City of Hope

THIRD ANNUAL

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International Society for the Study of Pleura and Peritoneum

KEYNOTE LECTURE

Primary and Metastatic Pleural Malignancies

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Grant/Research support from Genentech for clinical trial (LCMC 3).

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or its product(s) and/or other business interests.

- Serve on DSMC for 2 UK trials (MARS 2, RAMON)

- Co-Chair, NCI Thoracic Malignancy Steering Committee (TMSC)

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Communication issues.
- Common oversight of early diagnosis in underserved and socioeconomically depressed patients.

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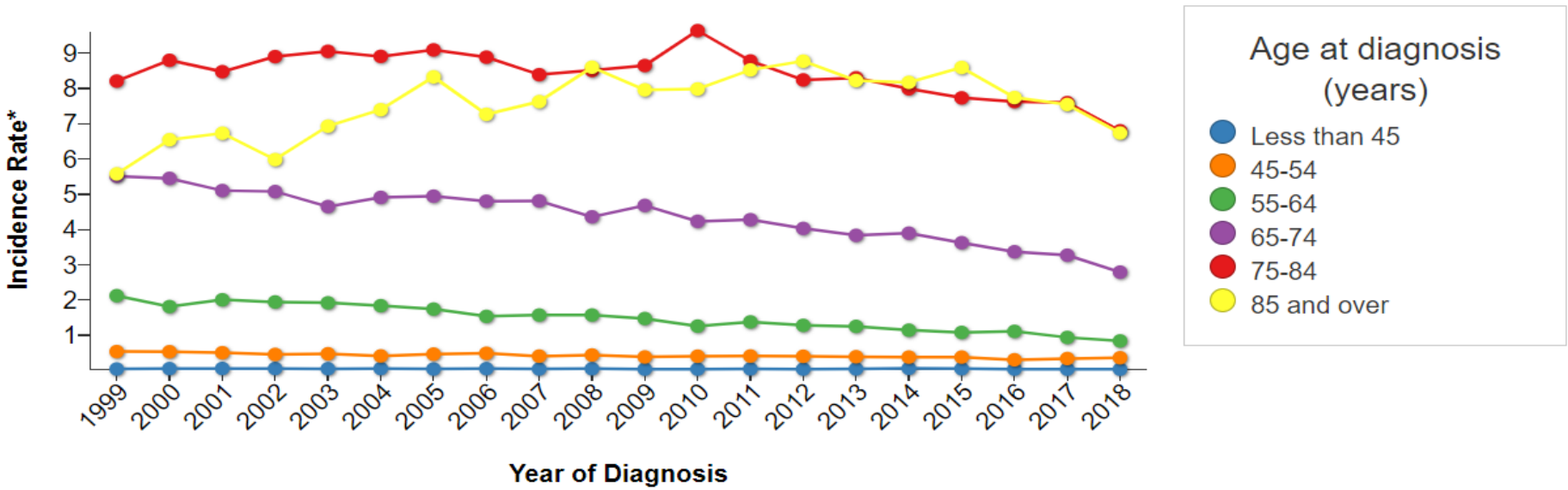
Metastatic and primary pleural malignancies

- Pleural metastases occur from many solid tumors
- Metastatic lung and breast cancers most common
  - recent advances in tumor biology and in systemic therapy (TKIs, IO) usually supersede considerations of intrapleural therapy
  - in most instances, locoregional treatment focuses on symptom control (pleural effusion) via PleurX insertion or chemical pleurodesis (bedside or VATS)
- Occasional role for surgical resection, e.g. metastatic thymic malignancies
  - few systemic therapy options
  - more indolent clinical course
  - disease that usually remains intrathoracic
- Focus of today's discussion: malignant pleural mesothelioma (MPM)

Challenges of studying and treating MPM: a rare disease

Figure 2. Rate of New Malignant Mesothelioma Cases by Age at Diagnosis, United States, 1999–2018



Source: US Cancer Statistics; cdc.gov/cancer/about/databriefs March, 2022 (~2,800 cases annually)

*New mesothelioma cases per 100,000 population. Based on 47 registries that met high-quality data criteria for all years 1999–2018, covering 97% of the U.S. population.

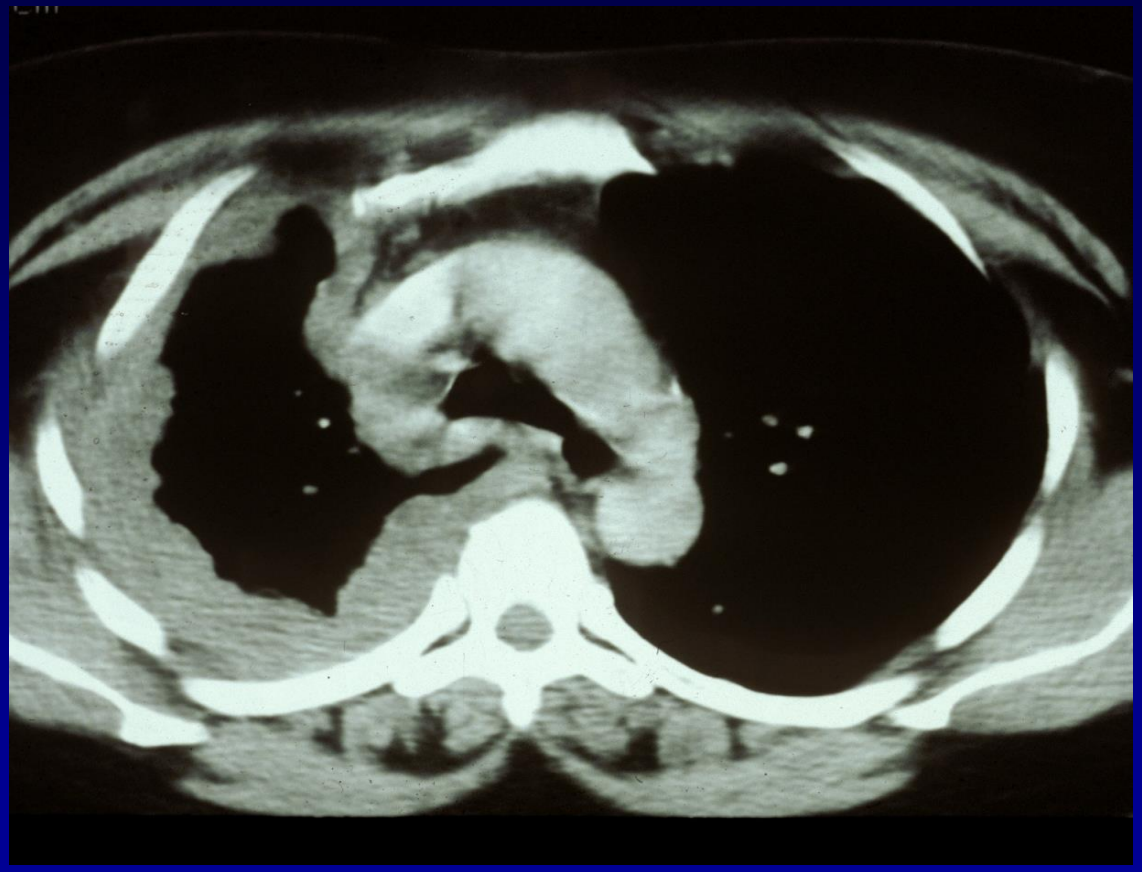
- By virtue of risk factors (occupational asbestos exposure), patients predominantly male, Caucasian
  - aging patient population (due to asbestos control legislation in Western countries)
  - frequent medical comorbidities
- Female patients either have idiopathic disease or history of second-hand asbestos exposure
- Cancer survivors (s/p mantle RT for Hodgkin's) form special MPM patient subgroup

MPM: *Defining the unmet needs*

Historical context

	1982	2022
Accurate path diagnosis	Difficult: required electron microscopy	Routine, supported by IHC
Knowledge of tumor biology	None	Evolving (BAP-1, etc); still does not significantly affect clinical care
Staging system	None	TNM system internationally accepted but needs refinement
Pre-treatment staging	Very limited (CXR, CT)	CT, PET, MRI, laparoscopy, EBUS; still need greater accuracy in clin staging
Role of surgery? M&M?	Not defined; EPP primary operation; high M&M	Better defined; EPD primary operation; low M&M
Role of RT?	None	Well studied: adjuvant hemithoracic RT feasible, improves local control
Effective systemic therapy / multimodality therapy	None	Cis-pem and ipi-nivo standard Rx, with modest OS benefits; chemo + surgery feasible

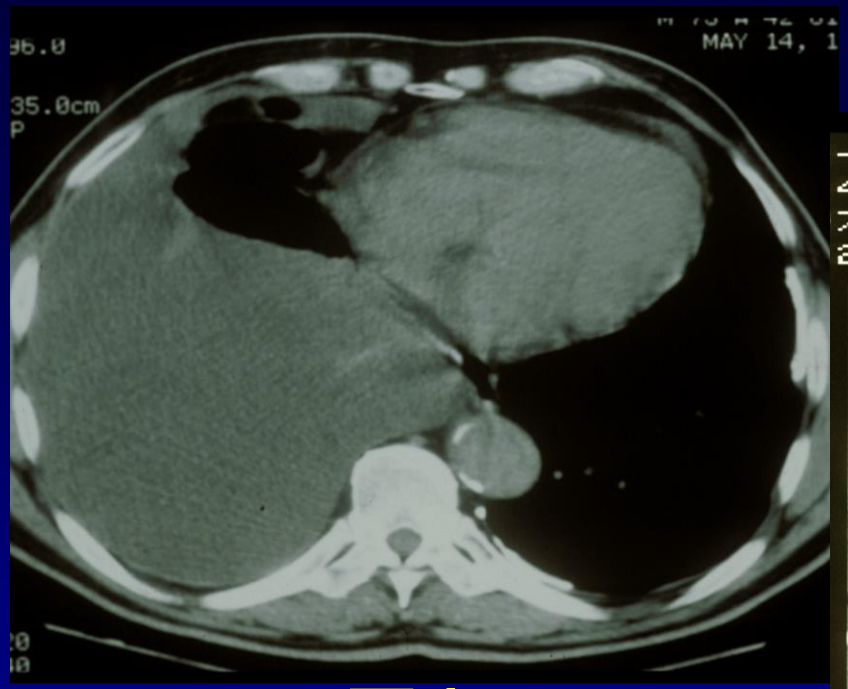
Typical appearance of MPM ??



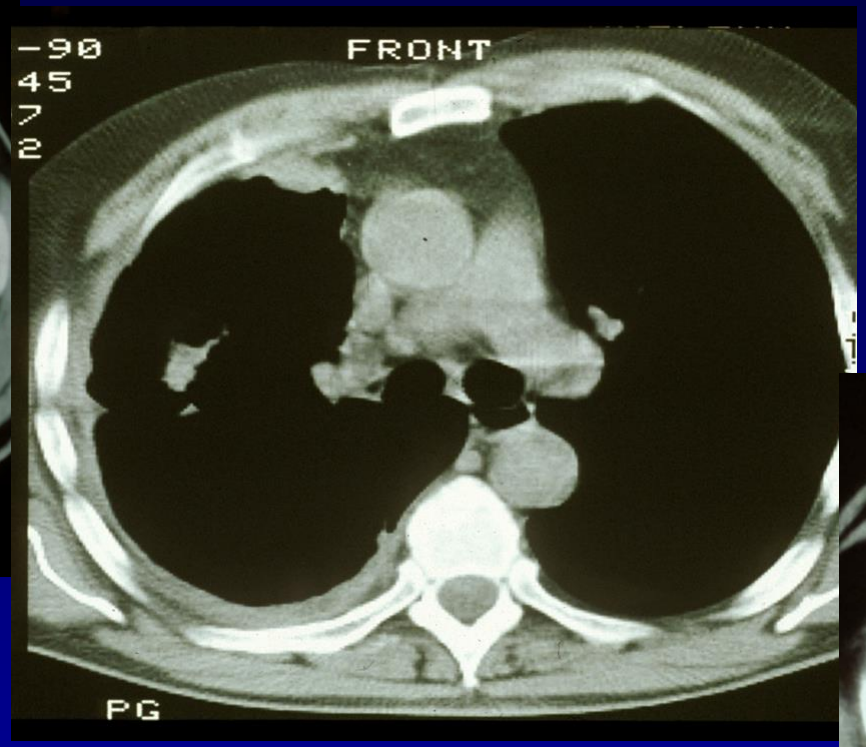
Often described as:

