What’s (old and) new?
Lung metastases

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TOGA symposium 20/10/17
What’s new?
Lung metastases

- history - controversy - evidence
- retrospective data
- how to do it?
- treatment algorithm
- how to improve local control?
What’s new?
Lung metastases

• history - controversy - evidence
• retrospective data
• how to do it?
• treatment algorithm
• how to improve local control?
Surgery for pulmonary metastases

1786  J. Hunter

Allen E. The case books of J.Hunter. London 1993
## Surgery for pulmonary metastases

### History

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Procedure/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1786</td>
<td>J. Hunter</td>
<td>case of pulm. mets</td>
</tr>
<tr>
<td>1927</td>
<td>J. Divis</td>
<td>resection pulmonary mets</td>
</tr>
<tr>
<td>1939</td>
<td>J. Barney - E. Churchill</td>
<td>lobectomy - metastasis kidney: nephrectomy</td>
</tr>
<tr>
<td>1965</td>
<td>N. Thomford</td>
<td>205 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-year survival 30.3 %</td>
</tr>
</tbody>
</table>
Surgery for pulmonary metastases

- Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness?
  T. Treasure et al. Thorax 2014; 69:946-9

- Pulmonary metastasectomy: a call for better data collection, presentation and analysis.

- Pulmonary metastasectomy: where is the evidence?
Surgery for pulmonary metastases

- retrospective case series
- selection bias
- no level 1 evidence, no control group

“There is reason to believe that any perceived survival benefit may simply be due to patient selection. This is an insecure foundation of which to justify ablative therapies.”

Surgery for pulmonary metastases

• no large randomized trials to prove survival benefit compared to conservative treatment

• also for thymoma, mesothelioma, even early stage lung cancer!

• N2 disease: 3 large RCT; still highly controversial

• reverse statement not proven: 
  absence of evidence ≠ evidence of absence

30% of all cancer patients will develop lung metastases

5-year survival rates
- untreated: 5 - 10%
- resected: 30 - 50%

*selection bias??*

Surgery for pulmonary metastases

Selection criteria

- able to withstand the operation planned (cardiac, functional evaluation)
- complete resection of all pulmonary mets
- primary tumor and extrapulmonary mets must be controlled or controllable
- no better treatment available offering the same chance of cure or superior palliation

What’s new?
Lung metastases

- history - controversy - evidence
- retrospective data
- how to do it?
- treatment algorithm
- how to improve local control?
Long-Term Results of Lung Metastasectomy: Prognostic Analyses Based on 5206 Cases

The International Registry of Lung Metastases*
Writing Committee:
Ugo Pastorino, MD
Marc Buyse, ScD
Godhard Friedel, MD
Robert J. Ginsberg, MD
Philippe Girard, MD
Peter Goldstraw, MD
Michael Johnston, MD
Patricia McCormack, MD
Harvey Pass, MD
Joe B. Putnam, Jr., MD

Objectives: The International Registry of Lung Metastases was established in 1991 to assess the long-term results of pulmonary metastasectomy. Methods: The Registry has accrued 5206 cases of lung metastasectomy, from 18 departments of thoracic surgery in Europe (n = 13), the United States (n = 4) and Canada (n = 1). Of these patients, 4572 (88%) underwent complete surgical resection. The primary tumor was epithelial in 2260 cases, sarcoma in 2173, germ cell in 363, and melanoma in 328. The disease-free interval was 0 to 11 months in 2199 cases, 12 to 35 months in 1857, and more than 36 months in 1620. Single metastases accounted for 2383 cases and multiple lesions for 2726. Mean follow-up was 46 months. Analysis was performed by Kaplan-Meier estimates of survival, relative risks of death, and multivariate Cox model. Results: The actuarial survival after complete metastasectomy was 36% at 5 years, 26% at 10 years, and 22% at 15 years (median 35 months); the corresponding values for incomplete resection were 13% at 5 years and 7% at 10 years (median 15 months). Among complete resections, the 5-year survival was 33% for patients with a disease-free interval of 0 to 11 months and 45% for those with a disease-free interval of more than 36 months; 43% for single lesions and 27% for four or more lesions. Multivariate analysis showed a better
Surgery for pulmonary metastases
International Registry

