



Malignant Pleural Mesothelioma

Role of surgery

Ricardo M. Terra

Professor Livre-Docente da Disciplina de Cirurgia Torácica
Faculdade de Medicina da USP

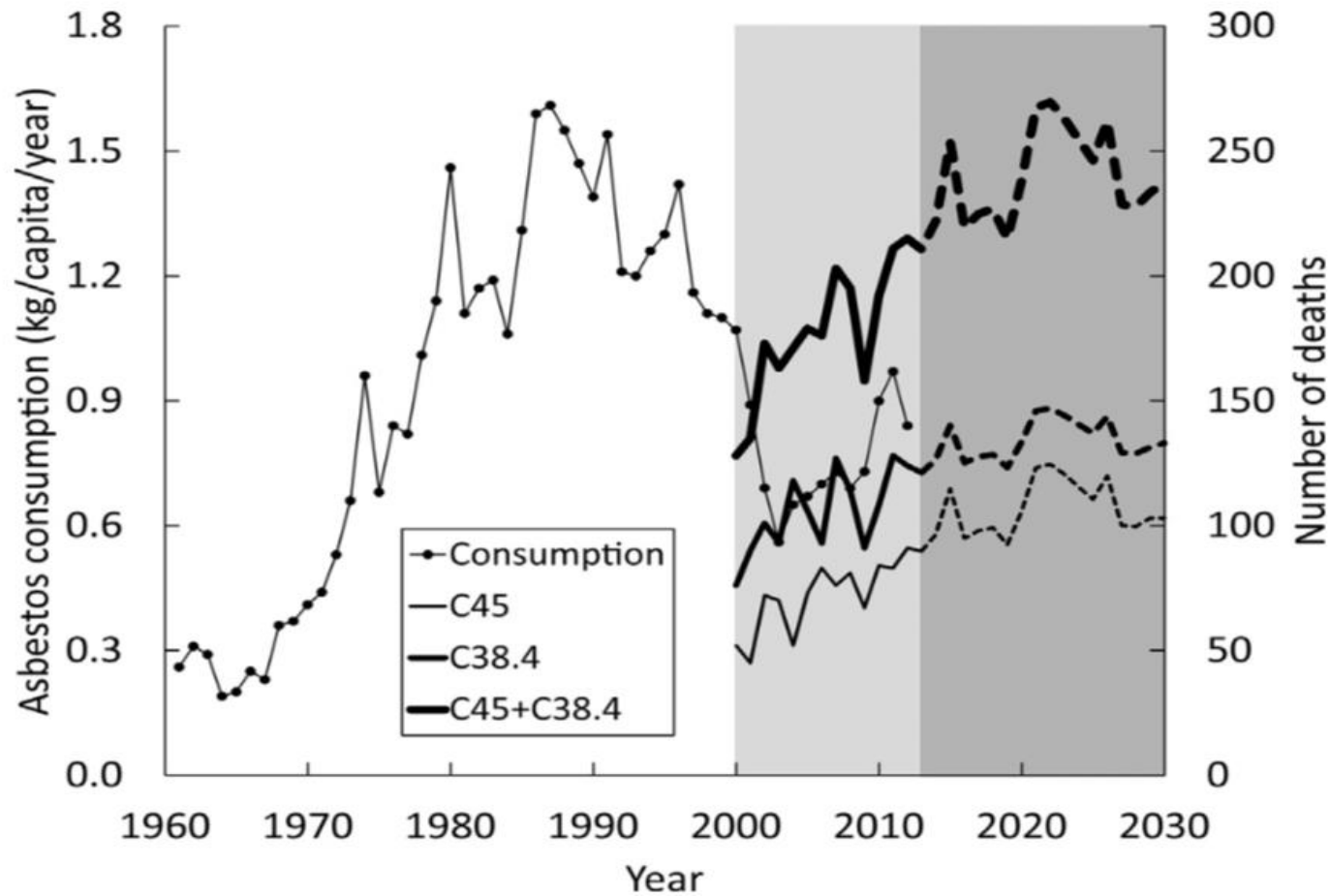


Disclosure

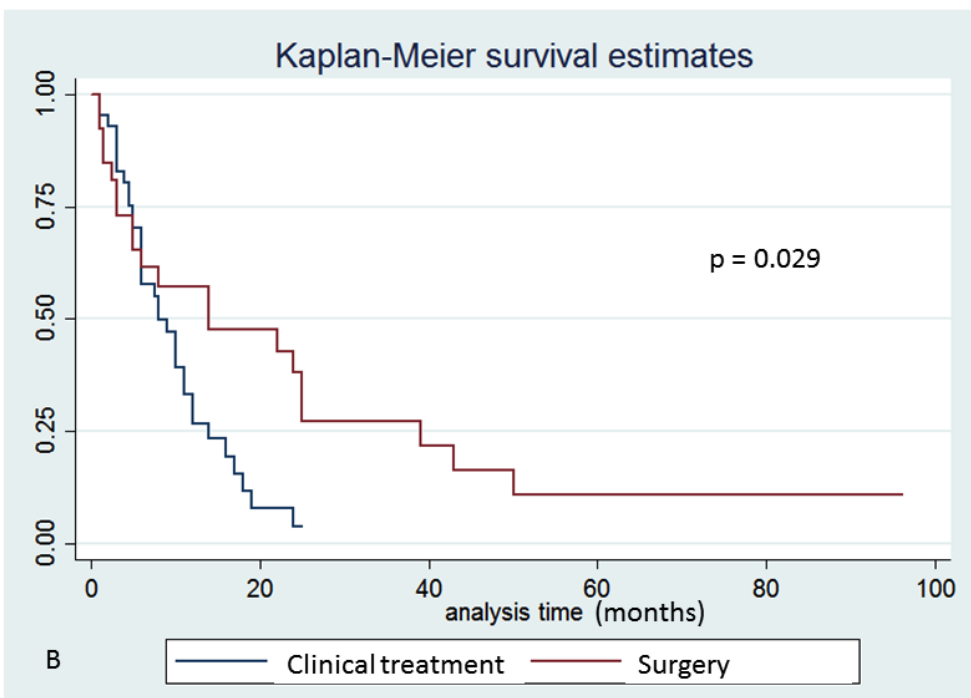
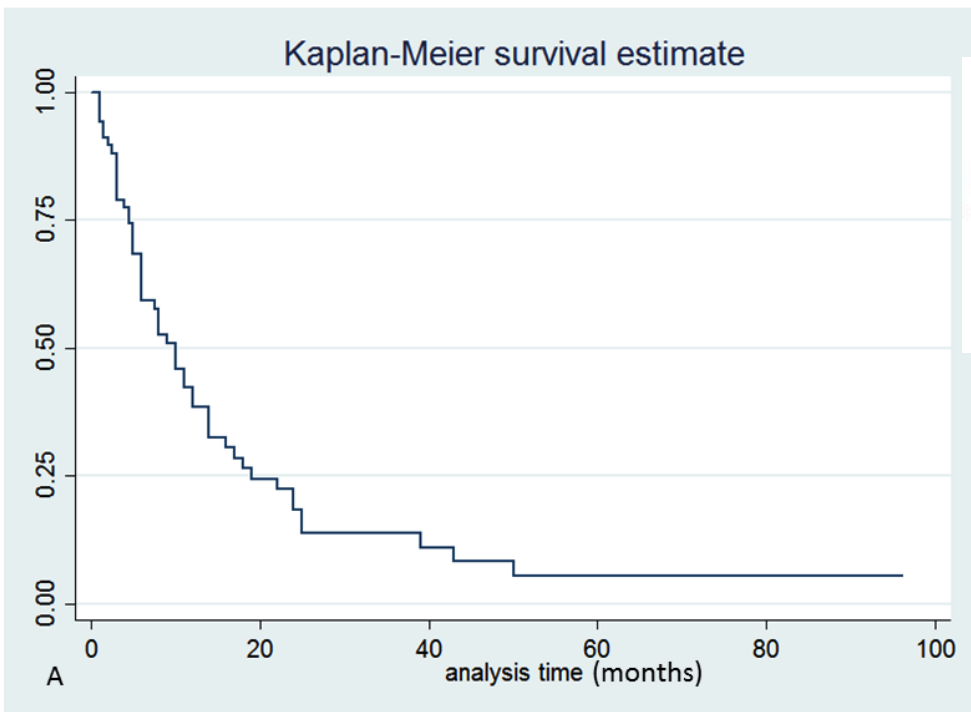
- Advisory Board: Johnson&Johnson
- Speaker Bureau: Medtronic,
H.Strattner/Intuitive, Astra Zeneca, Boehringer

The next mesothelioma wave: Mortality trends and forecast to 2030 in Brazil

Eduardo Algranti^{a,*}, César Akiyoshi Saito^b, Ana Paula Scalia Carneiro^c, Bruno Moreira^c, Elizabethete Medina Coeli Mendonça^a, Marco Antonio Bussacos^d



N=85
pacientes
FMUSP

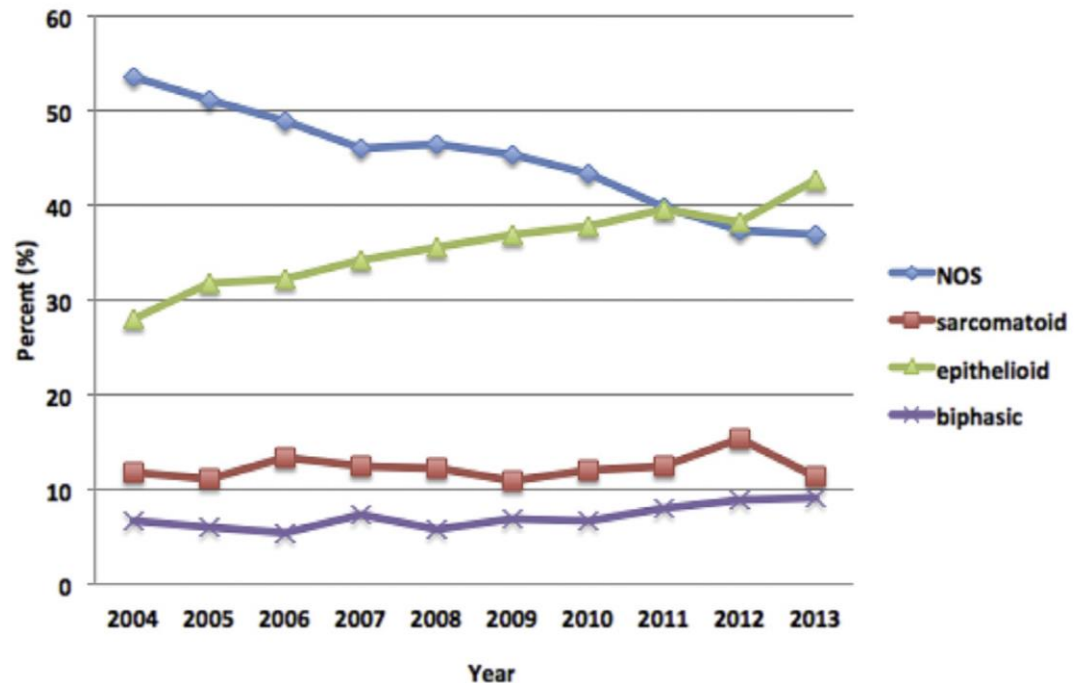


National Trends in the Epidemiology of Malignant Pleural Mesothelioma: A National Cancer Data Base Study

Sahar A. Saddoughi, MD, PhD, Zaid M. Abdelsattar, MD, MS, and Shanda H. Blackmon, MD, MPH

Division of General Thoracic Surgery, Mayo Clinic, Rochester, Minnesota

- Retrospective analysis – National Cancer Database
- 2004-2013
- N=19134 patients

