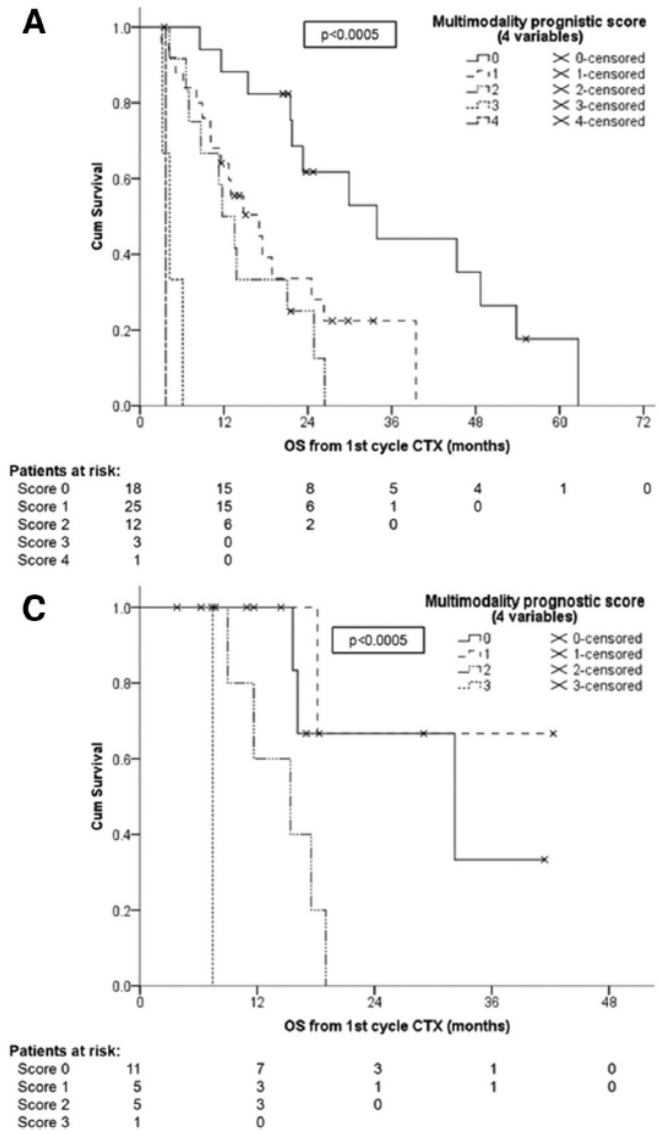
35.93 months vs. 7.86 months OS

Ghanim, Hoda et al, Ann Surg. 2012

EPP - Selection

- TU Volume
- Histology
- CRP
- Response to CHT

Opitz,....Hoda... et al; JTO 2015



	(A) Patients treated with induction chemotherapy followed by EPP (Zurich)	(B) Patients of the intention to treat group (Zurich)	(C) Patients treated with induction chemotherapy followed by EPP (Vienna)
number of patients	59	37	22
	Median survival time in months (95% CI)		
Score 0	34 (18-50)	21 (6-36)	32 (8-56)
Score 1	17 (9-25)	11 (7-14)	- (-)
Score 2	12 (8-16)	10 (8-12)	15 (7-24)
Score 3	4 (3-6)	10 (0-21)	7 (-)
Score 4	4 (-)	3 (-)	

Outcome and Morbidity after trimodality treatment

Table 2 Summary of survival and perioperative outcomes of patients with malignant pleural mesothelioma who underwent trimodality therapy involving neoadjuvant or adjuvant chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy

Author	Median survival (months)			Disease free survival (months)	Perioperative mortality	Perioperative morbidity		Length of stay
						Overall	Major	
Lang-Lazdunski (7)	12.8[DD]			NR	4.5%	68%	NR	14
Treasure (8)	14.4[DR]			7.6	12.5%	69%	42%	NR
van Schil (9)	ITT: 18.4[RE]	NC+EPP: NR	TMT: 33	13.9	6.5%	82.6%	NR	NR
Krug (10)	ITT: 16.8[CC]	NC+EPP: 21.9	TMT: 29.1	10.1	3.7%	NR	NR	NR
Buduhan (11)	25[DD]			NR	4.3%	80%	54%	9.2[MV]
de Perrot (12)	14[CC]			NR	6.7%	NR	33%	NR
Rea (13)	ITT: 25.5[CC]	NC+EPP: 27.5	TMT: NR	16.3	0%	52.4%	23.8%	NR
Weder (14)	ITT: 19.8[CC]	NC+EPP: 23	TMT: NR	13.5	2.2%	NR	35%	NR
Ambrogi (15)	19.5[DB]			NR	3.4%	NR	41%	NR
Patel (16)	23.2[DB]			15	NR	NR	NR	NR
Rena (17)	20			14	5%	62%	NR	9
Tonoli (18)	46.9[DB]			NR	NR	NR	NR	NR
Luckraz (19)	19.5[DB]			NR	8.2%	53%[TMT]	NR	10
Batirel (20)	ITT: 17.2	EPP+AC: 19.6	TMT: 23.9	10	5%	55%	NR	NR
Pagan (21)	20[DB]			NR	4.5%	50%	36.3%	11.5[MV]
Sugarbaker (22)	19[DB]			NR	3.8%	50%	24.5%	9

