INTRODUCTION

- Malignant mesothelioma is an aggressive tumor originating in the serosal membranes → More than 90% of reported mesothelioma cases occur in the pleura
- The current epidemic of malignant mesothelioma is closely associated with past occupational exposure to asbesto
- Malignant pleural mesothelioma (MPM) → median survival of 9 months after diagnosis
- MPM presents unique challenges with regard to diagnosis and treatment

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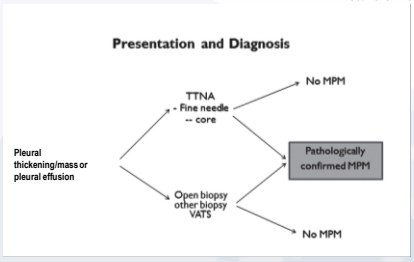
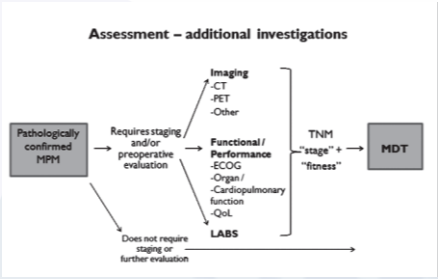
DIAGNOSIS

Journal of Thoracic Disease 2013



Recommendations	Grade*
1. CT-guided core biopsy or VAT-guided pleural biopsy is recommended—depending on the clinical circumstances—to obtain adequate tissue for histological analysis including immunohistochemistry, and has high sensitivity and specificity for the diagnosis of MPM.	A
2. Cytological recognition of an atypical mesothelial proliferation in pleural effusion fluid from patients may be sufficient for diagnosis in some patients when correlated with the clinical background and imaging studies, and when biopsy is considered inadvisable or unnecessary.	C



Recommendations	Grade*
14. FDG-PET is a more sensitive modality than CT to detect possible lymph node involvement and distant metastatic disease, and should be performed when the presence of disease in these sites will influence a management plan.	A
15. FDG-PET-CT should be used in preference to FDG-PET where available.	A

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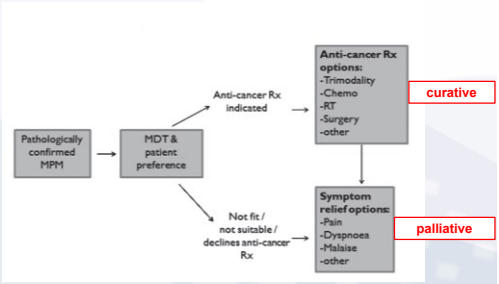
MULTIDISCIPLINARY TEAM



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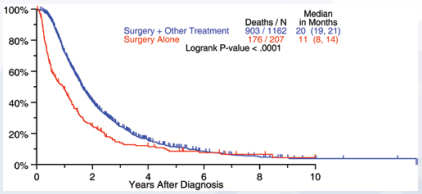
it is virtually impossible to resect the pleura with an adequate margin. Treatment strategies have therefore been developed to consolidate local control from surgery with radiotherapy and chemotherapy → trimodality treatment

Survival for patients managed with curative-intent surgery only versus multimodality therapy



p < 0.0001

Rusch, J Thorac Oncol 2012

Prospective multicenter phase II trials of radical trimodality treatment in MPM - CT + EPP + RT -

Variable	SAKK trial [11]	USA phase II trial [20]	EORTC 08031
Patients/institutions n/n	61/6	77/9	59/11
Induction regimen	Cis-gem ×3	Cis-pem ×4	Cis-pem ×3
Compliance to induction chemotherapy	95	83	93
EPP	45 (74)	54 (70)	42 (74)
Operative mortality	2.2	7	6.5
pCR rate	2.2	5	4.8
PORT completed	36 (59)	40 (52)	37 (65)
OS months			
ITT	19.8 (14.6-24.0)	16.8 (13.6-23.2)	16.4 (15.6-32.1)
PP	23.0 (16.6-32.9)	21.9 (16.8-29.1)	21.5 (17.6-NR)
Local relapse n (% PP)	NS	11 (28)	6 (16)
PFS months			
ITT	13.5 (10.2-18.8)	10.1 (8.6-15.0)	13.9 (10.9-17.2)
Median overall treatment time (range) days	NS	NS	193 (162-220)