- associated with SOB, chest pain
- universally fatal
- median OS 12 mos or less

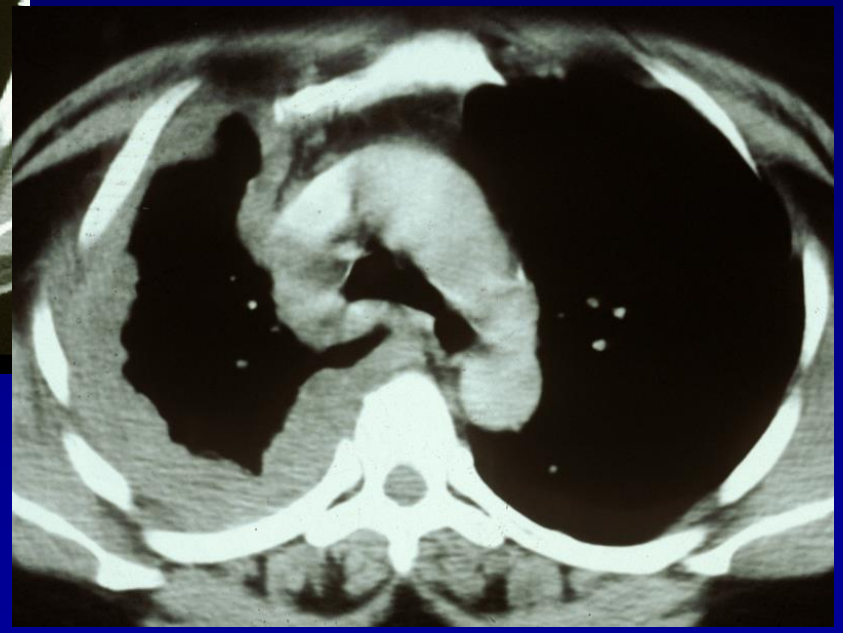
CT appearance of MPM is related to tumor extent (and histology)



T1



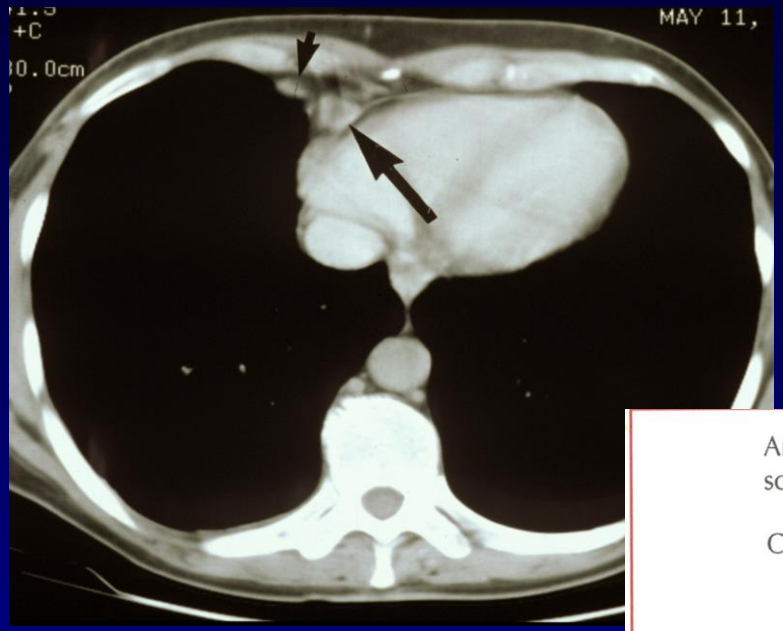
T2



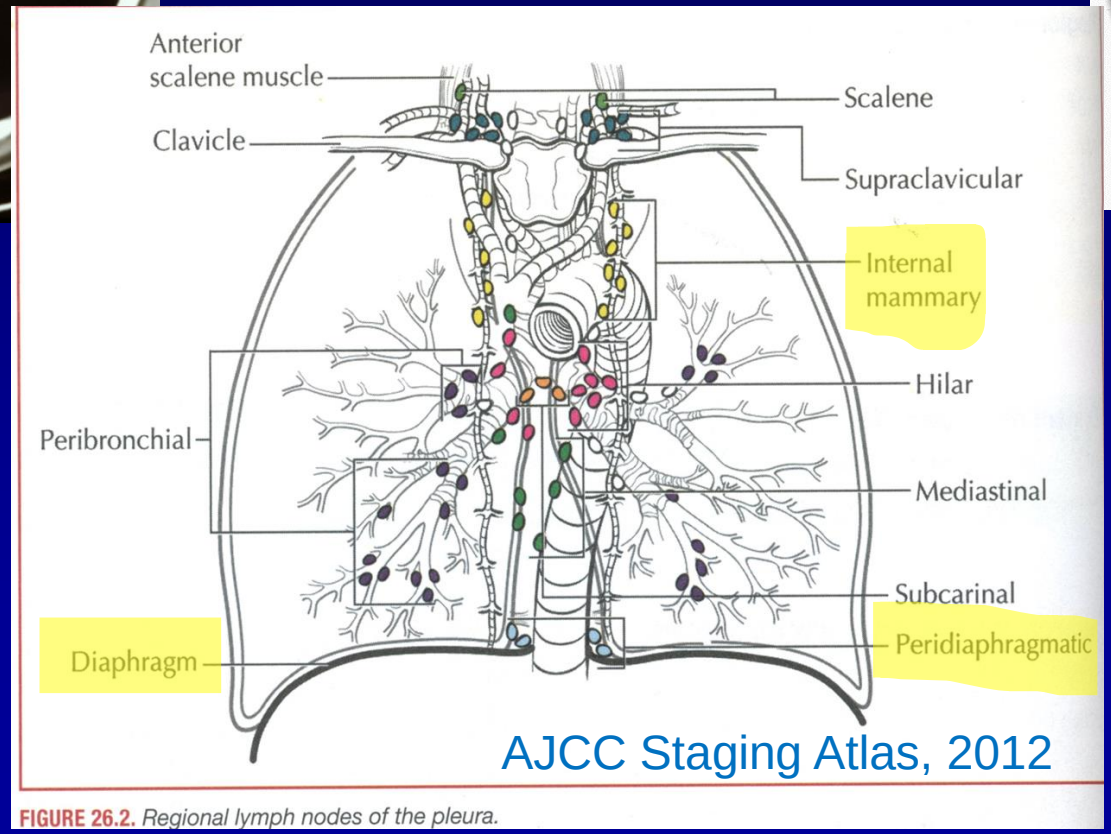
T3 or T4

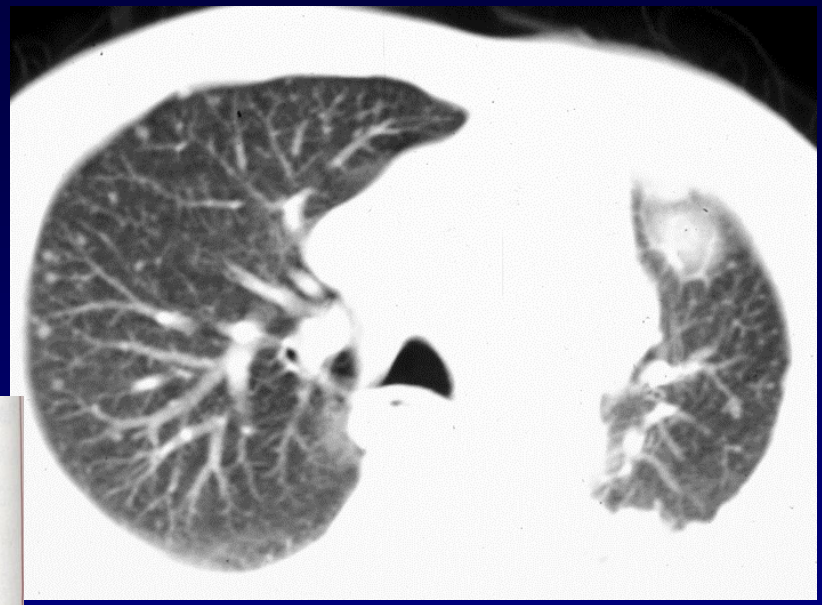
Epithelioid MPM may have bulky but not invasive pleural masses; sarcomatoid MPM may be low volume but invasive into chest wall

Initial presentations differ from those of other thoracic malignancies (e.g. NSCLC) *



Mediastinal nodal mets common, more so than hilar/ peribronchial nodes





M1 (lung)

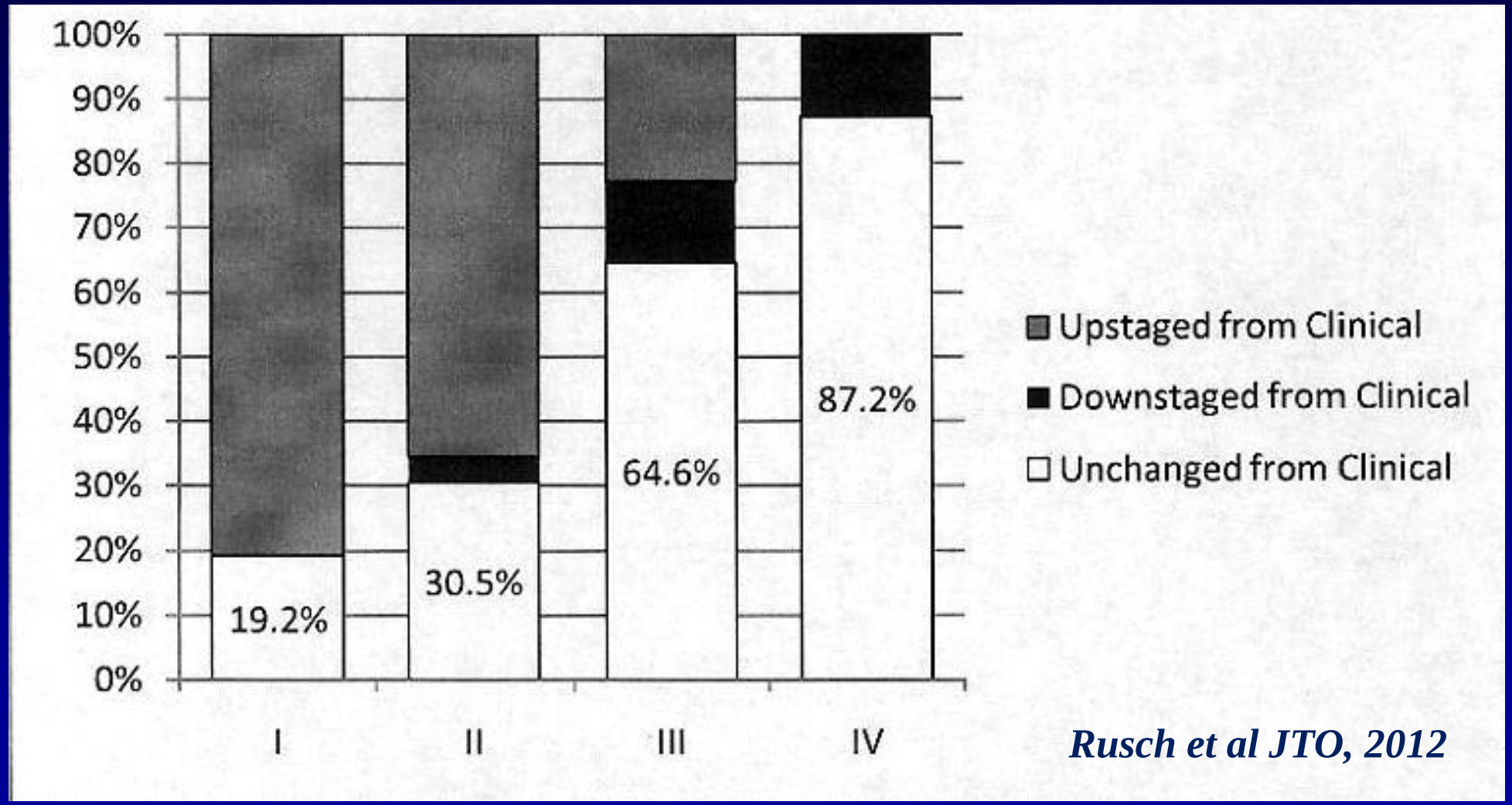
Metastatic disease uncommon at presentation

Sites of mediastinal nodal involvement different from those in lung cancer – often in areas not accessible by mediastinoscopy or EBUS

** Most thoracic surgeons and med/ rad oncologists not familiar with nuances of MPM*

Correlation of stage between cTNM (by CT) and p TNM

IASLC Mesothelioma Staging Database



Rusch et al JTO, 2012

FDG PET in MPM
Staging and Prognosis

- Unsuspected extrathoracic disease detected in 6/63 patients (10%):
  - M1: 2 patients (peritoneum and bone)
  - N3 (supraclavicular): 4 patients
- In subsequent analysis (n>100 patients), SUV >10 was independent prognostic indicator of poor survival (in patients managed surgically)

