EPP or P/D
in early-stage malignant pleural mesothelioma?

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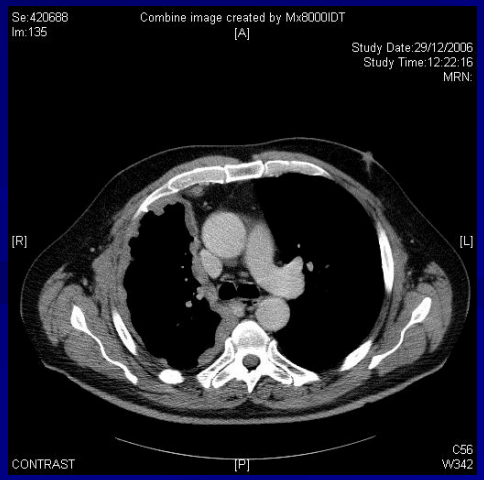
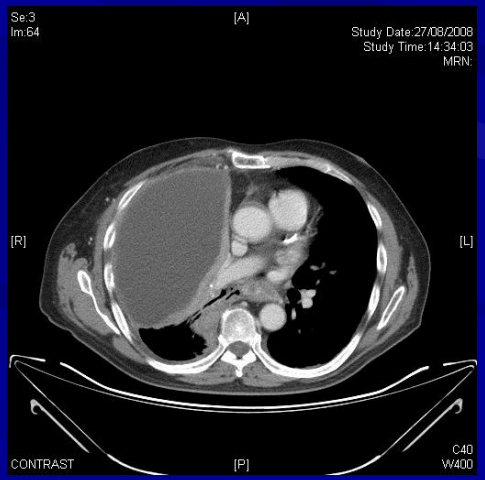
The legacy of asbestos

- The asbestos-related cancer malignant mesothelioma remains a major health problem worldwide, 50 years after Wagner recognised the link between asbestos and mesothelioma in South-African miners (1960).
- The epidemic is expected to reach its peak within 10 years, eventually > 250 000 mesothelioma deaths expected in Europe. More than 1.8m people exposed to asbestos every year in Britain (source: Health and Safety Executive, 2011).
- In Britain, more than 2200 mesothelioma deaths registered yearly, highest incidence worldwide. By 2015, >2500 deaths per year expected in Britain, due to asbestos (HSE). Majority of malignant pleural mesotheliomas > peritoneal mesotheliomas.
- Asbestos banned in most Western countries, but uncontrolled use in many countries: China, Russia, Quebec are mining asbestos. India imports > 100,000 tonnes per year.

Malignant pleural mesothelioma: presentations

- Dyspnea
- Pain
- Cough
- Systemic symptoms: fever, sweats, weight loss
- 2 different presentations: solid tumour or haemorrhagic pleural effusion (70%)





Malignant pleural mesothelioma: histological subtypes

- Pathologists have classified mesothelioma into different subgroups:
- Epithelioid (70%), pure epithelial proliferation
- Biphasic (20%), mixed epithelial and sarcomatoid proliferation
- Sarcomatoid (10%), predominantly sarcoma-like proliferation
- Differentiation is extremely important as each subtype is associated with a different prognosis (best=epithelioid, worse=sarcomatoid, median survival 6 months)
- Recently it has been recognized that a subtype of epithelioid mesothelioma: pleiomorphic, has a particularly bad prognosis

Malignant pleural mesothelioma treatments

- Surgery
- Radiotherapy
- Chemotherapy
- Immunotherapy
- Targeted therapies
- Best supportive care (pain control)

- Only the fittest patients can be offered multimodality therapy (20-25% ?)

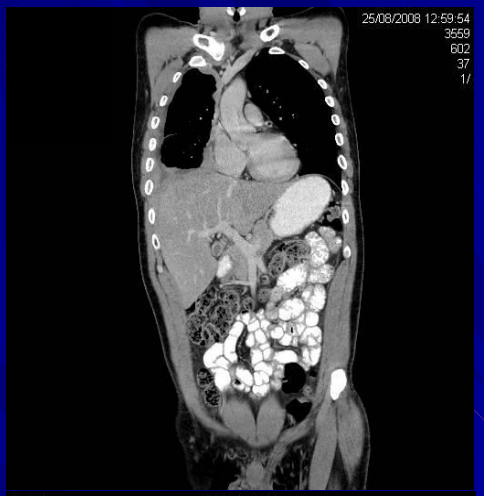
- For the majority of patients, treatment will consist in pleurodesis followed by some palliative chemotherapy or supportive care / pain control with opioids and/or palliative radiotherapy

