



U F I M

Unità Funzionale
Interaziendale
Mesotelioma



Malignant Pleural Mesothelioma

COMBINED TREATMENT

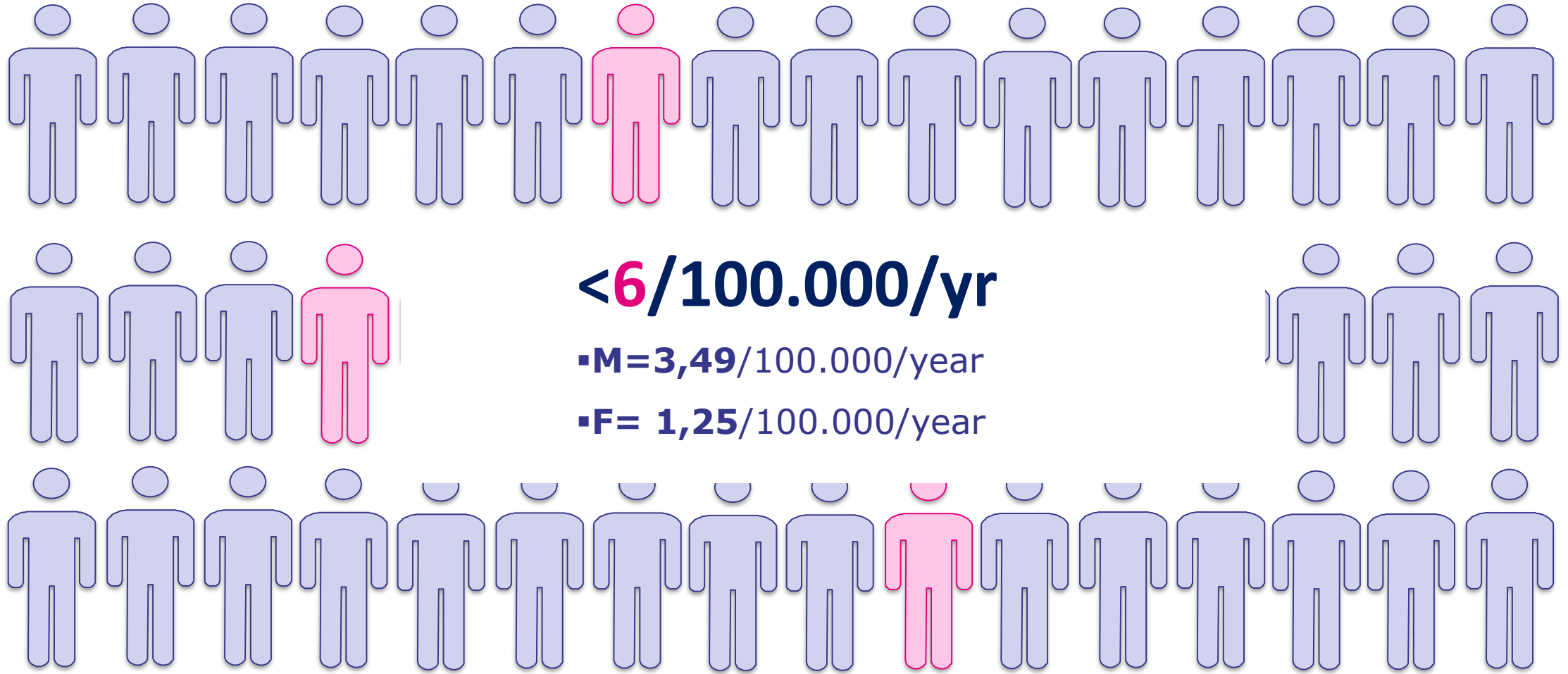
Federica Grosso



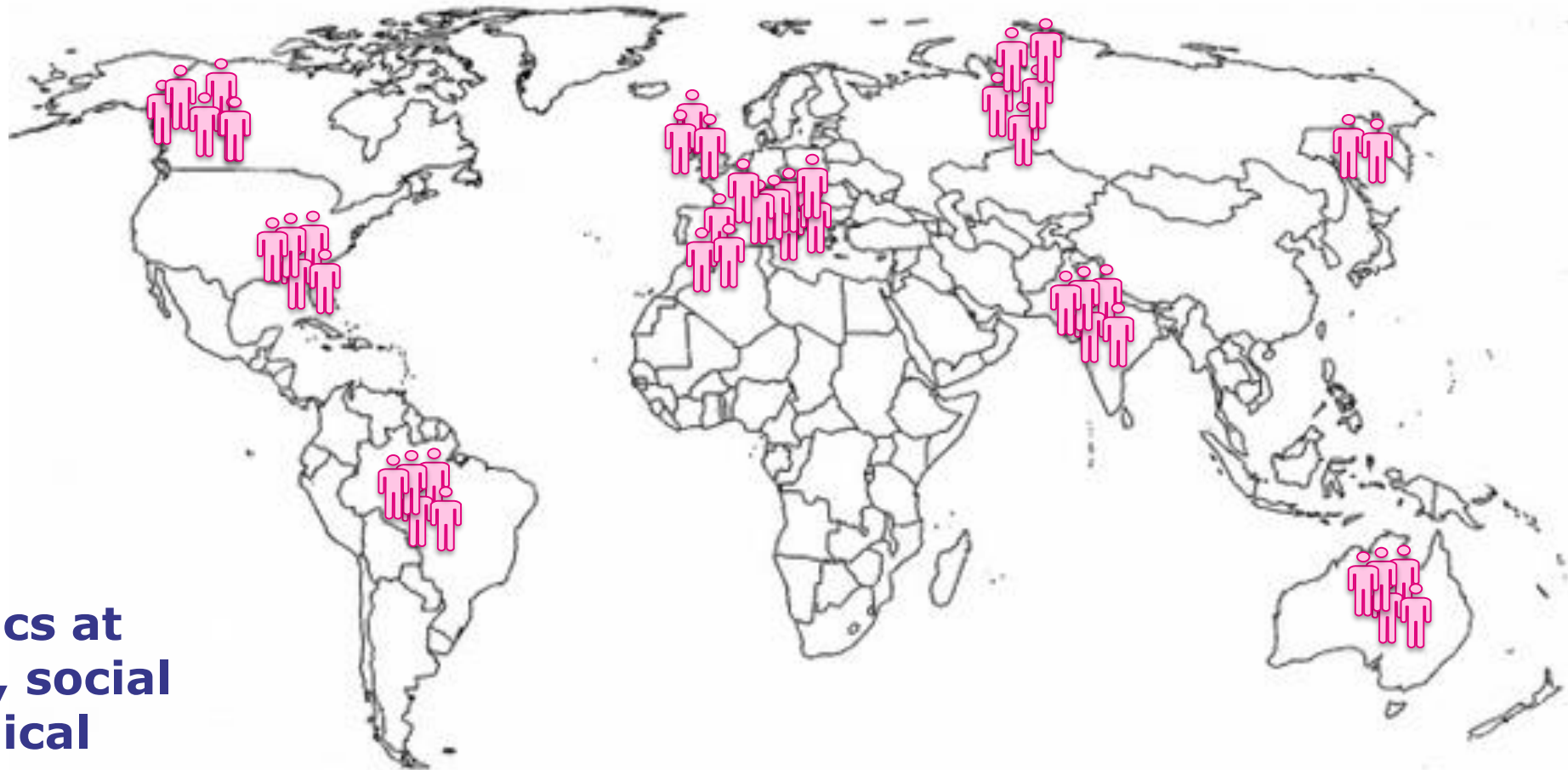
Azienda Ospedaliera Nazionale
SS. Antonio e Biagio e Cesare Arrigo
Alessandria



incidence



Distribution of cases

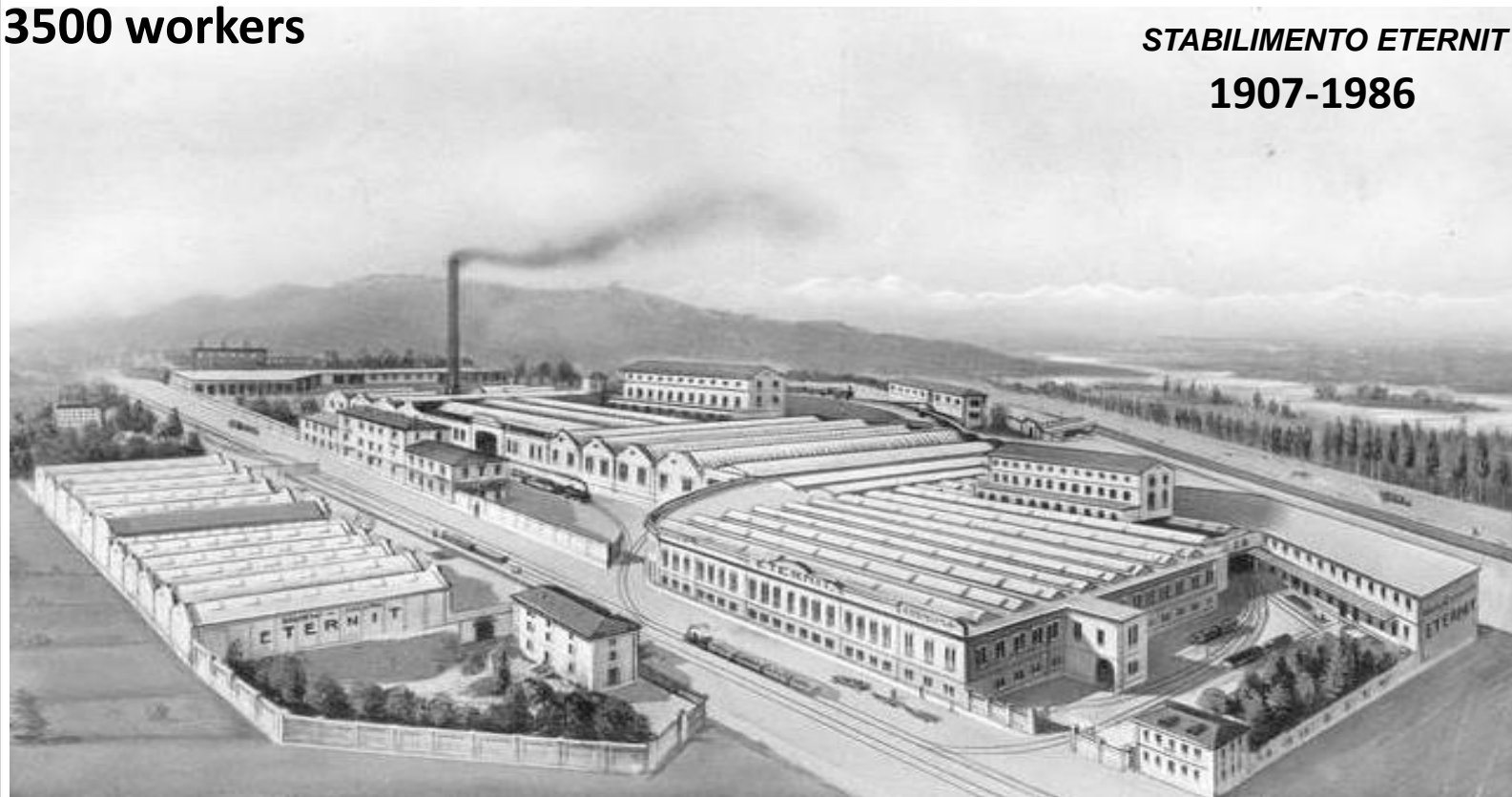


True epidemics at high medical, social and psychological burden

Casale Monferrato – Alessandria (Italy)

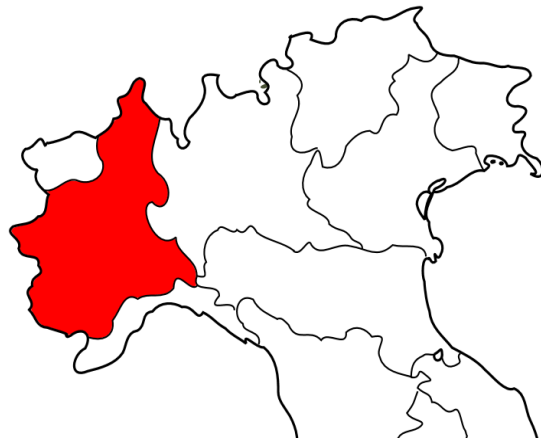


3500 workers



STABILIMENTO ETERNIT
1907-1986

In my region

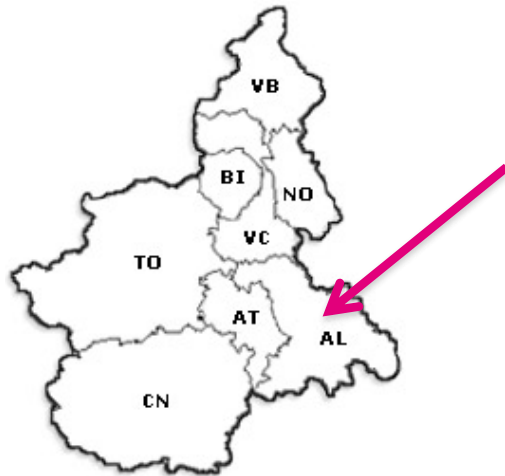


250 new cases/year

▪ **M= 5,3/100.000/yr**

▪ **F= 1,9/100.000/yr**

70% professional exposure



▪ **M= 89,3/100.000/yr**

▪ **F= 34,6/100.000/yr**

80% environmental exposure

State of the art

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline

Hedy L. Kindler, Nofisat Ismaila, Samuel G. Armato III, Raphael Bueno, Mary Hesdorffer, Thierry Jahan, Clyde Michael Jones, Markku Miettinen, Harvey Pass, Andreas Rimmer, Valerie Rusch, Daniel Sterman, Anish Thomas, and Raffit Hassan

ABSTRACT

Purpose

To provide evidence-based recommendations to practicing physicians and others on the management of malignant pleural mesothelioma.