- 5206 cases of lung metastasectomy
- mean follow-up : 46 months
- complete resection : 4572 (88 %)
- male : 2392 (56 %) female : 2274 (44 %)
- mean age : 44 years (range 2-93)

Surgery for pulmonary metastases
International Registry

- **primary tumor**
  - epithelial 2260 43%
  - sarcoma 2173 42%
  - germ cell 363 7%
  - melanoma 328 6%

- **DFI**
  - 0-11 mos. 1603 31%
  - 12-35 1857 36%
  - > 36 1620 31%

Surgery for pulmonary metastases
International Registry

- single metastasis 2383 46%
- multiple 2726 52%
  - 4 or more 1353 26%
  - 10 or more 457 9%

- hilar or mediastinal nodes: 239 (5%)

Surgery for pulmonary metastases
International Registry

<table>
<thead>
<tr>
<th></th>
<th>5 - year</th>
<th>10 - year</th>
<th>median</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete</td>
<td>36%</td>
<td>26%</td>
<td>35 mos</td>
</tr>
<tr>
<td>incomplete</td>
<td>13%</td>
<td>7%</td>
<td>15 mos</td>
</tr>
<tr>
<td>DFI 0-11 mos</td>
<td>33%</td>
<td>27%</td>
<td>29 mos</td>
</tr>
<tr>
<td>12 - 35</td>
<td>31%</td>
<td>22%</td>
<td>30 mos</td>
</tr>
<tr>
<td>&gt; 36</td>
<td>45%</td>
<td>29%</td>
<td>49 mos</td>
</tr>
</tbody>
</table>

overall mortality 1.0%

### Surgery for pulmonary metastases

**International Registry**

<table>
<thead>
<tr>
<th>Type</th>
<th>5-year</th>
<th>10-year</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>43%</td>
<td>31%</td>
<td>43 mos</td>
</tr>
<tr>
<td>2 or 3</td>
<td>34%</td>
<td>24%</td>
<td>31 mos</td>
</tr>
<tr>
<td>4 or more</td>
<td>27%</td>
<td>19%</td>
<td>27 mos</td>
</tr>
</tbody>
</table>

*Pastorino U. J Thorac Cardiovasc Surg 1997; 113:37-49*
Surgery for pulmonary metastases
International Registry

- multivariate analysis complete resection
- significant prognostic factors
  - 1ary tumor type (germ cell, Wilms)
  - DFI (>36 mos)
  - number of mets (single)

Surgery for pulmonary metastases
International Registry

**prognostic groups**

<table>
<thead>
<tr>
<th>group</th>
<th>Description</th>
<th>MST (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>single and DFI &gt; 35 mos.</td>
<td>61</td>
</tr>
<tr>
<td>II</td>
<td>single or DFI &gt; 35 mos.</td>
<td>34</td>
</tr>
<tr>
<td>III</td>
<td>multiple, DFI &lt; 36 mos.</td>
<td>24</td>
</tr>
<tr>
<td>IV</td>
<td>incomplete resection</td>
<td>14</td>
</tr>
</tbody>
</table>

Surgery for pulmonary metastases
International Registry

Surgery for pulmonary metastases

Lung mets: recent series

- 575 pts    708 pulmonary metastasectomies
- retrospective review 1998 – 2008
- open resection 83.3%    DFI 46.6 months
- results:
  5-year survival complete resection 46%
  multivariate analysis: complete resection
  germ cell tumors
  DFI ≥ 36 months
- not significant: n mets, n of metastasectomies

What’s new?
Lung metastases

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## Surgery for pulmonary metastases

### International Registry

**Surgical approach**

- Unilateral thoracotomy: 3111 (58%)
- Bilateral or staged: 576 (11%)
- Median sternotomy: 1415 (27%)
- VATS: 93 (2%)

Surgery for pulmonary metastases

- median sternotomy
- thoracotomy
- "clam shell" incision
- thoracoscopy (VATS)
- robotic da Vinci® system
Surgery for pulmonary metastases
International Registry