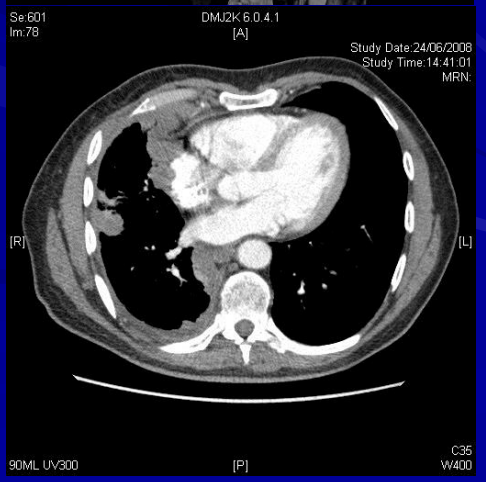
Survival in MPM

- Survival is stage-dependant: stage I: 35 months, stage II: 16 months, stage III: 11 months and stage IV: 6 months (Rusch, J Thorac Cardiovasc Surg 1996)
- Prognostic factors: epithelioid histology, N0 disease, but also Hb, WBC count, platelet count, weight loss (EORTC / Curran, J Clin Oncol 1998).
- With best palliative care: around 7 months (MSO-1 Muers, Lancet 2008)
- With best chemotherapy combinations: median survival around 12 months in the palliative setting (Vogelzang, J Clin Oncol 2003; Van Meerbeeck J Clin Oncol 2004)
- With intra-pleural immunotherapy: median survival 15-18 months (Astoul, Cancer 1998)
- With multimodality therapy (EPP): median survival 10 to 29 months, but few patients can complete the trimodality therapy courses (Krug, J Clin Oncol 2009: 52%, Weder, Ann Oncol 2007: 59%, De Perrot, J Clin Oncol 2009: 50%)
- With multimodality therapy (P/D): median survival 9 to 32 months

Diagnostic investigations / Staging

- Biopsy to prove diagnosis of malignant pleural mesothelioma:
  CT-guided biopsy, VATS or open pleural biopsy (cytology not reliable)
- Chest CT , MRI rarely (diaphragm/great vessels?)
- ^{18}FDG-PET and PET-CT (SUVmax prognostic value, TGV)
- EBUS, EUS, mediastinoscopy or VATS for nodal staging
- Bronchoscopy
- Laparoscopy, pericardioscopy (rarely)



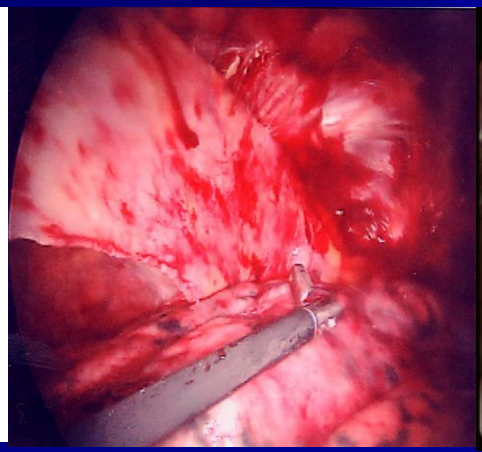
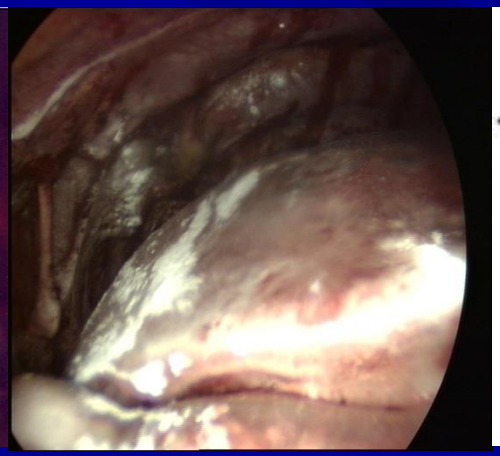
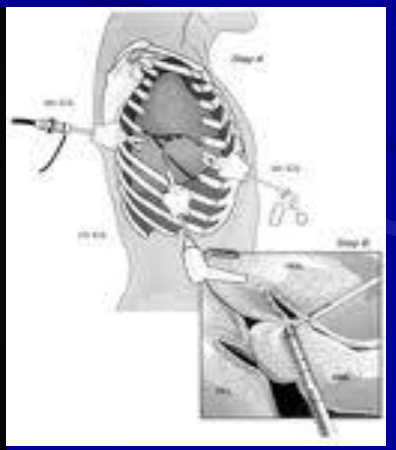


Radical surgery. Is the patient fit enough?

