Fundación GECP
lung cancer research

Reassessing multidisciplinary approaches in Mesothelioma

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Conflicts of interest

Research funding: Roche, Pfizer, Merck-Serono, Bristol Myers Squibb

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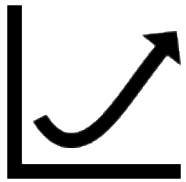
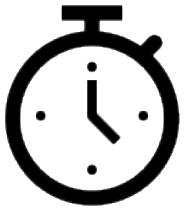
Views expressed in the session are mine, and/or are based on unbiased, peer reviewed and published literature.

Facts on malignant pleural mesothelioma, a distinct neoplasm



- Rare cancer (2.14 / 100,000) but incidence is on the rise

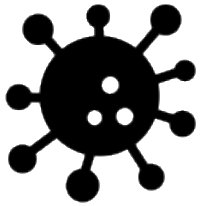


- Long latency from asbestos exposure to the onset of disease

- Histology is a major prognostic factor, non-epithelioid are a very aggressive neoplasm

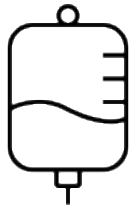
- Systemic therapies are the most effective treatment and surgery is very controversial

- Tumor dominated by TSG inactivation (p16, NF2, BAP1) and low TMB



- TME is dominated by immune suppressive cells

- Platinum and pemetrexed has been the SoC for decades



- ICI were effective and the most important advance during the last years

Treatment patterns and prognosis of pleural mesothelioma in Spain

Lung Cancer 147 (2020) 83–90

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Malignant pleural mesothelioma: Treatment patterns and outcomes from the Spanish Lung Cancer Group

J. Remon[a], E. Nadal[b], M. Dómine[c], J. Ruffinelli[b], Y. García[d], J.C. Pardo[e], R. López[f], A. Cilleruelo[g], R. García-Campelo[h], P. Martín[i], O. Juan[j], J.L. González-Larriba[k], M. Provencio[l], E. Olmedo[m], S. Ponce[n], D. Cumplido[o], C. Barenys[p], M. Majem[q], B. Massutti[r], D. Rodriguez-Abreu[s], R. Porta[t], M.A. Sala[u], M. Martinez-Kareaga[v], P. Lianes[a], N. Reguart[w,x,*]

Patients' characteristics:

N=560 patients

Median age 68y

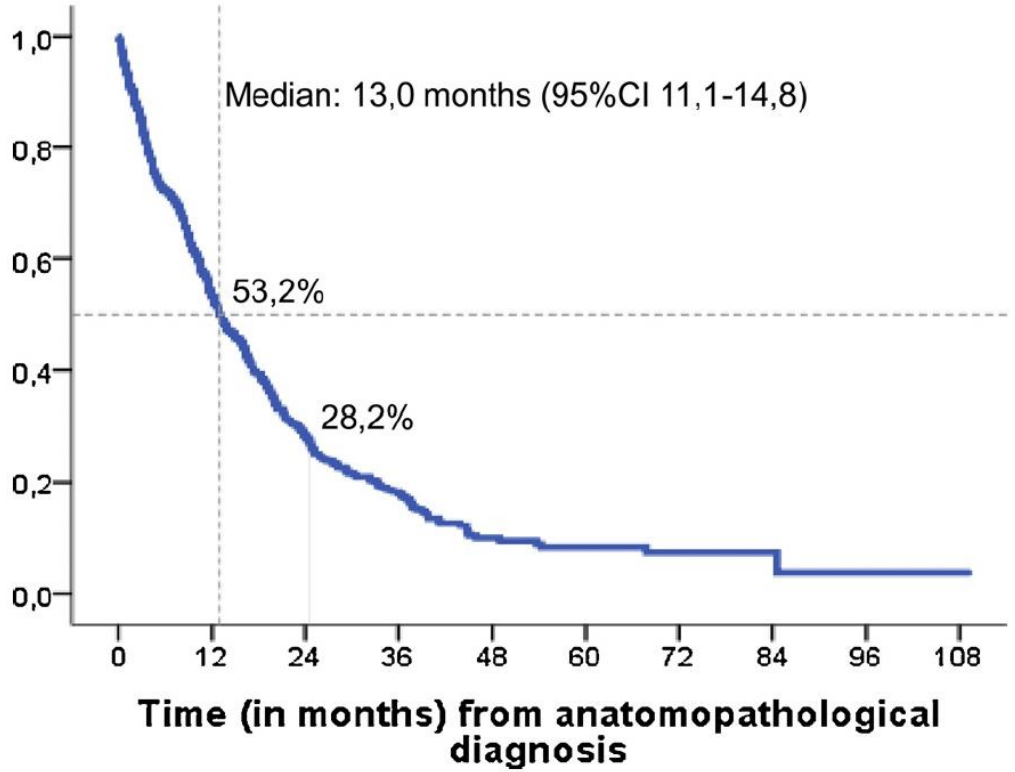
62% Epithelioid meso

204 (36%) got surgery

59 (10.5%) surgery with curative intent (28 EPP)

