Postgraduaat medische oncologie

WORK-UP, STAGING AND SURGICAL TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

November 21; 2020

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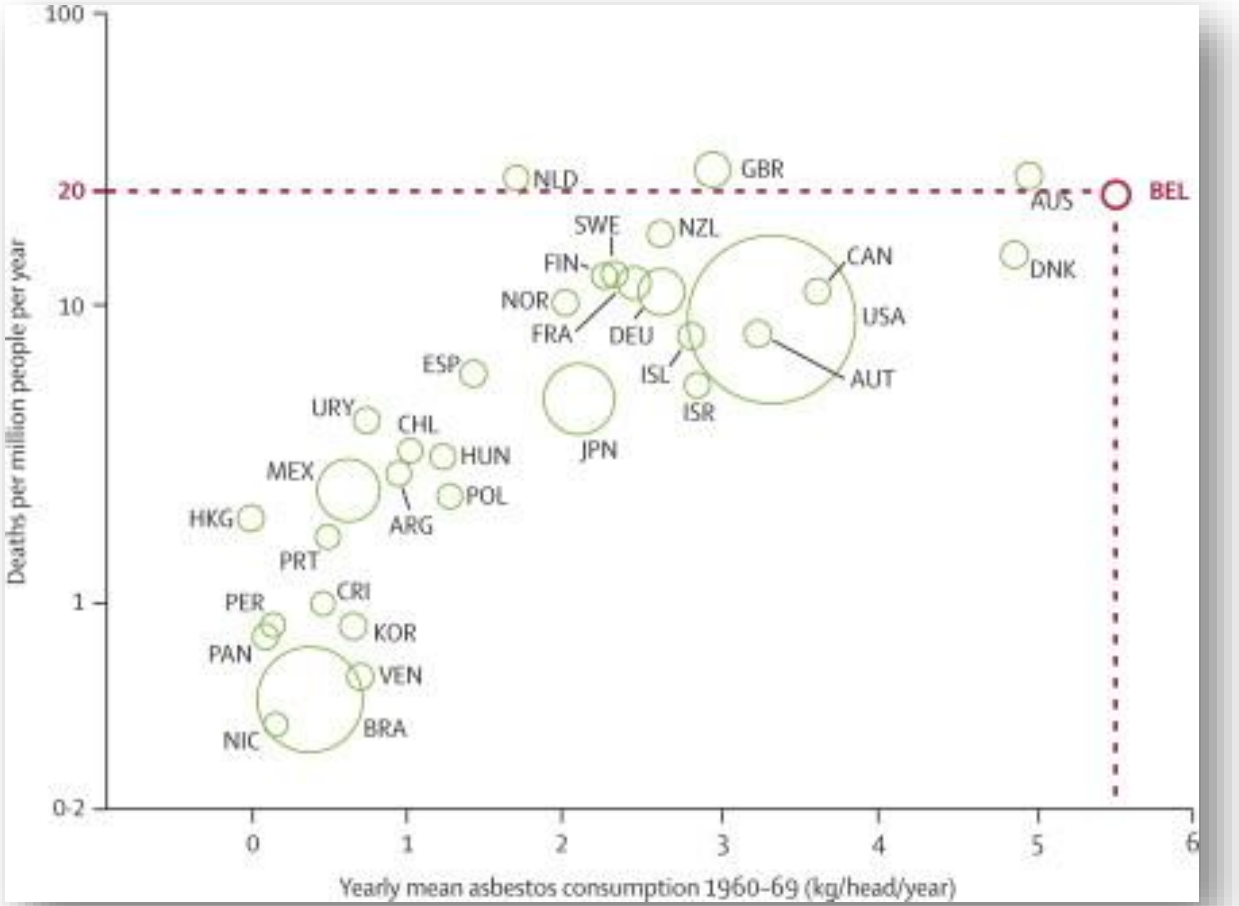
Introduction

- Introduction
- Place for surgery?
- Staging
- UZLeuven work-up, staging and treatment protocol
- EPP and ePD
- Leuven experience

The Belgian issue



Nawrot, Lancet 2007

Treatment

- Low incidence → no golden standard treatment
- Multiple treatment options:
  - Chemotherapy
  - Radiotherapy
  - Immunotherapy
  - Surgery
  - ……..

Multi (TRI) modality treatment

- EPP - chemotherapy – radiotherapy

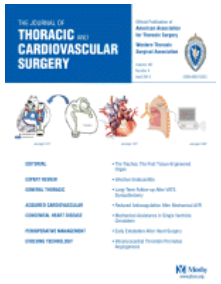
  (different schemes) (30-40-14Gy)

N=176	2 year-	5 year-survival	
General	38%	15%	
Epithelial, R0, N0	68%	46%	median 51 mo
Sarcomatous, mixed:	20%	0%	

BUT:

Low tolerance to adjuvant treatment

Recurrences



Sugarbaker, J Thorac Cardiovasc Surg 1999

Multimodality treatment

- Chemotherapy-EPP-radiotherapy

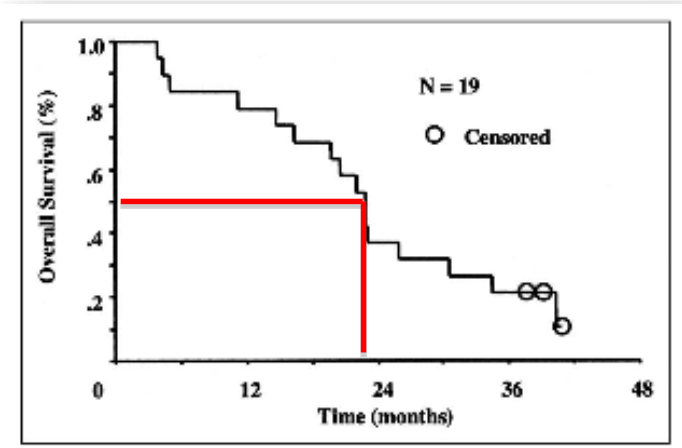
  (cisplatin-gemcitabin) (30-20 Gy)

n=72 1999-2003 T1-T3, N0-2,M0, all types

Response rate: 32%

Postoperative mortality: 6,25%

Overall median survival: 23 months



Weder, J Clin Oncol 2004

MARS trial

Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study

*Tom Treasure, Loic Lang-Lazdunski, David Waller, Judith M Bliss, Carol Tan, James Entwisle, Michael Snee, Mary O'Brien, Gill Thomas, Suresh Senan, Ken O'Byrne, Lucy S Kilburn, James Spicer, David Landau, John Edwards, Gill Coombes, Liz Darlison, Julian Peto, for the MARS trialists**

Interpretation In view of the high morbidity associated with EPP in this trial and in other non-randomised studies a larger study is not feasible. These data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.

Treasure, Lancet Oncol 2011

BUT….

- Feasibility study
- No “intention to treat” analysis
  - 42% of patients were randomized
- Limited number of patients (EPP 16 patients)
- Chemotherapy non standardized
  - Type, duration, interval, …
- Non-surgical arm were operated (N=3)
- Mortality EPP: 18%?

Weder, Lancet Oncol 2011

Place for surgery?

- Introduction
- Place for surgery?
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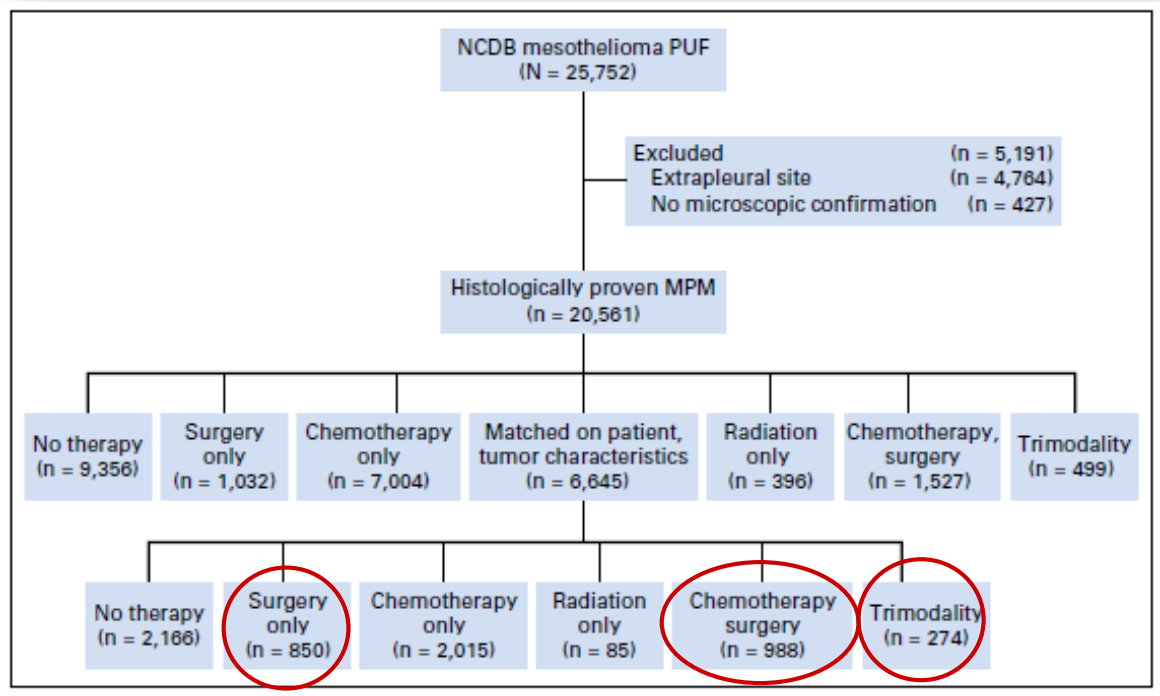
Is surgery necessary?

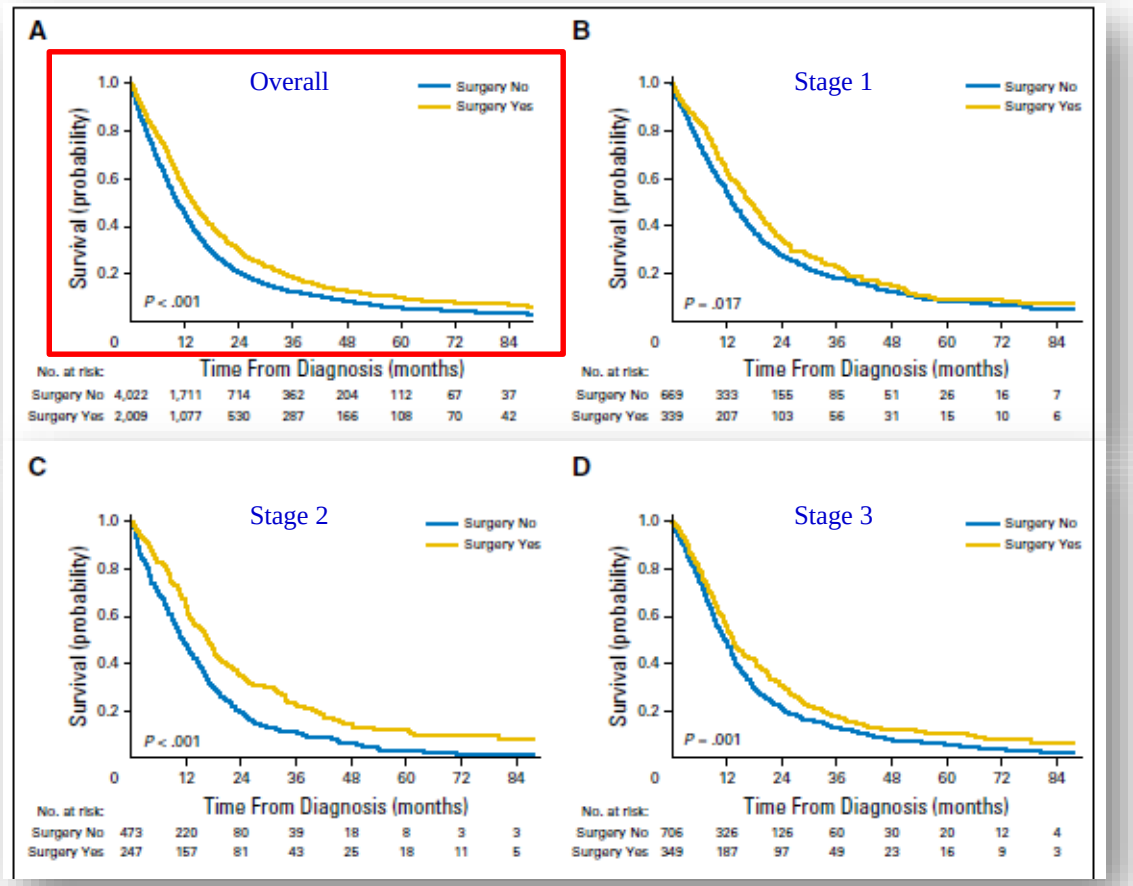
- National Cancer Database (ACS) 2004-2014
- 1:2 match (surgical vs non-surgical)