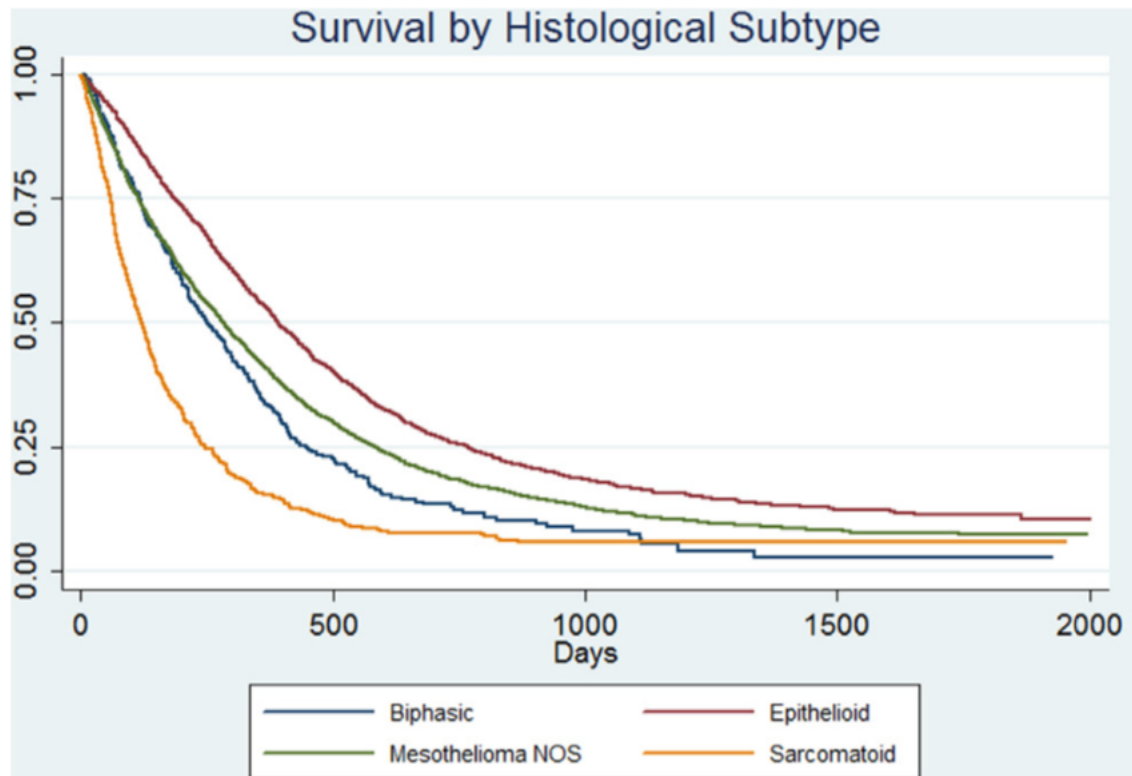


Demographics, management and survival of patients with malignant pleural mesothelioma in the National Lung Cancer Audit in England and Wales

P. Beckett^{a,b,*}, J. Edwards^c, D. Fennell^d, R. Hubbard^e, I. Woolhouse^{b,f}, M.D. Peake^{b,g}

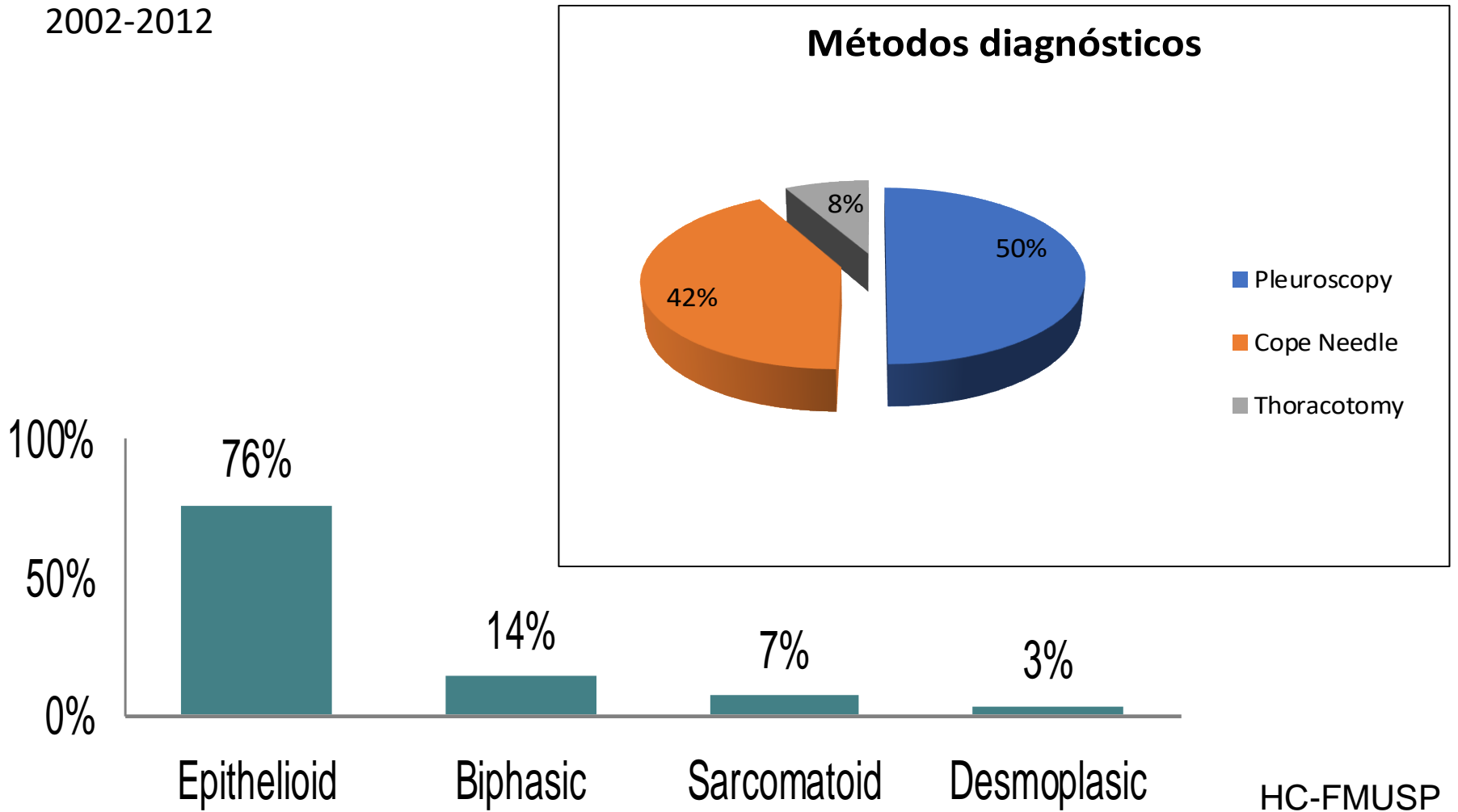
Database analysis: 2008-2012

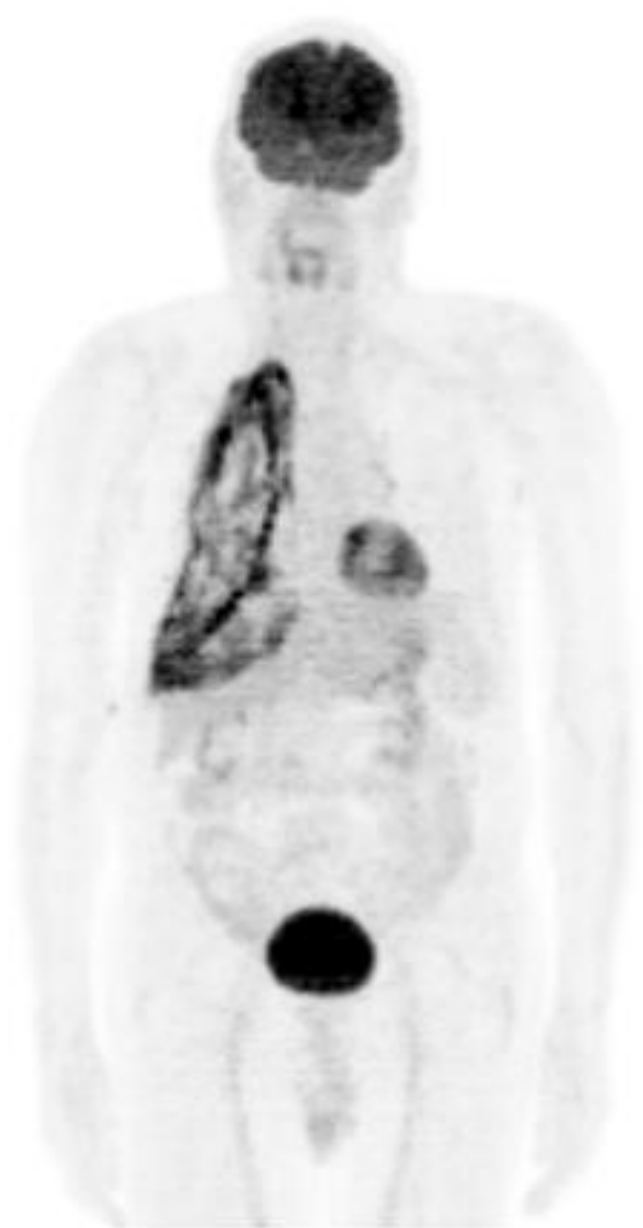
N=8740



Histology

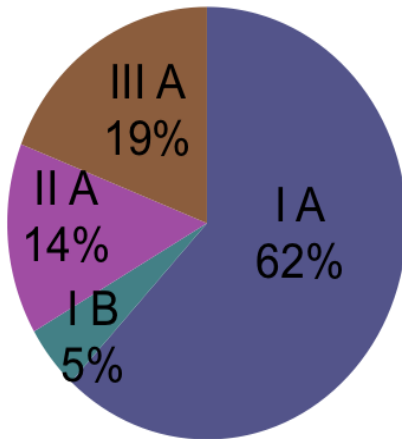
N=59
2002-2012



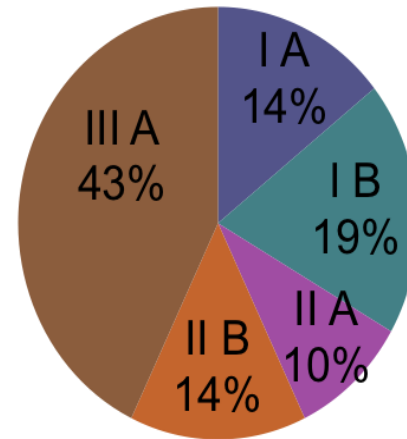


Staging

Estadiamento Pré-op.



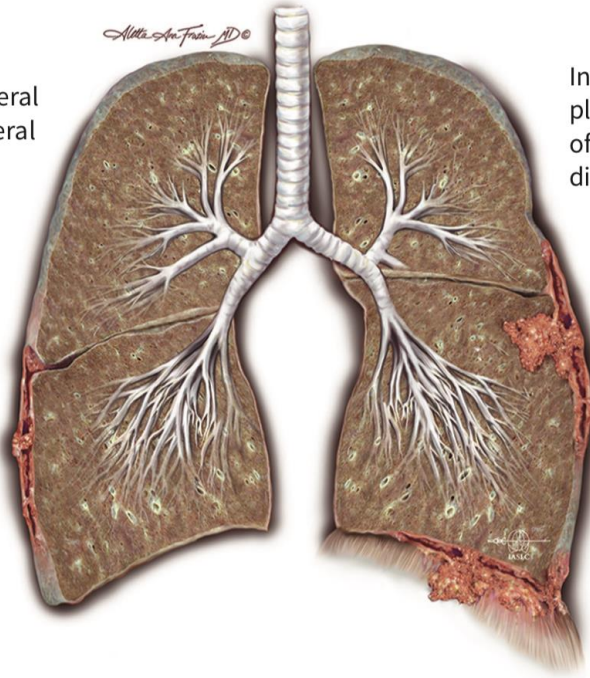
Estadiamento Pós-op.