399 (71.3%) received chemotherapy

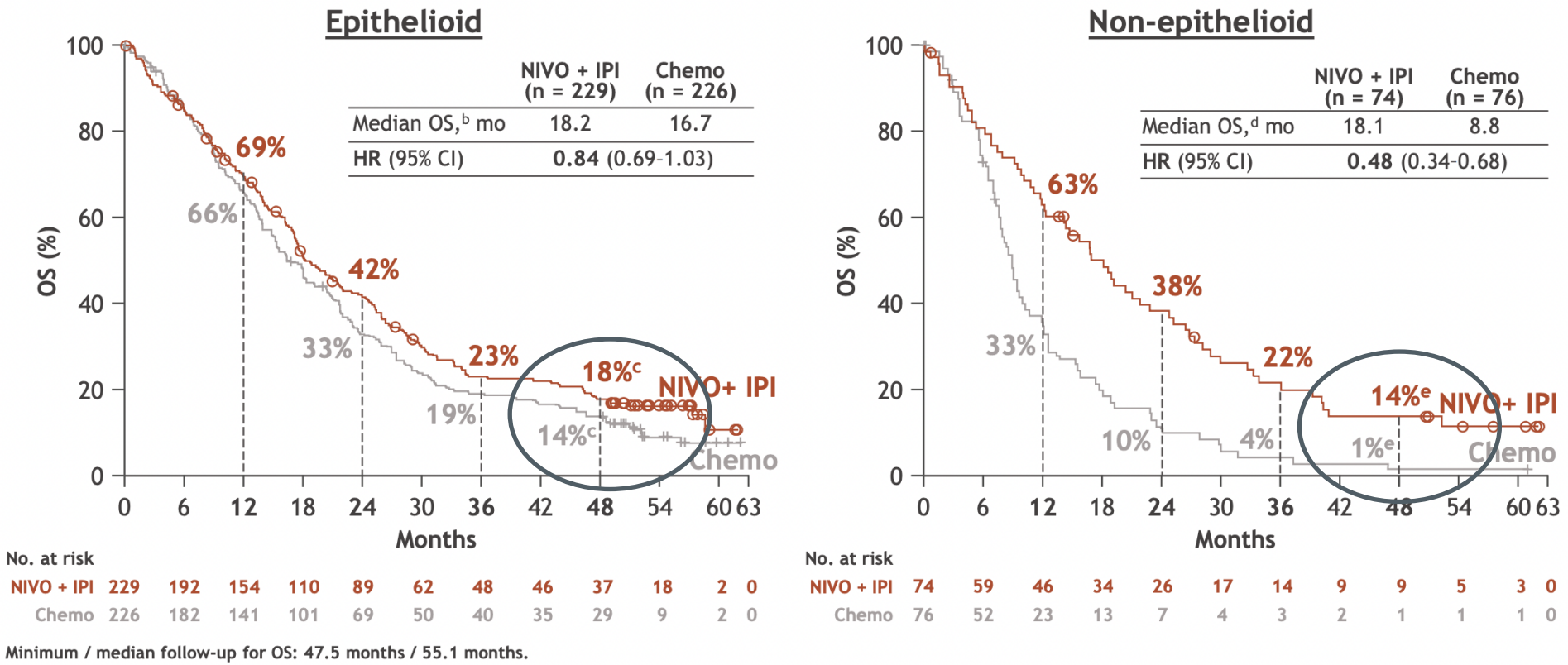
100 (25%) received perioperative chemo



Remon et al. Lung cancer 2020

For patients not candidates to surgery, dual ICI improved OS compared to chemotherapy, particularly in non-epithelioid mesothelioma

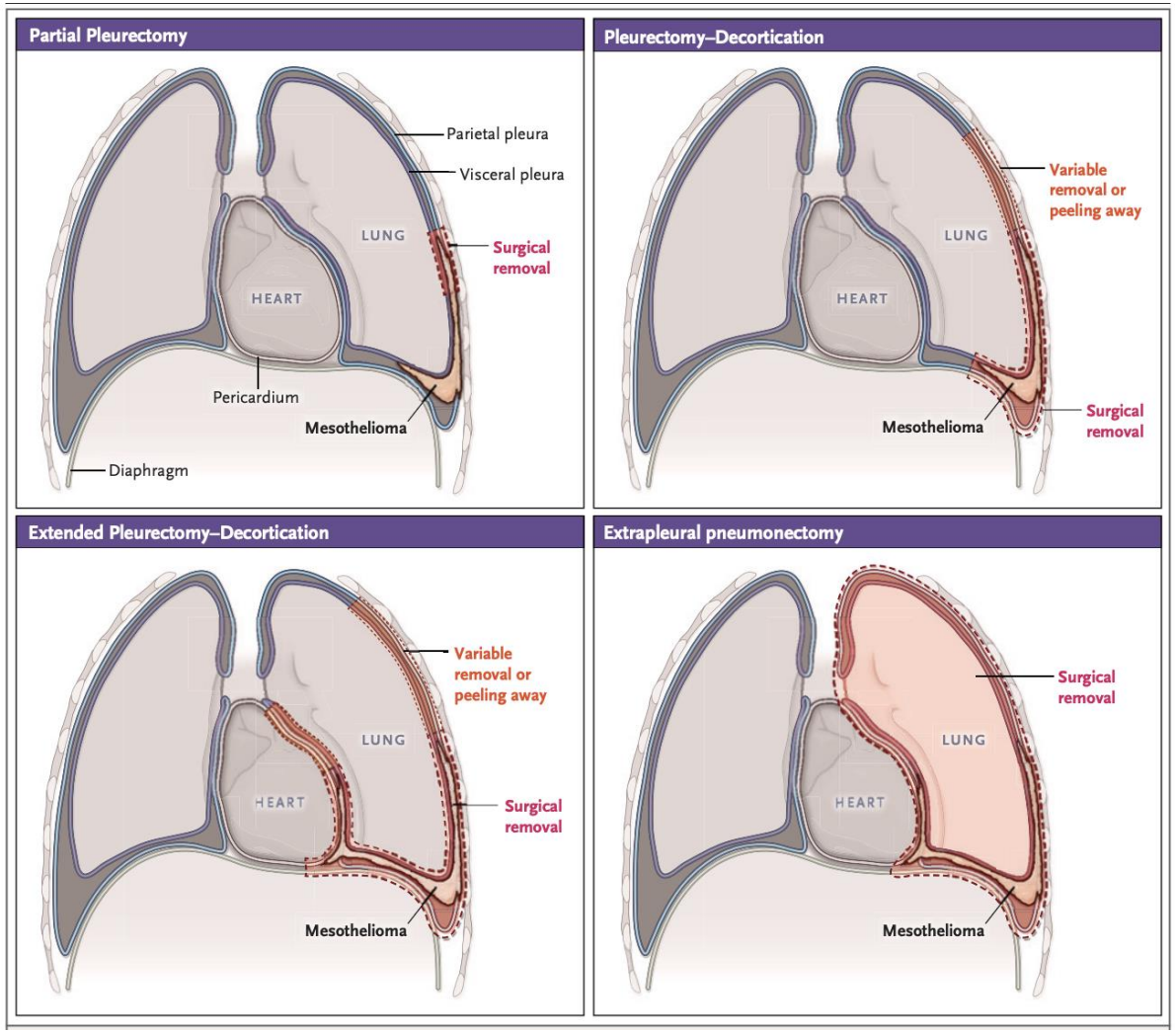
4-year update: OS by histology[a]



Minimum / median follow-up for OS: 47.5 months / 55.1 months.