SAKK trial → Weder W, Ann Oncol 2007
USA phase II trial →Krug LM, J Clin Oncol 2009
EORTC 08031 → Van Schil P, Eur Resp J 2010

PROGNOSTIC FACTORS

TABLE 3. Cox Regression Model of Survival, Including Best Stage, Histology, Sex, and Age (n = 2107)

Variable	Hazard Ratio	p
II vs. I	1.16	0.1153
III vs. I	1.47	<.0001
III vs. II	1.27	0.0002
IV vs. I	1.86	<.0001
IV vs. III	1.26	0.0008
Other histology vs. epithelial	1.70	<.0001
Male vs. female	1.28	0.0002
Age, yrs		
50–45 vs. <50	1.23	0.0058
65+ vs. <50	1.31	0.0006
65+ vs. 50–64	1.07	0.2500
Palliative vs. curative surgery	1.71	<.0001

Rusch, J Thorac Oncol 2012

Overall tumor stage ($p < 0.0001$), tumor histology ($p < 0.0001$), patient sex ($p = 0.0002$) and age ($p = 0.0025$), and type of operation (curative versus palliative, $p < 0.0001$) had a statistically significant impact on survival.

SURGERY

- VATS + pleurodesis/pleurectomy → palliative
- Pleurectomy/decortication → debulking/radical
- Extrapleural pneumonectomy → radical

curative

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Initial Analysis of the International Association For the Study of Lung Cancer Mesothelioma Database

Valerie W. Rusch, MD,* Dorothy Giroux,† Catherine Kennedy,‡ Enrico Ruffini,§ Ayten K. Cangir,‖ David Rice,¶ Harvey Pass,# Hisao Asamura,** David Waller,†† John Edwards,†† Walter Weder,‡‡ Hans Hoffmann,§§ Jan P. van Meerbeeck,‖‖ on behalf of the IASLC Staging Committee and participating institutions

J Thorac Oncol 2012

Data included 3101 patients (15 centers, 4 continents)

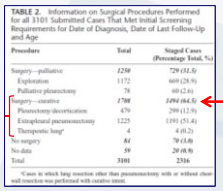
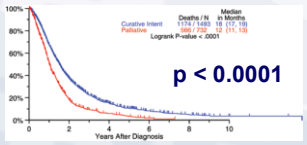


TABLE 2. Information on Surgical Procedures Performed for all 3101 Submitted Cases That Met Initial Screening Requirements for Date of Diagnosis, Date of Last Follow-Up and Age

Procedure	Total	Staged Cases (Percentage Total, %)
Surgery—palliative	1250	729 (31.5)
Exploration	1172	669 (28.9)
Palliative pleurectomy	78	60 (2.6)
Surgery—curative	1708	1094 (64.3)
Pleurectomy/decortication	670	299 (12.9)
Extrapleural pneumonectomy	1225	1191 (51.4)
Therapeutic lung*	4	4 (0.2)
No surgery	84	78 (3.4)
No data	59	20 (0.9)
Total	3101	2316

*Cases in which lung resection other than pneumonectomy with or without chest wall resection was performed with curative intent.



This is the largest international database examining outcomes in surgically managed MPM patients.

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

Raja M. Flores, MD,* Harvey I. Pass, MD,† Venkatraman E. Seshan, PhD,‡ Joseph Dycoco, BA,* Maureen Zakowski, MD,* Michele Carbone, MD,† Manjit S. Bains, MD,* and Valerie W. Rusch, MD*

J Thor Cardiovasc Surg 2008

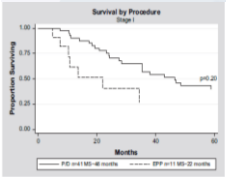
From 1990 to 2006, 663 consecutive patients underwent resection

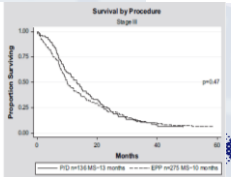
The operative mortality → 7% for EPP (27/385)
4% for P/D (13/278)

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

	EPP (n = 298) n (%)	P/D (n = 130) n (%)
Local recurrences	73 (33%)	46 (65%)
Ipsilateral chest	66 (31%)	84 (63%)
Pericardium	5 (2%)	2 (2%)
Distant recurrences	146 (64%)	47 (35%)
Contralateral lung/pleura	49 (22%)	14 (11%)
Peritoneum	57 (28%)	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.





