Isolated lung perfusion and related techniques for treatment of pulmonary metastases. Is survival really improved?

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on behalf on EACTS lung perfusion working group

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no conflicts of interest
Isolated lung perfusion and related techniques for treatment of pulmonary metastases. Is survival really improved?

- survival data: the problem
- how to improve local control?
- phase II study of ILuP
- conclusions
Isolated lung perfusion and related techniques for treatment of pulmonary metastases. Is survival really improved?

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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?
Pulmonary metastasectomy: where is the evidence?

- 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*

- prospective registries (ITMIG, IASLC)

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

## 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>

### Table II. Relapse after metastasectomy

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Epithelial</th>
<th></th>
<th>Sarcoma</th>
<th></th>
<th>Germ cell</th>
<th></th>
<th>Melanoma</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<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>
<td>84</td>
<td>21</td>
<td>180</td>
<td>8</td>
</tr>
<tr>
<td>Single intrathoracic</td>
<td>111</td>
<td>12</td>
<td>191</td>
<td>16</td>
<td>18</td>
<td>21</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Multiple intrathoracic</td>
<td>291</td>
<td>32</td>
<td>607</td>
<td>50</td>
<td>30</td>
<td>36</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>515</td>
<td>36</td>
<td>420</td>
<td>34</td>
<td>36</td>
<td>43</td>
<td>132</td>
<td>73</td>
</tr>
<tr>
<td>Second metastasectomy</td>
<td>260</td>
<td>28</td>
<td>642</td>
<td>53</td>
<td>34</td>
<td>40</td>
<td>28</td>
<td>16</td>
</tr>
</tbody>
</table>

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Alternative treatments

Optimizing systemic + local control

- induction or adjuvant systemic chemotherapy
- alternative techniques: SRT, RFA
- chemoembolisation
- isolated lung perfusion (high local drug concentration)
- regional drug delivery (pulm. art. infusion)
Alternative techniques: chemo-embolisation

- chemo-embolisation with degradable starch microspheres + cytotoxic drugs (carboplatin) in a rat model
  - more effective than i.v. and $= ILuP$

  Schneider P. Clin Cancer Res 2002; 8:2463-8

- transpulmonary chemo-embolisation
  - 106 unresectable lung metastases in 52 pts
  - 5-10 mg mitomycin C + 5-10 ml iodized oil + microspheres
  - no complications, well tolerated
  - partial response in 16 pts., stable disease 11, progression 25
  - median survival 21 months

Isolated lung perfusion (ILuP)

Experimental animal studies

rat model ILuP

Weksler B. J Appl Physiol 1993; 74: 2736-9
phase II  ILuP: method

- **lung isolation**
  - heparinisation
  - cannulation of pulm. artery and both veins
  - central clamping
  - snaring of main bronchus

- **centrifugal pump** and a closed circuit

- 45 mg melphalan at 37°C for 30 min followed by washout
  - alkylating agent
  - also used with isolated limb and liver perfusion
Isolated lung perfusion (ILuP)

den Hengst W. J Thorac Oncol 2014; 9:1547-53
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phase II  ILuP: procedure – follow-up

• phase II single arm, *resectable* lung mets colorectal cancer and sarcoma
• 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 mos
• follow-up CT scans to evaluate local and distant disease progression
phase II  ILuP: patients

- 107 pts  136 procedures: Leiden, Rotterdam, Nieuwegein, NL
  Antwerp, B

n=57            n = 50

- 29 bilateral procedures
- ♂  63 pts     ♀   44 pts
- mean age 51 years (range 19-78)
- mean DFI: 18 mos (range 0-168)
- median of 2 active mets on pathology (range: 0-17)
phase II ILuP: results

• Safety:
  – no perioperative mortality
  – 12 (8.8%) severe complications (grade III or higher)
  – recovery of lung function within 12 months

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

Table 1: LUNG FUNCTION 12 MONTHS AFTER ILUP

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of preoperative value</td>
<td>% of preoperative value</td>
<td>% of preoperative value</td>
</tr>
<tr>
<td>FEV1</td>
<td>91.06</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 3: SURVIVAL DATA ACCORDING TO TUMOR HISTOLOGY

<table>
<thead>
<tr>
<th>Tumor Type</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 ± 5%</td>
</tr>
</tbody>
</table>

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

\(^1\) Time in months

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Table 4: LOCATION OF FIRST RECURRENCE

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of patients</th>
<th>% of total patients</th>
<th>No. of patients</th>
<th>% of total patients</th>
<th>No. of patients</th>
<th>% of total patients</th>
<th>No. of patients</th>
<th>% of total patients</th>
<th>No. of patients</th>
<th>% of total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral lung</td>
<td>41</td>
<td>30</td>
<td>18</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>18</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local (primary)</td>
<td>5</td>
<td>4</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sites</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
phase II ILuP: results

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

<table>
<thead>
<tr>
<th></th>
<th>Median TTLPP¹ (95% CI)</th>
<th>3-year PPFS (95% CI)</th>
<th>Median TTP¹ (95% CI)</th>
<th>3-year DFS (95% CI)</th>
<th>MST¹ (95% CI)</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</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</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><strong>Sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>NR</td>
<td>60 ± 10%</td>
<td>15 (7-24)</td>
<td>14 ± 9%</td>
<td>48 (38-58)</td>
<td>35 ± 15%</td>
</tr>
<tr>
<td>Bilateral</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: 12-52 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%
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phase II ILuP: conclusions

• **ILuP with melphalan** combined with metastasectomy is feasible and safe
  - no perioperative † - postoperative complications ≈ regular thoracic procedures
  - no long-term pulmonary toxicity

• compared to historical controls, ILuP with melphalan is beneficial in pts with colorectal and sarcoma tumours
  - ILuP better local control compared to retrospective literature data, especially in unilateral disease.
  - for sarcoma patients this local control markedly diminished general disease progression; long-term survival?

• further evaluation of **locoregional lung perfusion techniques** with other chemotherapeutic drugs and adjuvant IV therapy is warranted.
Alternative techniques: future prospects

Pulmonary artery infusion

- high-dose unilateral pulmonary chemotherapy (infusate)
- catheter-based pulmonary artery control in dog model
- 75% of tracer remained in lung after 30 min. dwell time

- blood flow occlusion in rat model with gemcitabine
- MTD 40 mg, lung saturated after 20 min
- ↓ plasma levels and ↑ lung levels compared with iv injection