Zalcman et al. ESMO 2022

Distinct surgical modalities have been used in mesothelioma



Surgical resection for mesothelioma is always incomplete and should be considered palliative

Cytoreductive surgery does not clearly extend OS in patients with pleural mesothelioma

Janes et al. NEJM 2021

Trimodal therapy (EPP) in expert centers yielded an OS ranging 17-26 m

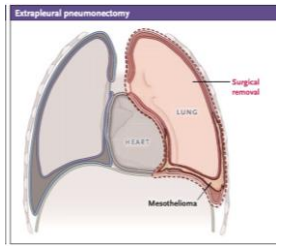
	Stage	Number of patients			ITT median survival (95% CI)	EPP operative mortality
		Chemotherapy	EPP	Radiotherapy		
Weder and colleagues[1]	T1–3, N0–2	19 (100%)	16 (84%)	13 (68%)	23	0%
Weder and colleagues[2]	T1–3, N0–2	61 (100%)	45 (74%)	36 (59%)	19·8 (14·6–24·5)	2·2%
Rea and colleagues[3]	T1–3, N0–2	21 (100%)	17 (81%)	15 (71%)	25·5	0%
Batirel and colleagues[4]	T1–3, N0–2	20 (100%)	16 (80%)	12 (60%)	17	5%
Krug and colleagues[5]	T1–3, N0–2	77 (100%)	57 (74%)	44 (57%)	16·8 (13·6–23·2)	3·7%
Van Schil and colleagues[6]	T1–3, N0–2	59 (100%)	42 (73%)	38 (64%)	18·4 (15·6–32·9)	5%

ITT=intention to treat. Median survival is in months.

Table: **Prospective studies of trimodality therapy of malignant pleural mesothelioma including neoadjuvant chemotherapy, extrapleural pneumonectomy (EPP), and radiotherapy**

Weder et al. Lancet Oncol 2011

MARS trial: EPP vs no surgery



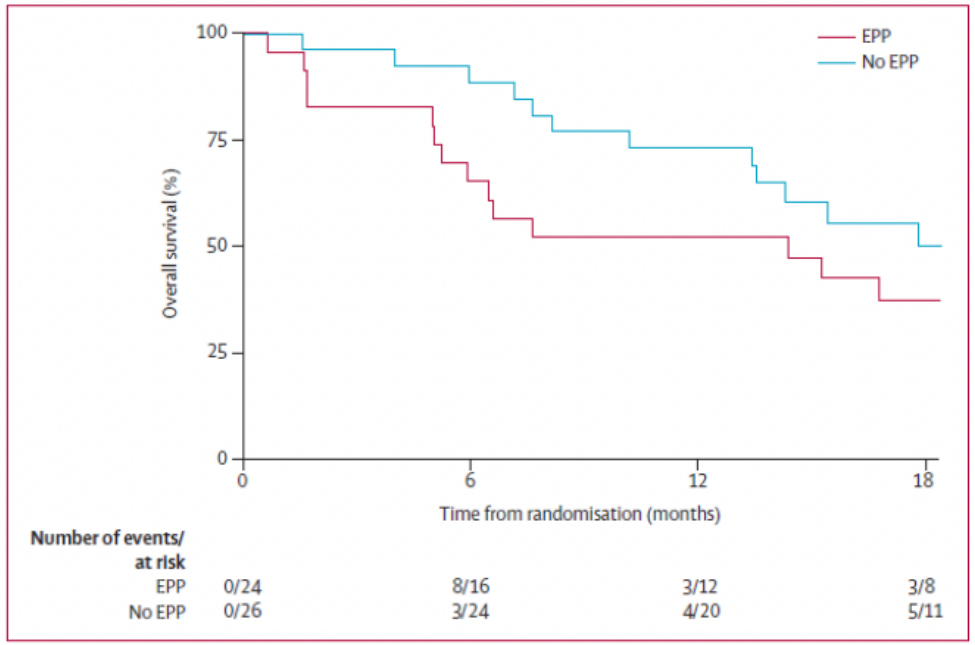
Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study

*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**

EPP → hemithorax RT

Induction Chemo

No EPP



Feasibility trial = 3 years to accrue 50 patients!!!

N=112 patients registered, but only 50 randomized (powered?)

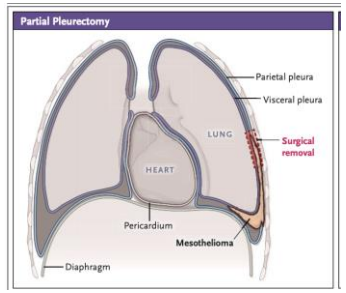
EPP completed only in 16/24 (66%) assigned to this arm

Worse median OS with EPP vs no EPP (14.4 vs 19.5 months)
Adjusted HR for OS =2.75 (95% CI 1.21 – 18.9; p=0.016)