- maximal resected volume
  - sublobar: 3922 (76%)
  - (bi)lobectomy: 1109 (21%)
  - pneumonectomy: 133 (3%)

- extended resection
  - chest wall, diaphragm, LN: 446 (9%)

Surgery for pulmonary metastases

Controversies

- unilateral versus bilateral exploration
- simultaneous versus staged resections
- open versus closed
Surgery for pulmonary metastases
Role of VATS

- accuracy of VATS peripheral lung mets
- 28 pts CT scan: ≤ 3 solitary mets
  ≤ 3 cm, peripheral nodules
- VATS + confirmatory thoracotomy
- VATS: 10 technically impossible
  1 carcinoid
  17 confirmatory thoracotomy

Surgery for pulmonary metastases
Role of VATS

- confirmatory thoracotomy 17
  complete resection by VATS 12
  residual disease 5
- success rate: 1 lesion 11/12 correct
  > 1 lesion 1/5 correct
- VATS: solitary pulmonary metastasis
  ≤ 3 cm, peripheral nodule

Surgery for pulmonary metastases

Role of VATS

observer blinded study

- oligometastatic pulmonary disease
- VATS + thoracotomy (different team)
- 89 pts  CT 140 suspicious nodules
- VATS  122 nodules palpated (87%)
- thoracotomy:  67 additional nodules
  22 mets (33%) 43 benign (64%) 2 lung cancers (3%)
- VATS : inadequate to resect all pulmonary metastases

Surgery for pulmonary metastases

Lymph node dissection

- complete mediastinal lymph node dissection advised
- 883 pts resection lung metastases
  - 70 pts (7.9%) complete lymphadenectomy
  - 20 + LN (28.6%) 9 N1 8 N2 3 N1+2

- 3-year survival
  - LN 69%
  - + LN 38 % p<.001

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Surgery for pulmonary metastases

Treatment algorithm

Lung metastases

↓ operative risk

1-2 mets (peripheral)

VATS

open intervention

> 2 mets

↑ operative risk

RFA/SRT

recurrent lung mets after prior resection

repeat resection

What’s new?
Lung metastases

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- treatment algorithm
- how to improve local control?
Surgery for pulmonary metastases
Case report

° 27-07-62 ♂

- 1983 orchiectiony L + retroperit. lymph-adenectomy (teratocarcinoma)
- 1985 shortness of breath
  pulmonary mets; chemotherapy
- 1986 L thoracotomy (mature teratoma)
Surgery for pulmonary metastases
Case report

alphafetoprotein: 4/90 1.4 ng/ml
5/94 5220 ng/ml

- 3 cycles chemotherapy (2 BEP, 1 VIP)
- 7/94 R pneumonectomy
  - metastases RUL
  - mature teratoma subcarinal
persisting embryonal carcinoma  RUL
Lung metastasectomy - recurrences

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Epithelial</th>
<th>Sarcoma</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Single Intrathoracic</td>
<td>5</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Multiple Intrathoracic</td>
<td>45</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Intra-and Extrathoracic</td>
<td>17</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>33</td>
<td>36</td>
<td>40</td>
</tr>
</tbody>
</table>

Table II. Relapse after metastasectomy

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Epithelial</th>
<th>Sarcoma</th>
<th>Germ cell</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>All sites</td>
<td>917</td>
<td>12</td>
<td>1218</td>
<td>16</td>
</tr>
<tr>
<td>Single intrathoracic</td>
<td>111</td>
<td>32</td>
<td>191</td>
<td>50</td>
</tr>
<tr>
<td>Multiple intrathoracic</td>
<td>291</td>
<td>56</td>
<td>607</td>
<td>34</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>515</td>
<td>28</td>
<td>420</td>
<td>53</td>
</tr>
<tr>
<td>Second metastasectomy</td>
<td>260</td>
<td>28</td>
<td>642</td>
<td>53</td>
</tr>
</tbody>
</table>
Surgery for pulmonary metastases
Alternative treatments

Optimizing systemic + local control

- induction or adjuvant chemotherapy
- alternative techniques: SBRT, RFA
- biological techniques (inhaled interleukins)
- molecular or genetic therapy
- isolated lung perfusion (high local drug concentration)
- regional drug delivery (pulm.art. blood flow occlusion)
Isolated Lung Perfusion