Cao et al 2012

Own experience

- 3-Institution experience (Vienna, Toronto, Zurich)

Extrapleural Pneumonectomy After Induction Chemotherapy: Perioperative Outcome in 251 Mesothelioma Patients From Three High-Volume Institutions

Table 2. Morbidity and Mortality After Induction Chemotherapy Followed by Extrapleural Pneumonectomy (n = 251)

Morbidity/Mortality	n	(%)
30-day mortality	12	(5)
90-day mortality	21	(8)
Major morbidity	76	(30)
Empyema	35	(14)
BPF	20	(8)
Chylothorax	13	(5)
Patch failure	12	(5)
Bleeding	9	(4)
Pulmonary embolism	9	(4)
ARDS	3	(1)

Lauk, Hoda et al. Ann Thorac Surg 2014

Intracavitary options

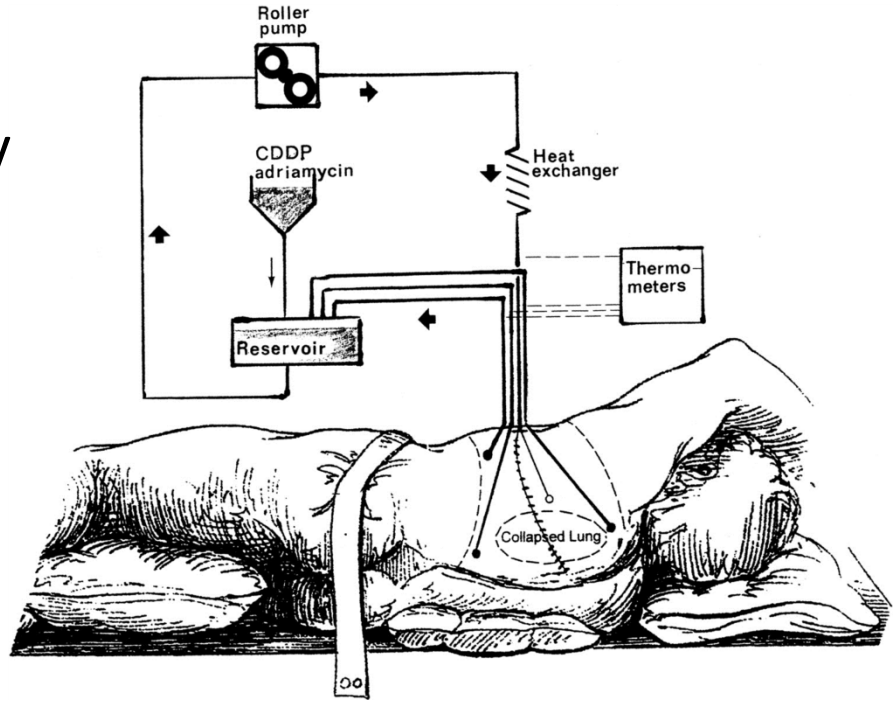
Rationale and procedures

- Methods of loco-regional control (experience in abdominal malignancies)

- In combination with both procedures (EPP, P/D) and neoadjuvant or adjuvant treatment modalities
  - **Hyperthermic intraoperative intracavitary cisplatin perfusion (HIOC)**
  - **Hyperthermic pleural lavage with povidone-iodine (P-I)**
  - **Intraoperative Photodynamic Therapy (PDT)**
  - **Intrapleural Immunotherapy (BCG, IL-2, INF-α, INF-γ)**
  - **Intrapleural Gene Therapy (viral, non-viral vectors)**
  - **Use of Doxorubicin or Paclitaxel as nano – or microparticles**

HITOC

- Platinum-based, in combination with EPP or P/D
- Morbidity (13-85%) – renal toxicity
- Mortality (0-29%)



Rice et al 1994, Richards et al 2006, Tilleman 2009, Opitz 2010, deBree E et al 2002

HITOC – most recent experience

- **Sugarbaker et al, JCTVS 2013:**
  - HIOC effect on interval to recurrence and OS among patients with favorable prognostic factors
  - 103 low risk patients: 72 pts with HIOC vs. 31 without HIOC
  - HIOC pts: significant longer interval to recurrence (27.1 vs 12.8 months) and longer OS (35.3 vs 22.8 months)
  - Note: improved results particularly in subgroups of patients not receiving hemithoracic radiotherapy and pathologic N1 or N2 lymph node mets.

