Pleural Mesothelioma

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University Hospital Zurich, Division of Thoracic Surgery
John G. Edwards «How Has the «Mars» Trial Affected the Surgical Approach to Malignant Pleural Mesothelioma»

MS12.1: How Has the 'MARS' Trial Affected the Surgical Approach to Malignant Pleural Mesothelioma?

Mr. John G. Edwards PhD FRCS(C/Th)
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Northern General Hospital
United Kingdom

Sheffield Teaching Hospitals NHS
Sheffield Thoracic Institute
NHS Foundation Trust
British Randomised Trials of Surgical Resection of MPM

- EPP feasibility
- VATS Partial Pleurectomy phase III
- Extended P/D

MARS reported 14th WCLC
MesoVATS reported 15th WCLC
MARS-2 opens 2013/4
Current and Future Trials

- Current Phase II trials:
  - NCT00895648  Toronto  Trimodality (?)
  - NCT00797719  Toronto  IMRT then EPP
  - NCT01258868  NIHCC  Adjuvant autologous tumour cell vaccine (?)
  - NCT01644994  Zurich  intracavitary chemo after P/D
  - NCT00859495  Columbia NY  intracavitary/systemic chemo after P/D
  - NCT01265433  MSKCC  WT-1  vaccine after P/D or EPP
  - NCT00715611  MSKCC/MDACC  chemo +/- P/D

www.clinicaltrials.gov
Answered Questions

• A prospective RCT of EPP in the UK is not feasible

• There may be a role for “MesoVATS” VATS Partial Pleurectomy in symptom control
Unanswered Questions

• Does Extended Pleurectomy/Decortication improve survival and quality of life, compared to no surgery?

• Does a role remain for EPP in Stage I MM?
Pleurectomy Decortication vs. Extrapleural Pneumonectomy

JESSICA S. DONINGTON MD,
NYU SCHOOL OF MEDICINE,
DEPARTMENT OF CARDIOTHORACIC SURGERY,
NEW YORK, NY, USA,
What do we do?

- Preferentially P/D for minimal bulky disease with diaphragm and pericardial resection (if invaded) and MLND
- This is our first choice if it is possible in the OR

- Preferentially EPP for moderate to major bulky disease with diaphragm and pericardial resection and MLND
Recommendations

IASLC/IMIG
• P/D or EPP should be performed with the goal of obtaining MCR, and as part of a multimodality treatment approach
• Type of resection should be selected on the basis of
  ✤ disease distribution,
  ✤ institutional experience
  ✤ surgeon preference and experience

Rusch V, JTO, 2012.
Future Directions

- **MARS-2**
  Induction chemo + Ext-P/D vs. chemo alone

- **EORTC 1205**
  cT1-3No-2M0
  UICC TNM

  4 cycle cisp/pem → P/D
  P/D → 4 cycle cisp/pem
Allan Price «Locoregional Management of Malignant Pleural Mesothelioma»
Perioperative radiotherapy in MPM - conclusions

- Evidence base for surgery very poor
  - EPP high early mortality
  - Pleurectomy anecdotal reports only
- Evidence base for radiotherapy zero
  - No completed prospective studies
  - Complexity of techniques which might be useful constrains prospective studies
- Randomised trial of chemotherapy ± pleurectomy + secondary randomisation to VMAT
- Or just carry on as now without any evidence at all
EXPOSURE-RESPONSE RELATIONSHIP OF AMATUXIMAB IN COMBINATION WITH Pemetrexed and Cisplatin in Patients with Unresectable Pleural Mesothelioma

Bruce A. Wallin, Julia D. Maltzman, Anubha Gupta, Jason Wustner, Raffit Hassan
MORAb-009-003 Trial Design

- Amatuximab 5mg/kg Days 1 and 8 of 21 day cycle
- Pemetrexed 500mg/m2 on Day 1 of cycles 1-6
- Cisplatin 75mg/m2 on Day 1 of 1-6 cycles
- Folic Acid, B12, and Dexamethasone