- pulmonary metastases (PM)
  - CRC: 5-15%
  - sarcoma: 20-50%
- high pulmonary recurrence (up to 66%) due to undetected micrometastases
- surgical resection limited due to decrease in lung function
- systemic chemotherapy limited due to decrease in lung function
Isolated Lung Perfusion

Phase II clinical trial

A multicentre phase II clinical trial of isolated lung perfusion with melphalan in 107 patients with resectable lung metastases
Isolated Lung Perfusion

**Method**

- Lung isolation
  - Heparinisation
  - Cannulation of pulmonary artery and two pulmonary veins
  - Central clamping
  - Snaring main bronchus
- Centrifugal pump and closed circuit
- 45 mg melphalan at 37 °C for 30 minutes followed by a 5-minute washout
Phase II trial

Methods

- Pulmonary metastasectomy with lymphadenectomy
- Postoperative complications were scored using the extended Clavien-Dindo classification
- Lung function was measured preoperatively and at 1, 3, 6, 9 and 12 months
- Follow-up CT scans were performed to evaluate local and distant disease progression
Phase II trial

Goals

- evaluation
  - local control:
    - time to local pulmonary progression (TTLPP)
    - pulmonary progression-free survival (PPFS)
  - distant control:
    - time to progression (TTP)
    - disease-free survival (DFS)
  - overall survival:
    - median survival time (MST)
    - rate of overall survival
- confirm
  - safety
  - feasibility
Phase II trial

Patients

• 107 patients; 136 procedures
  – CRC: n=57
  – sarcoma: n=50
• 29 bilateral procedures
• male – female: 63-44
• mean age: 51 years (range: 19-78)
• mean DFI: 18 months (range: 0-168)
• median of 2 active metastases were found on pathology
Phase II trial

Results

- safety:
  - no perioperative mortality
  - recovery of lung function within 12 months
  - 12 (8.8%) severe complications

### Table 1: LUNG FUNCTION 12 MONTHS AFTER ILUP

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>91.08</td>
<td>16.11</td>
</tr>
<tr>
<td>VC</td>
<td>91.72</td>
<td>14.16</td>
</tr>
<tr>
<td>TLC</td>
<td>91.14</td>
<td>13.78</td>
</tr>
<tr>
<td>DLCO</td>
<td>93.24</td>
<td>2.50</td>
</tr>
<tr>
<td>KCO</td>
<td>103.61</td>
<td>19.28</td>
</tr>
</tbody>
</table>

ILUP: Isolated lung perfusion; SD: Standard deviation; FEV1: Forced expiratory volume in 1 second; VC: Vital capacity; TLC: Total lung capacity; DLCO: Diffusing capacity; KCO: DLCO/VA

### Table 2: SEVERE COMPLICATIONS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Complication</th>
<th>Treatment</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>Atelectasis</td>
<td>Bronchoscopy</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>Bronchoscopy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
<td>New chest tube</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td>New chest tube</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fibrotic lung</td>
<td>Pleural puncture, Diuretics</td>
<td>1</td>
</tr>
<tr>
<td>IIIb</td>
<td>Postoperative bleeding</td>
<td>Reoperation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chest tube sutured to skin</td>
<td>Reoperation</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>ARDS</td>
<td>ICU admission</td>
<td>1</td>
</tr>
<tr>
<td>IVa</td>
<td>Perioperative anaphylactic shock</td>
<td>Fluids, medication, ICU admission postoperatively</td>
<td>1</td>
</tr>
</tbody>
</table>
Phase II trial

