Surgery for Lung Cancer and Malignant Pleural Mesothelioma

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I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.
Summary provided in:

ESMO Thoracic Tumors: Essentials for Clinicians
Chapter 5
Hoda & Klepetko
available at Oncology PRO or by......
Overview
Surgery for early stage NSCLC
Surgery for locally advanced disease
Surgery for oligometastatic disease
Palliative treatment options
Role of surgery in SCLC
Summary
NSCLC – Outcome and treatment depends on staging

Goldstraw et al, JTO 2015

Can we do better?
Old treatment paradigm

Stage

I
Surgery

II

III
Radiotherapy
Chemotherapy

IV
Modern treatment algorithm

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>IB</th>
<th>IIA</th>
<th>IIB</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IIC</th>
<th>IVA</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>Chemo</td>
<td>RT</td>
<td>Chemo</td>
<td>Chemo</td>
<td>RT</td>
<td>Chemo-, Immuno- and targeted therapy</td>
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</tbody>
</table>

Surgery
# The New Kids on the Block

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>Immuno TKI</td>
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<tr>
<td>IIB</td>
<td>Immuno TKI</td>
</tr>
<tr>
<td>IIIA</td>
<td>Chemo, TKI, TKI</td>
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<tr>
<td>IIIB</td>
<td>TKI</td>
</tr>
<tr>
<td>IIIC</td>
<td>TKI</td>
</tr>
<tr>
<td>IVA</td>
<td>Chemo-, Immuno-, and targeted therapy</td>
</tr>
<tr>
<td>IVB</td>
<td>Chemo-, Immuno-, and targeted therapy</td>
</tr>
</tbody>
</table>

Surgery
Surgery for early stage NSCLC
Gold standard for Stage I NSCLC

What determines the oncological outcome? ? ?
Gold standard for Stage I NSCLC

Primary radical resection + mediastinal lymphadenectomy
(regardless of surgical access)
Lobectomy vs. limited resection

- Anatomical resection is generally accepted as the optimal procedure for early stage NSCLC


Fig 1. Time to death (from any cause) by treatment for 247 eligible patients.
Surgical options for Stage I NSCLC

- **Wedge Resection**: Lesion < 2cm, Peripheral location, Marginal patient
- **Segmentectomy**: Lesion < 2cm, More central location (Marginal patient)
- **Lobectomy**: Lesion > 2cm
Surgical techniques - wedge resection

Lesion < 2cm
Peripheral location
Marginal patient

Stapler line
Surgical techniques - anatomical segmentectomy

Lesion < 2cm
More central location (Marginal patient)
Surgical techniques - lobectomy

Lesion > 2cm
The type of surgery is selected based on tumor size and C/T ratio.

C/T ratio = Max. consolidation diameter / max. tumor diameter

C/T ratio < 0.25 were considered to be non-invasive in tumors < 2 cm. (specificity 98.7%)

Maybe also important to determine extent of surgery
PET SUV
Serum CEA


Limitations of segmentectomies – important issues

- **Tumor size**: larger than 2cm – higher local recurrence rate
- **Tumor location**: in relation to the hilum/pleural surface
  - WR or AS only when tumors are located in the outer 1/3
- **Histological subtype**: ADC is not ADC!
  - AIS, MIA have more favourable outcomes
- **Anatomy**: preop 3D-reconstruction and modelisation
- **Margins**: definition of correct interseg. plane, intraop LN assessment
- **Nodal involvement**

• 164 extended segmentectomies compared to lobectomy
• Incidence of locoregional recurrence according to location of resected site
• 21.9 % locoregional recurrence:
  – RUL: 21.9 %
  – LUL: 15.8 %
  – Bilat. basal segments: 20.8 % and 37.5 %
  – Lowest recurrence rates: bilat. S6

Lobectomy vs. anatomical segmentectomy


- Prospective multicenter study
- 55 patients included with peripheral cT1N0M0 NSCLC (<2cm) from 1992-1994
- Follow up: 5 years at least
- 5-year DFS: 91.8%
- Postoperative loss of lung function: FEV1 -13.4%

**Conclusion**: Extended segmentectomy is viable as a standard operation for patients with small peripheral lung tumors, and causes minimal loss of lung function.
... but the last word is not yet spoken

- Comparison of Different Types of Surgery in Treating Patients With Stage IA Non-Small Cell Lung Cancer (JCOG 0802, Japan)

- A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (CATGB 140503, USA)

- Comparison of Lobectomy and Segmentectomy for cT1aN0M0 Peripheral NSCLC (China)
FIGURE 4. Design of JCOG0802/WJOG4607L, a Randomized Trial to Compare the Prognoses and Postoperative Function After Segmentectomy or Lobectomy for Non–Small Cell Lung Cancer \( \leq 2 \) cm Diameter

**Non-inferiority design**

**PI:** Asamura H.

**Stratified factors:**
- Institute
- Gender
- Histology (Ad vs. Non-ad)
- Solid or non-solid

**Endpoints:**
- Primary: OS
- Secondary: pulmonary function

**Sample size:** 1,100

**Abbreviation:** OS, overall survival.
Lobectomy vs. anatomical segmentectomy - Vienna Data

Stage IA and IB NSCLC, propensity score matched cohort retrospective data (2006 – 2013)

Median OS
77.3 vs 87.1 months
p=0.302, HR 1.26

3-year survival
79% vs 84%

5-year survival
69% vs 76%
Anatomical segmentectomy vs. wedge

Retrospective review of a prospective database (2000-2014) for cT1N0 patients
289 patients including WR in 160, and AS in 129

Although AS is associated with a more thorough lymph node dissection, this did not translate to a survival benefit in this patient population with a low rate of nodal metastases.

