Multidisciplinary Management of Locally Advanced Mesothelioma

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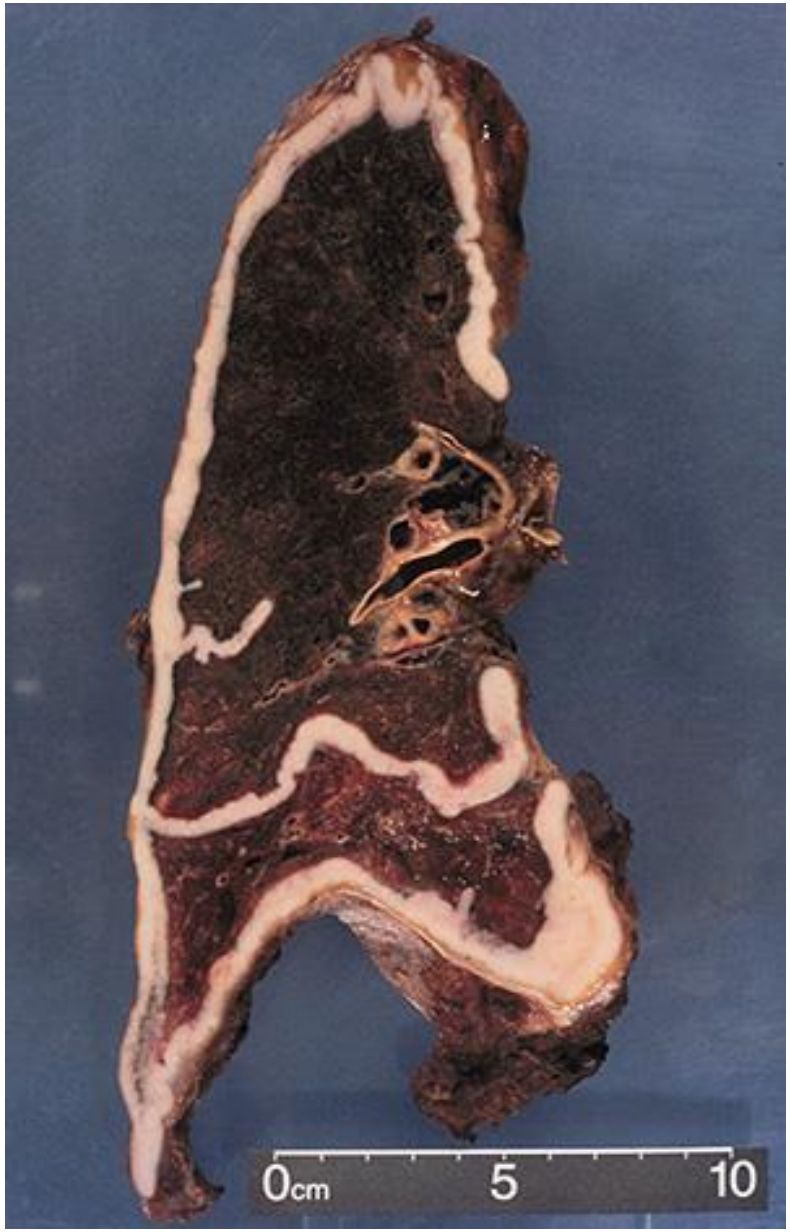
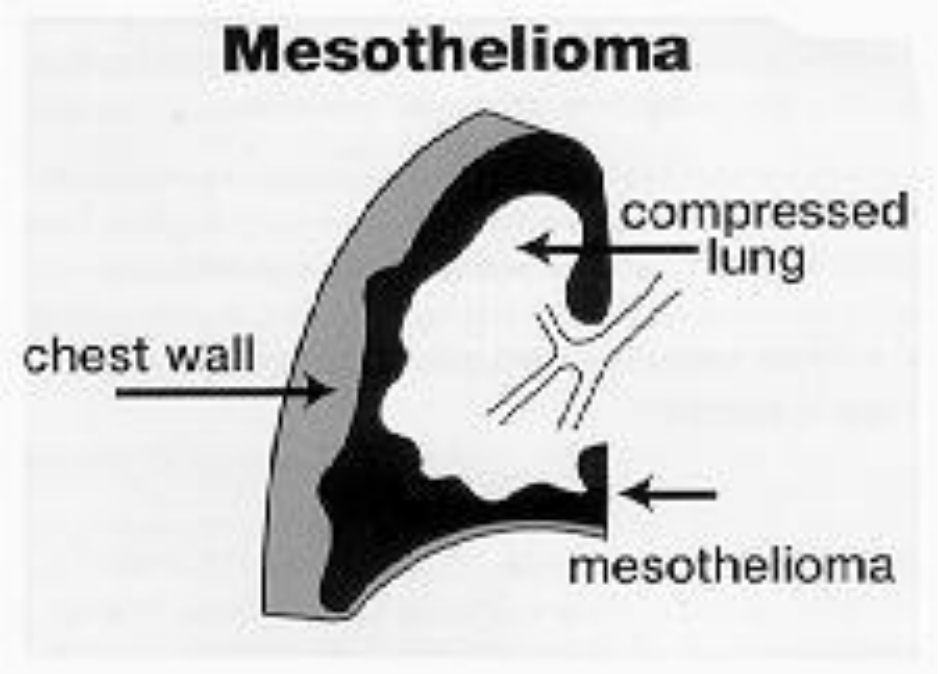
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

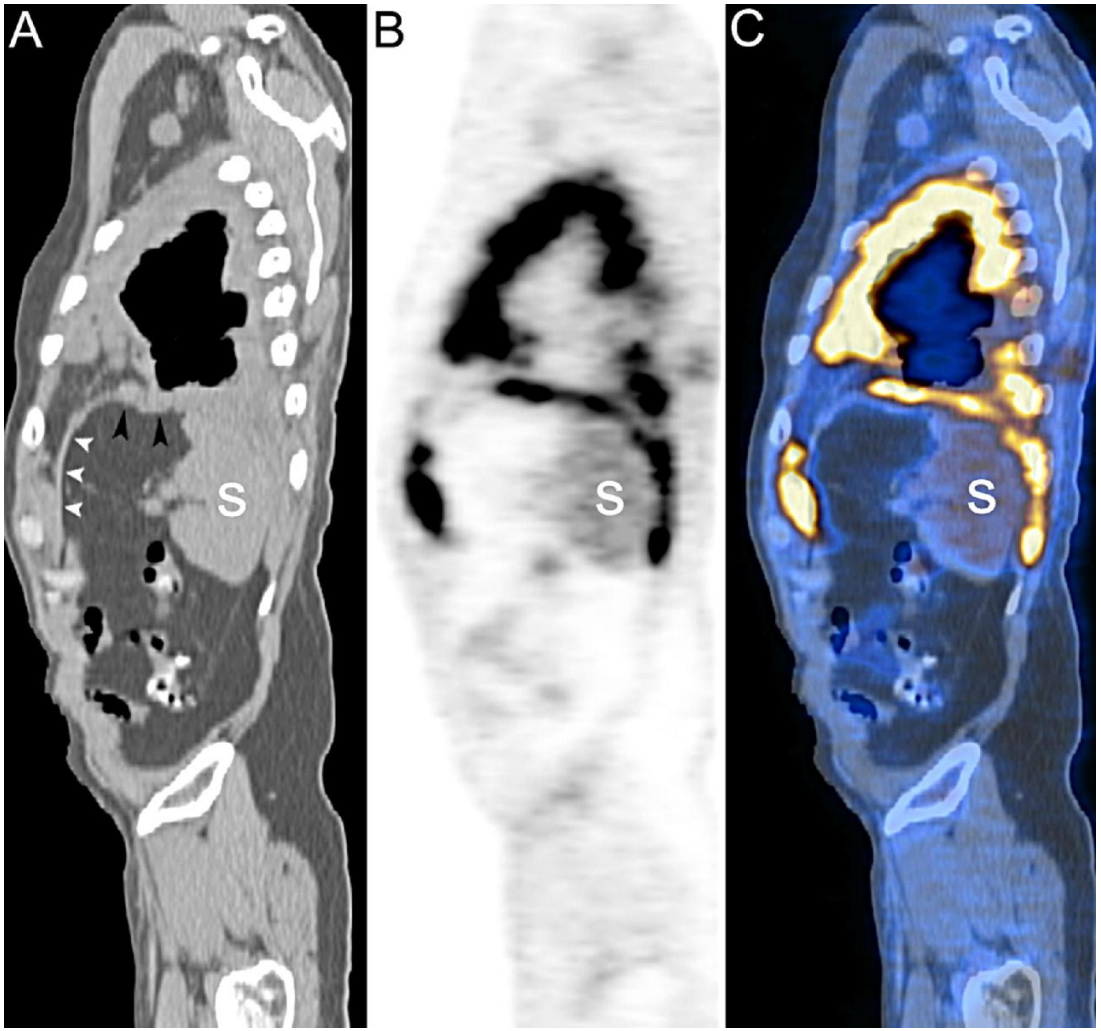
Disclosures

Honoraria for advisory board work or speaker bureau activites from Pfizer, Roche, AZD, Boehringer, BMS, MSD



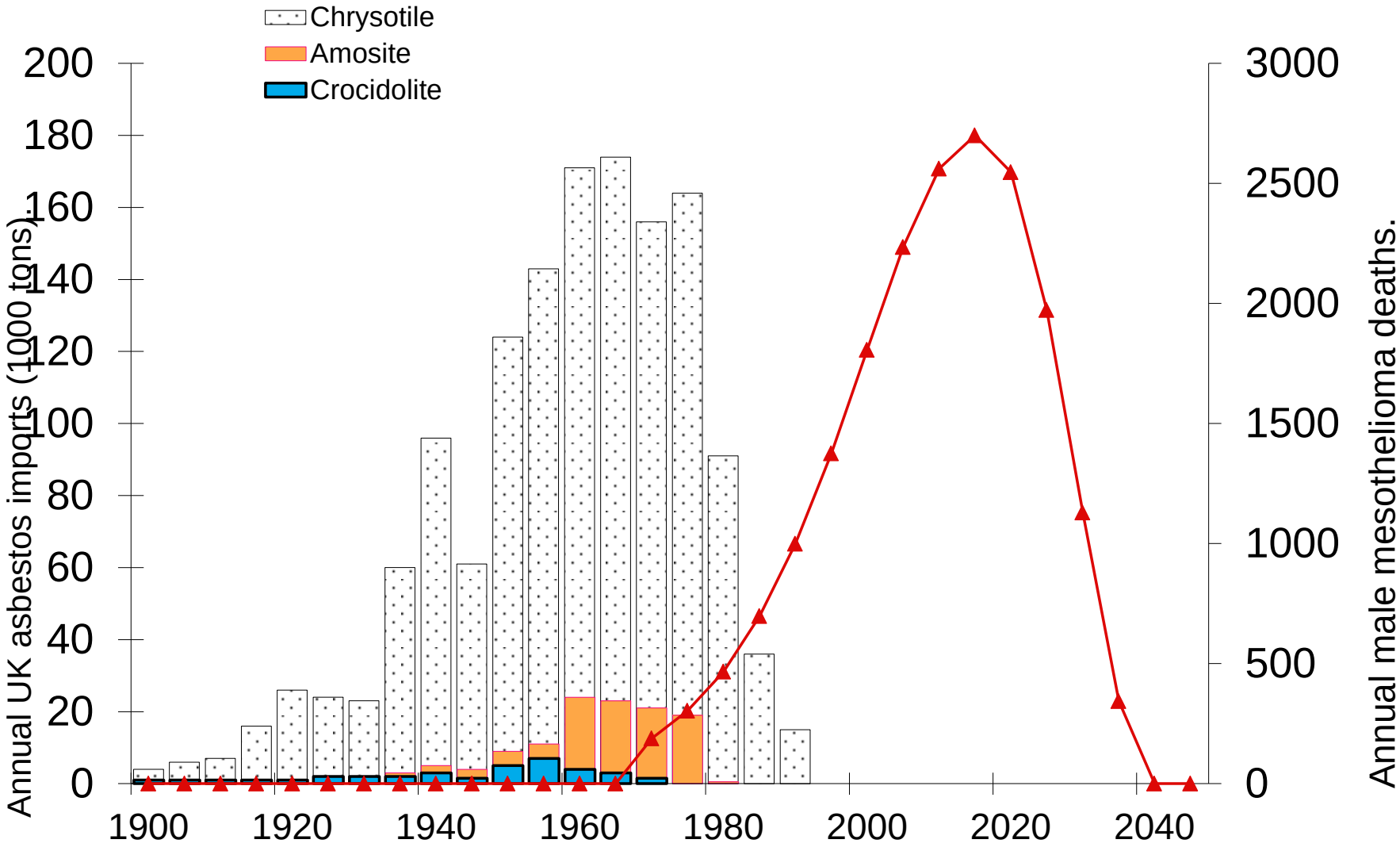


Sagittal CT (A), PET (B), and integrated CT-PET (C) show diffuse uptake of FDG in malignant pleural mesothelioma (MPM)



Erasmus JJ et al, J Thorac Cardiovasc Surg 2005;129:1364-1370

UK asbestos imports & predicted mesothelioma deaths in men born before 1953



Source: Peto et al

UK National Lung Cancer Audit

- 8740 cases MPM 2008-2012
- 83% male, median age 73 years
- 70% PS 0-2, 54% PS 0-1
- 192 (2.4%) pleurectomy/decortication
- 9 (0.1%) EPP

- Median survival for PS-0, epithelioid variant is 18.3 months

How do we Define Locally Advanced Disease in Mesothelioma?

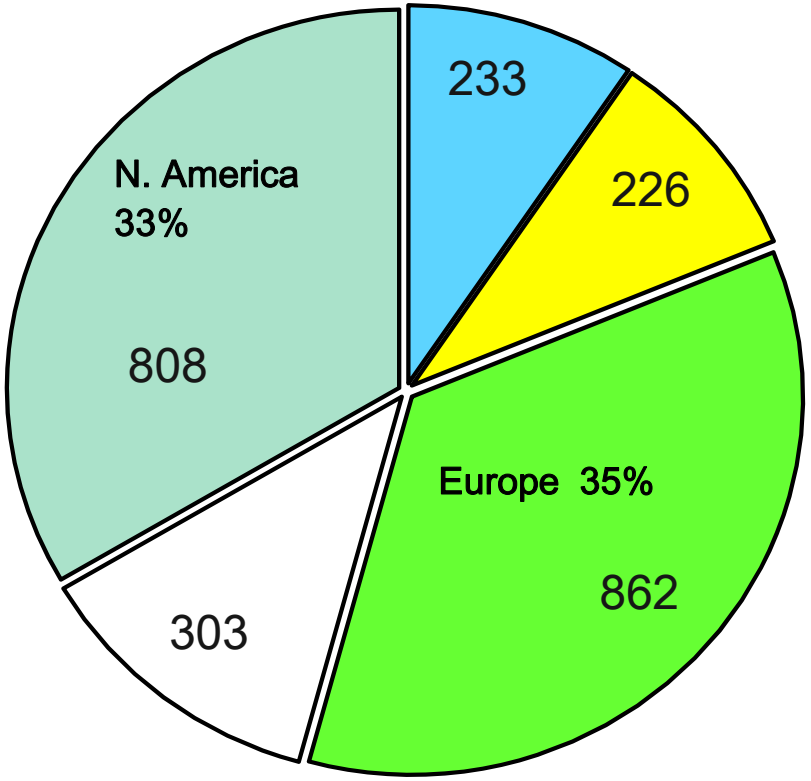
Analysis of the IASLC Malignant Pleural Mesothelioma Database

Valerie Rusch, Kari Chansky, Anna Nowak,
David Rice, Hedy Lee Kindler, Harvey Pass
on behalf of the Mesothelioma Domain (MD)
of the IASLC International Staging and Prognostic Factors Committee (ISC)

Memorial Sloan-Kettering Cancer Center, New York, New York, USA
Cancer Research and Biostatistics, Seattle, Washington, USA
University of Western Australia, Perth, Australia
MD Anderson Cancer Center, Houston, Texas, USA
University of Chicago, Chicago, Illinois USA
NYU School of Medicine, New York, New York, USA

Presentation Number: 1734 ... Presentation Title: IASLC Meso Database Presenting Au...