Experience: povidone-iodine lavage

Pleurectomy/Decortication, Hyperthermic Pleural Lavage with Povidone-Iodine Followed by Adjuvant Chemotherapy in Patients with Malignant Pleural Mesothelioma

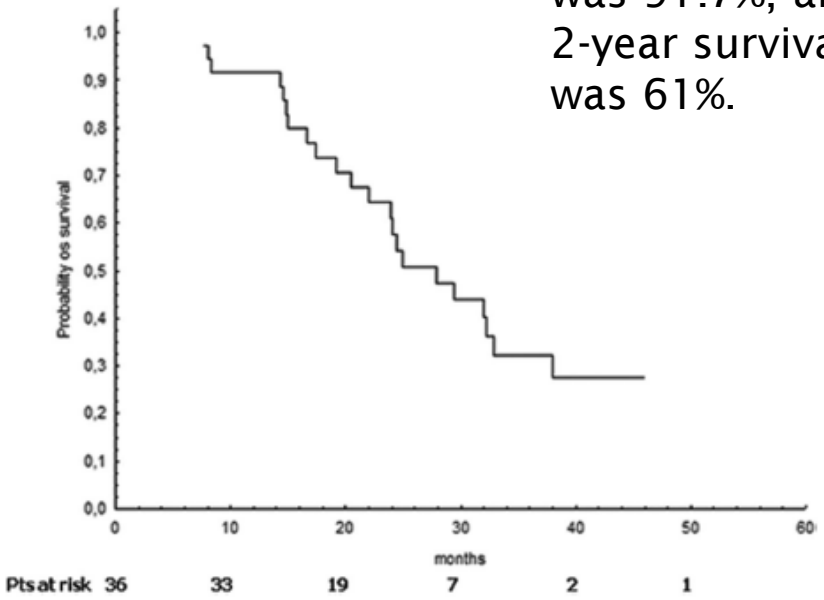
Loïc Lang-Lazdunski, MD, PhD, FRCS, Andrea Bille, MD, Elizabeth Belcher, MRCP, PhD, FRCS, Paul Cane, FRCPath, David Landau, FRCP, Jeremy Steele, PhD, FRCP, Henry Taylor, FRCP, and James Spicer, PhD, FRCP

(*J Thorac Oncol.* 2011;6: 1746–1752)

n=35
Overall median survival: 24 mo
One-year survival was 91.7%, and 2-year survival was 61%.

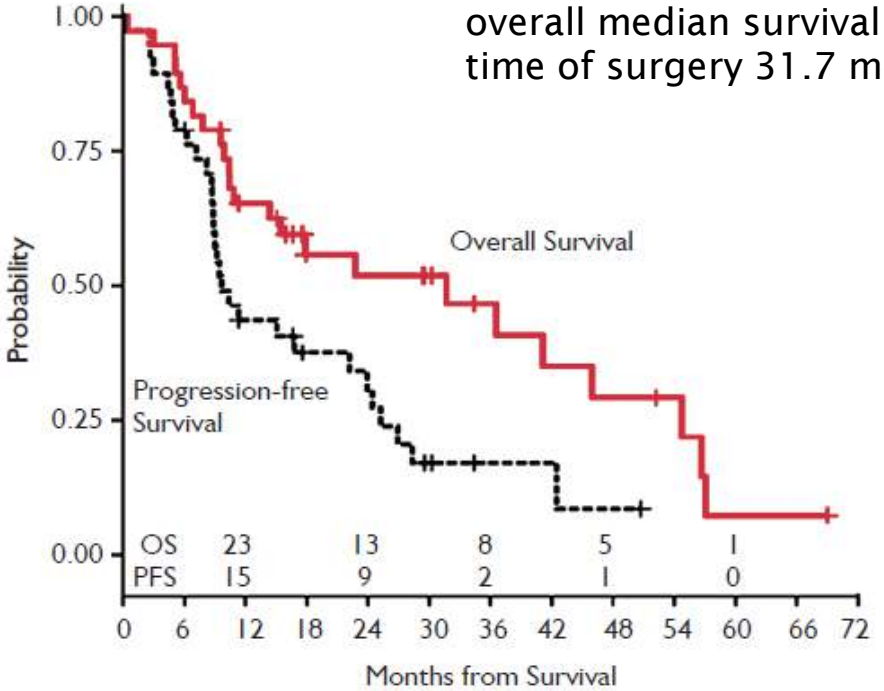
CONCLUSION

In our experience, P/D with hyperthermic pleural lavage with povidone-iodine and adjuvant chemotherapy is a well-tolerated multimodality scheme. It is associated with low morbidity and mortality. This treatment plan could represent an alternative to the classical trimodality regimen involving chemotherapy, EPP, and adjuvant radiotherapy if our results were to be confirmed in larger trials and by other groups. Further studies are warranted to compare this treatment protocol to chemotherapy only and make sure that radical P/D can significantly improve life expectancy. Further treatments are needed to reduce local recurrence after radical P/D.



Photodynamic therapy

N=38
97% Stage III or IV disease
18% nonepithelial histology
overall median survival from the time of surgery 31.7 months.