- Full medical history (familial history of cancer, comorbidities, diabetes)
- Clinical examination (cardiac murmur, arteriopathy, COPD, …?)
- Performance status, nutritional status, psychological status
- Blood tests: FBC, coagulation, renal function + liver function tests
- ECG. Echocardiogram, coronary angiogram only if coronary artery disease, valvulopathy or heart failure
- Pulmonary function tests / spirometry and gas transfer factor:
  when FEV 1 < 60% predicted or TLCO < 60% predicted, I do a cardiopulmonary exercise test with measurement of VO_2max
- Lung ventilation/perfusion scan

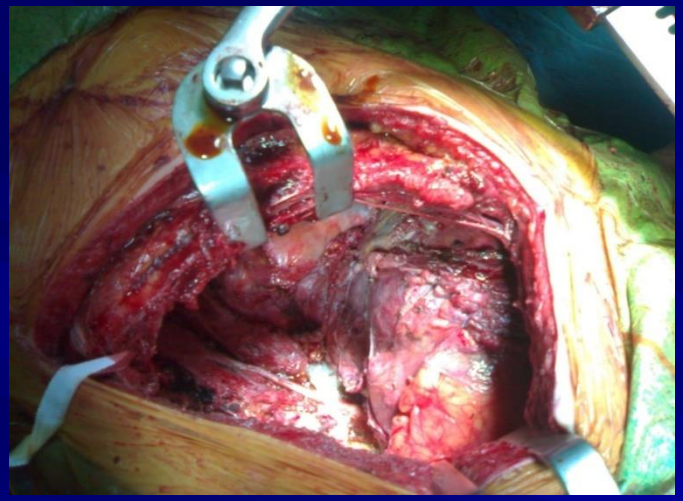
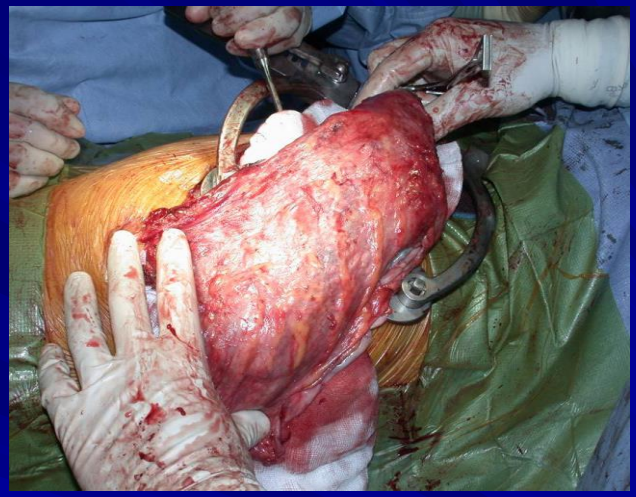
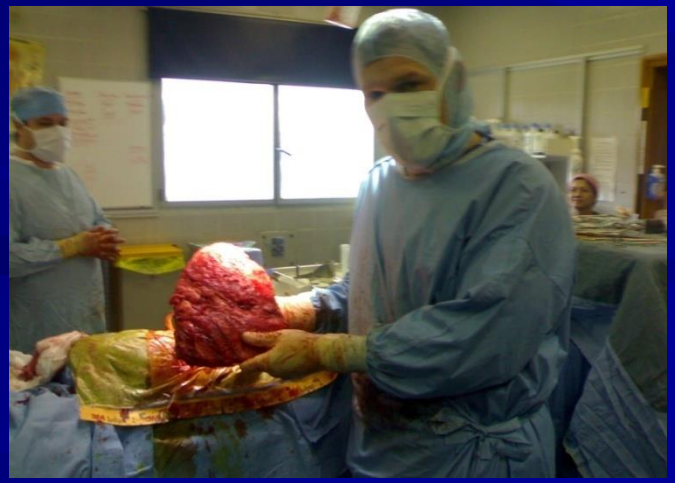
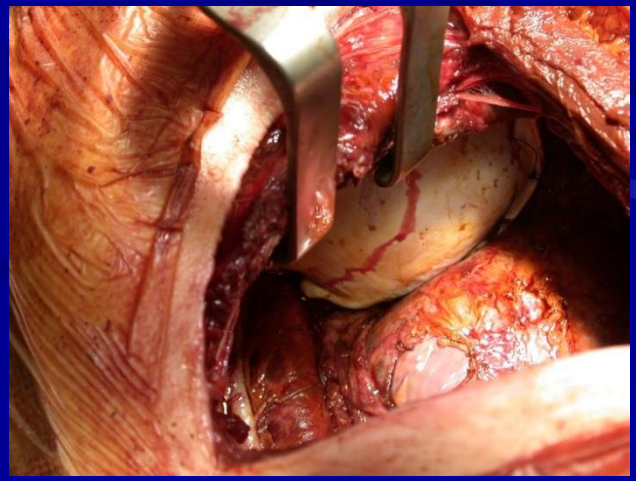
Palliative surgery in MPM

- VATS talc pleurodesis
- VATS pleurectomy (trapped lung, high output effusion / bleeding)
- The role of talc pleurodesis vs VATS pleurectomy has been evaluated in the MesoVATS trial, paper in press in the Lancet: VATS pleurectomy does not improve survival, but freedom from effusion and QoL at 6 and 12 months (Rintoul, Lancet 2014).
- When the lung is trapped the alternative is to insert a pleur-X catheter, if patients is not fit for pleurectomy
- Open palliative debulking pleurectomy/decortication if PS<2 and life expectancy > 6 mo