Altorki et al, JTO 2016
... a few words on minimally invasive surgery

VATS lobectomy may be associated with …

Less pain

Better quality of life

Bendixen et al. Lancet Oncol 2016
### Complications VATS lobectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>VATS</th>
<th>Thoracotomy</th>
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<tbody>
<tr>
<td></td>
<td>Studies No.</td>
<td>Patients No.</td>
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<td>Overall survival, %</td>
<td>9</td>
<td>867</td>
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<tr>
<td>1-year</td>
<td>11</td>
<td>1486</td>
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<tr>
<td>2-year</td>
<td>13</td>
<td>1623</td>
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<tr>
<td>3-year</td>
<td>8</td>
<td>759</td>
</tr>
<tr>
<td>4-year</td>
<td>5</td>
<td>531</td>
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<tr>
<td>5-year</td>
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<td>Overall complications, %</td>
<td>11</td>
<td>2149</td>
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<tr>
<td>Atrial fibrillation, %</td>
<td>7</td>
<td>1095</td>
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<tr>
<td>Pneumonia, %</td>
<td>7</td>
<td>1005</td>
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<tr>
<td>Persistent air leak, %</td>
<td>8</td>
<td>709</td>
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<tr>
<td>Chest tube duration, d</td>
<td>9</td>
<td>713</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>12</td>
<td>2218</td>
</tr>
</tbody>
</table>

VATS lobectomy in patients with impaired lung function - a meta-analysis

Mortality

Overall morbidity

Pulmonary morbidity

Zhang et al. PLOS one 2014
Awake VATS for SPN

Feasibility and Results of Awake Thoracoscopic Resection of Solitary Pulmonary Nodules

Eugenio Pompeo, MD, Davide Mineo, MD, Paola Rogliani, MD, Alessandro F. Sabato, MD, and Tommaso C. Mineo, MD
Division of Thoracic Surgery and Multidisciplinary Pulmonary Program, Polyclinic Tor Vergata University, Rome, Italy

RCT
n=60
Epidural anaesthesia vs GA+DLI

0% mortality

Pompeo et al, ATS 2004
Parenchyma sparing procedures – sleeve lobectomy

- Bronchoplastic techniques are currently procedures of choice in anatomically suitable patients in order to preserve lung parenchyma.

- Bronchoplastic resections are performed in 3% - 13% of patients with resectable lung tumors.
Bronchoplastic and angioplastic resection of centrally located tumors
## Bronchoplastic resection after neoadjuvant treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Title</th>
<th>n</th>
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<tbody>
<tr>
<td>Milman S.</td>
<td>Ann Thorac Surg</td>
<td>2009</td>
<td>The incidence of perioperative anastomotic complications after sleeve lobectomy is not increased after neoadjuvant chemoradiotherapy</td>
<td>64</td>
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<td>Burfeind W.</td>
<td>Ann Thorac Surg</td>
<td>2005</td>
<td>Low morbidity and mortality for bronchoplastic procedures with and without induction therapy</td>
<td>73</td>
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<tr>
<td>Ohta M.</td>
<td>JTCVS</td>
<td>2003</td>
<td>Efficacy and safety of tracheobronchoplasty after induction therapy for locally advanced lung cancer</td>
<td>48</td>
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<tr>
<td>Veronesi G.</td>
<td>Lung Cancer</td>
<td>2002</td>
<td>Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer</td>
<td>55</td>
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<tr>
<td>Rendina E.</td>
<td>JTCVS</td>
<td>1997</td>
<td>Safety and efficacy of bronchovascular reconstruction after induction chemotherapy for lung cancer</td>
<td>68</td>
</tr>
</tbody>
</table>
Conclusion resection for stage I NSCLC

- Numerous publications suggest that sublobar resection for early lung cancer may be an adequate surgical treatment.
- No difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumors of <2 cm.
- Tumors with a GGO appearance on CT are reported to have 100% survival at 5 yrs after resection.

Primary radical resection + mediastinal lymphadenectomy
(regardless of surgical access)
Stage II – old and new concepts
Adjuvant treatment in stage II NSCLC

Douillard et al. Lancet Oncol. 2006. ANITA Trial, Adjuvant cis/vino in completely resected NSCLC
Adjuvant treatment in stage II NSCLC – current concept

Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 3, 15, 22, every 28 days for 4 cycles
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1, 8, every 21 days for 4 cycles
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles
Emerging use of TKIs and Immunotherapy in early stage NSCLC due to encouraging results in stage IV
Neoadjuvant Immunotherapy

Forde et al. NEJM 2018. Neoadjuvant Nivolumab in resectable stage I-IIIA NSCLC
Pilot study, n=21

**Conclusion**: Neoadjuvant nivolumab was associated with few side effects, did not delay surgery, and induced a major pathological response in 45% of resected tumors
Targeted therapy as adjuvant treatment in mut+ NSCLC

Conclusion Stage II

- Currently adjuvant chemotherapy is standard of care in completely resected stage II NSCLC.
- Targeted- and Immunotherapy are powerful tools and selected cases might benefit from (neo)adjuvant individualized treatment based on their individual tumor features (i.e. molecular pathology, mutational burden, PD-L1 expression, etc...).
Surgery for locally advanced NSCLC
What is stage III from now?

<table>
<thead>
<tr>
<th>Descriptor in 7th edition</th>
<th>Proposed T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 ≤ 1 cm</td>
<td>T1a</td>
<td>IA (IA)</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T1 &gt; 1-2 cm</td>
<td>T1b</td>
<td>IA2 (IA)</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T1 &gt; 2-3 cm</td>
<td>T1c</td>
<td>IA3 (IA)</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T2 &gt; 3-4 cm</td>
<td>T2a</td>
<td>IB</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T2 &gt; 4-5 cm</td>
<td>T2b</td>
<td>IB (IB)</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T2 &gt; 5-7 cm</td>
<td>T3a</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
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<tr>
<td>T3 structures</td>
<td>T3b</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
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<tr>
<td>T3 &gt; 7 cm</td>
<td>T4</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIIA)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T3 diaphragm</td>
<td>T4</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIIA)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T3 endobronchial: location/atelectasis 3-4 cm</td>
<td>T3a</td>
<td>IIIB (IIIA)</td>
<td>IIIA (IIIB)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T3 endobronchial: location/atelectasis 4-5 cm</td>
<td>T3b</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIIA)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>T4</td>
<td>T4</td>
<td>IIIA (IIB)</td>
<td>IIIA (IIIA)</td>
<td>IIIB (IIIA)</td>
<td>IIIB (IIIA)</td>
</tr>
<tr>
<td>M1a</td>
<td>M1a</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
</tr>
<tr>
<td>M1b single lesion</td>
<td>M1b</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
<td>IVA (IV)</td>
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<tr>
<td>M1c multiple lesions</td>
<td>M1c</td>
<td>IVB (IV)</td>
<td>IVB (IV)</td>
<td>IVB (IV)</td>
<td>IVB (IV)</td>
</tr>
</tbody>
</table>
... and even more complicating...