IASLC Staging System

T1

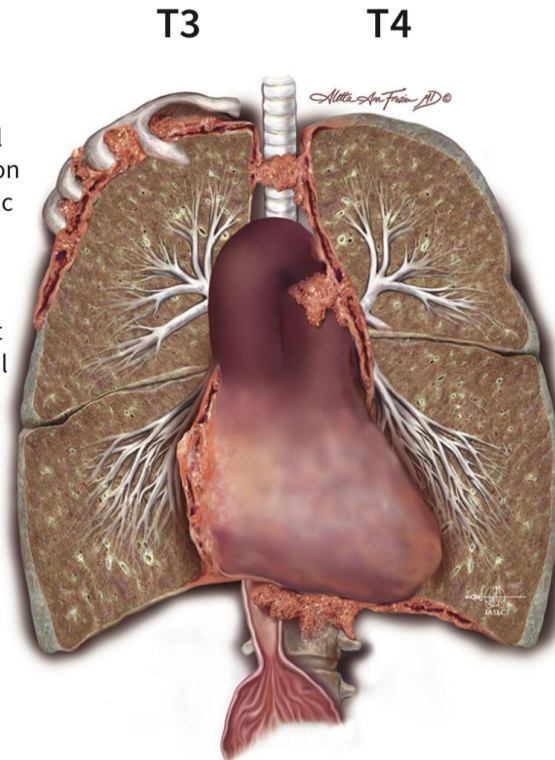
Involves ipsilateral parietal or visceral pleura only



T2

Involves ipsilateral pleura with invasion of lung and/or diaphragmatic muscle

Involves ipsilateral pleura with invasion of the endothoracic fascia, the chest wall (solitary, resectable focus extending into soft tissue), mediastinal fat and/or non-transmural invasion of the pericardium



T3

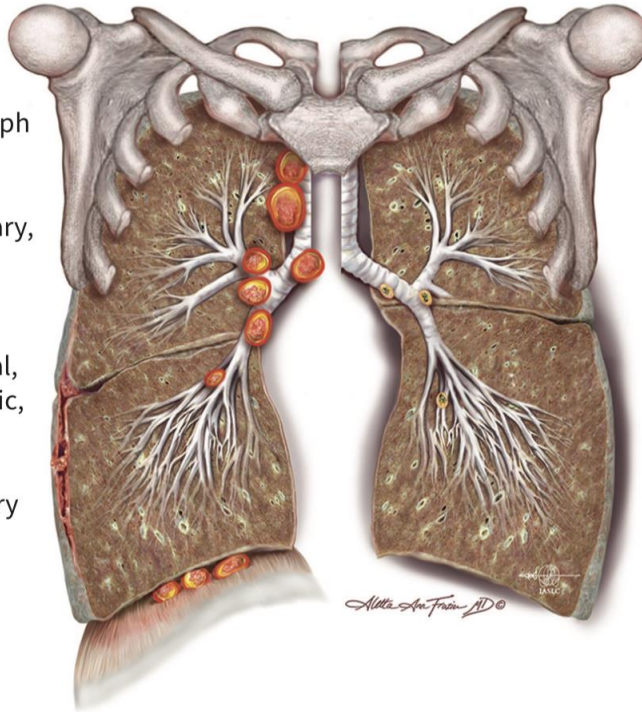
T4

Involves ipsilateral pleura with diffuse, multifocal invasion of the chest wall, invasion of the contralateral pleura, peritoneum, mediastinal organs, spine, transmural invasion of the pericardium (with or without pericardial effusion) and/or myocardium

IASLC Staging System

N1

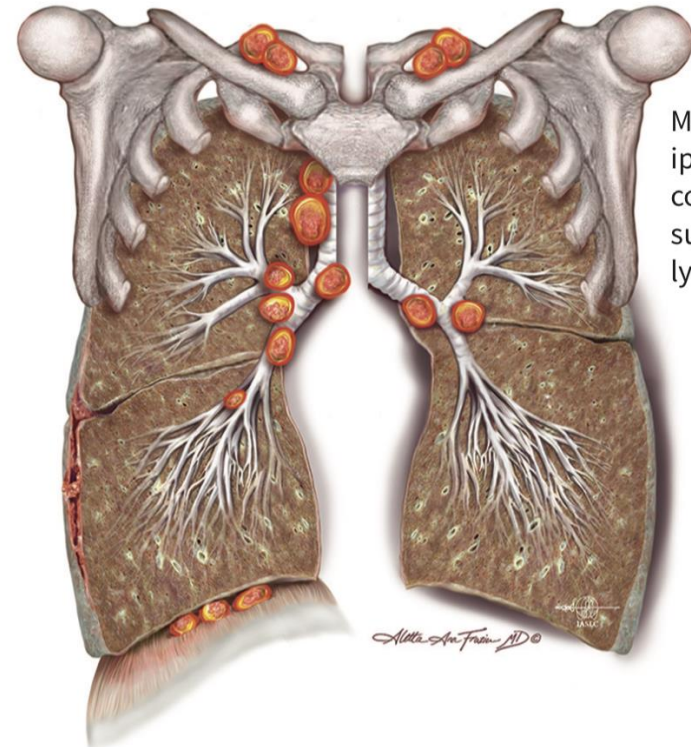
Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, para-oesophageal, peridiaphragmatic, pericardial, intercostal and internal mammary lymph nodes)



N2

Metastases to ipsilateral or contralateral supraclavicular lymph nodes

Metastases to contralateral intrathoracic lymph nodes



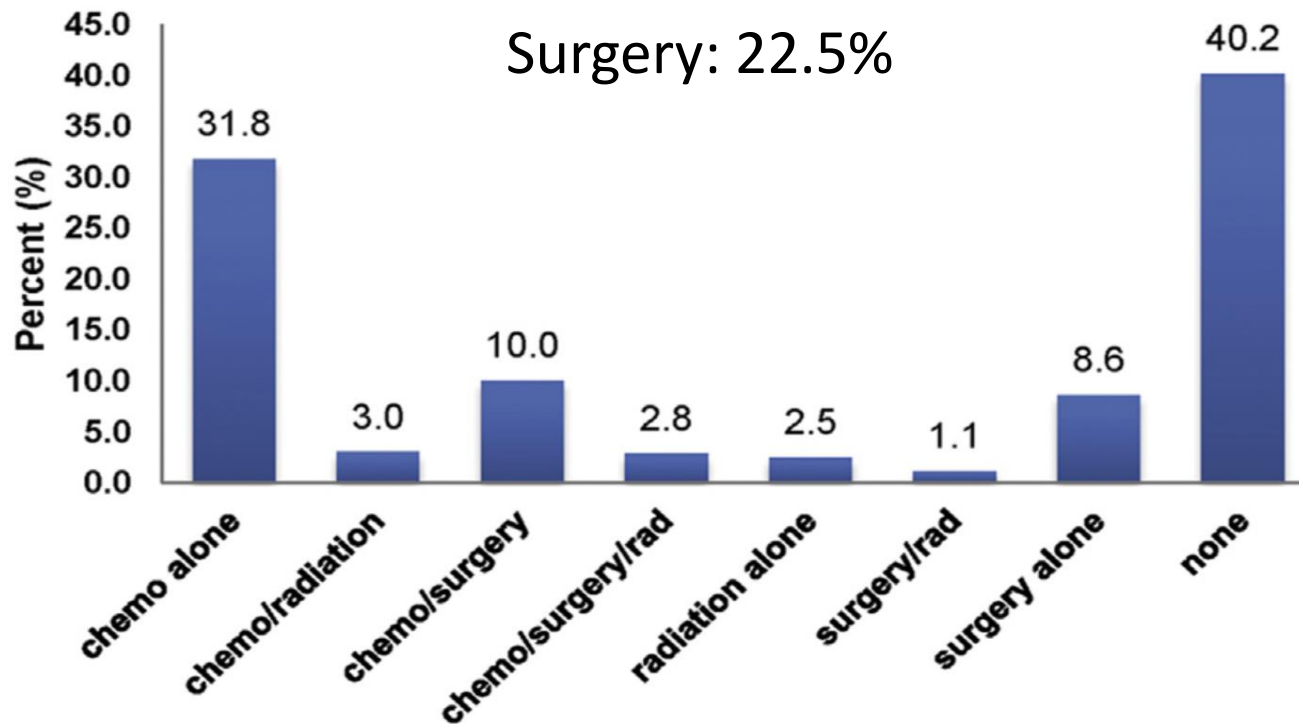
IASLC Staging System

Stage IA	T1	N0	M0
Stage IB	T2, T3	N0	M0
Stage II	T1, T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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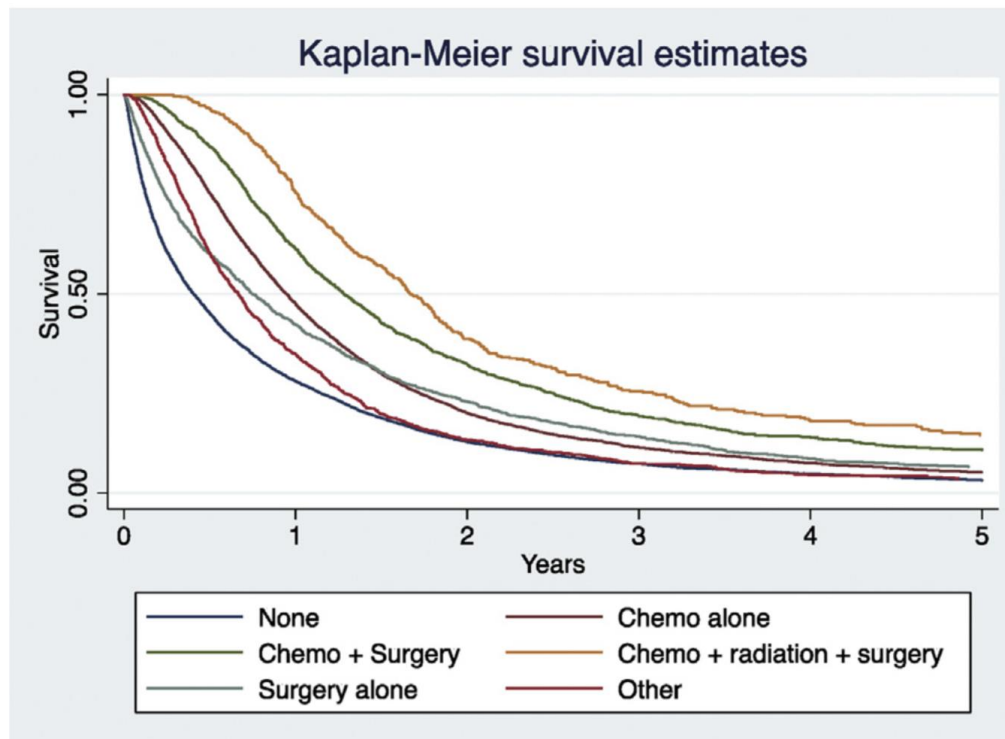


Demographics, management and survival of patients with malignant pleural mesothelioma in the National Lung Cancer Audit in England and Wales