IASLC Mesothelioma (MPM) Staging Data Base
Regional Representation, Eligible Cases



3,427 cases total
2,184 analyzable

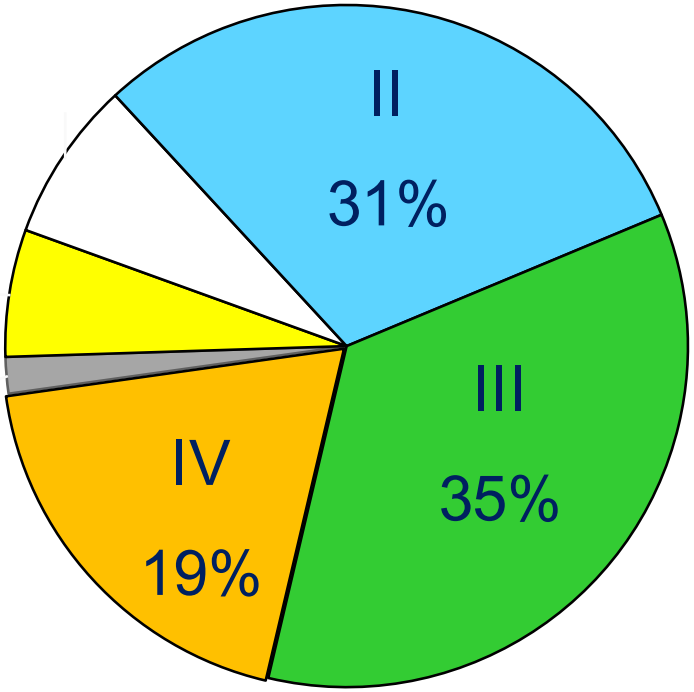
Cases predominantly from 2000-13

Data cutoff: June 30, 2013

Clinical staging only: 1/3
Path staging only: 1/3
Clinical + path staging: 1/3

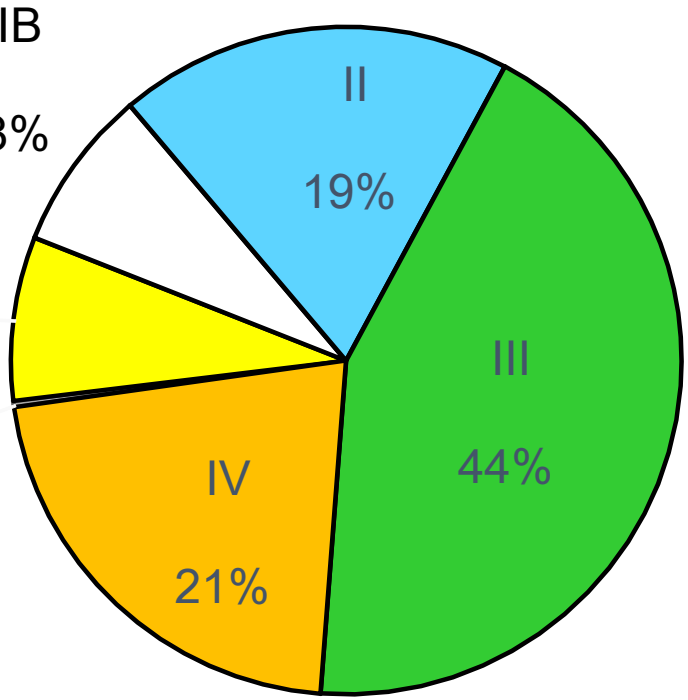
IASLC Mesothelioma Staging Data Base
Stage Distribution

Clinical Stages



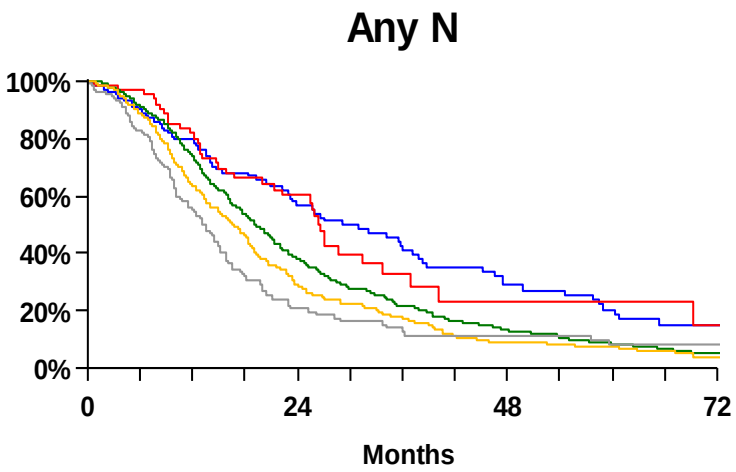
IA
8%
I
0%

Path Stages



44% of patients had EPP or EPD or P/D

Current T categories: Clinical Staging
Restricted Subset: Cases With T Descriptor Support

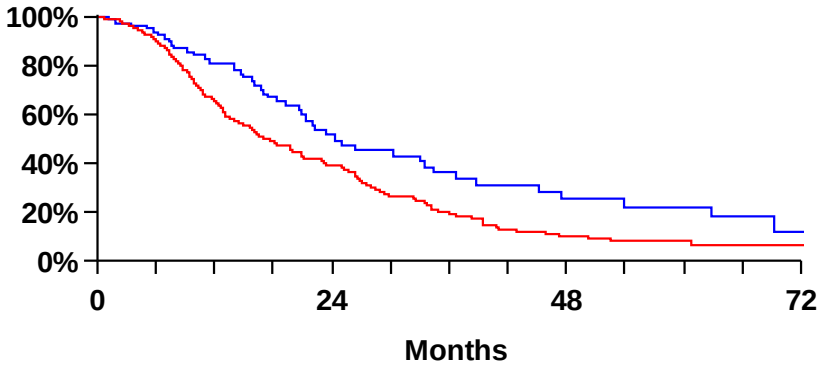


cT	Events / N	MST	24 Month	60 Month
T1a	70 / 107	29.1	57%	20%
T1b	37 / 67	26.5	60%	23%
T2	388 / 508	19.0	38%	9%
T3	247 / 325	16.7	29%	8%
T4	109 / 144	13.4	21%	8%

Comparisons for Adjacent T Stage categories (Adjusted for R0/1 vs Others, including non-surg)

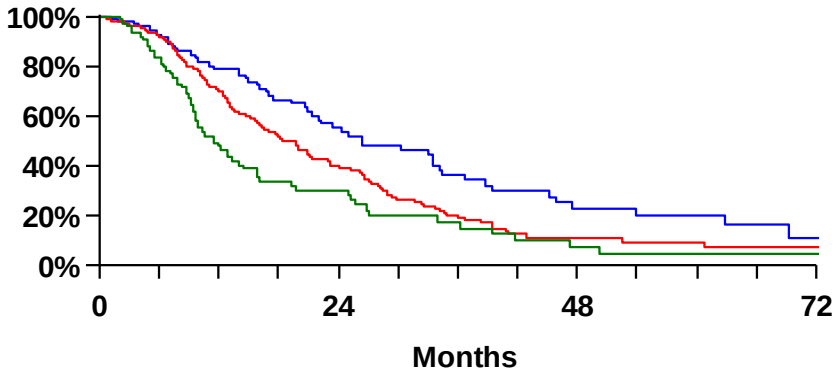
comparison	HR	P
T1b vs T1a	1.05	0.8117
T2 vs T1b	1.45	0.0304
T3 vs T2	1.23	0.0126
T4 vs T3	1.21	0.0998

Maximum Thickness of Three Levels With Best Cutpoint - M0 Any N



Max (mm)	Events / N	MST	24 Month	60 Month
<5.1	47 / 81	24.2	51%	22%
>=5.1	259 / 391	17.7	39%	8%

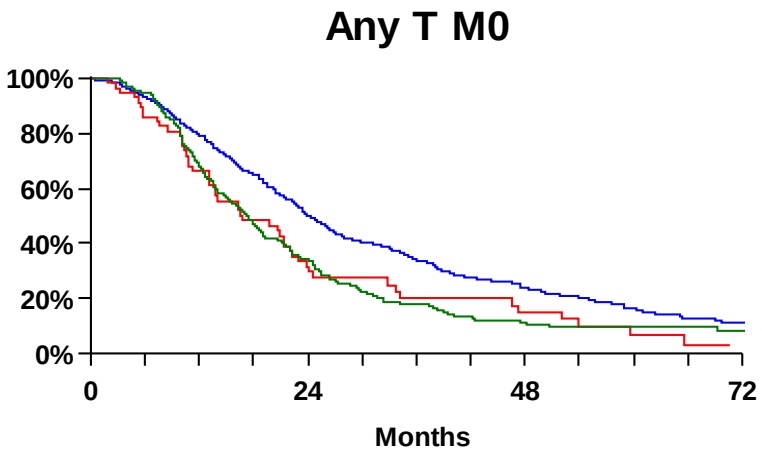
Sum of Thickness Levels With Best Cutpoints - M0 Any N



Sum (mm)	Events / N	MST	24 Month	60 Month
<13	56 / 98	26.3	55%	20%
13-60	190 / 296	18.5	40%	9%
60+	60 / 78	11.5	30%	5%

By either method, increasing pleural thickness is associated with increasing frequency of (+) lymph nodes (range of 13.5 to 47.4%)

Pathologic N Stage Comparisons* (7th Edition)



pN	Events / N	MST	24 Month	60 Month
N0	406 / 530	24.0	50%	16%
N1	49 / 58	16.9	32%	7%
N2	208 / 256	17.4	34%	10%

Single vs. multi station nodal involvement

comparison	HR	P
N2 Single vs N0*	1.21	.24
Other N1/N2 vs N2 Single	1.36	.07

N1 vs. N2 nodal involvement

comparison	HR	P
N1 vs N0	1.51	.0063
N2 vs N1	0.99	0.99

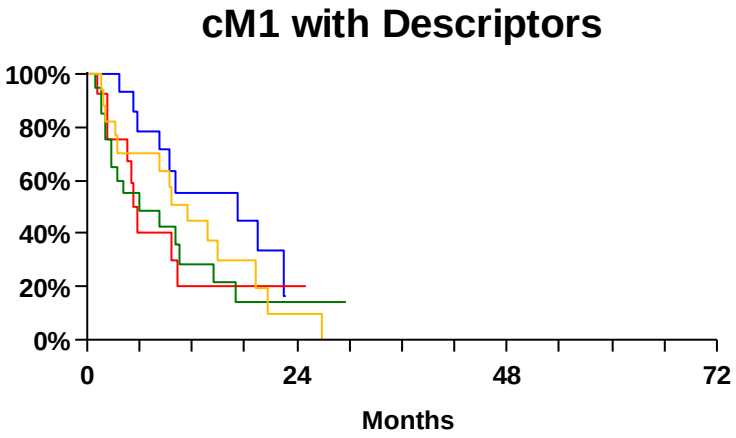
*** Unstable comparison due to small #**

In Summary:

N2 vs N0 HR = 1.51 P<.0001

N+ vs N0 HR = 1.51 P<.0001

Metastatic Sites: Pre-Treatment Stage



M0 vs. all M1 significantly different OS

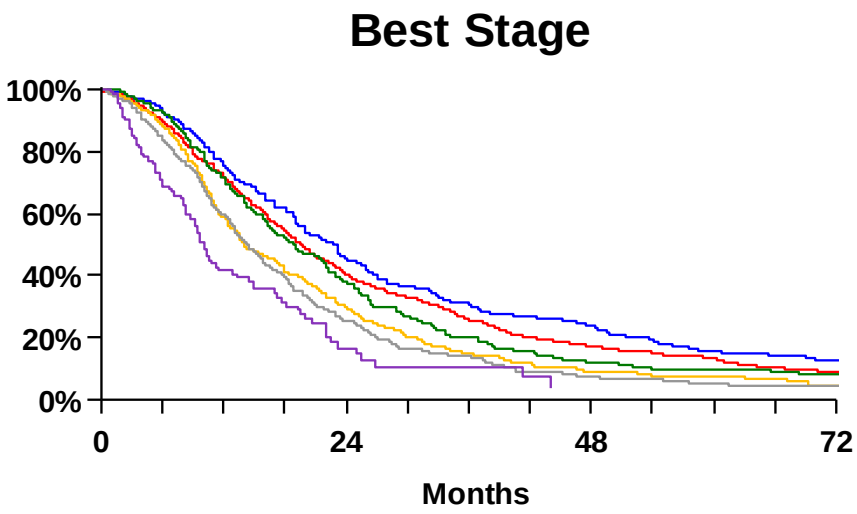
	Events / N	MST	24 Month	60 Month
1.Single lesion, single site	9 / 18	17.3	0	0
2.Multiple lesions, single site	9 / 14	5.8	20%	0
3.Multiple sites	15 / 21	6.1	14%	0
4.Single site, lesions NOS	14 / 17	11.5	10%	0%

Proposed Stage Groupings for the 8th Edition

(developed via recursive partitioning analysis)

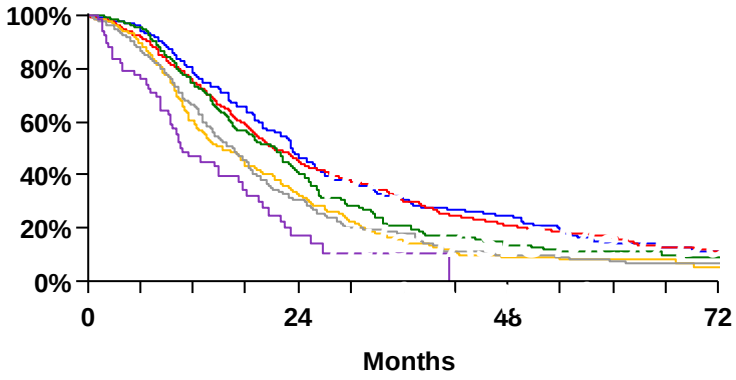
	N0		N1/2 (new N1)		N3 (new N2)	
	v7	v8	v7	v8	v7	v8
T1	I (A,B)	IA	III	II	IV	IIIB
T2	II	IB	III	II	IV	IIIB
T3	II	IB	III	IIIA	IV	IIIB
T4	IV	IIIB	IV	IIIB	IV	IIIB
M1	IV	IV	IV	IV	IV	IV

- *T1 a, T1b consolidated into T1*
- *All ipsilat. LN now N1*
- *Contralat. / supraclav LN now N2*



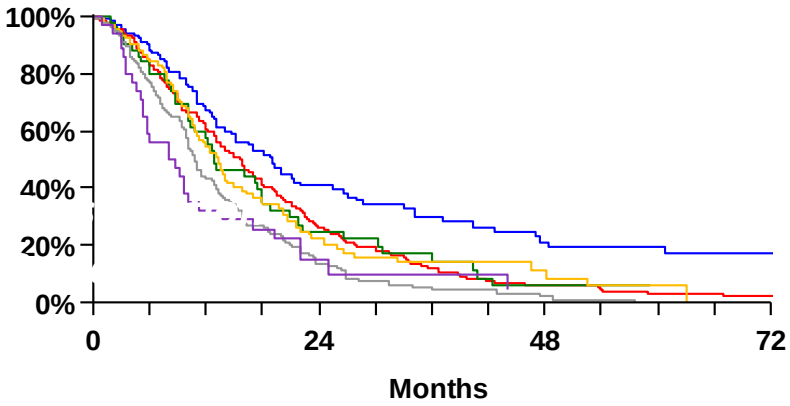
Proposed Stage Groupings for the 8th Edition
Histology Subsets

Best Stage - Epithelioid



	Events / N	MST	24 Month	60 Month
IA	181 / 253	23.3	48%	14%
IB	499 / 676	21.1	46%	17%
II	147 / 203	21.6	41%	11%
IIIA	189 / 228	15.4	33%	8%
IIIB	253 / 335	16.6	31%	8%
IV	49 / 70	10.7	17%	0%

Best Stage - Non-Epithelioid



	Events / N	MST	24 Month	60 Month
IA	73 / 103	19.0	41%	19%
IB	195 / 230	15.5	27%	3%
II	42 / 51	12.9	25%	0%
IIIA	76 / 90	13.2	22%	6%
IIIB	126 / 138	10.8	14%	0%
IV	30 / 37	8.7	15%	0%

Systematic Review: Lancet 2004

Pleural mesothelioma: little evidence, still time to do trials

Tom Treasure, Artyom Sedrakyan

Lancet 2004; 364: 1183–85

Cardiothoracic Unit, Guy's Hospital, London SE1 9RT, UK (Prof T Treasure MD); and School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA (A Sedrakyan MD)
Tom.Treasure@ukgateway.net

Context The incidence of malignant pleural mesothelioma is increasing throughout most of the world. This cancer is uniformly fatal, and characterised by progressive breathlessness and unremitting pain in the chest wall. From the onset of symptoms, survival is from a few weeks to a few years. Desperation by patients and doctors has driven a search for effective treatments. Clinical benefits are marginal and evidence of a good quality is lamentably lacking.

Starting point David Sugarbaker is the world's leading proponent of extrapleural pneumonectomy (EPP), an operation in which all the pleura is removed with the lung, pericardium, and diaphragm. He has recently reported the complications of this radical surgery in a series of 496 operations (*J Thorac Cardiovasc Surg* 2004; 128: 138–46). Although EPP as part of trimodality therapy (preoperative chemotherapy and postoperative radiation) is thought to be the best that can be offerred and is regarded as the standard of care for selected patients given the morbidity associated with it, evidence for benefit is needed to justify its wider use.