Methods

ASCO convened an Expert Panel of medical oncology, thoracic surgery, radiation oncology, pulmonary, pathology, imaging, and advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 1990 through 2017. Outcomes of interest included survival, disease-free or recurrence-free survival, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

Results

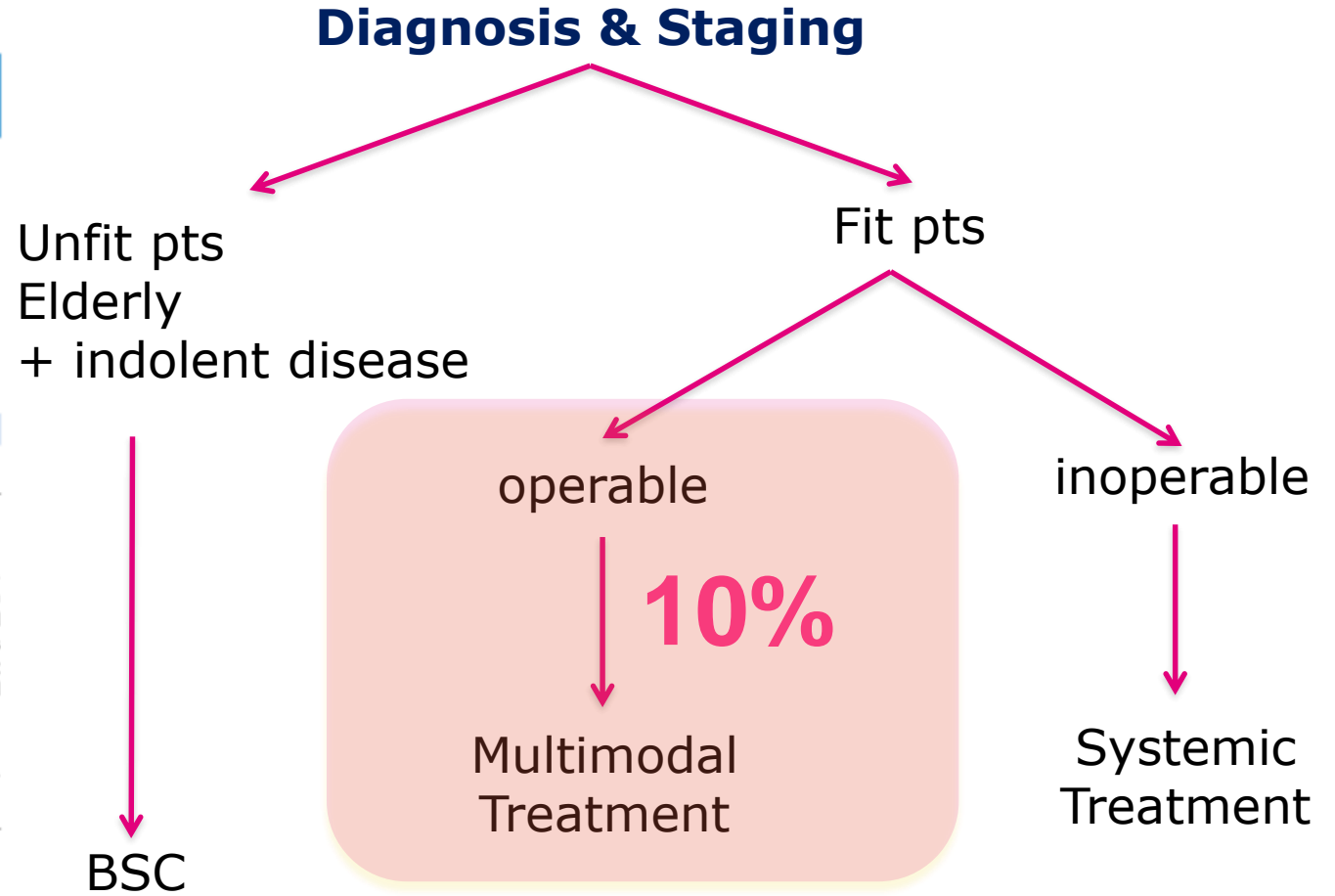
The literature search identified 222 relevant studies to inform the evidence base for this guideline.

Recommendations

Evidence-based recommendations were developed for diagnosis, staging, chemotherapy, surgical cytoreduction, radiation therapy, and multimodality therapy in patients with malignant pleural mesothelioma.

Additional information is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

J Clin Oncol 36:1343-1373. © 2018 by American Society of Clinical Oncology



* Clinical trial suggested at all levels



Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 18, 2018.

Hedy L. Kindler and Raffit Hassan were Expert Panel co-chairs.

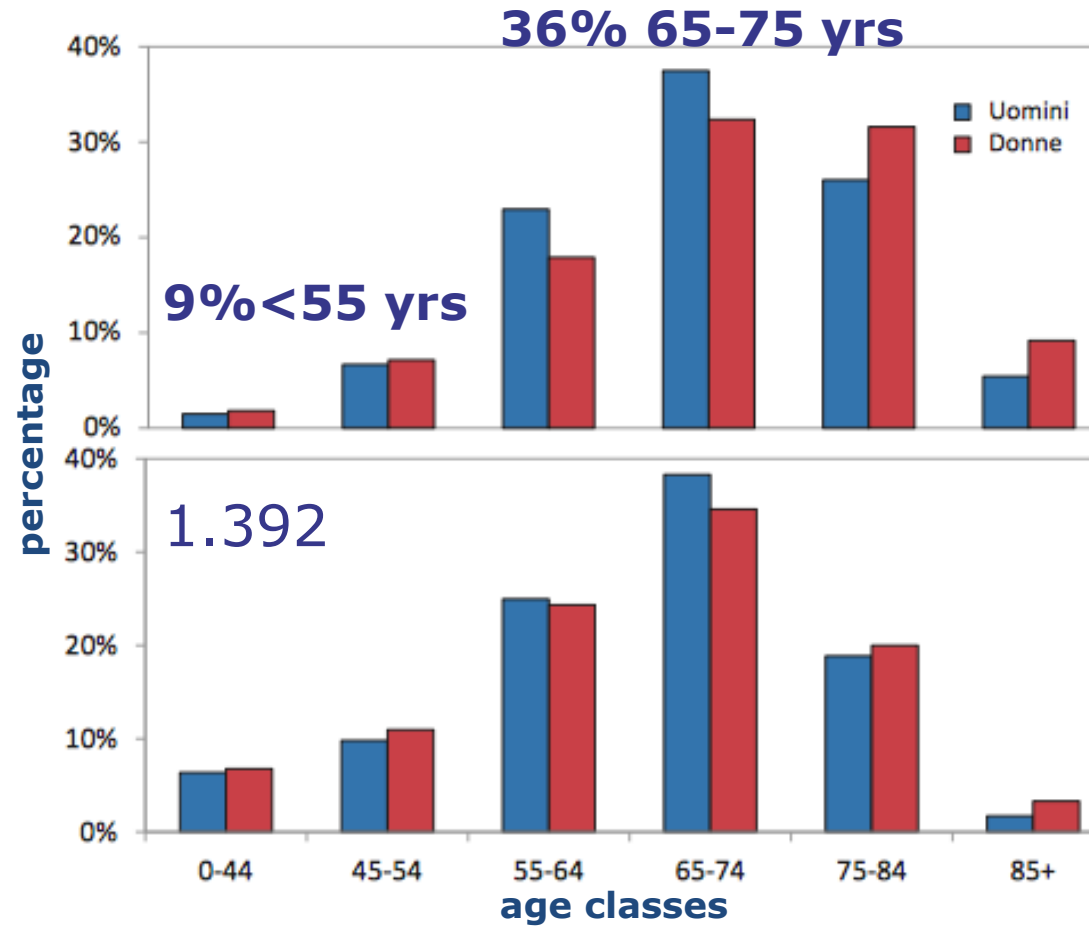
Clinical Practice Guideline Committee Approved: October 16, 2017.

Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

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Elderly



m-age 69,2

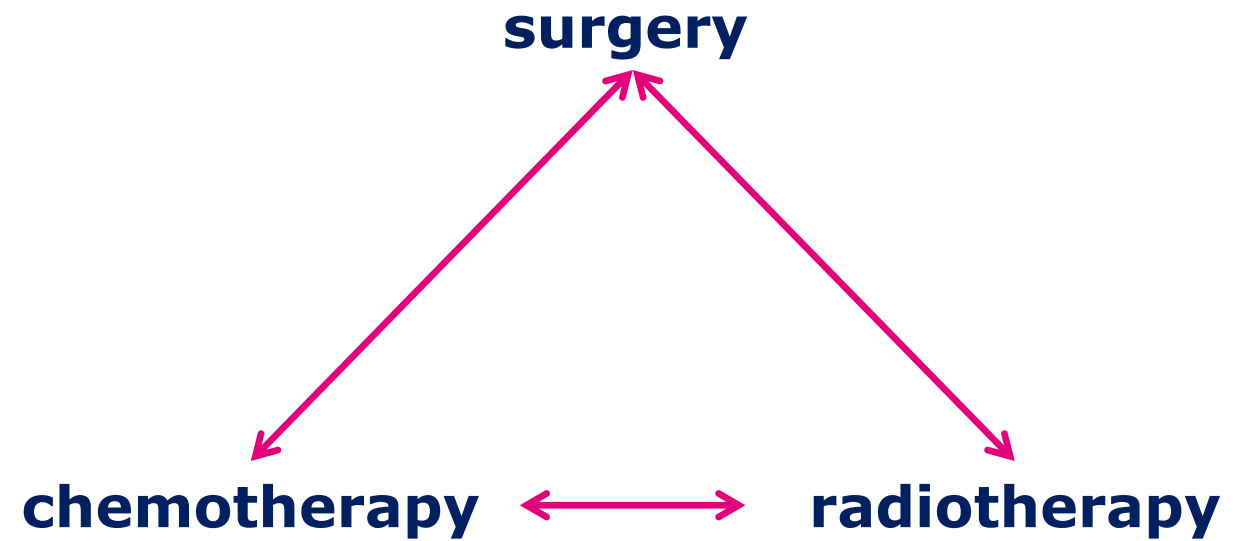
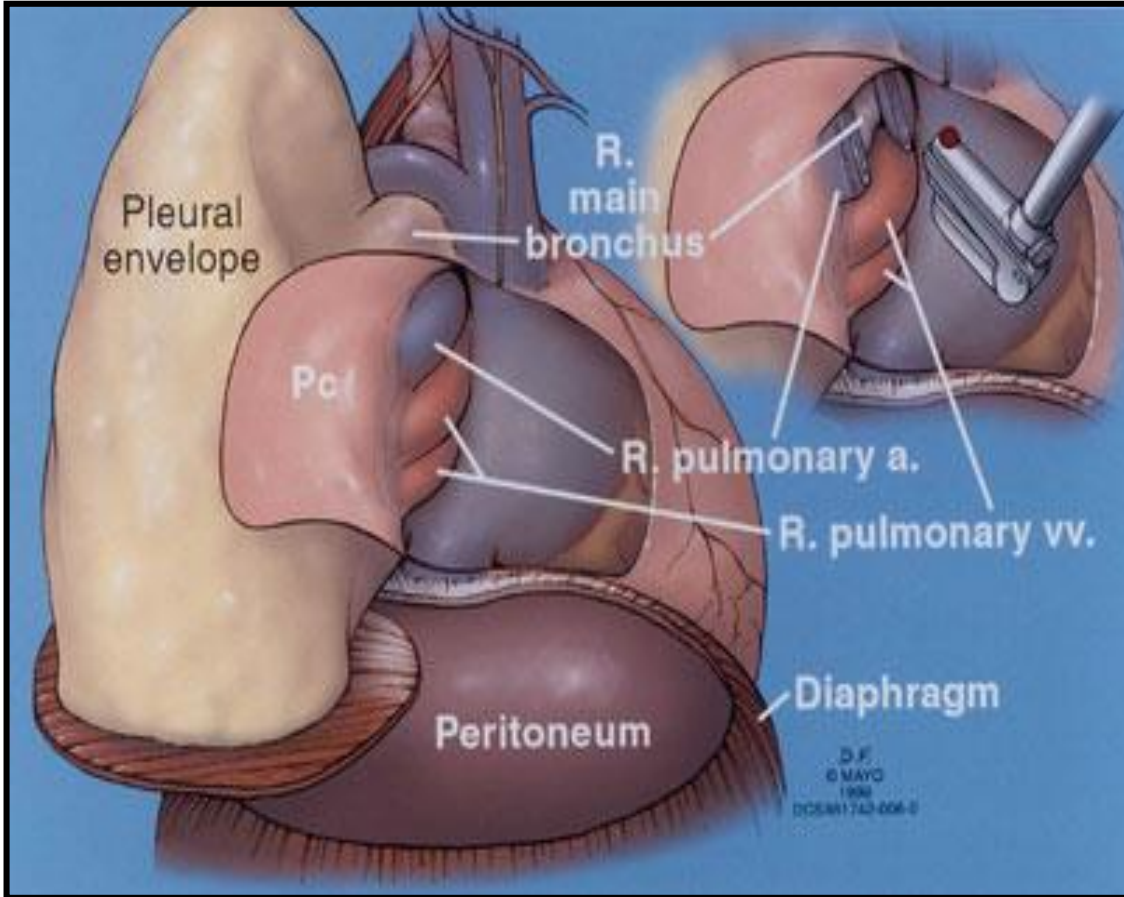
Pleura

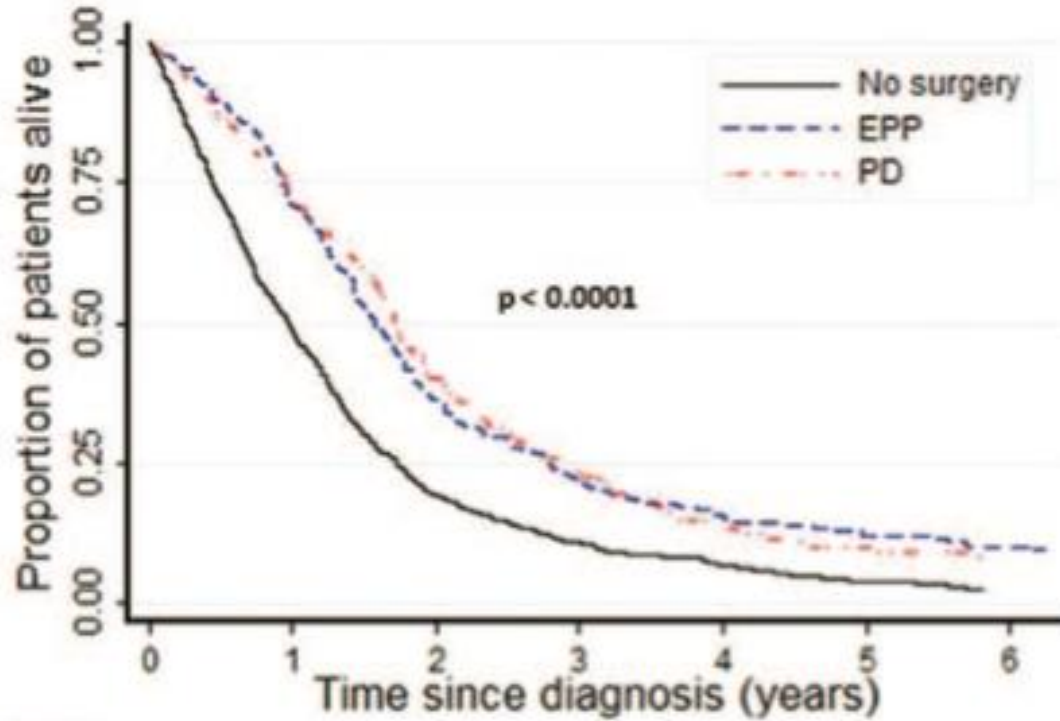
39% >75 yrs

Peritoneum

Italy 1993-2012
21.463 cases

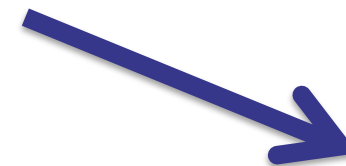
Multimodal treatment: rational





Number at risk		0	1	2	3	4	5	6
No surgery	782	375	145	80	47	25	11	
EPP	290	202	98	53	32	21	13	
PD	155	106	56	29	18	11	8	