Results

**Table 3: SURVIVAL DATA ACCORDING TO TUMOR HISTOLOGY**

<table>
<thead>
<tr>
<th></th>
<th>Median TTLPP(^1) (95% CI)</th>
<th>3-year PPFS (%)</th>
<th>Median TTP(^1) (95% CI)</th>
<th>3-year DFS (%)</th>
<th>MST(^1) (95% CI)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>22 (10-34)</td>
<td>42 ± 7%</td>
<td>12 (7-17)</td>
<td>27 ± 6%</td>
<td>78 (35-121)</td>
<td>57 ± 9%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>NR</td>
<td>60 ± 8%</td>
<td>12 (7-18)</td>
<td>28 ± 7%</td>
<td>42 (29-55)</td>
<td>34 ± 8%</td>
</tr>
<tr>
<td>Overall</td>
<td>34 (4-64)</td>
<td>50 ± 5%</td>
<td>12 (9-15)</td>
<td>27 ± 4%</td>
<td>50 (36-64)</td>
<td>46 ± 6%</td>
</tr>
</tbody>
</table>

\(^1\) Time in months

MST: median survival time; OS: overall survival; TTP: time to progression; TTLPP: time to local pulmonary progression; DFS: disease-free survival; CRC: colorectal carcinoma; NR: not reached

**Table 4: LOCATION OF FIRST RECURRENTCE**

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral lung</th>
<th>Contralateral lung</th>
<th>Local (primary)</th>
<th>Other</th>
<th>Multiple sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>41</td>
<td>18</td>
<td>5</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>% of total patients</td>
<td>30</td>
<td>13</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>% of total recurrence</td>
<td>48</td>
<td>21</td>
<td>6</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>
Phase II trial

Results

Table 5: SURVIVAL DATA FOR SPREAD OF DISEASE ACCORDING TO TUMOR HISTOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Median TTLPP(^1) (95% CI)</th>
<th>3-year PPFS (95% CI)</th>
<th>Median TTP(^1) (95% CI)</th>
<th>3-year DFS (95% CI)</th>
<th>MST(^1) (95% CI)</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral disease</td>
<td>NR</td>
<td>59 ± 10%</td>
<td>23 (0-83)</td>
<td>48 ± 10%</td>
<td>NR</td>
<td>73 ± 9%</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>18 (12-24)</td>
<td>26 ± 9%</td>
<td>11 (7-17)</td>
<td>7 ± 5%</td>
<td>51 (24-78)</td>
<td>34 ± 11%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral disease</td>
<td>NR</td>
<td>60 ± 13%</td>
<td>15 (7-24)</td>
<td>14 ± 9%</td>
<td>48 (38-58)</td>
<td>35 ± 15%</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>NR</td>
<td>60 ± 10%</td>
<td>10 (6-14)</td>
<td>35 ± 9%</td>
<td>38 (25-51)</td>
<td>32 ± 9%</td>
</tr>
</tbody>
</table>

\(^1\) Time in months

TTLPP: time to local pulmonary progression; PPFS: pulmonary progression free survival; TTP: time to progression; DFS: disease free survival; MST: median survival time; OS: overall survival; HVC: high volume centre; LVC: low volume centre; CRC: colorectal carcinoma

Literature:
- **CRC**
  - TTLPP: 12-19 mos
  - 3-year PPFS:
    - Unilateral: 55%
    - Bilateral: 12%
  - TTP: 12-32 mos
  - 3-year DFS: 44%
    - 1 study
    - 26% bilateral procedures
  - MST: 31-75 mos
  - 5-year OS: 34-68
- **Sarcoma**
  - TTLPP: 13-18 mos
  - 3-year PPFS: 44-45%
  - TTP: 7-8 mos
  - 3-year DFS: 25-26%
  - MST: 19-48 mos
  - 5-year OS: 22-53%
Phase II trial

Conclusions

- isolated lung perfusion with melphalan combined with metastasectomy is feasible and safe
  - no perioperative † - postoperative complications ≈ regular thoracic procedures
  - no long-term pulmonary toxicity
Phase II trial

Conclusions

• compared to historical controls, ILuP with melphalan combined with pulmonary metastasectomy seems beneficial in pts with PM from CRC and sarcoma tumours
  – ILuP shows better local control compared to retrospective literature data, especially in unilateral disease
  – for sarcoma patients this local control markedly diminished general disease progression
Phase II trial

Conclusions

- treatment of undetected micrometastases is needed
- further evaluation of locoregional lung perfusion techniques with other chemotherapeutic drugs, a RCT and with adjuvant intravenous therapy is warranted