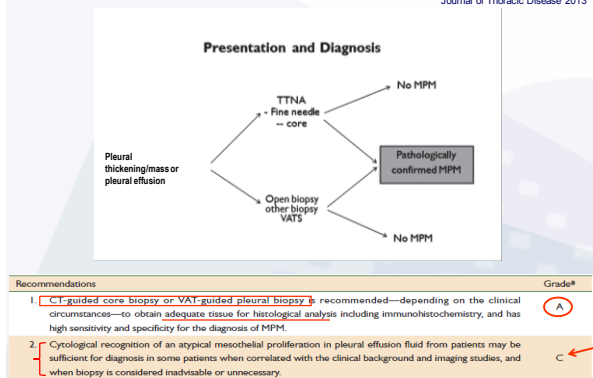


INTRODUCTION

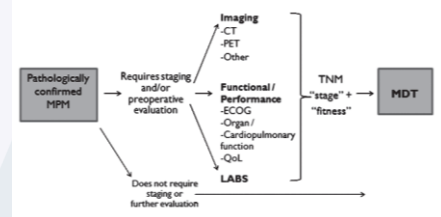
- Malignant mesothelioma is an aggressive tumor originating in the serosal membranes → More than 90% of reported mesothelioma cases occur in the pleura
- The current epidemic of malignant mesothelioma is closely associated with past occupational exposure to asbestos
- Malignant pleural mesothelioma (MPM)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

DIAGNOSIS

Journal of Thoracic Disease 2013



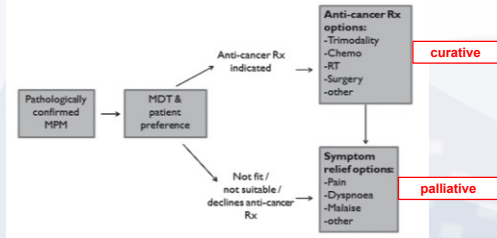
Assessment – additional investigations



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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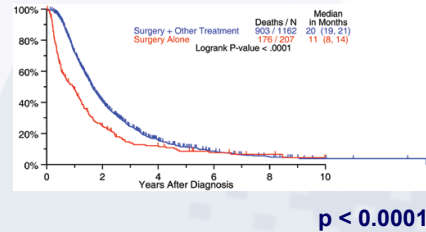
MULTIDISCIPLINARY TEAM



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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-pem ×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)	42 (52)	37 (63)
OS months	19.8 (14.6-24.9)	15.8 (13.6-23.2)	15.4 (15.6-32.3)
ITT	23.9 (16.6-32.5)	21.9 (16.8-29)	21.3 (17.6-148)
PP			
Local relapse n (% PP)	NS	11 (26)	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

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

Valerie W. Rusch, MD,* Dorothy Ginn,† Catherine Kennedy,‡ Enrico Ruffini,§ Aron K. Garg,|| David B. S. Harvey,¶ David R. Hoon,||§§ David Haffner,||§ John Edwards,||§§ Walter Hudes,||§§ Hans Hoffmann,||§§ Jan P. van Meerbeek,||§§ on behalf of the IASLC Staging Committee and participating institutions

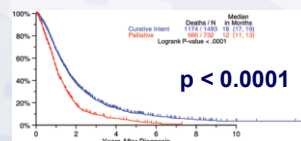
J Thorac Oncol 2012

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	Surgical Cases (Percentage Total, %)
Surgery—palliative	1238	729 (59.8)
Expleurotomy	1172	603 (51.4)
Pleurotomy/decortication	78	40 (51.3)
Surgery—curative	1768	1494 (84.5)
Pleurotomy/decortication	476	299 (62.8)
Extrapleural pneumonectomy	1225	1191 (97.2)
Thymoplastic lung*	4	4 (100)
No surgery	84	79 (94.0)
No data	29	29 (100)
Total	3101	2316

*Cases in which lung resection after first resection 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,* Venkatesan E. Seshan, PhD,* Joseph Dwyer, BA,* Maureen Zakowski, MD,* Michele Carbone, MD,* Manjiv S. Bains, MD,* and Valerie W. Rusch, MD*

J Thor Cardiovasc Surg 2008

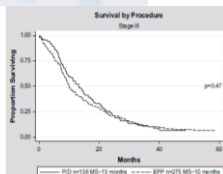
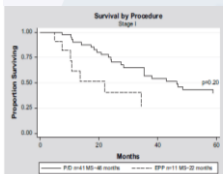
From 1990 to 2006, 663 consecutive patients underwent resection