- Single N1
- Multiple N1
- Single N2 (+/- N1)
- Multiple N2
- (Number of involved LNs)
Surgical point of view

<table>
<thead>
<tr>
<th></th>
<th>N0</th>
<th>N1</th>
<th>N2 single</th>
<th>N2 multiple</th>
<th>N3</th>
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<tr>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIB</td>
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<tr>
<td>T3</td>
<td>IIIA</td>
<td></td>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td>Smaller TUs (&lt; 5cm)</td>
<td></td>
<td></td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
</tbody>
</table>

**Issues in stage III:**

- Locally advanced T4 / no LNs
- Locally advanced T3/T4 / N1 (single vs. multiple)
- Smaller TUs (< 5cm) / N2 (single vs. multiple)
- Locally advanced T3/T4 / N2 (but still technically resectable)

- Impact of INDUCTION TREATMENT and RESPONSE?!
N2 and stage III

N2 disease itself is a heterogeneous disease but now stage III is even more heterogeneous.
T3/T4
Locally advanced disease: stage IIIA/B – according to T or N

1. Surgical approach depending on tumor localisation requiring different surgical approaches
   
   **Pancoast:**
   - Paulson (posterior), Hemiclamshell, Dartevelle (anterior)
   
   **Carina:**
   - Carinal resection or Sleeve-pneumonectomy
   
   **Invasion of Atrium and greater vessels:**
   - Vascular reconstruction, ev. extracorporal circulation (ECMO/HLM)
   
   **Chest wall infiltration:**
   - Resection und reconstruction
   
   **Infiltration of the spine:**
   - Laminectomy ± Vertebrectomy

2. Inductionchemo- ± radiation

---

**T3/4 N0, N1**

**N2**

“No surgery” ?
In highly qualified centers, radical surgery of T4 N0/N1 NSCLC can be performed with a 4% MR and may yield a 43% 5-year survival. These results seem to indicate primary surgery as the treatment of choice for T4 non–small cell lung carcinoma, whenever a complete resection is thought to be technically feasible and the patient’s condition is compatible with the extent of the planned surgery.

Yildizeli et al, ATS 2008
Induction C/RT Primary Surgery

<table>
<thead>
<tr>
<th>Survival</th>
<th>Induction C/RT</th>
<th>Primary Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y survival</td>
<td>61%</td>
<td>22%</td>
</tr>
<tr>
<td>10 y survival</td>
<td>50%</td>
<td>14%</td>
</tr>
<tr>
<td>Median survival</td>
<td>90 months</td>
<td>22 months</td>
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</tbody>
</table>

Aggressive treatment of node-negative invasive T3 and T4 NSCLC with induction chemo radiotherapy may significantly prolong survival. This approach should be evaluated in a prospective multicenter national trial.

Daly et al, JCTVS 2011
Radical en bloc Resection for Lung Cancer Invading the Spine

Grunenwald et al, JCTVS 2002
Long term follow up of prosthetic replacement of vena cava

- N = 28 patients (1998-2008)
- PTFE grafts
- Perioperative mortality = 3.5% (1 patient)
- Graft thrombosis = 1 patient

Pastorino et al., EJCTS 2010
Sleeve Pneumonectomy – Carinal resection

SCC Carina  cT4N1
Inductionchemotherapy
Carinal resection + reconstruction as neocarina on central ECMO
Pancoast/Sulcus superior tumors
Pancoast Tumor – Advances in Treatment

- 1930 – 1950
  - Considered inoperable
  - Radiotherapy only
  - Disappointing results

- 1950 – 1980
  - Induction radiotherapie (30 Gy) +
  - “en bloc” Resection;
  - R0 only in 60%

- Late 1980s – 2000
  - New surgical techniques
  - (Resection of vertebrae, vessels, …)

- 2000 –
  - Chemoradiotherapy + Surgery
  - R0 in > 90%

Tamura, Hoda, Klepetko, EJCTS 2011
## Trimodality Treatment for Pancoast Tumors

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>n</th>
<th>Complete Resection (%)</th>
<th>2 year survival (%)</th>
<th>5 year survival (%)</th>
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<tr>
<td>Martinez-Monge</td>
<td>1994</td>
<td>18</td>
<td>77</td>
<td>NR</td>
<td>56 (4y)</td>
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<td>Attar</td>
<td>1998</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>72</td>
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<td>Wright</td>
<td>2002</td>
<td>15</td>
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<td>Barnes</td>
<td>2002</td>
<td>8</td>
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<td>86</td>
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<td>Miyoshi</td>
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<td>11</td>
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<td>73</td>
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<td>Kwong</td>
<td>2005</td>
<td>36</td>
<td>97</td>
<td>58</td>
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<td>Rusch</td>
<td>2007</td>
<td>83</td>
<td>76</td>
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<td>Marra</td>
<td>2007</td>
<td>31</td>
<td>94</td>
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<td>Kunitoh</td>
<td>2008</td>
<td>57</td>
<td>68</td>
<td>61 (3y)</td>
<td>56</td>
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<td>Pourel</td>
<td>2008</td>
<td>72</td>
<td>98</td>
<td>62</td>
<td>51 (3y)</td>
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<tr>
<td>Kappers</td>
<td>2009</td>
<td>22</td>
<td>100</td>
<td>70</td>
<td>37</td>
</tr>
</tbody>
</table>
n_ = 46 (28 T4)
30-day mortality was 0%, major surgical complications in 9 (19.6%) patients.
OS at 5-years was 63%.
DFS at 5-years was 45%.
multivariate cox regression analysis
adjusted for clinical factors, T factor (T3/T4) and extended surgical procedures did not impact survival.
However, pathological positive N stage had a negative impact on OS and lack of pathological response negatively impacted both OS and DFS.
Pancoast-TU

Trimodality therapy
Pancoast-Tumor: anterior approach
Vascular reconstruction
### Perioperative issues

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Etiology</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>Lung atelectasis</td>
<td>Thoracic wall resection ± Resection of the phrenic nerve</td>
<td>BSK</td>
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<td></td>
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<td>Intensified Physiotherapy</td>
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<tr>
<td>Local pain</td>
<td>Extended resection</td>
<td>i.v. pain medication (pain pump)</td>
</tr>
<tr>
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<td>Neural injuring</td>
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<tr>
<td>Headache</td>
<td>Neural fluid loss</td>
<td>Fluids</td>
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<td>Conservative medication</td>
</tr>
<tr>
<td>Unilateral venous congestion</td>
<td>Graft occlusion</td>
<td>Adequate anticoagulation</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Resection of the recurrent nerve</td>
<td>Logopedic treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Late vocal cord plastic (implants)</td>
</tr>
<tr>
<td>Impaired mobility of shoulder</td>
<td>Osteo-muscular resection</td>
<td>Special individualized physiotherapy</td>
</tr>
</tbody>
</table>