Where next? With the increase in the number of cases there is increasing awareness of the disease, leading to earlier diagnosis, and an expectation that something must be done. Survival is short and the treatments on offer are onerous. The only responsible approach from a scientific, compassionate, or economic view (and why not combine all three?) is to find evidence of effectiveness to avoid futile and distressing treatment when possible.

Treasure and Sedrakyan
Lancet 2004;**364**:1183-5

Surgery

Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients

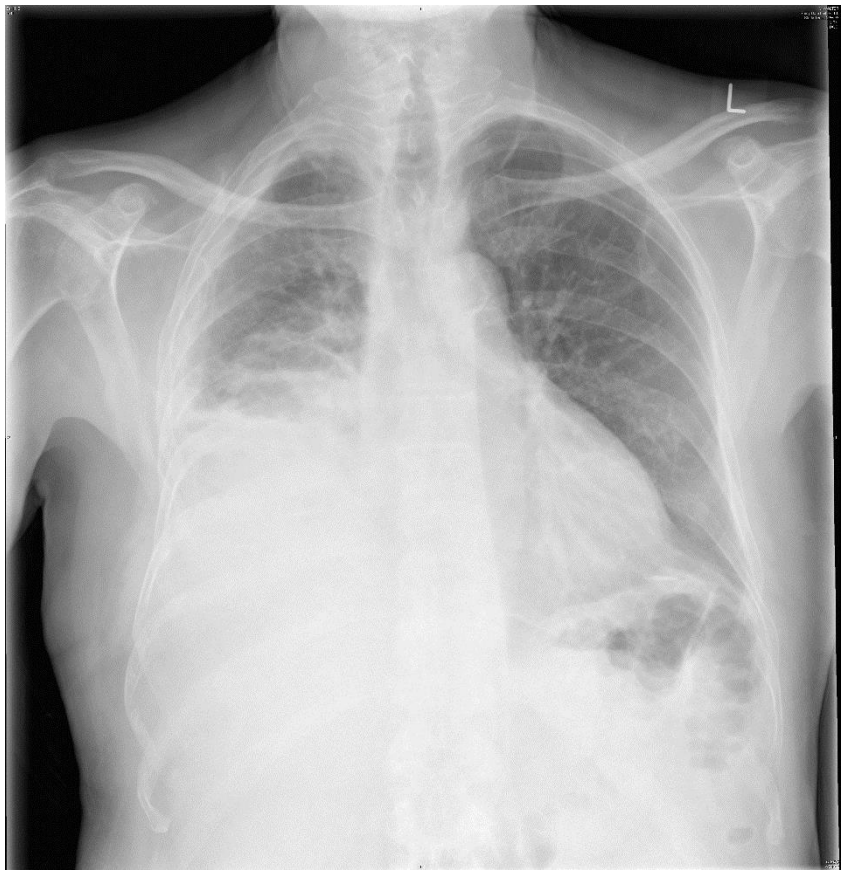
Taioli E, Wolf AS, Camacho-Rivera M, Kaufman A, Lee DS, Nicastri D, Rosenzweig K, Flores RM

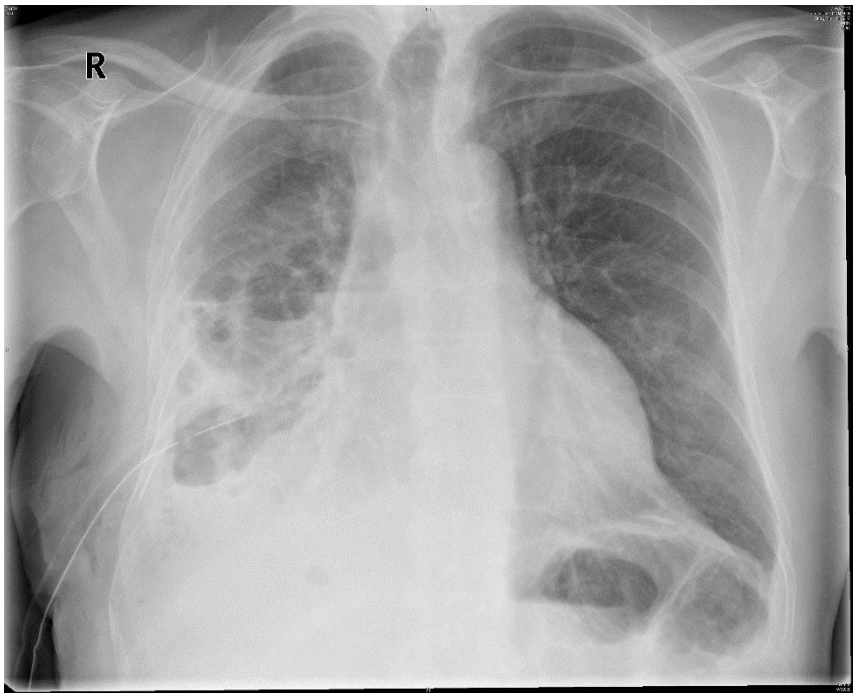
PLoS One. 2015 Dec 14;10(12):e0145039. doi: 10.1371/journal.pone.0145039. eCollection 2015.

Summary of Results

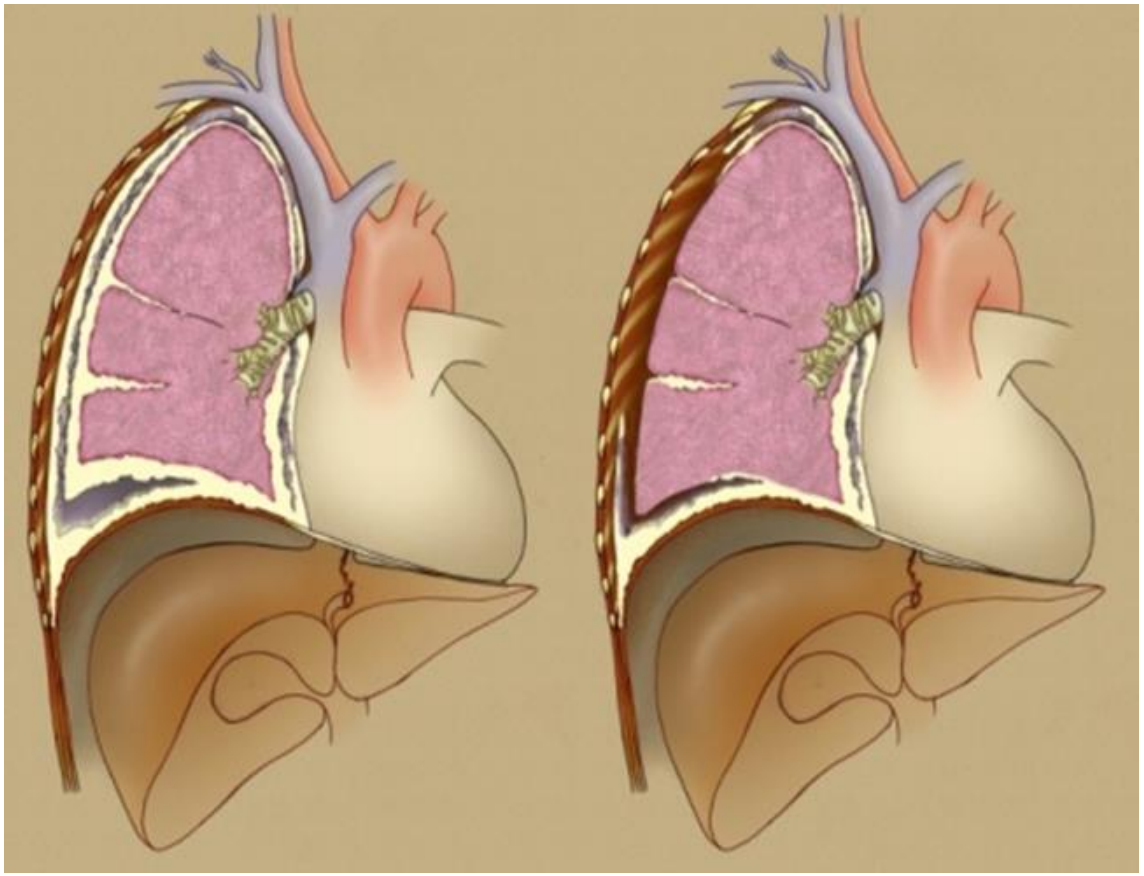
- Despite developments in surgical and radiation techniques, the prognosis for MPM patients has not improved over the past 4 decades.
- Cancer-directed surgery is independently associated with better survival, suggesting that multimodal surgery-based therapy can benefit these patients
- Surgery and radiation combined had similar survival as surgery alone
- Further research in adjuvant treatment is necessary to improve prognosis in this challenging disease
  - ***However Surgery performed on highly selected fit patients; hence a significant bias***

Pre & Post Talc Thoracoscopic Pleurodesis





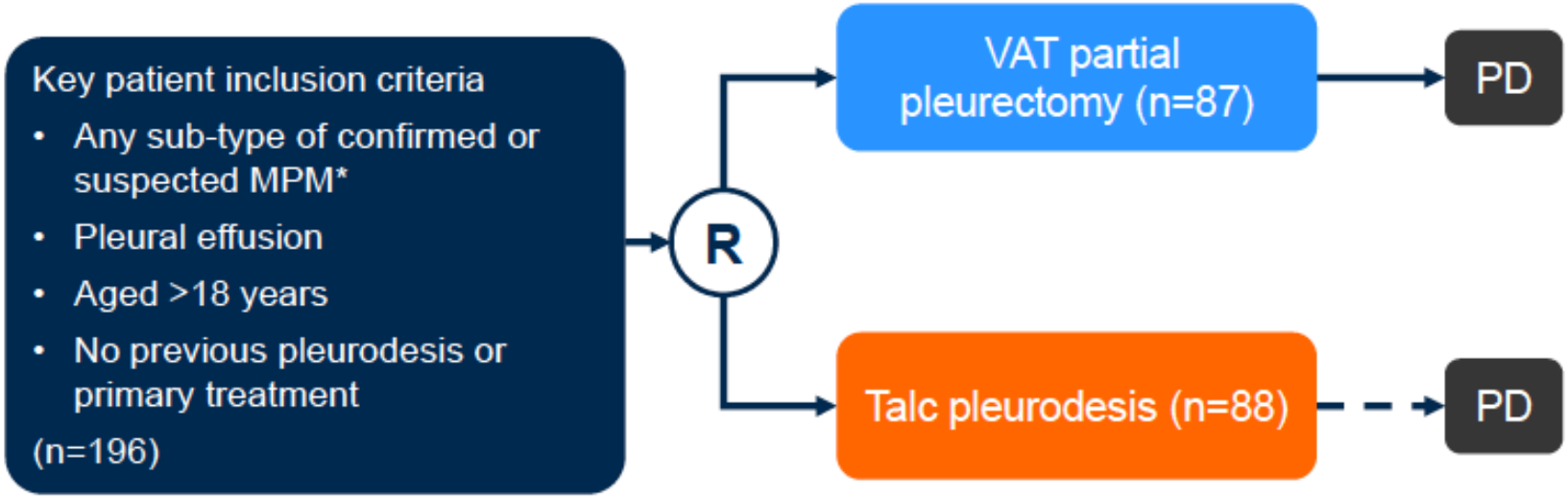
Video assisted thoracoscopic partial pleurectomy



PL03.03 MesoVATS: A multi-centre randomised controlled trial of video assisted thoracoscopic pleurectomy versus talc pleurodesis in malignant pleural mesothelioma – *Rintoul RC et al*

Randomised, open-label, parallel-group, controlled, multicentre study

Objective: To compare video-assisted thoracoscopic (VAT) pleurectomy with talc pleurodesis in patients with malignant pleural mesothelioma (MPM)



Primary endpoint

- 1-year survival

Secondary endpoints

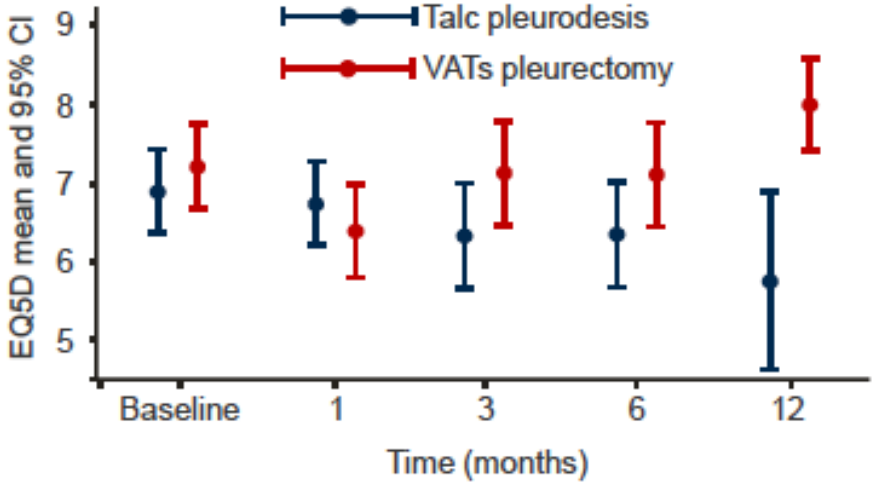
- QoL, control of pleural effusion, complications, length of hospital stay, lung function

*21 suspected cases were confirmed not to be MPM and were excluded from the main analysis

Rintoul et al. J Thorac Oncol 8, 2013; (Suppl 2; PL03.03)

MesoVATS: results

- **Key results**
  - Survival at 12 months was not significantly different between talc pleurodesis (57%) and VAT (52%, log-rank test p=0.83)



Time period	Difference VATs-Talc, adjusted for baseline (95% CI)	p-value
1 month (n=137)	–0.06 (–0.13, 0.004)	0.06
3 months (n=129)	0.04 (–0.03, 0.12)	0.267
6 months (n=109)	0.08 (0.003, 0.16)	0.042
12 months (n=68)	0.19 (0.05, 0.32)	0.006

  - Pleural effusion was significantly controlled with VAT compared with talc pleurodesis at 1 month (59% vs. 37%; p=0.008) and 6 months (76% vs. 57%; p=0.04), but control was similar at 9 and 12 months
  - Compared with talc pleurodesis, hospital stays were significantly longer (6 vs. 8 days, p<0.001) and complications (e.g. air leak) were more common with VAT; the incidence of serious AEs did not differ between groups
- **Key conclusions**
  - Overall survival did not differ between VAT partial pleurectomy and talc pleurodesis, but control of pleural effusion and QoL were improved by VAT partial pleurectomy

Rintoul et al. J Thorac Oncol 8, 2013; (Suppl 2; PL03.03)

Radical surgery

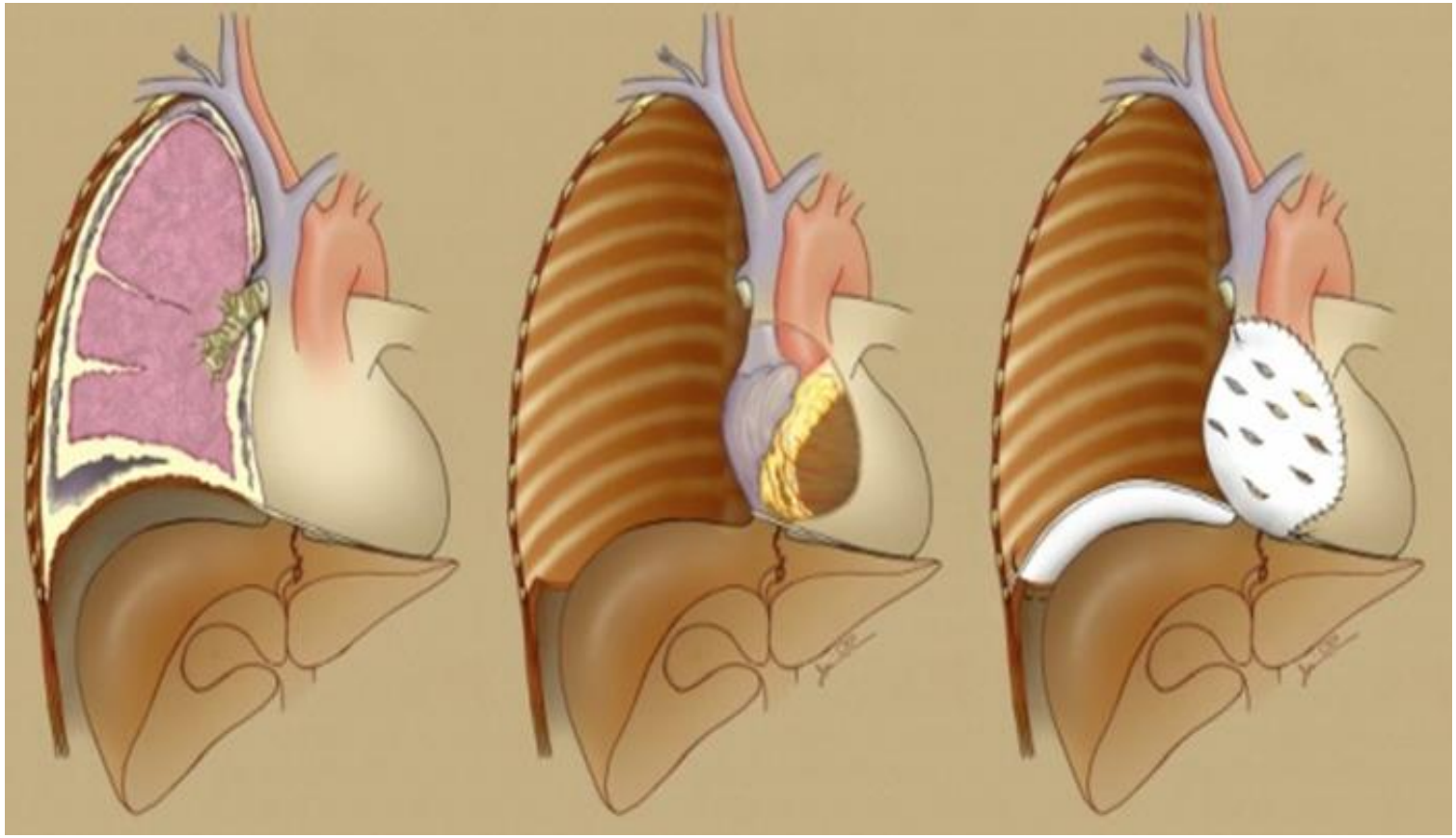
Extra Pleural Pneumonectomy

EPP

Extrapleural Pneumonectomy

- En bloc resection of ipsilateral pleura, lung, hemidiaphragm, and pericardium
- Considerable mortality and morbidity
- Reserved for fit patients with early disease