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 = 385) (%)	P/D (n = 278) (%)
Local recurrences	73 (19%)	46 (16%)
Ipsilateral chest	68 (18%)	41 (15%)
Pericardium	5 (1%)	2 (1%)
Distant recurrences	166 (43%)	147 (53%)
Contralateral lung/pleura	10 (3%)	14 (5%)
Pleurectomy	37 (10%)	24 (9%)
Parietal/visceral + chest	17 (4%)	1
Abdominal viscera	12 (3%)	4 (1%)
Bone	1 (0%)	1
Brain	1	1
Cervical (distal)	1	1
Other	2	2 (1%)

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



P/D



EPP

- 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

- 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

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

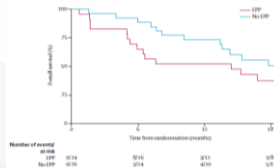
See [https://doi.org/10.1016/j.lan.2016.06.011](#) for the full-text version of this article, which includes the following supplementary information:

Summary
Background: The effects of extra-pleural pneumonectomy (EPP) on survival and quality of life in patients with malignant pleural mesothelioma have, to our knowledge, not been assessed in a randomised trial. We aimed to assess the clinical outcomes of patients who were randomised to EPP or no EPP in the context of intracavitary therapy in the Mesothelioma and Radical Surgery (MARS) feasibility study.

Methods: MARS was a randomised controlled trial in 12 UK hospitals. Patients aged 18 years or older who had pathologically confirmed mesothelioma and were deemed fit enough to undergo intracavitary therapy were included in a pre-randomisation registration phase. All patients underwent induction platinum-based chemotherapy followed by intracavitary therapy. After further consent, patients were randomised to EPP or no EPP followed by postoperative intracavitary therapy or to no EPP. Randomisation was done centrally with computer-generated permuted blocks stratified by surgical centre. The main outcome was feasibility of randomising patients to 1-year (median) survival in another cohort, proportion randomised who received treatment, proportion (range) improved who proceeded to randomisation, postoperative morbidity, and quality of life. Patients and investigators were not recruited to treatment allocation. This is the principal report of the MARS study; all patients have been treated. Analyses were by intention to treat. The trial is registered, number ISRCTN18315124.

Findings: Between Oct 1, 2005, and Nov 1, 2008, 111 patients were registered and 50 were subsequently randomised assigned to no EPP or to no EPP. The main reasons for not proceeding to randomisation were disease progression (11 patients), inoperability (five patients), and patient death (19 patients). EPP was completed successfully in 30 of 41 patients assigned to EPP in the patients EPP or no EPP group. Two patients in the EPP group died within 30 days and a further patient died of disease before hospital. The patient in the no EPP group died preoperatively while awaiting EPP and died in a care-home setting. The hazard ratio (HR) for overall survival between the EPP group and the no EPP group was 1.06 (95% CI 0.33–3.53; one-sided 95% CI 0.05–0.95). Median survival was 14 months (5–18.7) for the EPP group and 15 months (5–18.7) for the no EPP group. One patient in the EPP group and 10 in the no EPP group completed the quality of life questionnaire. Although median quality of life scores were lower in the EPP group than in the no EPP group, no significant difference in quality of life scores was reported in the quality of life analyses. There were no serious adverse events reported in the EPP group and two in the no EPP group.

Interpretation: In view of the high morbidity associated with EPP in this trial and in other non-randomised studies, a large trial is not feasible. These data, although limited, suggest that radical surgery in the form of EPP with intracavitary therapy offers no benefit and possible harm to patients.