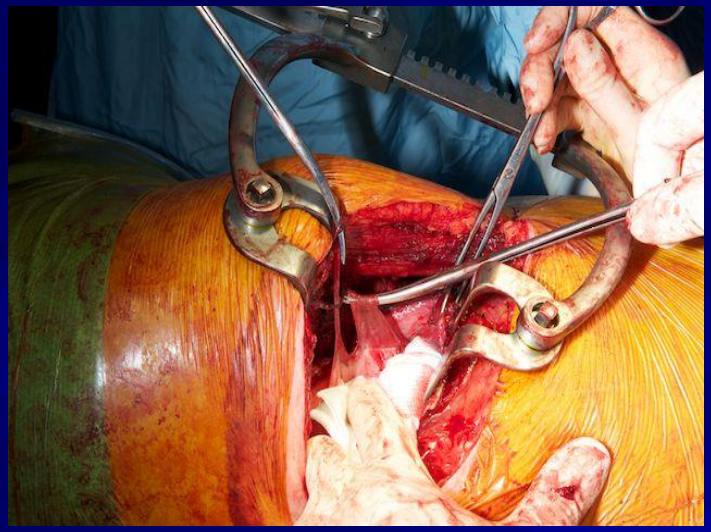





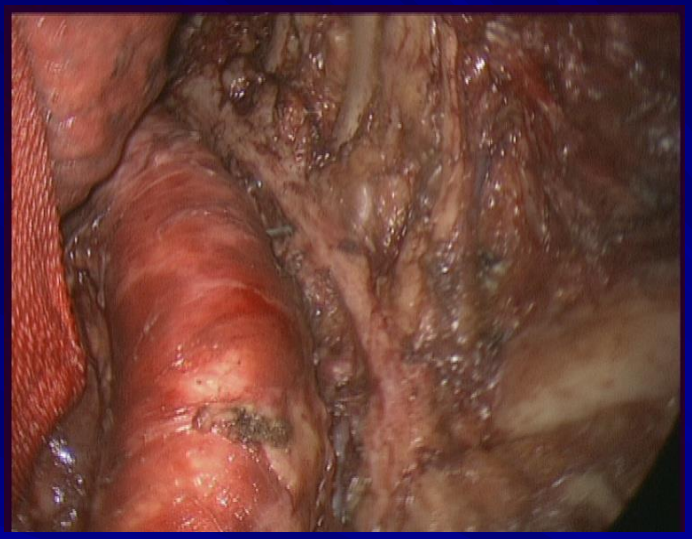
Radical surgery in malignant pleural mesothelioma: EPP

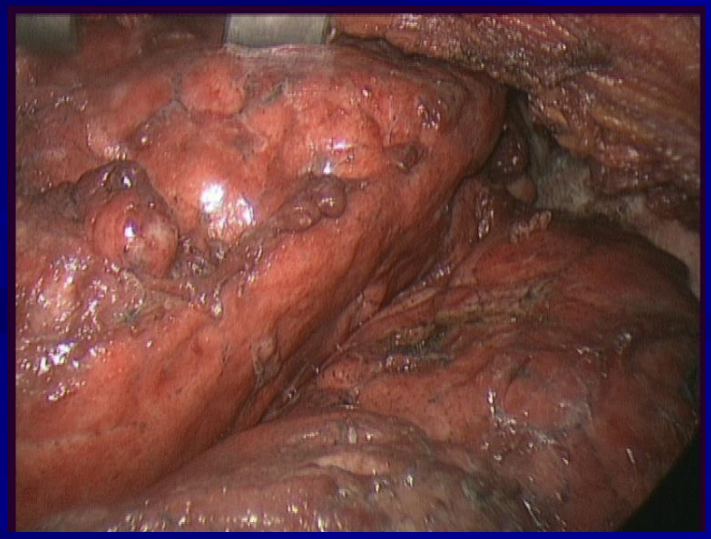
- Extrapleural pneumonectomy: en-bloc resection of pleura, lung, diaphragm and pericardium