Surgery 2112 pts

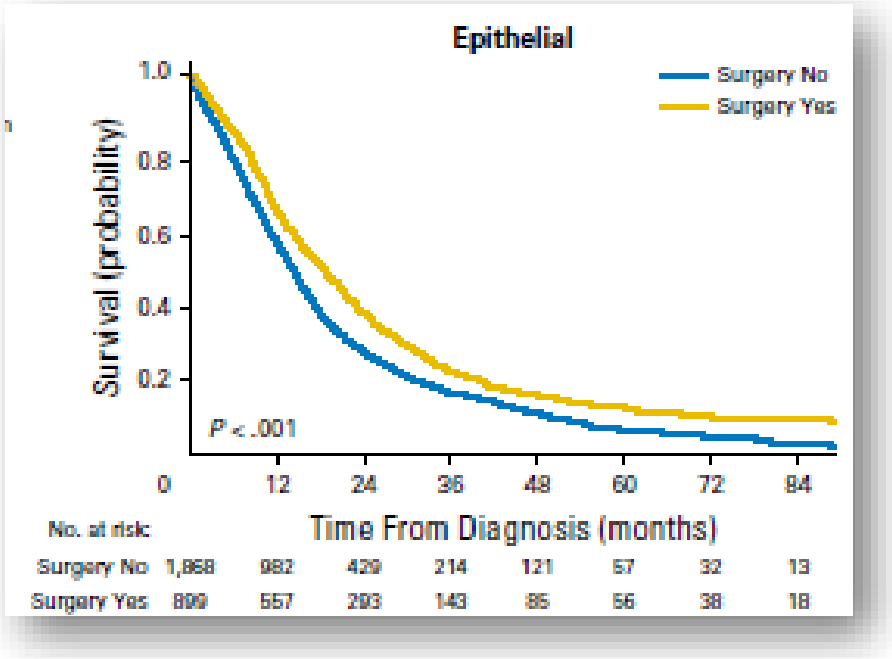
Nelson, J Clin Oncol 2017

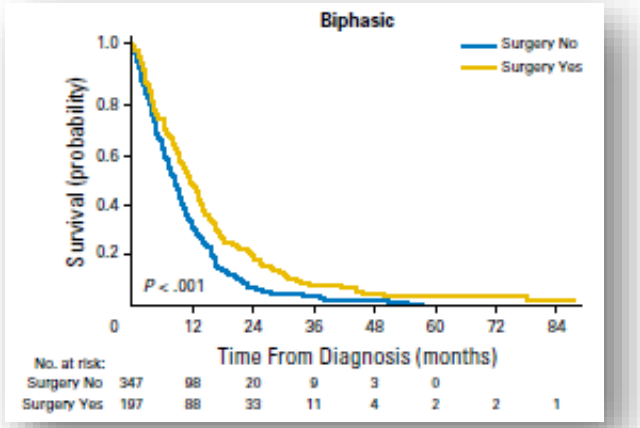
Impact surgery on survival

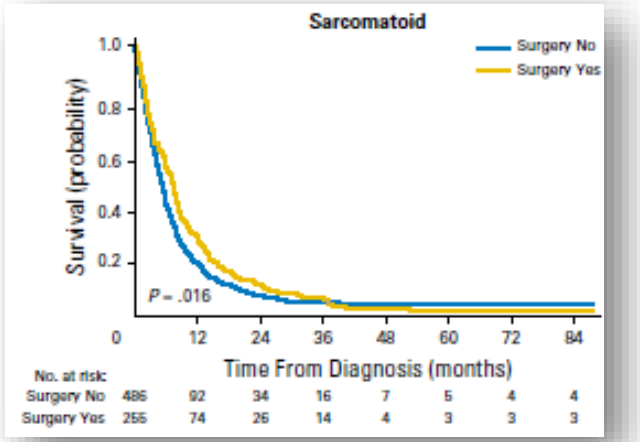


Nelson, J Clin Oncol 2017

Impact of MPM type





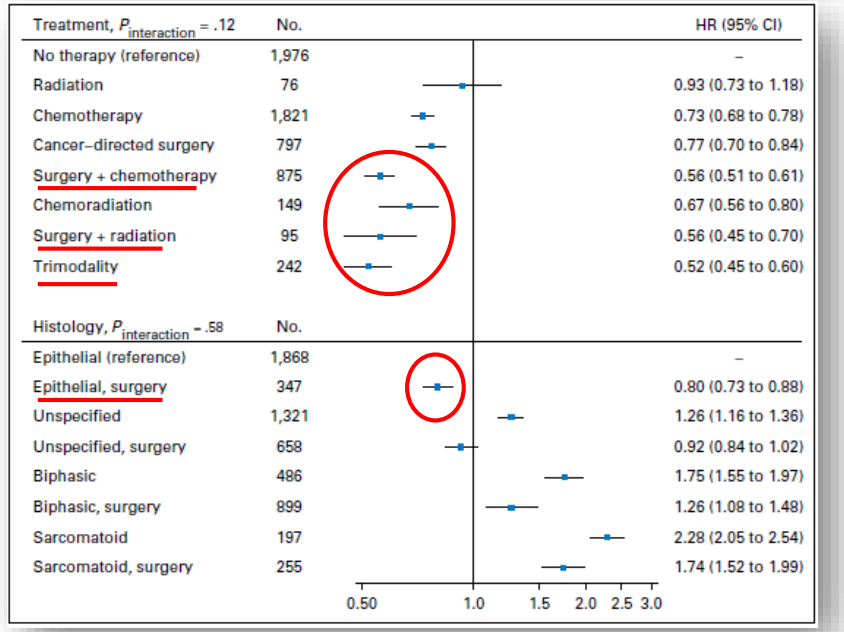


Nelson, J Clin Oncol 2017

Impact multimodality treatment

Table 3. Median Survival, Stratified By Cancer-Directed Surgery and Trimodality Therapy

Therapy	Overall	Stage I	Stage II	Stage III	Stage IV	Epithelial	Biphasic	Sarcomatoid
No surgery	10.45	13.24	11.24	11.73	8.31	13.70	8.11	5.06
Cancer-directed surgery	13.86	17.15	16.76	13.34	11.53	18.17	11.24	7.26
No trimodality	11.17	14.32	12.68	11.79	9.20	14.46	8.71	5.59
Trimodality	20.8	23.56	18.86	21.42	17.71	23.36	13.86	10.81



Nelson, J Clin Oncol 2017

Staging

- Introduction
- Place for surgery?
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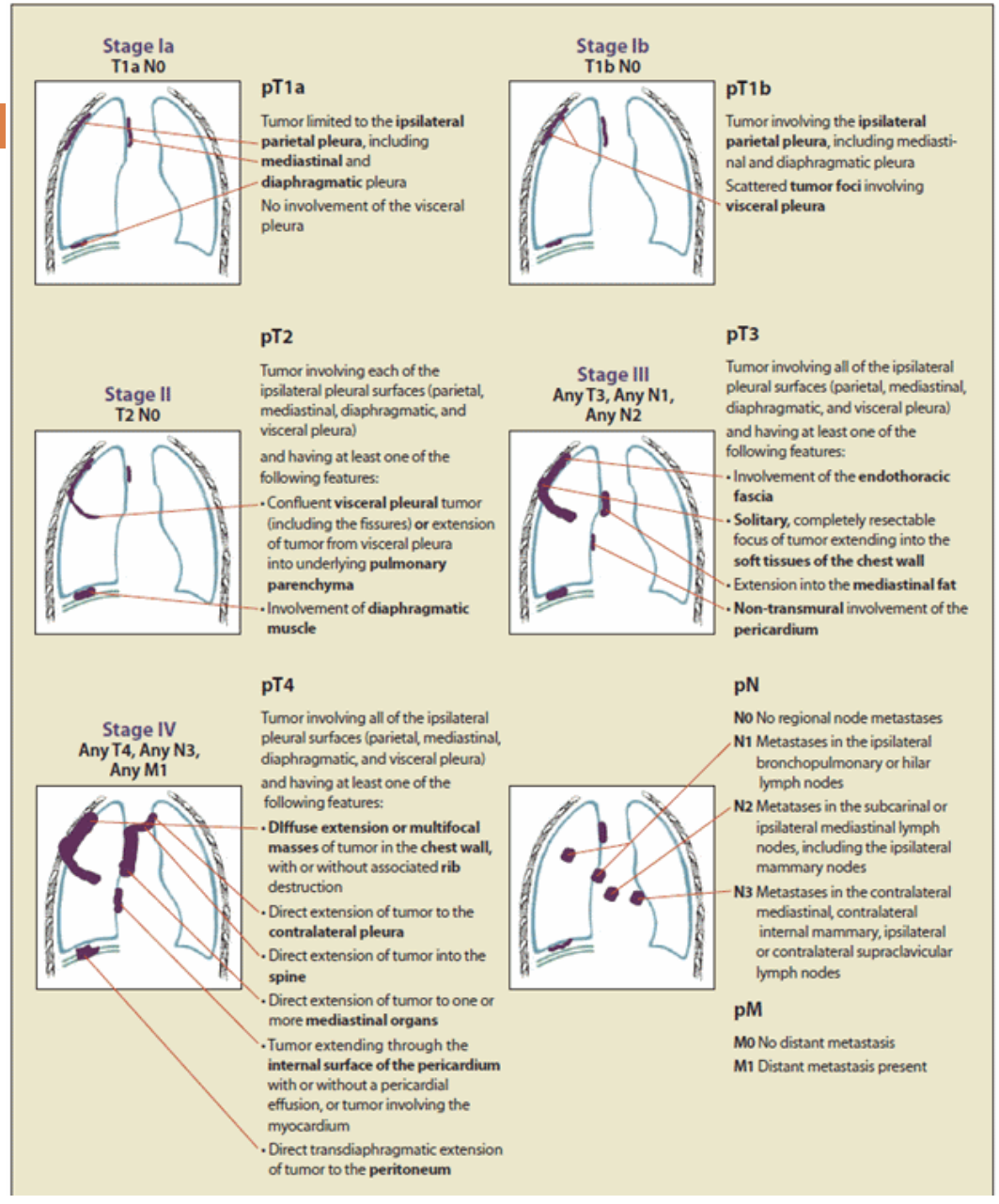
Importance of staging

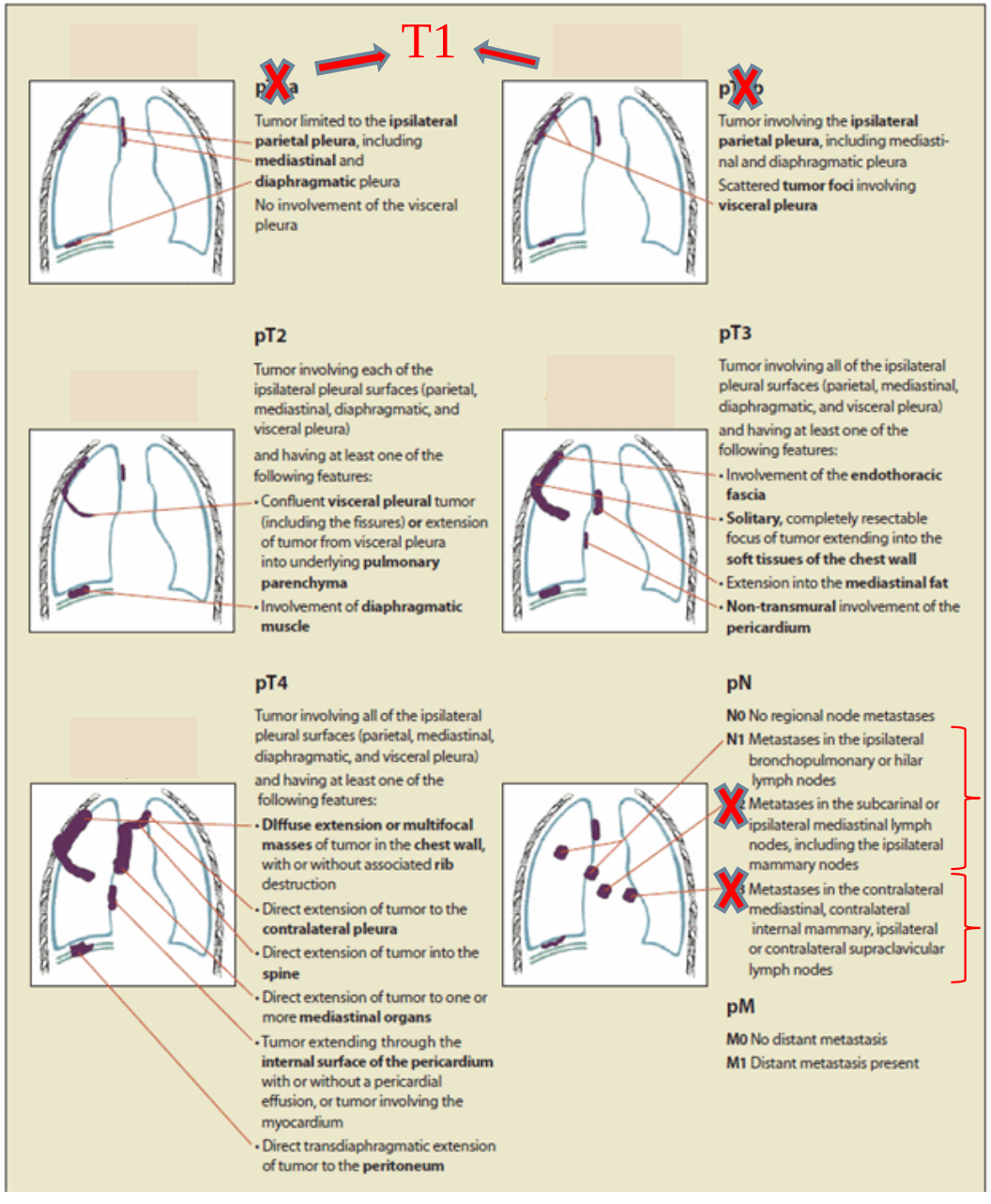
- Accurate staging is essential:
  - Define best treatment option
  - Evaluate response to treatment
    - Modified RECIST criteria
  - Accurate selection of patients

