Surgery for Lung Cancer and Malignant Pleural Mesothelioma

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Department of Thoracic Surgery and Thoracic Endoscopy
(Director: Prof. Dr. Clemens Aigner)
Disclosure

- I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.
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Surgery for lung cancer
AGENDA

Overview

Surgery for early stage NSCLC

Surgery for locally advanced disease

Surgery for oligometastatic disease

Palliative treatment options

Role of surgery in SCLC

Summary
Lung Cancer Mortality since 1930

Male Cancer Death Rates Among Men, US, 1930-2006

Female Cancer Death Rates Among Women, US, 1930-2006
## Classical treatment protocol for Lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0</td>
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<tr>
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<td>T3N0M0</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>IIA</td>
<td>Surgery</td>
</tr>
<tr>
<td>IIB</td>
<td>Surgery</td>
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<table>
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<tr>
<th>Stage</th>
<th>TNM</th>
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<tbody>
<tr>
<td>IIIA</td>
<td>T1-3N2M0</td>
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<td>IIB</td>
<td>T3N1M0</td>
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<td>T1-3N3M0</td>
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<td></td>
<td>T4anyNM0</td>
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Modern Treatment Algorithm for Lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgery</th>
<th>Adjuvant Chemotherapy</th>
<th>Radiotherapy + Second-line Chemotherapy</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
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<td></td>
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<td>IB</td>
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<td></td>
<td></td>
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<tr>
<td>IIA</td>
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<tr>
<td>IIB</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IIIA₁-₂</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IIIA₃</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IIIA₄ - B</td>
<td></td>
<td>neoadjuvant treatment</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
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</table>
Surgery for early stage NSCLC
Standard of care:
Lobectomy + mediastinal lymph node dissection (MLND)

Standard of care – new developments

- Minimal invasive resections (incl. awake)
- Sublobar resection (limited resections)
- Parenchyma sparing options
Minimal invasive surgery (MIS)
Video assisted thoracic surgery (VATS)

VATS: 3-portal (Hansen et al, 2011)

VATS: uniportal (Gonzalez-Rivas et al, 2013)
Robotic assisted thoracic surgery (RATS)
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, Policlinico Tor Vergata University, Rome, Italy

RCT
n=60
Epidural anaesthesia vs GA+DLI

0% mortality

Pompeo et al, ATS 2004
Lobectomy: MIS vs. open surgery

Is VATS Lobectomy Better: Perioperatively, Biologically and Oncologically?

Natasha M. Rueth, MD, and Rafael S. Andrade, MD
Ann Thorac Surg 2010;89:S2107–11
The currently available clinical evidence indicates that VATS lobectomy for early-stage NSCLC is associated with fewer postoperative complications and less negative biologic impact on patients than open lobectomy. Furthermore, all data to date strongly suggest oncologic equivalence of VATS versus open lobectomy for patients with early-stage NSCLC.

Ann Thorac Surg 2010;89:S2107–11
Sublobar resections
Sublobar resections

- Tendency towards less invasive resections for radiological non-invasive tumors
- Tendency towards lung parenchyma sparing resections i.e. segmental (anatomic) resections
- More candidates for surgery (limited lung function e.g.)
- Key question: Are these approaches really oncological radical?
Of special interest to thoracic surgeons are the new categories; adenocarcinoma \textit{in situ} and minimally invasive adenocarcinoma that represent small ($\leq 3$ cm), solitary adenocarcinomas consisting purely of lepidic growth without invasion or no greater than a 0.5-cm invasion, respectively. Usually, they correspond to GGO lesions on chest computed tomography.

\textbf{Adenocarcinoma \textit{in situ} and minimally invasive adenocarcinoma: 100% or near 100\% 5-year disease-free survival, respectively, if completely resected.}
Future Prospects

- Lobectomy is still considered the standard surgical treatment for tumours of <2 cm that have a solid appearance on chest CT because such tumours are invasive carcinomas.