- Unresected MPM
- No prior systemic therapy
- Epithelial or biphasic type

Phase 2, open-label, multicenter, single-arm trial
- 89 subjects

After 6 cycles, continue maintenance Amatuximab days 1 and 8 of 21 day cycle until PD
Amatuximab Exposure – OS relationship

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>1st Quartile</th>
<th>Median</th>
<th>2nd Quartile</th>
<th>Max</th>
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<tbody>
<tr>
<td>Observed Cmin (µg/mL)</td>
<td>0.10</td>
<td>8.08</td>
<td>38.2</td>
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<td>136</td>
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Amatuximab Average Pre-infusion Concentration for Last Three Assessment

Total N = 38 (out of the 39 enrolled)

log rank test p = 0.0202
**Amatuximab Exposure – PFS relationship**

<table>
<thead>
<tr>
<th>Observed Cmin (µg/mL)</th>
<th>Min</th>
<th>1st Quartile</th>
<th>Median</th>
<th>2nd Quartile</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.10</td>
<td>7.28</td>
<td>32.9</td>
<td>74.6</td>
<td>136</td>
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</table>

**Amatuximab Average Pre-infusion Concentration for Last Three Assessment**

Total N = 76 (out of the 89 enrolled)

log rank test p = 0.000 852
In the group of subjects in MORAb-009-003 who had Cmin concentrations above the population median Cmin:

- Median OS is 583 days (90% CI 418 – NE) or approximately 6 months better than what would be expected with standard of care (pemetrexed plus cisplatin)
- Median PFS is 238 days (90% CI 193-322) or 2 months better than what would be expected with standard of care (pemetrexed plus cisplatin)

By achieving this Cmin we anticipate that Amatuximab should provide a benefit in both OS and PFS
Andrea Billè «Does Surgery Improve Survival of Patients with Malignant Pleural Mesothelioma? A Multicenter Retrospective Analysis of 1365 Consecutive patients»

2962: Does surgery improve survival of patients with malignant pleural mesothelioma? A multicenter retrospective analysis of 1365 consecutive patients.

Andrea Billè MD

Department of Thoracic Surgery
Chief Dr. Ugo Pastorino
Fondazione IRCCS Istituto Nazionale dei Tumori
Milano
Material and Methods:

- 1365 consecutive patients with histologically proven MPM between September 1982 and September 2012 at six Italian Institutions
- Tissue diagnosis achieved by thoracoscopy \( n=1282 \) or open pleural biopsy \( n=83 \) under general anesthesia.
- 862 patients received medical treatment alone, consisting in either chemotherapy \( n=172 \) or best supportive care \( n=690 \); 503 patients received surgical treatment with or without chemotherapy, consisting in either P/D \( n=202 \) or EPP \( n=301 \)
- Sixty-eight patients \( n=19 \) in non surgical group, \( n=46 \) in P/D group, \( n=3 \) in EPP group) were lost at follow-up. The remaining 1297 patients were followed up until death or for a minimum period of one year.
Survival curves according to the treatment (non surgical treatment vs EPP vs P/D)

Median survival of the entire study population: 14.5 months

**Overall median survival**
- Non surgical group: 11.7 mo
- P/D group: 20.5 mo
- EPP group: 18.8 mo

**2 year survival rate**
- Non surgical group: 19%
- P/D group: 40%
- EPP group: 37%

2882: Does surgery improve survival of patients with malignant pleural mesothelioma? A multicenter retrospective analysis of 1366 consecutive patients. Andrea Billè, MD
Results

- Pemetrexed determined an improvement in survival in all 3 groups.

- In the EPP group the overall and major perioperative morbidity were 21.6% and 7.6% and the crude perioperative mortality at 30 and 90 days was 4.1% and 6.9%, respectively.