*BSK: Better Surgical Knowledge*

*ESO-ESMO EEBP Masterclass 2019*
Proposed algorithm – Vienna protocol for locally advanced lung cancer

Therapy in locally advanced NSCLC

N0 / N1

- T3: Primary surgery
- T4: Induction Chemo/Radiation

N2 A1-2

- Primary surgery
- Adjuvant Chemo/Radiation

N2 A3-4

- Induktions Chemo/Radiation
  - Response
  - no Response

- Primary surgery
  - Adjuvant Chemo/Radiation
  - Response
  - Definitive Chemo/Radiation

- Resection
  - Adjuvant Chemo/Radiation
  - Resection
Surgery for oligometastatic disease & palliative surgical options
Surgery Stage IV NSCLC

- Palliative
  - Airway obstruction ± haemoptysis
  - Intrapulmonary cavitation ± infection
  - Pleural effusion
  - Pericardial effusion

- Potentially curative
  - Single (brain) metastasis
  - Contralateral metastasis
  - Pleural involvement ?
Definition of oligometastatic NSCLC – distinct cohorts

- **Oligometastases** = diagnosed with oligometastatic disease
- **Oligorecurrence** = relapsed oligometastatic disease
- **Oligoprogressive** = status after cytoreductive therapy

These cohorts have probably different prognoses
Rationale behind local control for oligometastatic NSCLC

- Controls usual disease progression at the primary site
- Controls major disease burden (primary site)
- If new metastases are to occur from metastases, then control of metastases should impact clinical outcome
- Decreasing tumor burden, may make systemic therapy more effective (immunotherapy)
- Prevents development of resistant clones
- Provides maximum anti-tumor effect
Principles of surgery for oligometastatic NSCLC

- Patient selection (physiologic status, age, PFTs, cardiac function …)
- Primary tumor location (lobe, hilum…)
- Extent of metastatic disease (brain, lung, adrenal …)
- Tumor histology, targetable mutations, PD-L1, TMB, other biomarkers
- Therapeutic options available and previously received (chemotherapy, immunotherapy, targeted therapy, radiation)
- Therapy duration and sequence (to maximize effect and limit resistance)
- Choice of procedure (VATS, RATS, open?)
- What is the goal of surgical therapy? What can be achieved? What is the morbidity and expected QOL
- Return to other indicated therapy
• 43,538 metastatic NSCLC
• SEER 2004-2007

<table>
<thead>
<tr>
<th>Surgery</th>
<th>%</th>
<th>5y OS</th>
<th>Med Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>89%</td>
<td>2%</td>
<td>11.1</td>
</tr>
<tr>
<td>Metastasis only</td>
<td>6.7%</td>
<td>4%</td>
<td>14.7</td>
</tr>
<tr>
<td>Primary only</td>
<td>3.5%</td>
<td>13%</td>
<td>29.4</td>
</tr>
<tr>
<td>Primary and Metastasis</td>
<td>0.8%</td>
<td>20%</td>
<td>34.9</td>
</tr>
</tbody>
</table>

Shen H, Medicine, 2016
Surgery for ologometastatic NSCLC: long-term results from a single center experience

N=53
1997-2010
Majority: brain, adrenal (n=47)
feasible and safe

In combination with multimodality protocols

Good survival:
- Complete resection of primary
- Radical control of distant met
- Weight loss – prognostic factor
NSCLC with contralateral lesion

1. Histological proof mandatory
2. Genetic analysis
3. Extent of surgical resection?
Surgery Stage IV NSCLC

Palliative

- Airway obstruction ± haemoptysis
- Intrapulmonary cavitation ± infection
- Pleural effusion
- Pericardial effusion

Potentially curative

- Single (brain) metastasis
- Contralateral metastasis
- Pleural involvement?
Patients with advanced-stage lung cancer (metastatic or locally-advanced) under normal circumstances not being considered for surgery

- massive haemoptysis
- large cavitated or infected tumour
- no other treatment option after chemo and/or radiotherapy
- tumors compressing: vertrebral body, treachea, great vessels
- tumors with chest wall infiltration causing pain

precluding safe administration of palliative chemotherapy due to the risk of sepsis or tumor perforation

surgical intervention seems justified if patient has a life expectancy of >3 months
Typical scenarios
Malignant pleural effusion

- Malignant pleural effusion is staged M1a in the new TNM classification.

- A very common problem in thoracic surgical practice and third common cause of dyspnea in lung cancer patients.

- Surgical pleurodesis slightly more successful than application of talc slurry with 75-100% success rate.

- In patients fit for a surgical procedure, a videothoracoscopy under general anaesthesia, can be offered to drain the effusion, obtain multiple pleural biopsies for histopathology and mutational analysis and to perform pleurodesis.

Examples
Other options than VATS

Thoracoscopic Talc Versus Tunneled Pleural Catheters for Palliation of Malignant Pleural Effusions

Ben M. Hunt, MD, Alexander S. Farivar, MD, Eric Vallières, MD, Brian E. Louie, MD, Ralph W. Aye, MD, Eva E. Flores, LPN, and Jed A. Gorden, MD

Division of Thoracic Surgery and Interventional Pulmonology, Center for Pleural Diseases, Swedish Cancer Institute, Swedish Medical Center, Seattle, Washington
Surgery for small cell lung cancer
The Role of Surgery in the Treatment of Limited Disease Small Cell Lung Cancer

Time to Reevaluate

Eric Lim, FRCS (C-Th), Elizabeth Belcher, FRCS, Yoon Khoong Yap, MRCS, Andrew G. Nicholson, FRCPath, and Peter Goldstraw, FRCS

n = 59
Stage IA – IIIB
1y surv: 76%
5y surv: 52%
1y DFS: 76%
5y DFS: 46%

JTO 2008
Surgery vs. no surgery

Schreiber et al., survival outcomes with the use of surgery in LD SCLC: should its role be re-evaluated? Cancer 2010.
Conclusions Surgery in SCLC

- R0 resection essential
- Surgery only recommended for T1-2, N0-N1 (limited disease)
- Evidence is limited
- Gold standard of treatment not yet defined
- Further prospective trials needed
## Proposed classification

<table>
<thead>
<tr>
<th>Incidental SCLC</th>
<th>SCLC incidentally found during surgery</th>
<th>-&gt; Primary resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verified SCLC</td>
<td>Single nodule stage I (N0) SCLC</td>
<td>-&gt; Primary resection, adjuvant treatment</td>
</tr>
<tr>
<td>Limited disease (N0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verified SCLC</td>
<td>Stage IIA – IIB (N1) SCLC Complete response after induction</td>
<td>-&gt; Resection after induction CHT/RT</td>
</tr>
<tr>
<td>Limited disease (N1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verified SCLC</td>
<td>SCLC with proven N2/N3 disease</td>
<td>-&gt; CHT/RT</td>
</tr>
<tr>
<td>Advanced disease (N2/3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Controversies in oncology: surgery for small cell lung cancer? It's time to rethink the case