- Any change in this standard care awaits the results of two randomised trials (Japan Clinical Oncology Group identifier JCOG 0802/West Japan Oncology Group identifier WJOG3406L in Japan and Cancer and Leukemia Group B identifier CALGB 140503 (www.clinicaltrials.gov identifier NCT00499330) in North America) that randomise such patients into either lobectomy or sublobar resection.
Impact of tumor size on outcomes after anatomic lung resection for stage 1A non–small cell lung cancer based on the current staging system

Shamus R. Carr, MD, a Matthew J. Schuchert, MD, a Arjun Pennathur, MD, a David O. Wilson, MD, b Jill M. Siegfried, PhD, c James D. Luketich, MD, a and Rodney J. Landreneau, MD a

### TABLE 1. Patient demographics and operative data by T descriptor

<table>
<thead>
<tr>
<th></th>
<th>T1a (n = 284)</th>
<th>T1b (n = 145)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>.009</td>
</tr>
<tr>
<td>Mean</td>
<td>67.0</td>
<td>69.4</td>
<td></td>
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<tr>
<td>Range</td>
<td>28–88</td>
<td>43–88</td>
<td></td>
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<tr>
<td>Gender</td>
<td>123 male, 161 female</td>
<td>75 male, 70 female</td>
<td>.10</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>121 (42.6%)</td>
<td>57 (39.3%)</td>
<td>.54</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>163 (57.4%)</td>
<td>88 (60.7%)</td>
<td></td>
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<tr>
<td>Approach</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VATS</td>
<td>142 (50.0%)</td>
<td>62 (42.8%)</td>
<td>.18</td>
</tr>
<tr>
<td>Open</td>
<td>142 (50.0%)</td>
<td>83 (57.2%)</td>
<td></td>
</tr>
</tbody>
</table>

VATS, Video-assisted thoracoscopic surgery.

Carr et al, JCTVS 2012
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.
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>
</tr>
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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>
</tr>
<tr>
<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>
Surgery for locally advanced NSCLC: T3/T4
T4 Lung cancer
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

1. Inductionchemo- ± radiation

“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
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
Induction chemotherapy
Carinal resection + reconstruction as neocarina on central ECMO
Extended Resections – Invasion der Aorta (T4)
Extended Resections – Invasion der Aorta (T4)
T4 surgery: largest experience in Europe

Spaggiari et al, Ann Thorac Surg 2013

n = 125, extended resections for NSCLC
Pancoast/Sulcus superior tumors
Pancoast’s Syndrome

- Brachial plexus (arm and shoulder pain)
- Vertebral body
- Vagus nerve
- Sympathetic trunk (Horner’s syndrome)
- Recurrent nerve (vocal cord paralysis)
- Subclavian artery and vein

V subclavia
A subclavia
V jugularis
V subclavia
V cava
Pancoast-TU ➔ Trimodality therapy
Pancoast Tumor – Advances in Treatment

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

- **1950 -1980**
  - Induction radiotherapy (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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<tbody>
<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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<tr>
<td>Attar</td>
<td>1998</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>72</td>
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<tr>
<td>Wright</td>
<td>2002</td>
<td>15</td>
<td>93</td>
<td>93</td>
<td>84</td>
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<tr>
<td>Barnes</td>
<td>2002</td>
<td>8</td>
<td>NR</td>
<td>86</td>
<td>NR</td>
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<tr>
<td>Miyoshi</td>
<td>2004</td>
<td>11</td>
<td>NR</td>
<td>73</td>
<td>53</td>
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<tr>
<td>Kwong</td>
<td>2005</td>
<td>36</td>
<td>97</td>
<td>58</td>
<td>50</td>
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<td>Rusch</td>
<td>2007</td>
<td>88</td>
<td>76</td>
<td>55</td>
<td>44</td>
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<td>Marra</td>
<td>2007</td>
<td>31</td>
<td>94</td>
<td>74</td>
<td>46</td>
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<td>Kunitoh</td>
<td>2008</td>
<td>57</td>
<td>68</td>
<td>61 (3y)</td>
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<tr>
<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%.

Waseda et al, JSO 2017
## 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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<tr>
<td></td>
<td></td>
<td>Intensified Physiotherapy</td>
</tr>
<tr>
<td>Local pain</td>
<td>Extended resection</td>
<td>i.v. pain medication (pain pump)</td>
</tr>
<tr>
<td></td>
<td>Neural injuring</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Neural fluid loss</td>
<td>Fluids</td>
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<tr>
<td></td>
<td></td>
<td>Conservative medication</td>
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<tr>
<td>Unilateral venous congestion</td>
<td>Graft occlusion</td>
<td>Adequate anticoagulation</td>
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<tr>
<td>Hoarseness</td>
<td>Resection of the recurrent nerve</td>
<td>Logopedic treatment</td>
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<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>
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</table>
Surgery for locally advanced NSCLC: N2
N2 disease is a very heterogeneous entity!
Stage IIIA (N2)