Extra pleural pneumonectomy



Study	Number of patients	Age (years)	Female (%)	Epitheloid cancer (%)	Treatment	In-hospital death (%)	Median survival (months)
Sugarbaker et al, 1999[18]	183	57 (mean)	23	56	EPP+chemotherapy+radiotherapy	3·8	19
Maggi et al, 2001[25]	32	53 (median)	33	100	Mostly EPP+chemotherapy+radiotherapy	6·2	Not clear
Rusch et al, 2001[26]	61	62 (median)	17	68	EPP+radiotherapy	7·9	17*
Aziz et al, 2002[20]	51	<60	..	54	EPP+chemotherapy	9·1	35
Lee et al, 2002[27]	26	69 (median)	19	73	EPP+chemotherapy+radiotherapy	6·9	18
Ahamad et al, 2003[28]	28	59 (mean)	7	79	EPP+radiotherapy	NA	24†
Stewart et al, 2004[29]	53	57 (median)	..	87	EPP+radiotherapy (not extensive)	7·5	17

*Demographics presented for 88 patients and survival calculated for 61 patients (surgery was not done in 21 patients, 1 dropped out, and 5 had pleurectomy and were not included in survival analyses). †Only patients surviving surgery were enrolled. EPP=extrapleural pneumonectomy. Chemotherapy was mostly cisplatin-based; radiation was on average around 54 Gy with some differences in techniques.

***Table 2:* Mesothelioma treatment**

- No randomised trials
- Completed protocol analysis defined retrospectively
- No intention to treat analysis
- Conditional on survival to that point

Treasure and Sedrakyan
Lancet 2004;**364**:1183-5

J Thorac Cardiovasc Surg 1999;117:54-65

GENERAL THORACIC SURGERY

RESECTION MARGINS, EXTRAPLEURAL NODAL STATUS, AND CELL TYPE DETERMINE POSTOPERATIVE LONG-TERM SURVIVAL IN TRIMODALITY THERAPY OF MALIGNANT PLEURAL MESOTHELIOMA: RESULTS IN 183 PATIENTS

David J. Sugarbaker, MD, Raja M. Flores, MD, Michael T. Jaklitsch, MD, William G. Richards, PhD, Gary M. Strauss, MD, Joseph M. Corson, MD, Malcolm M. DeCamp, Jr, MD, Scott J. Swanson, MD, Raphael Bueno, MD, Jeanne M. Lukanich, MD, Elizabeth Healey Baldini, MD, MPH, Steven J. Mentzer, MD

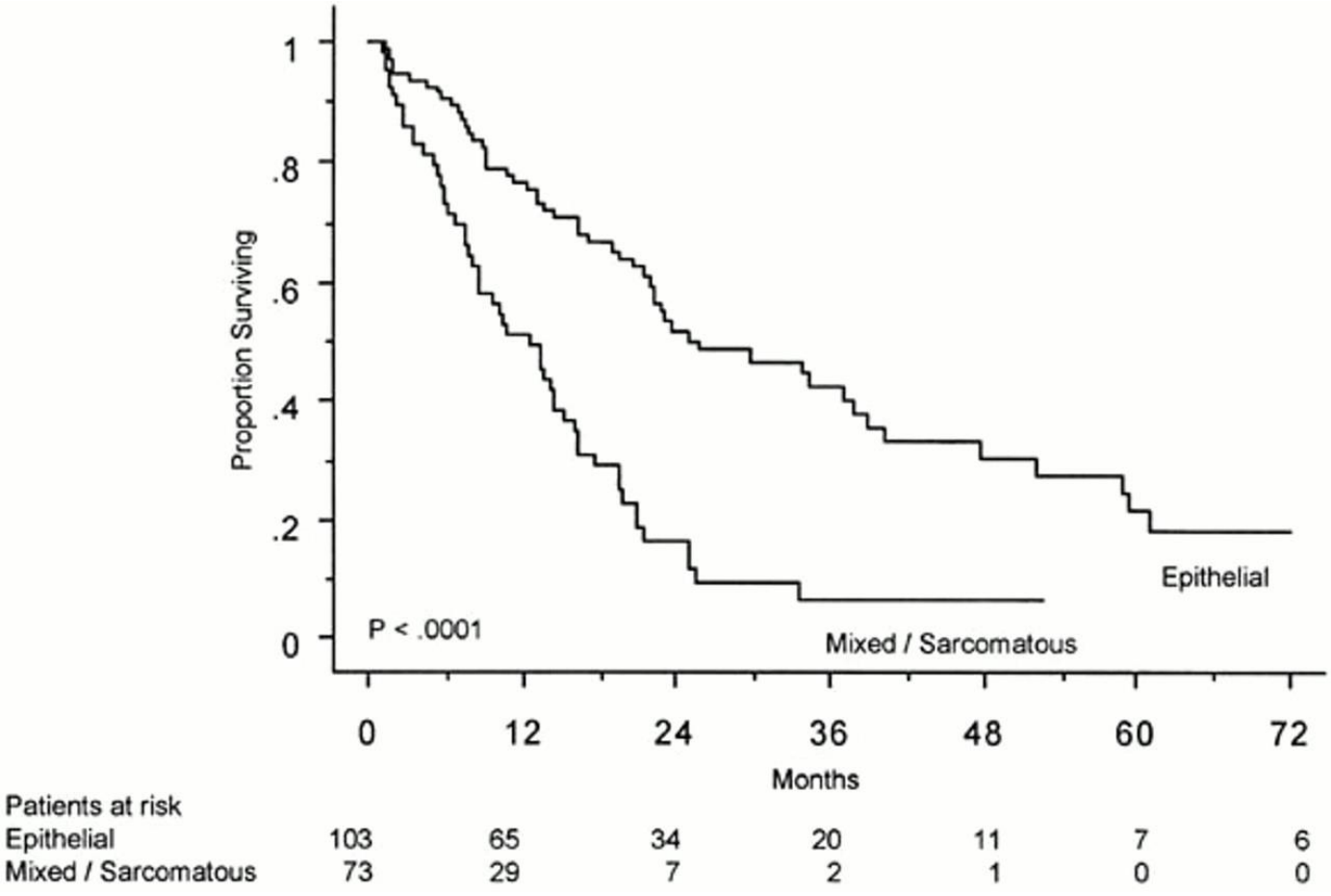
From the Division of Thoracic Surgery and the Department of Pathology, Brigham and Women's Hospital; Surgical Services and the Department of Adult Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Mass; and Hematology-Oncology, University of Massachusetts, Worcester, Mass.

Read at the Seventy-eighth Annual Meeting of The American Association for Thoracic Surgery, Boston, Mass, May 3-6

The 1999 Sugarbaker paper

- 183 cases selected for surgery
- 176 survived 30 days and are reported
- Multivariate analysis determined three features asssociated with longer survival

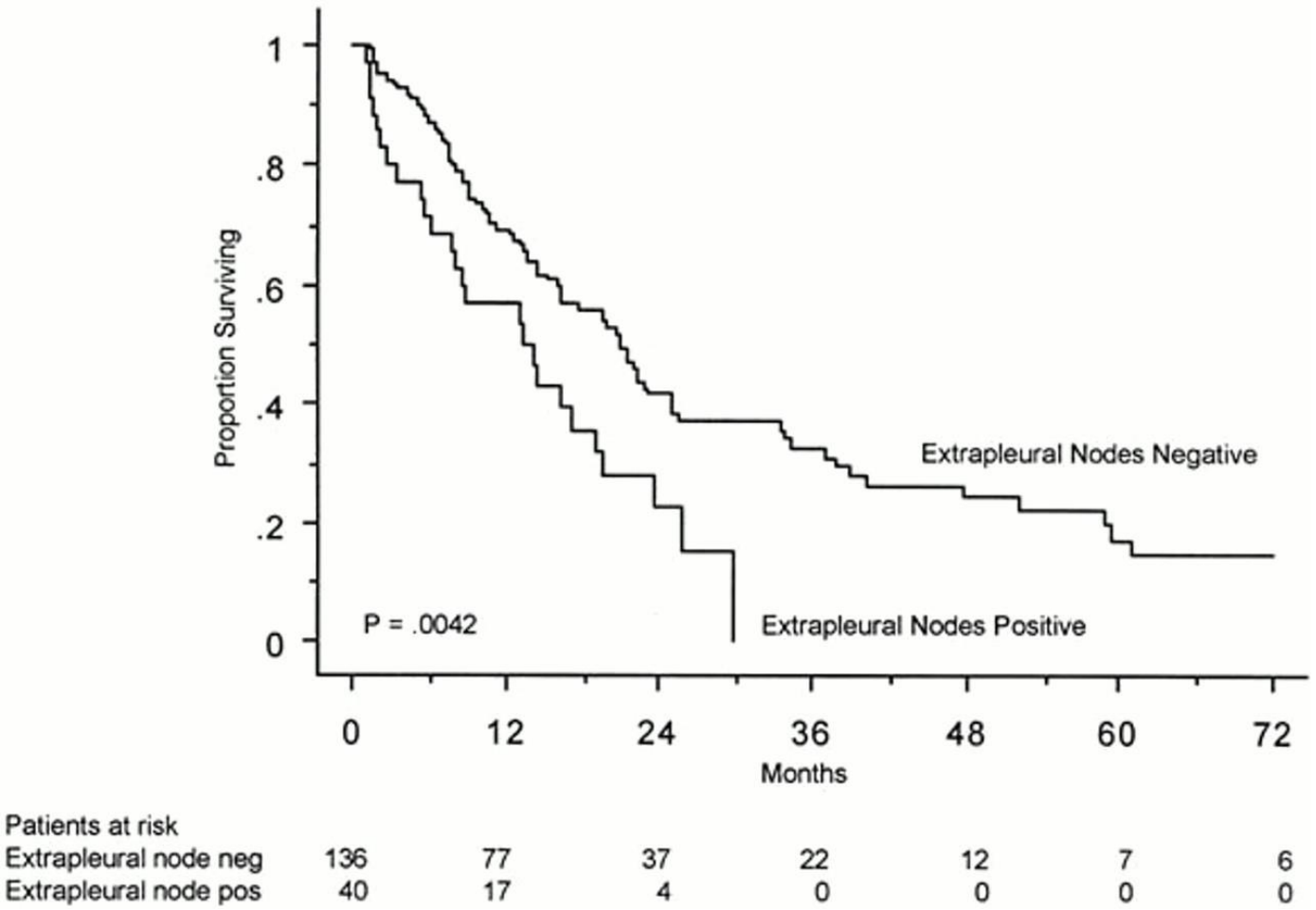
Type of Mesothelioma (Histology)



Patients at risk							
Epithelial	103	65	34	20	11	7	6
Mixed / Sarcomatous	73	29	7	2	1	0	0

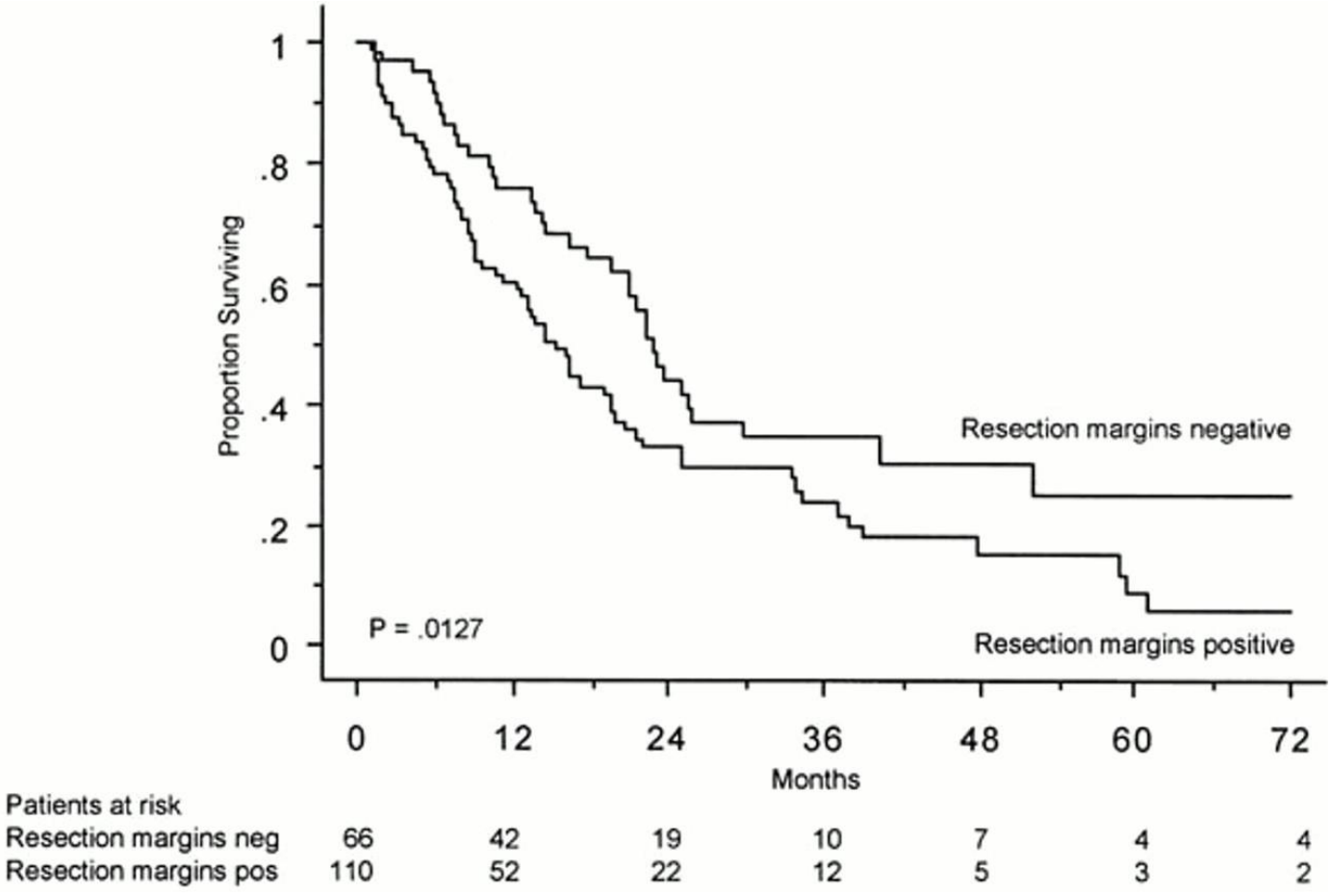
Sugarbaker D. J. et al.; J Thorac Cardiovasc Surg 1999;117:54-65

Mediastinal Nodal Status (N Stage)



