Metastatic colorectal cancer: special clinical situations

Primary tumor with synchronous metastases

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Comparison of 15 scoring systems of prognosis (1996 - 2009)

The occurrence of prognostic factors in the analysis of the selected studies proposing predictive models for outcome after liver resection for colorectal cancer metastases.

<table>
<thead>
<tr>
<th>Number of liver metastases</th>
<th>Total number of patients</th>
<th>Highest level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies (prospective ones)</td>
<td>12 (4)</td>
<td>6086</td>
</tr>
<tr>
<td>CRC spread to lymph nodes</td>
<td>10 (2)</td>
<td>5228</td>
</tr>
<tr>
<td>Maximum size of metastases</td>
<td>6 (1)</td>
<td>4340</td>
</tr>
<tr>
<td>Interval between CRC operation and detection of liver metastases</td>
<td>5 (0)</td>
<td>3040</td>
</tr>
<tr>
<td>Preoperative CEA-level</td>
<td>5 (3)</td>
<td>2890</td>
</tr>
<tr>
<td>Extravasation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor perioperative condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significantly elevated ALP levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic lymph node metastases</td>
<td>2 (1)</td>
<td>1031</td>
</tr>
<tr>
<td>Bilobar spread</td>
<td>2 (0)</td>
<td>454</td>
</tr>
</tbody>
</table>

High risk of recurrence after/during surgery

+= factor identified as predictive, -= factor identified as not predictive, blank field = factor not analysed.
Case Report MHH 1991

UICC IV rectal cancer

rectal cancer

synchronous

- large liver metastases
- Infiltration of diaphragm

- Abdomino-perineal resection simultaneous extended right hepatectomy
- postoperative chemotherapy; 5-FU
- died of recurrence 1 year postoperatively
38-year-old female; **unresectable** liver metastases

**asymptomatic** adenocarcinoma of sigma (15-20cm ab ano) (06/2011)

Chemotherapy with Folfiri + Cetuximab from 06/2011 to 12/2011
Case Report UMM 2011

CT after 3 cycles Folfiri + Cetuximab

significant response!!
Surgery February 2012:

- Extended right hepatectomy + reconstruction of left hepatic vein + wedge resections segments II and III

Surgery March 2012:

- low anterior rectal resection

ypT3 ypN0 G2 R0
R0-resection of both primary tumor and liver metastases offers the only chance for cure!

Therapeutic strategies:

- curative situation:
  - resection and potential cure, lowering the risk for recurrence

- potentially curative situation:
  - increasing resectability
  - lowering the risk for local and systemic recurrence

- noncurable disease:
  - prolongation of survival
  - optimizing quality of life

No randomized studies!
UICC IV - different scenarios
Value of neoadjuvant CRT in UICC IV?

Primary chemotherapy
Liver first
Rectal resection first
Simultaneous resection

Neoadjuvant RT/CRT
asymptomatic primary
symptomatic primary

UICC IV - different scenarios
Primary chemotherapy  
(CRC resection first)  
Simultaneous resection  

Liver first  
(Neoadjuvant RT/CRT)  

Colostomy if symptomatic  

Rectal resection
Primary chemotherapy
( Rectal resection first)
Simultaneous resection

Colostomy if symptomatic
UICC IV - different scenarios

Liver resection first
Rectal resection first
Simultaneous resection

Colostomy?

Neoadjuvant RT/CRT

Rectal resection
Stage IV colorectal carcinoma (liver only)

Rationale for traditional approach („primary first“)
- Treatment/prevention of tumor related symptoms
- Primary tumor is „trigger“ of metastases
- Recovery time after resection of primary tumor:
  - „selection period“ (to avoid unnecessary liver resections)
  - Disease progression to unresectable hepatic disease

Rationale for „liver first“
- Liver metastases determine prognosis
- „better“ condition for RCTx (rectal cancer)
- Chemotherapy also effective on primary tumor
- Laparoscopic CRC resection more difficult after open liver resection

Rationale for synchronous resection
- Only one operation
- Increased morbidity?
- Early recurrence in aggressive tumors before/ despite CTx
CRT in rectal cancer

- undertreatment of liver metastases (low-dose CTx)
- 1/3 of patients did not receive adjuvant CRT