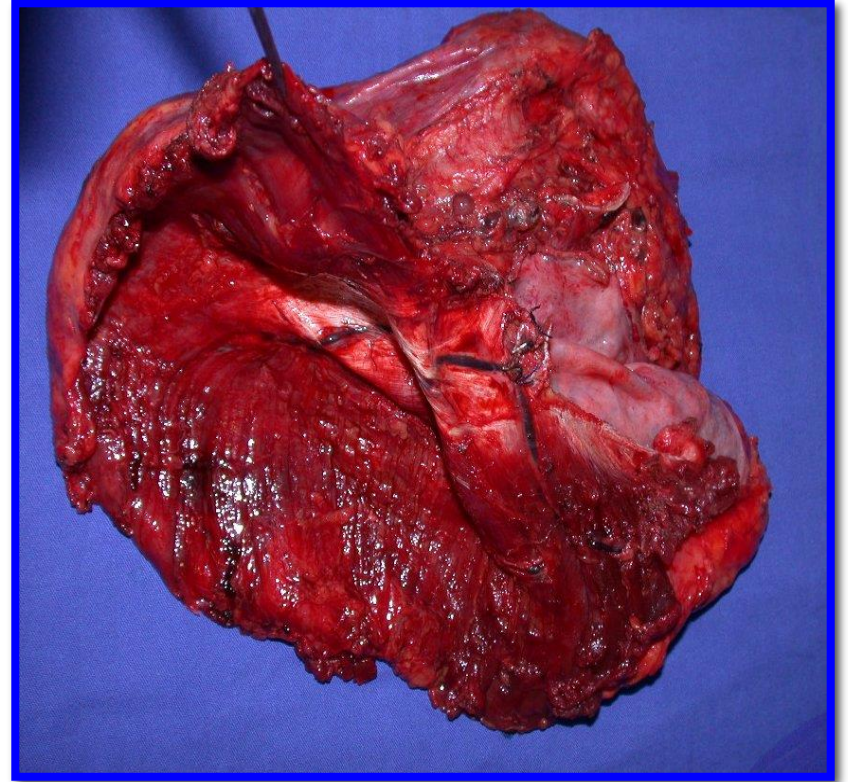
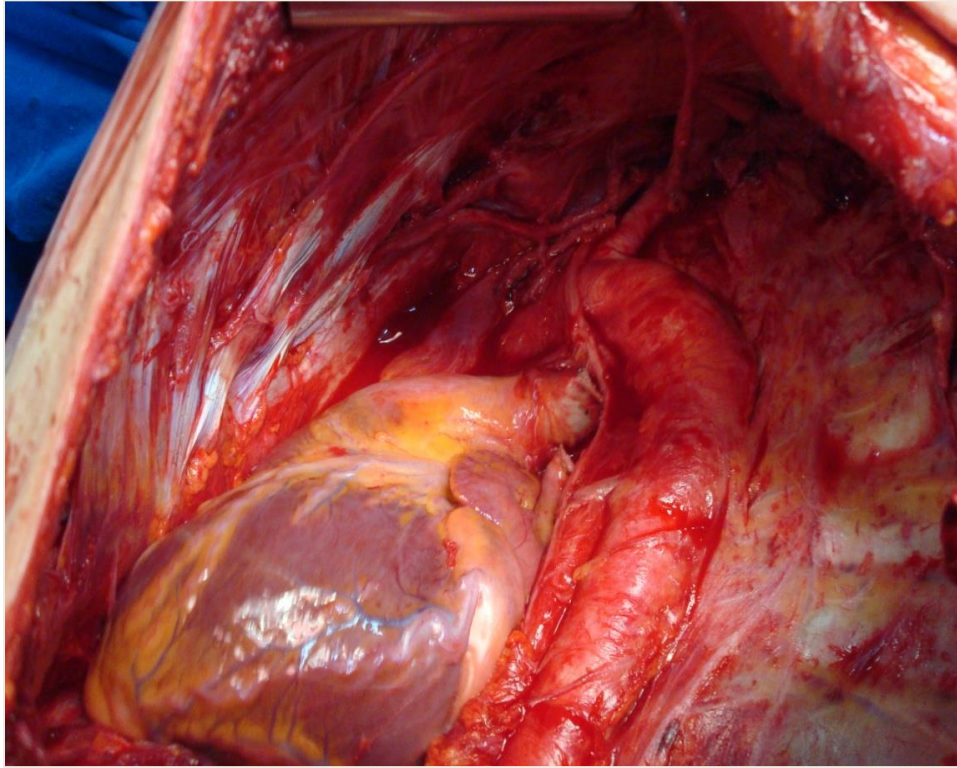
P. Beckett^{a,b,*}, J. Edwards^c, D. Fennell^d, R. Hubbard^e, I. Woolhouse^{b,f}, M.D. Peake^{b,g}

Database analysis: 2008-2012

N=8740



Extrapleural pneumonectomy



**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

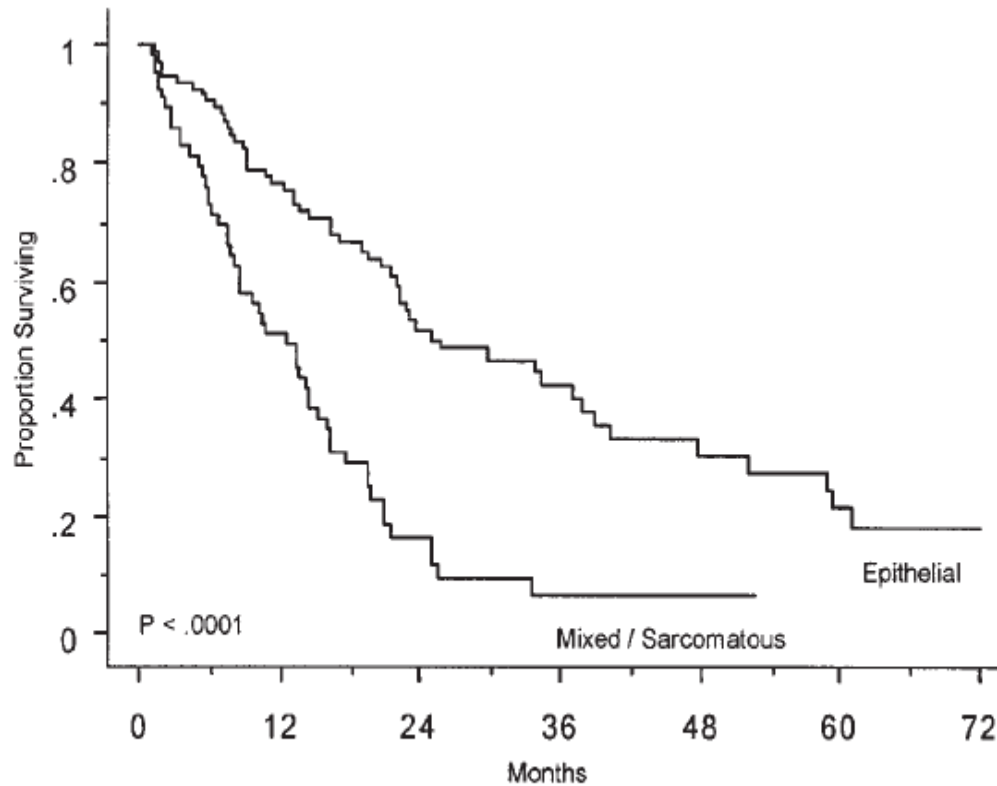
Raja M. Flores, MD

- Coorte retrospectivo;
- Objetivo: identificar variáveis prognósticas para sobrevida a longo prazo em pacientes tratados com EPP seguida de quimio e radioterapias adjuvantes;
- 183 pacientes.

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

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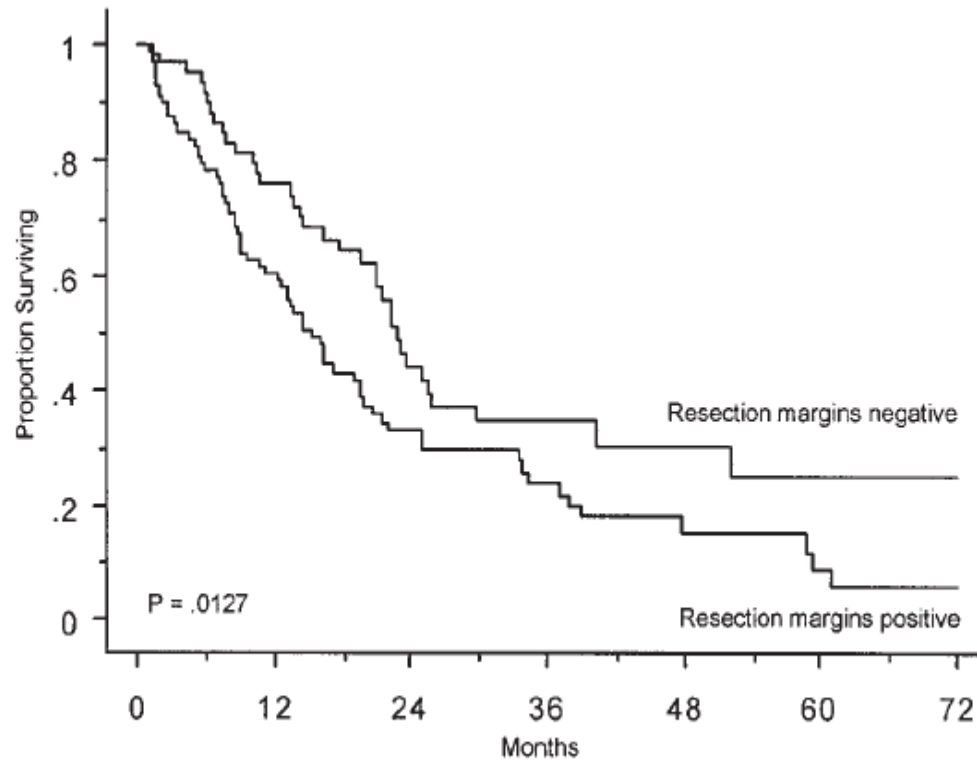
Raia M. Flores, MD



Patients at risk	0	12	24	36	48	60	72
Epithelial	103	65	34	20	11	7	6
Mixed / Sarcomatous	73	29	7	2	1	0	0

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
Raia M. Flores, MD

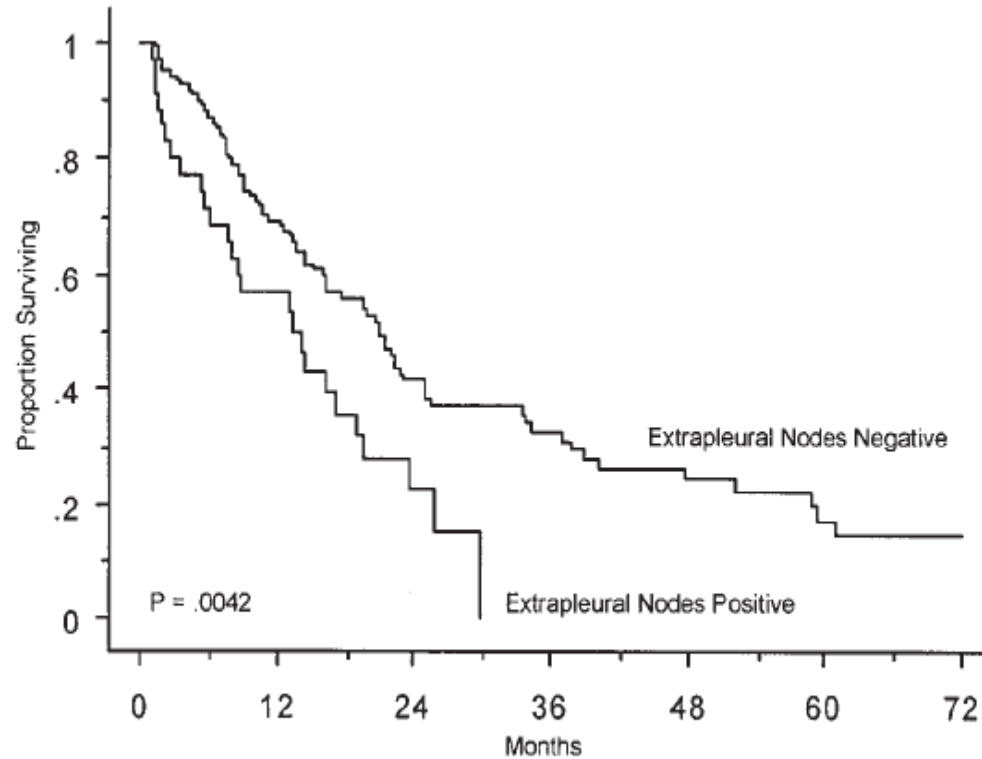


Patients at risk	0	12	24	36	48	60	72
Resection margins neg	66	42	19	10	7	4	4
Resection margins pos	110	52	22	12	5	3	2