_____ NO Sur 11.7 mos
 - - - - - PD 20.5 mos
 - - - - - EPP 18.8 mos



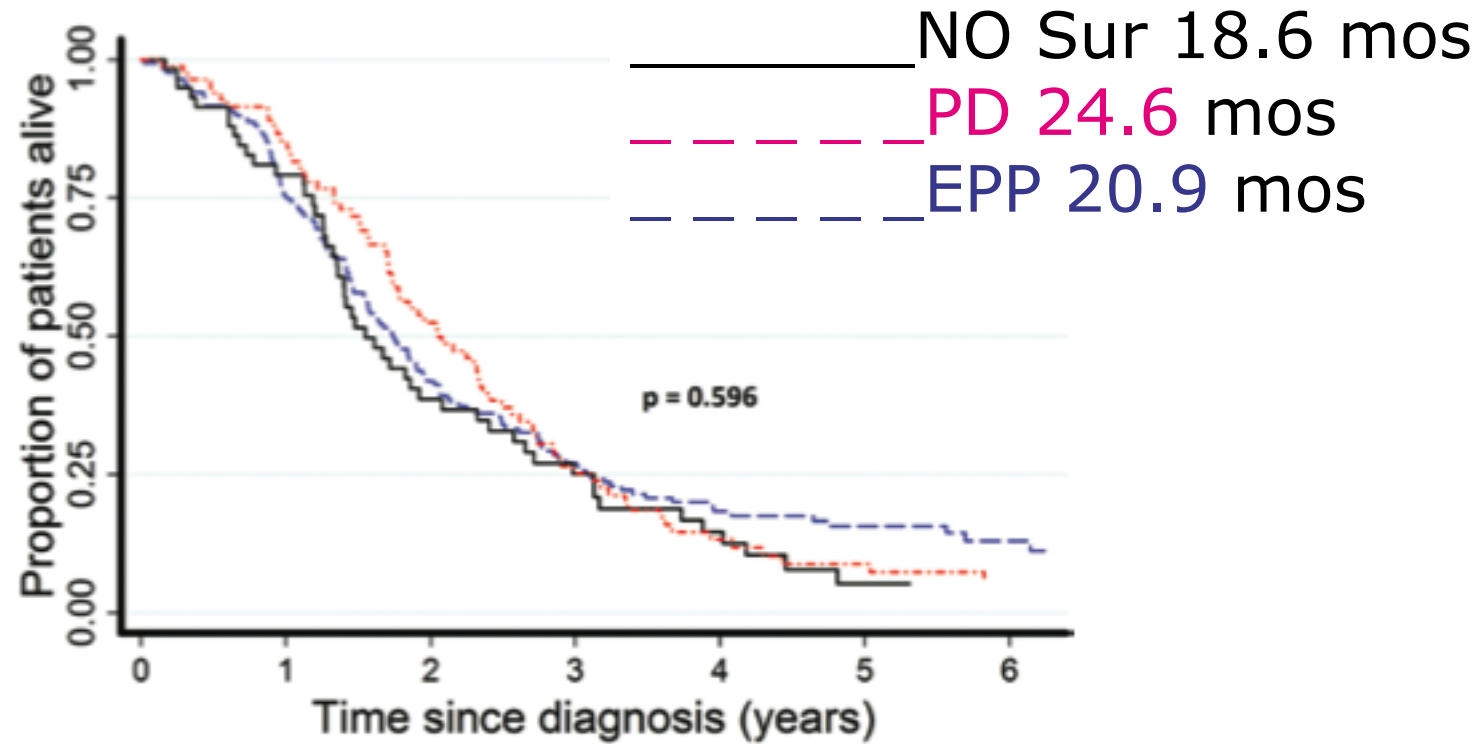
- FP +**

 - Age < 70 yrs
 - Epit hist
 - CT

6 H Ita 1982-2012 FUP 6.7 YRS

1365 pts 172 CT, 690 BSC, SURG 503 **EPP 301 P/D 202**

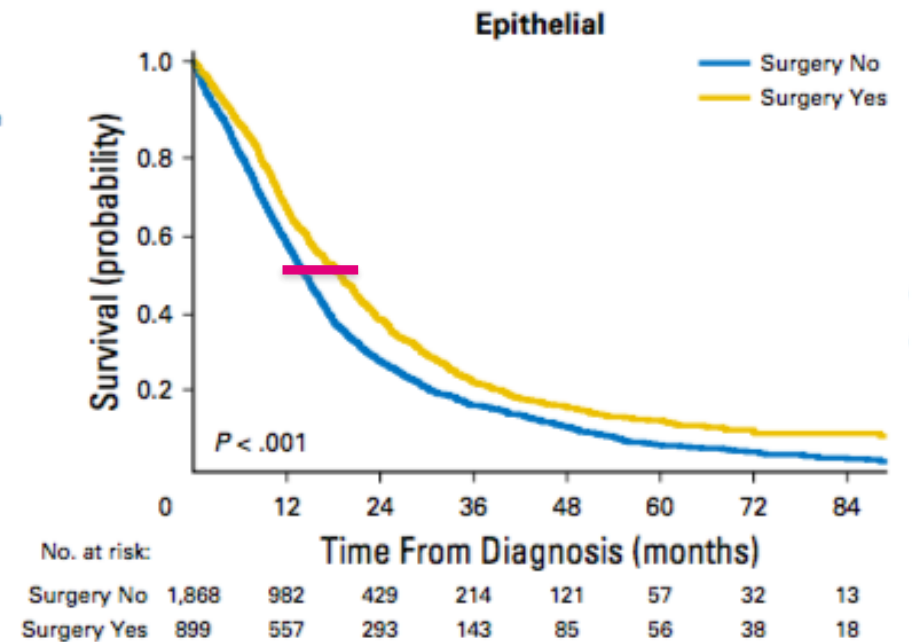
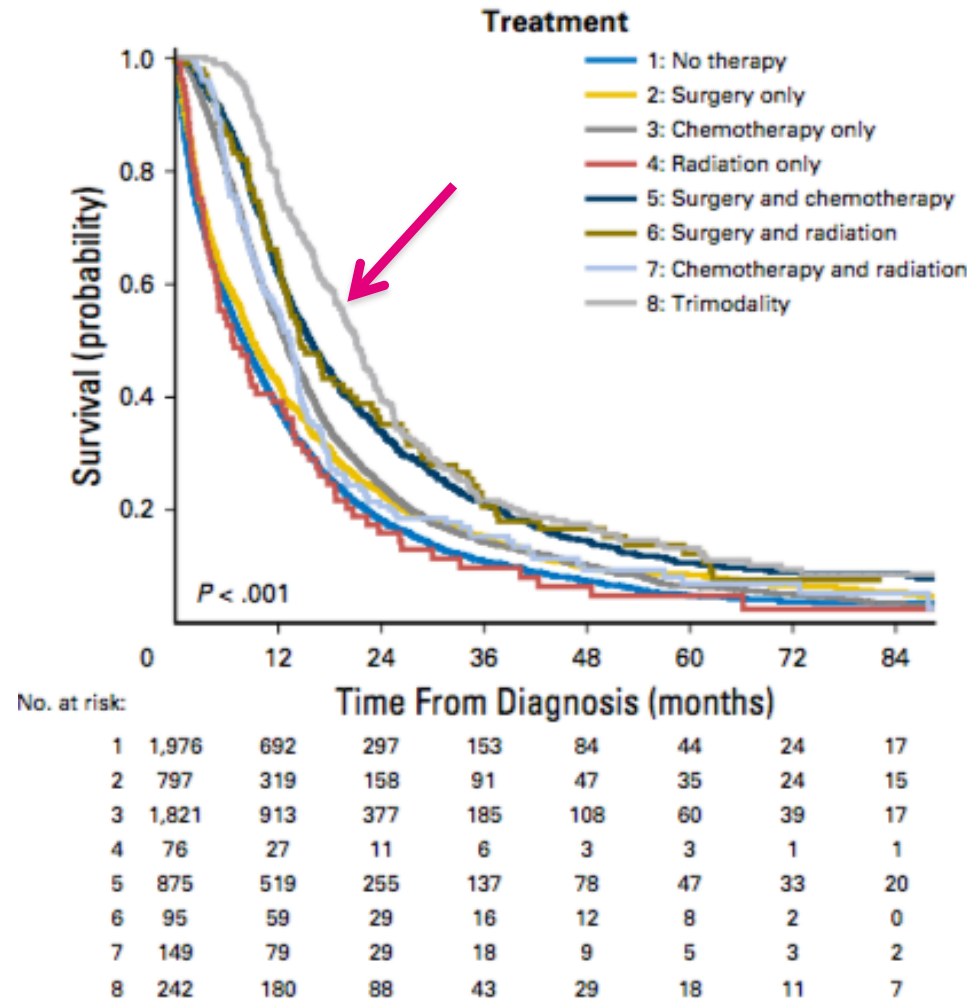
m-OS # 313 PF +



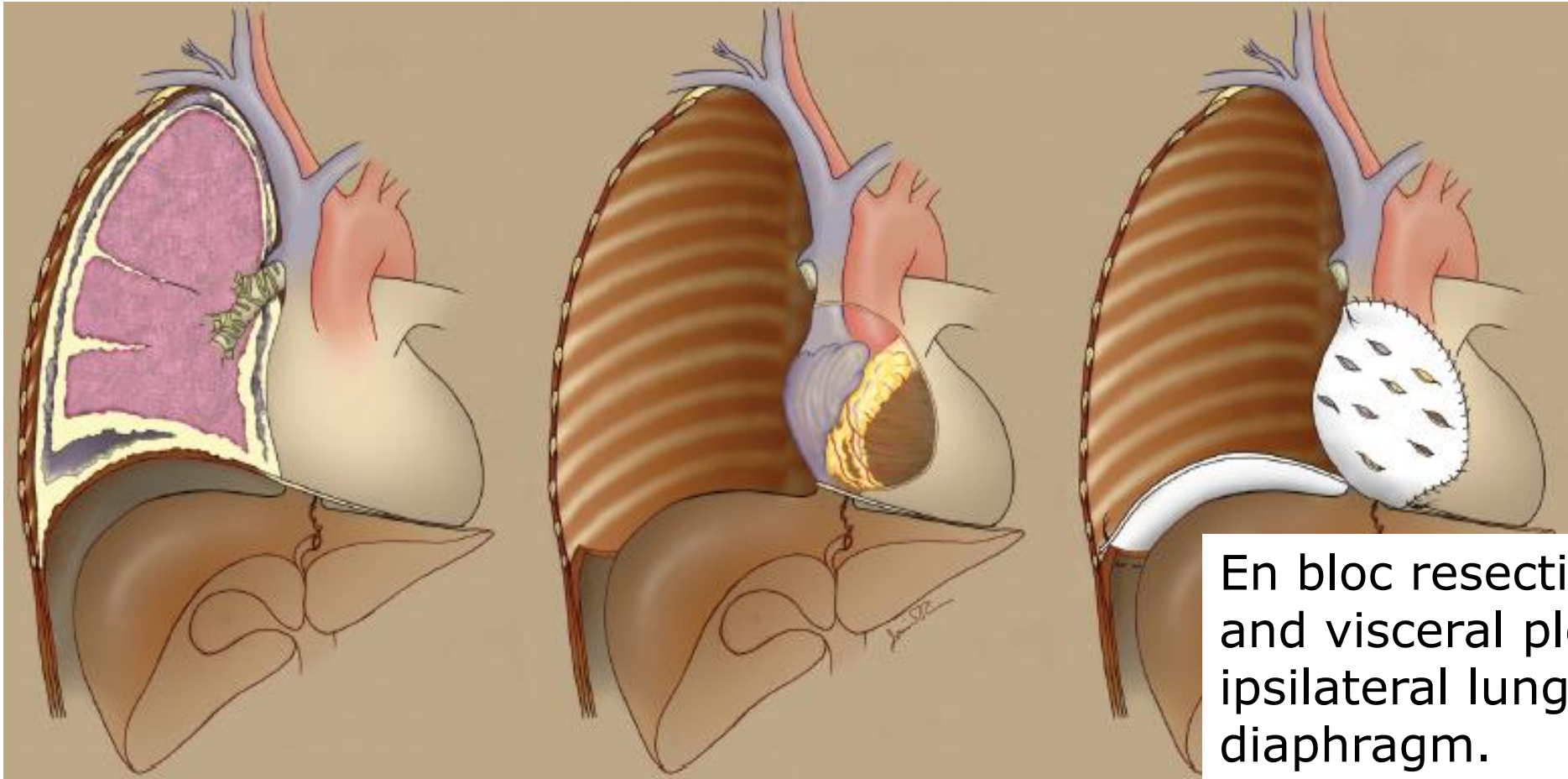
Number at risk		0	1	2	3	4	5	6
No surgery	58	44	20	13	7	2	1	
EPP	169	125	65	39	22	14	8	
PD	86	69	41	19	10	6	4	

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Extrapleural pneumonectomy (EPP)



En bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm.

EPP: Brigham's experience

Table 4. Trimodality therapy in MPM: Brigham's study [ref 88]

Prognostic variable	n	mSv (months)	2-Yr Sv (%)	5-Yr Sv (%)	Odds ratio (CI)
Histology					
→ Epithelial	103	NR	52	21	
Mixed/sarcomatous	73		16	0	3.0 (2.0–4.5)
Resection margins					
→ Negative	66	NR	44	25	
Positive	110		33	9	1.7 (1.2–2.6)
Extrapleural nodes					
→ Negative	136	NR	42	17	
Positive	40		23	0	2.0 (1.3–3.2)
Three positive prognostic factors	31	51	68	46	-
All patients	176	19	38	15	-

Abbreviations: CI, 95% confidence interval; MPM, malignant pleural mesothelioma; mSv, median survival; NR, not reported; Sv, survival rate.