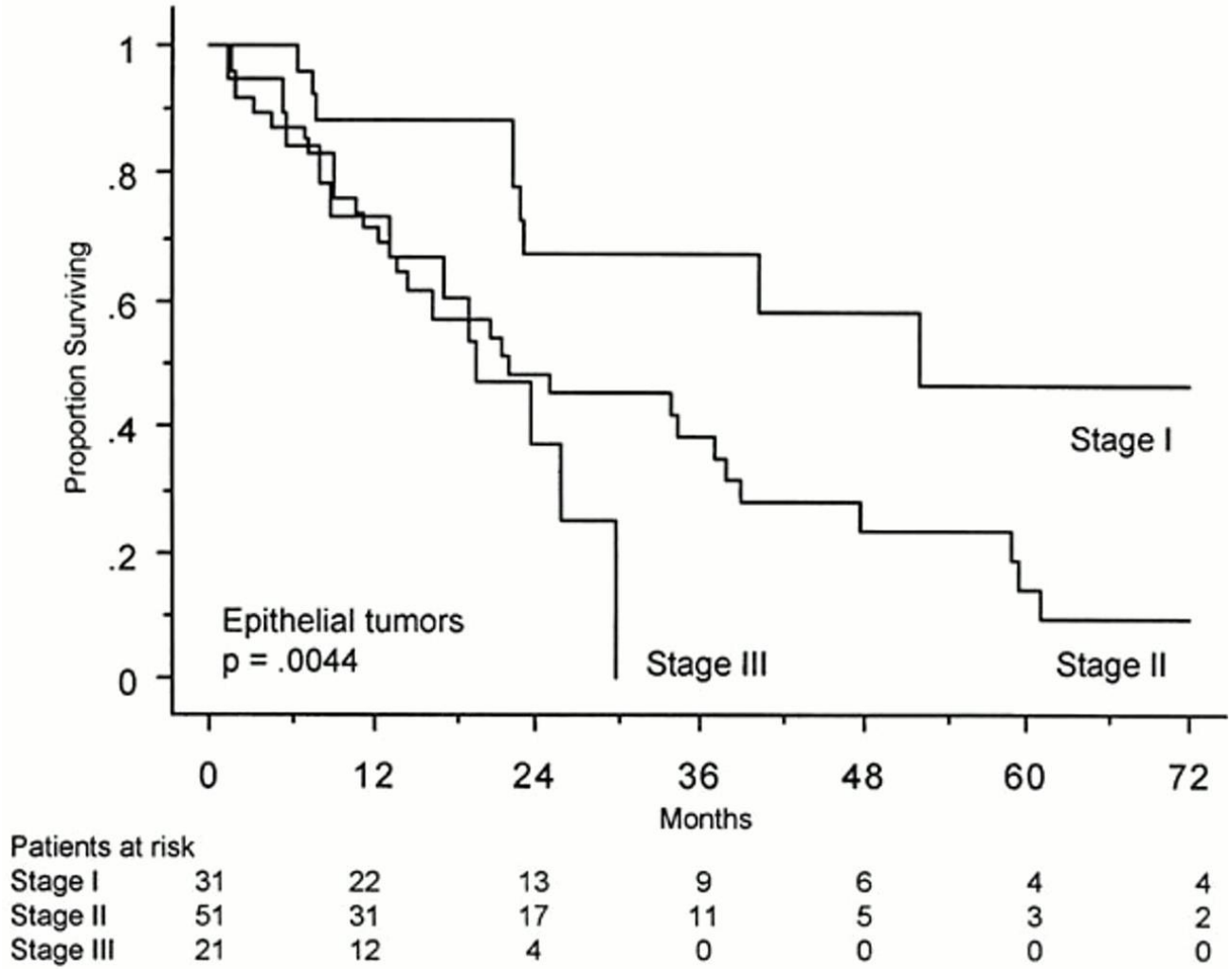
Sugarbaker D. J. et al.; J Thorac Cardiovasc Surg 1999;117:54-65

Surgical Clearance (R0/R1)



Sugarbaker D. J. et al.; J Thorac Cardiovasc Surg 1999;117:54-65

Figure 6



Sugarbaker D. J. et al.; J Thorac Cardiovasc Surg 1999;117:54-65

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

Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, Snee M, O'Brien M, Thomas G, Senan S, O'Byrne K, Kilburn LS, Spicer J, Landau D, Edwards J, Coombes G, Darlison L, Peto J and for the MARS Trialists

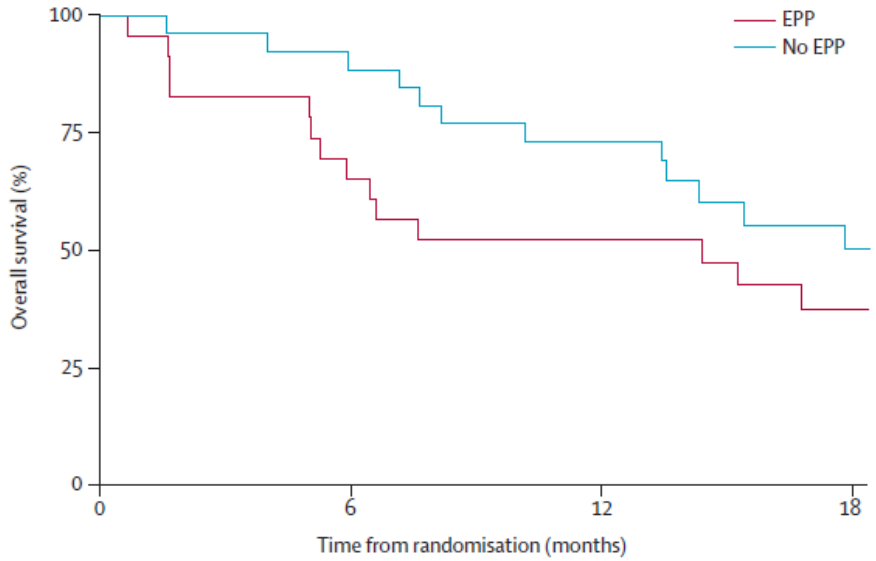
Lancet Oncol. 2011 Aug; 12(8): 763–772.
doi:10.1016/S1470-2045(11)70149-8 PMCID: PMC3148430

- 12 UK centres (2005-2008)
- 112 patients, 50 randomised
- 24 EPP, 26 no EPP

- Possible to recruit, but stopped for futility
- Large attrition between registration and surgery
- Questions on surgical quality, fidelity and outcomes

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

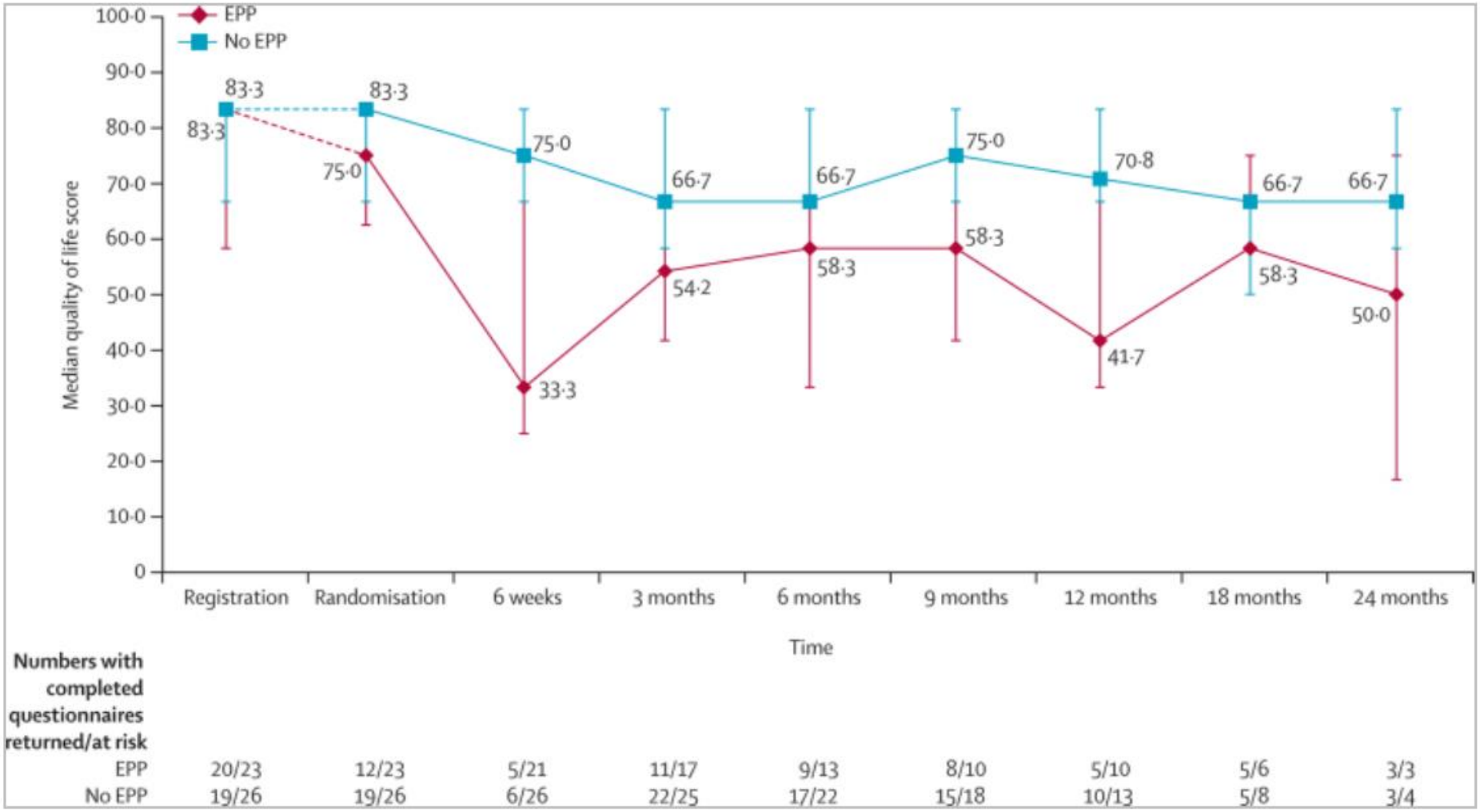
*Tom Treasure, Loic Lang-Lazdunski, David Waller, Judith M Bliss, Carol Tan, James Entwisle, Michael Snee, Mary O'Brien, Gill Thomas, Suresh Senan, Ken O'Byrne, Lucy S Kilburn, James Spicer, David Landau, John Edwards, Gill Coombes, Liz Darlison, Julian Peto, for the MARS trialists**



Number of events/ at risk				
EPP	0/24	8/16	3/12	3/8
No EPP	0/26	3/24	4/20	5/11

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.

Lancet Oncol 2011; 12: 763–72

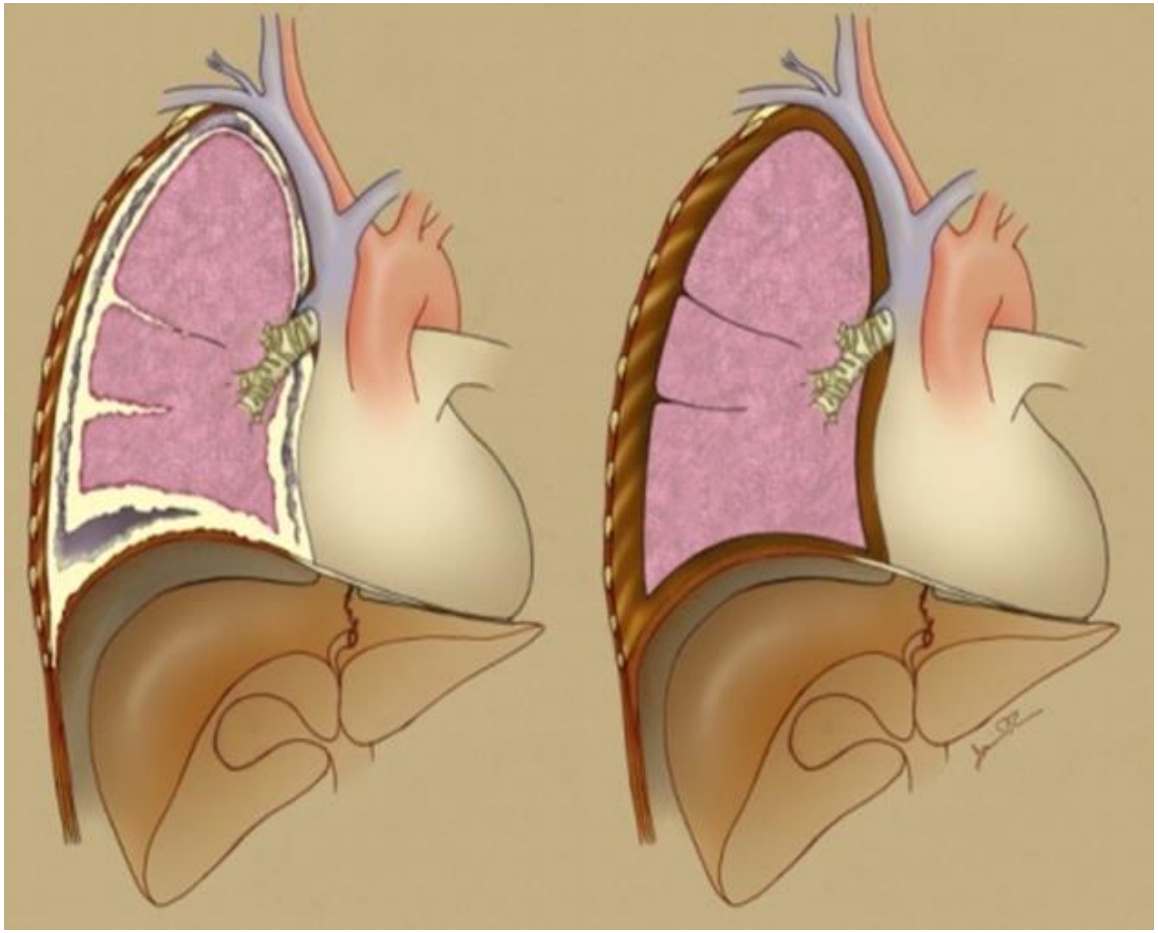


Numbers with completed questionnaires returned/at risk									
EPP	20/23	12/23	5/21	11/17	9/13	8/10	5/10	5/6	3/3
No EPP	19/26	19/26	6/26	22/25	17/22	15/18	10/13	5/8	3/4

Quality of life

Are there published series robust enough to guide therapy?

Extended Pleurectomy Decortication



Extended Pleurectomy Decortication

- Lung left behind
- Remove all gross evidence of tumour
- Pericardium and diaphragm left behind if they can be separated from the pleura
- Aim to get the lung fully expanded
- Used for palliation and ‘cure’

The effects of an intentional transition from extrapleural pneumonectomy to extended pleurectomy/decortication

Sharkey AJ, Tenconi S, Nakas A, Waller DA.

Eur J Cardiothorac Surg. 2015 Dec 3. pii: ezv403

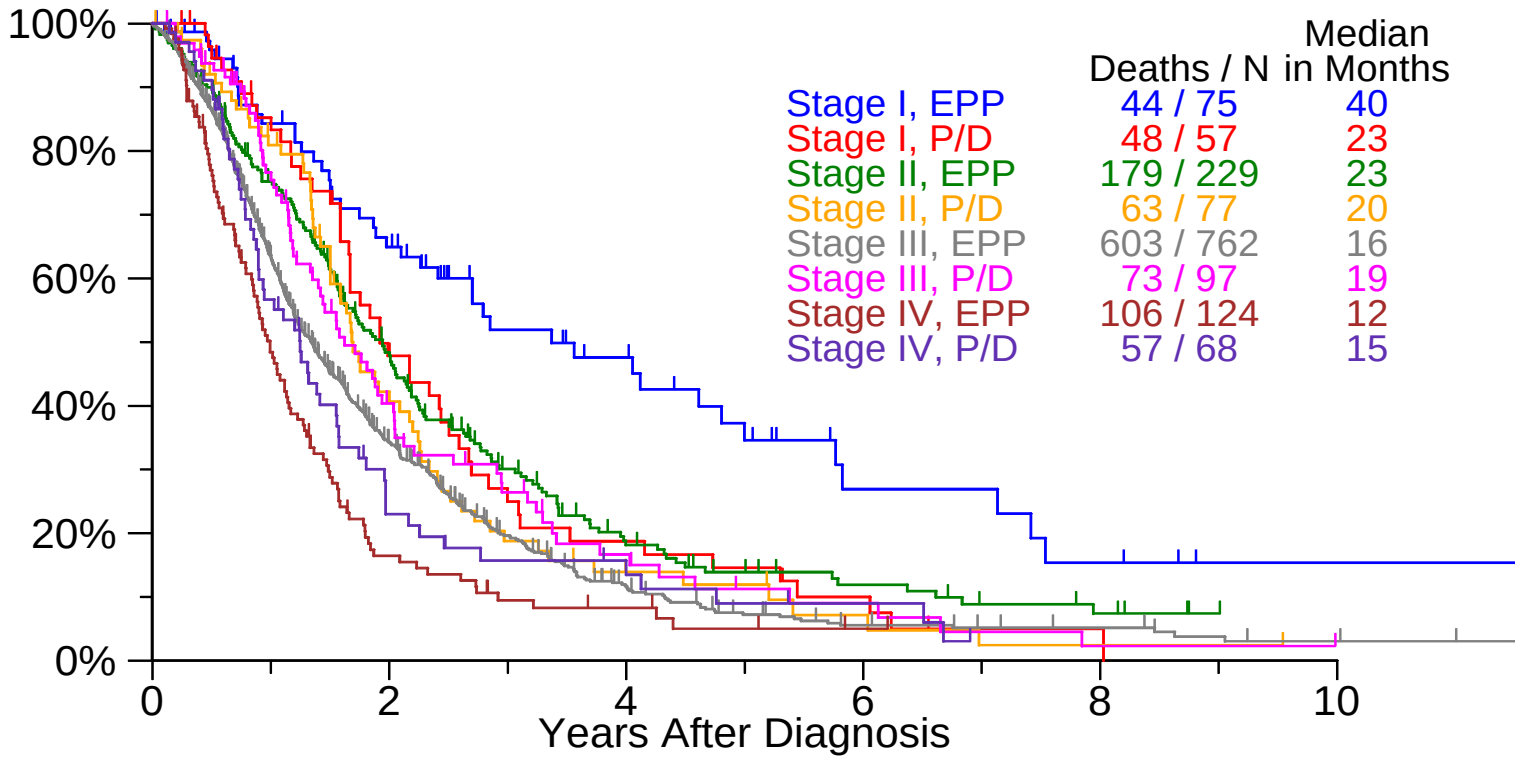
Summary of Results (1)