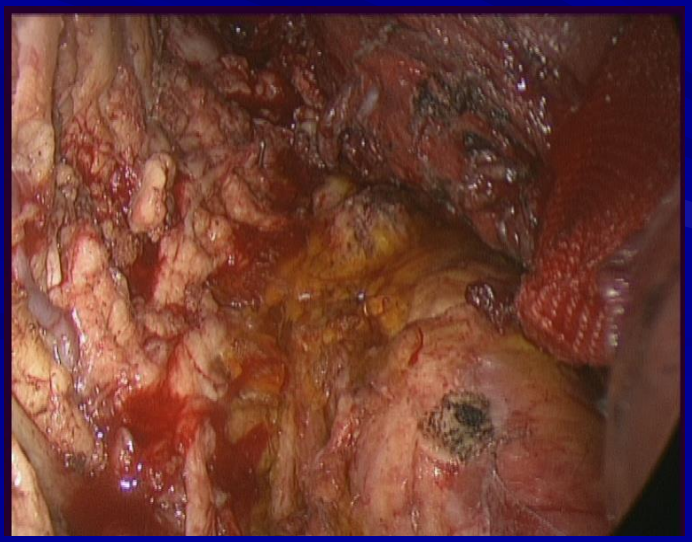





Radical surgery in malignant pleural mesothelioma: P/D







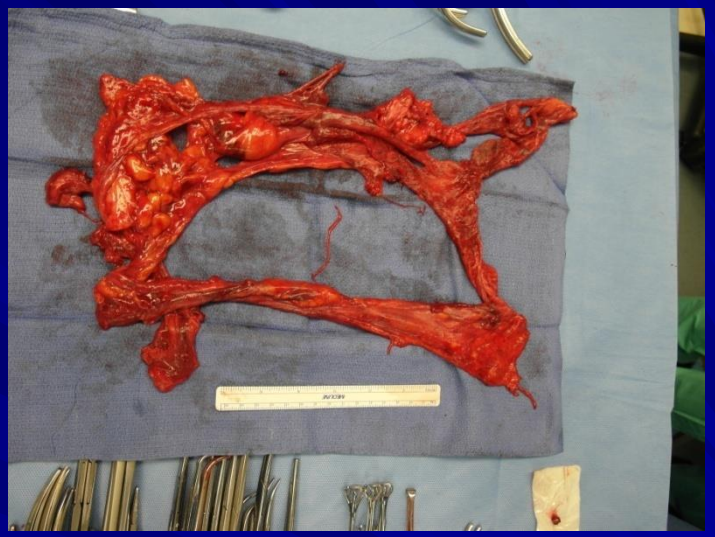


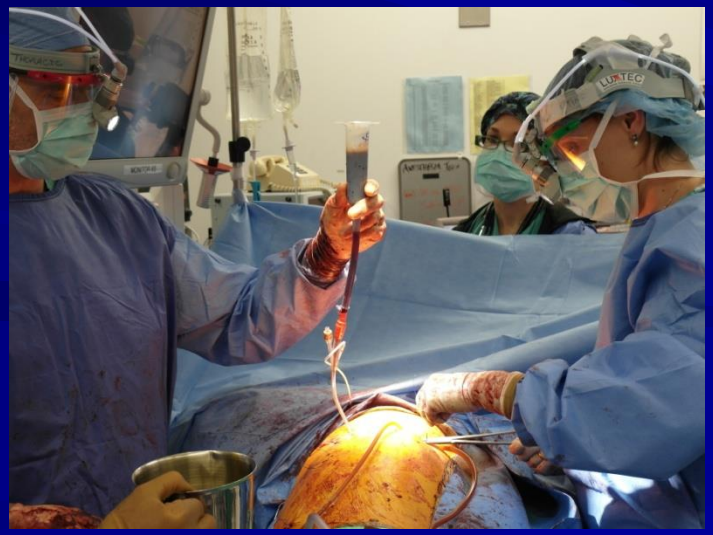
Adjuncts: intra-pleural therapies

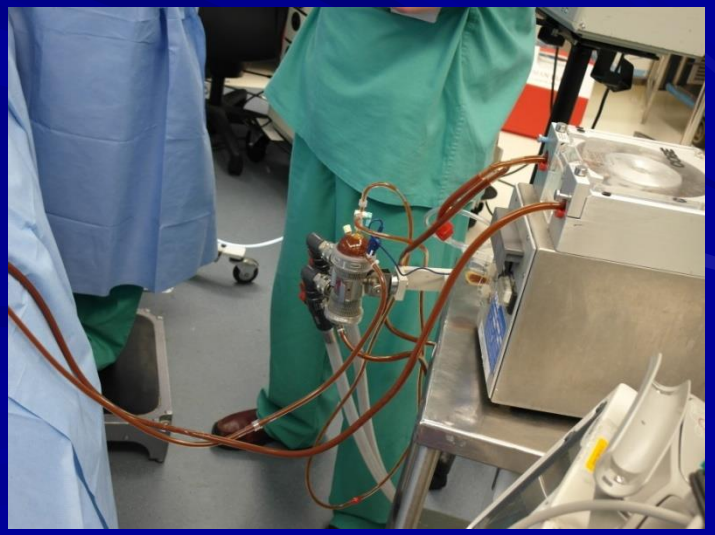
Hyperthermic intra-pleural chemotherapy

Photodynamic therapy

Hyperthermic lavage with povidone-iodine







Radical surgery in MPM

- EPP was reported in mid 70's with mortality rate of 33%
- Mortality dropped significantly and is less than 5% at most specialist centres
- Significant morbidity (>60%)
- Accepted treatment as part of multimodality therapy
- Induction chemotherapy used at most centres
- Most institutions use adjuvant radiotherapy at 6-8 weeks following EPP
- Relapses mainly at distant sites (abdomen, contralateral hemi-thorax, mediastinum)

- P/D has been performed since the 70's with low mortality
- Mortality is less than 3% at most specialist centres
- Morbidity is low (<25%)
- Accepted as "adequate procedure" in early stage (stage Ia and Ib)
- Adjuvant radiotherapy (30-45 Gy) not routinely recommended, but "lung sparing" radiotherapy currently being evaluated
- Chemotherapy used at most centres (adjuvant)
- Relapses, mainly local

