Resection of liver limited metastases

H.-R. Raab
Segmental anatomy of the liver
Principles of liver resection

Examinations before resection of the liver
- CT + MRI with liver specific contrast media
- 3D-reconstruction for selected cases
- intraoperative US to definitively decide about extent of resection

Functional demands
- sufficient residual parenchyma
- Blood supply via hepatic artery and portal vein
- venous drainage via at least one hepatic vein
- bile drainage

Dissection of parenchyma and control of bleeding
- different possibilities for both
- blood transfusions should be a rare exception
Extent of resection

Atypical (non-anatomical) resections
- subsegmental resections
  (so called “wedge resections”)

Anatomical resections
- segmental resections
- bisegmental resections (sectorectomies)
- right or left hepatectomy
- extended hepatectomie (trisectorectomie)
Anatomical resections

right liver lobe  left liver lobe

VII  VIII  I_r  I_i  IVa  II
VI  V  IVb  III

V-VIII about 60%

right hepatectomy

II u. III

left-lateral resection

I-IV

segm. I-IV

left hepatectomy

IV-VIII about 70%

segm. IV-VIII

right trisectorectomie
Surgical access and dissection of the parenchyma
Right hepatectomy
Proof that resection of CRC liver mets can be curative

Scheele et al. 1995, data from Erlangen

Survival

Years after operation

Curative resection (n = 226)
Resectable, untreated (n = 62)
Not resectable (n = 921)

p < 0.0001
Evidence that even R1/2-resection of CRC liver mets can prolong survival

Own results (early 80s, unselected)

- **RO-resection**
- **R1/2 resection**
- **exploration only**

Survival over months:

0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Liver resection of colorectal liver metastases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>5-YSR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheele</td>
<td>1995</td>
<td>434</td>
<td>39</td>
</tr>
<tr>
<td>Nordlinger</td>
<td>1996</td>
<td>1568</td>
<td>28</td>
</tr>
<tr>
<td>Geoghegan</td>
<td>1998</td>
<td>Review of lit.</td>
<td>40</td>
</tr>
<tr>
<td>Fong</td>
<td>1999</td>
<td>1001</td>
<td>37</td>
</tr>
<tr>
<td>Choti</td>
<td>2002</td>
<td>226</td>
<td>40</td>
</tr>
<tr>
<td>Adam</td>
<td>2003</td>
<td>615</td>
<td>28</td>
</tr>
<tr>
<td>Pawlik</td>
<td>2005</td>
<td>557</td>
<td>58</td>
</tr>
<tr>
<td>Wei</td>
<td>2006</td>
<td>423</td>
<td>47</td>
</tr>
<tr>
<td>Tomlinson</td>
<td>2007</td>
<td>612</td>
<td>37</td>
</tr>
<tr>
<td>De Haas</td>
<td>2008</td>
<td>436</td>
<td>39</td>
</tr>
<tr>
<td>Robertson</td>
<td>2009</td>
<td>3957</td>
<td>26</td>
</tr>
<tr>
<td>Fortner</td>
<td>2009</td>
<td>293</td>
<td>35</td>
</tr>
<tr>
<td>Giuliani</td>
<td>2009</td>
<td>251</td>
<td>39</td>
</tr>
<tr>
<td>Thomas</td>
<td>2010</td>
<td>432</td>
<td>48</td>
</tr>
<tr>
<td>Swan</td>
<td>2011</td>
<td>1202</td>
<td>42</td>
</tr>
<tr>
<td>Kulik</td>
<td>2011</td>
<td>939</td>
<td>32 (&gt;70 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38 (&lt;70 years)</td>
</tr>
</tbody>
</table>
## Liver metastases of CRC: Scores

<table>
<thead>
<tr>
<th>Autor</th>
<th>Alter (p)T</th>
<th>(p)N</th>
<th>Grad</th>
<th>Intervall</th>
<th>CEA</th>
<th>Anzahl</th>
<th>DM</th>
<th>Dist?</th>
<th>Rand</th>
<th>EHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordlinger I</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nordlinger II</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Nordlinger III</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Fong</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Iwatsuki</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nagashima</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Lee</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Rees I</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Rees II</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Konopke</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Jena</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

nach Altendorf-Hofmann et al., 2010
Liver metastases of CRC: Clinical risk score (Fong)

Clinical criteria: 1 point each

- Lymph node metastases of the primary tumor (N+)
- Disease-free interval between resection of the primary and diagnosis of liver metastases <12 months
- Number of liver metastases in the preoperative scans >1
- Peroperative CEA level >200ng/ml
- Diameter of the largest metastasis >5cm

0 points  good prognosis
1-2 points  intermediate prognosis
3-5 points  worse prognosis

The Fong-score discriminates prognostic groups, but ...