TNM 7



TNM 8

Trans Lung Cancer Res 2018; 7: 543



Stages

Table 4 Comparison of stage groupings as defined by the seventh and eighth edition of the TNM classification

Stage	Stage grouping for the seventh edition			Stage grouping for the eighth edition		
	T	N	M	T	N	M
I						
IA	T1a	N0	M0	T1	N0	M0
IB	T1b	N0	M0	T2,3	N0	M0
II	T2	N0	M0	T1,2	N1	M0
III						
IIIA	T1,2	N1,2	M0	T3	N1	M0
IIIB	T3	N0–2	M0	T1–3	N2	M0
IV	T4	Any N	M0	T4	N0–2	M0
	Any T	N3	M0			
	Any T	Any N	M1	Any T	Any N	M1

SURGERY

UZLeuven work-up, staging and treatment protocol

- Introduction
- Place for surgery?
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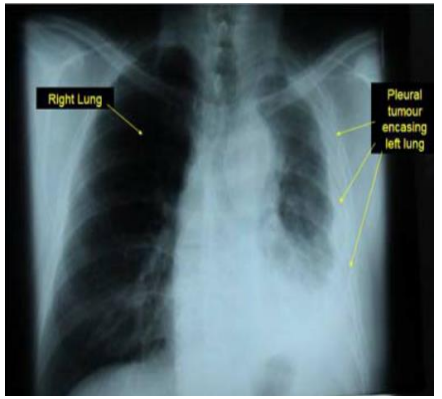
Pre-op evaluation: ERS/ESTS/EACTS/ESTRO guidelines

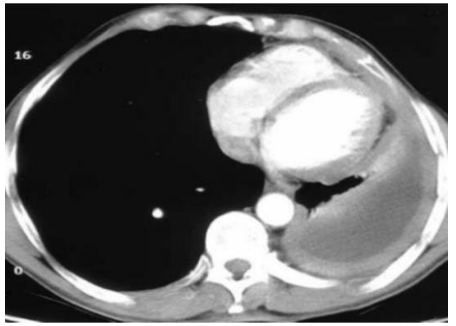
Scherpereel, Eur Respir J 2020

- Before any type of treatment

- **X ray**: unilateral, concentric pleural thickening



- **Chest CT/PET-CT:** Concentric pleural thickening, pleural effusion



Biopsy

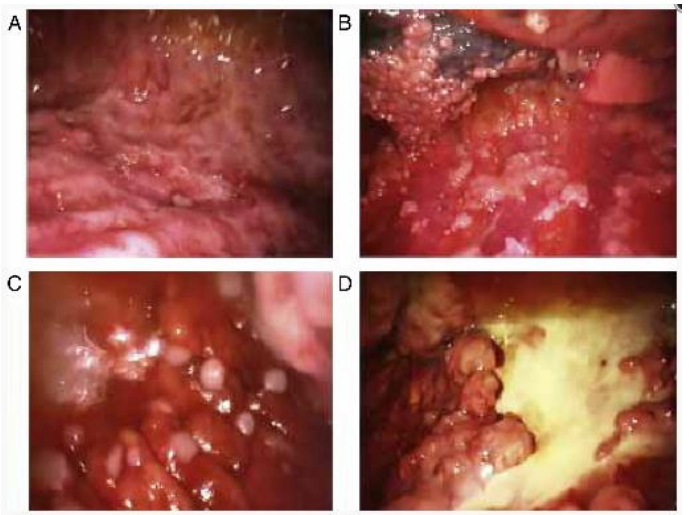
- Needle biopsy (CT-guided)

- VATS biopsy + TALCAGE

  CAVE/ Local soiling

=> UNIPORTAL (5th/6th IC space)

Decreases morbidity and renders ePD more feasible



Pre-op evaluation: ERS/ESTS/EACTS/ESTRO guidelines

Scherpereel, Eur Respir J 2020

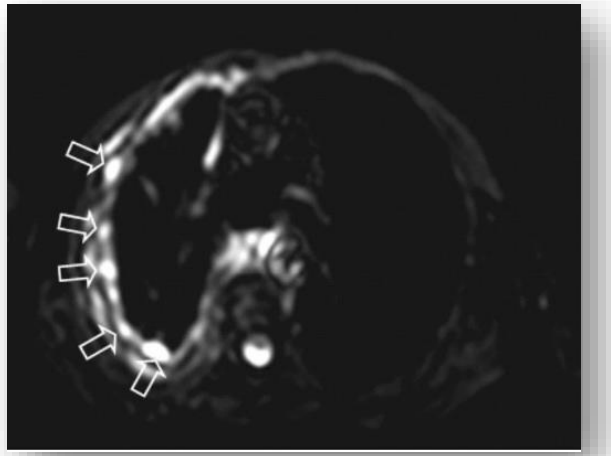
- If suitable for surgery/chemotherapy

- **PET-CT**: unilateral, concentric pleural thickening

! Low sensitivity for stage N1(38%) and T4 (67%)

! If talc pleurodesis => sensitivity decreases

- **MRI:** Concentric pleural thickening, pleural effusion



Superior for disease margins (vessels, diaphragm, multifocal chest wall invasion)

- **Brain CT/MRI**: excluding metastases

Role of PET-MRI ?? => research

Coolen, Radiology 2012

Functional evaluation (after talcage)

- Spirometry
- Cyclo-ergometry
- Cardiac ultrasound (+ carotic vessels)
- V/Q scintigraphy
- Age? (estimate biological age); no strict limit

First MOC

Scherpereel, Eur Respir J 2020

Epithelioid
Biphasic

Sarcomatoid

SURGERY

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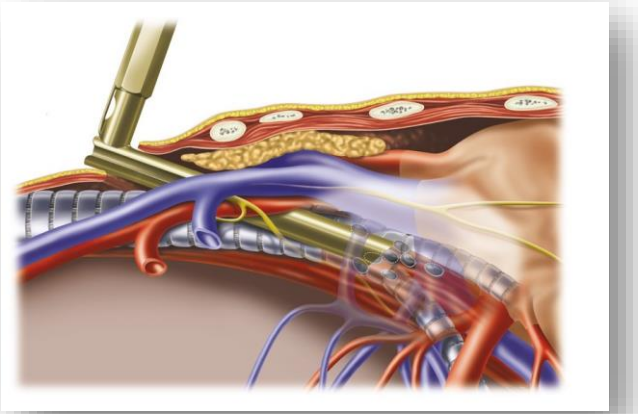
IV	T4	Any N	M0	T4	N0–2	M0
	Any T	N3	M0			
	Any T	Any N	M1	Any T	Any N	M1

Invasive surgical staging

- **Videomediastinoscopy** n=82
  - Downstaging 3.66% (n=3)
  - Upstaging 10.96% (n=9)
- **Laparoscopy** n=74
  - Invasion 2.70% (n=2)
  - M^+ perit 2.70% (n=2)

Δ of treatment in19.28% (n=16)

→ 3 surgical + 13 non-surgical



Nafteux, Ceulemans
unpublished data

Invasive surgical staging: NEGATIVE

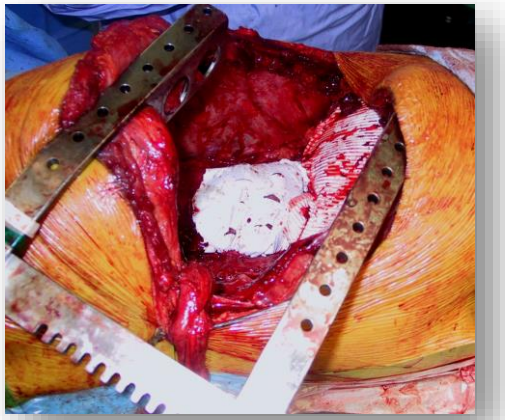
- **Bi-modal therapy**
  - **Induction chemotherapy**

Cisplatin / Pemetrexed; 3 cycles/3weeks

PET-CT / MRI (modified RECIST, volumetry)

SECOND MOC

  - **Surgery**
    - **EPP / extended PD**



EPP versus ePD technique

- Introduction
- Place for surgery?
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Surgical technique

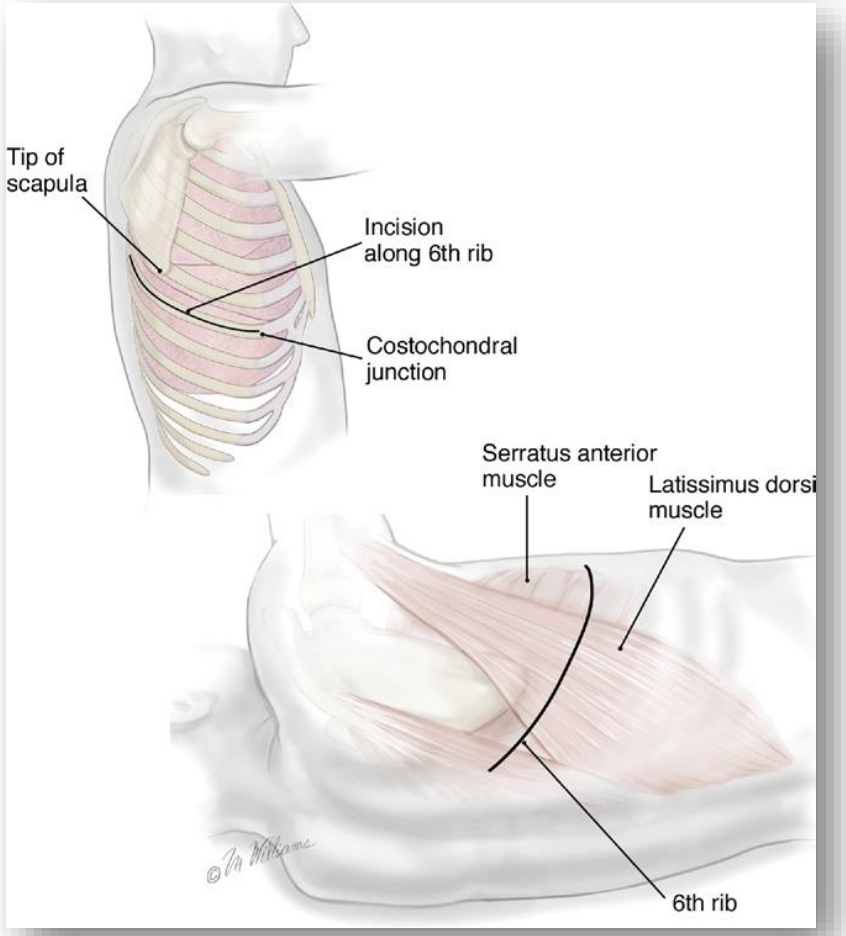
- Extrapleural pneumonectomy (EPP)
  - Pneumonectomy
  - Diaphragmatic/pericardial resection

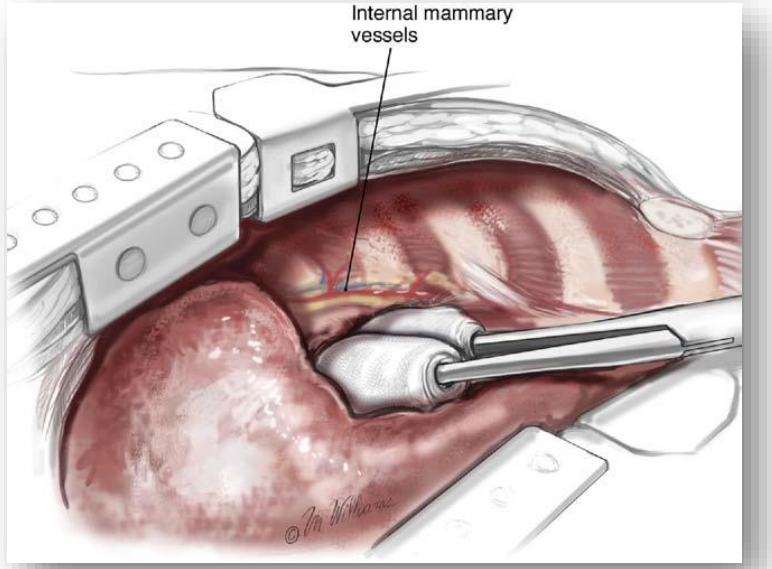
- (extended) pleurectomy/decortication (e P/D)
  - Lung-savind
  - Diaphragmatic/pericardial resection