Outcomes following multimodality therapy (EPP)

Author	Year	Chemotherapy	EPP (n)	TMT/ITT (%)	30-day mortality (%)	Median survival, ITT (month)
Sugarbaker	1999	adjuvant	183	?	3.8	19
Rusch	2001	no, adj radiother	62	61%	11.3	17
Pagan	2006	adjuvant	44	57%	4.5	20
Weder	2007	neoadjuvant	45	59%	2.2	19.8
Edwards	2007	adj/neoadjuvant	105	?	6.7	? after EPP 14.5
Rice	2007	not standard	100	<63%	8	10.2
Rea	2007	neoadjuvant	17	71%	0	25.5
De Perrot	2009	neoadjuvant	45	50%	6.7	14
Krug	2009	neoadjuvant	54	52%	3.7	16.8
Trousse	2009	adj/neoadjuvant	83	?	4.8	? after EPP 14.5
Hasani	2009	adjuvant	18	64%	11	? After EPP 20.4
Tilleman	2009	IHC	96	76%	4.3	12.8
Buduhan	2009	neoadjuvant	46	69%	4.3	? After EPP 24
Van Schil	2010	neoadjuvant	42	65%	6.5 (90d)	18.4
Sugarbaker	2013	IHC	72	?	?	35.3
Cho	2014	Adjuvant to N2	25	100%	0	?

Outcomes following multimodality therapy (P/D)

Author	Year	Chemotherapy / radiotherapy	P/D (n)	TMT/ITT (%)	Morbidity (%)	30 day mortality (%)	Median survival, ITT (month)
Hilaris	1984	intraoperative brachytherapy adjuv radiother 45 Gy	41	100%	15	0	21
Rusch	1994	intraoperative chemo adjuvant chemo	28	64%	?	3.5	17
Lee	2002	adjuvant chemo Intraoperative and adju radiotherapy 45 Gy	32	37.5%	15	6.2	18.1
Richards	2006	intraoperative chemo	44	72%	41	11	9
Lucchi	2007	adj chemo and IL-2 adj radiotherapy 30 Gy	49	100%	10	0	26
Nakas	2008	adjuvant chemo prophylactic radiotherapy	51	? 46%	55	5.9	15.3
Bolukbas	2011	adjuvant chemo prophylactic radiotherapy	35	94%	20	2.9	30
Lang-Lazdunski	2011	adjuvant chemo prophylactic radiotherapy	36	100%	25	0	24
Friedberg	2012	adjuvant PDT, chemotherapy	38	!00%		2.7%	31.7
Minatel	2014	Adjuvant IMRT and chemo	20	95%		0	33

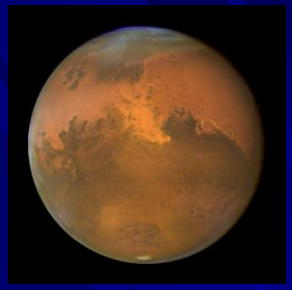
Radical surgery in malignant pleural mesothelioma. Have we got enough evidence?

- Most trials are retrospective
- Single-institution trials. Staging differ (Butchard, BWH, IMIG,)
- Patients pre-selected, denominator not known
- Many patients do not receive the full treatment agreed initially
- Poor recording of QoL data.
- Morbidity/mortality of other treatment modalities?
- Two separate panels (IASLC and CCOP) have concluded that there was no convincing evidence to support the role of EPP in MPM (Lung Cancer 2005)
- The ESTS and ERS recommend that EPP is offered only as part of a clinical trial (Scherpereel , Eur Resp J 2010)

- It seemed logical to design a randomised trial to assess the role of surgery (EPP) as a treatment modality versus no surgery (chemotherapy, palliative radiotherapy allowed)

The MARS feasibility study

Treasure, Lancet Oncol 2011



Originally, the MARS randomized study was supposed to enrol 670 patients

More than 300 patients were screened between October 2005 and November 2008

112 patients registered after first consent

A majority of patients did not proceed to random allocation (n=62, 55%)

Heterogeneity of chemotherapy regimes and number of cycles

50 patients (45%) randomised, 24 to EPP and 26 to no EPP

19 patients started EPP, with a final 30-day mortality of 10.5% and morbidity of 69%

23% of patients in the no EPP group had surgery off trial (3 EPP and 3 P/D)

Median survival by intention to treat was 18 months for the EPP group, 23 months for the no EPP group (from registration). The hazard ratio was 2.75 for EPP after adjustments.