Data from Erlangen1995-2006
Courtesy of Mrs. Altendorf-Hofmann
The Fong-score discriminates prognostic groups, but ...

Data from Erlangen 1995-2006
Courtesy of Mrs. Altendorf-Hofmann

The Fong-score is not not a suitable means to exclude patients from liver resection
Development of resection rates for colorectal liver metastases

![Graph showing percentage of patients undergoing liver resection from 1990 to 2006. The graph demonstrates an increase in resection rates over time, with fluctuations in certain years.](image-url)
Development of resection rates for colorectal liver metastases

Actually at least 25%, probably up to 50% or even more CRC liver mets are resectable.

Kopetz et al. JCO 2009
Resection rates of colorectal liver metastases according to the level of care

- Liver center (n=197): 46.6%
- Regional Hospital (n=177): 22.0%
- Total (n=374): 26.2%
Resection of CRC liver metastases

Former contraindications

- More than 3 metastases
- Safety distance less than 1 cm
- Extrahepatic tumor manifestations
- Recurrent metastases

No evidence to support those limitations. Most contraindications are based on unproven assumptions!
Contraindication number of metastases?

Scheele et al. (patients from Erlanger)
Contraindication number of metastases?

Survival (%)

Years

number of metastases

- 1
- 2-3
- ≥ 4

Contraindication limited safety distance?

Survival years after R0 – liver resection

- 0 - 9 mm
- ≥ 10 mm

Scheele et al. (patients from Erlangen)
**FIGURE 4.** Survival stratified by margin status. Median survival was 49.6 months in patients with positive margins and not yet reached in patients with negative margins ($P = 0.005$). No significant difference in survival was seen in patients with a negative surgical margin, regardless of the width of the margin (all $P > 0.5$).
Contraindication extrahepatic tumor?

Scheele et al. (patients from Erlangen)
Liver mets + resectable lung metastases?

131 Patients
- median survival 3.8 years
- 5-year survival 35%
Contraindication recurrent metastases?
Liver resection for colorectal metastases

PROVEN FACTS

Liver resection improves survival.

Chance of cure by R0-resection

- about 25-45% of all patients with metastases, depending on selection

Realistic chance of cure only after R0-resection
Possibilities if metastases are irresectable

- **Transplantation** (no chance to get an organ)
- **Local destruction**
  - Microwave ablation
  - Radio frequency ablation (RITA)
  - Interstitial LASER therapy (LITT)

Extended possibilities of resection
  (staged procedure, split procedure, hypothermic perfusion)

- Neoadjuvant chemotherapy

No realistic chance of cure
“Un-resectable“ metastases can be made resectable

**FIGURE 2.** a. A 40-year-old man presenting huge liver metastases not amenable to primary resection because of too large liver involvement and close contact with portal bifurcation, hepatic veins, and vena cava. (b) Tumor downstaging by chemotherapy allowed secondary liver resection by right hepatectomy. The patient is currently alive without recurrence at 5.5 years.

**Rescue surgery for unresectable colorectal liver metastases**
Pat. C.S. born 1942

July 2010: Liver metastases

February 2012, after Ctx
Rescue surgery for „unresectable“ CRC liver mets

Neoadjuvant Ctx in the treatment of liver metastases

Chemotherapy of 1104 patients with initially irresectable liver metastases

- Secondary resectable: 12.5%
- Survival after curative resection: 33%
- 4 independent prognostic factors:
  - primary in the rectum
  - more than 3 mets
  - greatest diameter of metastasis > 10 cm
  - Ca 19-9 >100 U/l
10 year-survival: Resectable versus primary un-resectable mets

![Survival Graph]

- Resectable: 335 patients
- Initially non-resectable: 138 patients

<table>
<thead>
<tr>
<th>Years</th>
<th>Non-resectable</th>
<th>Resectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Yr</td>
<td>138</td>
<td>335</td>
</tr>
<tr>
<td>1 Yr</td>
<td>124</td>
<td>282</td>
</tr>
<tr>
<td>3 Yrs</td>
<td>69</td>
<td>168</td>
</tr>
<tr>
<td>5 Yrs</td>
<td>37</td>
<td>90</td>
</tr>
<tr>
<td>8 Yrs</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>10 Yrs</td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>
Neoadjuvant Ctx for **resectable** liver metastases?