MARS trial

Articles

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



12 H UK – 2005-2008
#112 registered
#50 randomized
24 EPP vs 26 nil

*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**

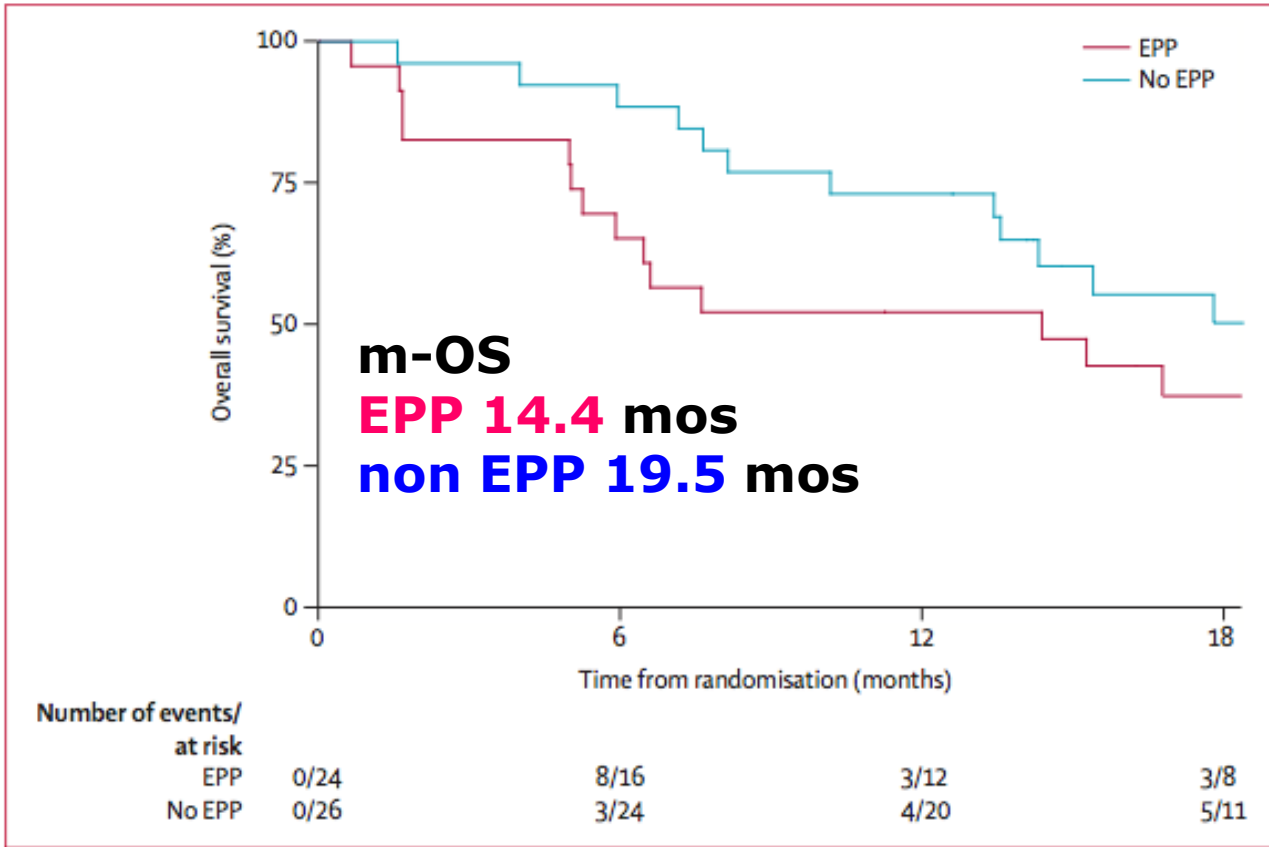


Figure 4: Overall survival
EPP=extra-pleural pneumonectomy.

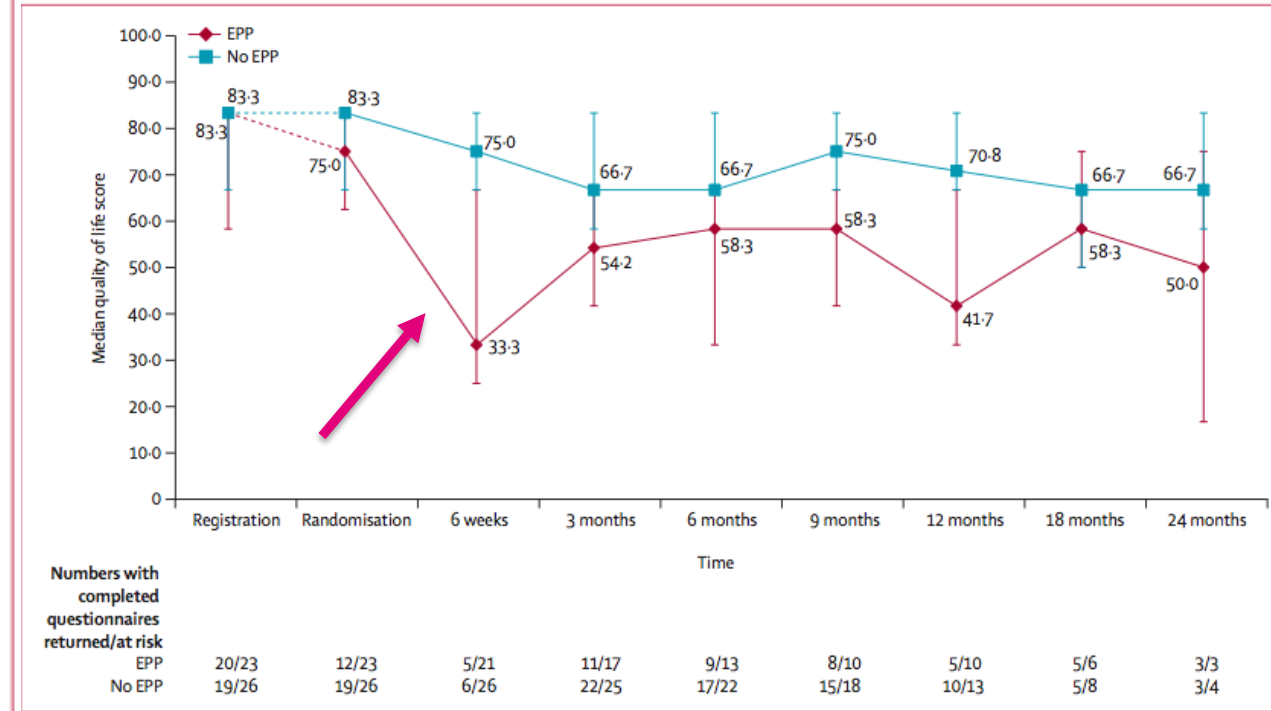


Figure 6: Quality of life

“Radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients”.

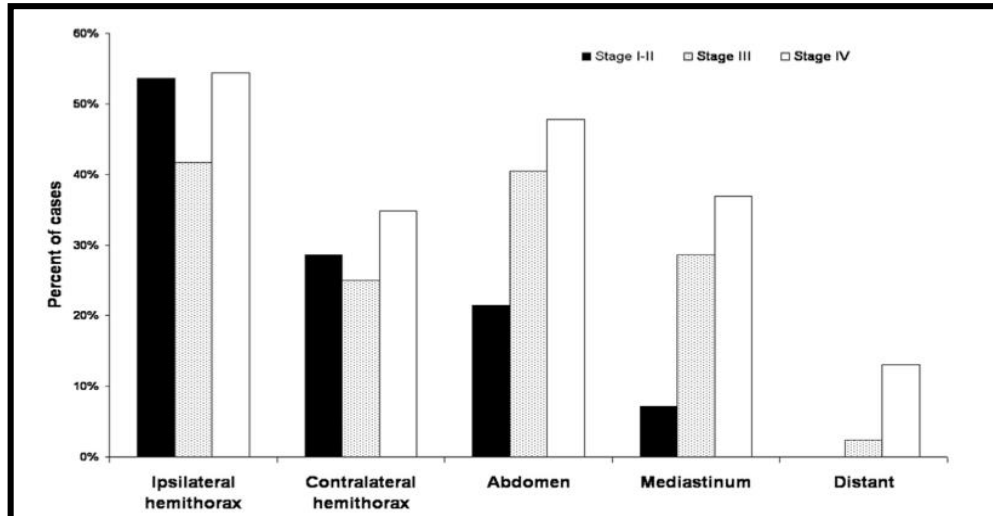
Relapse pattern after EPP

Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma

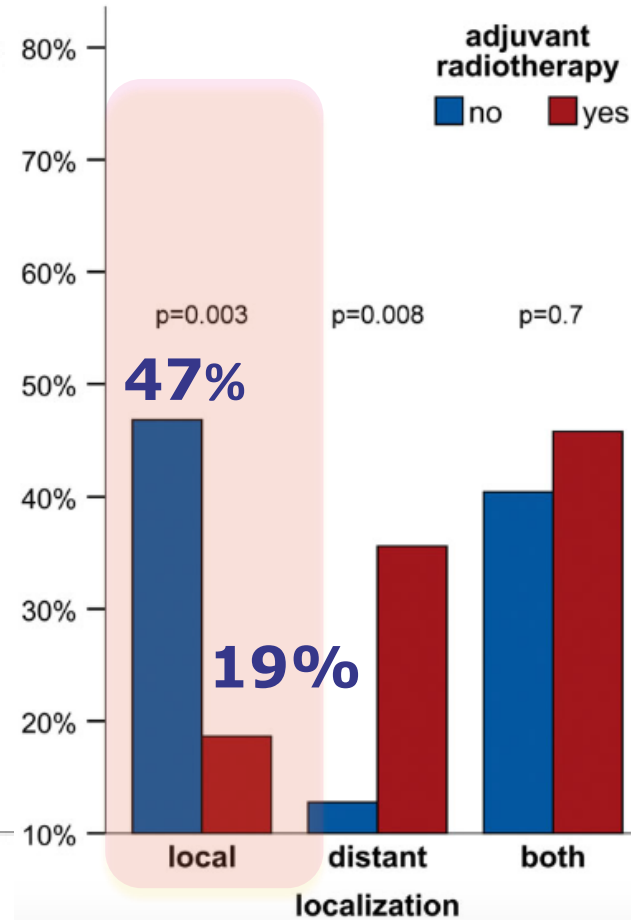
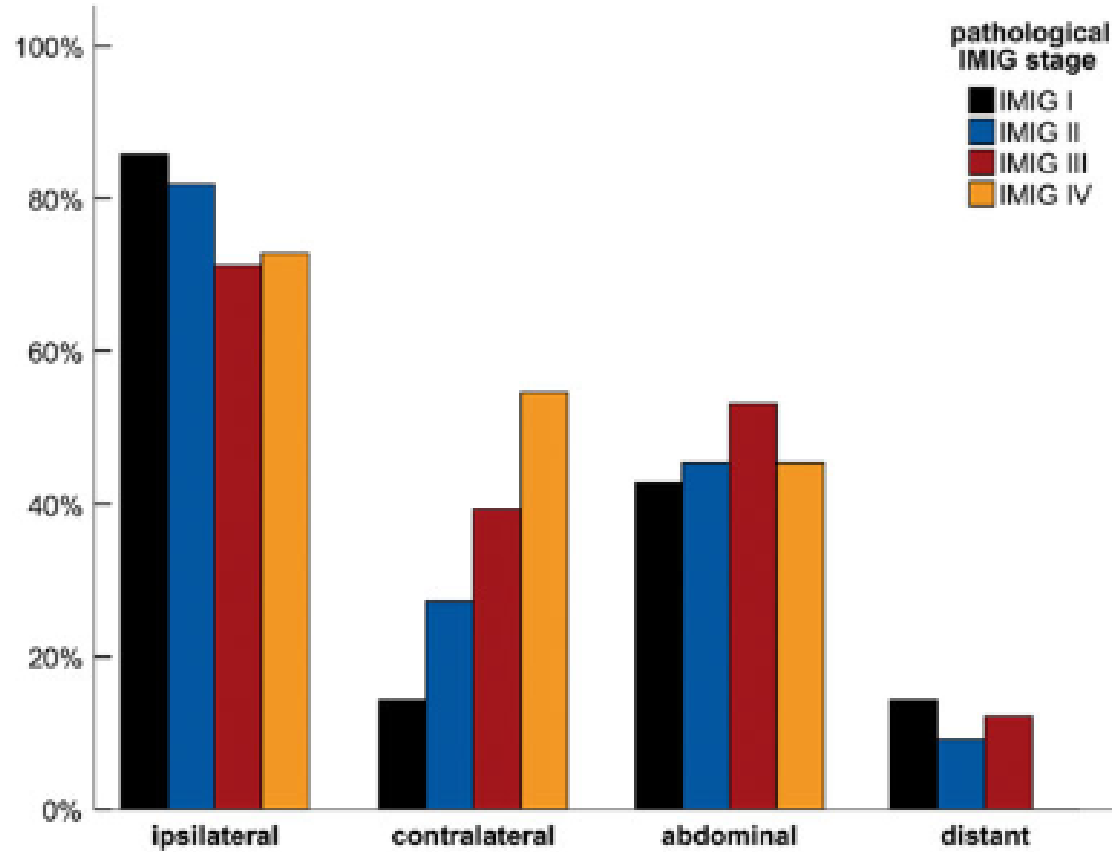
Elizabeth H. Baldini, MD, MPH,^a William G. Richards, PhD,^b Ritu R. Gill, MD, MPH,^c Brian M. Goodman, MD,^d Olivia K. Winfrey, MPH,^e Hannah M. Eisen, MS,^b Raymond H. Mak, MD,^a Aileen B. Chen, MD, MPP,^a David E. Kozono, MD, PhD,^a Raphael Bueno, MD,^b and David J. Sugarbaker, MD^f

retrospective (2001-2010)
#169 EPP
#158 evaluable pts 118 (75%)
recurred

mTTR 12.1 mos
mOS 15 mos



Site of Failure	N	% of all Patients (n=158)	% of all Failures (n=118)	% of all Failures from 1997 report (n=49) ¹⁰
Ipsilateral Hemithorax +/- Mediastinum (Local Failure)	85	54%	72%	67%
Abdomen	62	39%	53%	50%
Contralateral Hemithorax	45	28%	38%	33%
Distant	8	5%	7%	8%