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

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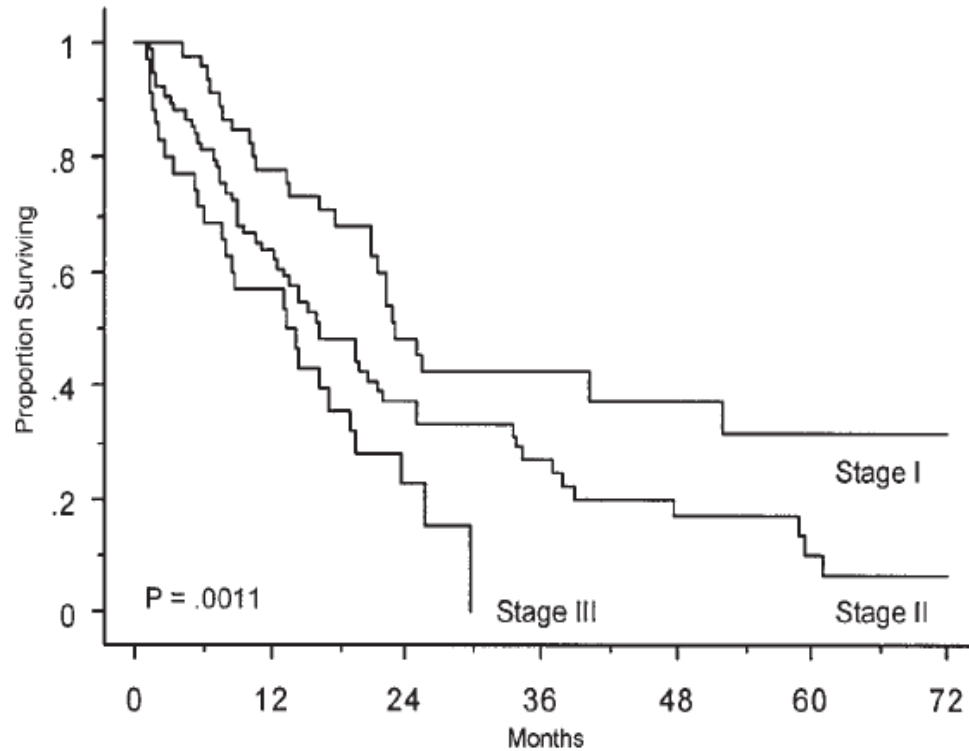
Patients at risk

Extrapleural node neg	136	77	37	22	12	7	6
Extrapleural node pos	40	17	4	0	0	0	0

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



Patients at risk		Months						
	0	12	24	36	48	60	72	
Stage I	52	34	17	10	7	4	4	
Stage II	84	43	20	12	5	3	2	
Stage III	40	17	4	0	0	0	0	

**RESECTION MARGINS, EXTRAPLEURAL NODAL STATUS, AND CELL TYPE DETERMINE
POSTOPERATIVE LONG-TERM SURVIVAL IN TRIMODALITY THERAPY OF MALIGNANT PLEURAL
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Raja M. Flores, MD

Conclusão

- Tratamento multimodal com Qt e Rt adjuvantes é viável: **3,8%** mortalidade peri-operatória e 24,5% morbidades maiores;
- Subgrupo de pacientes com tipo epitelioide, margens cirúrgicas completas e sem acometimento linfonodal → Benefício na sobrevida;
- Avaliação pré-operatória dos linfonodos é importante.

Multicenter Phase II Trial of Neoadjuvant Pemetrexed Plus Cisplatin Followed by Extrapleural Pneumonectomy and Radiation for Malignant Pleural Mesothelioma

Lee M. Krug, Harvey I. Pass, Valerie W. Rusch, Hedy L. Kindler, David J. Sugarbaker, Kenneth E. Rosenzweig, Raja Flores, Joseph S. Friedberg, Katherine Pisters, Matthew Monberg, Coleman K. Obasaju, and Nicholas J. Vogelzang

- Prospectivo
- Estadios T1-3 N0-2, VEF₁ ≥ 35% e performance 0 ou 1
- Objetivos: analisar a viabilidade e eficácia do tratamento multimodal com Cisplatina e Pemetrexed neoadjuvantes seguido de EPP e radioterapia
- 77 iniciaram quimioterapia → 57 realizaram EPP → 44 iniciaram radioterapia → 40 completaram todos os tratamentos

Multicenter Phase II Trial of Neoadjuvant Pemetrexed Plus Cisplatin Followed by Extrapleural Pneumonectomy and Radiation for Malignant Pleural Mesothelioma

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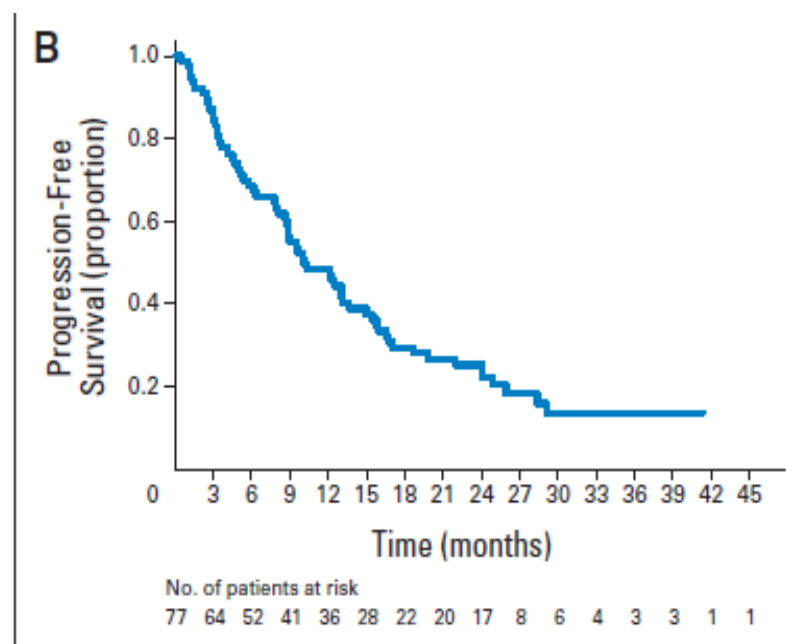
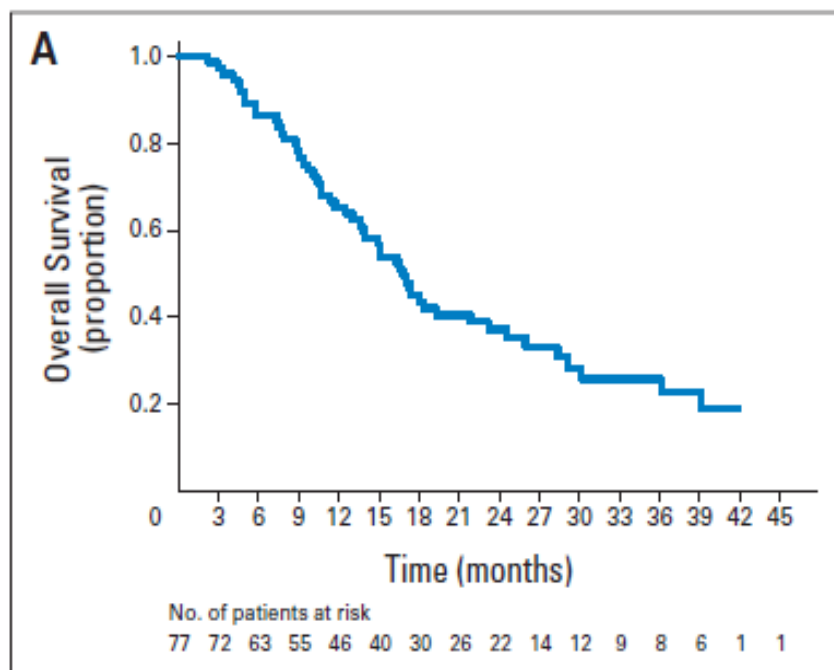


Fig 2. (A) Kaplan-Meier overall survival, intent-to-treat (ITT) population (median, 16.8 months; 95% CI, 3.6 to 23.2 months). (B) Kaplan-Meier progression-free survival, ITT population (median, 10.1 months; 95% CI, 8.6 to 15.0 months).

Multicenter Phase II Trial of Neoadjuvant Pemetrexed Plus Cisplatin Followed by Extrapleural Pneumonectomy and Radiation for Malignant Pleural Mesothelioma

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Table 4. Trimodality With Extrapleural Pneumonectomy and Radiation Therapy for Malignant Pleural Mesothelioma

Author	No. of Patients	Stage of Disease	Chemotherapy Regimens Used	No. With EPP	% of ITT	Key Results
Weder et al ¹³	19	I-III	Neoadjuvant gemcitabine 1,000 mg/m ² days 1, 8, 15 plus cisplatin 80 mg/m ² day 1, 28-day cycle × 3	16	84	RR = 32%, OS = 23 months for ITT
Flores et al ²²	19	III-IV	Neoadjuvant gemcitabine 1,250 mg/m ² days 1, 8 plus cisplatin 75 mg/m ² day 8, 21-day cycle × 4	8	42	PR = 26%, SD = 32%, OS = 19 months for ITT
Weder et al ²³	61	I-III	Neoadjuvant gemcitabine 1000 mg/m ² days 1, 8, 15 plus cisplatin 80 mg/m ² day 1, 28-day cycle X 3	45	74	OS = 19.8 months for ITT and 23 months for EPP
Rea et al ²⁴	21	I-III	Neoadjuvant gemcitabine 1,000 mg/m ² days 1, 8, 15 plus carboplatin AUC 5 day 1, 28-day cycle × 3	17	81	PR = 33%, SD = 67%, OS = 25.5 months for ITT
Batirel et al ²⁵	20	I-III	Adjuvant gemcitabine 1,250 mg/m ² days 1, 8 plus cisplatin 75 mg/m ² day 1, 21-day cycle × 3. After 2005, adjuvant pemetrexed 500 mg/m ² day 1 plus cisplatin 75 mg/m ² day 1 × 3	16	80	OS = 17.2 months for ITT and 23.9 months for EPP
Current study	77	I-III	Neoadjuvant pemetrexed 500 mg/m ² day 1 plus cisplatin 75 mg/m ² day 1 × 4	54	70	pCR = 5.3%, RR = 32.5%, OS = 16.8 months for ITT and 21.9 months for EPP

Abbreviations: EPP, extrapleural pneumonectomy; ITT, intent to treat; RR, response rate; OS, overall survival; PR, partial response; SD, stable disease; AUC, area under the curve; pCR, pathologic complete response.