Mir Alireza Hoda, Thomas Kikovits, Walter Klepetko

ESMO Open
2018;3:e000366. doi:10.1136/esmoopen-2018-000366
# Summary: Surgery for lung cancer

<table>
<thead>
<tr>
<th>Early stages</th>
<th>Lobectomy (VATS), sublobar resections, parenchyma sparing options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local advanced stages</td>
<td>Multimodality treatment including surgery in selected cases</td>
</tr>
<tr>
<td>Oligometastatic disease</td>
<td>Combined Surgery and multimodality treatment reasonable in selected cases</td>
</tr>
<tr>
<td>Palliation and control of symptoms</td>
<td>Talc –Pleurodesis, PleurX Cath. Impl., Salvage resection</td>
</tr>
<tr>
<td>SCLC</td>
<td>Good long term results for radically resected early SCLC</td>
</tr>
</tbody>
</table>
Surgery for malignant pleural mesothelioma
Outline

- Overview
- Diagnosis and Staging
- Surgical procedures
- Multimodality treatment
- Intracavitary treatment options
- New approaches
- Summary
Malignant Pleural Mesothelioma

- Etiology: 50-70% pos. anamnesis of asbestos exposure
- Latency period between exposure and diagnosis: approx. 20-35 y.
- In early stage, MPM forms multiple small nodules mostly in parietal pleura
- In advanced stage, MPM is characterized by thick tumor gross surrounding the whole lung
- Mean survival without therapy: 6-7 Mo
- Trimodality treatment: 11-22 Mo.
- 5 year survival rate: 5%

Source: http://mesoblog.org/mesothelioma/pleural-mesothelioma.php
## Epidemiology

<table>
<thead>
<tr>
<th>Country or Region</th>
<th>Incidence cases/million population</th>
<th>Predicted Peak Years</th>
<th>Predicted No. of Deaths in Next 40 Yr †</th>
<th>Predicted Cost‡ billions of U.S. dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>15</td>
<td>2004</td>
<td>72,000</td>
<td>200</td>
</tr>
<tr>
<td>Europe</td>
<td>18§</td>
<td>2015-2020</td>
<td>250,000</td>
<td>80</td>
</tr>
<tr>
<td>Japan</td>
<td>7</td>
<td>2025</td>
<td>103,000</td>
<td>—</td>
</tr>
<tr>
<td>Australia</td>
<td>40</td>
<td>2015</td>
<td>30,000</td>
<td>5–10</td>
</tr>
</tbody>
</table>

Histological characteristics

- First description of MPM in 1767
- First subclassification in 1931
- Immunohistochemical examination as a gold standard in differentiating MPM from metastatic disease of another primary cancer
- Established markers: Calretinin (positive), MOC31 (negative), BerEP4 (negative), D2-40 (positive), TTF-1 (negative), Cytokeratine (positive) und WT-1 (positive)
- Histological subtypes:
  - Epitheliod: ~ 50%
  - Sarcomatoid: ~ 25%
  - Biphasic: ~ 25%

Feldman et al JCO 2003
Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012 (n=3101)
Therapy for MPM

- Survival 9-12 months
- Therapy: nihilism to multimodality therapy
- Chemotherapy Pemetrexed & Cisplatin
- **Trimodality therapy**
  - Induction chemotherapy
  - Cytoreductive surgery (EPP vs. P/D)
  - Adjuvant Radiotherapy
- Outcome after treatment strongly varies
- Only around 50% are able to complete trimodality therapy
- Benefit of multimodality therapy recently was questioned (M.A.R.S.-Trial)

## Prognostic factors

**TABLE 7. Final Model of Clinical, Pathologic, and Laboratory Variables (n = 550)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic stage II vs. I</td>
<td>1.48</td>
<td>0.0802</td>
</tr>
<tr>
<td>Pathologic stage III vs. I</td>
<td>2.20</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pathologic stage IV vs. I</td>
<td>2.49</td>
<td>0.0001</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other histology vs. epithelial</td>
<td>1.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>1.70</td>
<td>0.0006</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 50 vs. younger</td>
<td>1.61</td>
<td>0.012</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative vs. curative intent</td>
<td>1.67</td>
<td>0.0008</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs. yes</td>
<td>1.70</td>
<td>0.0002</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 400 vs. &lt;400</td>
<td>1.50</td>
<td>0.0004</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15.5 vs. &lt;15.5</td>
<td>2.39</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

WBC, white blood cell count.

Prognostic Variables for Pleural Mesothelioma: A Report from the IASLC Staging Committee JTO 2014
Diagnostic algorithm

Patient: asbestos exposure, pleural effusion, pain, ...

CT scan

Cytology and/or biopsy negative

VATS
VATS biopsy
Malignant Pleural Mesothelioma

Heterogenous disease

Classification by staging?
Staging modalities

- **Non-invasive**: imaging modalities (CT, PET-CT, MRI)

- **Invasive**: ultrasound-guided biopsy, EBUS-TBNA, mediastinoscopy, VATS, laparoscopy
**TNM (7th edition) – T descriptors**

**T1a**
- potentially resectable
- only parietal pleura
- no viszeral or mediastinal pleural involvement

**T1b**
- potentially resectable
- parietal pleura and
- scattered foci of visceral pleural involvement

Rusch V et al, Chest 1995
**TNM (7th edition) – T descriptors**

**T2**
- *potentially resectable*
  - parietal and visceral pleural involvement, and / or
  - pulmonary parenchymal involvement and/or
  - diaphragmatic muscle involvement

**T3**
- *potentially resectable*
  - localised tumour extension into endothoracic fascia and / or
  - localised non-transmural involvement of pericardium and / or
  - localised extension into mediastinal fat, soft tissue chest wall

*Rusch V et al, Chest 1995*
T4

unresectable
– multiple foci of extension into chest wall +/- rib destruction and/or
– extension through diaphragm into peritoneum and/or
– extension into contralateral pleura and/or
– extension into mediastinal organs and/or
– extension through pericardium +/- direct extension into heart

**TNM (7th edition) – N descriptors**

**N0**: no evidence of nodal involvement

**N1**: ipsilateral bronchopulmonary or hilar nodal involvement

**N2**: subcarinal or ipsilateral mediastinal / internal mammary or peridiaphragm or pericardial or intercostal nodes

**N3**: contralateral mediastinal / internal mammary nodes, or ipsilateral / contralateral supraclavicular nodes

Rusch V et al, Chest 1995
## TNM (7th edition) – M descriptors and stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1,T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1,T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0-2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any</td>
<td>M1</td>
</tr>
</tbody>
</table>

**M0:** no evidence of distant metastasis

**M1:** distant metastasis

(contralateral lung (pleura), brain, liver, spleen, thyroid, Bone, extrathoracic LN (other than supraclav.))