- involvement of single/ multiple stations
- +/- microscopic / full thickness / transcapsular

Induction CT (n=47)

- Censored
- pN2 single level (n=33)
- pN2 multilevel & pN3 (n=14)

Decaluwe et al. EJCTS 2009
## Subsets of Stage IIIA (N2)

<table>
<thead>
<tr>
<th>Subset</th>
<th>Description</th>
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<tbody>
<tr>
<td>IIIA&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Incidental nodal metastases found on final pathologic examination of the resection specimen</td>
</tr>
<tr>
<td>IIIA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Nodal (single station) metastases recognized intraoperatively</td>
</tr>
<tr>
<td>IIIA&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)</td>
</tr>
<tr>
<td>IIIA&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Bulky or fixed multistation N2 disease</td>
</tr>
</tbody>
</table>

Surgery for N2 positive NSCLC

Stage IIIA: Based on N2

III A_1

Surgery

III A_2

neoadjuvant chemo-/radiotherapy

Responders

Adjuvant Chemo or radiotherapy

Non-Responders

Surgery

III A_3

neoadjuvant chemo-/radiotherapy

Responders

Surgery

Local radiotherapy ± Second-line chemotherapy

Non-Responders

Surgery in highly selected cases

Local boost radiotherapy ± Second-line chemotherapy

III A_4

neoadjuvant chemoradiotherapy

Responders

Non-Responders
Results – MUV

Median OS
82.0 vs 29.0 months

p=0.003

Median RFS
54.8 vs 15.3 months

p = 0.019
Proposed algorithm – Vienna protocol

Therapy in locally advanced NSCLC

- **N0 / N1**
  - **T3**
    - Primary surgery
    - Adjuvant Chemo
  - **T4**
    - Induction Chemo/Radiatio
    - Resection

- **N2 A₁-₂**
  - Primary surgery
  - Adjuvant Chemo/Radiatio
  - Response
  - no Response

- **N2 A₃-₄**
  - Induction Chemo/Radiatio
  - Response
  - no Response
  - Definitive Chemo/Radiatio
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?
**Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

G. D’Addario¹, M. Früh², M. Reck³, P. Baumann⁴, W. Klepetko⁵ & E. Felip⁶

On behalf of the ESMO Guidelines Working Group*

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**isolated adrenal metastasis**

Systemic chemotherapy is recommended. In selected fit patients adrenalectomy can be considered, if lung disease is resectable as well.

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**lungs**

Solitary lesions in the contralateral lung should be considered as secondary primary and treated with curative intention if both tumours are potentially curable.

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**solitary brain metastasis**

- Resection or stereotactic radiosurgery (SRS) are the primary alternatives.
- If the primary tumour is resectable (i.e. T1–3 N0–1): surgery with or without chemotherapy is an option in highly selected, fit patients. Alternatively, radiotherapy or chemoradiation is an option in selected patients with localized thoracic disease. In other patients chemotherapy is recommended [III, C].

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*Annals of Oncology 21 (Supplement 5): v116–v119, 2010*
NSCLC with Single brain metastasis: Metaanalysis

153 relevant papers 1035 patients

✓ Curative intent group median survival 23,12 ± 3,3 mo.
  1y and 5y survival 63,9 ± 5,6% and 18 ± 5,7%

✓ Palliative group median survival 10,3 +/- 2.9 mo.
  1y and 5y survival 35,3 +/- 3,8 % and 0 %

In absence of mediastinal LN involvement combined surgical resection improved prognosis.

Parameters for good prognosis:

* Adenocarcinoma
  • low CEA levels at presentation
  • high Karnofsky performance score
  • response to induction CR

NSCLC with single brain metastasis

- Gamma Knife
- Stereotactic Rx
- Surgical removal

Limited surgical resection + CX

Definitive CX or CX/Rx
Surgery for oligometastatic 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

Congedo , JTCVS 2012
NSCLC with contralateral lesion

1. Histological proof mandatory
2. Genetic analysis
3. Extent of surgical resection?
Synchronous bilateral lung cancer

Retrospective study 1990 – 2007

- 57 patients with bilateral lesion identified
- 15 unilateral resection only
  - 6 benign disease unilaterally
- 36 with bilateral NSCLC resected
  - Same histology 18
  - Different histology 18

- Postoperative mortality: 2.8%
- Median survival: 25.4 months
- 5-year survival: 38%
- No significant difference between different vs. same histology

Selected patients with bilateral lung cancer benefit from an aggressive approach.