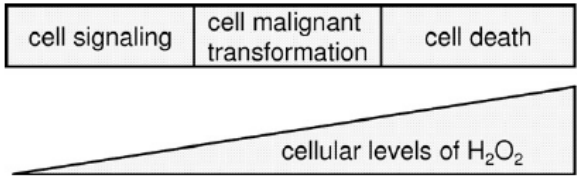


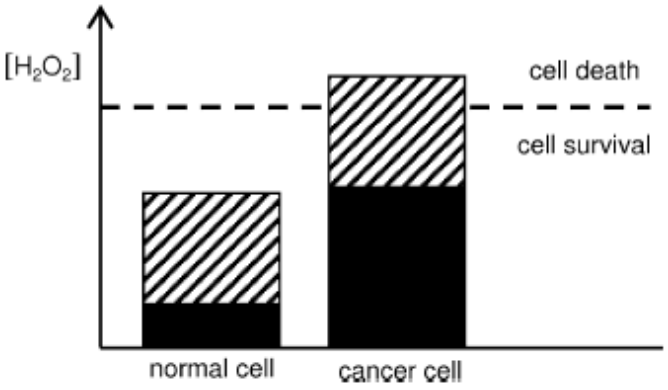
Photodynamic therapy = light based cancer treatment
A photosensitizer is excited by a light source of a defined wavelenght -> production of reactive oxygen species

Friedberg JS. Ann Cardiothorac Surg 2012

Background hydrogen peroxide (H_2O_2)

- Antiseptic, antibacterial properties, leads to release of oxidative O2 radicals (concentration: 1.5 – 6%)
- Dual role in cancer
- Different concentrations - diverse cellular effects
- Increase of cellular levels is important for cancer development
- High levels of H_2O_2 in cancer cells are incompatible with cell survival and lead to suscetibility of these cells to H_2O_2 –induced cell death compared to normal cells
- Unclear which specific concentrations are selectively killing cancer cells
- Every approach which leads to elevation of cellular H_2O_2 levels may induce selective cell death in cancer cells and may be exploited therapeutically



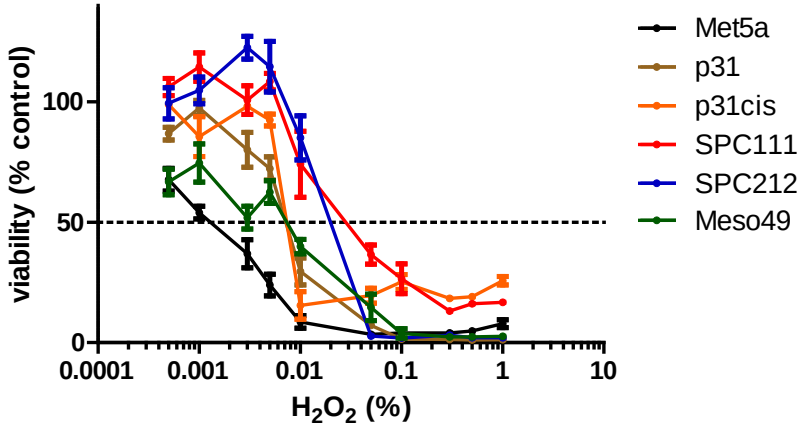


Lopez-Lazaro M et al, 2007

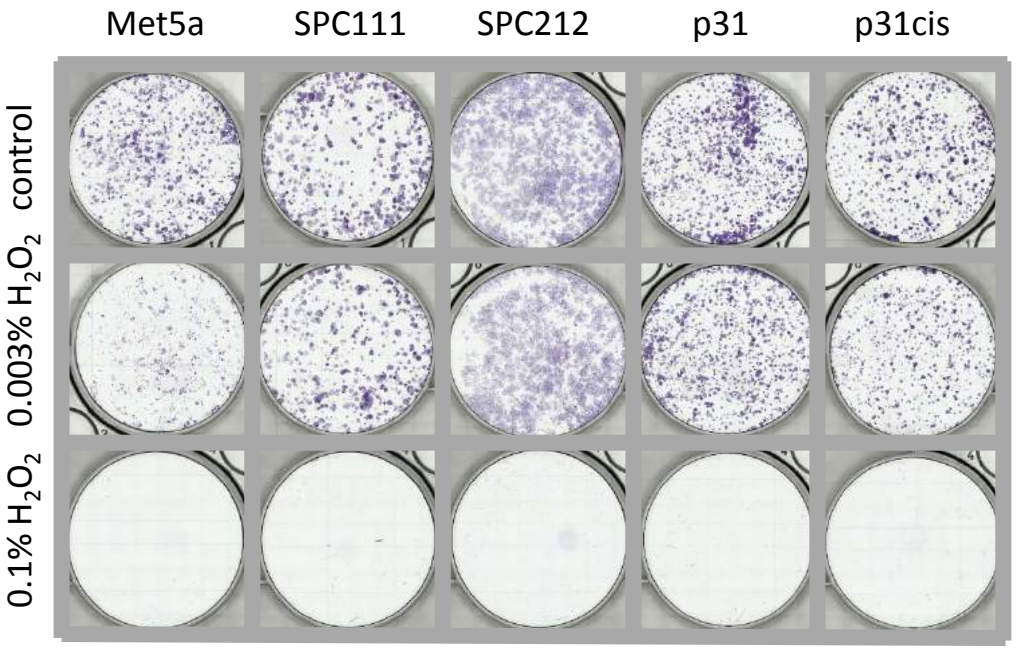
Comparison intracavitary treatment options