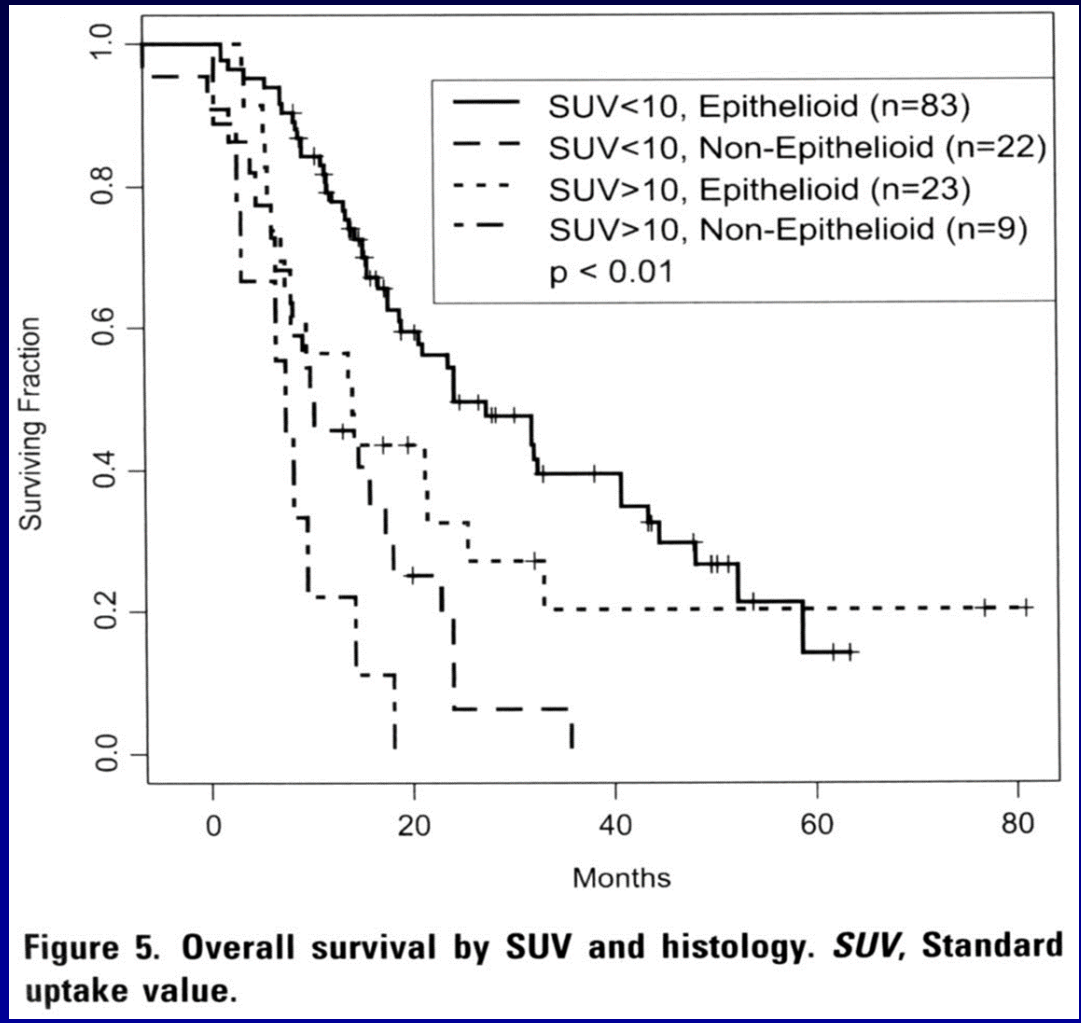
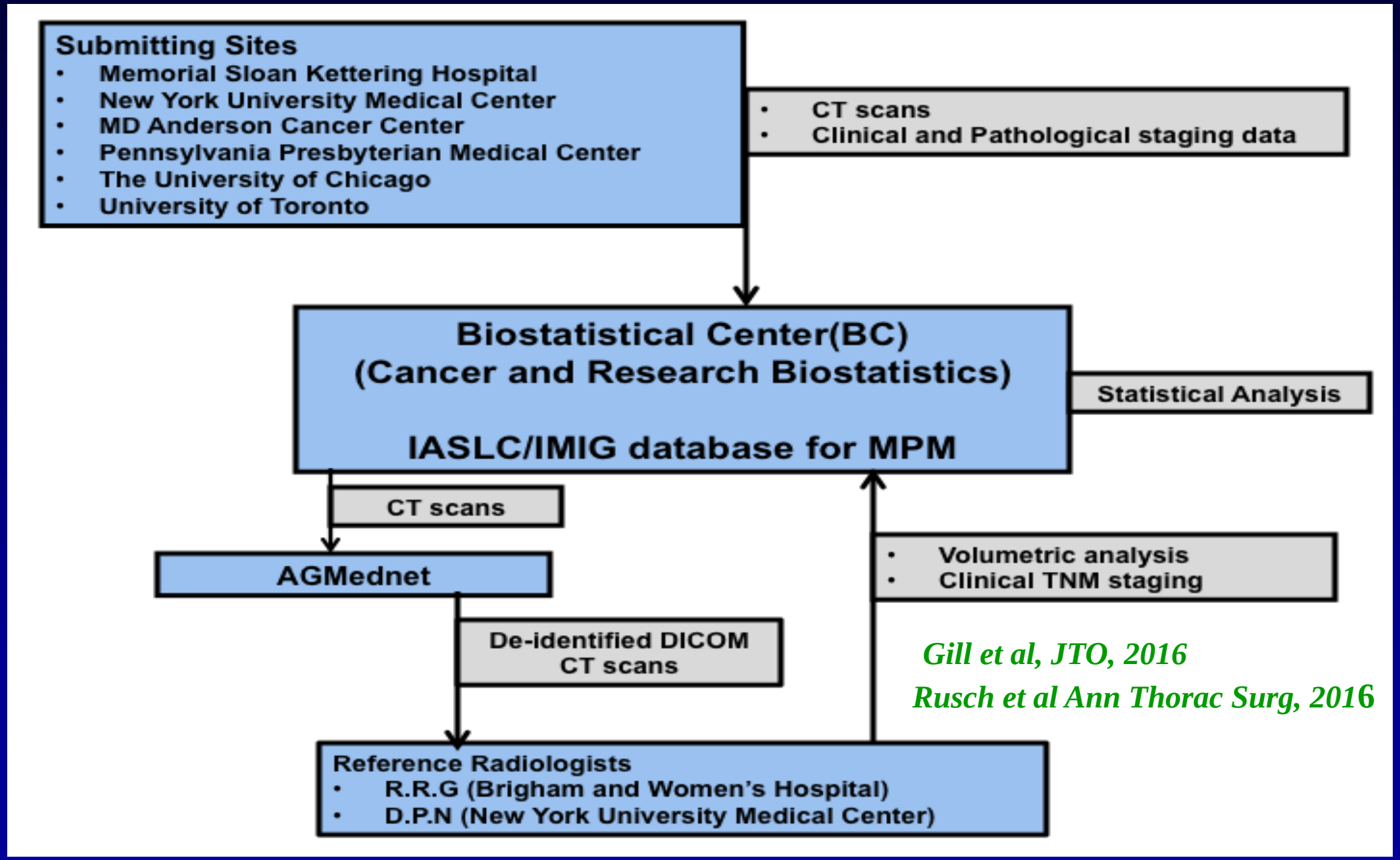


Figure 5. Overall survival by SUV and histology. *SUV*, Standard uptake value.

Flores, Rusch et al. JTCVS 2003;126: 11-16

Flores, Rusch et al. *JTCVS* 2006;132:763-768.