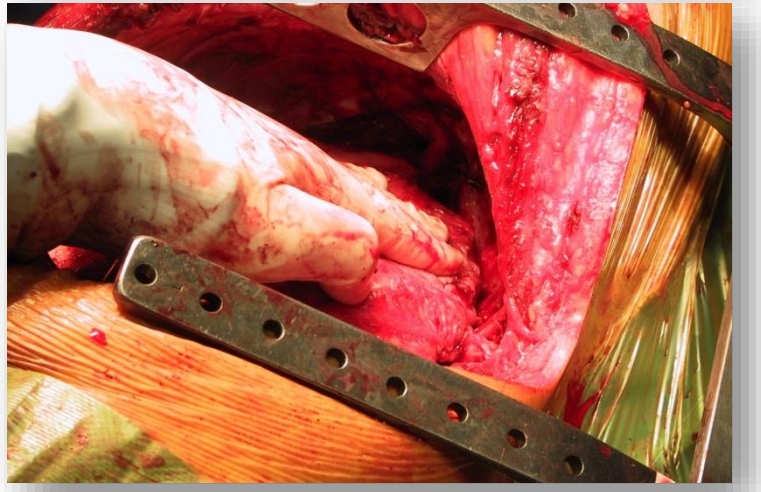
INTRA-OP Decision

e P/D additional value for those with functional limitation

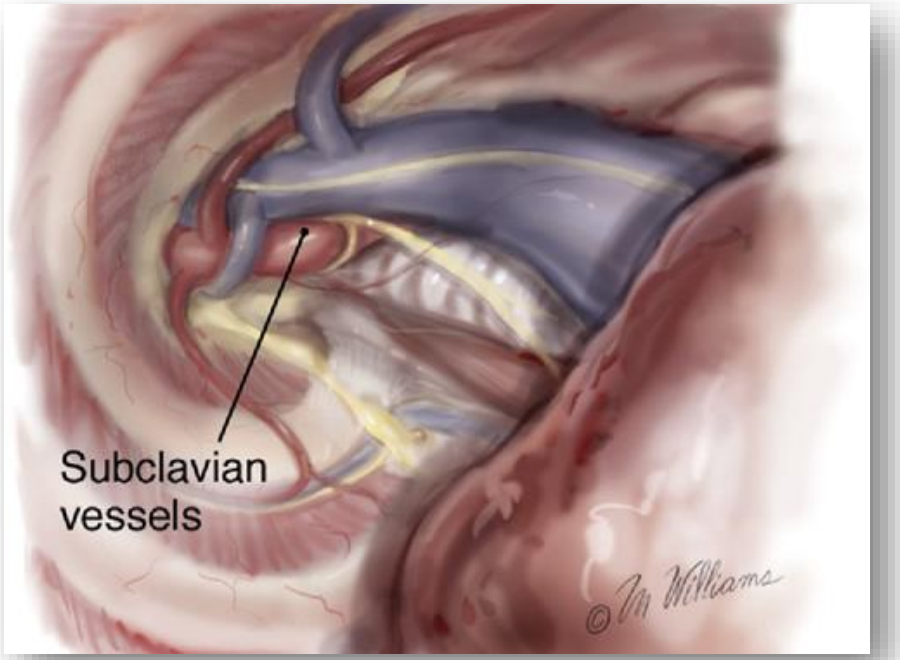
First step: extrapleural dissection

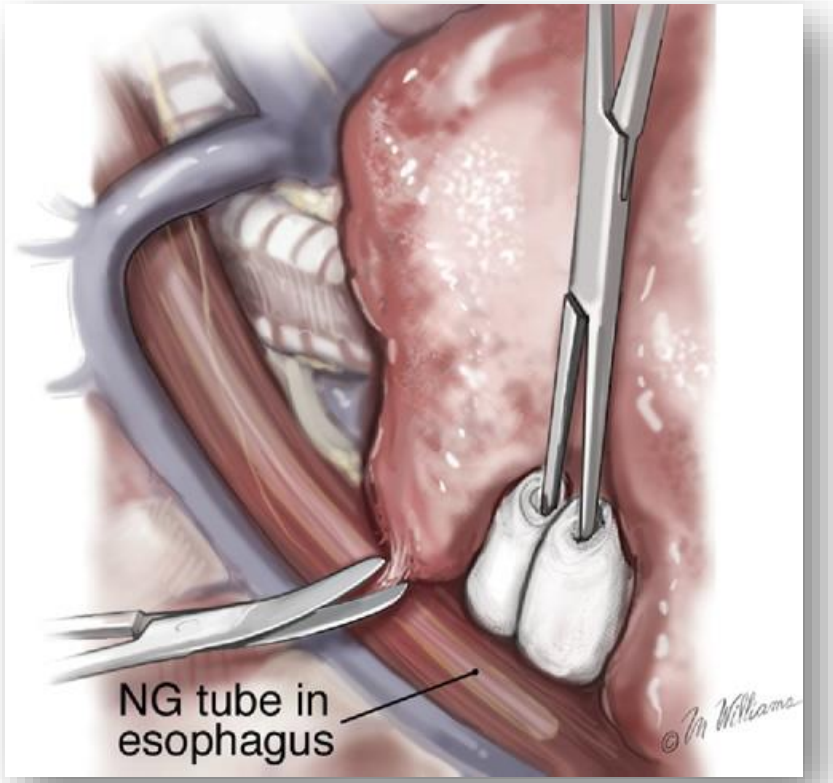






EPP-eP/D: extrapleural dissection





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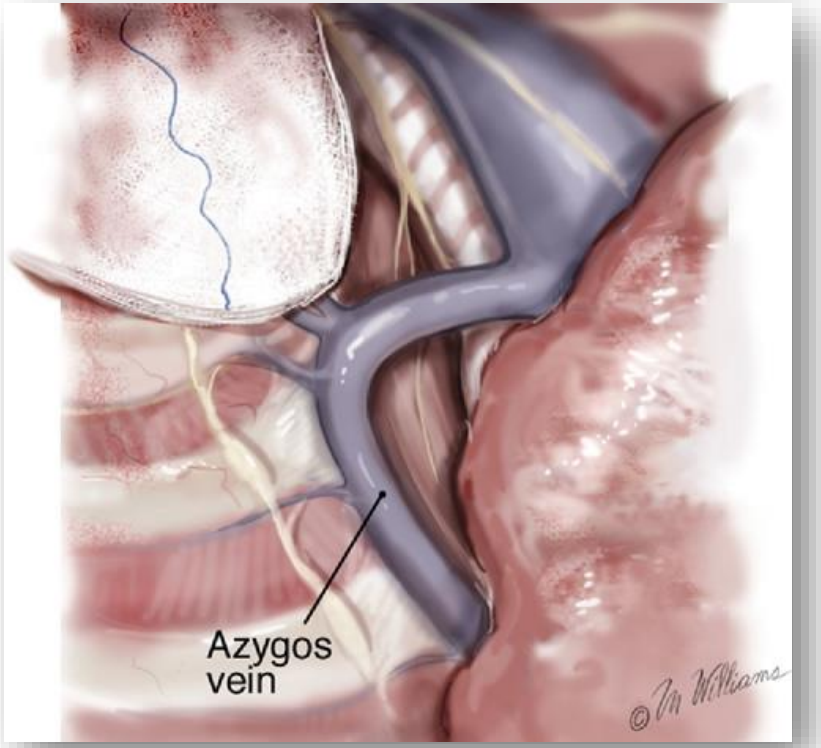
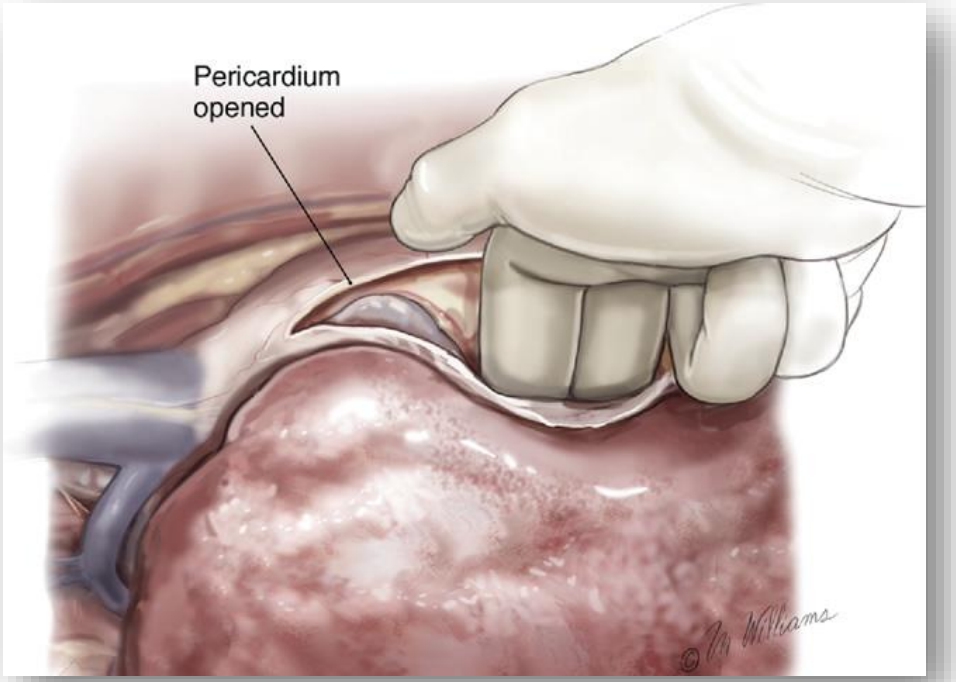
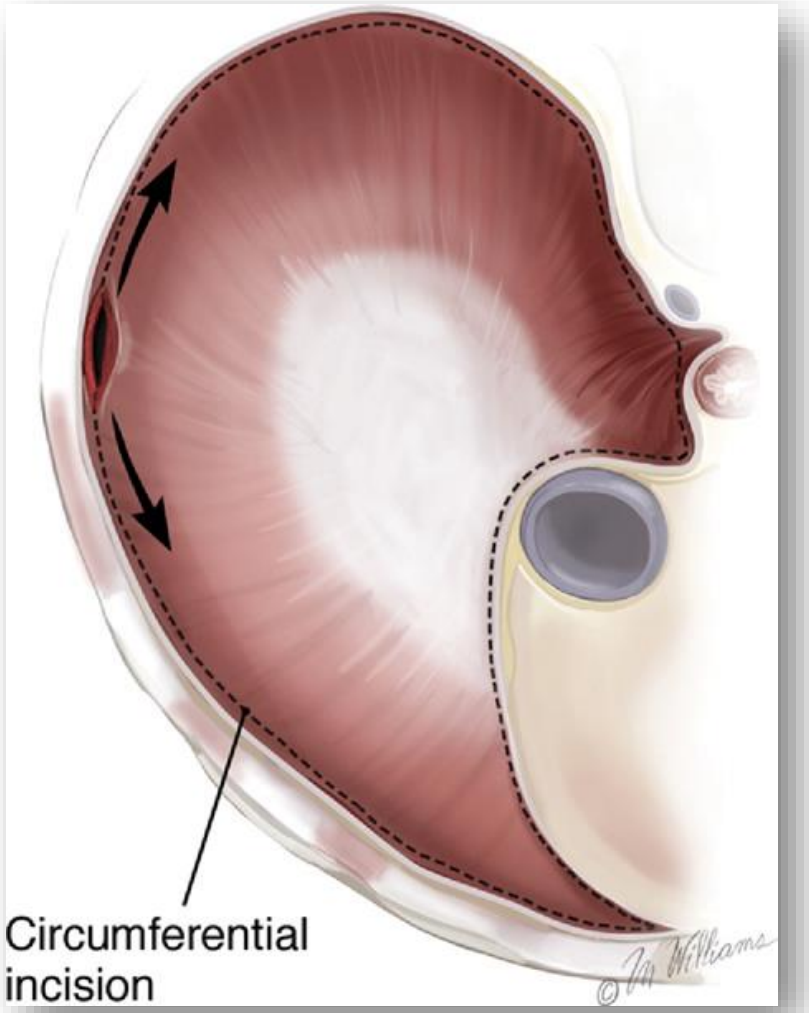
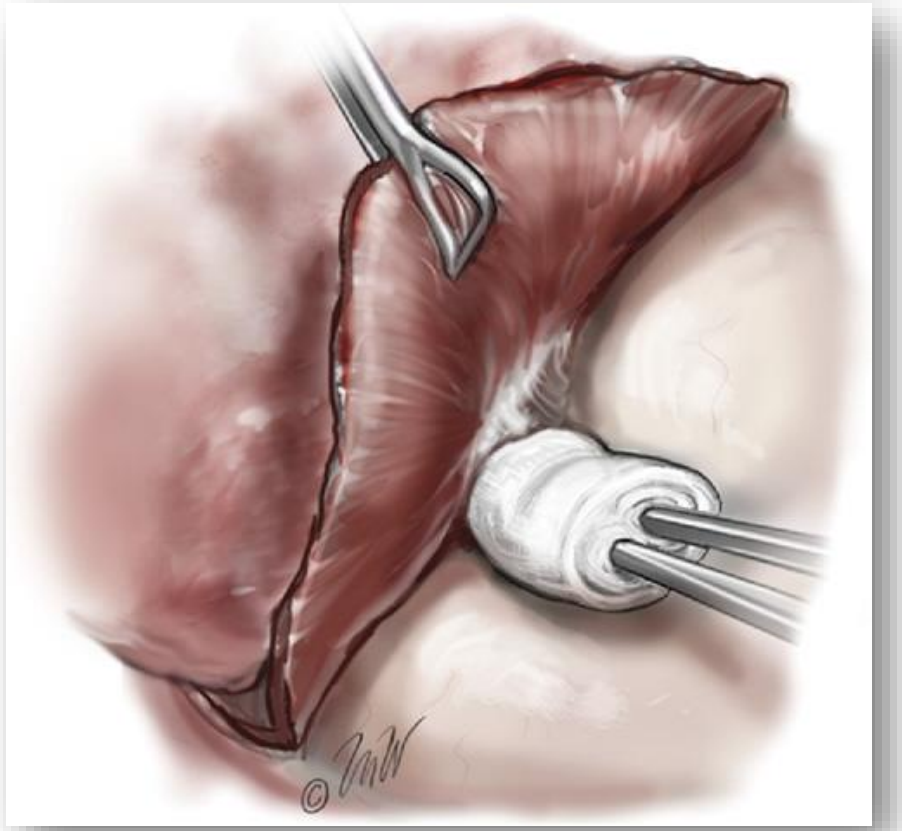