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P/D

- Adequate cytoreduction, especially for patients with earlier stage tumors
- Associated with a lower morbidity and mortality than EPP
- Part of a multimodality treatment program in conjunction with therapies such as intrapleural or systemic chemotherapy, and intensity-modulated radiation therapy

EPP

- More frequently allows a complete removal of all gross tumor (R0/R1 resection)
- Advanced stage
- Increasingly acceptable rates of morbidity and mortality
- Facilitates the administration of postoperative high-dose hemithoracic radiation → excellent local control

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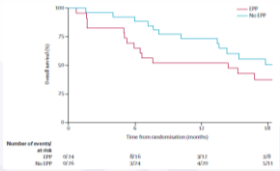
Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study



Bias

- EPP-associated morbidity (11/16; 69%) and mortality (3/16; 19%) were much higher than reported in the literature
- Quality control of the surgery in the MARS trial was not reported
- Neither final histologic type nor disease stage was reported for the patients who underwent surgery
- The chemotherapy regimens applied were uncontrolled

It was designed as a pilot feasibility trial to examine the potential benefits of EPP compared with chemotherapy alone → 55,4% did not proceed to random

Nine Italian referral centers 2000 and 2010

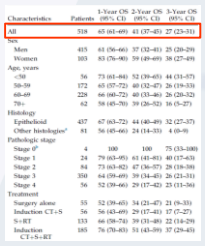
↓

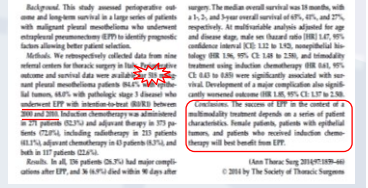
518 EPP

Morbidity (major) 26%
90 days mortality 6.9%

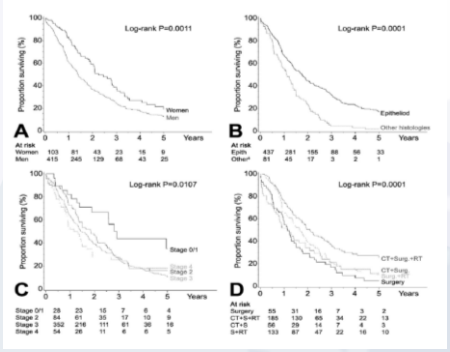
Extrapleural Pneumonectomy for Malignant Mesothelioma: An Italian Multicenter Retrospective Study

Lorenzo Spaggiari, MD, PhD, Giuseppe Marulli, MD, Pietro Bovolato, MD, Marco Alloisio, MD, Vittore Pagan, MD, Alberto Oliaro, MD, Giovanni Battista Ratto, MD, Francesco Facciolo, MD, Rocco Sacco, MD, Daniela Brambilla, MS, Patrick Maisonneuve, Eng, Felice Mucilli, MD, Gabriele Alessandrini, MD, Giacomo Leoncini, MD, Enrico Ruffini, MD, Paolo Fontana, MD, Maurizio Infante, MD, Gian Luca Parisenti, MD, Monica Casiraghi, MD, and Federico Rea, MD, PhD





Median OS 18 months



Conclusions

- All patients with the diagnosis of MPM should be initially evaluated in a multidisciplinary setting, including medical oncology, radiation oncology, and surgery.
- Clinical staging (lymph node sampling, positron emission tomography, magnetic resonance imaging) should be performed before therapy.
- The histologic subtype should be identified by tissue biopsy before initiation of therapy.
- Surgical macroscopic complete resection and control of micrometastatic disease play a vital role in the multimodality therapy of MPM→ trimodality treatment
- The type of surgery (EPP or P/D) depends on clinical factors and on individual surgical judgment and expertise

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Thank you!!!