VolCT in Staging MPM: Study Schema



Gill et al, JTO, 2016

Rusch et al Ann Thorac Surg, 2016

VolCT for Staging MPM

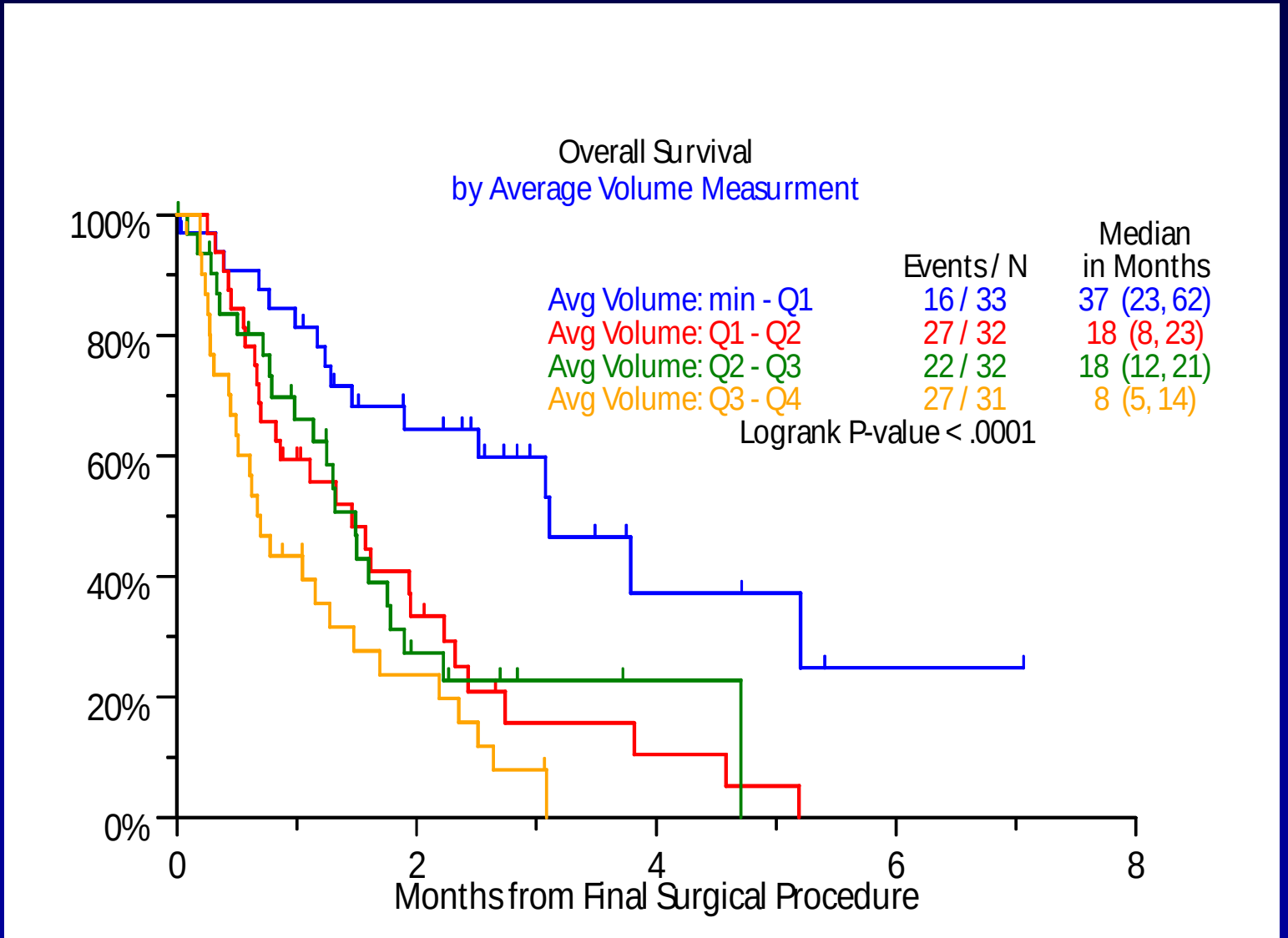
Tumor volume predicts OS

- **Best separation for OS is by 3 groups:**

Q1 = 91.2cm^3

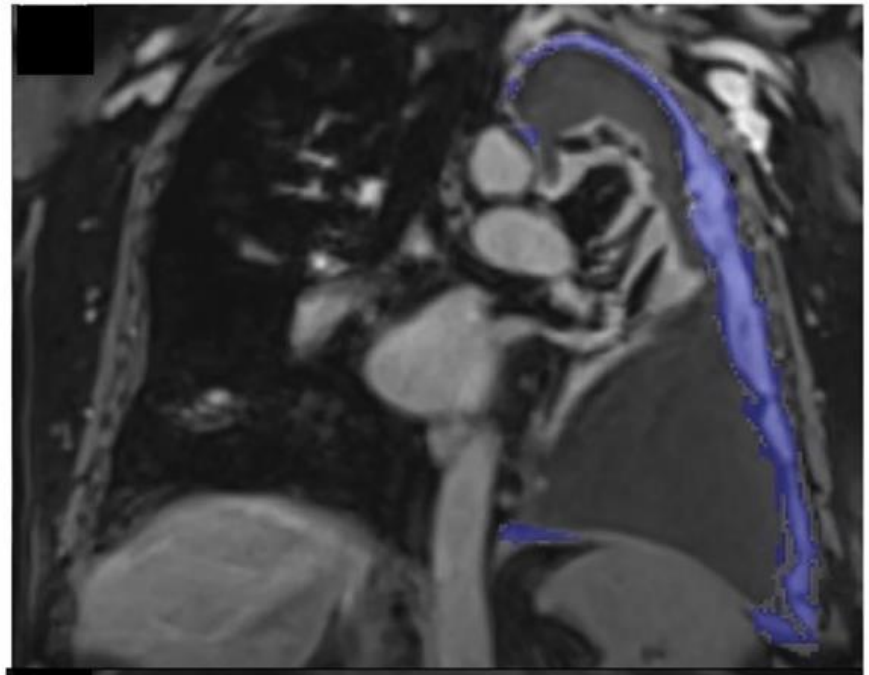
Q2 /Q3 (median)=245.35cm^3

Q4 = 511.35 cm^3



MRI tumor volume segmentation in MPM predicts OS

A



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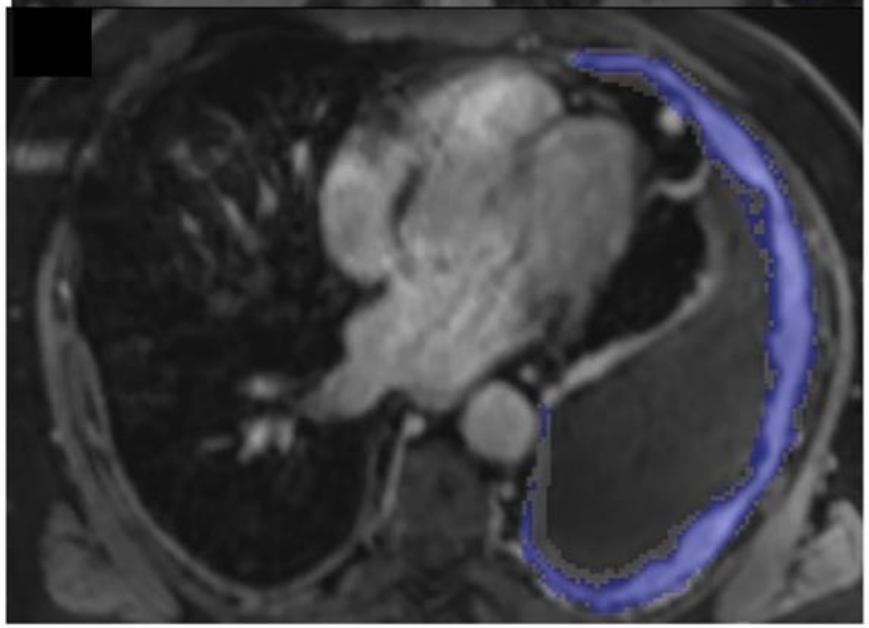

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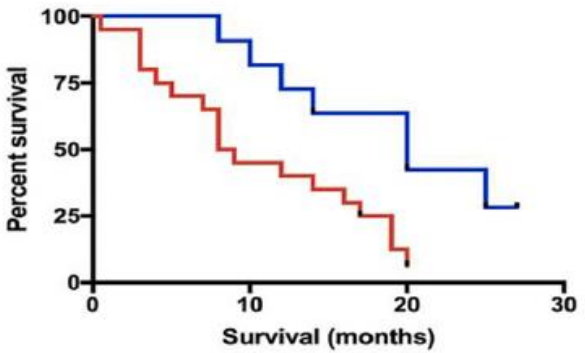
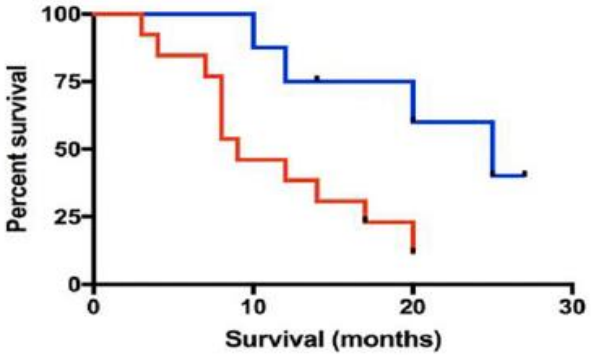


Volume ≥300cm^3 (n = 20)
Volume <300cm^3 (n = 11)

All patients (n=31)

Median Survival
20 months vs. 8.5 months
p=0.0088

D

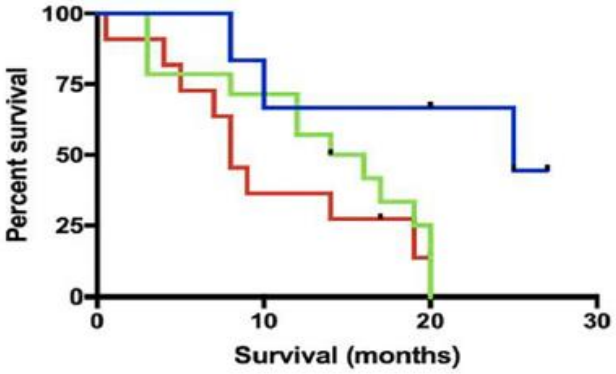


Volume ≥300cm^3 (n = 13)
Volume <300cm^3 (n = 8)

Epithelioid MPM (n=21)

Median Survival
25 months vs. 9 months
p=0.017

E



≤250cm^3 (n = 6)
>250 - 400cm^3 (n = 14)
≥400cm^3 (n = 11)

All patients (n=31)

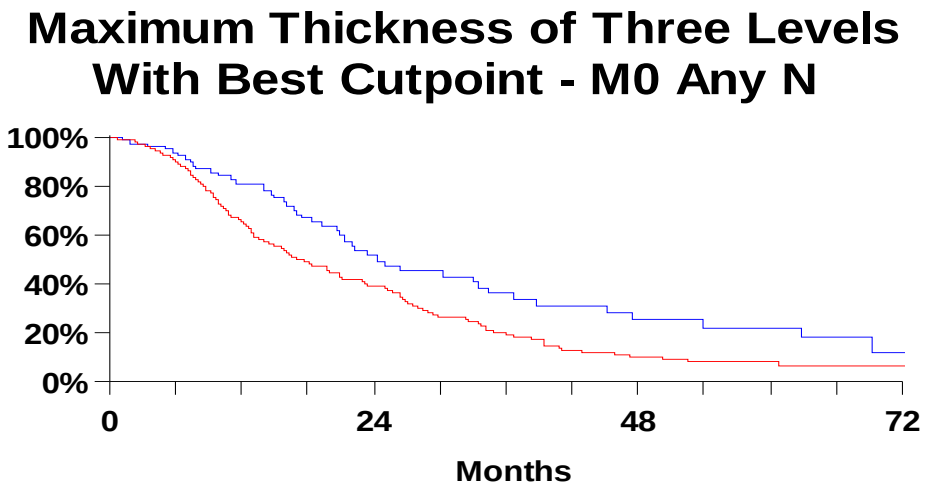
Log-rank for trend
p=0.0232

Contrast enhanced MRI with semi-automated volumetry faster and more reproducible than CT

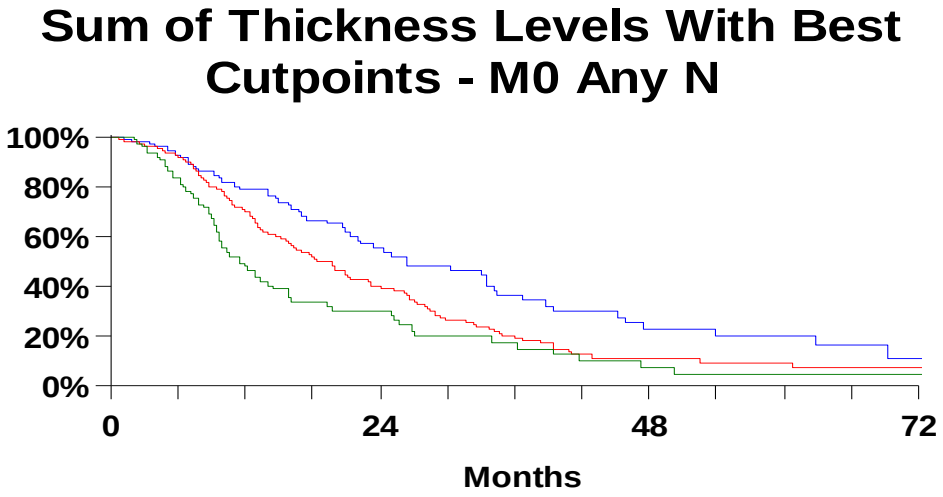
Armato et al.
Lung Cancer
2022; 164:76-83

The "low tech" approach to assessing pleural tumor volume: Pleural thickness measurements

Exploratory analyses of IASLC database for 8th edition of MPM staging system



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 (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%)

N = 472 MO cases

Nowak et al JTO 2016;11(12A): 2089-2099

MALIGNANT PLEURAL MESOTHELIOMA

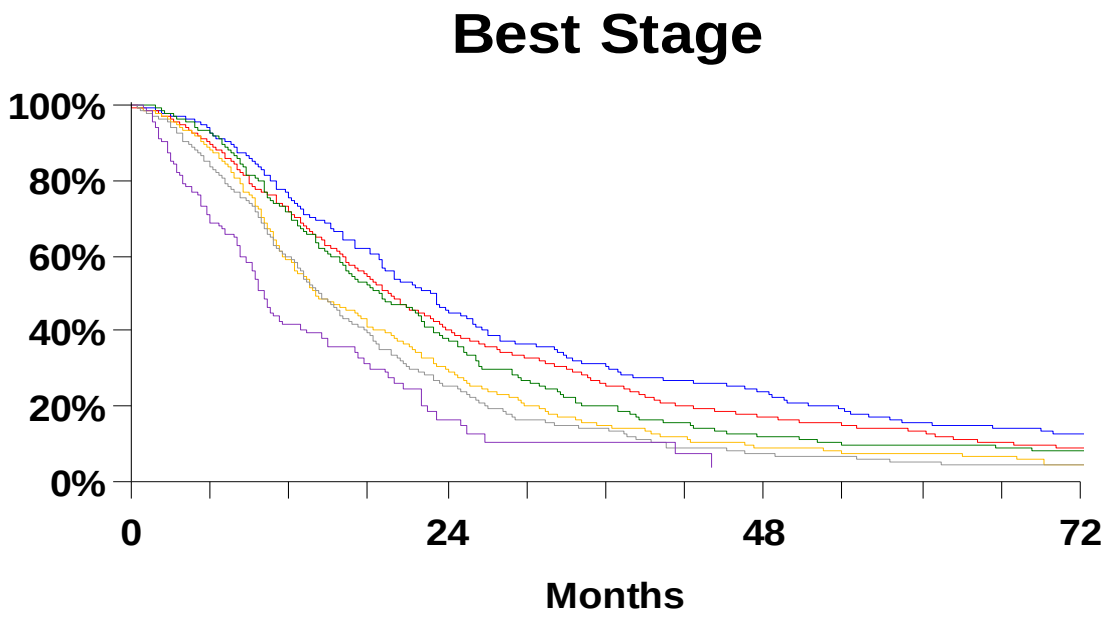
Staging Methods

- **CT scan (chest + upper abdomen)**
  - Standard imaging study
- **MRI (chest, abdomen, brain)**
  - Some prefer for assessing chest wall / diaphragm invasion
- **PET / CT**
  - detects metastases not seen on CT or MRI (~ 10% patients)
  - SUV is prognostic
- **Mediastinoscopy / EBUS**
  - Identifies some but not all N1 / N2 disease
- **Laparoscopy**
  - Identifies peritoneal disease in ~ 10% patients

Stage Groupings for the AJCC / UICC 8th edition of MPM staging system

	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

- T1a and T1b consolidated into T1
- All ipsilateral LN now N1
- All contralateral and supraclav LN now N2
- Major changes in stage groupings, including creation of IIIA, IIIB



Rusch et al. JTO 2016; 11(12): 2112-2119

Supplementary Prognostic Variables

Based on analyses of IASLC database

- 3 models depending on extent of available information

- *(1) Clinical + surg /path stage info*:
  - Path stage, histology, sex, age, type of surgery, adjuvant treatment, WBC, platelet count
- *(2) No surgical staging info:*
  - Clinical stage, histology, sex, age, type of surgery, adjuvant treatment, WBC, Hgb, platelet count
- *(3) Limited clinical info*:
  - Histology, sex, age, WBC, Hgb, platelet count

