WORK-UP, STAGING AND SURGICAL TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA
Department Thoracic Surgery, Leuven, Belgium

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Introduction

- Introduction
- Place for surgery?
- Staging
- UZLeuven work-up, staging and treatment protocol
- EPP and ePD
- Leuven experience
The Belgian issue

Nawrot, Lancet 2007
Treatment

- Low incidence → no golden standard treatment
- Multiple treatment options:
  - Chemotherapy
  - Radiotherapy
  - Immunotherapy
  - Surgery
  - ........
Multi (TRI) modality treatment

- **EPP - chemotherapy – radiotherapy**
  - (different schemes)
  - (30-40-14Gy)

<table>
<thead>
<tr>
<th></th>
<th>2 year-survival</th>
<th>5 year-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Epithelial, R0, N0</strong></td>
<td>68%</td>
<td>46% median 51 mo</td>
</tr>
<tr>
<td><strong>Sarcomatous, mixed:</strong></td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**BUT:**

Low tolerance to adjuvant treatment
Recurrences

Sugarbaker, J Thorac Cardiovasc Surg 1999
Multimodality treatment

- Chemotherapy-EPP-radiotherapy
  (cisplatin-gemcitabin) (30-20 Gy)

n=72 1999-2003 T1-T3, N0-2,M0, all types

Response rate: 32%
Postoperative mortality: 6.25%
Overall median survival: 23 months

Weder, J Clin Oncol 2004
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*

**Interpretation** In view of the high morbidity associated with EPP in this trial and in other non-randomised studies a larger study is not feasible. These data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.
BUT....

- Feasibility study
- No “intention to treat” analysis
  - 42% of patients were randomized
- Limited number of patients (EPP 16 patients)
- Chemotherapy non standardized
  - Type, duration, interval, ...
- Non-surgical arm were operated (N=3)
- Mortality EPP: 18%?

Weder, Lancet Oncol 2011
Place for surgery?

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Is surgery necessary?

- National Cancer Database (ACS) 2004-2014
- 1:2 match (surgical vs non-surgical)
Impact surgery on survival

Nelson, J Clin Oncol 2017
Impact of MPM type

Nelson, J Clin Oncol 2017
Impact multimodality treatment

Nelson, J Clin Oncol 2017
Staging

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Importance of staging

- **Accurate staging is essential:**
  - Define best treatment option
  - Evaluate response to treatment
    - Modified RECIST criteria
  - Accurate selection of patients
TNM 7

Stage Ia
T1a N0
- Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura
- No involvement of the visceral pleura

Stage Ib
T1b N0
- Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura
- Scattered tumor foci involving visceral pleura

Stage II
T2 N0
- Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) and having at least one of the following features:
  - Confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into underlying pulmonary parenchyma
  - Involvement of the visceral pleura
  - Involvement of the diaphragmatic muscle

Stage III
Any T3, Any N1, Any M1
- Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) and having at least one of the following features:
  - Involvement of the esophageal fascia
  - Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
  - Extension into the mediastinal fat
  - Non-transmural involvement of the pericardium

Stage IV
Any T4, Any N2, Any M1
- Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) and having at least one of the following features:
  - Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
  - Direct extension of tumor to the contralateral pleura
  - Direct extension of tumor into the mediastinum
  - Direct extension of tumor to one or more mediastinal organs
  - Tumor extending through the internal surface of the pericardium or with or without a pericardial effusion, or tumor involving the myocardium
  - Direct transdiaphragmatic extension of tumor to the peritoneum

TNM 8

T1
- Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura
- No involvement of the visceral pleura

Stage II
T2 N0
- Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) and having at least one of the following features:
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N1
- Metastasis in the ipsilateral bronchopulmonary or hilar lymph nodes

N2
- Metastasis in the ipsilateral mediastinal lymph nodes
- Metastasis in the ipsilateral paratracheal lymph nodes
- Metastasis in the ipsilateral subcarinal lymph nodes
- Metastasis in the ipsilateral external lymph nodes, including the ipsilateral paratracheal and contralateral supraclavicular lymph nodes
Table 4 Comparison of stage groupings as defined by the seventh and eighth edition of the TNM classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage grouping for the seventh edition</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>I</td>
<td>T1a</td>
<td>N0</td>
</tr>
<tr>
<td>IA</td>
<td>T1b</td>
<td>N0</td>
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<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
</tr>
<tr>
<td>III</td>
<td>T1,2</td>
<td>N1,2</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0–2</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>Any N</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N3</td>
</tr>
</tbody>
</table>
UZLeuven work-up, staging and treatment protocol

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Pre-op evaluation:
ERS/ESTS/EACTS/ESTRO guidelines

- Before any type of treatment

  - X ray: unilateral, concentric pleural thickening

  - Chest CT/PET-CT: Concentric pleural thickening, pleural effusion
Biopsy

- Needle biopsy (CT-guided)

- VATS biopsy + TALCAGE
  
  CAVE/ Local soiling

  => UNIPORTAL (5th/6th IC space)

  Decreases morbidity and renders ePD more feasible
If suitable for surgery/chemotherapy

- **PET-CT**: unilateral, concentric pleural thickening

  ! Low sensitivity for stage N1 (38%) and T4 (67%)

  ! If talc pleurodesis => sensitivity decreases

- **MRI**: Concentric pleural thickening, pleural effusion

  Superior for disease margins (vessels, diaphragm, multifocal chest wall invasion)

- **Brain CT/MRI**: excluding metastases

*Role of PET-MRI ?? => research*
Functional evaluation (after talcage)