This feasibility study failed to randomise 50 patients in 1 year and was not powered to show superiority of one group over another

This study has been misinterpreted by some and has infuriated thoracic surgeons supporting EPP, but it has prompted reflexion on the role of EPP in malignant pleural mesothelioma

Survival following multimodality therapy: EPP versus P/D (Flores, J Thorac Cardiovasc Surg 2008)

- Retrospective study, 663 patients at 3 different institutions over 27 years
- Mortality 7% for EPP and 4% for P/D
- Multivariate analysis showed a 1.4 hazard ratio for EPP, but selection bias...treatment heterogeneities, different protocols, ...
- P/D associated with better survival in early stage disease. Selection bias?

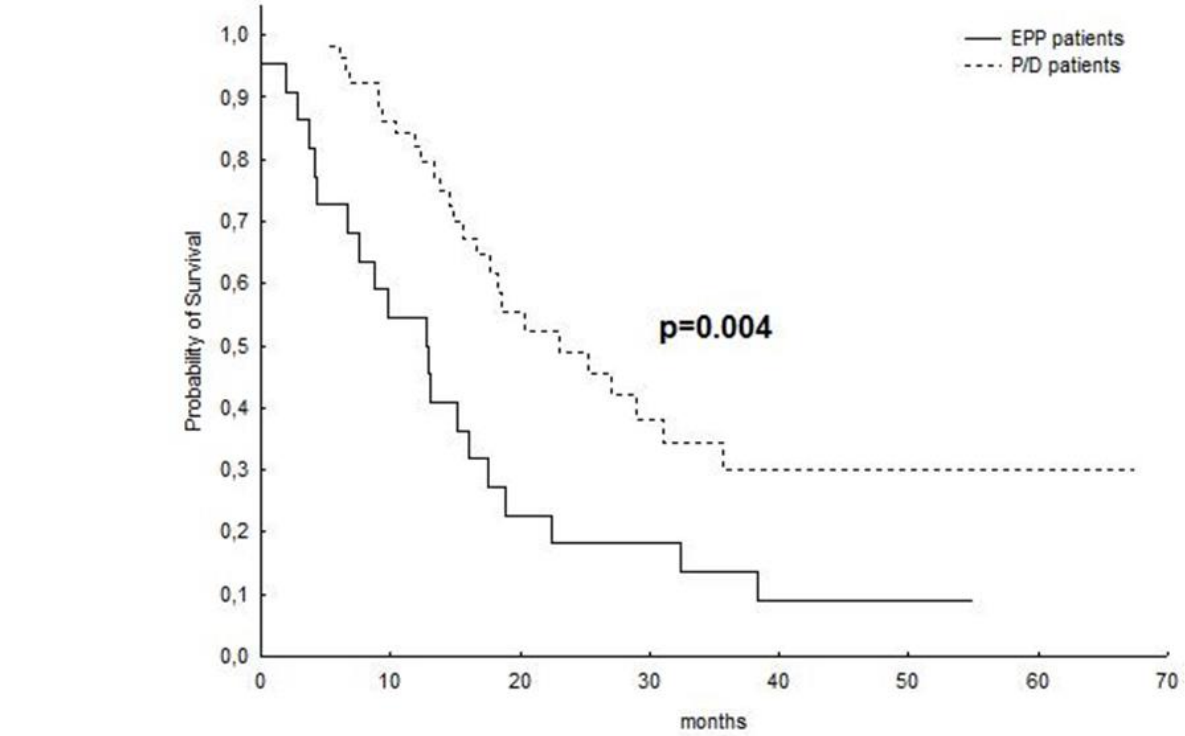
Survival following multimodality therapy: EPP versus P/D (Rusch, J Thorac Oncol 2012)

- Initial analysis of the IASLC database
- 3101 patients at 15 centres
- 1494 patients had surgery with curative intent
- No significant difference in survival for T1 and T2
- Significant difference for N0 versus N1/N2 and epithelioid versus non-epithelioid
- Superiority of EPP in early stage disease? Bias?