- Data from 362 patients undergoing radical surgery (229 EPD, 133 EPP) during 1999-2014 were included
- Median age of EPD significantly higher than EPP [57 years (range 14-70 years) vs 65 years (range 42-81 years), $P < 0.001$]
- Significantly higher proportion of patients with performance status ≥1 in the EPD group (46.3 vs 35.4%, $P = 0.047$)
- No difference in the median length of hospital stay between the two groups [14 days (range 1-133 days) vs 13 days (range 0-93 days), $P = 0.409$]
- No difference between the groups in terms of in-hospital mortality (EPP 5.3% and EPD 6.6%, $P = 0.389$), 30-day mortality [EPP 8 (6.0%) and EPD 8 (3.5%), $P = 0.294$] or 90-day mortality [EPP 18 (13.5%) and EPD 21 (9.2%), $P = 0.220$]

Summary of Results 2

- Significantly higher early reoperation rate in the EPP group (15.0 vs 6.2%, P = 0.008) but a significantly higher late reoperation rate in the EPD group (0.8 vs 5.3%, P = 0.037)
- No significant difference in overall survival or disease-free interval between the two groups (P = 0.899 and P = 0.399, respectively)
- Overall survival was significantly greater in patients over the age of 65 undergoing EPD (12.5 vs 4.7 months, P = 0.001).

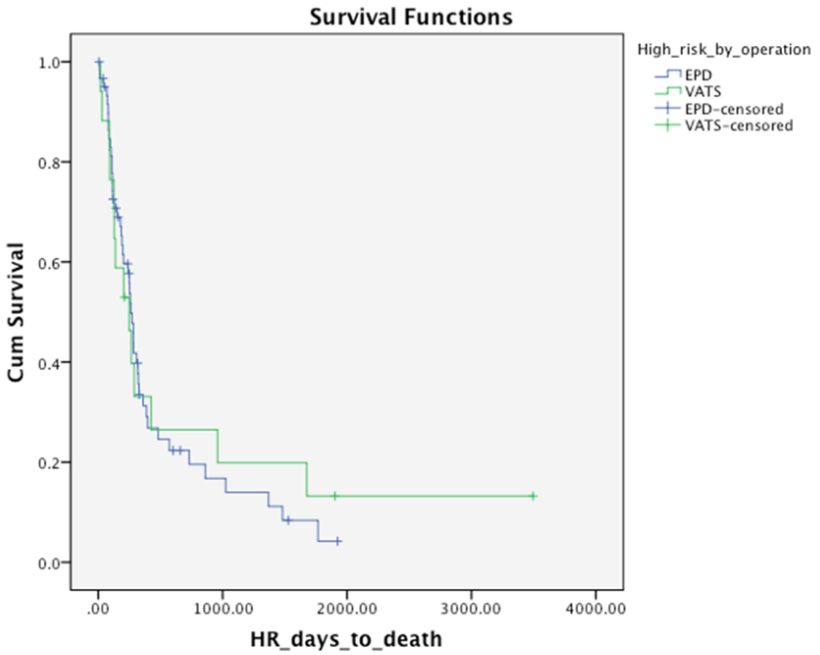
EPD equivalent to EPP except in Stage I



Initial analysis of the international association for the study of lung cancer mesothelioma database (Rusch VW,J Thorac Oncol. 2012 Nov;7(11):1631-9)

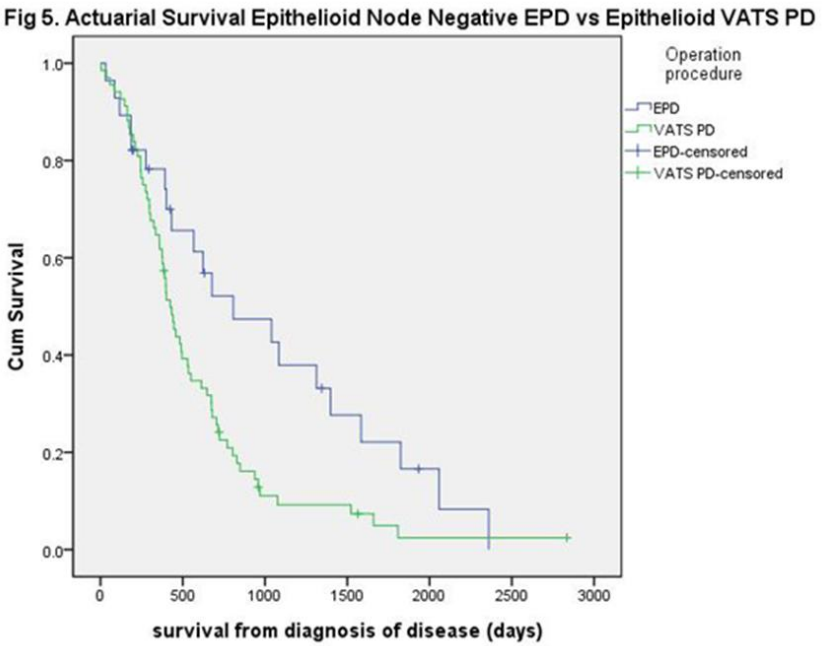
EPD may be an alternative to VATS in “good actors”

High risk



EPD 8.8mo v VAT 8.3mo

Low risk



EPD 27mo v VAT 14.4mo

To summarise surgical outcomes

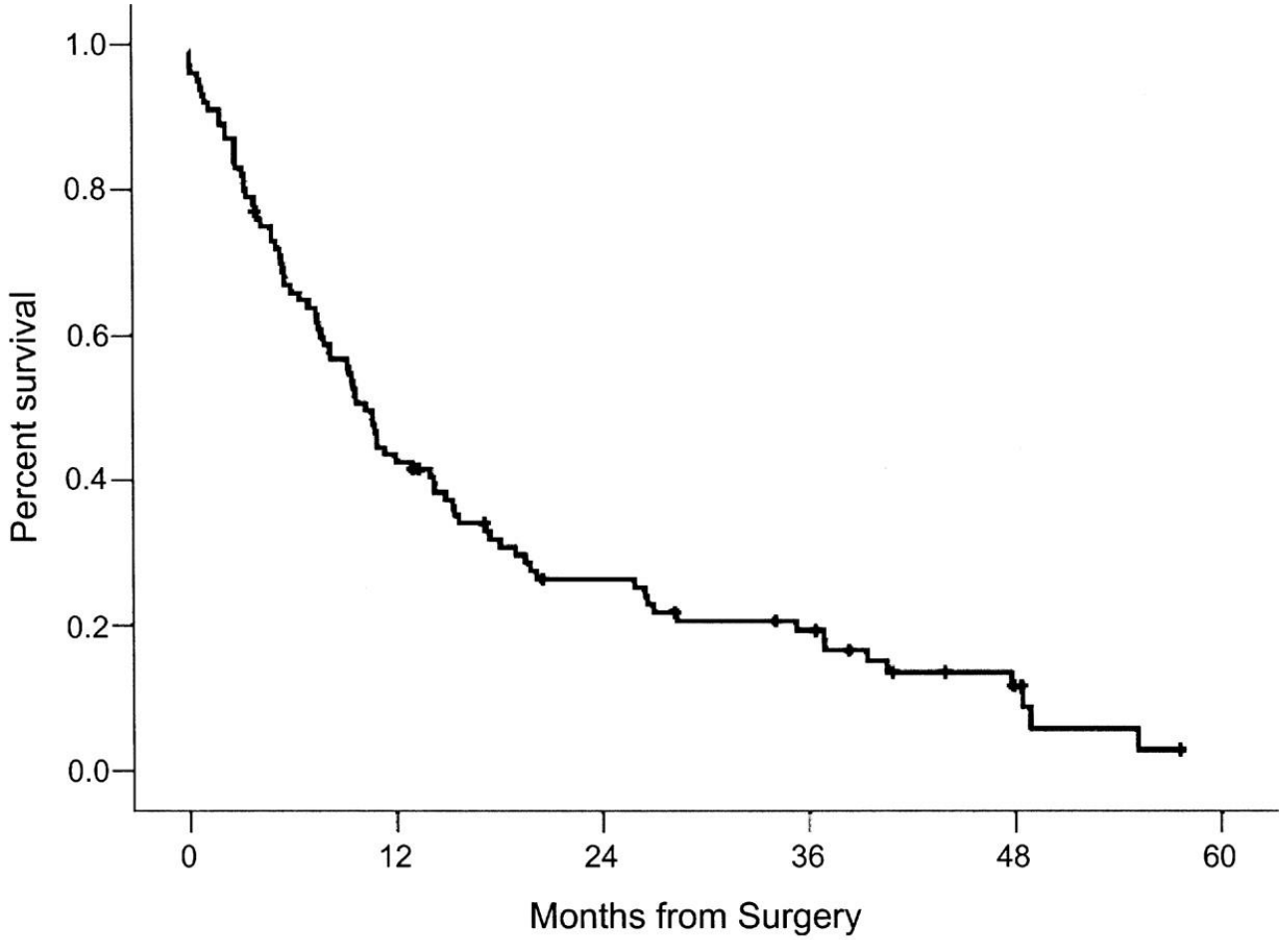
- There is no reliable evidence for the effectiveness of radical surgery in mesothelioma
  - The only randomised phase II trial suggested harm
- Patients should be informed of that fact
- Surgery should only be offered in a trial where its effectiveness can be tested
  - EPD appears at least as effective as EPP and probably should be considered as the operation of choice

Radiotherapy

Evidence Base Limited

- Mesothelioma appears exquisitely sensitive to radiotherapy
- Irradiation of site post drainage of effusion/biopsy reduces seeding/local occurrence of the tumour
- Symptom benefit with pain control of locally invasive disease into chest wall or mediastinum
  - No randomised data available
- IMRT feasible post EPP but data do not demonstrate any evidence of a survival benefit

Overall survival for the entire cohort, n = 100



Rice D. C. et al.; Ann Thorac Surg 2007;84:1685-1693

Systemic Therapy

MSO1 trial

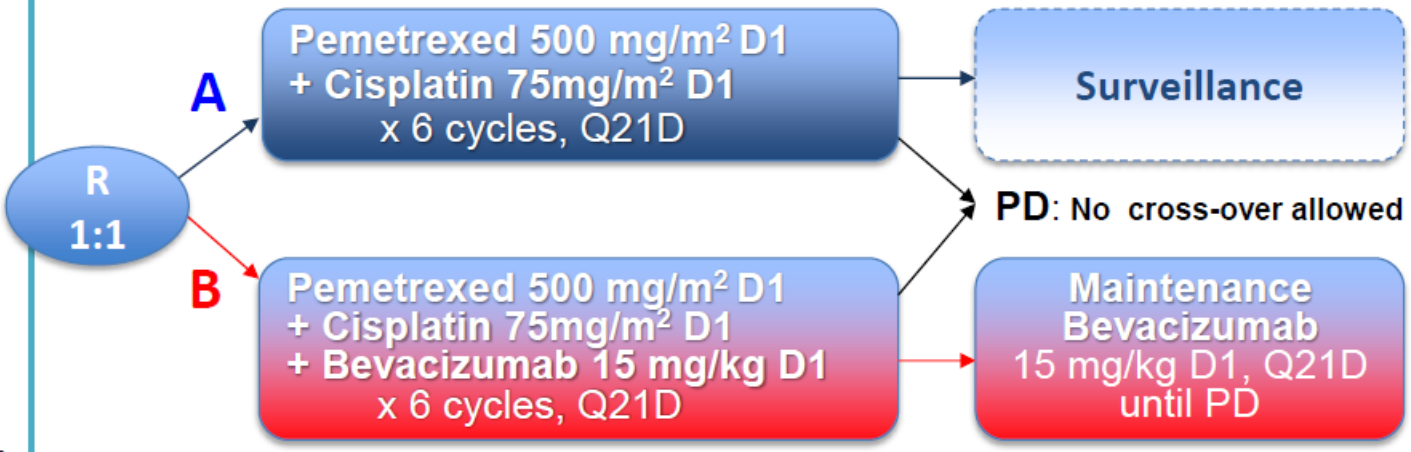
- Compared chemotherapy to best supportive care
  - No significant difference in survival
- Trend towards benefit in some subgroups
  - Optimal chemotherapy regimen (cis/pem) not employed
- Nonetheless benefit from chemotherapy limited
  - Cis/pem vs cisplatin alone – 4 months improvement in survival
    - ?cisplatin as a single agent harmful? – we'll never know

IFCT MAPS: Study design

- MPM proved by pleural biopsies (thoracoscopy...)
- Written informed consent
- Age ≥18 - <75 years
- PS 0 - 2
- Chemonaïve patients
- not candidate to curative intent surgery according to Multidisciplinary Board
- At least 1 evaluable or measurable lesion by CT
- Weight loss <10% within 3 months prior to enrolment
- No significant cardio-vascular comorbidity and/or other usual chemo or beva contra-indications (HTA, GI perforation...)
- Prophylactic radiotherapy (3 x 7 Gy) before chemo

IFCT-sponsored, open-label, multi-centre randomized phase II-III trial

(bevacizumab supplied by Roche)



CT-scan Q 3 cycles in both arms; Response assessed with modified RECIST criteria for MPM

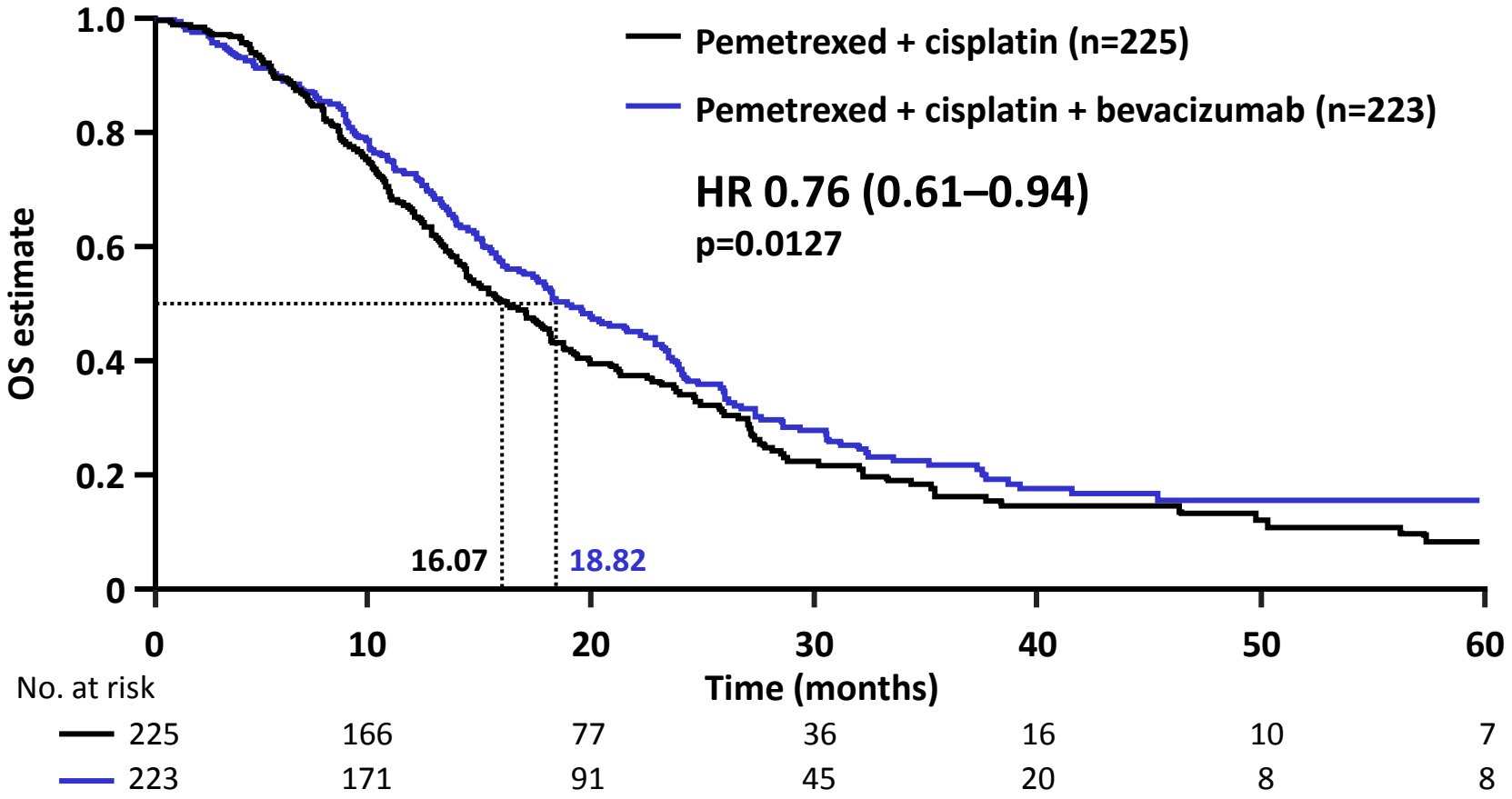
→ ***Phase 3 primary goal* = OS;** *Secondary goals:* PFS, QoL, ancillary studies