Patients with a single contralateral lesion should not be treated as disseminated disease – Stage IV.

Bilateral resection should be considered in otherwise fit patients.

Surgery Stage IV NSCLC

Palliative

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

Potentially curative

- Single (brain) metastasis
- Contralateral metastasis
- Pleural involvement?
Palliative Lung resections

- 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.

- 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. Gordon, MD

Division of Thoracic Surgery and Interventional Pulmonology, Center for Pleural Diseases, Swedish Cancer Institute, Swedish Medical Center, Seattle, Washington
VATS: biopsy and talc pleurodesis

Obtains diagnosis in combination with VATS biopsy (histology, Staging)
Therapeutic/palliative for persisting pleural effusion
Pericardial window

http://www.ctsnet.org/sections/clinicalresources/thoracic/expert_tech-32
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

FIGURE 1. Overall survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

FIGURE 2. Disease free survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

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.
## Tumor stages

<table>
<thead>
<tr>
<th>NSCLC</th>
<th></th>
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<tbody>
<tr>
<td><strong>„limited disease“</strong></td>
<td><strong>„advanced disease“</strong></td>
</tr>
<tr>
<td>N0</td>
<td>N0</td>
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<td>IA</td>
<td>IB</td>
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</tbody>
</table>

**Surgery** | **No surgery**

<table>
<thead>
<tr>
<th>SCLC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>„limited disease“</strong></td>
<td><strong>„advanced disease“</strong></td>
</tr>
<tr>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>IA</td>
<td>IB</td>
</tr>
</tbody>
</table>

**Surgery** | **No surgery**
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>→ Primary resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verified SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited disease (N0)</td>
<td>Single nodule stage I (N0) SCLC</td>
<td>→ Primary resection, adjuvant treatment</td>
</tr>
<tr>
<td>Verified SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited disease (N1)</td>
<td>Stage IIA – IIB (N1) SCLC Complete response after induction</td>
<td>→ Resection after induction CHT/RT</td>
</tr>
<tr>
<td>Verified SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced disease (N2/3)</td>
<td>SCLC with proven N2/N3 disease</td>
<td>→ CHT/RT</td>
</tr>
</tbody>
</table>
## Summary: Surgery for lung cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stages</td>
<td>Lobectomy (VATS), sublobar resections, parenchyma sparing options</td>
</tr>
<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:
  - Epithelioid: ~ 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: nullism 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>
<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>2.2</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>1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>1.7</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>1.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥400 vs. &lt;400</td>
<td>1.5</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

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

**M0**: no evidence of distant metastasis

**M1**: distant metastasis

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

<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 N</td>
<td>M1</td>
</tr>
</tbody>
</table>

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)

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

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

![Graph showing survival rates for different lesion types and stages.](image)

<table>
<thead>
<tr>
<th>Events / N</th>
<th>MST</th>
<th>24 Month</th>
<th>60 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Lesion, Single site</td>
<td>9 / 18</td>
<td>17.3</td>
<td>0%</td>
</tr>
<tr>
<td>Multiple Lesions</td>
<td>24 / 35</td>
<td>5.8</td>
<td>18%</td>
</tr>
<tr>
<td>Single Site, Number of Lesions Not Reported</td>
<td>14 / 17</td>
<td>11.5</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N0</th>
<th>N1/N2</th>
<th>N1</th>
<th>N3</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>v7</td>
<td>v8</td>
<td>v7</td>
<td>v8</td>
<td>v7</td>
</tr>
<tr>
<td>T2</td>
<td>IIA</td>
<td>III</td>
<td>II</td>
<td>IV</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3</td>
<td>II</td>
<td>IB</td>
<td>III</td>
<td>IIIA</td>
<td>IV</td>
</tr>
<tr>
<td>T4</td>
<td>IV</td>
<td>IIIB</td>
<td>IV</td>
<td>IIIB</td>
<td>IV</td>
</tr>
<tr>
<td>M1</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Rusch et al, JTO 2016
Surgical procedures for MPM
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

David Rice, MB, BCh,* Valerie Rusch, MD,† Harvey Pass, MD,‡ Hisao Asamura, MD,§ Takashi Nakano, MD,∥ John Edwards, MB, ChB, PhD,¶ Dorothy J. Giroux, MS,# Seiki Hasegawa, MD,** Kemp H. Kernstine, MD, PhD,†† David Waller, MD,‡‡ and Ramon Rami-Porta, MD§§, on behalf 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
Surgical cytoreduction is indicated when macroscopic complete resection is deemed achievable.
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
- 17 studies
- 13 centers