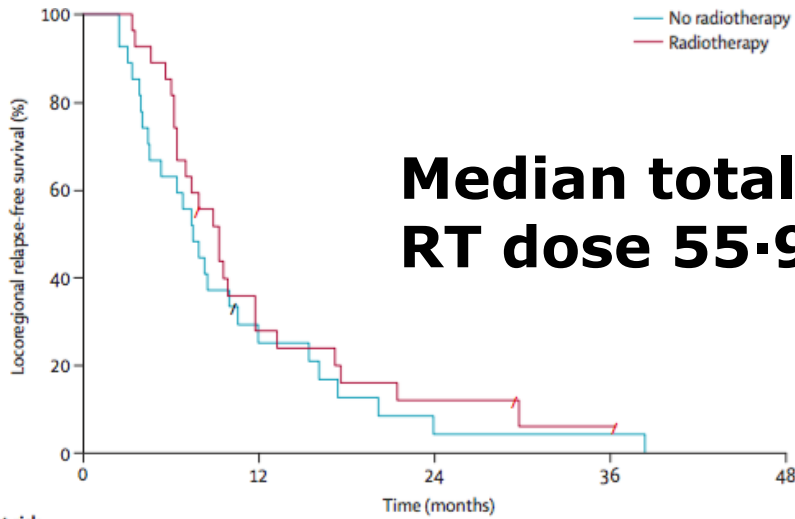


Single center retrospective 1999-2013
#136 EPP after induction CT
#106 recurrent disease (80%)
mFFR 9 mos
LR 31%
DR 26%
Both 43%

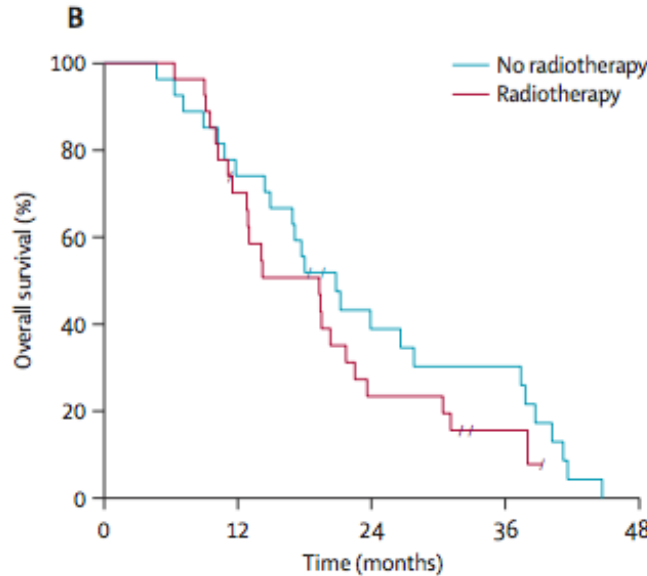
LR after RT 19% vs 47%
wo survival benefit

Role of RT after CT→EPP

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



Median total RT dose 55.9 Gy



Number at risk	0	12	24	36	48
No radiotherapy	27	7	2	1	0
Radiotherapy	27	7	3	1	0

Number at risk	0	12	24	36	48
No radiotherapy	27	20	9	7	0
Radiotherapy	27	18	6	2	0

2007-2012 14 H in Eu

#151 neoadj CT
#96 achieved MCR

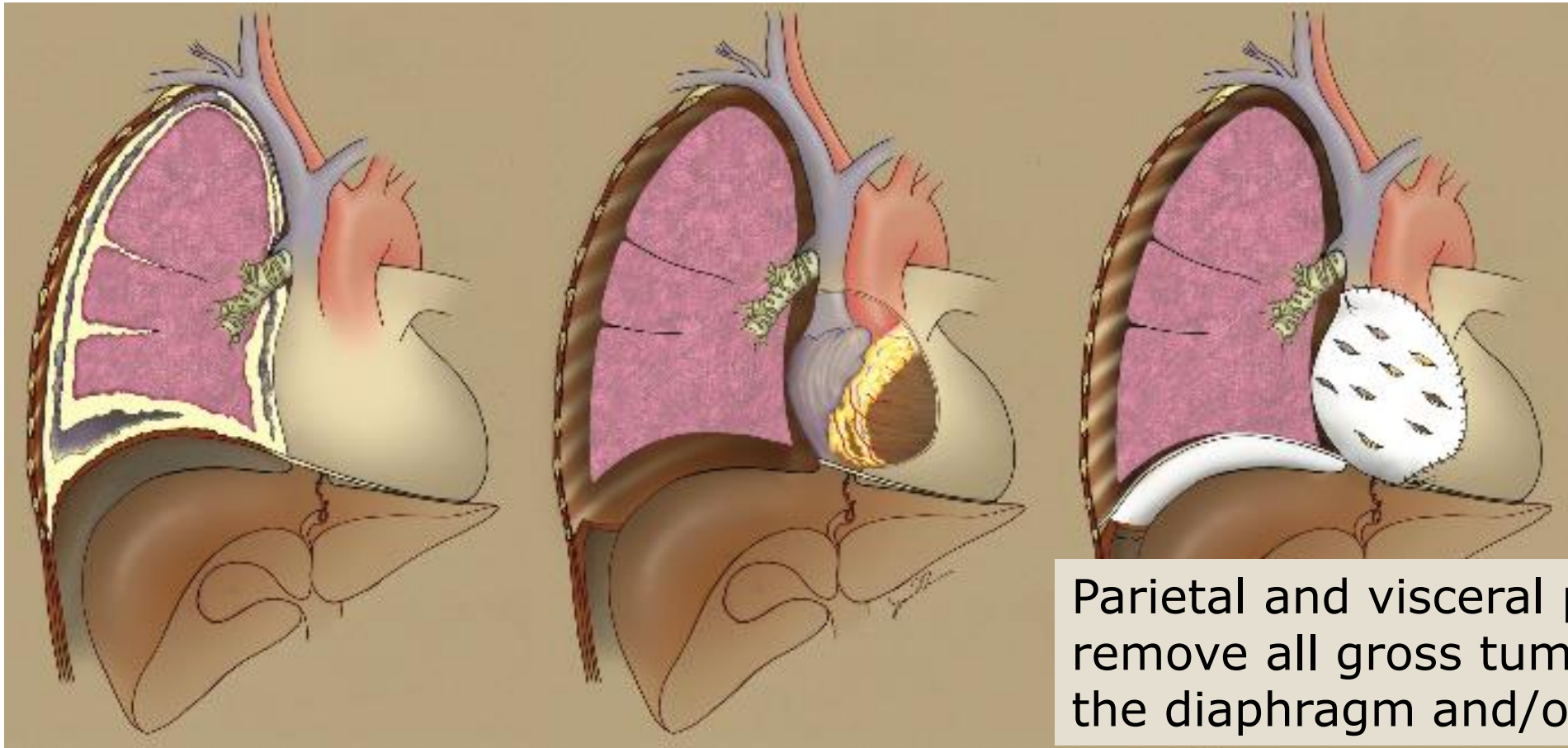
#54 were R to control (n=27) or RT (n=27 – 25 completed RT)

mLRFS 7.6 no RT vs 9.4 RT

mOS 20.8 noRT vs 19.3 RT

Routine use of hemithoracic RT after neoadjuvant CT and EPP is not supported by this trial

Pleurectomy/Decortication (P/D)



Parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium.



surgery

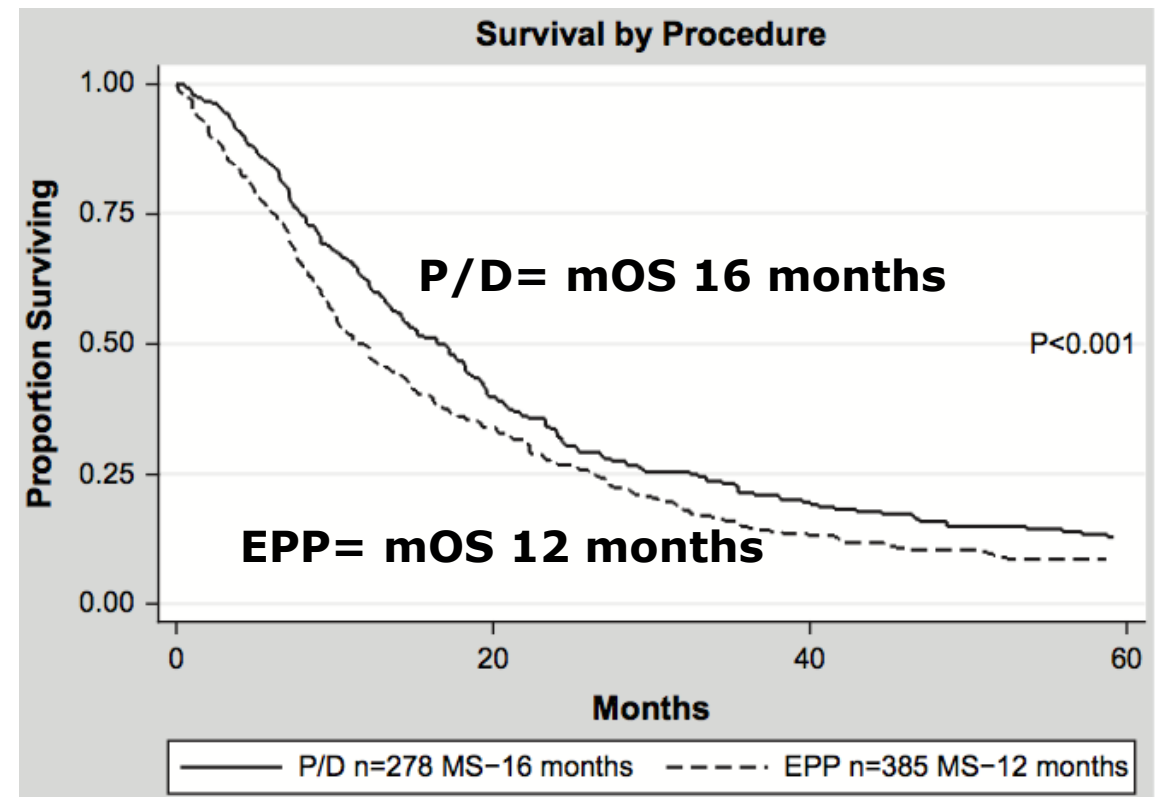
EPP

- Lung+pleura
- Major complic: 20-40%
- Mortality: 6%

e P/D

- Macroscopic disease
- Low morbidity
- Low mortality

Extrapleural pneumonectomy versus pleurectomy/ decortication in the surgical management of malignant pleural mesothelioma: Results in 663 patients



Flores, J Thor Cardiovas Surg,
2008

Cao C, Lung Cancer 2014

Taioli E et al., Ann Thor Surg 2015

Systemic review

A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma

Christopher Cao^{a,b,c,*}, David Tian^a, John Park^a, James Allan^a,
Kristopher A. Pataky^a, Tristan D. Yan^{a,d}

^a The Systematic Review Unit, Collaborative Research (CORE) Group, Macquarie University, Sydney, Australia

^b Department of Cardiothoracic Surgery, St George Hospital, Sydney, Australia

^c The Baird Institute for Applied Heart and Lung Surgical Research, Sydney, Australia

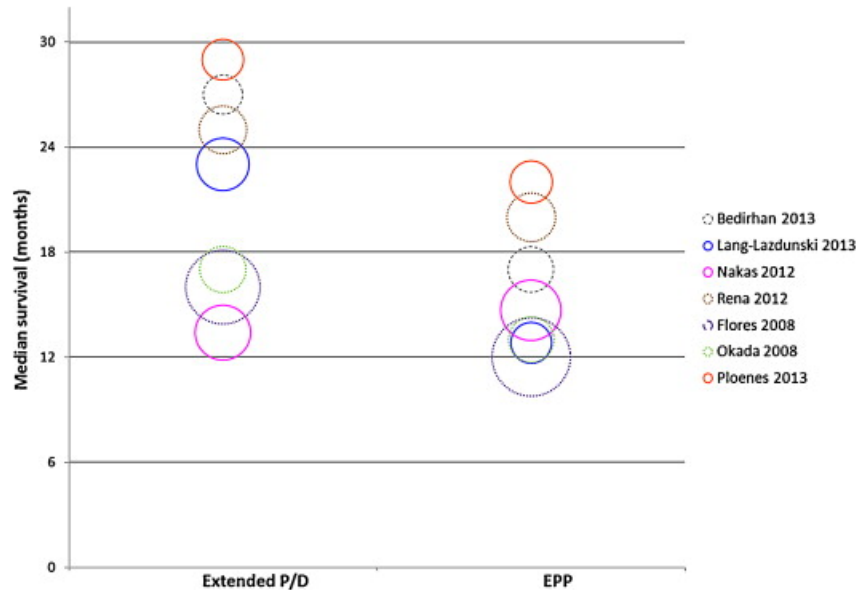
^d Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney, Australia

7 studies (2008-2013) comparing data on **513 P/D** vs **632 EPP**

Perioperative mortality
2.9% P/D vs 6.8% EPP

Morbidity
28% P/D vs 62% EPP

mOS ranges
13-29 mos PD vs 12-22 mos EPP



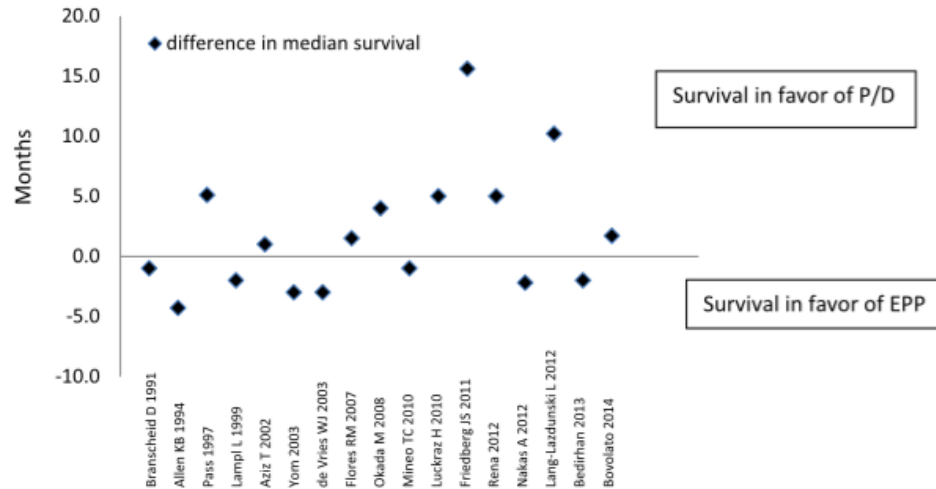
Meta-analysis

GENERAL THORACIC

Meta-Analysis of Survival After Pleurectomy Decortication Versus Extrapleural Pneumonectomy in Mesothelioma