Malignant Pleural Mesothelioma: Surgical Management in 285 Patients

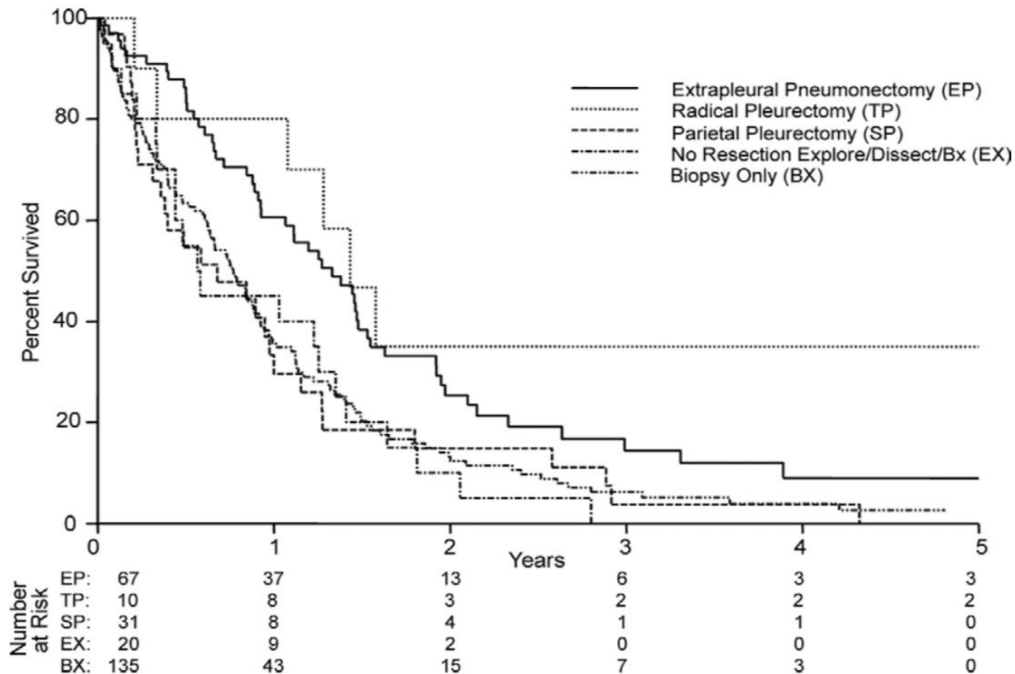
Paul H. Schipper, MD, Francis C. Nichols, MD, Kristine M. Thomse, BA, Claude Deschamps, MD, Stephen D. Cassivi, MD, Mark S. Allen, MD, and Peter C. Pairolero, MD

General Thoracic Surgery and Biostatistics, Mayo Clinic, Rochester, Minnesota

Retrospective study 1985-2003

EPP: 73 patients (26%) – Op. mortality: 8.1%

Pleurectomy: 10 patients (3%) – Op. mortality: 2.9%



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**

- Desenhado como ensaio clínico randomizado controlado de **viabilidade**
- Químio baseada em platina neoadjuvante → Randomização:
EPP e Radio adjuvante **X** Radio adjuvante
- 50 pacientes: EPP 24 X Não EPP 26

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

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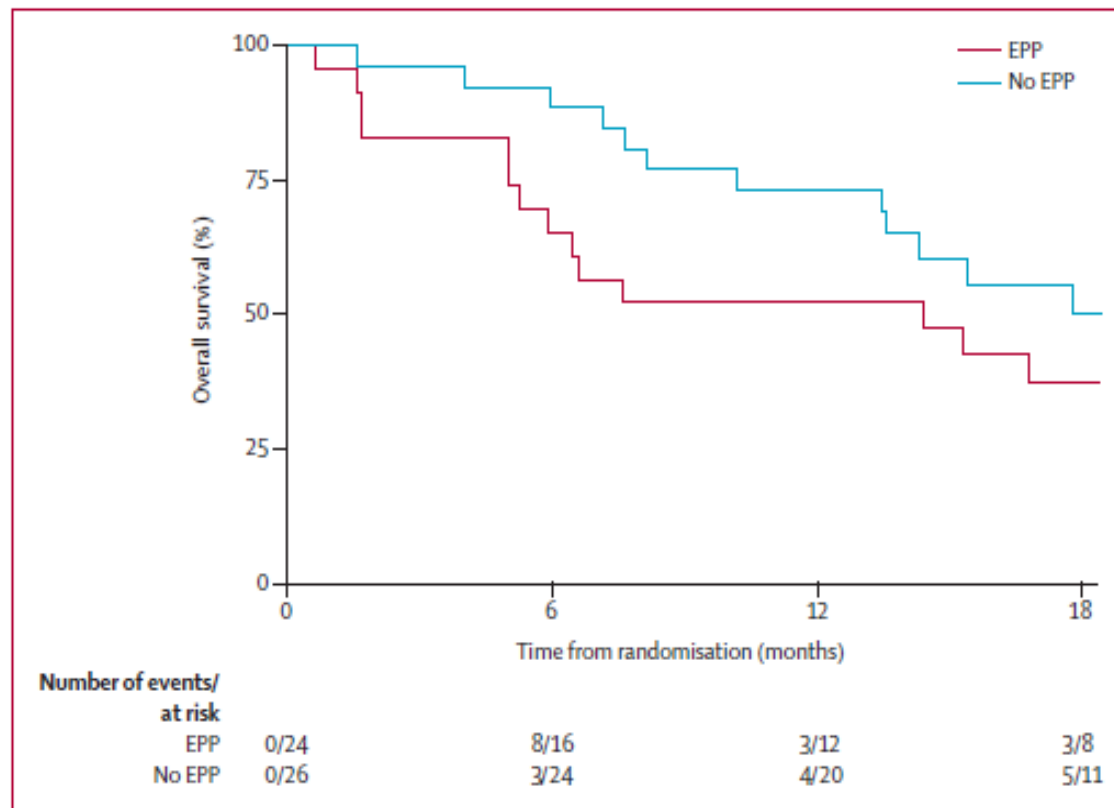


Figure 4: Overall survival
EPP=extra-pleural pneumonectomy.

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

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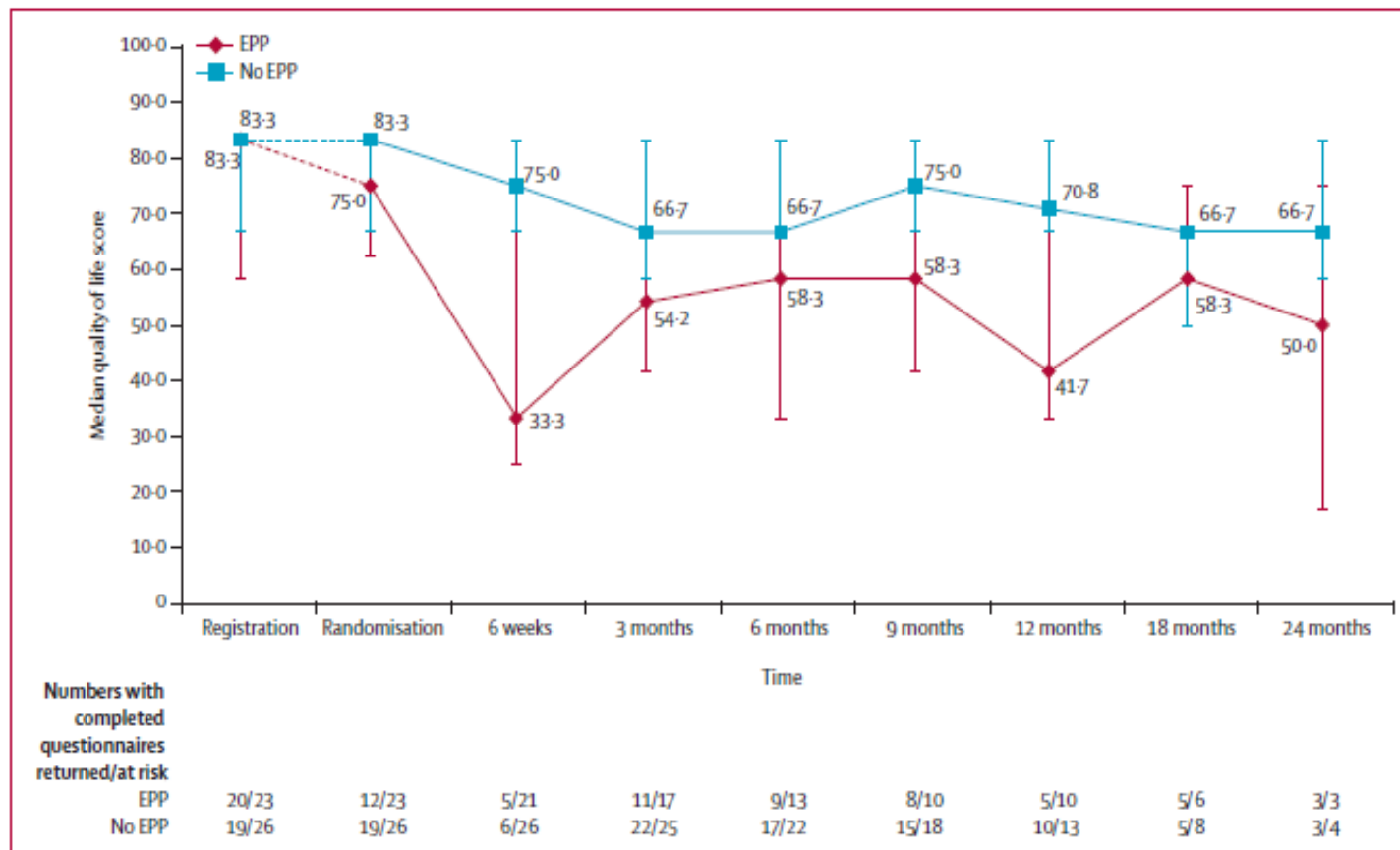
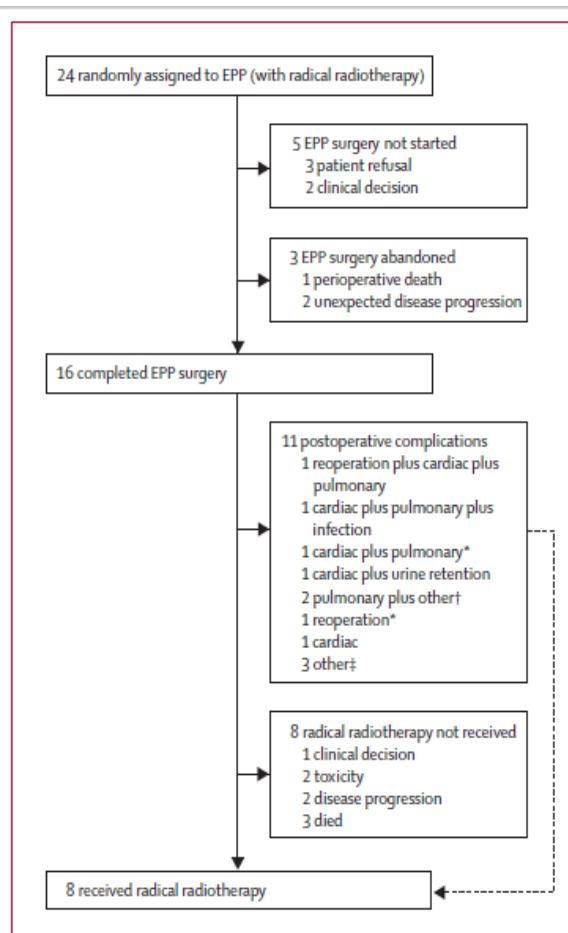


Figure 6: Quality of life

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

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- Apenas 50 dos 112 (42%) foram randomizados?
- Qt não padronizada e intervalo não informado
- Mortalidade cirúrgica EPP: **18%**
- Morbidade cirúrgica EPP: 69%

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

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Conclusão

- Sem benefício em sobrevida e qualidade de vida
- Alta morbi-mortalidade
- Não mostrou viabilidade na realização de um ensaio clínico comparando quimioterapia com EPP e radioterapia **X** quimioterapia com radioterapia

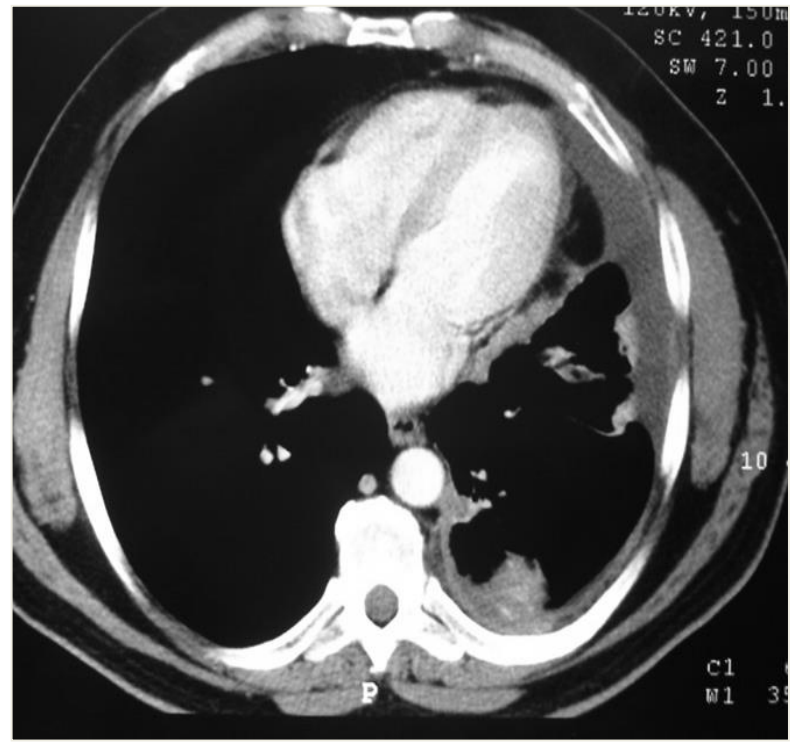
Tratamento do MPM Localizado

Pleuropneumonectomia

- Ressecção mais “radical”, em bloco;
- Viável em estadios mais avançados;
- Permite maior dose de radioterapia adjuvante.