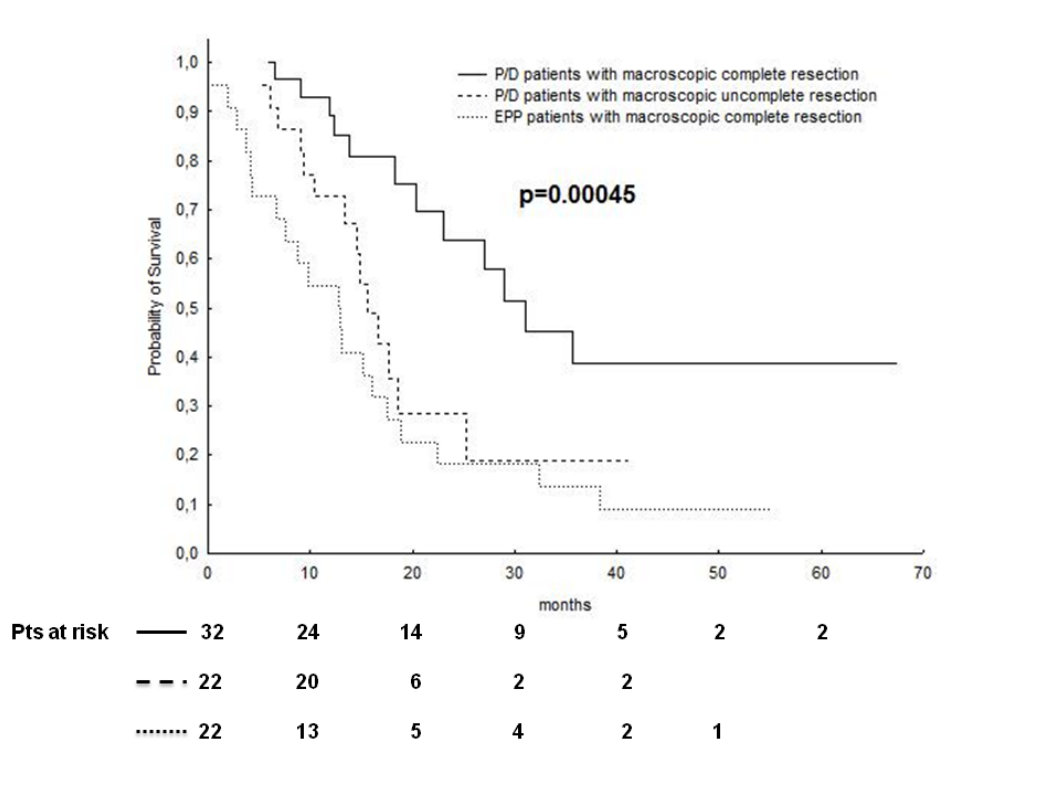
Survival following multimodality therapy: EPP versus P/D (Lang-Lazdunski, J Thorac Oncol 2012)

- Non-randomised prospective study of all patients offered radical surgery at Guy's 2004-2011 by a single thoracic surgeon
- 25 attempted EPP (22performed) and 54 P/D, populations similar in age, sex, stage, histology
- 30-day mortality 4.5% for EPP and nil for P/D
- Morbidity 68% with EPP versus 27.7% with P/D
- 97% of patients received trimodality therapy after P/D and 68% after EPP
- Overall median survival 23 months with P/D versus 12.8 months with EPP, 5-year survival 30.1% versus 9% (p=0.004)

Survival following multimodality therapy: EPP versus P/D (Lang-Lazdunski, J Thorac Oncol 2012)



Survival following radical P/D and hyperthermic lavage: impact of complete macroscopic resection



Radical surgery for mesothelioma:
personal experience 2004-2013

- More than 100 patients referred / treated yearly at Guy's & St Thomas' hospital.
  More than 1000 patients treated since programme started in October 2003.
- 25 multimodality treatments involving EPP 2004-2008: 30-day mortality 4.5%, overall median survival 12.9 months, 1-year survival 57%, 2-year survival 19%, 5-year survival 9%.
  68% of patients completed trimodality therapy.
- 102 multimodality treatments involving radical pleurectomy and HPL/Betadine 1% (41°C) 2004-2013: 30-day mortality nil, 96% received 4-6 cycles of adjuvant chemotherapy (+2 patients had 2 cycles), all patients had prophylactic radiotherapy within 6 weeks, overall median survival 32 months, 1-year survival 89%, 5-year survival 24.1%. In patients with epithelioid histology, median survival is 35.3 months and 5-year survival 42%. For non-epithelioid histology, median survival is 14.9 months and 5-year survival 7% . For those with epithelioid histology, N0 disease and CMR (n=47) median survival is 52.4 months.

Survival following multimodality therapy: EPP versus P/D (Cao, Lung Cancer 2014)

- Systematic review of the literature and meta-analysis
- Comparative data on 632 EPP and 513 P/D
- Significantly lower mortality of P/D 2.9% versus EPP 6.8% ($p=0.02$)
- Significantly lower morbidity of P/D 27.9% versus EPP 62% ($p<0.0001$)
- Median overall survival better with P/D (13-29 months) versus EPP (12-22 months) (NS)

Important questions to be answered in the future

- Is there a role for radical surgery in malignant pleural mesothelioma?
  MARS-2 randomized phase 3 study
- If yes, should it be EPP or radical pleurectomy/decortication ?
- Radical surgery in non-epithelioid patients?
- Timing of chemotherapy administration? EORTC L-1205 randomized phase 2 study
- Should the diaphragm and pericardium be resected routinely during P/D?
- Role for less invasive treatments in patients with early stage disease : vaccination, intrapleural therapies, immunotherapy, targeted therapies ?

Conclusions

- Patients with malignant pleural mesothelioma must be referred to a specialist centre
- Fit patients can have multimodality therapy adapted to their performance status, stage, tumour biology and life expectancy
- Considering the mortality and morbidity associated with EPP, P/D should be the default procedure in multimodality regimens (outside of a clinical trial)
- Treatments should be carefully evaluated, discussed in multi-disciplinary meetings and patients receiving new treatments should be enrolled into large randomised trials (involving translational research) and tumour / blood samples should be banked
- Prevention, Research +++