Emanuela Taioli, MD, PhD, Andrea S. Wolf, MD, and Raja M. Flores, MD

Department of Population Health, Hofstra North Shore-LIJ School of Medicine, Hempstead; and Department of Thoracic Surgery, Icahn School of Medicine, Mount Sinai Health System, New York, New York



24 data set (1990-2014)

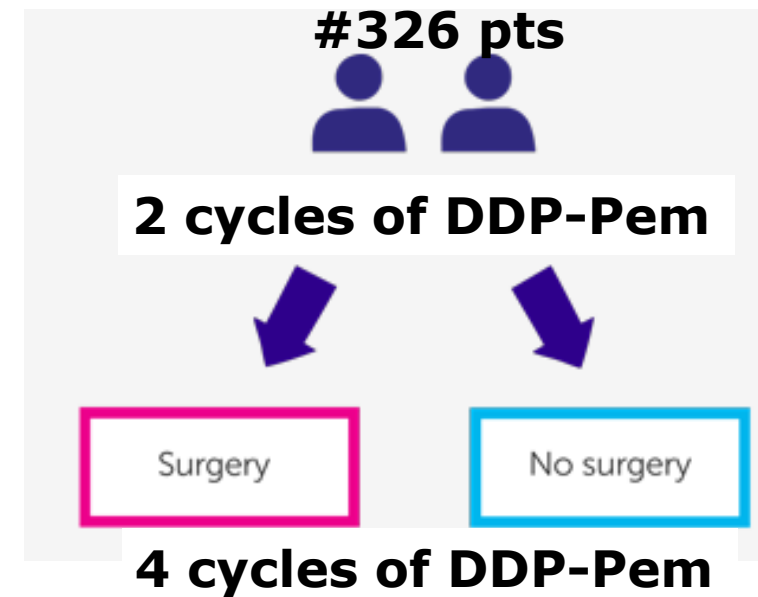
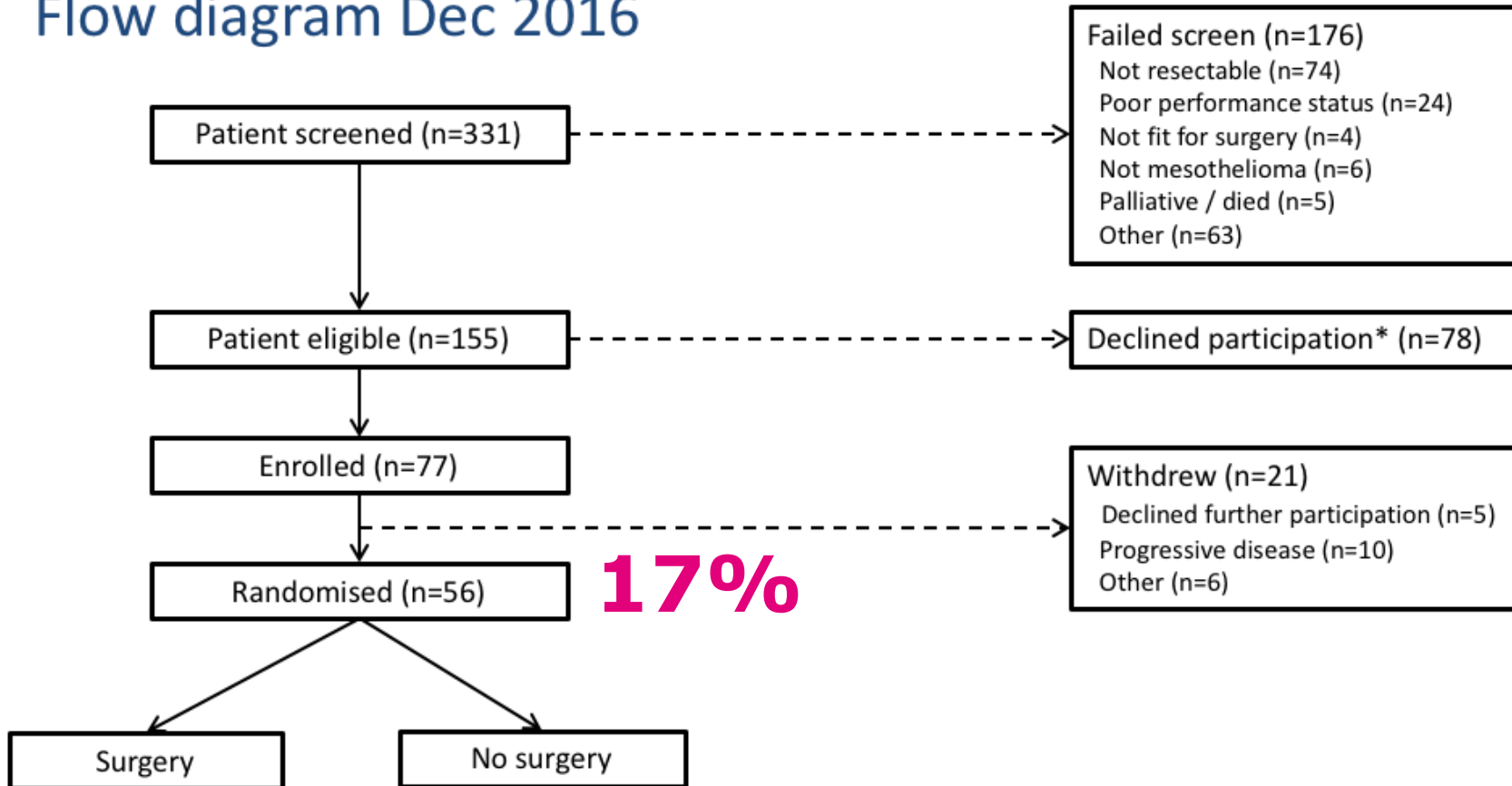
1512 P/D & **1391 EPP**

Short term mortality
4.5% EPP vs 1.7% P/D

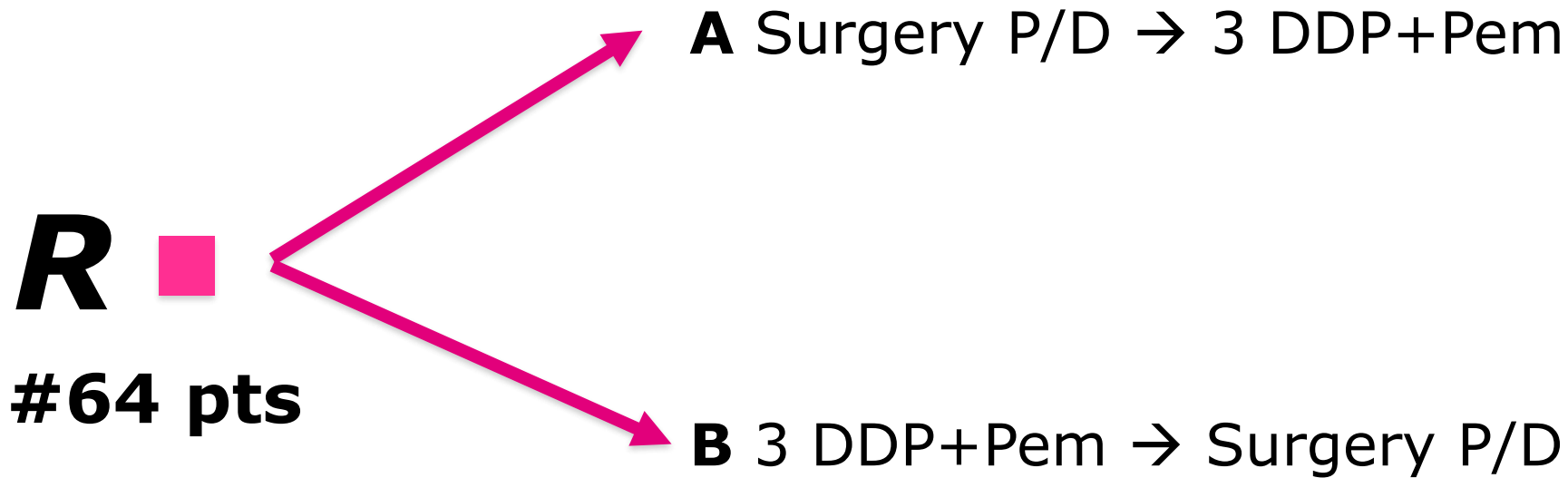
2 yr mortality
30% EPP vs 28% PD

MARS 2

Flow diagram Dec 2016



EORTC-1205-LCG

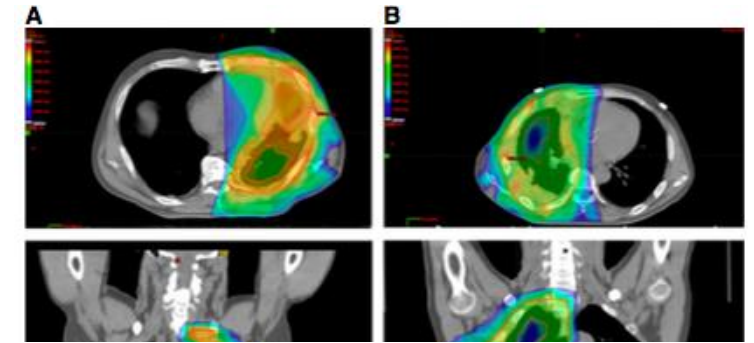
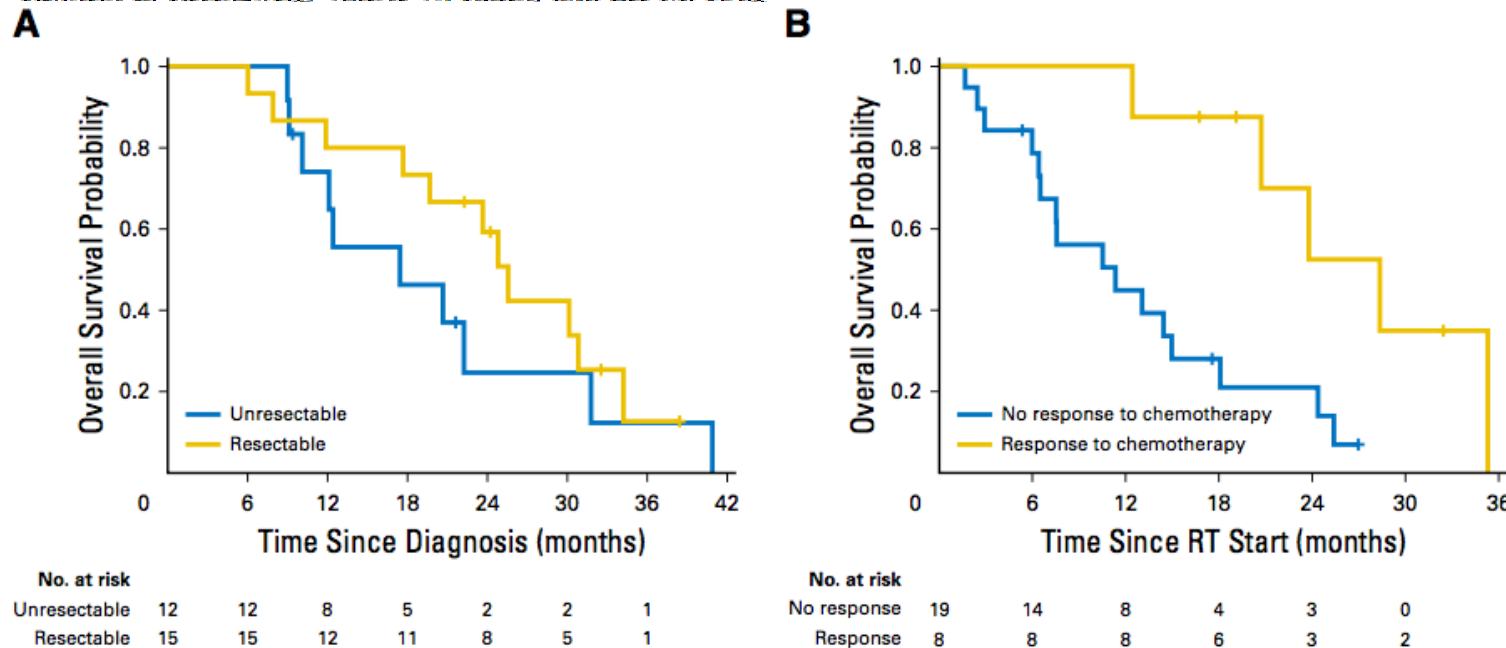


Primary end point: Rate of success to complete the full treatment
Secondary endpoints: Loco-regional failure free survival, OS, Side effects

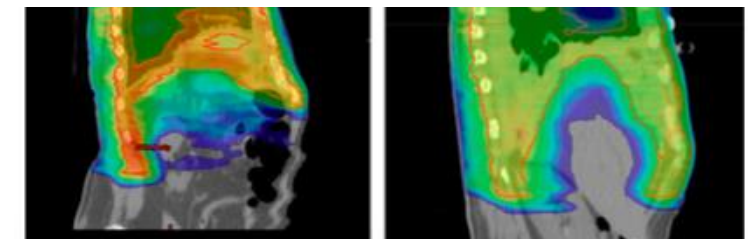
IMRT after P/D: MSKCC experience

Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma

Andreas Rimmer, Marjorie G. Zauderer, Daniel R. Gomez, Prasad S. Adusumilli, Preeti K. Parhar, Abraham J. Wu, Kaitlin M. Woo, Ronglai Shen, Michelle S. Ginsberg, Ellen D. Yorke, David C. Rice, Anne S. Tsao, Kenneth E. Rosenzweig, Valerie W. Rusch, and Lee M. Krue