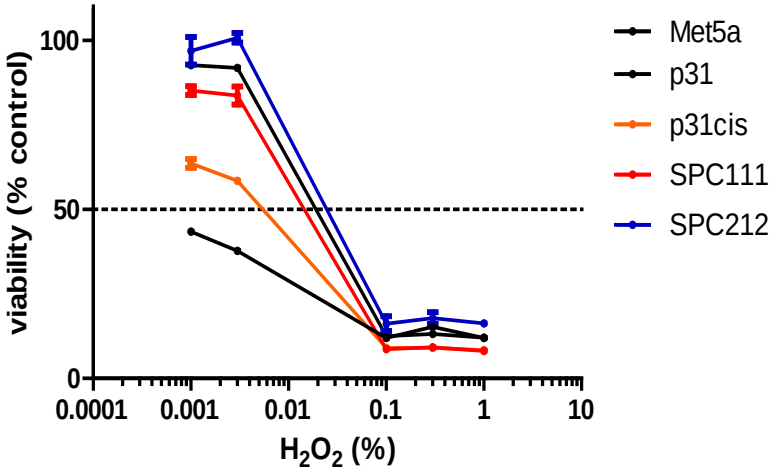
Author	n	Median OS (months)	Treatment	Morbidity (major)	Mortality (30d)
div. auhors (1994-2010)	>100	**9.3-13-2**	EPP, P/D, HIOC	13-85 %	0-29%
Sugarbaker et al (2013)	72	**35.3** No RT N1,N2 mets	EPP,P/D HIOC Neoadj.CHT (14%) Adj.CHT (57%) Adj.RT (57%)	NR Only lenght of stay as surrogate	4%
Lang-Lazdunski et al (2015)	102	**25**	**P**/D, hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy, and systemic treatment	29.4 %	0
Friedberg et al (2012)	38	**31.7**	RP + intra.op, PDT, adjuvant CHT (25), neaodjuvant CHT (4), both (6)	Resp.insuff. (16%) DVT+ PE (24%) chyle leak (5%)	3%
Hoda,Klikovits et al,(in preparation)	30	**31**	Neoadj.CHT, EPP, H2O2, adj.RT	17.6 %	0