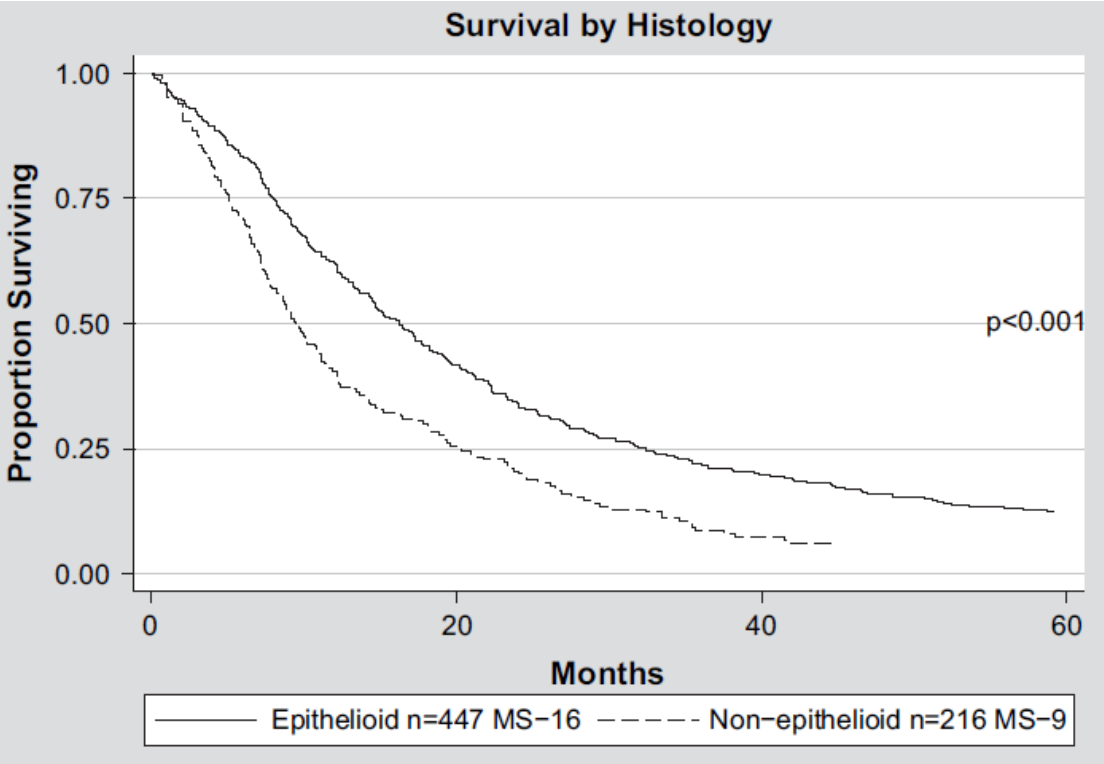
Pass et al JTO 2014; 9:856-864

Surgical Definitions

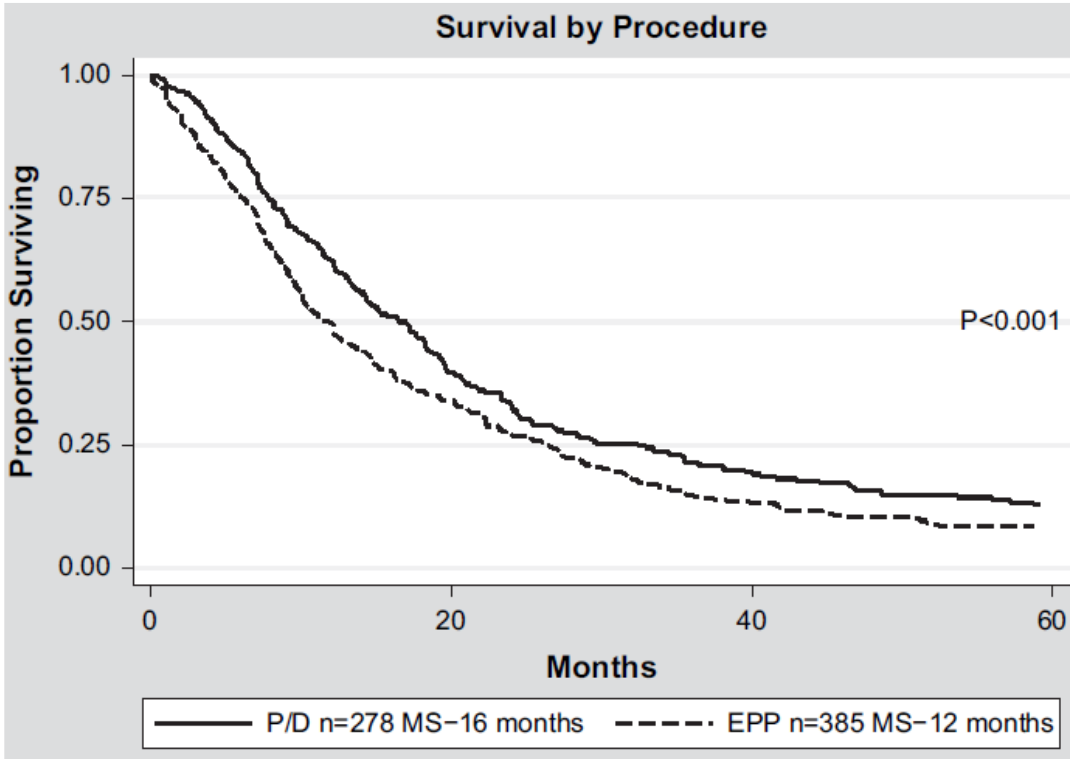
- ***EPP***
  - **Parietal and visceral pleurectomy with en bloc lymph node dissection +/-resection of diaphragm and pericardium**
- ***P/D***
  - **Parietal and visceral pleurectomy**
- ***EPD***
  - **Parietal and visceral pleurectomy with resection of diaphragm and / or pericardium**

IASLC Definitions:
Rice, D et al JTO 2011;6:1304-1312

EPP vs P/D for MPM: 663 Patients
Overall Survival



- 2 institution study: MSKCC & NYU
- Mortality: EPP (7%), P/D (4%)



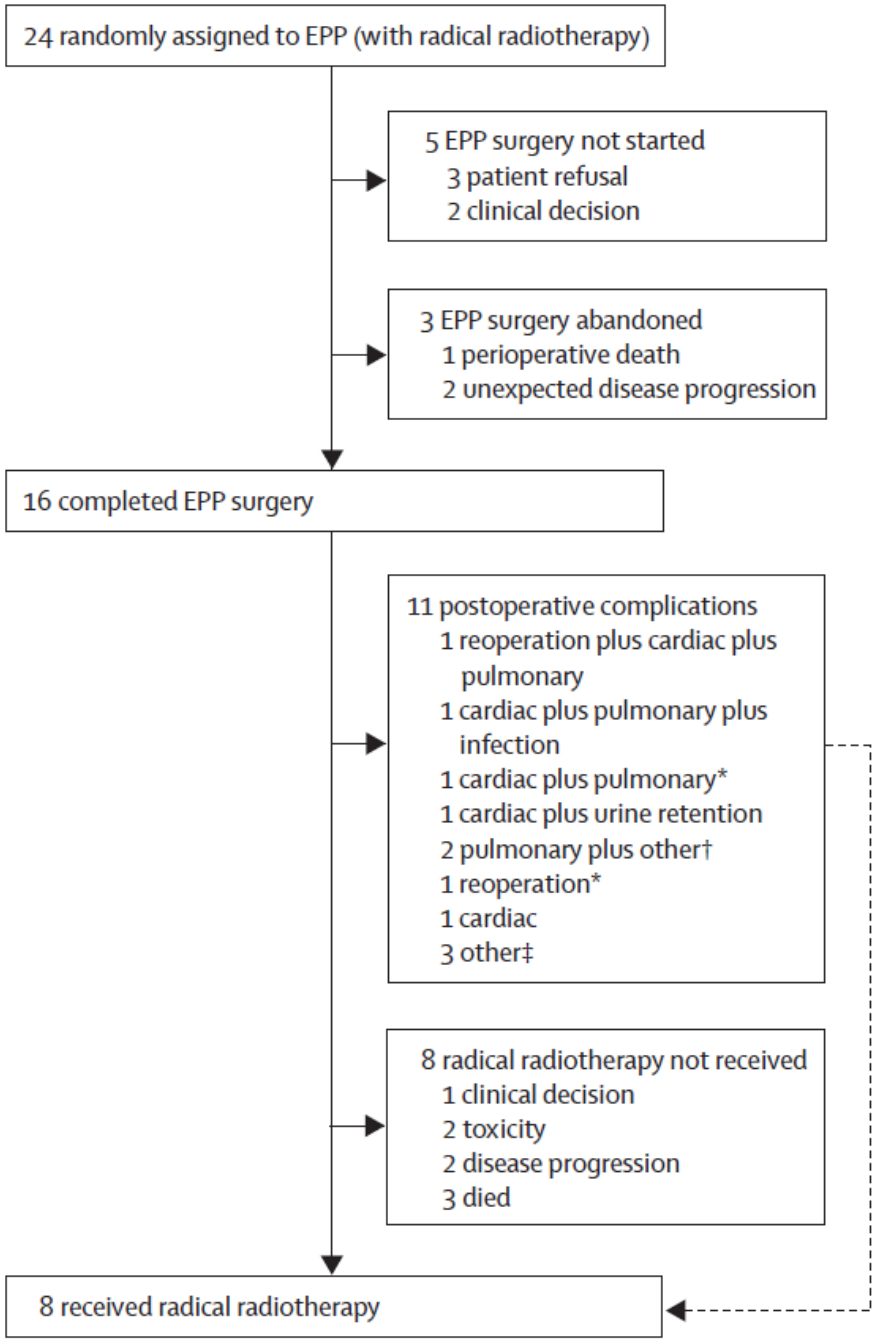
In MVA, HR for EPP = 1.4, controlling for stage, histology, gender and multimodality therapy

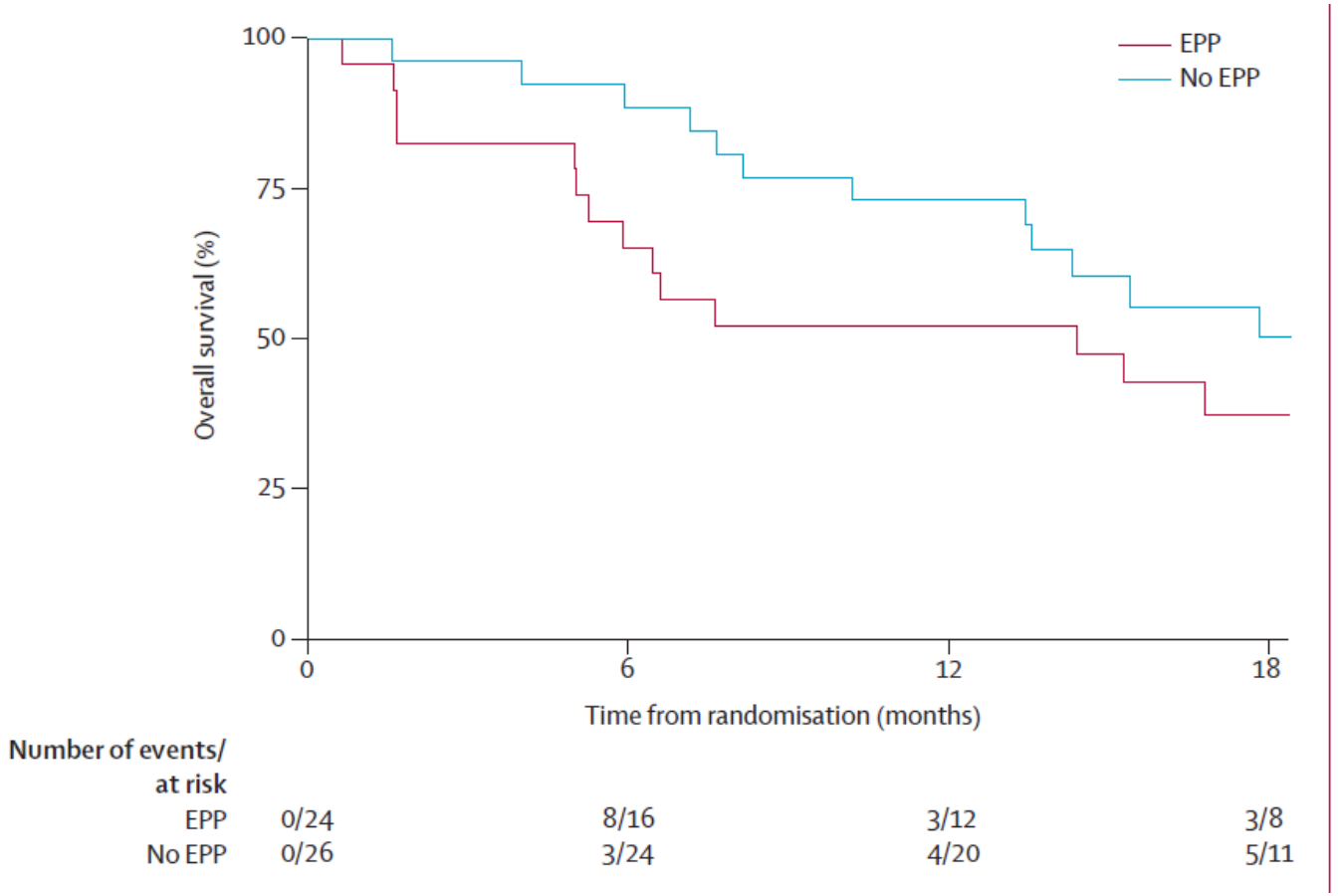
Corroborated by MDACC retrospective study of similar design: Zhou et al ATS 2022;113:200-8

Flores al. *J Thorac Cardiovasc Surg* 2008; 135:620-626.