45 pts enrolled
27 IMPRINT
6 G2 RP
2 G3 RP
mPFS 12.4 mos
mOS 23.7 mos





ORIGINAL ARTICLE

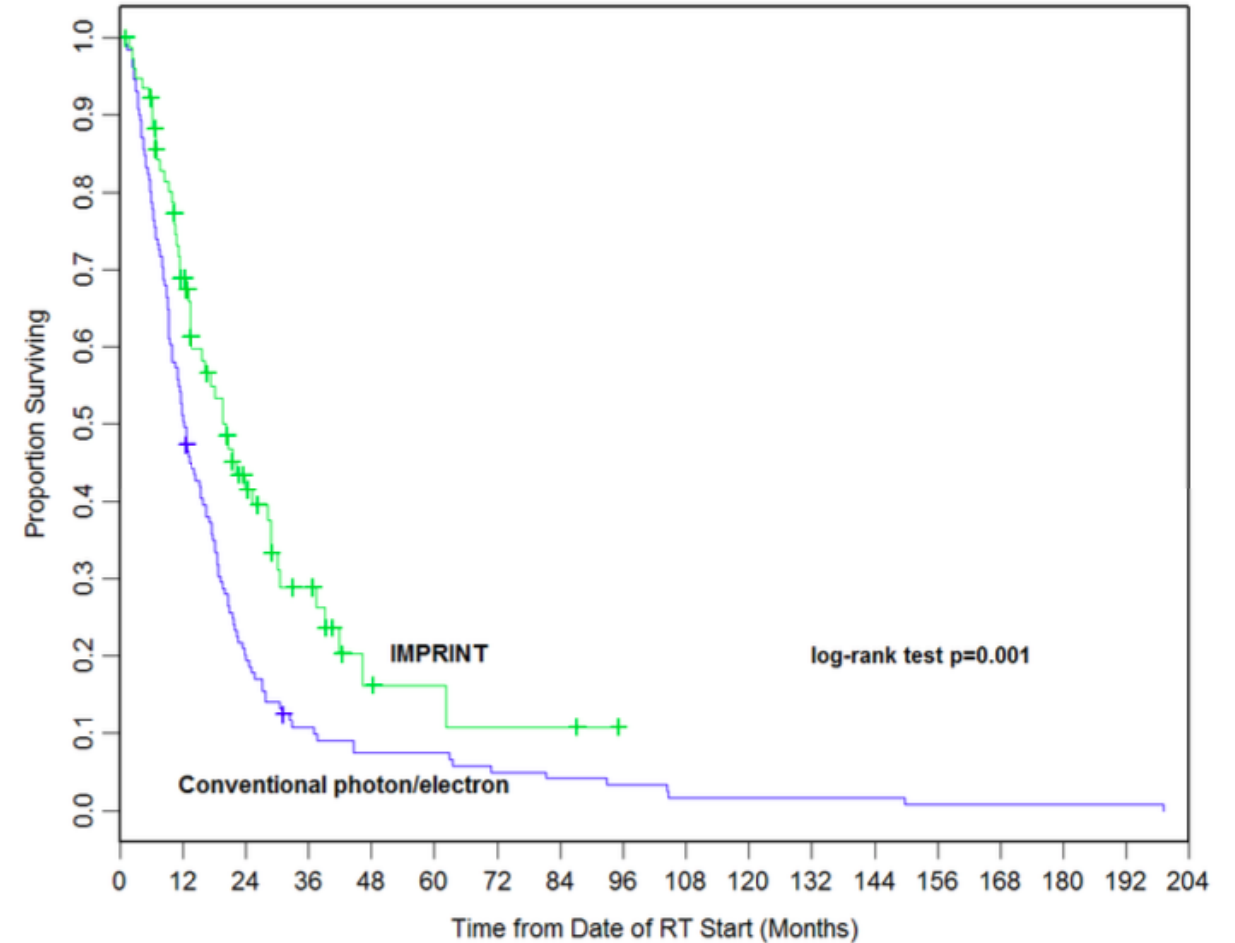
Improved Outcomes with Modern Lung-Sparing Trimodality Therapy in Patients with Malignant Pleural Mesothelioma

Fauzia Shaikh, MD,^a Marjorie G. Zauderer, MD,^{b,c} Donata von Reibnitz, BS,^a Abraham J. Wu, MD,^a Ellen D. Yorke, PhD,^d Amanda Foster, MS,^a Weiji Shi, MS,^e Zhigang Zhang, PhD,^e Prasad S. Adusumilli, MD,^f Kenneth E. Rosenzweig, MD,^g Lee M. Krug, MD,^{b,c} Valerie W. Rusch, MD,^f Andreas Rimner, MD^{a,*}

209 pts underwent P/D

1974-2015

#131 CONV vs 78 IMPRINT
mOS 12.3 vs 20.2 p=0.001



Outcomes following MMT (EPP)

Author	Year	Chemotherapy	EPP (n)	TMT/ITT (%)	30 days mortality	Median Survival ITT (months)
Sugarbaker	1999	Adjuvant	183	?	3.8	19
Rusch	2001	No adjuvant Radiotherapy	62	61%	11.3	17
Pagan	2006	Adjuvant	44	57%	4.5	20
Weder	2007	Neoadjuvant	45	59%	2.2	19.8
Edwards	2007	Adjuvant/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
Batirel	2008	Adjuvant	16	60%	5	17.2
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
Hasan	2009	Adjuvant	18	64%	11	? after EPP 20.4
Tillerman	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 (90 d)	18.4

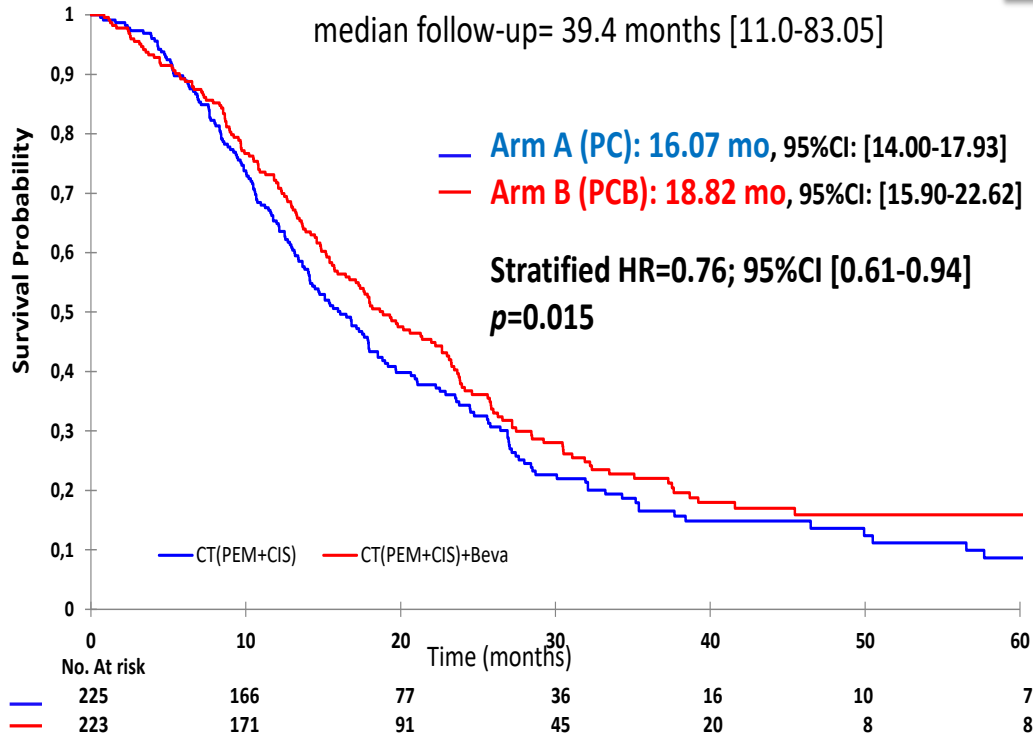
Outcomes following MMT (P/D)

Author	Year	Chemotherapy/radiotherapy	P/D (n)	TMT/ITT (%)	Morbidity (%)	30 days mortality (%)	Median survival ITT (months)
Hilaris	1984	Intraoperative brachytherapy Adjuvant radioth 45 Gy	41	100%	15%	0%	21
Rusch	1994	Intraoperative chemo adjuvant Chemo	28	64%	?	3.5%	17
Lee	2002	Adjuvant chemo intraoperative and adj radiotherapy 45 Gy	32	37.5%	15%	6.2%	18.1
Lucchi	2007	Adj chemotherapy and IL2 adj radiotherapy 30 Gy	49	100%	10%	0%	26
Nakas	2008	Adj chemo Prophylactic radiotherapy	51	?46%	55%	5.9%	15.3
Bolukbas	2011	Adj chemo Prophylactic radiotherapy	35	94%	20%	2.9%	30
Friedberg	2012	Intraoperative PDT adjuvant chemo	38	97%	28%	2.6%	31.7
Lang Lazdunski	2015	Adjuvant chemo Prophylactic RT	102	97%	28%	0%	32

Survival in modern clinical trials

Efficacy: ITT median Overall Survival (OS)

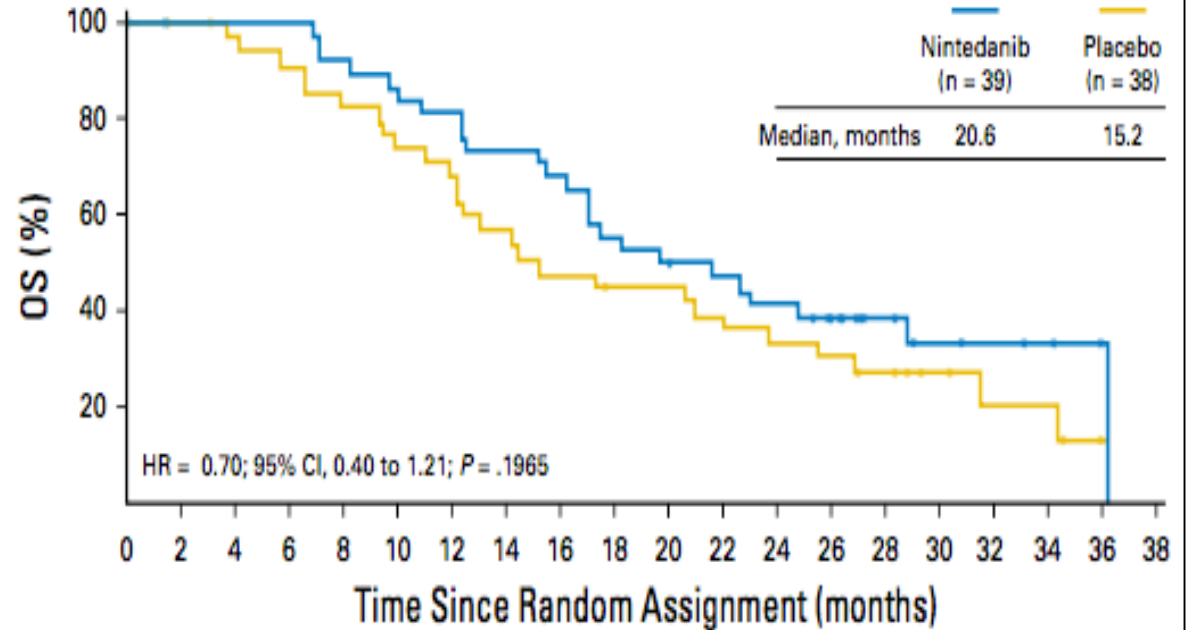
median follow-up= 39.4 months [11.0-83.05]



IFCT 0 01 'MAPS' randomized phase 3 trial

Zalcman et al., Lancet 2015

Epithelioid MPM

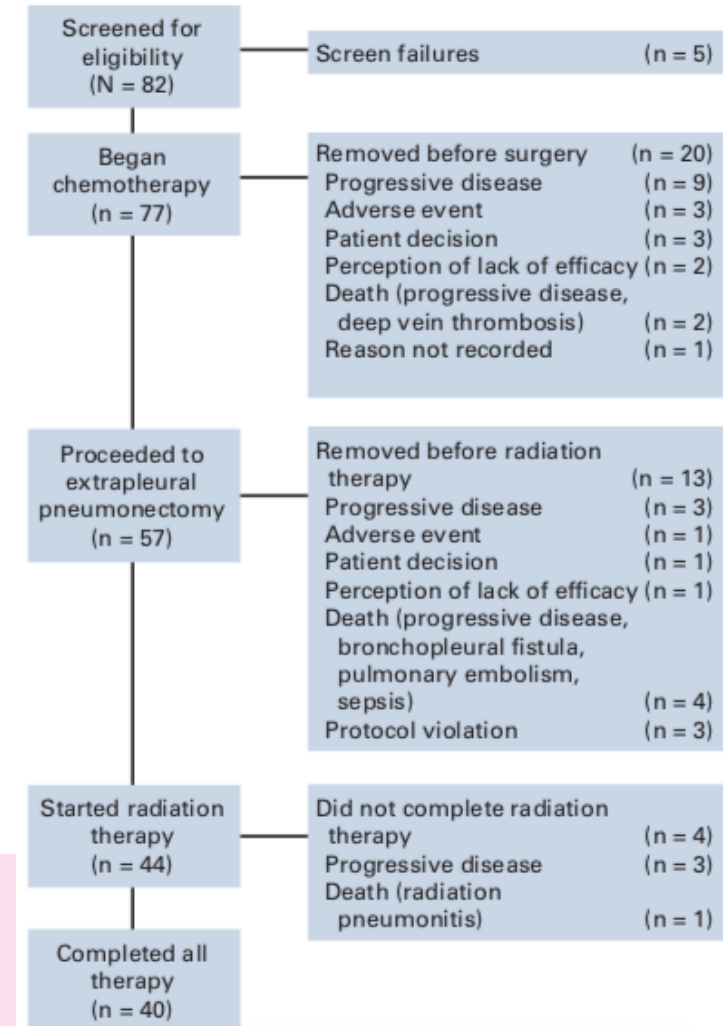
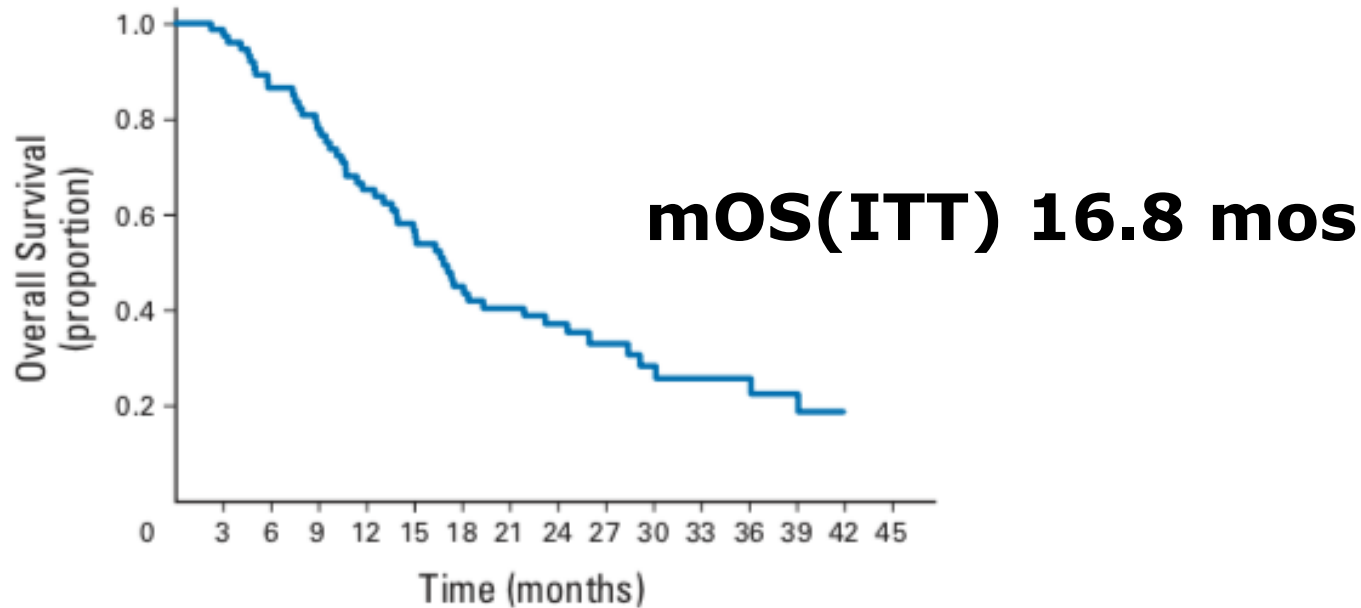