H2O2 impars cell proliferation in short- and long-term assays

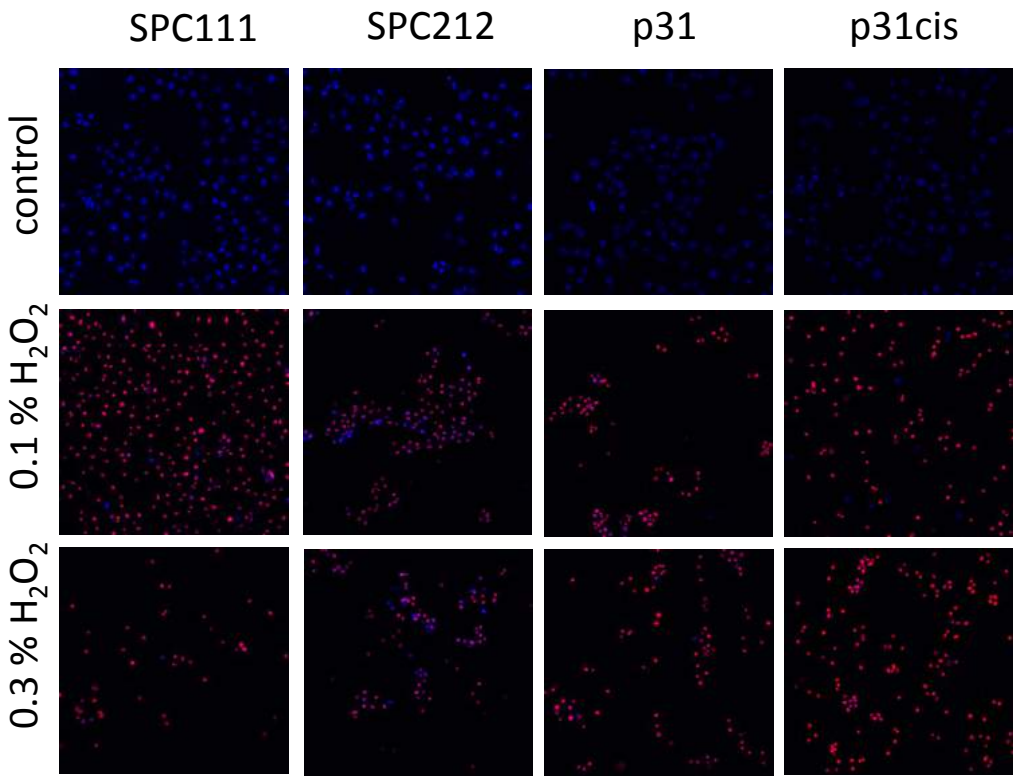


courtesy of Viktoria Laszlo, PhD

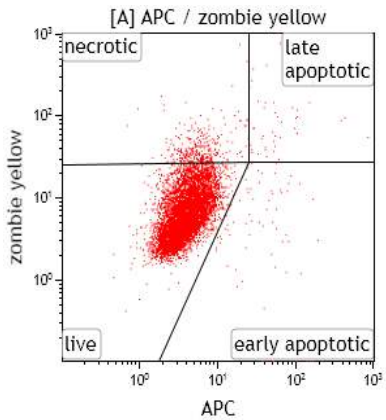




H2O2 leads to cell death - necrosis

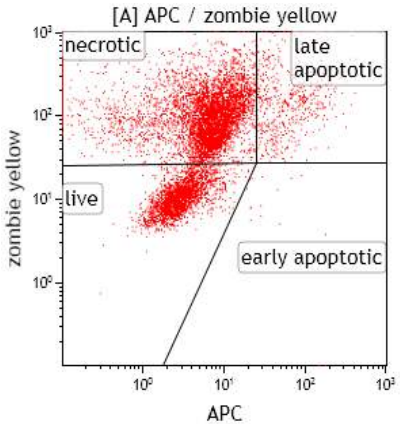


P31
control



Gate	Number	%Gated
All	8.643	100,00
early apoptotic	78	0,90
late apoptotic	44	0,51
live	8.161	94,42
necrotic	360	4,17

P31
0.3% H_2O_2

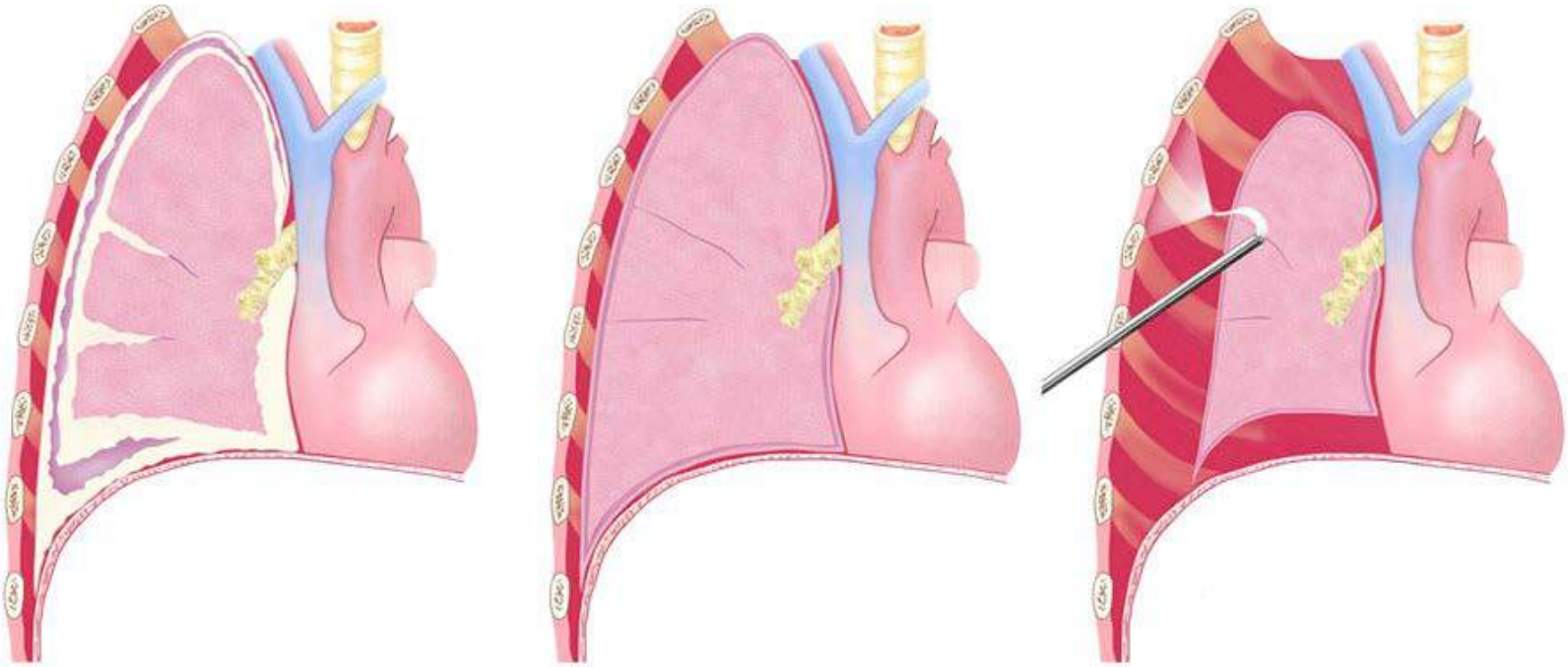


Gate	Number	%Gated
All	10.000	100,00
early apoptotic	16	0,16
late apoptotic	567	5,67
live	2.825	28,25
necrotic	6.592	65,92