- Spirometry
- Cyclo-ergometry
- Cardiac ultrasound (+ carotic vessels)
- V/Q scintigraphy
- Age? (estimate biological age); no strict limit
### Table 4: Comparison of stage groupings as defined by the seventh and eighth edition of the TNM classification

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<th>N</th>
<th>M</th>
<th>T</th>
<th>N</th>
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<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>T2,3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>T1,2</td>
<td>N1</td>
<td>M0</td>
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<td>Any N</td>
</tr>
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</table>
Invasive surgical staging

- **Videomediastinoscopy** $n=82$
  - Downstaging $3.66\%$ ($n=3$)
  - Upstaging $10.96\%$ ($n=9$)

- **Laparoscopy** $n=74$
  - Invasion $2.70\%$ ($n=2$)
  - $M^+$ perit $2.70\%$ ($n=2$)

$\Delta$ of treatment in $19.28\%$ ($n=16$)

$\rightarrow$ 3 surgical + 13 non-surgical

Nafteux, Ceulemans
unpublished data
Invasive surgical staging: NEGATIVE

- Bi-modal therapy
  - Induction chemotherapy
    *Cisplatin / Pemetrexed; 3 cycles/3 weeks*

- PET-CT / MRI (modified RECIST, volumetry)

SECOND MOC

- Surgery
  - EPP / extended PD
EPP versus ePD technique

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Surgical technique

- Extrapleural pneumonectomy (EPP)
  - Pneumonectomy
  - Diaphragmatic/pericardial resection

- (extended) pleurectomy/decortication (e P/D)
  - Lung-savind
  - Diaphragmatic/pericardial resection

INTRA-OP Decision

e P/D additional value for those with functional limitation
First step: extrapleural dissection
EPP-eP/D: extrapleural dissection
EPP-eP/D: extrapleural dissection
EPP-ePD: diaphragma resection
EPP: Intrapericardial pneumonectomy
EPP
Diaphragmatic reconstruction
Reconstruction after EPP
ePleurectomy-decortication
ePleurectomy-decortication
EPP vs ePD

Figure 3: This graph compares the various studies of EPP versus P/D in terms of median survival. The median survival scatter is greater with EPP but there is a very similar range between EPP and P/D with the vast majority of studies showing a median survival of between 8 and 21 months.
# EPP vs ePD: retrospective

<table>
<thead>
<tr>
<th>Primary author and year</th>
<th>Total number of patients</th>
<th>Number of patients (EPP/PD)</th>
<th>EPP/PD morbidity (%)</th>
<th>EPP/PD mortality (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flores, 2008 (6)</td>
<td>663</td>
<td>385/278</td>
<td>10/6.4</td>
<td>7/4</td>
<td>12/16*</td>
</tr>
<tr>
<td>Burt, 2014 (7)</td>
<td>225</td>
<td>95/130</td>
<td>Higher in EPP*</td>
<td>10.5/3.1</td>
<td>12/16*</td>
</tr>
<tr>
<td>Batirel, 2016 (8)</td>
<td>130</td>
<td>42/66</td>
<td>20/5</td>
<td>7/2</td>
<td>18.3/14.6</td>
</tr>
<tr>
<td>Sharkey, 2016 (9)</td>
<td>362</td>
<td>133/229</td>
<td>Higher in EPP*</td>
<td>6/3.5</td>
<td>12.9/12.3</td>
</tr>
</tbody>
</table>

Two of the studies (7,8) compared the results of two periods following an intentional transition from an EPP predominant practice to a P/D predominant practice. *, P<0.001; **, early and late reoperation, bleeding, bronchopleural fistula, ARDS, Sepsis, atrial arrhythmias, right heart failure and ileus were significantly higher in EPP patients, whereas prolonged air leak was higher in P/D patients. NS, not stated.

Batirel, Ann Transl Med 2016
EPP vs ePD: pro’s and con’s

- **EPP:**
  - More radical
  - More aggressive (mortality?, complications)

- **eP/D:**
  - More patients treated
  - Comparable survival
  - Less morbidity / less mortality (?)
  - Improved QoL

Wald, Annu Rev Med 2018
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**.
UZ Leuven experience

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Experience Leuven 2003-2014

- Neoadjuvant chemotherapy
  - Pemetrexed 500 mg/m² – cisplatin 75mg/m² 3 cycles, every 3 weeks

- Surgery
  - Extrapleural pneumonectomy (if no progression)

- Hemithoracic Radiotherapy
  - IMRT;
  - 54GY/1,8Gy

All histologic subtypes

Frick, EJCTS 2018
Complications

- **90-day mortality:** 3.6%
  - ARDS (n=1)
  - Empyema (n=1)

- **Morbidity:** 62.5%
  - Bleeding (n=1)
  - Chylothorax (n=1)
  - AF (n=18)
  - ARDS (n=3)
  - DVT (n=1)
  - > 48 h intubation (n=8)

Surgical complications: 5.2%
- No fistula
- No patch dehiscence
Overall survival, intention to treat

* 90-day mortality after EPP (n=2): 3.6%

CMT= combined modality treatment
Safety and impact of hemithoracic RT?

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

- Adjuvant RT no clinical benefit
- Increased morbidity
Conclusions

- maximal surgical cytoreduction should be performed (1,1)
- single modality generally insufficient (1,2)
- cytoreduction: EPP or eP/D (3,0)
- when possible: preferably eP/D (3,0)
- sarcomatoid type, N2, T4: no surgical indication (2,1)

Kindler, J Clin Oncol 2018
"...And one last thing, our health insurance doesn't cover mesothelioma. When can you start?"