---

Rusch et al, Chest 1995
Miller et al, Ann Am Thorac Soc. 2014
Finn et al, Chest 2012
**Changes in TNM (8th edition)**

**Changes T-descriptors**

- Collapse of T1a and T1b into a single T category (Tumor limited to ipsilateral parietal+/- visceral +/mediastinal +/- diaphragmatic pleura)

- Measurement of pleural tumor thickness (prognostic variable)

- Classification of pleural involvement pattern in minimal, nodular and rind-like (prognostic impact)

- cT better prognosis than pT

Nowak et al, JTO 2016
A Multicenter Study of Volumetric Computed Tomography for Staging Malignant Pleural Mesothelioma

Valerie W. Rusch, MD, Ritu Gill, MD, Alan Mitchell, MS, David Naidich, MD, David C. Rice, MB, BCh, Harvey I. Pass, MD, Hedy L. Kindler, MD, Marc De Perrot, MD, MS, and Joseph Friedberg, MD, on behalf of the Malignant Mesothelioma Volumetric CT Study Group*

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York; Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts; Cancer Research and Biostatistics, Seattle, Washington; Department of Radiology, New York University School of Medicine, New York, New York; Department of Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas; Department of Surgery, New York University School of Medicine and Comprehensive Cancer Center, New York, New York; Department of Medicine, The University of Chicago, Chicago, Illinois; Department of Surgery, Toronto General Hospital and Princess Margaret Hospital, Toronto, Ontario, Canada; and Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania

Rusch et al, ATS 2016
Changes in TNM (8th edition)

Changes N-descriptors

- Collapse of both clinical and pathological N1 and N2 into a single N category (ipsilateral, intrathoracic) = N1
- Previously N3 reclassified as N2
- Tumor thickness predicts risk of nodal metastasis
- No difference between single vs. multiple stations

Rice et al, JTO 2016
Changes in TNM (8th edition)

**Changes M-descriptors**
- No changes in M-descriptors
- Better prognosis in patients with only a single metastasis

**Changes in stage groups**
- Stage III changed to stage IIIA (T3N1M0) and stage IIIB (T1-3N2M0 and T4anyNM0)

Rusch et al, JTO 2016
Surgical procedures for MPM
Historical note

- Operative technique
- Survival advantage for epithelial type
- Mortality 31%


- Multimodality treatment
- 5y survival subgroup analysis) 46% *
- Mortality (3,8%)


Recommendations for Uniform Definitions of Surgical Techniques for Malignant Pleural Mesothelioma

A Consensus Report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group

- Online survey of surgeons experienced in MPM
- 62 answers, 39 centers, 14 nations
Definitions

- **EPP**: En bloc resection of the lung incl. parietal and visceral pleurae and pericardium/diaphragm

- **Extended P/D**: Parietal and visceral pleurectomy with resection of pericardium and diaphragm

- **P/D**: Parietal and visceral pleurectomy without resection of pericardium and diaphragm

- **Partial pleurectomy**: Resection of parts of parietal and/or visceral pleura for diagnostic or palliative purposes, no macroscopic complete resection
Surgery for MPM

Surgical cytoreduction is indicated when macroscopic complete resection is deemed achievable

Consensus Statement. Rush et al. JTCVS 2013
EPP
EPP: Indications

- Epithelial subtype and intrapleural localized disease with chance of a R0-Resection, regardless of LNN status (except N3)
- Sarcomatoid and mixed subtypes only in N0 or N1
- Only in combination with a multimodality treatment approach
- Good performance status (Karnofsky > 80%)
- Predicted postoperative FEV1 > 1 L
Summary of Prognostic Factors and Patient Selection for Extrapleural Pneumonectomy in the Treatment of Malignant Pleural Mesothelioma

Christopher Cao, BSc (Med), MBBS, Tristan D. Yan, BSc (Med), MBBS, PhD, Paul G. Bannon, MBBS, PhD, FRACS, and Brian C. McCaughan, MBBS, FRACS

TABLE 2 Summary of significant and nonsignificant prognostic factors on survival from referenced studies on extrapleural pneumonectomy for patients with malignant pleural mesothelioma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Significant</th>
<th>Nonsignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantitative factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging system</td>
<td>7, 8, 9, 10, 11, 18, 22</td>
<td>6, 13, 16, 21</td>
</tr>
<tr>
<td>T stage</td>
<td>7, 17*, 20</td>
<td>14, 16, 18, 21</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>7, 10, 11*, 12*, 13*, 14*, 16*, 18, 19*, 21*, 22</td>
<td>6, 17, 20</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>8, 9, 10, 11*, 12*, 13*, 14, 17*, 18, 21*, 22</td>
<td>6, 7, 15, 16, 19, 20</td>
</tr>
<tr>
<td><strong>Clinical factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>8 (E), 21*</td>
<td>8 (N), 9, 11, 14, 16, 18, 19, 20</td>
</tr>
<tr>
<td>Gender</td>
<td>8 (E), 11*, 14*, 17*</td>
<td>6, 8 (N), 9, 14, 16, 18, 19, 20, 21</td>
</tr>
<tr>
<td>Smoking history</td>
<td>19*</td>
<td>11, 18</td>
</tr>
<tr>
<td>Asbestos exposure</td>
<td>12</td>
<td>11, 18, 20</td>
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<tr>
<td>Performance status</td>
<td></td>
<td></td>
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<tr>
<td>Serological markers</td>
<td>8, 12*, 13*, 17*</td>
<td>10, 19, 21</td>
</tr>
<tr>
<td><strong>Treatment related factors</strong></td>
<td></td>
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</tr>
<tr>
<td>Completeness of resection</td>
<td>11*, 16, 18</td>
<td>10, 19</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>12*, 14, 19*, 20*, 22</td>
<td>21</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>7, 19*, 21</td>
<td></td>
</tr>
<tr>
<td>Interval to surgery</td>
<td>8 (E)</td>
<td>8 (N)</td>
</tr>
<tr>
<td>Surgical access site</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
EPP: Morbidity
Pulmonary embolism