courtesy of Viktoria Laszlo, PhD

New approaches on the block

Autologous Fibrin + Cisplatin



InfluenceMESO, PI: Isabelle Opitz,
Walter Weder, University of Zurich

New approaches on the block

A Feasibility Study Evaluating Surgery for Mesothelioma After Radiation Therapy

The "SMART" Approach for Resectable Malignant Pleural Mesothelioma

B. C. John Cho, MD, Ron Feld, MD,† Natasha Leighl, MD,† Isabelle Opitz, MD,‡ Masaki Anraku, MD,‡ Ming-Sound Tsao, MD,§ David M. Hwang, MD,§ Andrew Hope, MD,* and Marc de Perrot, MD‡*

Study Schema

ogically Proven, Previously Untreated
Malignant Pleural Mesothelioma (cT1-3 N0 M0)
Baseline Investigations, Informed Consent

Disease free survival (%)

ion

New approaches on the block

Combining multimodality with immunotherapy

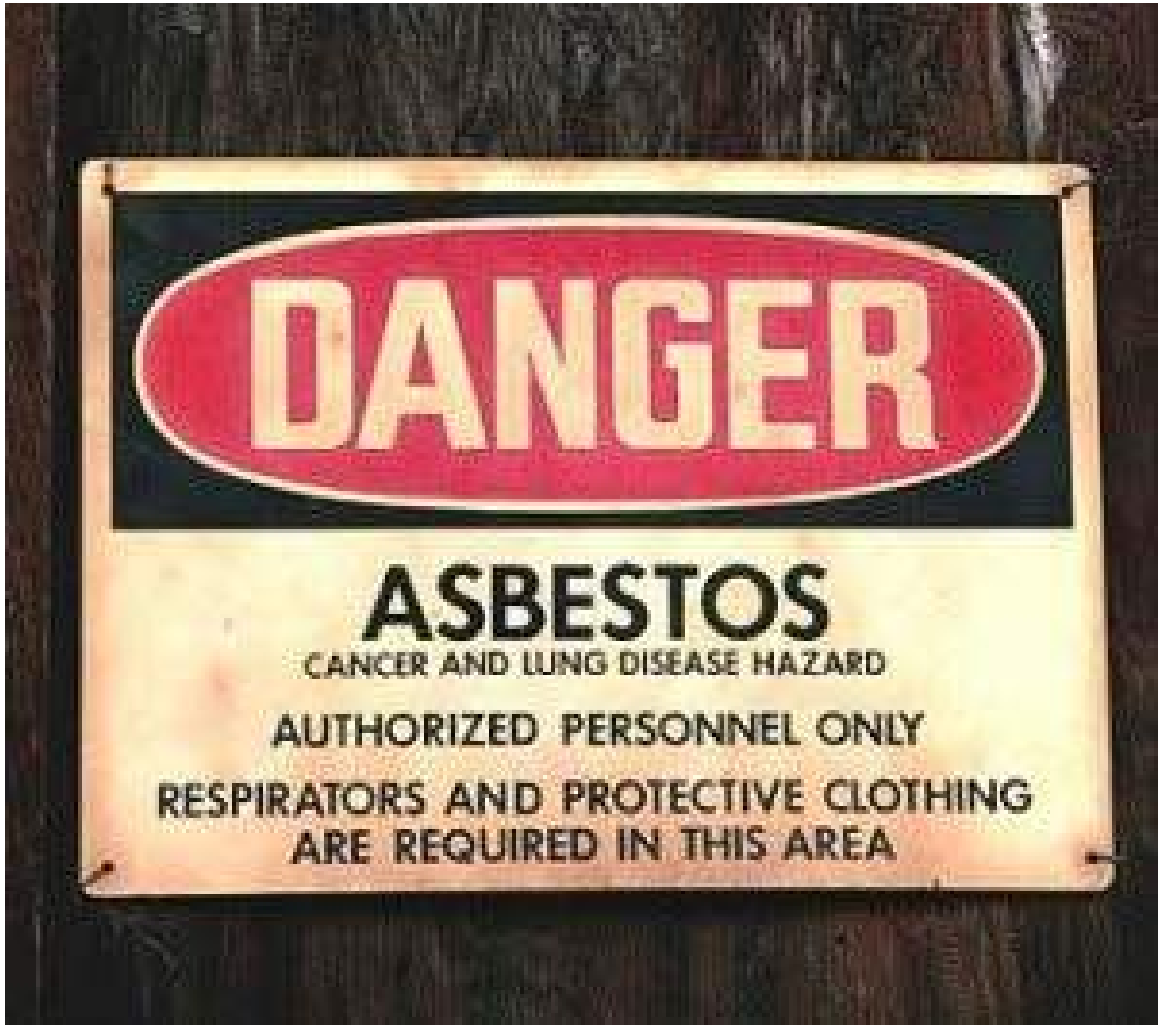
Wong RM et al.
Am J Respir Cell Mol Biol 2014