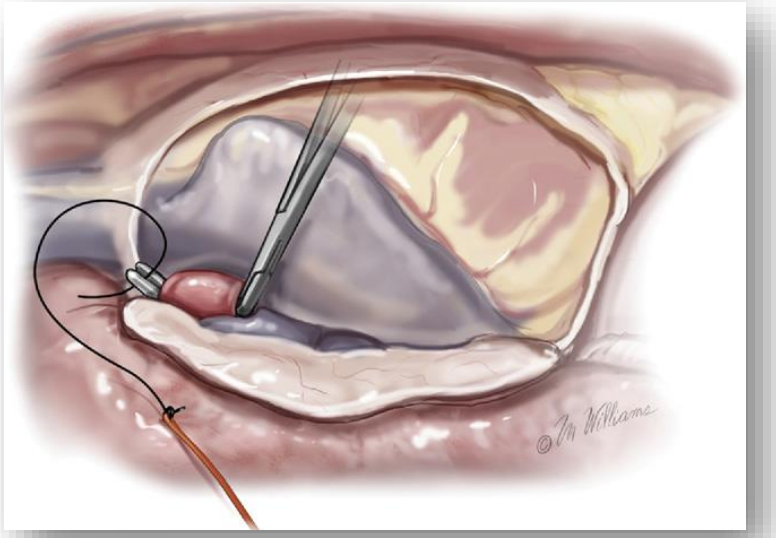


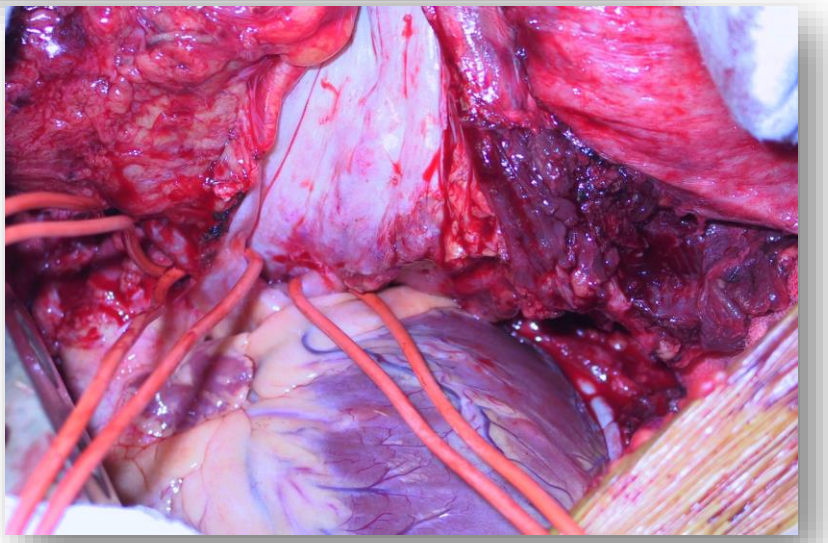
EPP-ePD: diaphragma resection

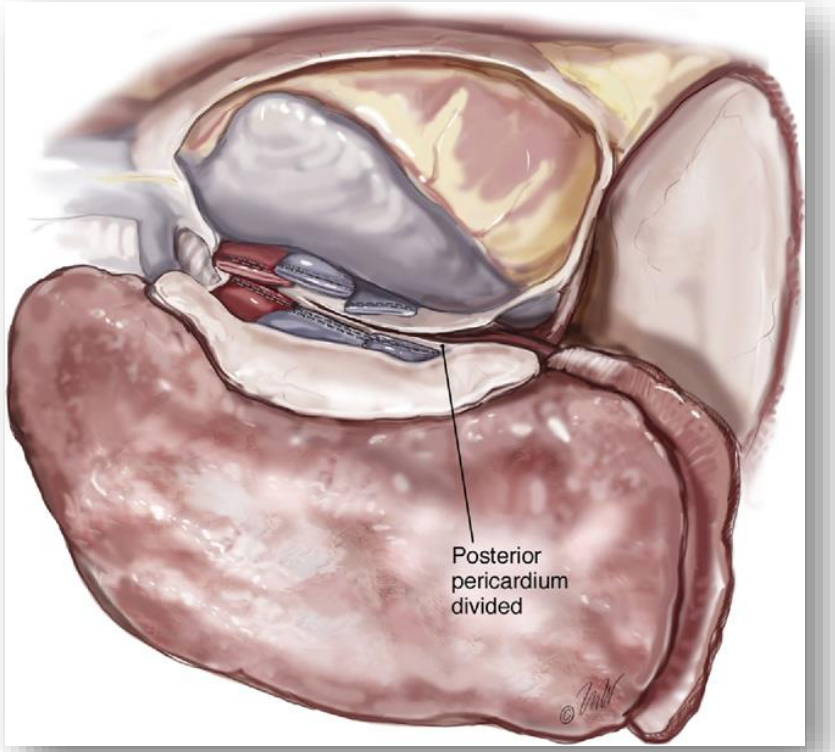




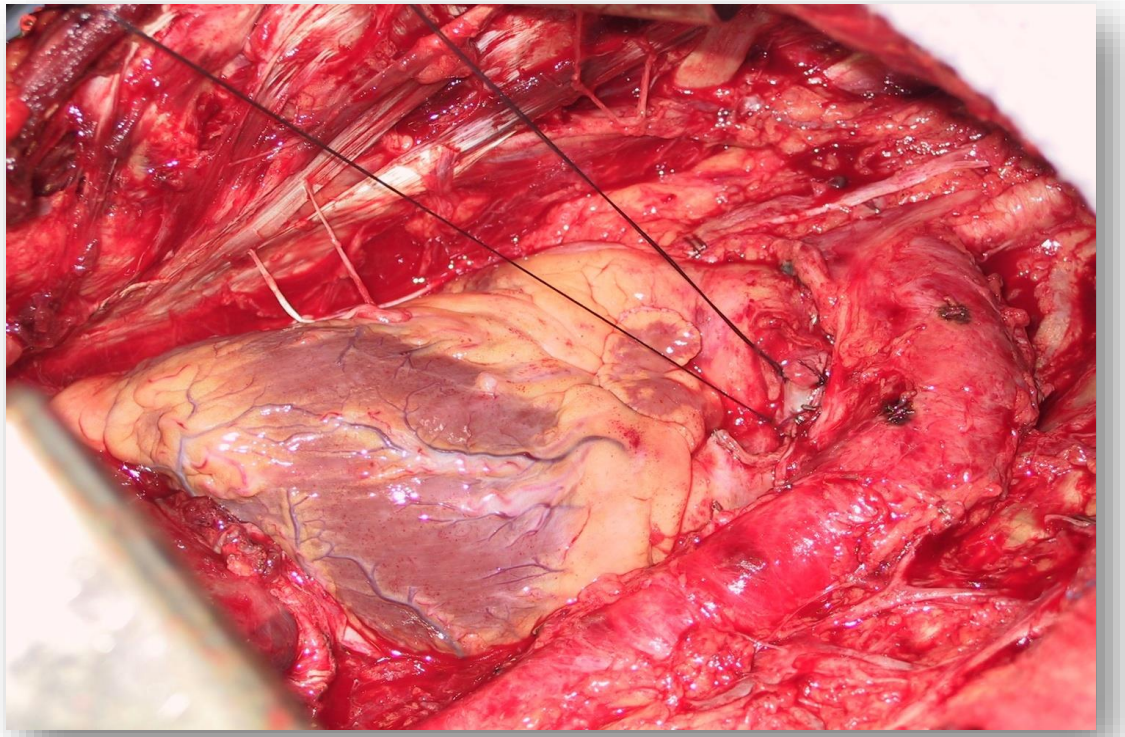
EPP: Intrapericardial pneumonectomy

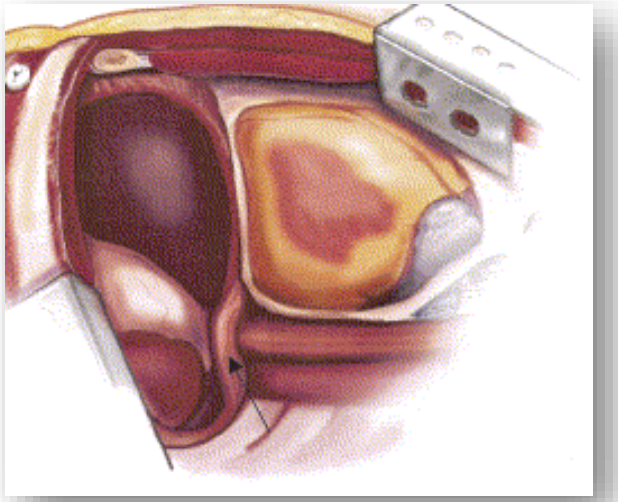


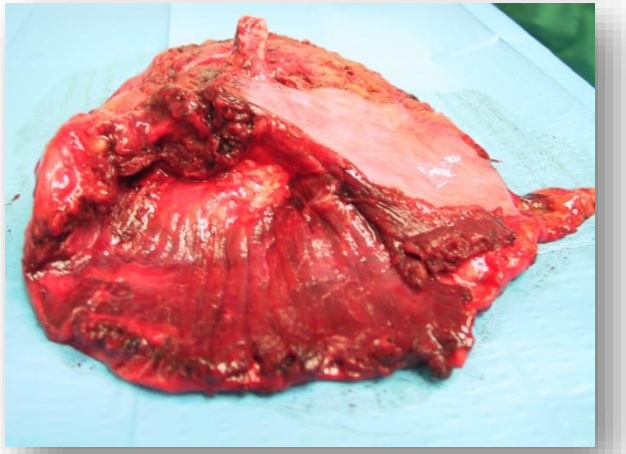




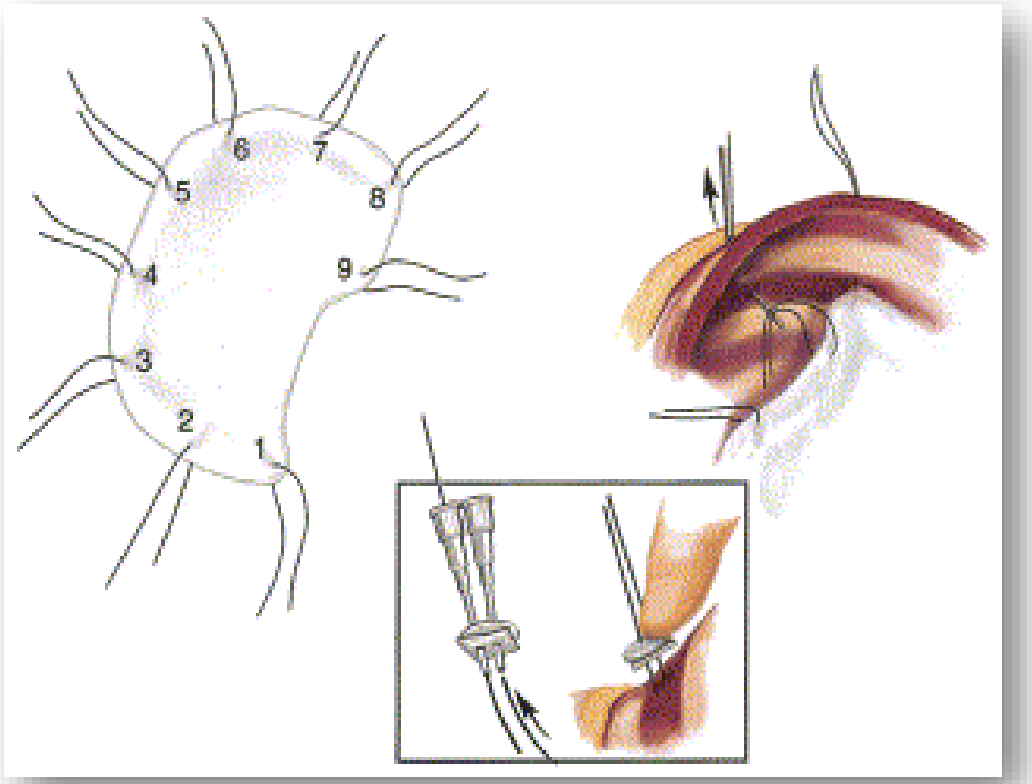
EPP



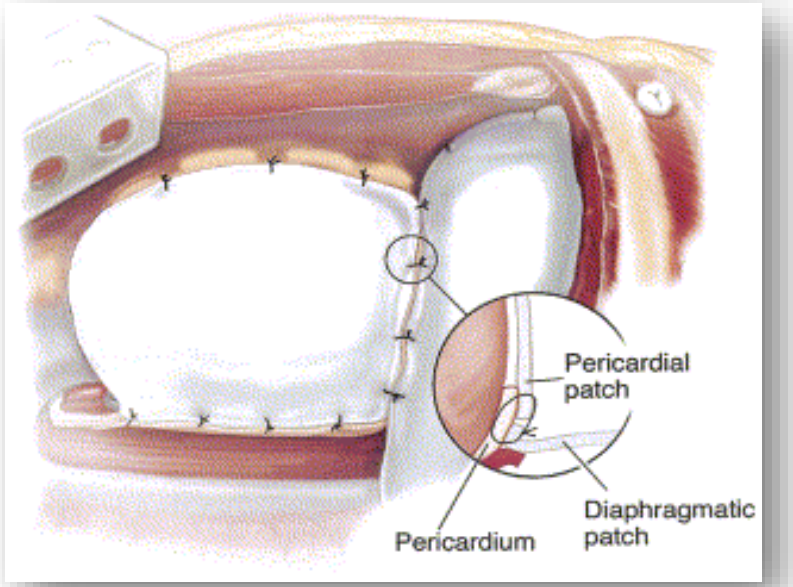


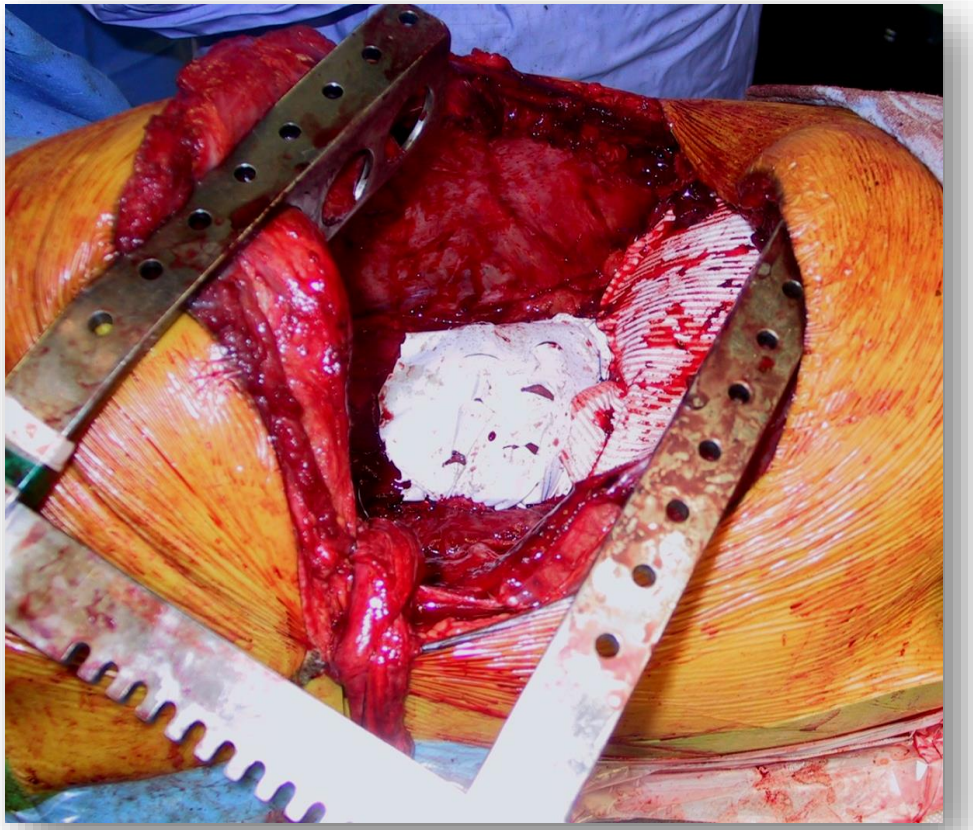


Diaphragmatic reconstruction

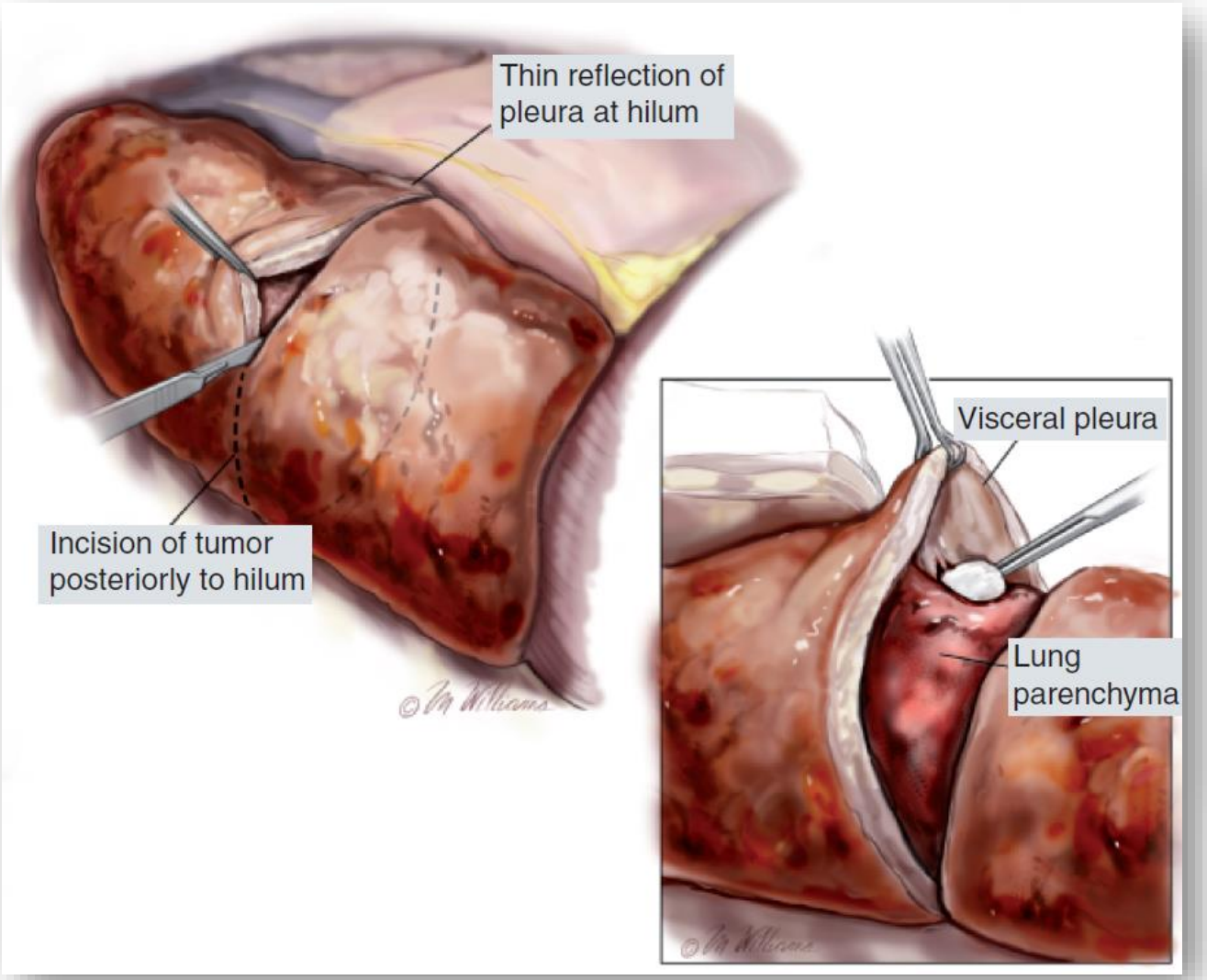


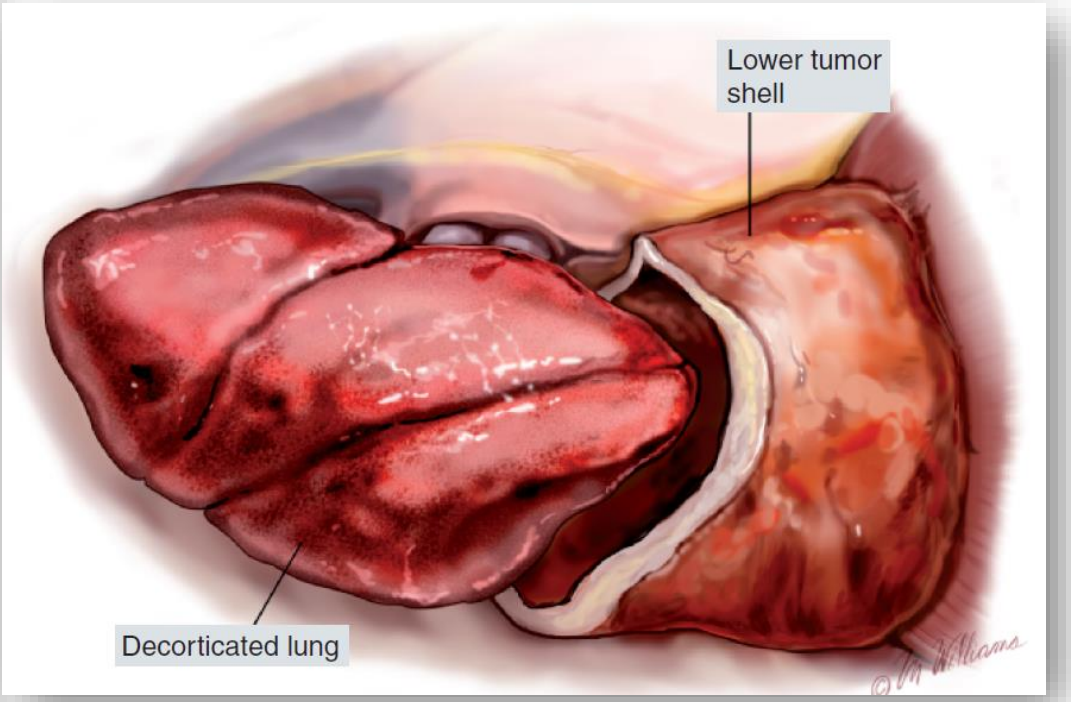
Reconstruction after EPP





ePleurectomy-decortication





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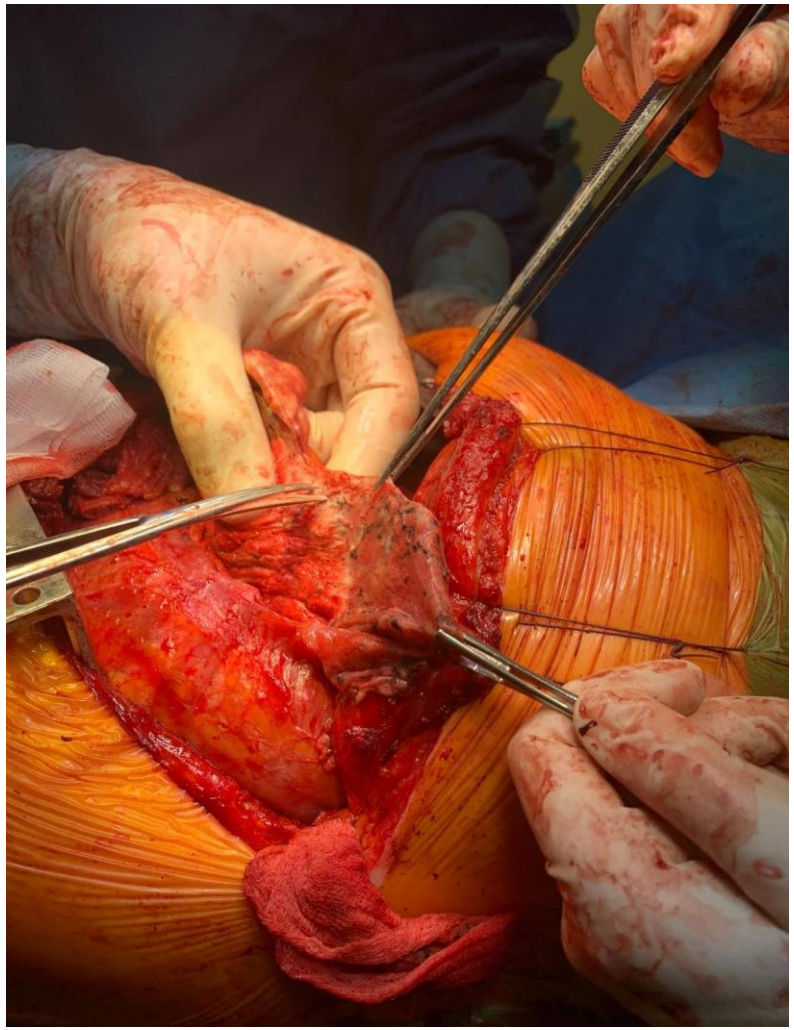
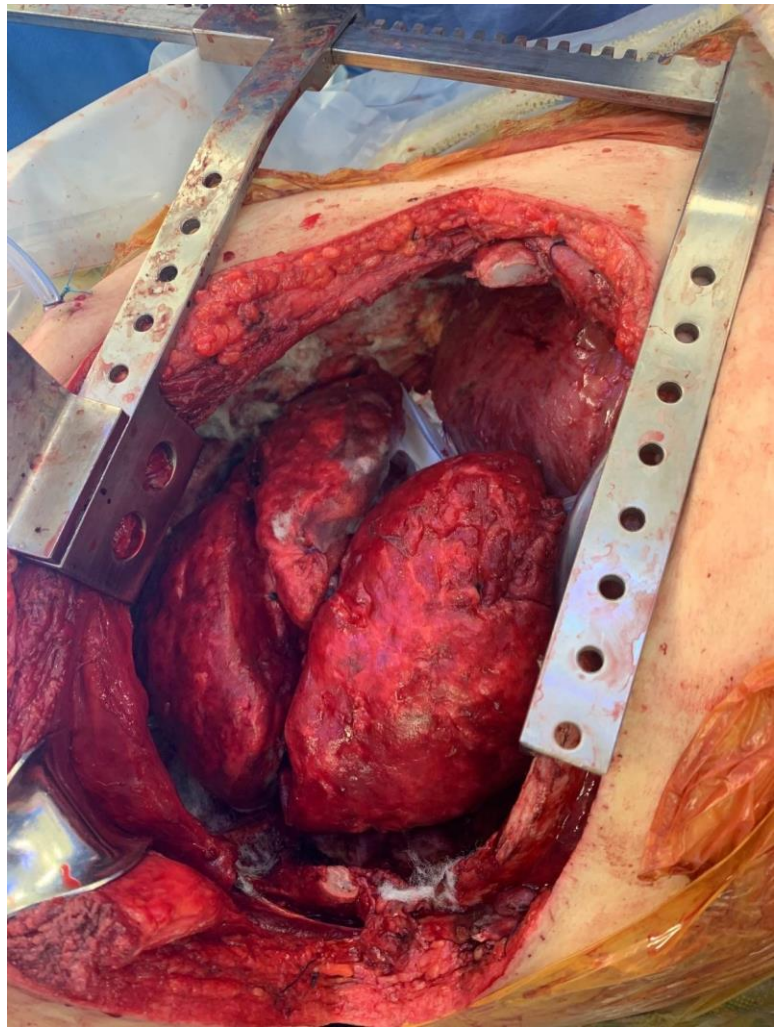
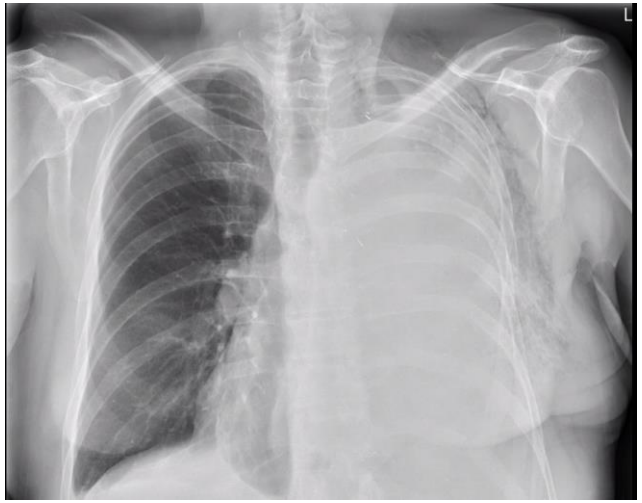
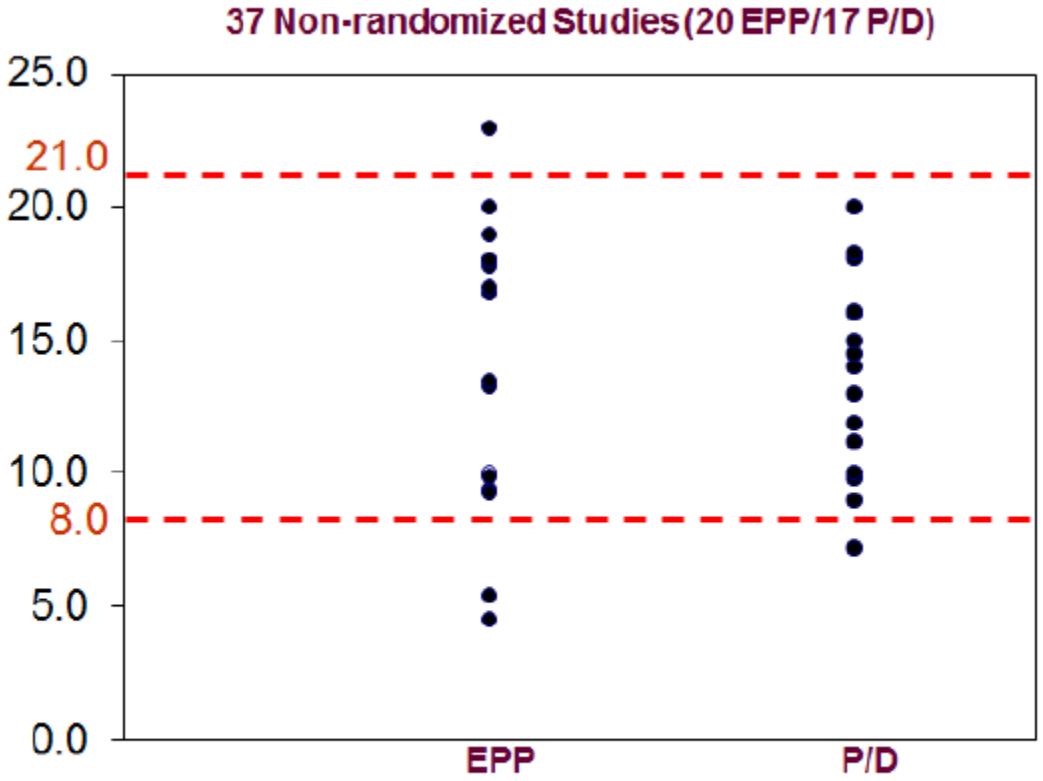




EPP vs ePD





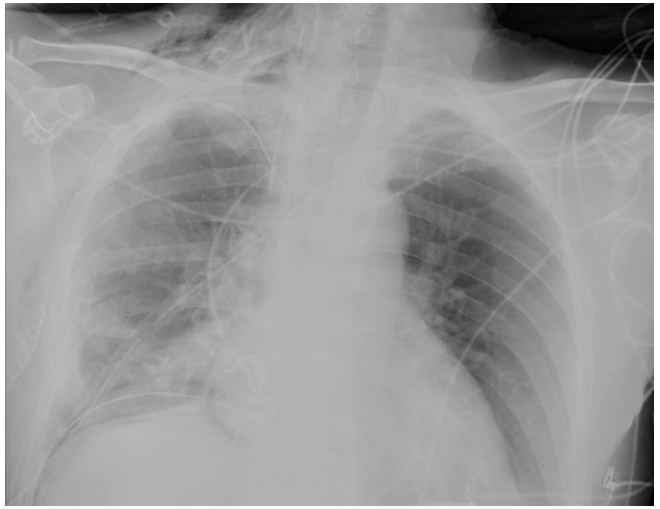
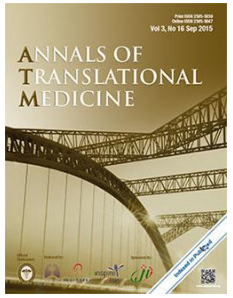


Figure 3: This graph compares the various studies of EPP versus P/D in terms of median survival. The median survival scatter is greater with EPP but there is a very similar range between EPP and P/D with the vast majority of studies showing a median survival of between 8 and 21 months.