EPP vs no EPP for MPM: MARS 1 Trial

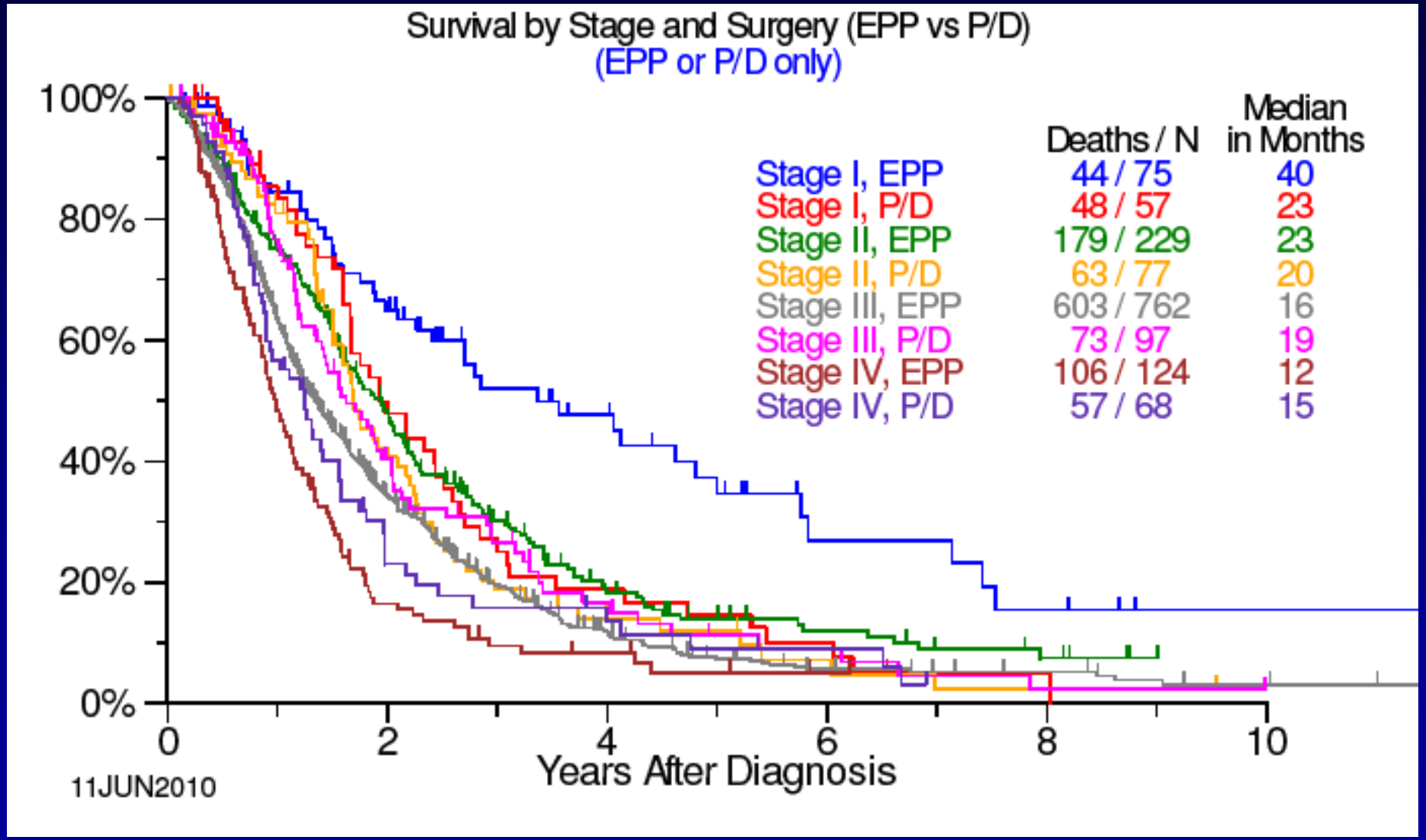
Feasibility of EPP surgery and radical radiotherapy treatment





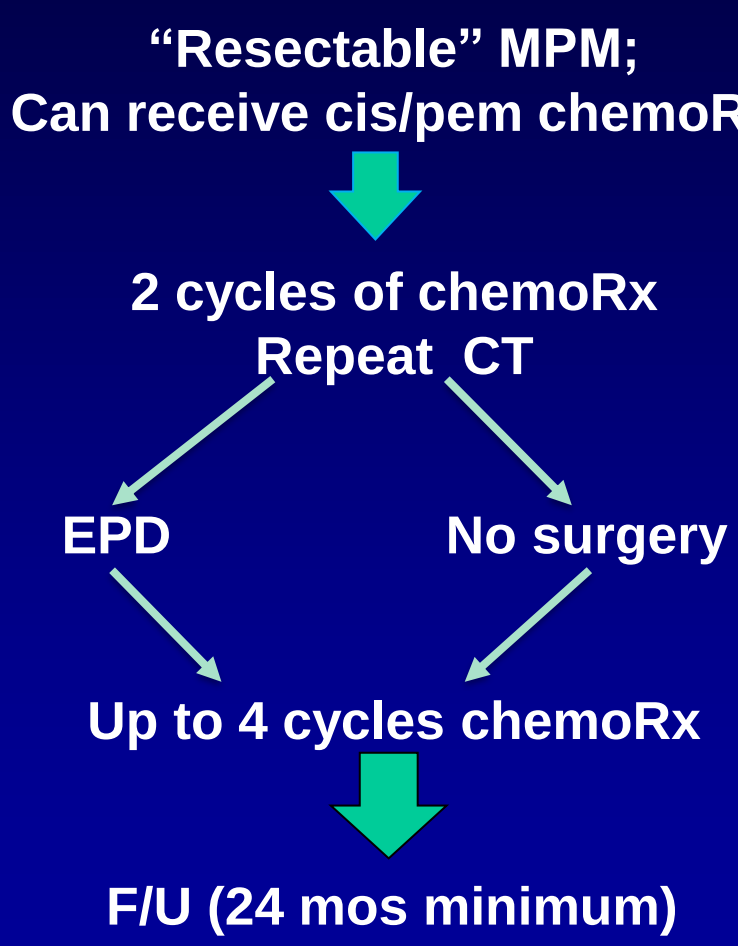
Treasure al. *Lancet Oncol* 2011; 12:763-72.

IASLC MPM Staging Database:
Analyses by Stage and Surgical Procedure



Rusch et al. JTO 2012; 7:1631-39

Does surgery (EPD) in addition to chemoRx benefit OS?
MARS2 trial (UK)



Endpoints:

- OS
- QOL
- Cost effectiveness

- Completed accrual as planned (despite COVID) with last randomization Jan 2021
- 335 randomized patients
- Currently awaiting analysis

TABLE 2. Site of first recurrence after extrapleural pneumonectomy versus pleurectomy/decortication

	EPP (n = 219) n (%)	P/D (n = 133) n (%)
Local recurrences	73 (33%)	86 (65%)
Ipsilateral chest	68 (31%)	84 (63%)
Pericardium	5 (2%)	2 (2%)
Distant recurrences	146 (66%)	47 (35%)
Contralateral lung/pleura	49 (22%)	14 (11%)
Peritoneum	57 (26%)	24 (18%)
Peritoneum + chest	17 (8%)	1
Abdominal viscera	12 (5%)	4 (3%)
Bone	7 (3%)	–
Brain	1	1
Cutaneous (distant)	1	1
Other	2	2 (2%)

EPP, Extrapleural pneumonectomy; *P/D*, pleurectomy/decortication.

Flores RM et al. *J Thorac Cardiovasc Surg* 2008;135:620-626.

MALIGNANT MESOTHELIOMA

MSKCC Trial (Surgery + RT)

- 1993-98: 88 patients entered
  62 tumors resected by EPP
- Adjuvant RT (54Gy) given to 57 patients
  Well tolerated except 1 esophageal fistula
- Relapse sites: locoregional = 1
  locoregional + distant = 6
- Median survival: 33.8 months, Stages I+II
  10 months, Stages III+IV

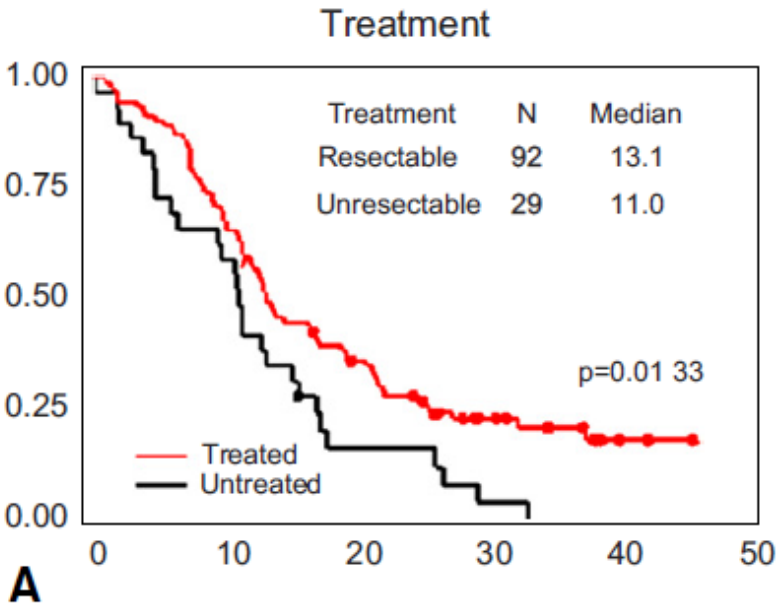
Rusch et al. JThCvS 2001;122:788-795

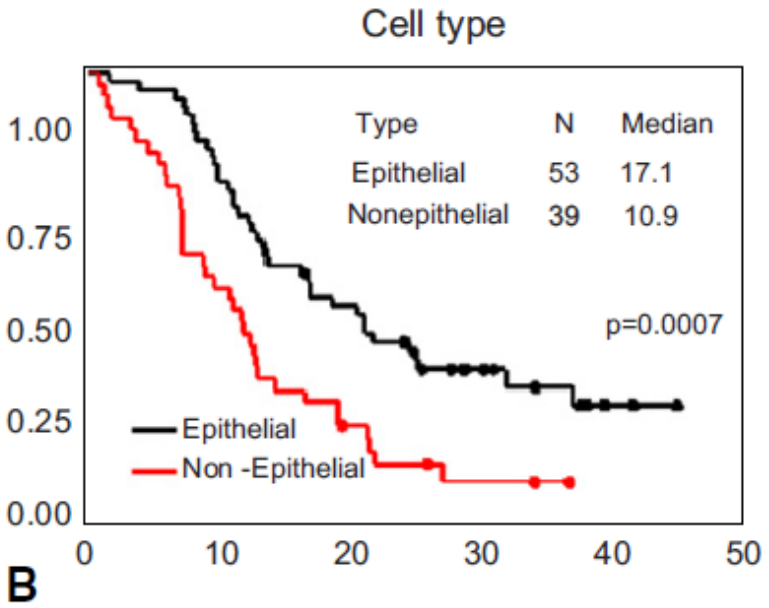
Selected Combined Modality Therapy Studies
(Induction chemotherapy + EPP +/- RT)