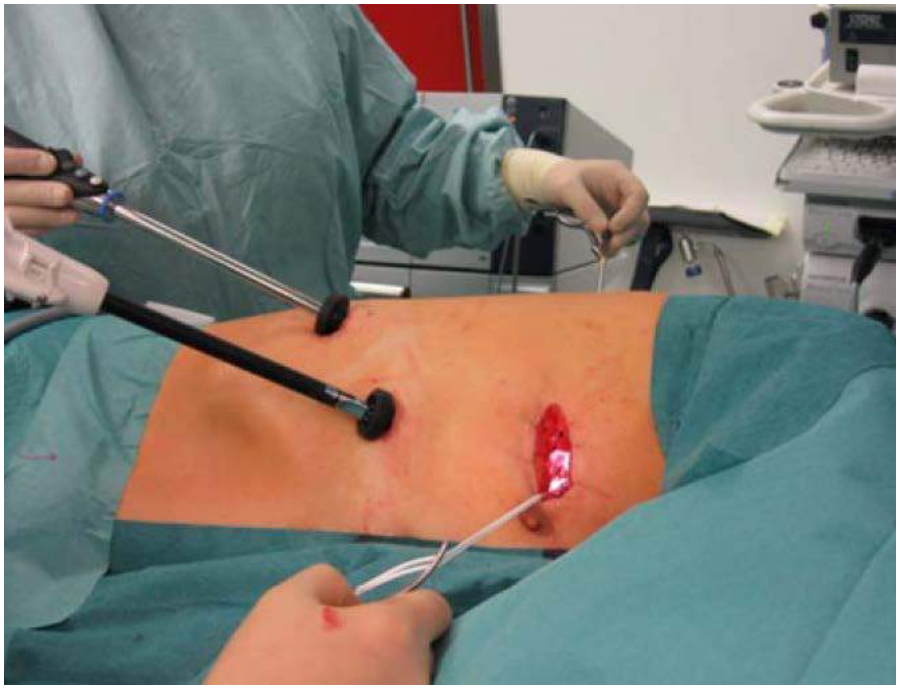
Multimodality regimen	Immunomodulatory/ antitumor effects	Reference
Radiation + immunotherapy		
Fractionated local irradiation + CTLA-4 blockade	Enhanced induction of tumor-specific T lymphocytes; delayed growth of nonirradiated distant tumor	37
Fractionated local irradiation + therapeutic vaccination	Transient systemic MDSC depletion; enhanced tumor-specific T-lymphocyte induction	38
Fractionated local irradiation + adoptive T lymphocyte transfer	Transient systemic Treg depletion; enhanced proliferation of donor T lymphocytes in recipients	39
Chemotherapy + immunotherapy		
Intratumoral Ad–IFN-α immunogene therapy followed by cisplatin + gemcitabine.	Systemic Treg and MDSC depletion; enhanced tumor-specific T-lymphocyte induction; increased intratumor T-lymphocyte infiltration	41
Cyclophosphamide + therapeutic vaccination	Systemic Treg depletion	42
Gemcitabine + CTLA-4 blockade	Systemic and intratumor Treg depletion; induction of protective immunologic memory	43
Surgical tumor reduction + immunotherapy		
Preoperative intratumoral Ad–IFN-β immunogene therapy + complete resection	Increased intratumor T-lymphocyte infiltration; induction of protective immunologic memory	44
Complete resection + postoperative therapeutic vaccination	Increased intratumor T-lymphocyte infiltration; delayed growth of recurrent and unresected distant tumor	45
Partial resection + postoperative gemcitabine + anti-CD40 agonist immunotherapy	Induction of protective immunologic memory	46
Cryoablation + CTLA-4 blockade	Increased intratumor Tlymphocyte infiltration; induction of protective immunologic memory	47

Summary

Diagnosis	**VATS & open biopsy**
Palliation and control of symptoms	**Talc -Pleurodesis**
Staging	**Mediastinoscopy, VATS, Laparascopy**
Cyto-reductive procedures **„Curative intent“**	**Pleurectomy / Decortication**
	Extrapleural Pneumonectomy within Multi-Modality-Treatment ± HIOC
Experimental therapy approaches	**Other Intracavitary therapies** **Neoadjuvant RT, Comb. IT**

Asbestos Awareness





Thank you for your kind attention!