More severe toxicities in EPP vs no EPP

Treasure et al. Lancet 2011

MesoVATS trial: VATS-PP vs talc pleurodesis

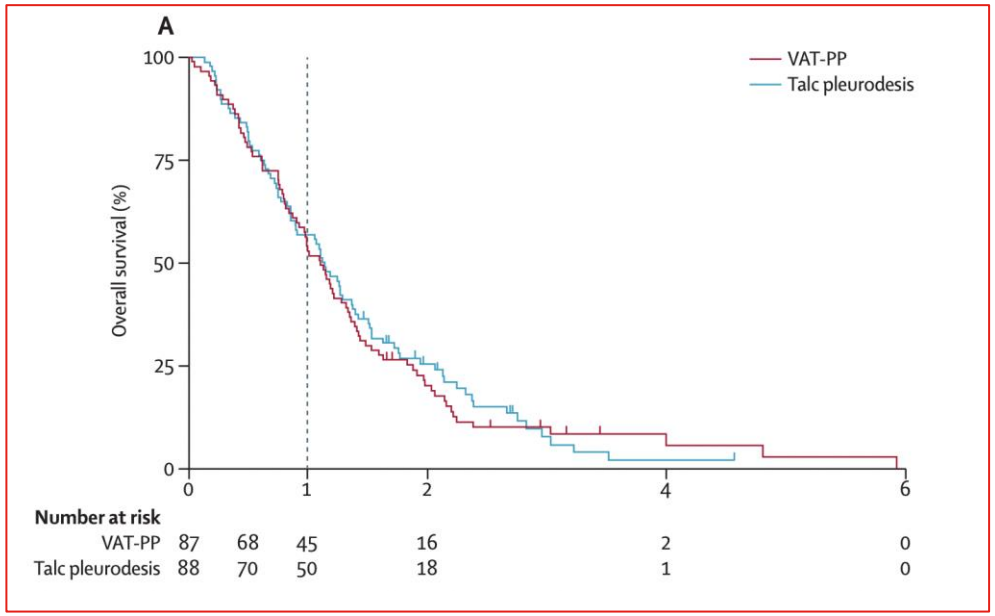


Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial

*Robert C Rintoul, Andrew J Ritchie, John G Edwards, David A Waller, Aman S Coonar, Maxine Bennett, Eleonora Lovato, Victoria Hughes, Julia A Fox-Rushby, Linda D Sharples, on behalf of the MesoVATS Collaborators**

Partial Pleurectomy (by VATs)

Talc pleurodesis



2003-2012, n=196 patients enrolled

No survival benefit with partial pleurectomy compared with talc pleurodesis: 1y OS 52% vs 57% (HR= 1.04; 95% CI 0.76–1.42)

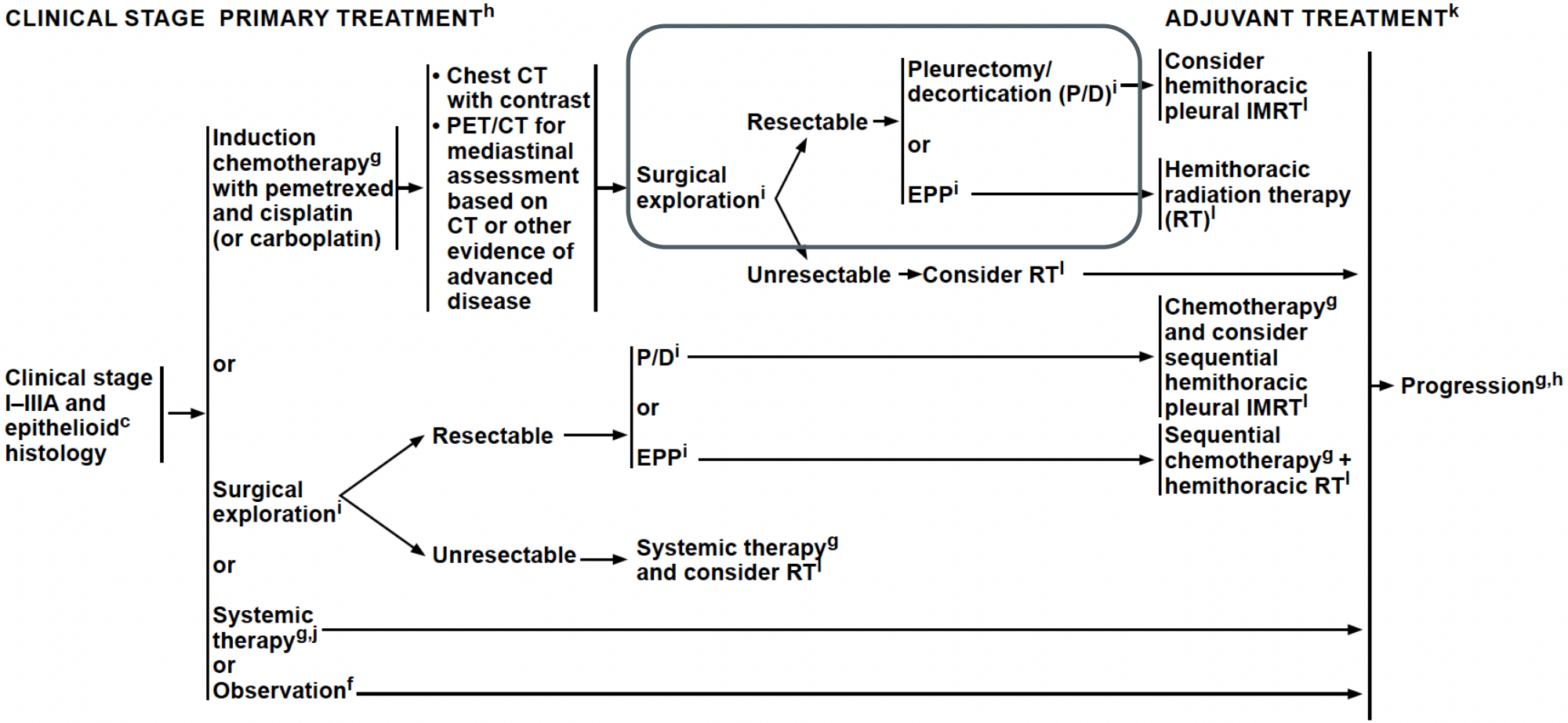
Longer median hospital stay (7 vs 3 days) with VATS-PP
Higher rate of complications with VATS-PP

Rintoul et al. Lancet 2014

The US perspective

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Mesothelioma: Pleural



NCCN Guidelines Version 1.2023

The European perspective

ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma

Remark: surgery may be appropriate for carefully and highly selected MPM patients. This would usually be EP/D rather than EPP, because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid-predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery other than in the context of research. However, as no single prognostic factor influences treatment allocation, prognostic scores encompassing several prognostic factors should be preferred (see sections on staging and allocation).

Scherpereel et al. Eur Resp J 2020

MARS 2 trial: Which is the role of pleurectomy/decortication?