Stratification: center, histology (epithelioid vs sarcomatoid/mixed), PS (0-1 vs 2), smoking status

IFCT = French Cooperative Thoracic Intergroup

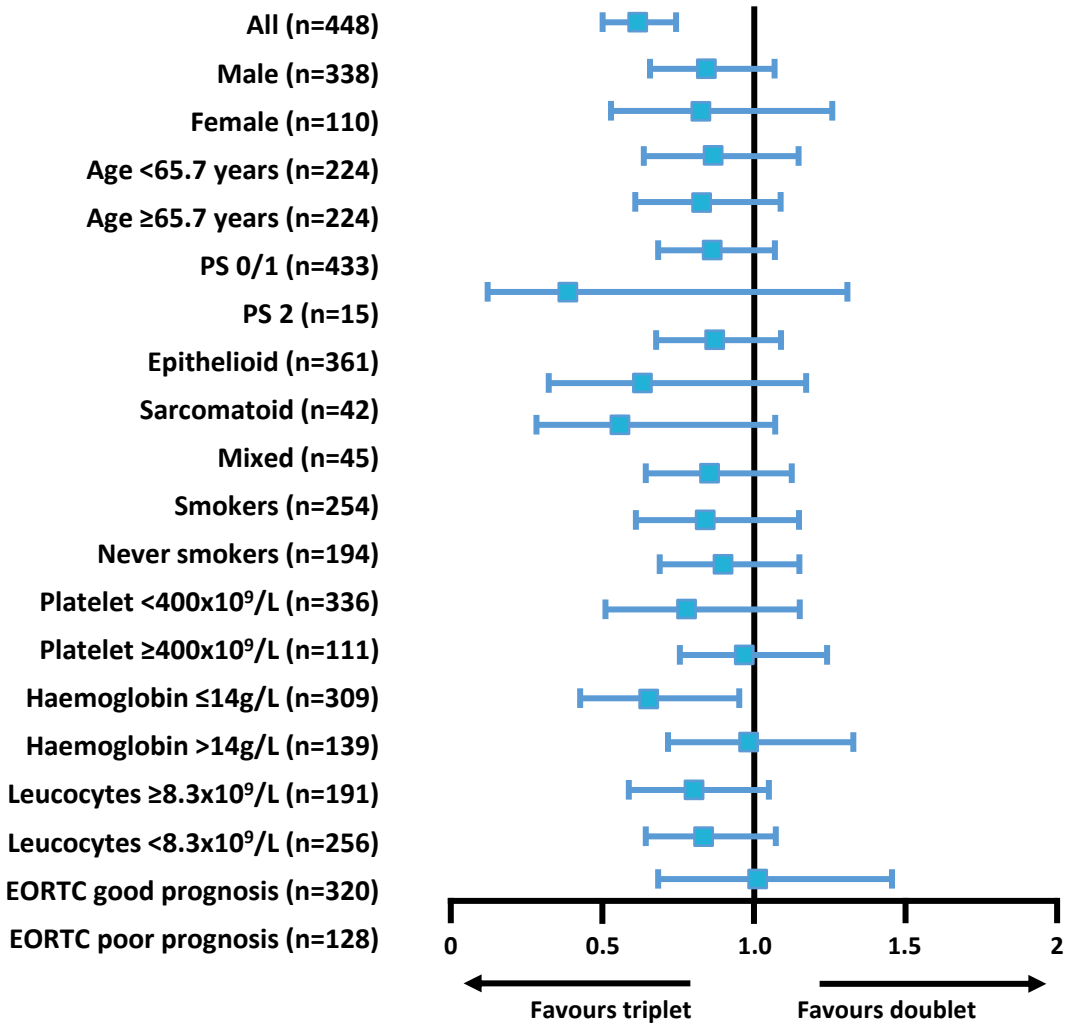
Scherpereel, et al. WCLC 2015

IFCT MAPS: OS



Scherpereel, et al. WCLC 2015

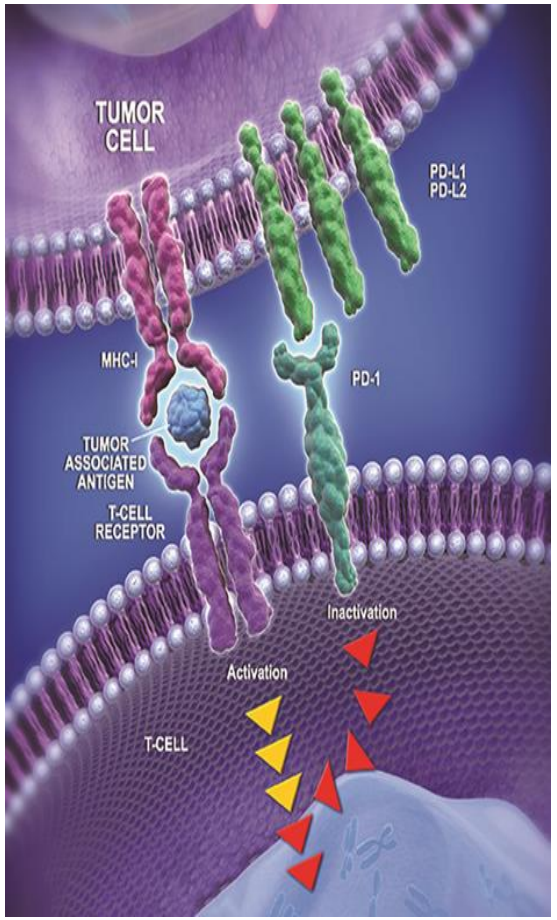
IFCT MAPS: OS by subgroup



Scherpereel, et al. WCLC 2015

PD1 Checkpoint Inhibitors

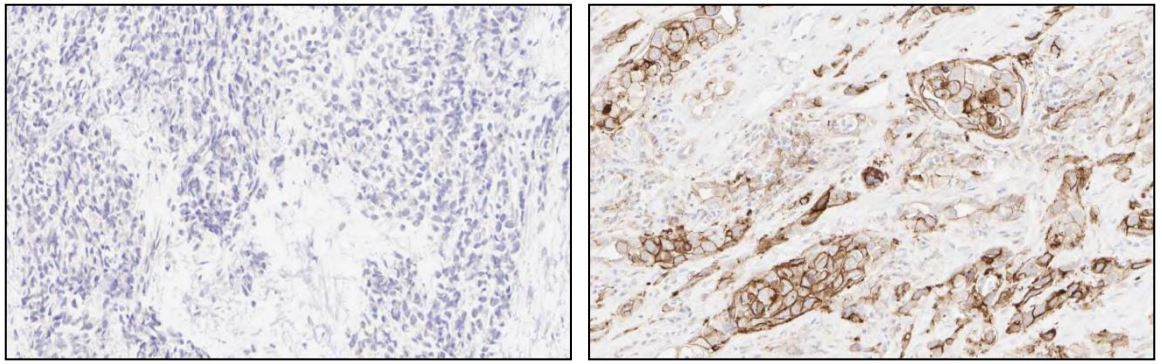
- T-cell inflamed phenotype and PD-L1 expression have been observed in MPM
- PD-L1 expression associated with poor prognosis in mesothelioma
  - Median OS: 5.0 months for PD-L1^{+} vs 14.5 mo for PD-L1^{-}
  - PD-L1 positivity an independent risk factor for OS: RR 1.71
- Anti–PD-1 antibody pembrolizumab has demonstrated robust antitumor activity and a favorable safety profile in multiple tumor types



Analysis of PD-L1 Expression

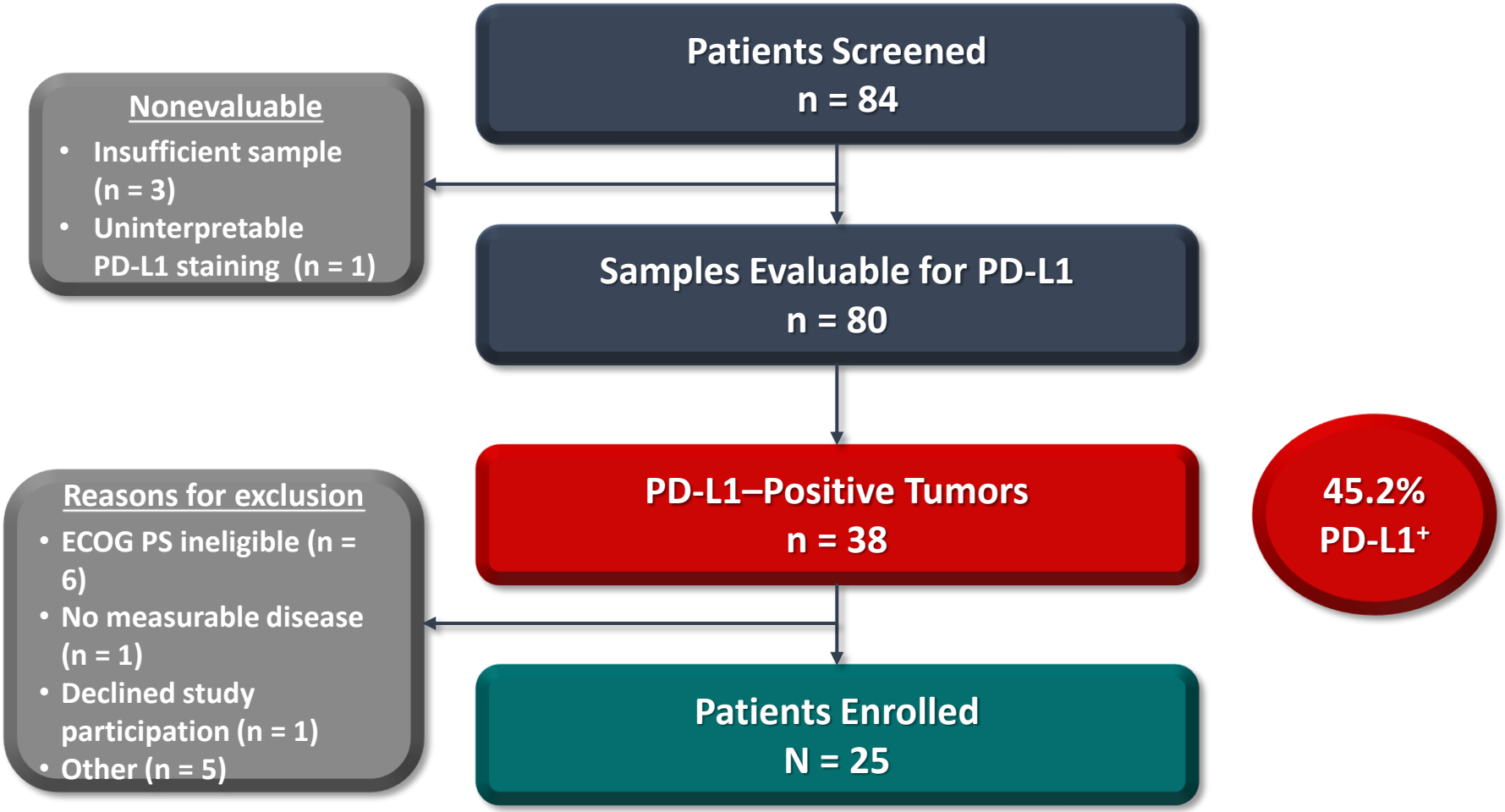
- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- MPM cohort: of 80 evaluable samples, 38 PD-L1 positive (45.2%)

Examples of PD-L1 Staining in MPM Specimens from KEYNOTE-028



PD-L1 Negative **PD-L1 Positive**

KEYNOTE-028 (NCT02054806) Phase 1b of Pembrolizumab in Solid tumours:
PD-L1 Screening: MPM Cohort



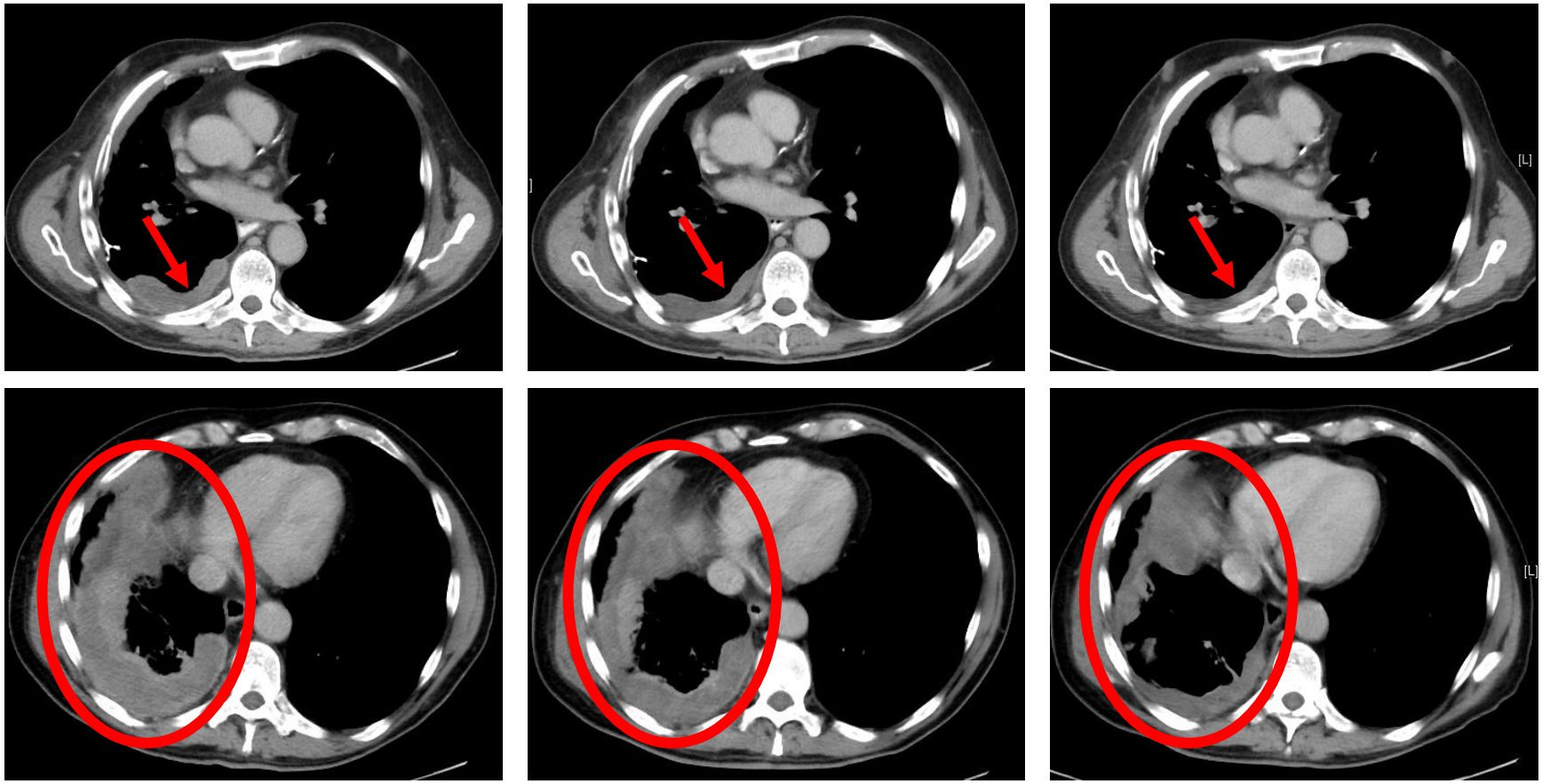
Antitumor Activity
(RECIST v1.1, Investigator Review)