EPP vs ePD: retrospective

Primary author and year	Total number of patients	Number of patients (EPP/PD)	EPP/PD morbidity (%)	EPP/PD mortality (%)	Median survival
Flores, 2008 (6)	663	385/278	10/6.4	7/4	12/16*
Burt, 2014 (7)	225	95/130	Higher in EPP$^{\alpha}$	10.5/3.1	NS
Batirel, 2016 (8)	130	42/66	20/5	7/2	18.3/14.6
Sharkey, 2016 (9)	362	133/229	Higher in EPP$^{\alpha}$	6/3.5	12.9/12.3

Two of the studies (7,8) compared the results of two periods following an intentional transition from an EPP predominant practice to a P/D predominant practice. *, P<0.001; $^{\alpha}$, early and late reoperation, bleeding, bronchopleural fistula, ARDS, Sepsis, atrial arrhythmias, right heart failure and ileus were significantly higher in EPP patients, whereas prolonged air leak was higher in P/D patients. NS, not stated.



Batirel, Ann Transl Med 2016

EPP vs ePD: pro's and con's

- EPP:
  - More radical
  - More agressive (mortality?, complications)

- eP/D:
  - More patients treated
  - Comparable survival
  - less morbidity / less mortality (?)
  - Improved QoL

Wald, Annu Rev Med 2018

Which one?

Editorials: Thoracic: Mesothelioma

Pleurectomy decortication for mesothelioma: The procedure of choice when possible

Raja M. Flores, MD

Flores, J Thorac Cardiovasc Surg 2016

Central Message

PD for mesothelioma is associated with greater lung preservation, lower morbidity and mortality, and similar or better survival to EPP.

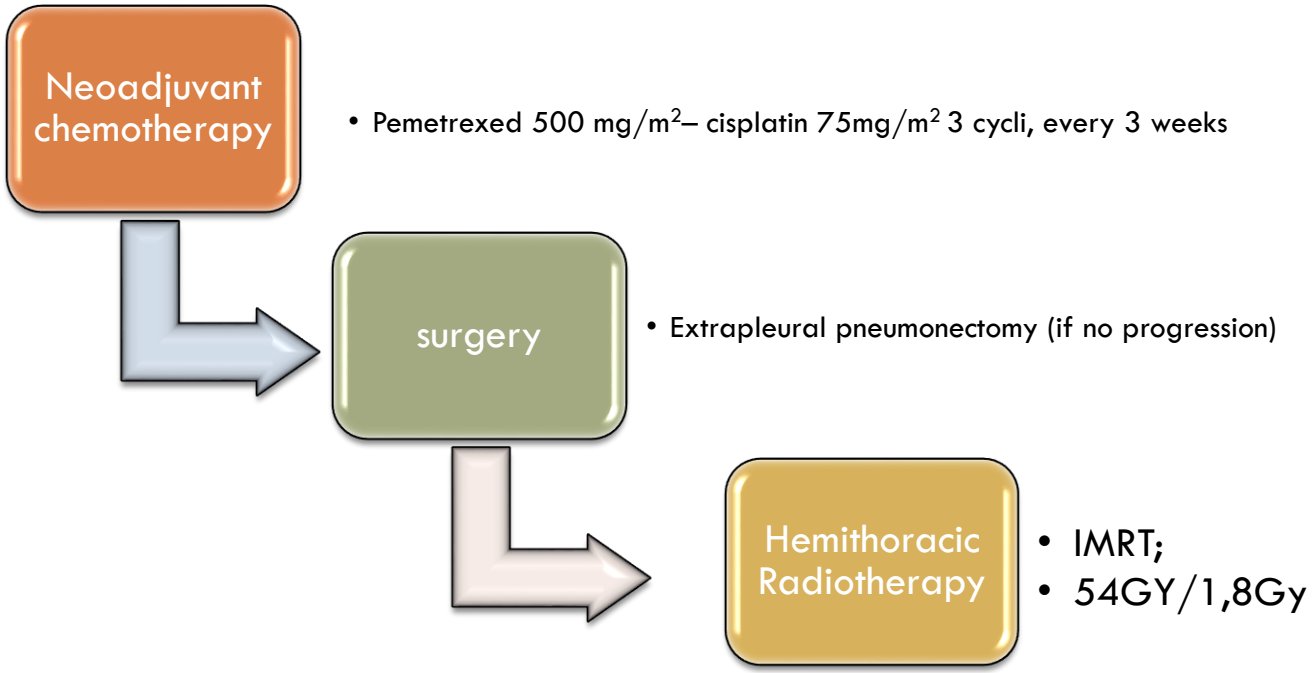
Surgery may be appropriate for carefully and highly selected MPM patients. This would usually be **EP/D rather than EPP**, because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as **part of multimodality treatment**

Scherpereel, Eur Respir J 2020

UZ Leuven experience

- Introduction
- Place for surgery?
- Staging
- UZLeuven work-up, staging and treatment protocol
- EPP and ePD
- Leuven experience

Experience Leuven 2003-2014



All histologic subtypes

Frick, EJCTS 2018

Complications

- 90-day mortality: 3.6%
  - ARDS (n=1)
  - Empyema (n=1)
- Morbidity: 62,5%
  - Bleeding (n=1)
  - Chylothorax (n=1)
  - **AF (n=18)**
  - ARDS (n=3)
  - DVT (n=1)
  - **> 48 h intubation (n=8)**