- In the P/D group the overall perioperative morbidity was 10.4%, the 30 and 90 day crude perioperative mortality rate was 2.6% and 6% after P/D.
Survival curves according to the treatment (non surgical treatment vs EPP vs P/D) considering only patients with independent favourable prognostic factors

Overall median survival

Non surgical group: 15.5 mo
P/D group: 19.4 mo
EPP group: 18.7 mo

Number at risk
No surgery 58
EPP 169
PD 86
Conclusions

➢ The best treatment for patients with malignant pleural mesothelioma remains controversial

➢ Our analysis confirmed that pemetrexed improved survival in all groups

➢ The multivariate analysis showed that age and histology were independent prognostic factors for survival

➢ Patients with positive prognostic factors showed a similar survival if they received chemotherapy alone, P/D or EPP. Survival might be slightly better for surgical patients

➢ In the surgical groups, our analysis showed similar survival after P/D or EPP with a lower postoperative morbidity and mortality after P/D.
Robert C. Rintoul «Randomized Controlled Trial of Video-assisted Thoracoscopic Pleurectomy Compared to Talc Pleurodesis in Patients with Confirmed or Suspected Malignant Pleural Mesothelioma: the MesoVATs Trial»
MesoVATs: Study objectives

Open label, parallel group, multicentre randomised controlled trial comparing VAT partial pleurectomy versus talc pleurodesis in malignant pleural mesothelioma

**Primary objective**: Survival at one year post randomisation

**Secondary objectives**:

- Quality of life at baseline and 1, 3, 6 and 12 months post treatment
- Control of pleural effusion at baseline and 1, 3, 6 and 12 months
- Complications
- Length of hospital stay
- Lung function at baseline and 1, 3, 6 and 12 months
MesoVATs: Randomisation

Randomised n=196

Confirmed n=120

Suspected n=76

Excluded
Non-Mesothelioma n=21
(10 Talc and 11 VAT pleurectomy)
Adenocarcinoma n=3
Benign n=15
Metastatic Carcinoma n=2
Unconfirmed malignancy at study endpoint n=1

Talc Pleurodesis n=88
Received Talc n=73

VAT Pleurectomy n=87
Received VATs n=78
MesoVATs: Overall survival

Kaplan-Meier survival estimates

Log-rank test, p=0.83

6m survival
Talc 80% VATs 78%

12m survival
Talc 57% VATs 52%

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<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>48</th>
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<tbody>
<tr>
<td>VAT Pleurectomy</td>
<td>87</td>
<td>68</td>
<td>45</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Talc Pleurodesis</td>
<td>88</td>
<td>70</td>
<td>50</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>
MesoVATs: Presence of pleural effusion

![Graph showing presence of pleural effusion over time with statistical significance](image)
MesoVATs: EQ5D QoL utility measure

![Graph showing EQ5D scores over time for Talc Pleurodesis and VATs Pleurectomy](image)

<table>
<thead>
<tr>
<th>Time period</th>
<th>Difference VATs-Talc, adjusted for baseline (95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td>1 month</td>
<td>-0.06 (-0.13, 0.004)</td>
<td>0.06</td>
</tr>
<tr>
<td>(N=137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>0.04 (-0.03, 0.12)</td>
<td>0.267</td>
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<tr>
<td>(N=129)</td>
<td></td>
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<tr>
<td>6 months</td>
<td>0.08 (0.003, 0.16)</td>
<td>0.042</td>
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<tr>
<td>(N=109)</td>
<td></td>
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<tr>
<td>12 months</td>
<td>0.19 (0.05, 0.32)</td>
<td>0.006</td>
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<tr>
<td>(N=68)</td>
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</table>
MesoVATs: Summary

There was no difference in overall survival between VAT partial pleurectomy and Talc pleurodesis

VAT partial pleurectomy improved control of pleural effusion and EQ5D quality of life

Should VAT partial pleurectomy be considered in patients with mesothelioma for symptom control?