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%

Characteristic	Patients	0-1 Year (%)	1-2 Year (%)	2-3 Year (%)	3-5 Year (%)	5-10 Year (%)
Age	518	65 (12.5)	43 (8.3)	27 (5.2)	27 (5.2)	27 (5.2)
Sex						
Male	435	61 (13.9)	37 (8.5)	21 (4.8)	20 (4.6)	20 (4.6)
Female	83	4 (4.8)	6 (7.2)	6 (7.2)	7 (8.4)	7 (8.4)
Age years						
<50	56	73 (13.0)	52 (9.3)	34 (6.1)	34 (6.1)	34 (6.1)
50-59	172	45 (26.2)	40 (23.3)	26 (15.1)	26 (15.1)	26 (15.1)
60-69	228	46 (20.2)	40 (17.5)	26 (11.4)	26 (11.4)	26 (11.4)
≥70	62	58 (93.9)	59 (95.2)	59 (95.2)	59 (95.2)	59 (95.2)
Histology						
Epithelial	437	67 (15.3)	44 (10.1)	32 (7.3)	32 (7.3)	32 (7.3)
Other histologies*	81	56 (69.0)	24 (29.6)	1 (1.3)	1 (1.3)	1 (1.3)
Pathologic stage						
Stage 0†	4	300 (75.0)	75 (18.8)	75 (18.8)	75 (18.8)	75 (18.8)
Stage 1	24	79 (32.9)	61 (25.4)	40 (16.7)	40 (16.7)	40 (16.7)
Stage 2	84	73 (86.9)	47 (56.1)	26 (31.0)	26 (31.0)	26 (31.0)
Stage 3	304	84 (27.6)	39 (12.8)	21 (6.9)	21 (6.9)	21 (6.9)
Stage 4	56	52 (92.9)	29 (51.8)	21 (37.5)	21 (37.5)	21 (37.5)
Treatment						
Surgery alone	55	32 (58.2)	34 (61.8)	21 (38.2)	21 (38.2)	21 (38.2)
Induction CT±S	56	54 (96.4)	29 (51.8)	17 (30.4)	17 (30.4)	17 (30.4)
S±P	133	46 (34.6)	39 (29.3)	22 (16.5)	22 (16.5)	22 (16.5)
Induction CT±S±P	185	76 (41.1)	51 (27.6)	27 (14.6)	27 (14.6)	27 (14.6)

Extrapleural Pneumonectomy for Malignant Mesothelioma: An Italian Multicenter Retrospective Study

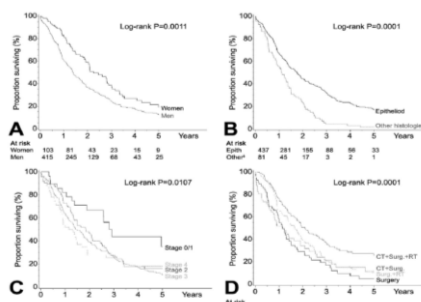
Luigi Spaggiari, MD, PhD, Giuseppe Marulli, MD, Pietro Boslata, MD, Marco Aliberti, MD, Vittorio Pagan, MD, Alberto Olivo, MD, Giovanni Battista Ratto, MD, Francesco Facchini, MD, Rocco Sacca, MD, Daniela Brambilla, MS, Patrick Maisonneuve, Eng, Felice Macrilli, MD, Gabriele Alessandrini, MD, Giacomo Leoncini, MD, Enrico Ruffini, MD, Paolo Fontana, MD, Maurizio Infante, MD, Gian Luca Pariscenti, MD, Monica Castagnoli, MD, and Federico Rea, MD, PhD

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Background: This study assessed postoperative outcome and long-term survival in a large series of patients with malignant pleural mesothelioma who underwent extrapleural pneumonectomy (EPP) to identify prognostic factors allowing better patient selection. **Methods:** We retrospectively collected data from nine selected centers for thoracic surgery in Italy. **Results:** Between 2000 and 2010, 518 patients underwent EPP for malignant pleural mesothelioma. Median survival was 18 months, with a 5-, 10-, and 15-year overall survival of 48%, 27%, and 21%, respectively. At multivariate analysis adjusted for age and disease stage, male sex (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.02 to 1.35), nonepithelial histology (HR 1.36, 95% CI 1.08 to 1.70), and intravital treatment using induction chemotherapy (HR 0.64, 95% CI 0.40 to 1.03) were significantly associated with survival. Development of a major complication also significantly increased mortality (HR 1.86, 95% CI 1.37 to 2.58). **Conclusions:** The reasons of EPP in the context of a multimodality treatment depend on a series of patient characteristics. Female patients, patients with epithelial tumors, and patients who received induction chemotherapy will benefit from EPP.

(Ann Thorac Surg 2014;97:1030-40)
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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 trimodality therapy of MPM → trimodality treatment
- The type of surgery (EPP or P/D) depends on clinical factors and on individual surgical judgment and expertise

Thank you!!!

Milano si colora
di Expo 2015