IASLC 2023 World Conference on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE

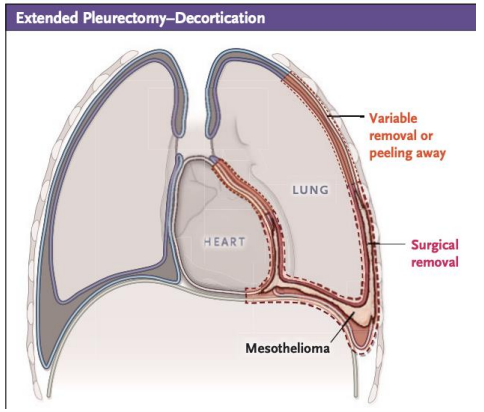
MARS 2 trial schema

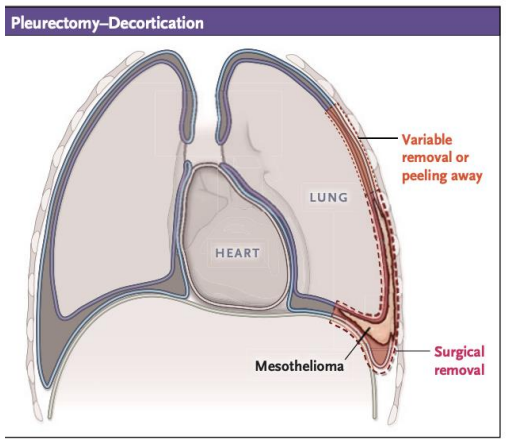
- Tissue confirmed mesothelioma
- Disease in one hemi-thorax
- Deemed surgically resectable
- PS (0-1)
- No end-organ failure

→ 2 cycles platinum + pemetrexed → CT (still resectable) → R

R → (extended) pleurectomy decortication → Up to 4 cycles platinum + pemetrexed

R → Up to 4 cycles platinum + pemetrexed





Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

Patients' characteristics:
Median age 69y
87% males
14% non-epitheloid
32% cT3
21% N1; 7% N2
3% M1

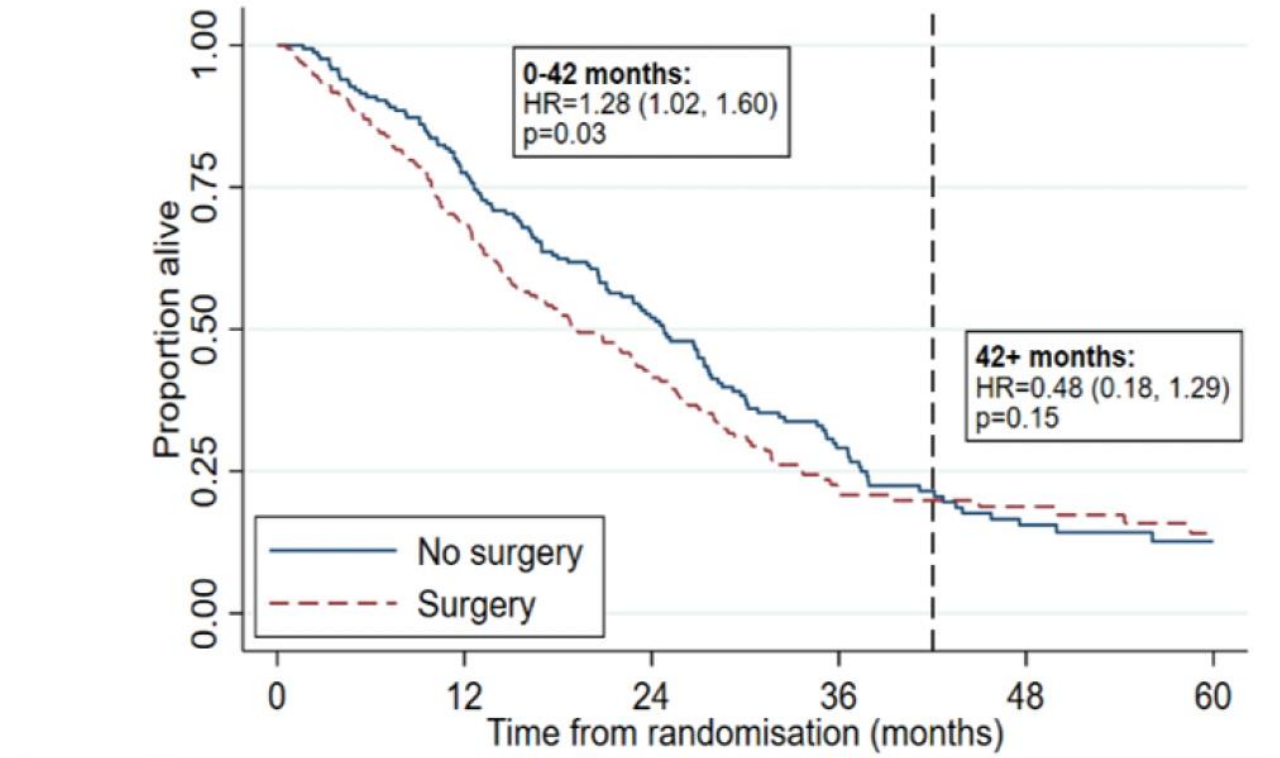
81% R1 surgery
16% R2 surgery

	Received surgery (n=158*)
Surgical procedure	
Extended pleurectomy/decortication	139/157 (88.5%)
Pleurectomy decortication	13/157 (8.3%)
Partial pleurectomy	3/157 (1.9%)
Exploration, no pleurodesis	1/157 (0.6%)
Other	1/157 (0.6%)
Resection and reconstruction	
Diaphragm resection	130/157 (82.8%)
Diaphragm reconstructed	128/157 (81.5%)
Pericardium resection	105/157 (66.9%)
Pericardium reconstructed	84/157 (53.5%)
Chest wall resection	19/157 (12.1%)
Chest wall reconstructed	9/157 (5.7%)
Other ipsilateral lung resection	67/157 (42.7%)
Wedge resection	64/67 (95.5%)
Bilobectomy	1/67 (1.5%)
Lobectomy	2/67 (3.0%)

Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

Surgery was associated with worse OS compared with chemotherapy



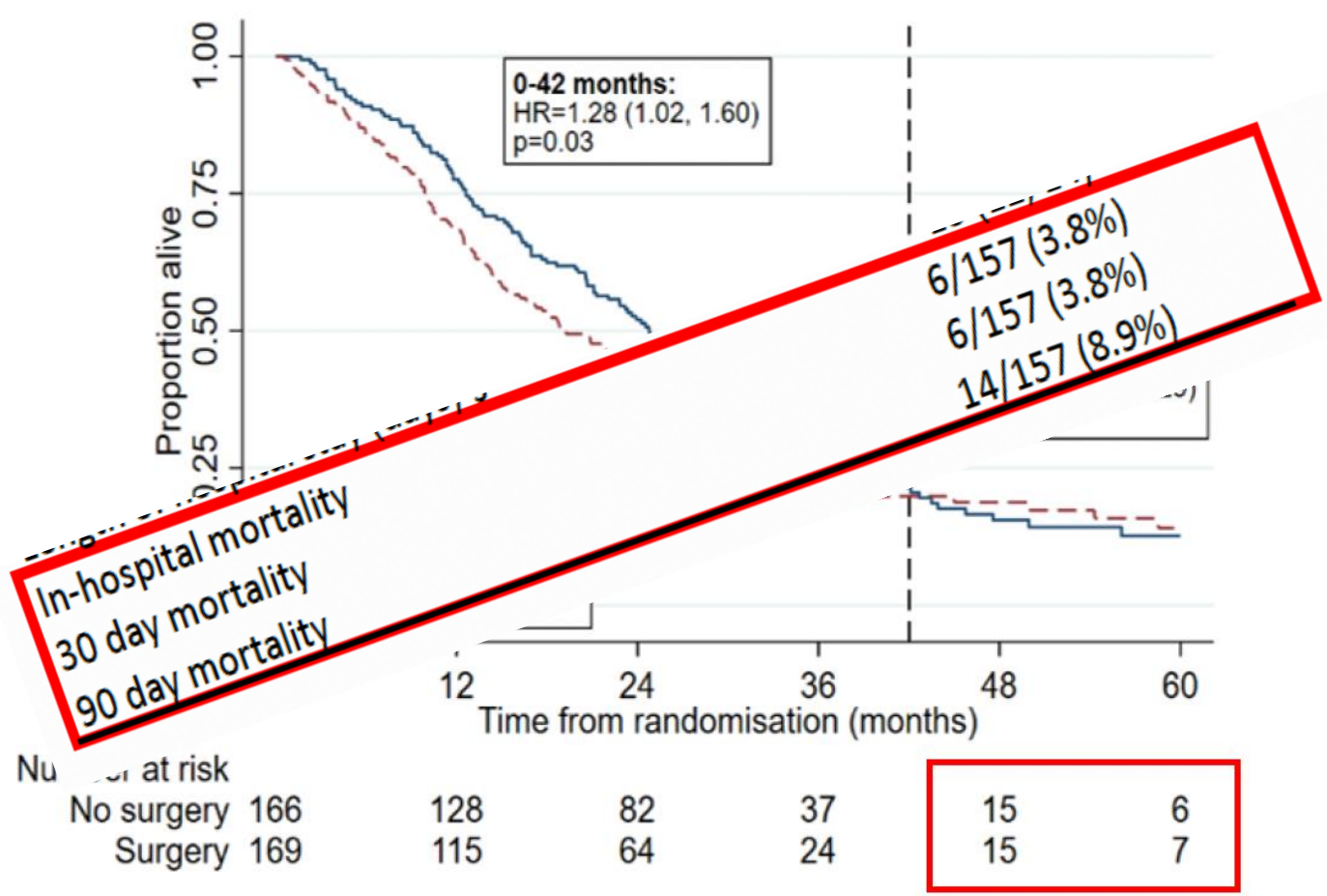
Number at risk

No surgery	166	128	82	37	15	6
Surgery	169	115	64	24	15	7

Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

Surgery was associated with worse OS – high early mortality in resected patients

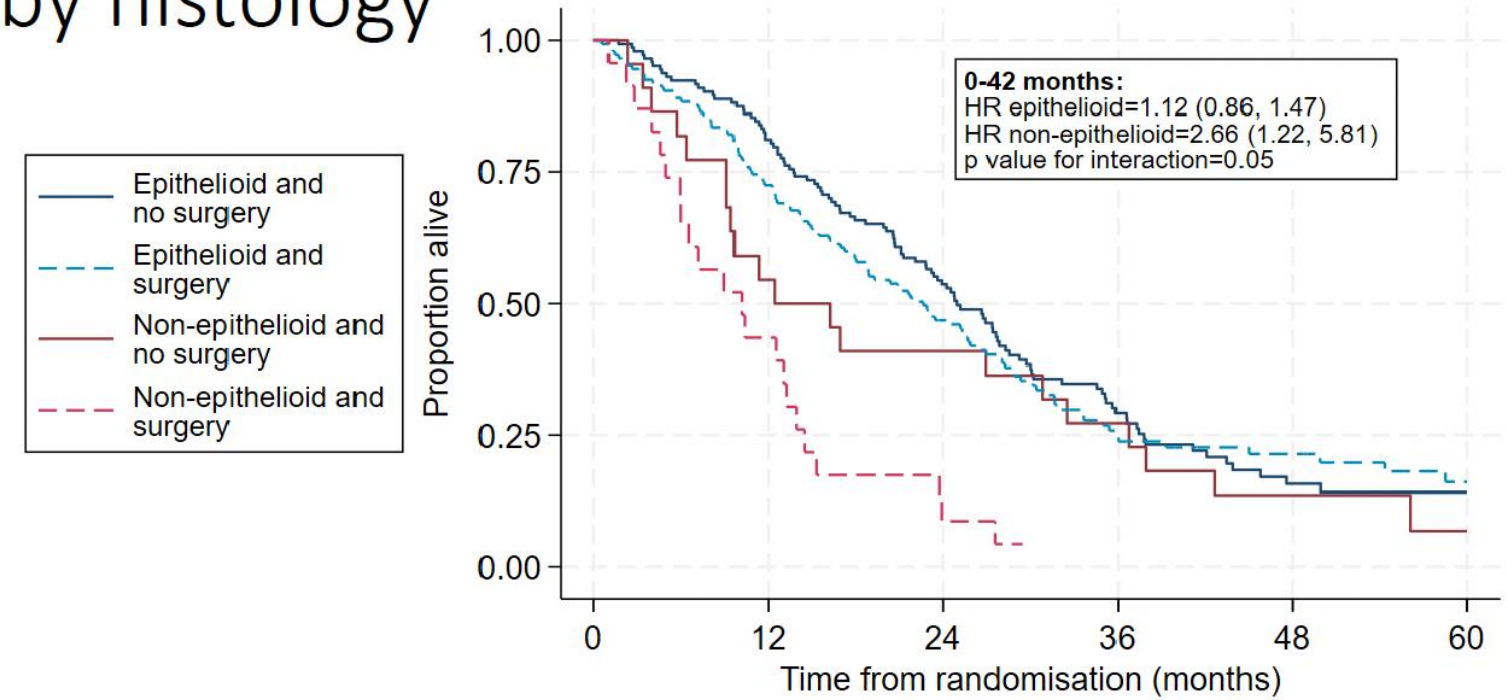


Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