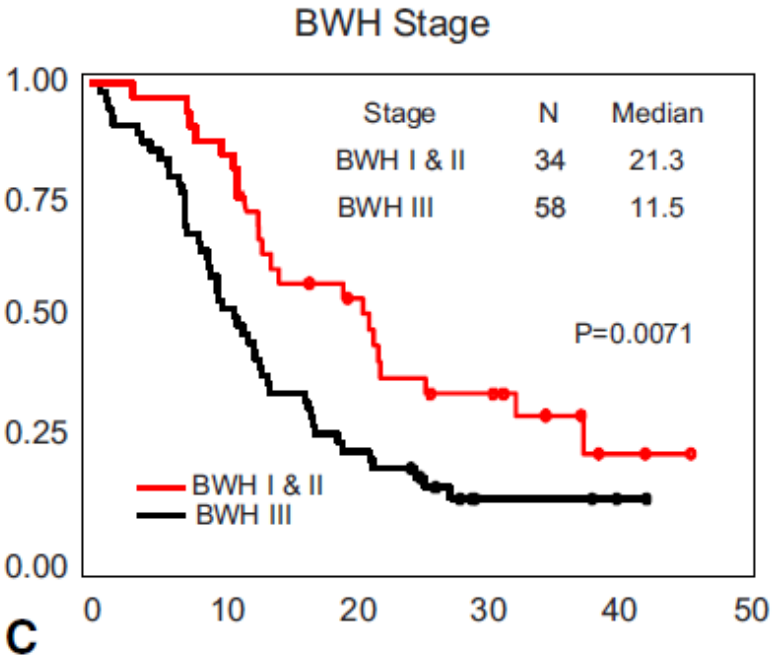
Study	pN2	Drug Regimen	EPP	Response Rate (%)	Adjuvant XRT	Median OS, Months
Krug * (n=75)	34	C+P	50	29.3	42	16.6
Weder (n=19)	0	C+G	16	32	13	23
Flores (n=21)	7	C+G	8	26	8	19
Weder * (n=61)	14	C+G	37	NR	36	19.8
Rea (n=21)	5	C+G	17	33	15	25.5

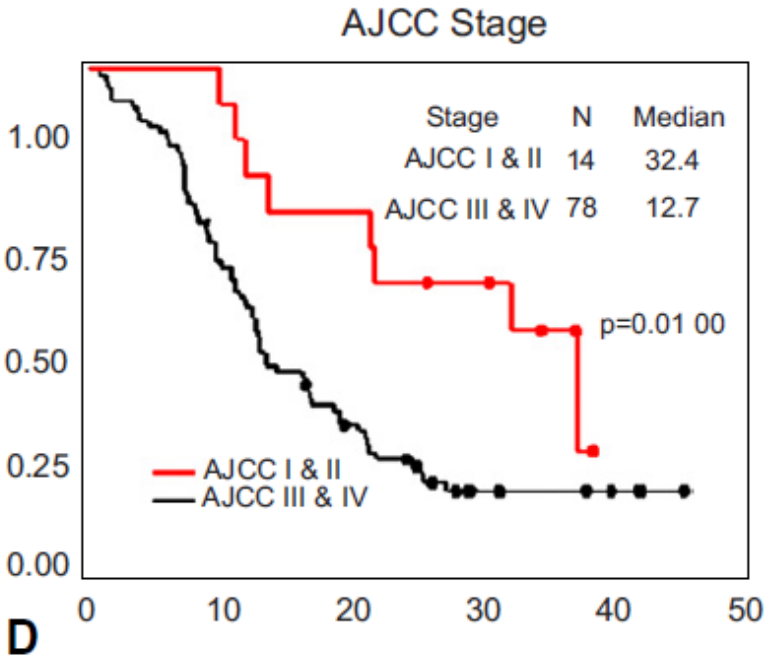
C=cisplatin; G=gemcitabine; P=pemetrexed
* = multicenter trials

Tsao et al. *Clin Lung Cancer* 2009;10(1):36-41.









EPP + hyperthermic intracavitary cisplatin for MPM (n=96): ***Survival Estimates***

Hospital mortality: 4.3%
Grade 3-4 AE: 49%
Median OS: 12.8 mos
Recurrence:
ipsilateral chest 34%
abdomen 51%

Tilleman et al (BWH).
JTCVS 2009; 138:405-411

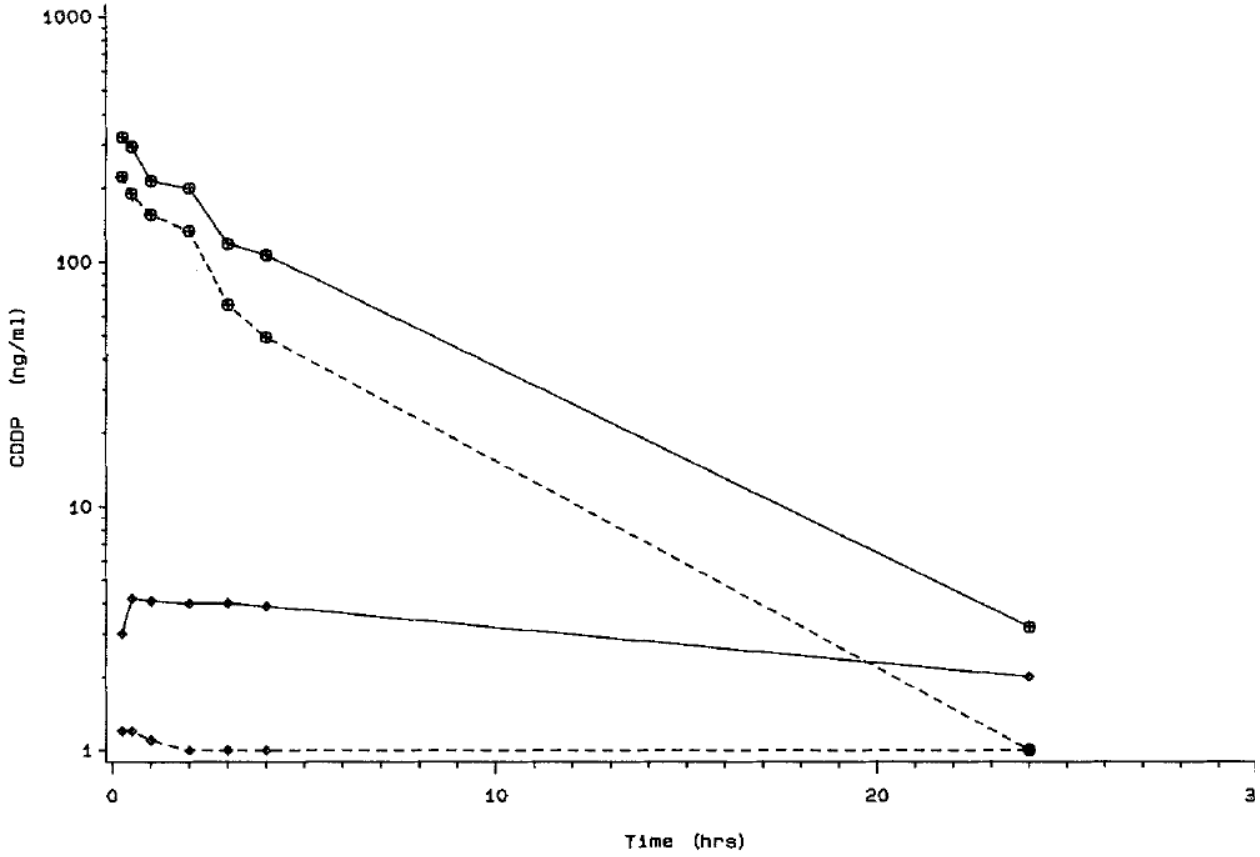
Selected Intrapleural Chemotherapy Trials

Study	N2 or Nx	Intra Chemo	Surg Type	Peri-op Mortal. %	Adjuvant Systemic Chemo	Adjuvant RT	Median OS, Months	3-Yr OS
Rusch (n=36)	16	C+M	P/D	3.7	C+M	None	18.3	40%
Lee (n=15)	0	C+CA	P/D	0	46%	73%	11.5	7%
Colleoni (n=20)	2	C+CA	P/D	0	E+M	None	11.5	NR
Rice (n=19)	5	C+M	P/D EPP	5	C	None	13	17%

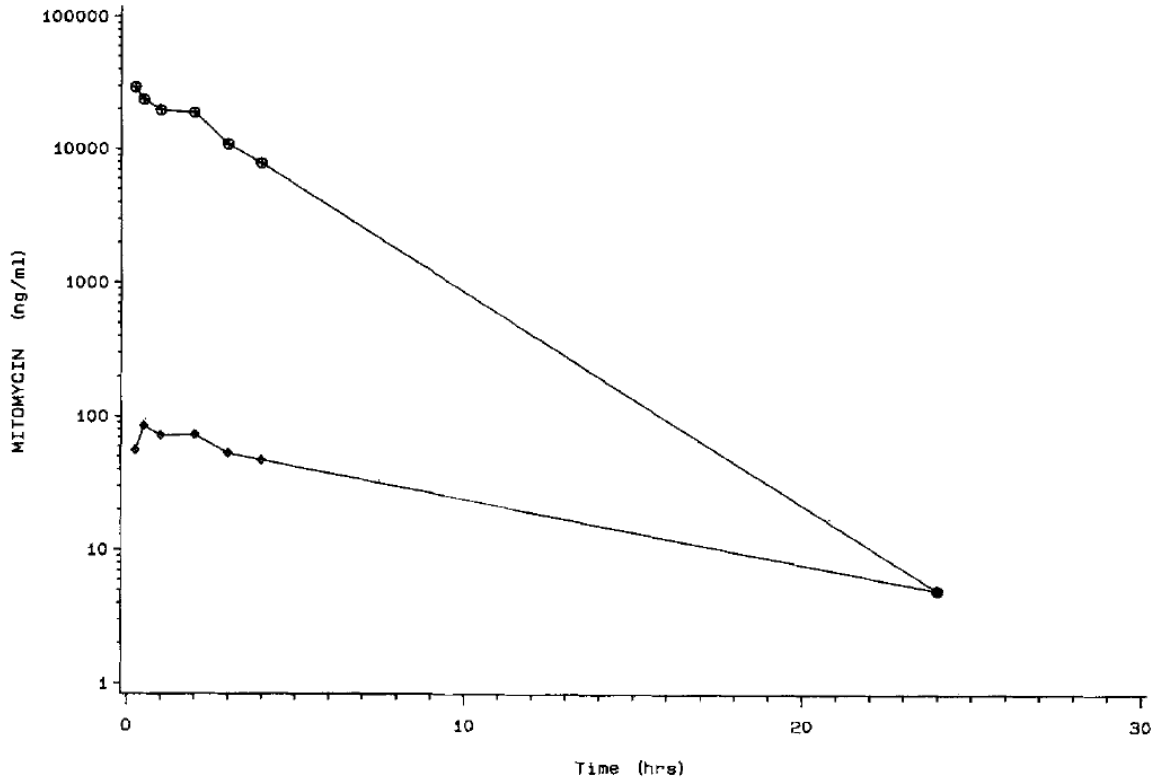
C=cisplatin; CA=cytosine arabinoside
M=mitomycin; E=epirubicin

Tsao et al. *Clin Lung Cancer* 2009;10(1):36-41.

Intrapleural Cisplatin and Mitomycin for MPM s/p EPD: Pleural and Plasma Elimination Curves