- 5% of cases

1.5 months after EPP
EPP outcome & morbidity

- Median overall survival: 9.4 – 27.5 months
- 1-year survival: 36 – 83%
- 3-year survival: 0 – 41%
- 5-year survival: 0 – 24%
- Median disease free survival: 7 – 19 months
- Perioperative mortality: 0 – 11.8%
- Major morbidity: 12.5 – 48%
EPP: Morbidity

- Morbidity overall (minor + major) about 50%
- Diaphragmatic patch dehiscence
- Mediastinal shift - Pleural effusion
- Chylothorax
- Hemothorax
- Vocal cord paralysis
- Subclavian vein thrombosis
- New onset AF
- Cardiac arrest – Luxation?
- PE
- Stroke
- Pneumonia
- Infection – intracavitary, chest wall, wound
- Bronchopleural Fistula
P/D: Indications

- Offered to patients who do not have the cardiopulmonary reserve to tolerate pneumonectomy
- Early-stage disease (confined to parietal pleura without lung infiltration) – lung sparing to decrease morbidity and mortality risk
- In combination with neoadjuvant or adjuvant treatment modalities
- Cytoreductive procedure (no R0 resection)
Partial Pleurectomy

Partial pleurectomy: partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind
Palliative Surgery

MesoVATS trial, Lancet 2014

- RCT, VATS partial Pleurectomy vs. Talc pleurodesis, n=175
RCT, VATS partial Pleurectomy vs. Talc pleurodesis, n=175

VAT-PP is not recommended to improve overall survival in patients with pleural effusion due to malignant pleural mesothelioma, and talc pleurodesis might be preferable considering the fewer complications and shorter hospital stay associated with this treatment.
**A systematic review of lung-sparing extirpative surgery for pleural mesothelioma**

Elaine Teh¹ • Francesca Fiorentino² • Carol Tan³ • Tom Treasure³

Mean survival all studies (26 papers):

- 1-year surv: 51%
- 2-year surv: 26%
- 3-year surv: 16%
- 4-year surv: 11%
- 5-year surv: 9%

<table>
<thead>
<tr>
<th>Author</th>
<th>Start year</th>
<th>End year</th>
<th>n</th>
<th>Op mort (%)</th>
<th>1 year survival (%)</th>
<th>2 year survival (%)</th>
<th>3 year survival (%)</th>
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</table>

Weighted average | 1-year surv: 51% | 2-year surv: 26% | 3-year surv: 16% | 4-year surv: 11% | 5-year surv: 9%
Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012
Multimodality approaches
(Tri)Multimodale Therapie

Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012 (n=3101)
Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. JTCVS 2008

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>Confidence interval</th>
<th>P value</th>
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<td>(1.01–1.02)</td>
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<td>Female gender</td>
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<td>(1.05–1.64)</td>
<td>$P = .02$</td>
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<td>(1.18–1.69)</td>
<td>$P &lt; .001$</td>
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<td>1.3</td>
<td>(1.11–1.60)</td>
<td>$P &lt; .001$</td>
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<td>1.4</td>
<td>(1.28–1.55)</td>
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<td>0.49</td>
<td>(0.38–0.54)</td>
<td>$P &lt; .001$</td>
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</table>

*EPP*, Extrapleural pneumonectomy.
What’s the best strategy?
Who should be selected?
CRP is a simple predictive biomarker


35.93 months vs. 7.86 months OS
EPP - Selection

- TU Volume
- Histology
- CRP
- Response to CHT

Opitz, Hoda... et al; JTO 2015
# Outcome and Morbidity after trimodality treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Median survival (months)</th>
<th>Disease free survival (months)</th>
<th>Perioperative mortality</th>
<th>Perioperative morbidity</th>
<th>Length of stay</th>
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<tr>
<td>Lang-Lazdunski (7)</td>
<td>12.8&lt;sup&gt;DD&lt;/sup&gt;</td>
<td>NR</td>
<td>4.5%</td>
<td>68%</td>
<td>14</td>
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<tr>
<td>Treasure (8)</td>
<td>14.4&lt;sup&gt;DR&lt;/sup&gt;</td>
<td>7.6</td>
<td>12.5%</td>
<td>69%</td>
<td>NR</td>
</tr>
<tr>
<td>van Schil (9)</td>
<td>ITT: 18.4&lt;sup&gt;RE&lt;/sup&gt;</td>
<td>NC+EPP: NR</td>
<td>TMT: 33</td>
<td>82.6%</td>
<td>NR</td>
</tr>
<tr>
<td>Krug (10)</td>
<td>ITT: 16.8&lt;sup&gt;OC&lt;/sup&gt;</td>
<td>NC+EPP: 21.9</td>
<td>13.9</td>
<td>8.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Buduwan (11)</td>
<td>25&lt;sup&gt;DD&lt;/sup&gt;</td>
<td>NR</td>
<td>4.3%</td>
<td>80%</td>
<td>9.2&lt;sup&gt;MW&lt;/sup&gt;</td>
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<tr>
<td>de Perrot (12)</td>
<td>14&lt;sup&gt;OC&lt;/sup&gt;</td>
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<td>52.4%</td>
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<td>Weder (14)</td>
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<td>NR</td>
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<td>62%</td>
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<td>53%&lt;sup&gt;TMT&lt;/sup&gt;</td>
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<td>50%</td>
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<td>50%</td>
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*NR = Not reported*
Own experience

- 3-Institution experience (Vienna, Toronto, Zurich)

Extrapleural Pneumonectomy After Induction Chemotherapy: Perioperative Outcome in 251 Mesothelioma Patients From Three High-Volume Institutions

<table>
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<th>Morbidity/Mortality</th>
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<td>90-day mortality</td>
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<td>(8)</td>
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<td>Major morbidity</td>
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<td>Empyema</td>
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<td>BPF</td>
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<td>(8)</td>
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<td>Chylothorax</td>
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<td>Patch failure</td>
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<td>(5)</td>
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<td>Bleeding</td>
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<td>(4)</td>
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<td>Pulmonary embolism</td>
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<td>(4)</td>
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<td>AKVs</td>
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Intracavitary options
Methods of loco-regional control (experience in abdominal malignancies)

In combination with both procedures (EPP, P/D) and neoadjuvant or adjuvant treatment modalities