No differences in terms of OS according to histology

Survival by histology

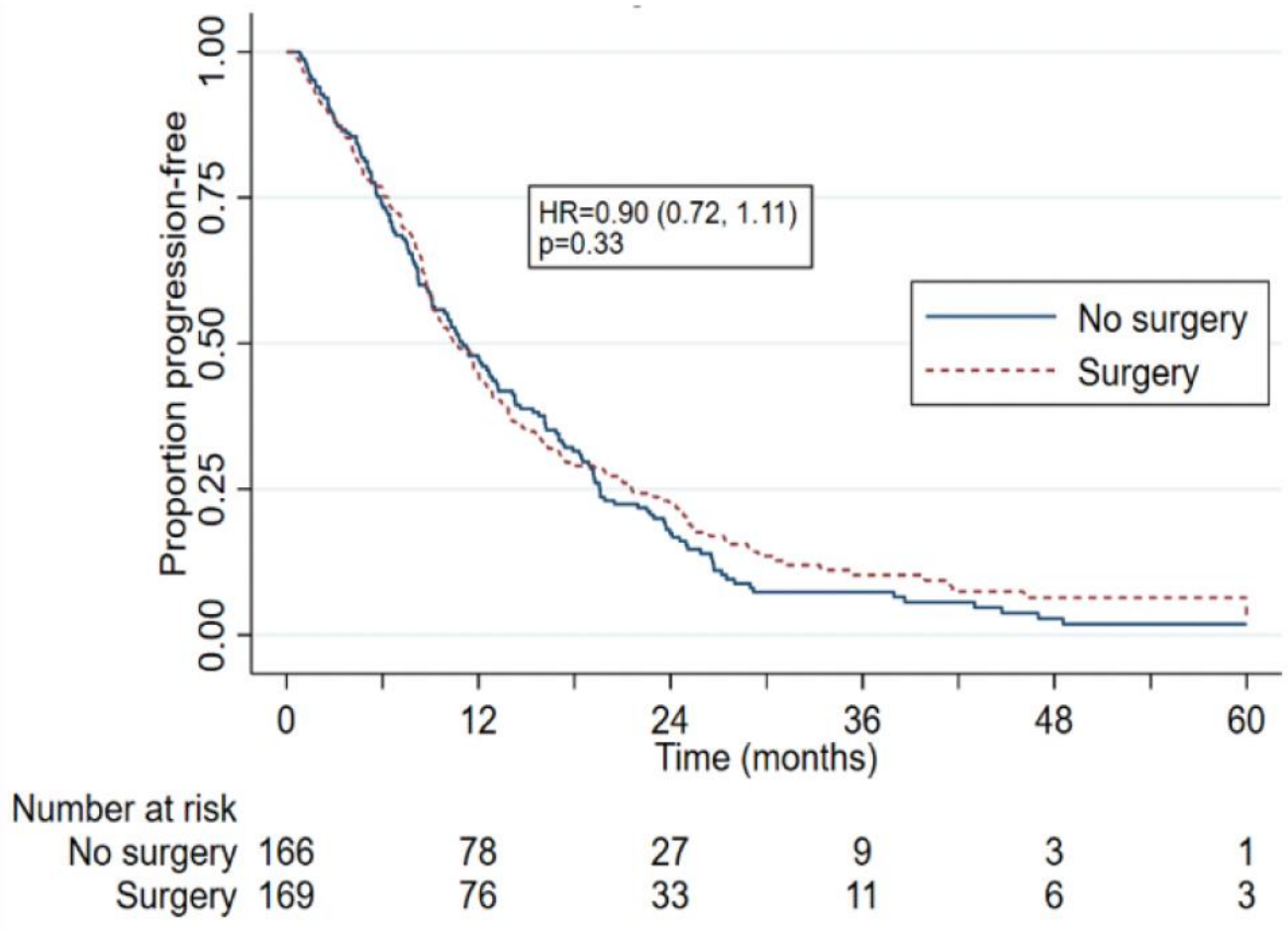


Number at risk						
Epithelioid and no surgery	144	116	73	31	12	5
Epithelioid and surgery	146	105	62	24	15	7
Non-epithelioid and no surgery	22	12	9	6	3	1
Non-epithelioid and surgery	23	10	2	0	0	0

Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

No differences in terms of PFS between surgery and no surgery



Lim et al. WCLC 2023

MARS 2 trial: Which is the role of pleurectomy/decortication?