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>Quantitative factors</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>Histopathology</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>Clinical factors</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, 13*, 17*</td>
<td>6, 8 (N), 9, 14, 16, 18, 19, 20, 21</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asbestos exposure</td>
<td>19*</td>
<td>11, 18</td>
</tr>
<tr>
<td>Performance status</td>
<td>12</td>
<td>11, 18, 20</td>
</tr>
<tr>
<td>Serological markers</td>
<td>8, 12*, 13*, 17*</td>
<td></td>
</tr>
<tr>
<td>Treatment related factors</td>
<td></td>
<td></td>
</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
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%
P/D vs. EPP

Initial analysis of the international association for the study of lung cancer mesothelioma database. JTO 2012
Multimodality approaches
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
Multimodality approaches

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>
</tr>
</thead>
<tbody>
<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>
</tr>
<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; NC+EPP: NR</td>
<td>TMT: 33</td>
<td>13.9</td>
<td>6.5%</td>
<td>82.6%</td>
</tr>
<tr>
<td>Krug (10)</td>
<td>ITT: 16.8&lt;sup&gt;OC&lt;/sup&gt; NC+EPP: 21.9</td>
<td>TMT: 29.1</td>
<td>10.1</td>
<td>3.7%</td>
<td>NR</td>
</tr>
<tr>
<td>Buduhan (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>
</tr>
<tr>
<td>de Perrot (12)</td>
<td>14&lt;sup&gt;CC&lt;/sup&gt;</td>
<td>NR</td>
<td>6.7%</td>
<td>33%</td>
<td>NR</td>
</tr>
<tr>
<td>Rea (13)</td>
<td>ITT: 25.5&lt;sup&gt;OC&lt;/sup&gt; NC+EPP: 27.5</td>
<td>TMT: NR</td>
<td>16.3</td>
<td>0%</td>
<td>52.4%</td>
</tr>
<tr>
<td>Weder (14)</td>
<td>ITT: 19.8&lt;sup&gt;CC&lt;/sup&gt; NC+EPP: 23</td>
<td>TMT: NR</td>
<td>13.5</td>
<td>2.2%</td>
<td>NR</td>
</tr>
<tr>
<td>Ambrogi (15)</td>
<td>19.5&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>NR</td>
<td>3.4%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Patel (16)</td>
<td>23.2&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rena (17)</td>
<td>20</td>
<td>14</td>
<td>5%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tonoli (18)</td>
<td>46.9&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Luckraz (19)</td>
<td>19.5&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>NR</td>
<td>8.2%</td>
<td>53%&lt;sup&gt;TMT&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>Batirel (20)</td>
<td>ITT: 17.2 EPP+AC: 19.6</td>
<td>TMT: 23.9</td>
<td>10</td>
<td>5%</td>
<td>55%</td>
</tr>
<tr>
<td>Pagan (21)</td>
<td>20&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>NR</td>
<td>4.5%</td>
<td>50%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Sunarhaker (22)</td>
<td>19&lt;sup&gt;DB&lt;/sup&gt;</td>
<td>NR</td>
<td>3.8%</td>
<td>50%</td>
<td>24.5%</td>
</tr>
</tbody>
</table>
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 2. Morbidity and Mortality After Induction Chemotherapy Followed by Extrapleural Pneumonectomy (n = 251)

<table>
<thead>
<tr>
<th>Morbidity/Mortality</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>12</td>
<td>(5)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>21</td>
<td>(8)</td>
</tr>
<tr>
<td>Major morbidity</td>
<td>76</td>
<td>(30)</td>
</tr>
<tr>
<td>Empyema</td>
<td>35</td>
<td>(14)</td>
</tr>
<tr>
<td>BPF</td>
<td>20</td>
<td>(8)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>13</td>
<td>(5)</td>
</tr>
<tr>
<td>Patch failure</td>
<td>12</td>
<td>(5)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>9</td>
<td>(4)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>9</td>
<td>(4)</td>
</tr>
<tr>
<td>ARDS</td>
<td>3</td>
<td>(1)</td>
</tr>
</tbody>
</table>

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 larger 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 = 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
Background hydrogen peroxide (H$_2$O$_2$)