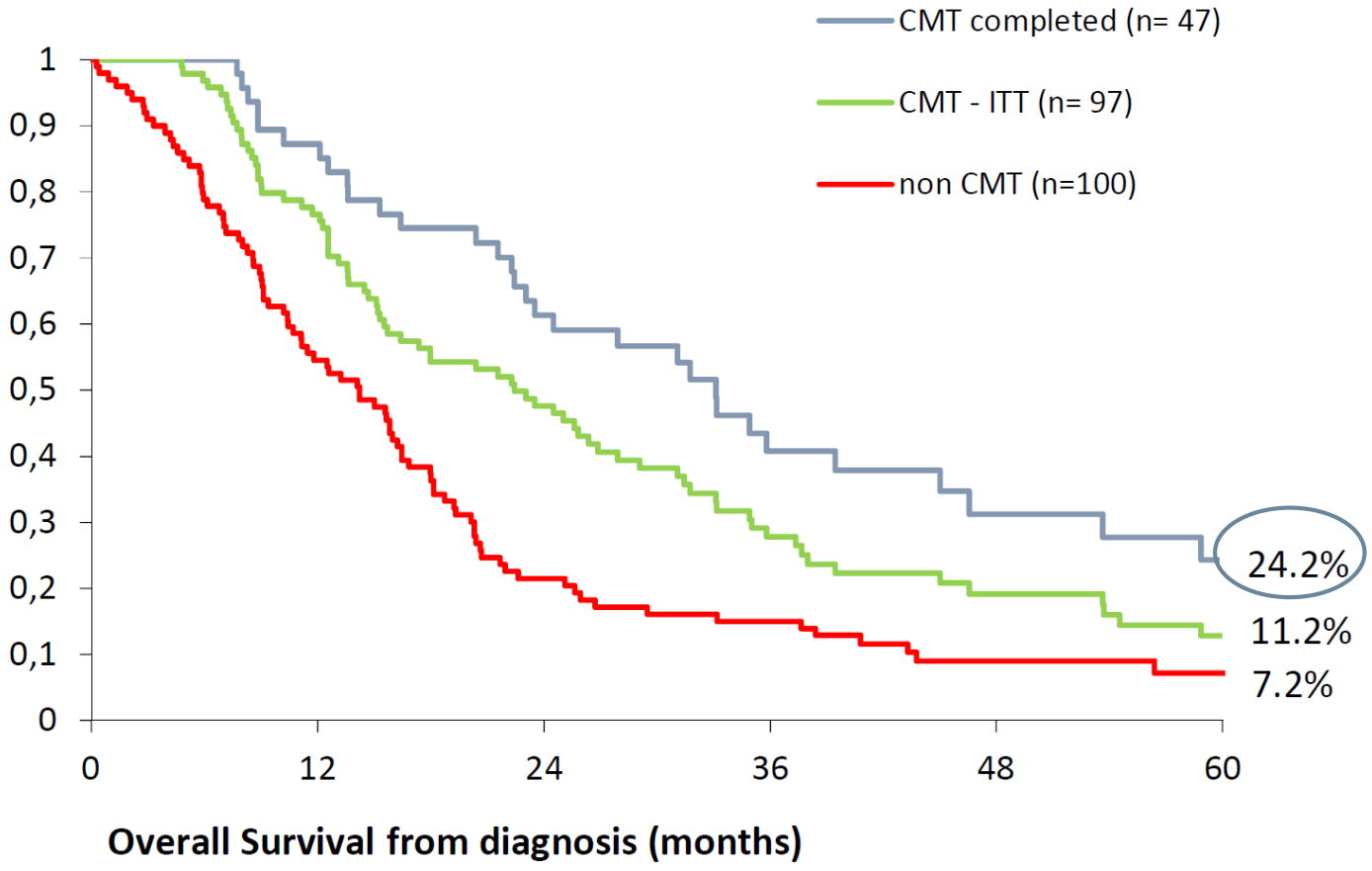
Surgical complicaties: 5,2%

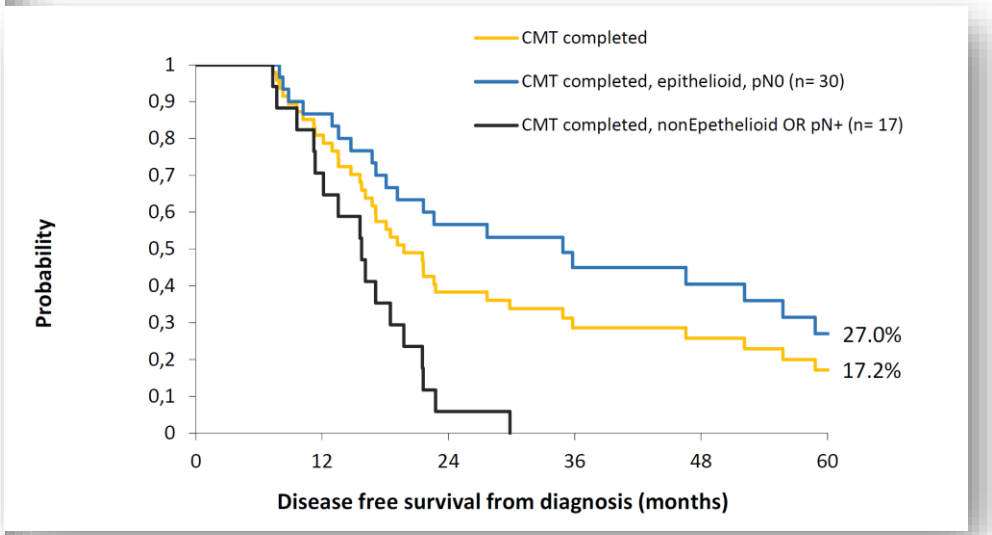
No fistula

No patch dehiscence

Overall survival, intention to treat

* 90-day mortality after EPP (n=2): 3.6%





CMT= combined modality treatment

Shift from Trimodality to Bi-modality:2015

- Safety and impact of hemithoracic RT?

Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial

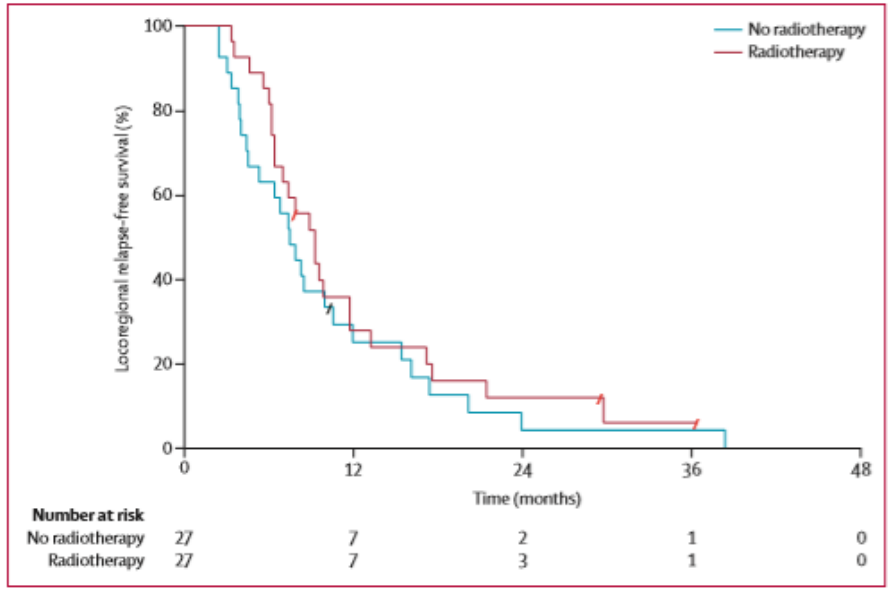


Figure 2: Kaplan-Meier analysis of locoregional relapse-free survival from surgery

	Grade 1–2	Grade 3	Grade 4	Grade 5
Anaemia	20 (74%)	--	--	--
Nausea or vomiting	8 (30%)	3 (11%)	--	--
Fatigue	6 (22%)	1 (4%)	--	--
Anorexia	7 (26%)	--	--	--
Oesophagitis	6 (22%)	2 (7%)	--	--
Radiation dermatitis	6 (22%)	--	--	--
Thrombocytopenia	5 (19%)	--	--	--
Weight loss	4 (15%)	1 (4%)	--	--
Leucopenia	4 (15%)	--	--	--
Increased creatinine concentration	4 (15%)	--	--	--
Pneumonitis	--	--	1 (4%)	1 (4%)
Dyspnoea	--	1 (4%)	--	--
Diarrhoea	--	1 (4%)	--	--
Increased alkaline phosphatase concentration	--	1 (4%)	--	--

Includes all grade 3 and grade 4 events as well as grade 1 and grade 2 events occurring in more than 10% of patients; highest grade per patient. n=27.

Table 4: **Adverse reactions to radiotherapy in part 2 of the study**

- Adjuvant RT no clinical benefit
- Increased morbidity

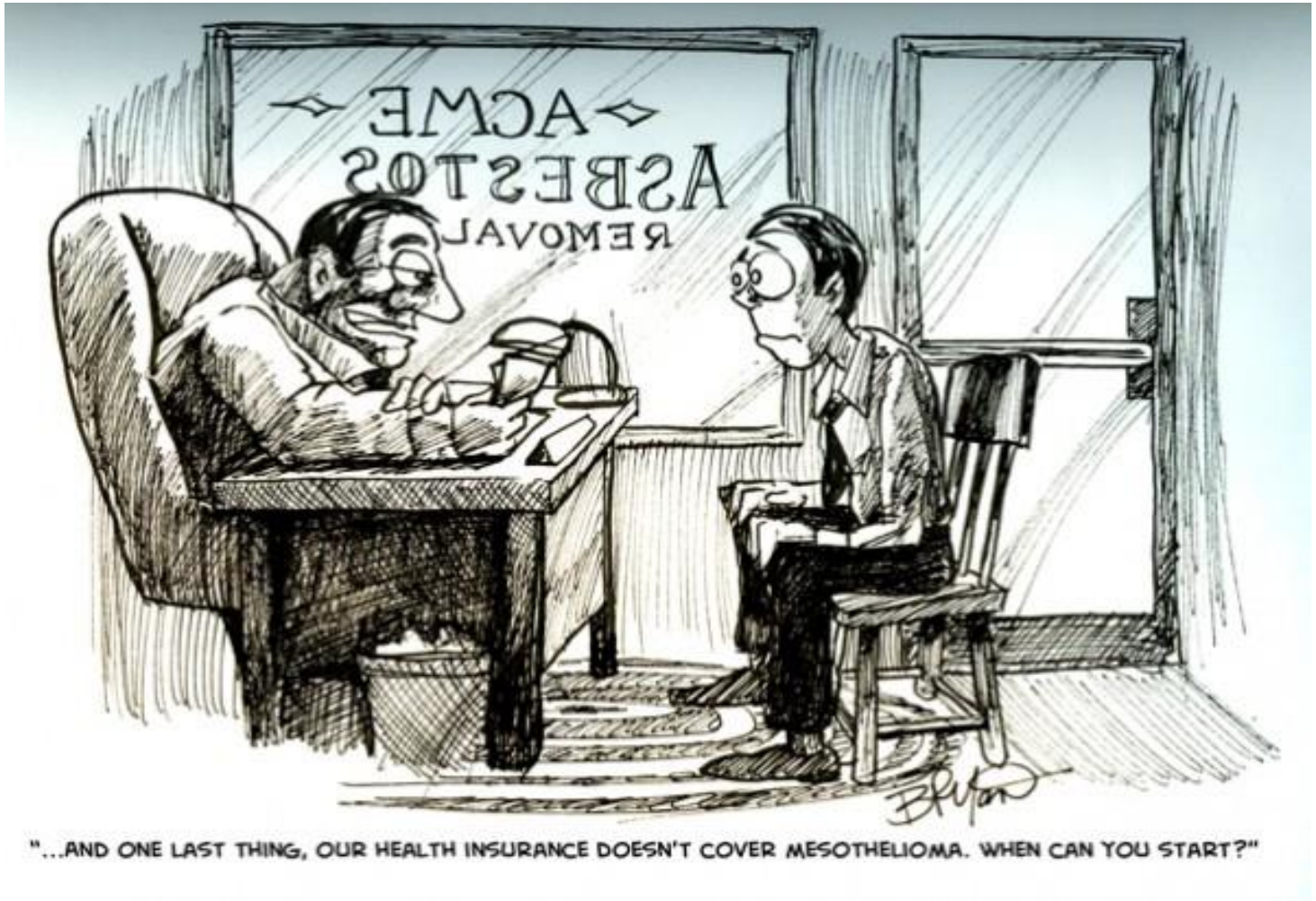
Stahel, Lancet Oncol 2015

Conclusions

- Maximal surgical cytoreduction should be performed (1,1)
- Single modality generally insufficient (1,2)
- Cytoreduction: EPP or eP/D (3,0)
- When possible: preferably eP/D (3,0)
- Sarcomatoid type, N2, T4: no surgical indication (2,1)

Kindler, J Clin Oncol 2018

Thank you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REMOVAL
"...AND ONE LAST THING, OUR HEALTH INSURANCE DOESN'T COVER MESOTHELIOMA. WHEN CAN YOU START?"