371(9617):1007-1016
Neoadjuvant Ctx for **resectable** liver metastases?

EORTC 40983 trial

<table>
<thead>
<tr>
<th>Eligible patients</th>
<th>Patients (N)</th>
<th>Deaths (n [%])</th>
<th>HR (95% CI)</th>
<th>Median overall survival (months [95% CI])</th>
<th>Estimated 5 year overall survival (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative chemotherapy</td>
<td>171</td>
<td>101 (59%)</td>
<td>0.87 (0.66-1.14)</td>
<td>63.7 (52.7-87.3)</td>
<td>52.4% (44.6-59.7)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>171</td>
<td>109 (64%)</td>
<td>1.00</td>
<td>55.0 (41.9-79.4)</td>
<td>48.3% (40.6-55.6)</td>
</tr>
</tbody>
</table>

**Overall survival**

Nordlinger et al., Lancet Oncol 2013
CASH (Chemotherapy-Associated Steatohepatitis) Costs

Yuman Fong, MD,* and David J. Bentrem, MD†

FIGURE 1. Development of CASH in a patient subjected to neoadjuvant chemotherapy. The development of steatohepatitis is clearly demonstrated by the decreased attenuation in the liver after 2 months of chemotherapy (B) as compared with before (A). The effects of chemotherapy on tumor are clear as demonstrated by the decrease in size of tumor in the scans (A, B), and in the tumor killing seen histologically (C). The effects on the noncancerous liver in terms of fat deposits are also clear (D).
Sinusoidal congestion caused by Oxaliplatin

Figure 1. (A) Low-power examination on trichrome Masson stain of the liver revealed areas of sinusoidal congestion involving centrilobular and mediolobular lobular surface. At high-power examination, sinusoidal congestion is severe, outlined by atrophic hepatocyte trabeculae. (B) The small hepatic vein is partially occluded by fibrous tissue; on the cut surface, the liver around and at the distance of the metastasis is diffusely nodular. (C) Nodules are outlined by congested areas. (D) In a third hepatectomy, performed in one patient 49 months after chemotherapy, extensive fibrous septa delimit parenchymal nodules on trichrome Masson.
### Risks of surgery after neoadjuvant Ctx

#### TABLE 4. Postoperative Complications in the 67 Patients According to the Preoperative Use of Chemotherapy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Chemotherapy Group (n = 45)</th>
<th>Control Group (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic failure</td>
<td>5</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural effusion requiring drainage</td>
<td>6</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Chest infection</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Subphrenic abscess</td>
<td>4</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Phlebothrombosis</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with complications</td>
<td>17</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay (mean ± SD) (days)</td>
<td>16.0 ± 8.2</td>
<td>15.7 ± 8.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant.
Risks of surgery after neoadjuvant Ctx

FIGURE 1. Influence of the number of cycles of CT on the percentage of postoperative morbidity.
Resection of liver metastases - Two stage hepatectomy -

**Concept**

- resection of all metastases of one lobe
- induction of liver hypertrophy
- resection of the contralateral lobe

Lang et al., Chirurg 2007
Chemotherapy:
- metastatic CRC
  n=879
- liver only
  n=425
- CTx responder and survival > 12 mo.
  n=207
- ≤70y., PS ≤2
  n=179
- no innumerable met’s
  n=62
- 06/2002-02/2010

Overall survival

Surgery (2-stage resection)

Chemo

Advanced bilateral CLM two-stage not completed (n=18)

Advanced bilateral CLM two-stage completed (n=47)

Advanced bilateral CLM chemotherapy-only (n=62)
Where are the borderlines?

Diseases desperate grown
By desperate appliance are relieved,
Or not at all.

William Shakespeare
Hamlet, Act 4, Scene 3
Liver resection with hypothermic perfusion

in situ  ante situm  ex situ
Liver resection with hypothermic perfusion

% Survival after R0-resection

- Conventional
- Hypothermic perfusion
  - n = 24 ex situ
  - n = 23 ante situm
  - n = 10 in situ

Survival over time (months)

6-90
Surgical resection of liver metastases, sometimes extended and/or repeated, is useful, if a R0-situation can be achieved. - possible in 25-50% or even more of all pts with CRC LM - cure for 25-45% of the patients - good palliation for many others

Means for thermoablation (RFA, LITT, MW ) are methods of second/third choice.

Multimodal concepts of therapy lead to an improvement of the results, up to now especially as neoadvant treatment of unresectable or borderline resectable metastases. Nevertheless, many questions are still open.