No. at risk:

Nintedanib	39	38	38	38	35	33	31	28	26	21	19	17	15	12	8	5	4	3	1	0
Placebo	38	36	34	32	29	26	24	20	17	15	15	13	11	10	8	5	3	3	0	0

Grosso et al., J Clin Oncol 2017

Patient selection for MMT: clinical variables



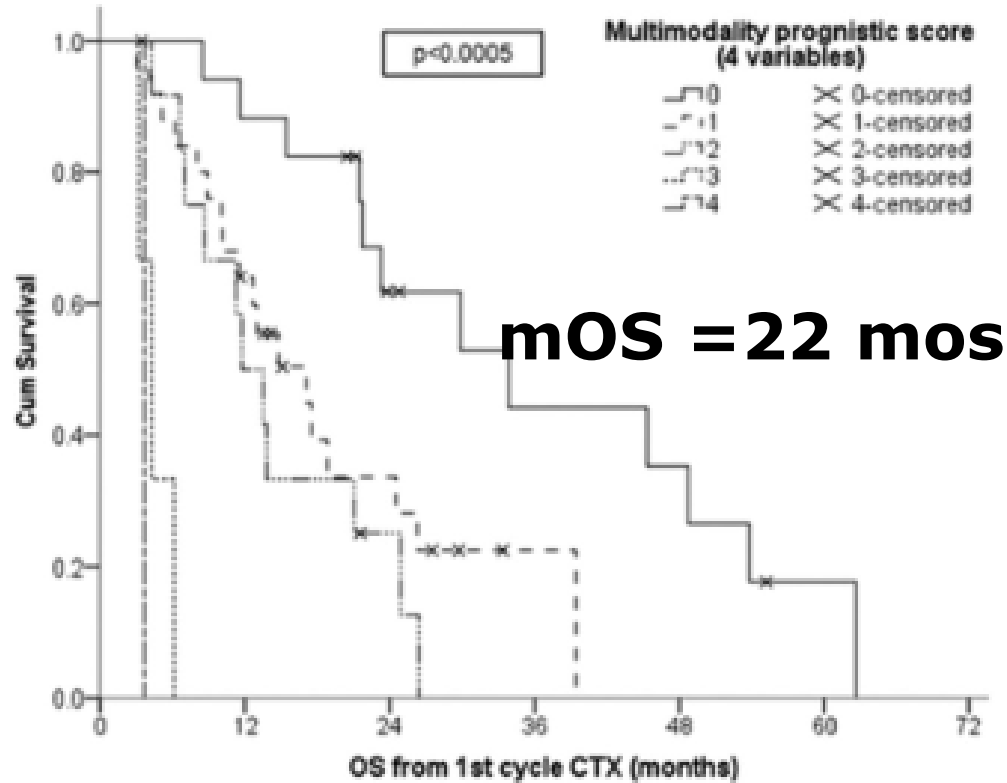
Conclusion

This multicenter trial showed that trimodality therapy with neoadjuvant pemetrexed plus cisplatin is feasible with a reasonable long-term survival rate, particularly for patients who completed all therapy. Radiologic response to chemotherapy, but not sex, histology, disease stage, or nodal status, was associated with improved survival.

Pts completing **all therapy**: **mOS 29.1 mos**
2-yr OS 61.2%.

Pts with **PR to CT**: **mOS 26.0** vs 13.9 SD/PD (p=.05)

Patient selection for MMT: clinical variables



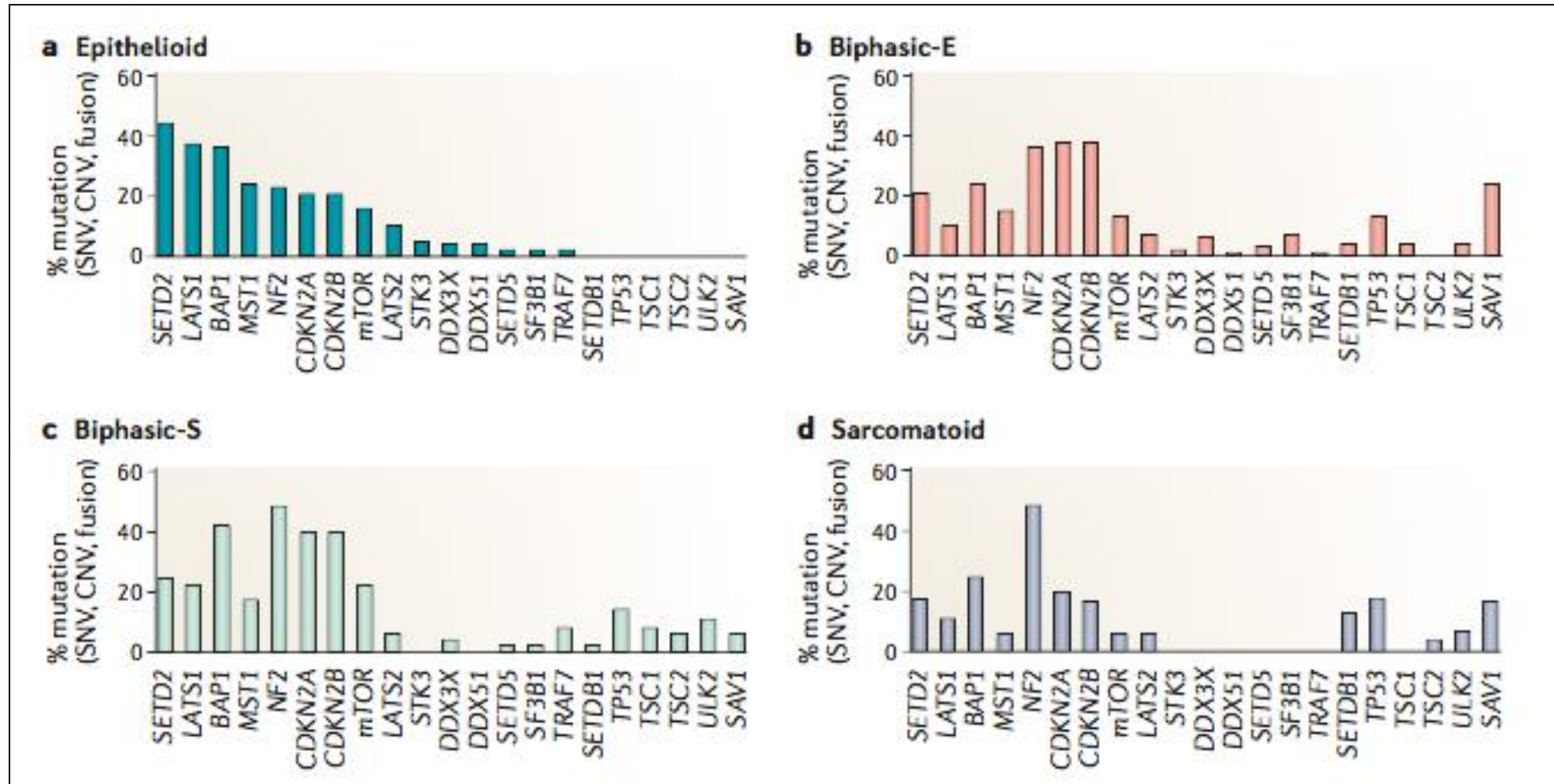
m-OS

Score 0 = 34 mos
Score 3-4 = 4 mos

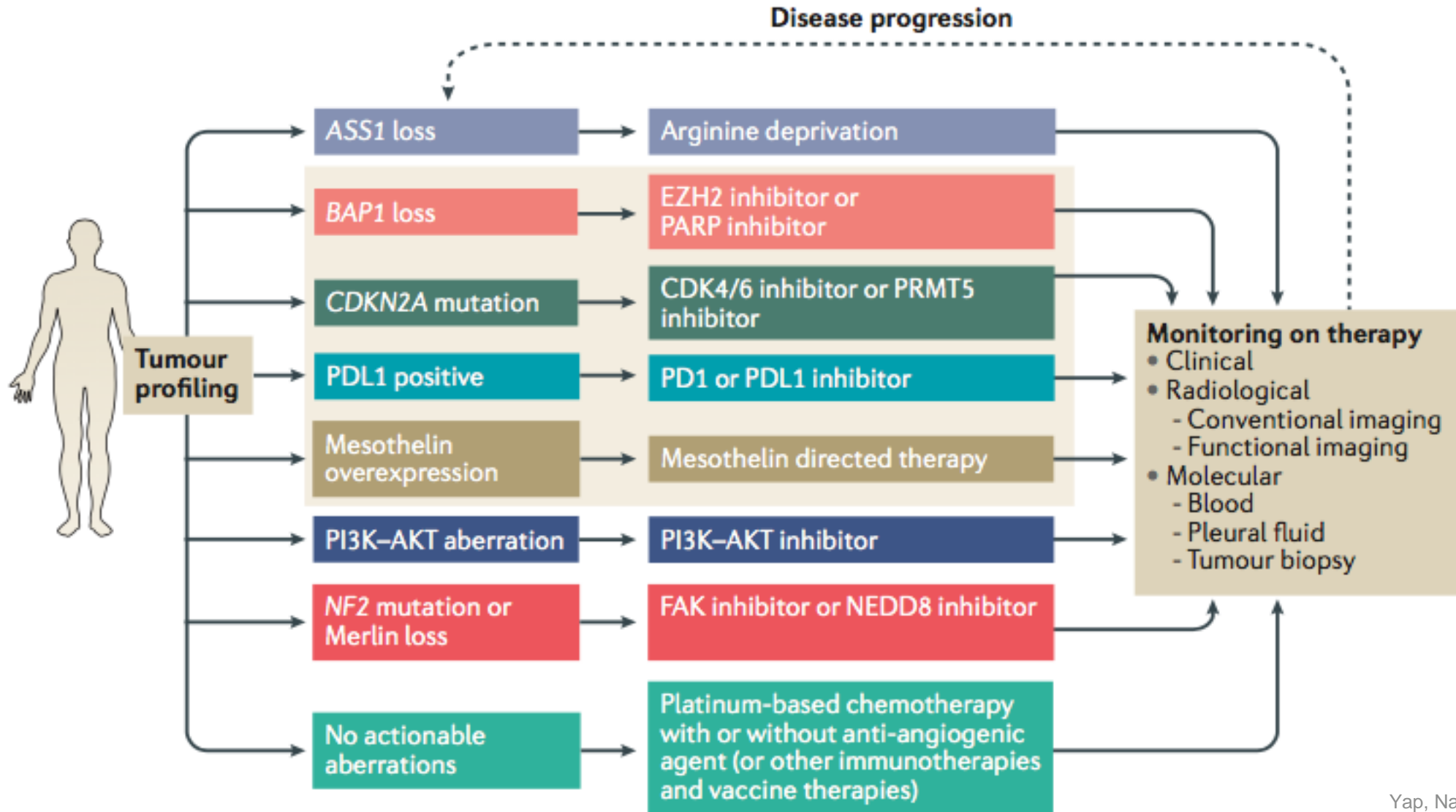
Four variables

- 1. Tumor volume** pre-CT > 500 ml;
- 2. PCR** pre-CT > 30 mg/liter;
- 3. Non-epithelioid** histology in pre-CT biopsy;
- 4. PD** to CT according to mRECIST

Patient selection for MMT: molecular profile



A potential molecularly stratified approach



Window of opportunity trials in MPM

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	<u>A Pilot Window-Of-Opportunity Study of the Anti-PD-1 Antibody Pembrolizumab in Patients With Resectable Malignant Pleural Mesothelioma</u>	<ul style="list-style-type: none"> • Pleural Mesothelioma 	<ul style="list-style-type: none"> • Drug: Pembrolizumab • Drug: Cisplatin and Pemetrexed 	<ul style="list-style-type: none"> • University of Chicago Chicago, Illinois United States
2	<input type="checkbox"/>	Completed	<u>Window of Opportunity Study of VS-6063 (Defactinib) in Participants With Surgical Resectable Malignant Pleural Mesothelioma.</u>	<ul style="list-style-type: none"> • Malignant Pleural Mesothelioma 	<ul style="list-style-type: none"> • Drug: VS-6063 	<ul style="list-style-type: none"> • Brigham and Women's Hospital Boston, Massachusetts United States
3	<input type="checkbox"/>	Recruiting	<u>MEDI4736 Or MEDI4736 + Tremelimumab In Surgically Resectable Malignant Pleural Mesothelioma</u>	<ul style="list-style-type: none"> • Mesothelioma 	<ul style="list-style-type: none"> • Drug: MEDI4736 • Drug: Tremelimumab • Other: Untreated arm (control) 	<ul style="list-style-type: none"> • Baylor St Lukes Houston, Texas United States

conclusions

- The role of MMT (surgery and radiotherapy) in MPM is still undefined: strategy for a minority of patients;
- Loco-regional control is still the main issue;
- Randomized trials very difficult in this setting; Extended Pleurectomy is under evaluation in the MARS2 trial;
- Role of IMRT promising, but consider pulmonary toxicity;
- Need for better (molecular) patient selection;
- Window of opportunity trials with new drugs.



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