- Antiseptic, antibacterial properties, leads to release of oxidative O$_2$ 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$_2$O$_2$ in cancer cells are incompatible with cell survival and lead to susceptibility of these cells to H$_2$O$_2$–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$_2$O$_2$ levels may induce selective cell death in cancer cells and may be exploited therapeutically

Lopez-Lazaro M et al, 2007
## Comparison intracavitary treatment options

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Median OS (months)</th>
<th>Treatment</th>
<th>Morbidity (major)</th>
<th>Mortality (30d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>div. auhors (1994-2010)</td>
<td>&gt;100</td>
<td>9.3-13-2</td>
<td>EPP, P/D, HIOC</td>
<td>13-85 %</td>
<td>0-29%</td>
</tr>
<tr>
<td>Sugarbaker et al (2013)</td>
<td>72</td>
<td>35.3</td>
<td>EPP, P/D HIOC, Neoadj.CHT (14%), Adj.CHT (57%), Adj.RT (57%)</td>
<td>NR</td>
<td>4%</td>
</tr>
<tr>
<td>Lang-Lazdunski et al (2015)</td>
<td>102</td>
<td>25</td>
<td>P/D, hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy, and systemic treatment</td>
<td>29.4 %</td>
<td>0</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>
H2O2 impairs cell proliferation in short- and long-term assays

courtesy of Viktoria Laszlo, PhD
H₂O₂ leads to cell death - necrosis

courtesy of Viktoria Laszlo, PhD
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 Leightl, MD,† Isabelle Opitz, MD,‡ Masaki Anraku, MD,‡ Ming-Sound Tsao, MD,§ David M. Hwang, MD,§ Andrew Hope, MD,* and Marc de Perrot, MD‡

Study Schema

- Logically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0)
- Baseline Investigations, Informed Consent
New approaches on the block

Combining multimodality with immunotherapy

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

<table>
<thead>
<tr>
<th>Multimodality regimen</th>
<th>Immunomodulatory/antitumor effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation + immunotherapy + Fractionated local irradiation + CTLA-4 blockade</td>
<td>Enhanced induction of tumor-specific T lymphocytes; delayed growth of nonirradiated distant tumor</td>
<td>37</td>
</tr>
<tr>
<td>Fractionated local irradiation + therapeutic vaccination</td>
<td>Transient systemic MDSC depletion; enhanced tumor-specific T-lymphocyte induction</td>
<td>38</td>
</tr>
<tr>
<td>Fractionated local irradiation + adoptive T lymphocyte transfer</td>
<td>Transient systemic Treg depletion; enhanced proliferation of donor T lymphocytes in recipients</td>
<td>39</td>
</tr>
<tr>
<td>Chemotherapy + immunotherapy Intratumoral Ad-IFN-α immunogene therapy followed by cisplatin + gemcitabine</td>
<td>Systemic Treg and MDSC depletion; enhanced tumor-specific T-lymphocyte induction; increased intratumor T-lymphocyte infiltration</td>
<td>41</td>
</tr>
<tr>
<td>Cyclophosphamide + therapeutic vaccination Gemcitabine + CTLA-4 blockade</td>
<td>Systemic Treg depletion</td>
<td>42</td>
</tr>
<tr>
<td>Surgical tumor reduction + immunotherapy Preoperative intratumoral Ad-IFN-β immunogene therapy complete resection</td>
<td>Increased intratumor T-lymphocyte infiltration; induction of protective immunologic memory</td>
<td>44</td>
</tr>
<tr>
<td>Complete resection + postoperative therapeutic vaccination</td>
<td>Increased intratumor T-lymphocyte infiltration; delayed growth of recurrent and unresected distant tumor</td>
<td>45</td>
</tr>
<tr>
<td>Partial resection + postoperative gemcitabine + anti-CD40 agonist immunotherapy</td>
<td>Induction of protective immunologic memory</td>
<td>46</td>
</tr>
<tr>
<td>Cryoablation + CTLA-4 blockade</td>
<td>Increased intratumor Tymphocyte infiltration; induction of protective immunologic memory</td>
<td>47</td>
</tr>
</tbody>
</table>
## 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

DANGER

ASBESTOS
CANCER AND LUNG DISEASE HAZARD
AUTHORIZED PERSONNEL ONLY
RESPIRATORS AND PROTECTIVE CLOTHING ARE REQUIRED IN THIS AREA
Thank you for your kind attention!