Decorticação e pleurectomia

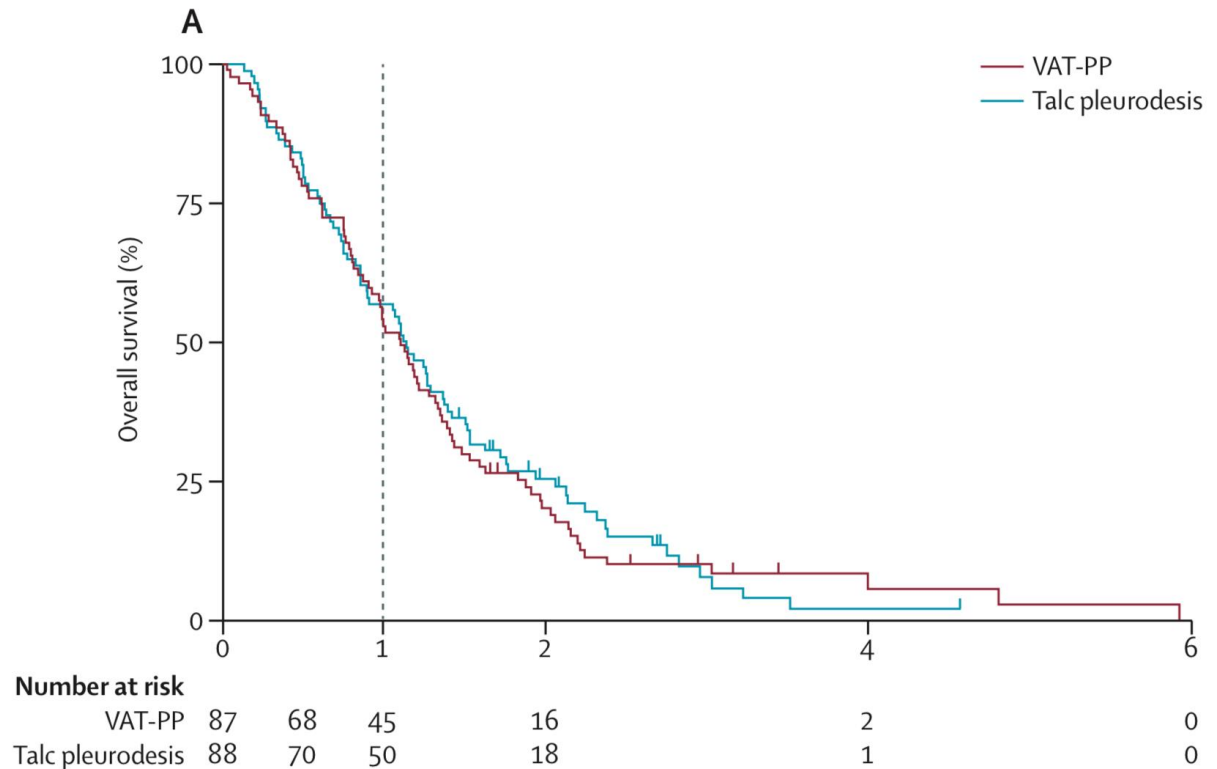
- Menor morbi-mortalidade cirúrgica;
- Viável em pacientes com pior reserva cardiopulmonar.



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*

RCT
 Multicentric
 N=196 randomized patients



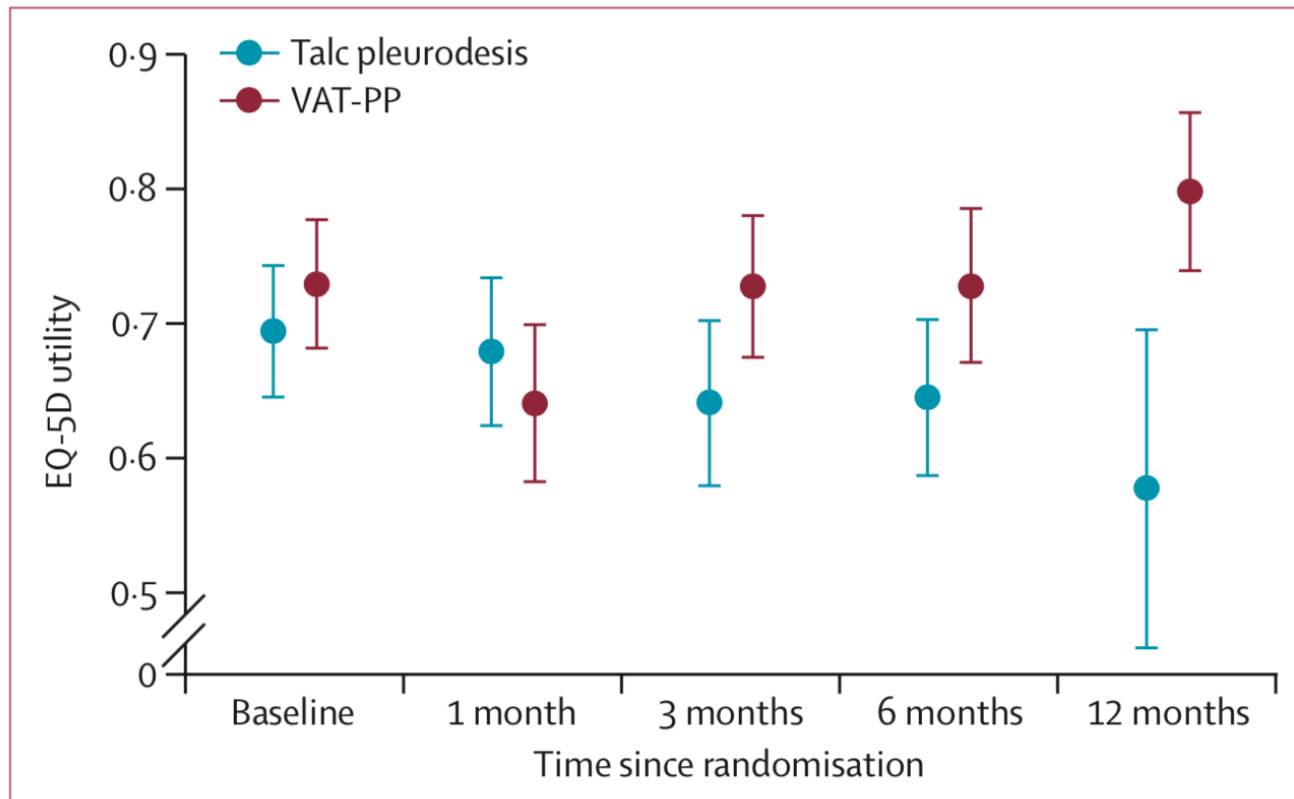
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	VAT-PP (n=78)	Talc pleurodesis (n=73)
Serious adverse events	13 (17%)	8 (11%)
Death	1 (1%)	0
Extended hospital stay		
Renal failure	1 (1%)	0
Surgical emphysema	1 (1%)	0
Repeat VAT-PP and subsequent CVA	2 (3%)	0
Fever and dyspnoea	0	1 (1%)

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

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

Raja M. Flores, MD,^a Harvey I. Pass, MD,^d Venkatraman E. Seshan, PhD,^b Joseph Dycoco, BA,^a
Maureen Zakowski, MD,^c Michele Carbone, MD,^e Manjit S. Bains, MD,^a and Valerie W. Rusch, MD^a

- Coorte retrospectiva
- Três centros dos EEUU
- Objetivos: análise de sobrevida e de fatores prognósticos
- 663 pacientes

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TABLE 1. Comparison of prognostic variables among patients undergoing extrapleural pneumonectomy and pleurectomy/decortication

	EPP (n = 385)	P/D (n = 278)	P value
Age (mean)	60 y	63 y	<.001
Male gender	316 (82%)	220 (79%)	.267
Epithelioid histology	269 (69%)	178 (64%)	.090
Early stage (I + II)	96 (25%)	98 (35%)	<.001
Asbestos exposure	231 (60%)	149 (54%)	.080
Laterality (right)	217 (56%)	173 (62%)	.156
Multimodality therapy	266 (69%)	161 (58%)	.002

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

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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.

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

Raja M. Flores, MD,^a Harvey I. Pass, MD,^d Venkatraman E. Seshan, PhD,^b Joseph Dycoco, BA,^a Maureen Zakowski, MD,^c Michele Carbone, MD,^e Manjit S. Bains, MD,^a and Valerie W. Rusch, MD^a

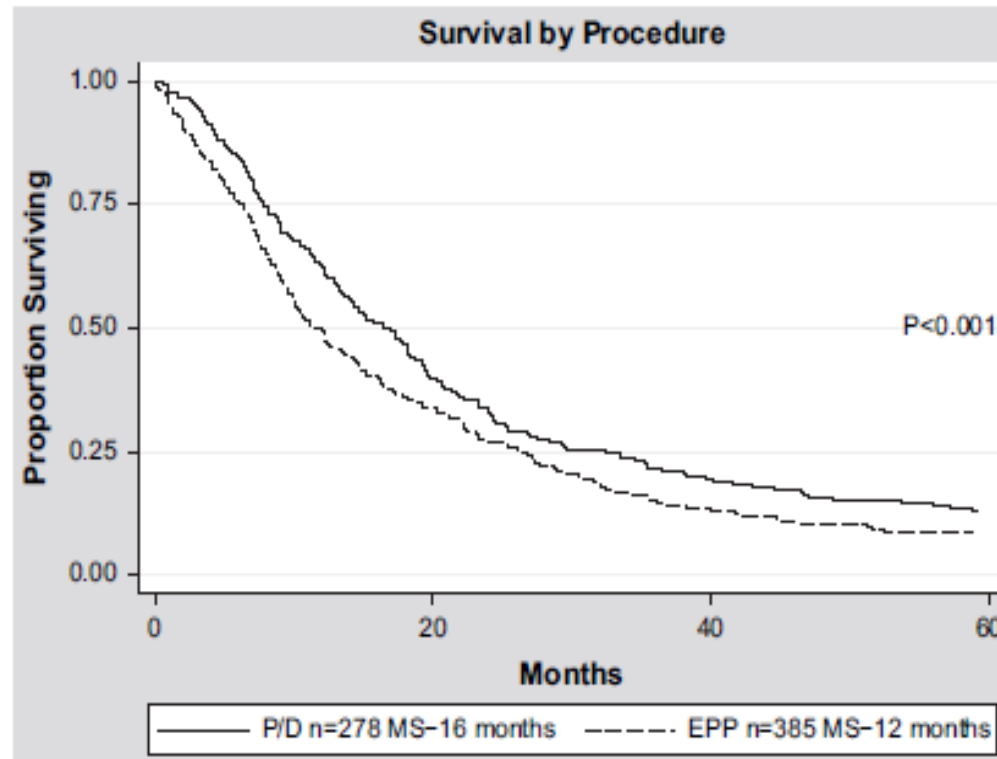


Figure 3. Overall survival of EPP versus P/D, by univariate analysis. *EPP*, Extrapleural pneumonectomy; *P/D*, pleurectomy/decortication.