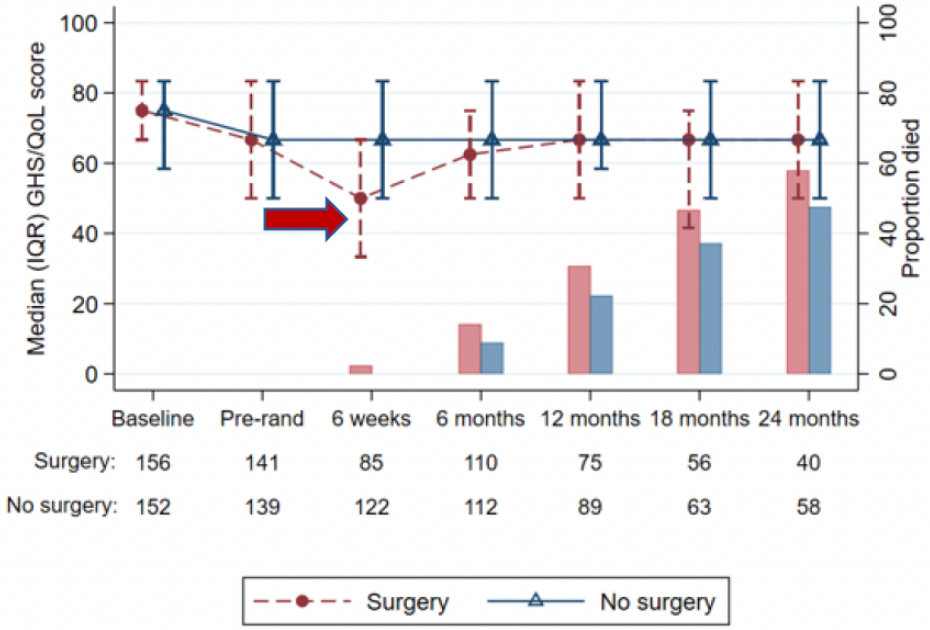
Surgery was associated with higher rate of G3-4 toxicity and worse QoL

Safety

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)
Number of CTCAE grade 3+ events	1 (0, 3)	0 (0, 2)
0	62/169 (36.7%)	86/166 (51.8%)
1	33/169 (19.5%)	38/166 (22.9%)
2	22/169 (13.0%)	17/166 (10.2%)
3	21/169 (12.4%)	12/166 (7.2%)
4+	31/169 (18.3%)	14/166 (7.8%)

31% vs 15%

Quality of life EORTC



Lim et al. WCLC 2023

However MARS2 trial has many flaws:

- ✓ Limited information on tumor staging (PET/CT, EBUS, mediastinoscopy)
- ✓ No clear definition of resectability in mesothelioma
- ✓ Poor-risk patients (like non-epithelioid, N2 or even M1) not excluded
- ✓ Some imbalances between both arms (more diaphragm involvement in control arm)
- ✓ Many centers with low experience in mesothelioma surgery
- ✓ Quality of surgery = unacceptably 90-day mortality (9%)

Lack of stardardization on tumor staging, lack of clear definition of resectable disease or macroscopic resection, need for neoadjuvant treatment or expert centers designation

Adapted from Paula Ugalde. WCLC 2023

Is surgery a good treatment for our patients with mesothelioma?

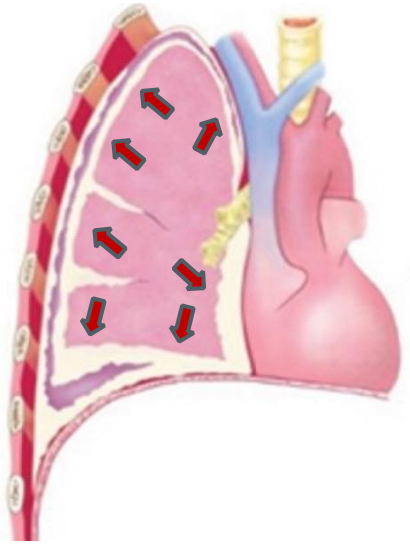
Is surgery a good treatment for our patients with mesothelioma?

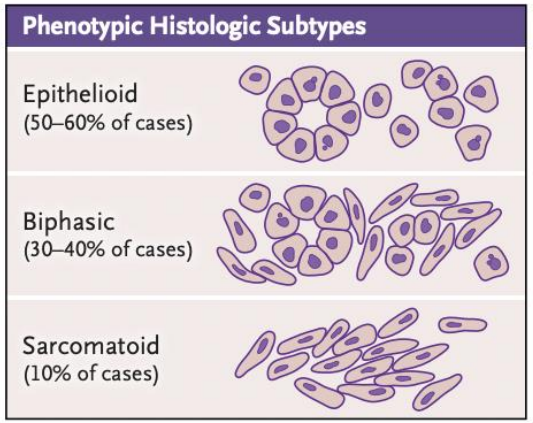
PROBABLY NOT

Clinical trials	Output
MARS	EPP – RT seems detrimental vs no EPP
Meso-VATS	No survival benefit & more complications with PP
MARS2	P/D seems detrimental vs no surgery

Why surgery underperforms in mesothelioma?

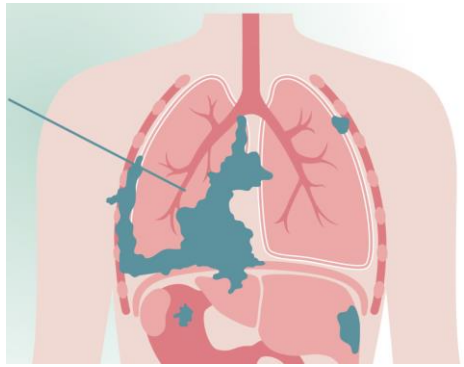
Multifocal disease
Clean margins realistic?

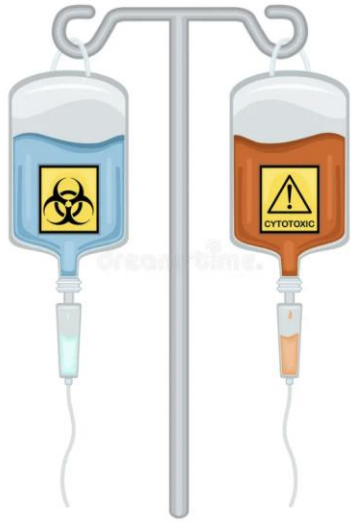




Intratumor heterogeneity
Lack of actionable genes

Surgery leads to serosal dissemination (peritoneum, contralateral lung)





Limited efficacy of systemic treatment

Adapted from Gary Lee. Lancet 2014

We should work into a multidisciplinary approach to mesotelioma… to move towards a more patient-centered management

Surgery should be conducted only in centers with significant volume and experience
Ideally in a clinical trial or academic study
(Only epithelioid and N0-1 disease)

To consider early palliative care support

Patient access to specialist nurse

Appropriate management of pleural effusion (pleurodesis, catheter)

To develop patient-focused information resources and improve communication with patients

Germline testing should be considered

More research needed
Promote patient access to clinical trials and innovative treatments

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MADRID

23&24 November 2023

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Fundación GECP lung cancer research

Muchas Gracias

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