- Hyperthermic intraoperative intracavitary cisplatin perfusion (HIOC)
- Hyperthermic pleural lavage with povidone-iodine (P-I)
- Intraoperative Photodynamic Therapy (PDT)
- Intrapleural Immunotherapy (BCG, IL-2, INF-α, INF-γ)
- Intrapleural Gene Therapy (viral, non-viral vectors)
- Use of Doxorubicin or Paclitaxel as nano- or microparticles
HITOC

- Platinum-based, in combination with EPP or P/D
- Morbidity (13-85%) – renal toxicity
- Mortality (0-29%)

HITOC – most recent experience

- **Sugarbaker et al, JCTVS 2013:**
  - HIOC effect on interval to recurrence and OS among patients with favorable prognostic factors
  - 103 low risk patients: 72 pts with HIOC vs. 31 without HIOC
  - HIOC pts: significant longer interval to recurrence (27.1 vs 12.8 months) and longer OS (35.3 vs 22.8 months)
  - Note: improved results particularly in subgroups of patients not receiving hemithoracic radiotherapy and pathologic N1 or N2 lymph node mets.
Experience: povidone-iodine lavage

Pleurectomy/Decortication, Hyperthermic Pleural Lavage with Povidone-Iodine Followed by Adjuvant Chemotherapy in Patients with Malignant Pleural Mesothelioma

Loïc Lang-Lazdunski, MD, PhD, FRCS, Andrea Bille, MD, Elizabeth Belcher, MRCP, PhD, FRCS, Paul Cane, FRCPath, David Landau, FRCP, Jeremy Steele, PhD, FRCP, Henry Taylor, FRCP, and James Spicer, PhD, FRCP

(J Thorac Oncol. 2011;6: 1746–1752)

CONCLUSION

In our experience, P/D with hyperthermic pleural lavage with povidone-iodine and adjuvant chemotherapy is a well-tolerated multimodality scheme. It is associated with low morbidity and mortality. This treatment plan could represent an alternative to the classical trimodality regimen involving chemotherapy, EPP, and adjuvant radiotherapy if our results were to be confirmed in large trials and by other groups. Further studies are warranted to compare this treatment protocol to chemotherapy only and make sure that radical P/D can significantly improve life expectancy. Further treatments are needed to reduce local recurrence after radical P/D.

n=35
Overall median survival: 24 mo
One-year survival was 91.7%, and 2-year survival was 61%.
Photodynamic therapy

Photodynamic therapy = light based cancer treatment
A photosensitizer is excited by a light source of a defined wavelength -> production of reactive oxygen species

Friedberg JS. Ann Cardiothorac Surg 2012

N=38
97% Stage III or IV disease
18% nonepithelial histology
overall median survival from the time of surgery 31.7 months.
Background hydrogen peroxide (H\textsubscript{2}O\textsubscript{2})

• Antiseptic, antibacterial properties, leads to release of oxidative O\textsubscript{2} radicals (concentration: 1.5 – 6%)

• Dual role in cancer

• Different concentrations - diverse cellular effects

• Increase of cellular levels is important for cancer development

• High levels of H\textsubscript{2}O\textsubscript{2} in cancer cells are incompatible with cell survival and lead to susceptibility of these cells to H\textsubscript{2}O\textsubscript{2} –induced cell death compared to normal cells

• Unclear which specific concentrations are selectively killing cancer cells

• Every approach which leads to elevation of cellular H\textsubscript{2}O\textsubscript{2} levels may induce selective cell death in cancer cells and may be exploited therapeutically

Lopez-Lazaro M et al, 2007
<table>
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<tr>
<th>Author</th>
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<th>Treatment</th>
<th>Morbidity (major)</th>
<th>Mortality (30d)</th>
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<td>4%</td>
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<td>Lang-Lazdunski et al (2015)</td>
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<td>P/D, hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy, and systemic treatment</td>
<td>29.4 %</td>
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<tr>
<td>Friedberg et al (2012)</td>
<td>38</td>
<td>31.7</td>
<td>RP + intra.op, PDT, adjuvant CHT (25), neoadjuvant CHT (4), both (6)</td>
<td>Resp.insuff. (16%), DVT+ PE (24%), chyle leak (5%)</td>
<td>3%</td>
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<tr>
<td>Hoda, Klikovits et al,(in preparation)</td>
<td>30</td>
<td>31</td>
<td>Neoadj.CHT, EPP, H2O2, adj. RT</td>
<td>17.6 %</td>
<td>0</td>
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</table>
New approaches on the block

Autologous Fibrin + Cisplatin

InfluenceMESO, PI: Isabelle Opitz, Walter Weder, University of Zurich
New approaches on the block

A Feasibility Study Evaluating Surgery for Mesothelioma After Radiation Therapy

The “SMART” Approach for Resectable Malignant Pleural Mesothelioma

B. C. John Cho, MD, * Ron Feld, MD, † Natasha Leighl, MD, † Isabelle Opitz, MD, † Masato Yumura, MD, † Ming-Sound Tsao, MD, § David M. Hwang, MD, § Andrew Hope, MD, * and Marc de Forcrand, MD †

Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0)
Baseline Investigations, Informed Consent

Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week)

1 week post-RT

Extrapleural Pneumonectomy

<26 weeks post-op

ypNO-1
ypN2

Observation
Adjuvant Chemotherapy

Overall survival

Survival by histology

Disease free survival by histology

Patients at risk 25

Survival (%)

Months after radiation

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

Patients at risk 16
Epithelial
12
5
3
Epithelial
16
11
5
2
Biphasic
3
1
1
Biphasic
9
2
0
0

Patients at risk 9

Survival (%)

Months after radiation

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

Patients at risk 9

Survival (%)

Months after radiation

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

Epithelial
16
11
5
2
Biphasic
9
2
0
0

Epithelial

Biphasic

p=0.0002

p<0.0001
New approaches on the block

Combining multimodality with immunotherapy

Wong RM et al. Am J Respir Cell Mol Biol 2014
## Summary

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>VATS &amp; open biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliation and control of symptoms</td>
<td>Talc - Pleurodesis</td>
</tr>
<tr>
<td>Staging</td>
<td>Mediastinoscopy, VATS, Laparascopy</td>
</tr>
<tr>
<td>Cyto-reductive procedures „Curative intent“</td>
<td>Pleurectomy / Decortication</td>
</tr>
<tr>
<td></td>
<td>Extrapleural Pneumonectomy within Multi-Modality-Treatment ± HIOC</td>
</tr>
<tr>
<td>Experimental therapy approaches</td>
<td>Other Intracavitary therapies Neoadjuvant RT, Comb. IT</td>
</tr>
</tbody>
</table>
Asbestos Awareness
Thank you for your kind attention!