Best Overall Response	n	%	95% CI
Complete response[a]	0	0	0.0–13.7
Partial response[a]	7	28.0	12.1–49.4
Stable disease	12	48.0	27.8–68.7
Progressive disease	4	16.0	4.5–36.1
No assessment[b]	2	8.0	1.0–26.0

Objective response rate: 28.0% (95% CI, 12.1–49.4)

Disease control rate: 76.0% (95% CI, 54.9–90.6)

Example of Pembrolizumab Antitumor Activity in a Patient With MPM

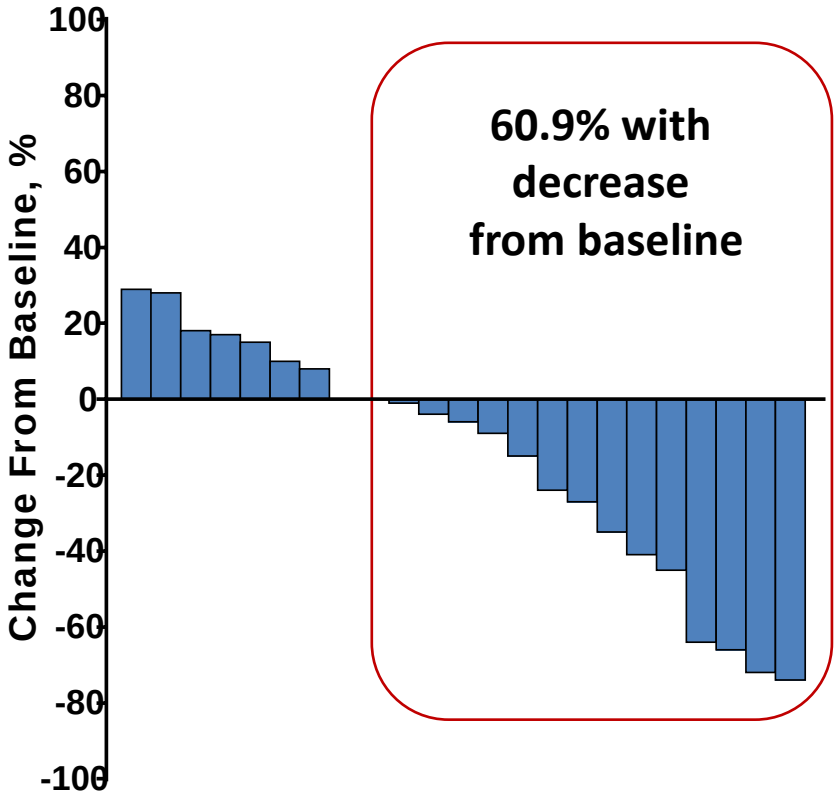


Pretreatment **Week 8** **Week 16**

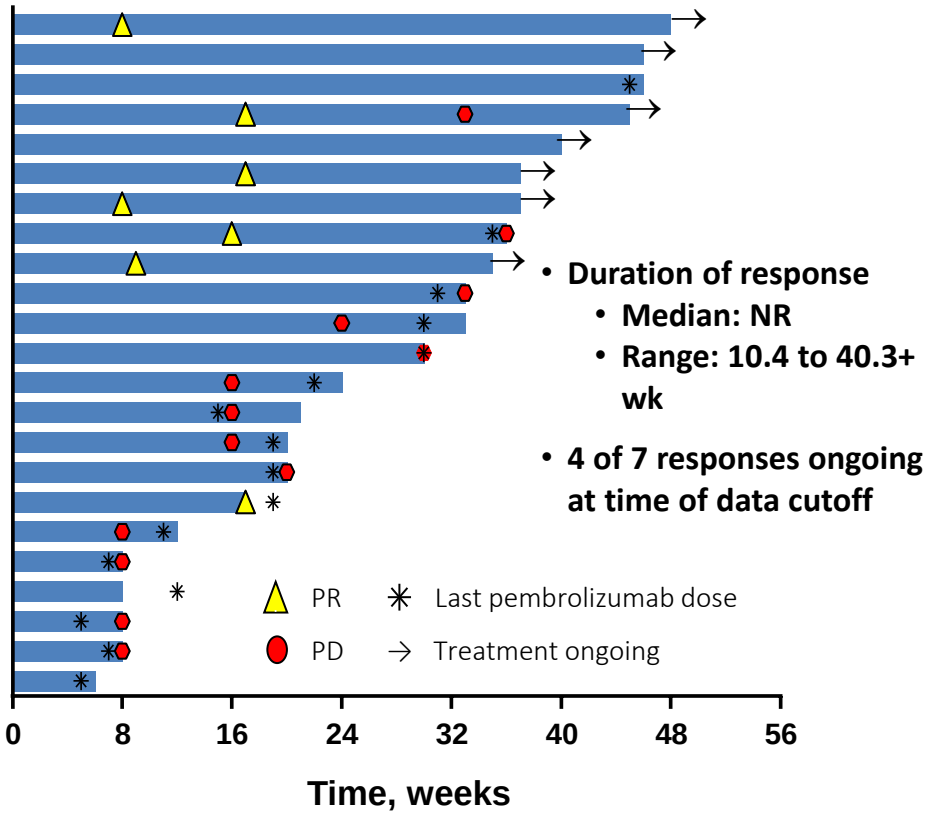
Antitumor Activity
(RECIST v1.1, Investigator Review)

PN028

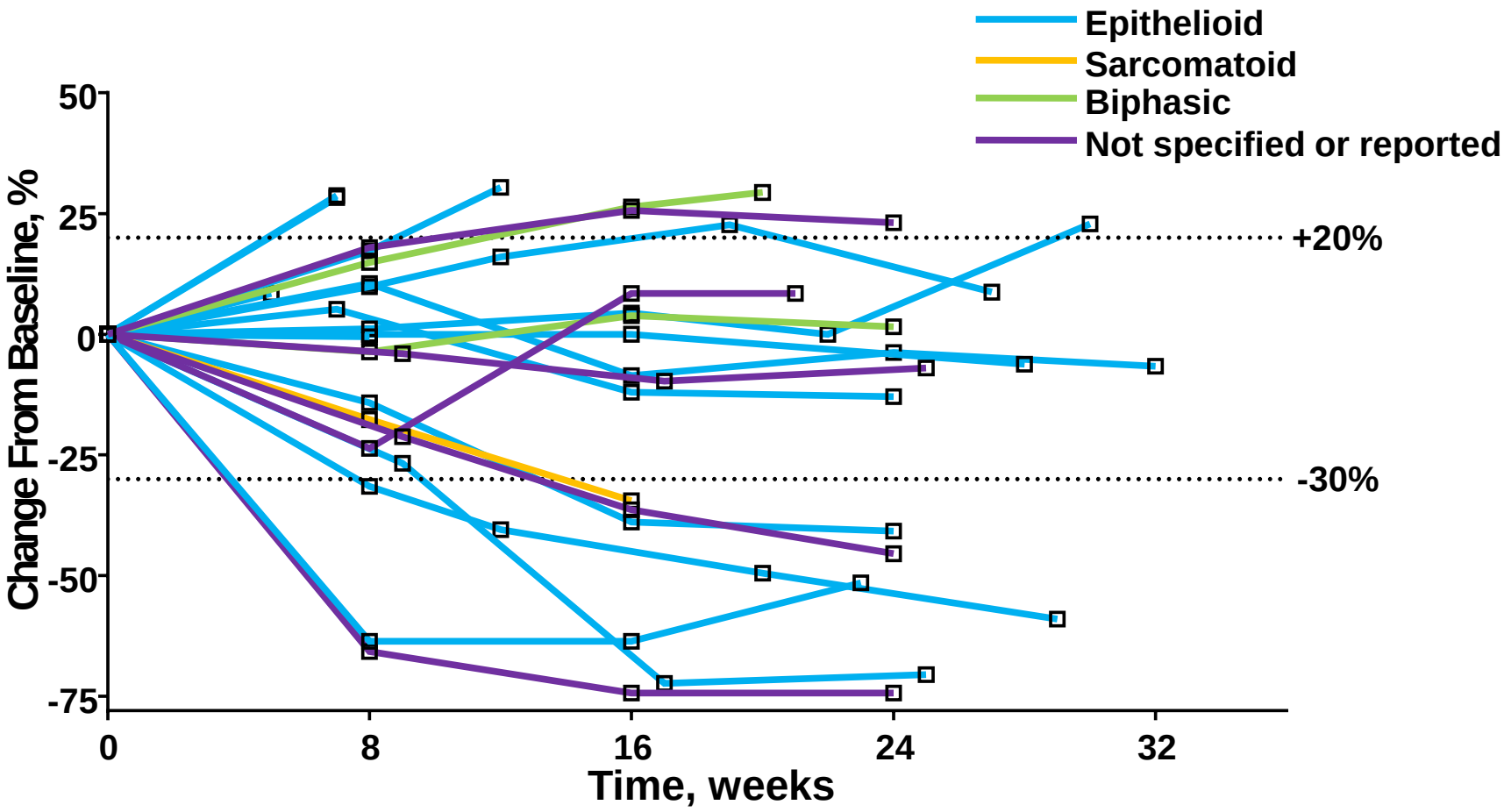
Change From Baseline in Tumor Size



Treatment Exposure and Response Duration[a]

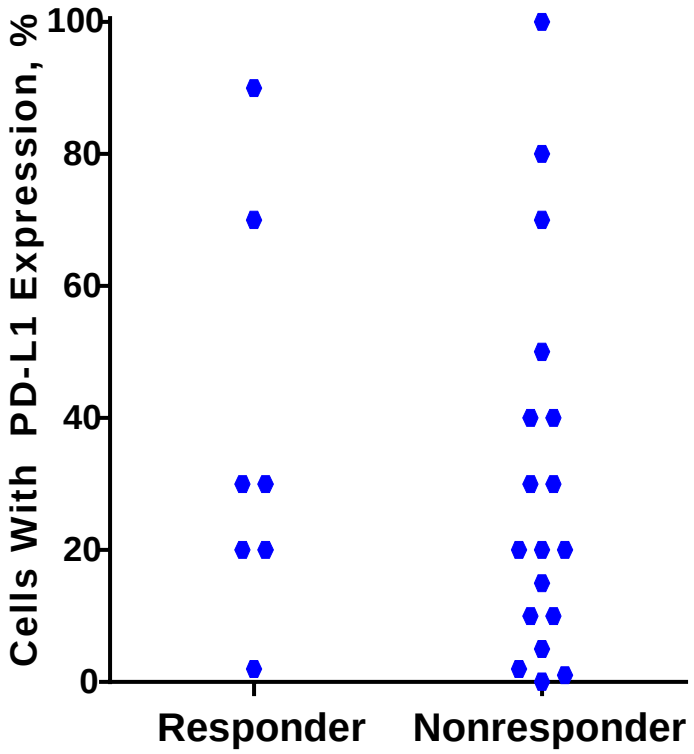


Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



Level of PD-L1 Expression and Response

- Using prototype IHC assay, no relationship between level of PD-L1 expression on tumor and immune cells within tumor nests and frequency of response
  - One-sided *P* = 0.284 by logistic regression



Patients were eligibile for enrollment if they had PD-L1 expression in ≥1% of tumor or immune cells in tumor nests or staining in the stroma.
Data cutoff date: June 24, 2015.

Other Novel Therapies

- Antibody drug conjugates
  - Warhead attached to mesothelin targeting antibodies or nanoparticles
- Arginine deiminase inhibition
  - Targeting tumours unable to produce their own arginine due to tumoural downregulation of the enzyme argininosuccinate synthetase
  - Effectively starves the tumour dependent on extracellular arginine
    - Significant promise in sarcomatoid disease

Clinical trials

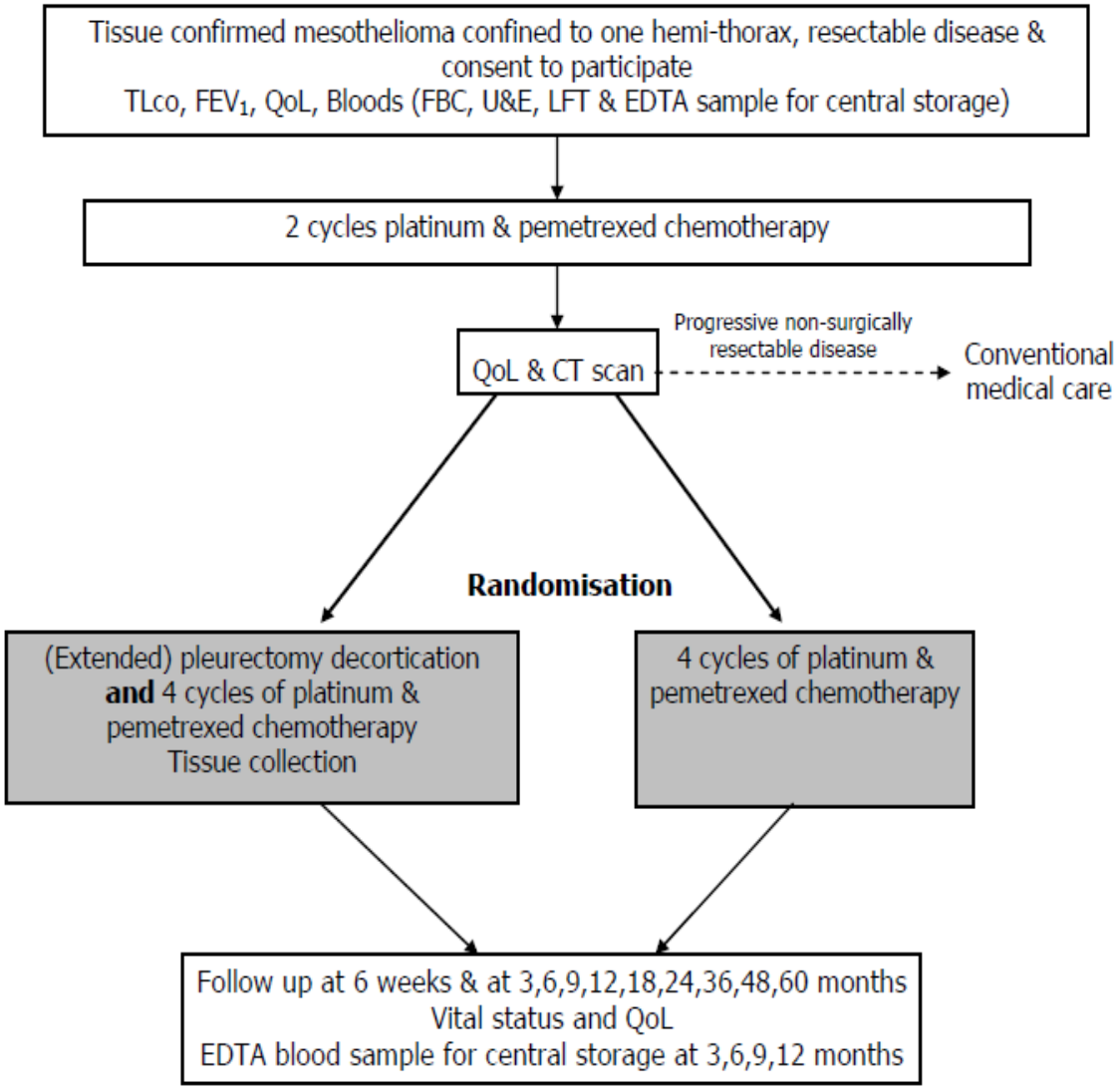
MARS 2 – pleurectomy decortication versus none

- 16 UK centres (2013 – 2018)
- Feasibility (50 pts within 2 years)
- Full (285 patients within 5 years)
- Co-primary outcomes
- Survival (30% improvement)
- QOL (10 point difference in EORTC QLQ C30)

- Continue with the momentum of surgical trials in mesothelioma
- Many centres from the outset
- Broad inclusion criteria
- Emphasis on demonstrating surgical quality and fidelity
- Continue to develop thoracic surgical trials community with support and training

MARS 2

- 2011 started work on MARS 2
- Randomised trial of surgery versus no surgery for mesothelioma
- N=314 (survival, QOL)
- Funded by CRUK initially as a feasibility study (n=50)



Summary

- Difficult to define ‘locally advanced mesothelioma’
- If stage III disease used as a definition then the role of surgery as a curative modality remains unproven
- VATS pleurectomy improves effusion control and Qol over time vs Talc pleurodesis
- If radical surgery undertaken EPD equivalent to EPP
- Systemic therapy may improve survival and Qol
- Radiotherapy stops seeding and may improve symptom control from locally invasive disease e.g. into chest wall or mediastinum

Conclusions

- Optimal current management of locally advanced mesothelioma
  - VATS pleurectomy for effusion control
  - Radiotherapy for local invasion
  - Systemic chemotherapy +/- bevacizumab
  - Radical surgery unproven and may do harm
    - Use only in clinical trials?
  - Palliative care involvement early
  - Trials, trials, trials: global effort required