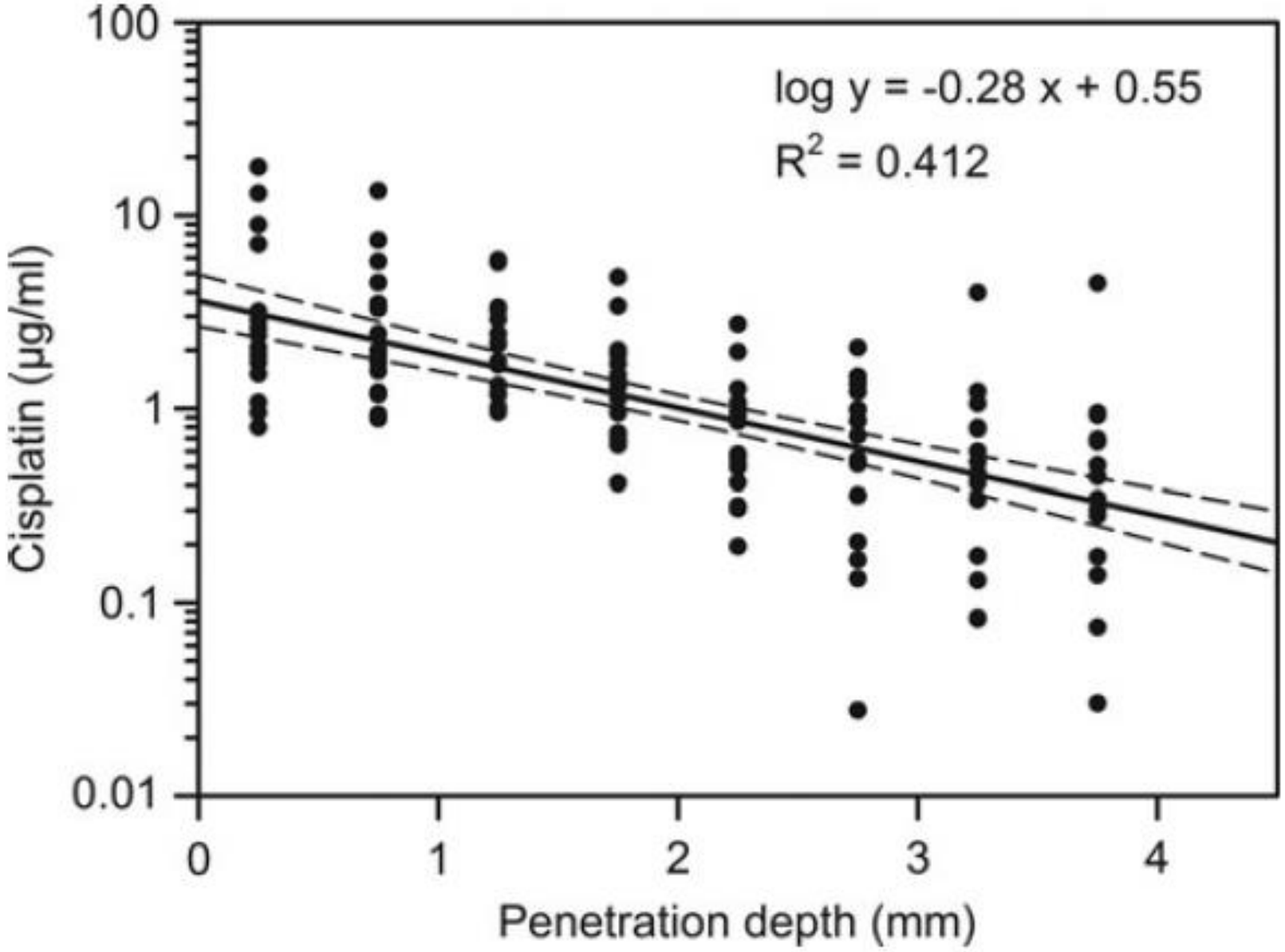


Total and Free Cisplatin



Mitomycin

Rusch et al. *J Clin Oncol* 1992;10:1001-1006.

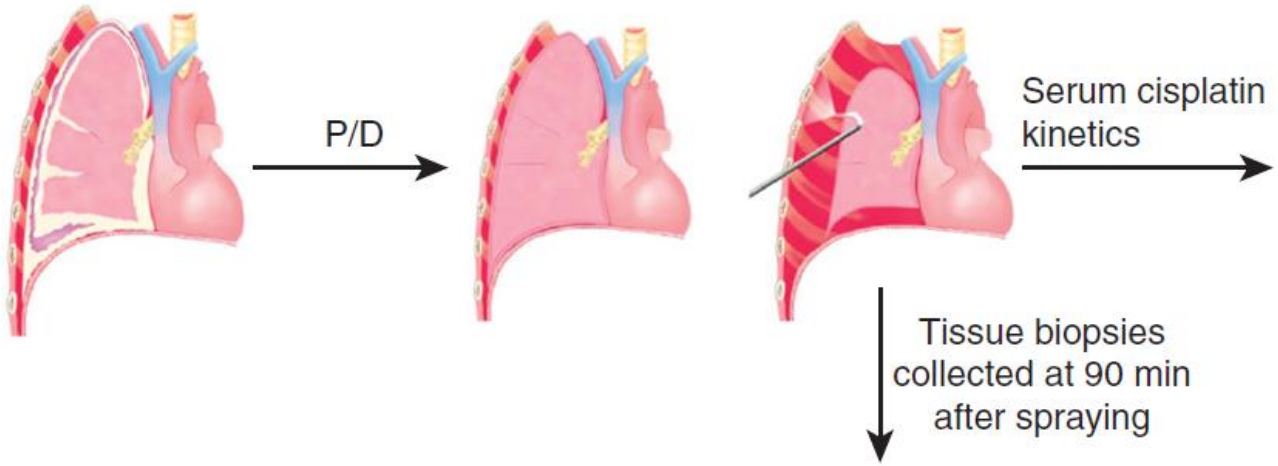


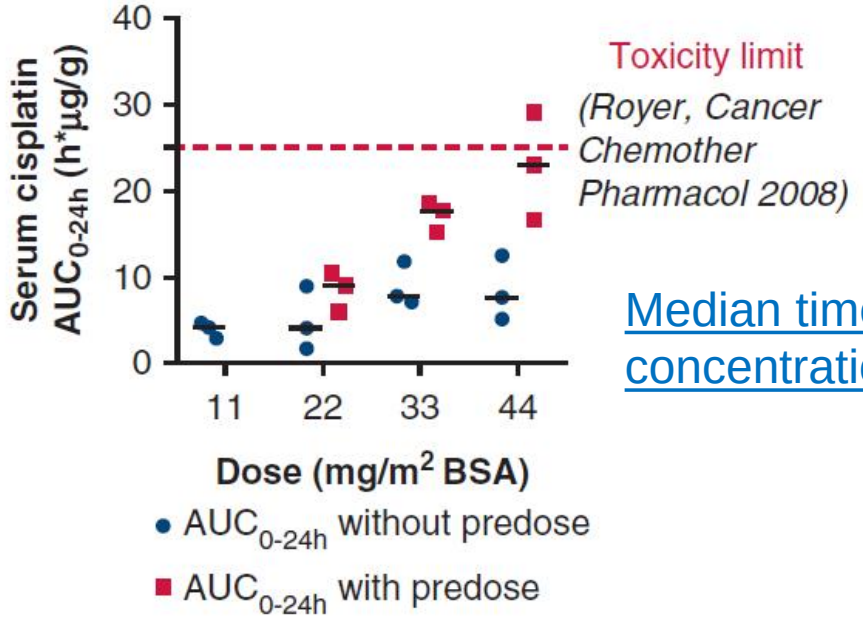
Cisplatin concentration in lung tissue after hyperthermic exposure: Estimation of platinum concentration

Ried et al. *Eur J Cardio-Thorac Surg 2015*; 47:563-566.

Intracavitary cisplatin-fibrin chemo after EPD for MPM **(Phase I, dose escalation, n=12)**

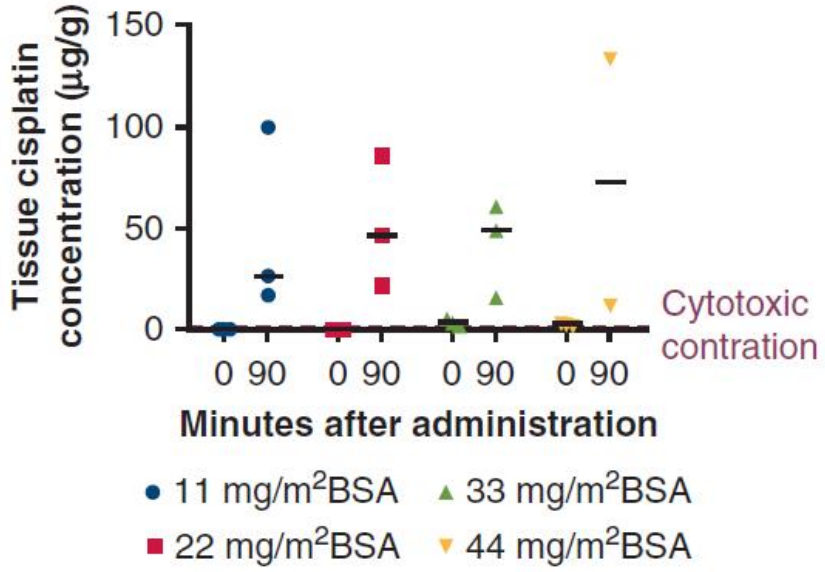
After EPP, cisplatin-fibrin was applied on the thoracic wall and the lung surface.





Median time to max serum concentration = 2 hrs

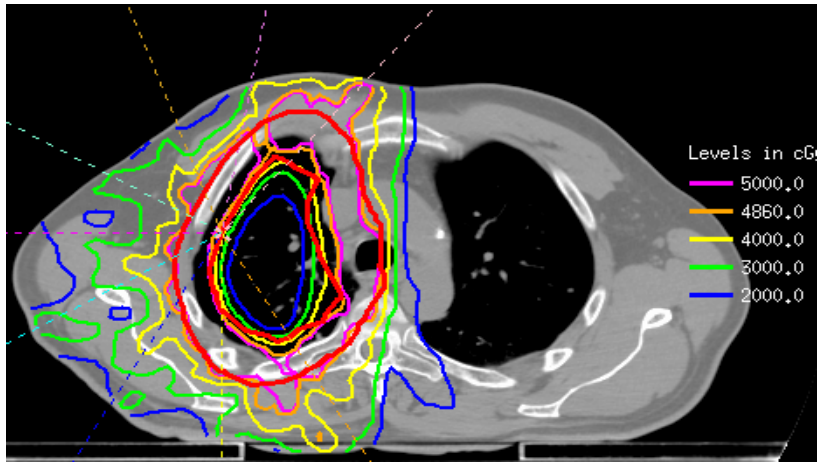
At 90 min

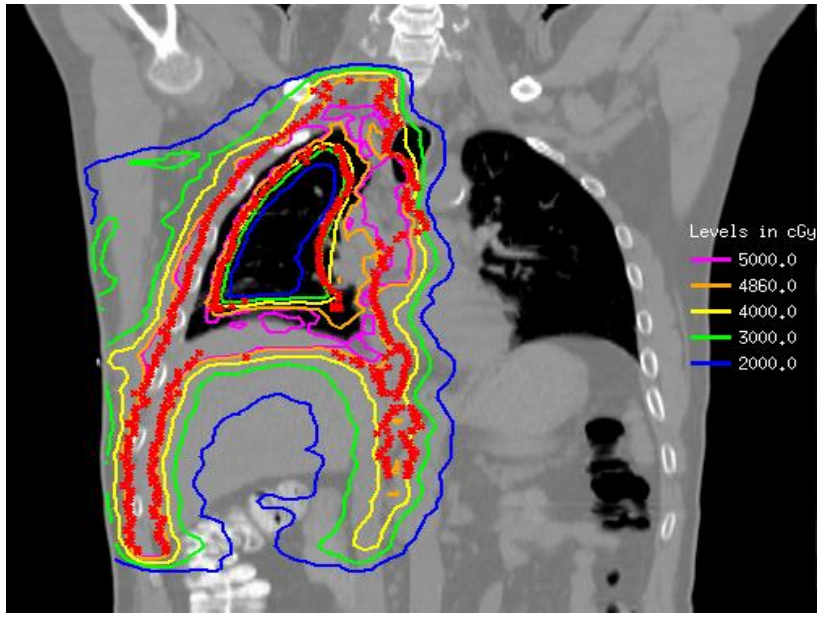


90 day mortality = 0
9 serious AE, none study related
High chest wall concentrations
Median OS 21 mos

Opitz et al. *J Thorac Cardiovasc Surg* 2020; 159:330-340.

Phase II trial hemithoracic intensity modulated pleural RT (IMPRINT) as part of lung sparing multimodality therapy in MPM





- 45 patients enrolled
  cis or carbo + pem (2-4 cycles)
- 21 pts: P/D or EPD
  27 pts. treated with IMPRINT
- No grade 4-5 toxicities
  12 pts. grade 2-3 pneumonitis, resolved with steroids
- Median PFS 12.4 mos
  Median OS 23.7 mos
- 2 yr. OS 59% for resectable tumors
  2 yr. OS 25% for unresectable

Rimner et al (MSKCC, MDACC) JCO 2016; 34:2761-2768

MULTIMODALITY THERAPY in MPM

Options: Summary

- ***EPP + hemithoracic RT***
  - excellent local control; suitable for selected patients; high risk of systemic relapse in stage III
- **EPD + IMRT**
  - Promising, awaiting further validation
- ***EPP or EPD + intrapleural +/- systemic chemoRx***
  - poor local control; ?? Impact on survival; investigational
- ***ChemoRx (pre or postop) + surgery +/- RT***
  - feasible; may improve OS especially stages II / III

MPM Unmet Needs

Summary

- Significant advances in pre-treatment evaluation and patient selection
  - Clinical staging still cumbersome and relatively imprecise
- Some insights into MPM tumor biology
  - Still no targetable molecular alterations
- Improving TNM staging system
  - A work in progress; recommendations for 9th edition staging system forthcoming
- EPD has largely supplanted EPP as method of surgical resection
  - MARS2 RCT results may soon provide definitive information about role of surgery

MPM Unmet Needs

Summary

- Some advances in both systemic therapies and RT modalities
  - Dual agent IO an important addition, needs further study
  - IMPRINT feasible after MCR, may improve local control, needs further study
- Multimodality therapy (chemo + surgery +/- RT) feasible
  - Many therapeutic combinations tested
  - Best treatment sequence still undefined
  - Therapeutic benefits appear real but still modest
- Still lots of room for very novel therapies in this disease