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TABLE 3. Multivariate analysis of prognostic variables that were significant by univariate analysis

	Hazard ratio	Confidence interval	<i>P</i> value
Age	1.0	(1.01–1.02)	<i>P</i> < .001
Female gender	1.3	(1.05–1.64)	<i>P</i> = .02
EPP	1.4	(1.18–1.69)	<i>P</i> < .001
Non-epithelioid	1.3	(1.11–1.60)	<i>P</i> < .001
Stage III/IV	1.4	(1.28–1.55)	<i>P</i> < .001
Multimodality therapy	.45	(0.38–0.54)	<i>P</i> < .001

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Conclusões

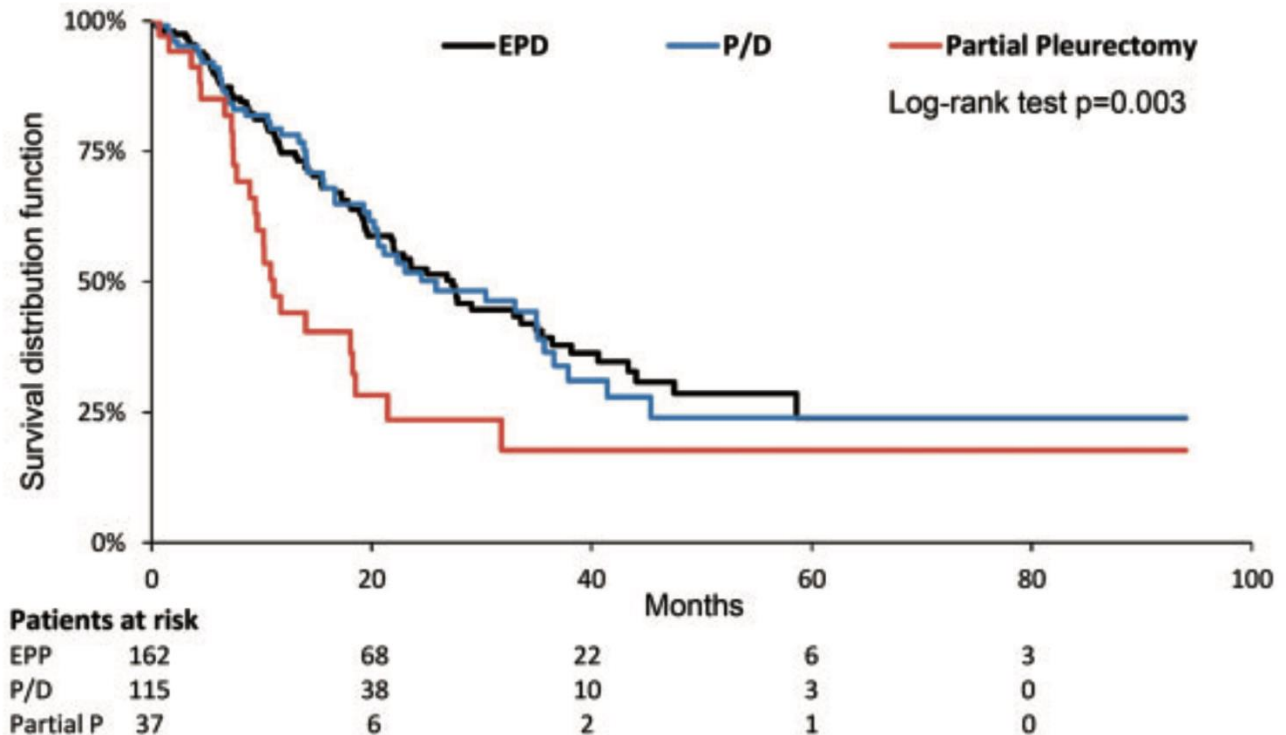
- Desfechos similares entre EPP e P/D
- Não permite definir melhor técnica

Pleurectomy-decortication in malignant pleural mesothelioma: are different surgical techniques associated with different outcomes?

Results from a multicentre study†

Giuseppe Marulli^{a,*}, Cristiano Breda^b, Paolo Fontana^b, Giovanni Battista Ratto^c, Giacomo Leoncini^c,
 Marco Alloisio^d, Maurizio Infante^d, Luca Luzzi^e, Piero Paladini^e, Alberto Oliaro^f, Enrico Ruffini^f,
 Mauro Roberto Benvenuti^g, Gianluca Pariscenti^g, Lorenzo Spaggiari^h, Monica Casiraghi^h, Michele Ruscaⁱ,
 Paolo Carbognaniⁱ, Luca Ampolliniⁱ, Francesco Facciolo^j, Giovanni Leuzzi^j, Felice Mucilli^k, Pierpaolo Campese^k,
 Paola Romanello^a, Egle Perissinotto^a and Federico Rea^a

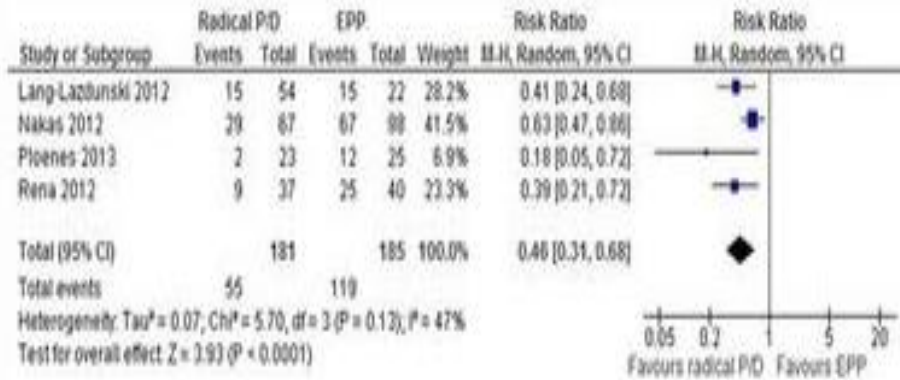
N=314
 Prospective



MO14.03 | Meta-analysis of extrapleural pneumonectomy versus radical pleurectomy for patients with resectable malignant pleural mesothelioma

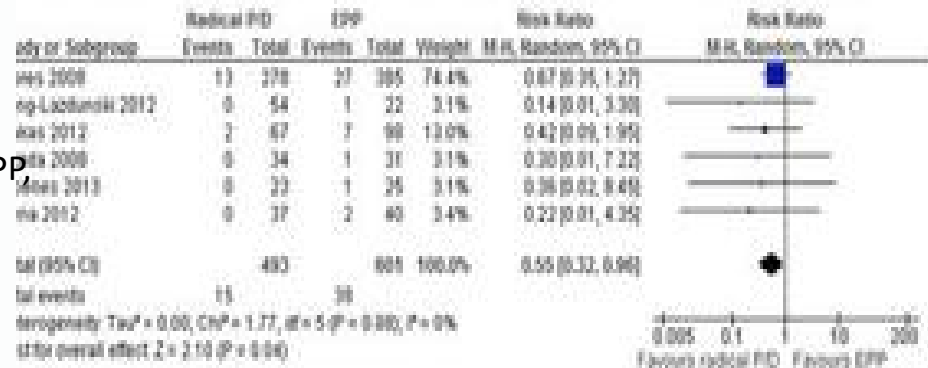
Authors: David Tian¹, Kristopher Pataky¹, Tristan D. Yan², Sheen Peeceeyen³, Christopher Cao¹

¹Collaborative Research Group, Sydney, NSW/AUSTRALIA, ²Collaborative Research Group, Sydney/AUSTRALIA, ³St. George Hospital, Sydney/AUSTRALIA



Significantly lower perioperative mortality (3.0% vs 6.5%, p=0.04) and overall morbidity (30.4% vs 64.3%, p<0.0001) for patients who underwent radical P/D compared to EPP.

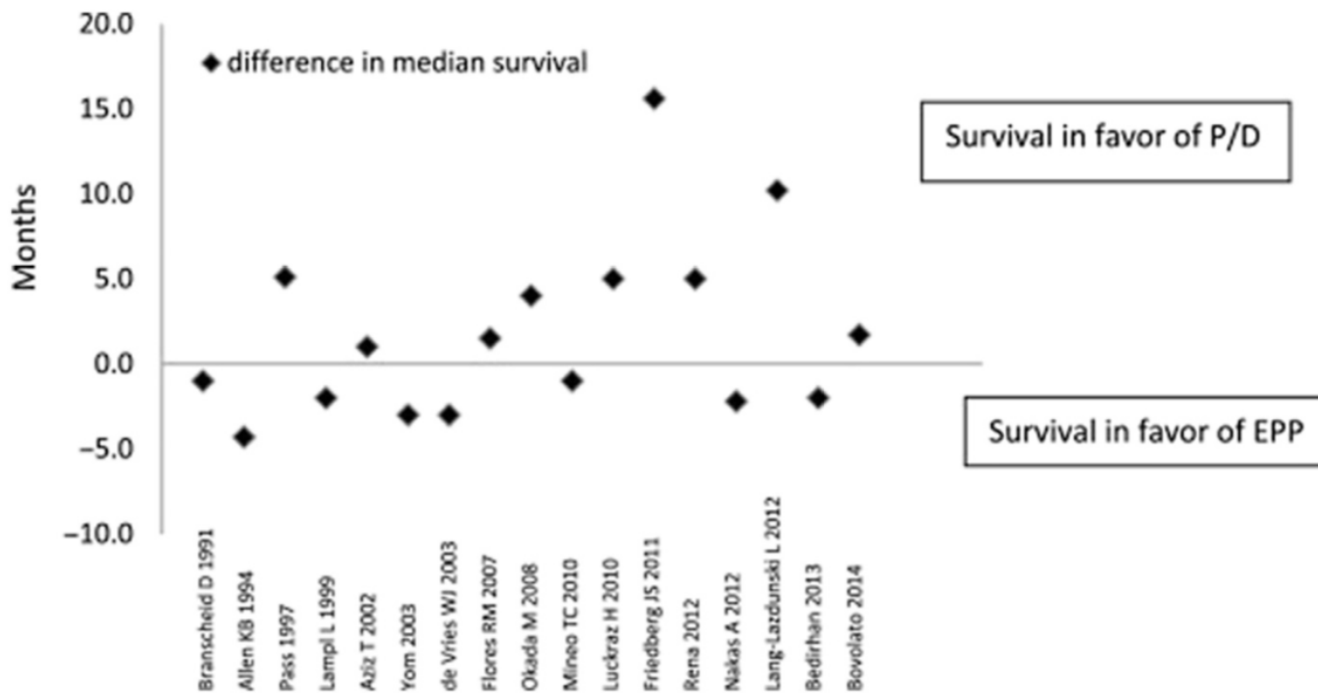
Median overall survival ranged between 13 – 29 months for radical P/D and 12 – 22 months for EPP with a strong trend favouring radical P/D.



Current Treatment of Mesothelioma

Extrapleural Pneumonectomy Versus Pleurectomy/Decortication

Andrea S. Wolf, MD, MPH, Raja M. Flores, MD*



Conclusion

- Overall Survival is low in spite of the treatment strategy
- Surgery supported by non-randomized evidence
- Uncertainty on the role of surgery and type of procedure
- EPP is associated with high morbi-mortality
- Radical pleurectomy emerges as na option