**Table 1. Patient and Tumor Characteristics According to Treatment Received**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preoperative CRT (n = 406)</th>
<th>Postoperative CRT (n = 248)</th>
<th>No Postoperative CRT (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
<td>30-77</td>
<td>30-77</td>
<td>30-77</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>293</td>
<td>203</td>
<td>165</td>
</tr>
<tr>
<td>Female</td>
<td>113</td>
<td>145</td>
<td>78</td>
</tr>
<tr>
<td>Distance from anal verge, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-&lt;5</td>
<td>117</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>5-&lt;10</td>
<td>199</td>
<td>102</td>
<td>66</td>
</tr>
<tr>
<td>10-16</td>
<td>85</td>
<td>79</td>
<td>45</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

**improvement of survival by intensifying systemic therapy!**

Outcome of surgery in patients with rectal cancer and simultaneous liver metastases

Overall survival (OS) all groups (n=57) 5 years 38%

Group 1 (n=29)
Primary tumor first
5-year OS 28%

Group 2 (n=8)
Simultaneous resection
5-year OS 73%

Group 3 (n=20)
Liver-first-approach
5-year OS 67%

Van der Pool et al., Br J Surg 2010
## Liver first - literature

<table>
<thead>
<tr>
<th>Author/year</th>
<th>patients</th>
<th>rectal/colon</th>
<th>Liver resection n (%)</th>
<th>completed sequence</th>
<th>prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentha 2008</td>
<td>n = 35</td>
<td>13/17</td>
<td>31 (89%)</td>
<td>30 / 85%</td>
<td>med. survival: 44 months; 1-, 2-, 3-, 4-, 5J-OS resect pat.: 100%, 89%, 66%, 44%, 30%</td>
</tr>
<tr>
<td>Verhoef 2009</td>
<td>n = 23</td>
<td>23/0</td>
<td>20 (87%)</td>
<td>17 / 73%</td>
<td>Median survival : 19 (7–56) months</td>
</tr>
<tr>
<td>Brouquet 2010</td>
<td>n = 41</td>
<td>28/13</td>
<td>27 (66%)</td>
<td>27 / 66%</td>
<td>4-year: 52%</td>
</tr>
<tr>
<td>De Jong 2011</td>
<td>n = 22</td>
<td>19/3</td>
<td>21 (95%)</td>
<td>16 / 73%</td>
<td>3-year.: 41%</td>
</tr>
<tr>
<td>Rosa 2013</td>
<td>n = 37</td>
<td>25/12</td>
<td>30 (81%)</td>
<td>24 / 65%</td>
<td>1-year-OS: 66% 3-year-OS: 30%</td>
</tr>
</tbody>
</table>

158 108/45 129 (82%) 114 (72%)
Liver first - summary

- no evidence-based data!
- usually CTx first!

- disadvantage:
  prognosis related factors of primary tumor remain unknown

- advantage:
  treatment of „prognostic most relevant“ tumor

Indication for liver first:
- in case of a risk for irresectability in case of (metastasis) progression
- in case of risk of simultaneous operation is too high
- in case of minor liver involvement but planned RCTx for rectal cancer
Response of primary tumor and metastases to chemotherapy

Simultaneous resection

Patient selection?!
Smaller tumors
„easier CRC resection“
Smaller liver resection

Laparoscopic vs. open liver resection

**Match-pair analysis**
Laparoscopic vs open resection for CRC-liver metastases
66 vs 66 patients

**OSLO-COMET Randomized trial**
Laparoscopic vs open resection for CRC-liver metastases
129 vs 144 patients

- **Complication rate**: 19% vs 31%  \( p=0.021 \)
- **Hospital stay**: 53h vs 96h  \( p<0.001 \)
- **Morphin equivalent**: 52 vs 170  \( p<0.001 \)


Simultaneous resection

Case report

- ♂, 79j
- (recto-) sigmoid cancer (15cm ab ano)
- Synchronous liver metastasis segment V

\[ pT3, pN0 \ (0/12), \ M1, \ G2, \ R0 \]

Discharge on POD 12
Liver first

Resectable liver metastases – advanced primary tumor

• 51-year-old female patient
• 04/10 diagnosis of non-obstructing adenocarcinoma of upper rectum
• synchronous liver metastases in segments I and IV-VIII
Liver first

Resectable liver metastases – advanced primary tumor

04/2010  extended right hepatectomy (R0-resection)

07/2010  low ant. rectal resection with partial right adnexectomy, partial peritonectomy in pelvis; loop ileostomy
  pT4a pN2b (11/16) G3 R0

07/2010  closure of ileostomy
  adjuvant chemotherapy: FOLFOX
Liver first

Resectable liver metastases, advanced primary tumor

- 47 – year-old male patient
- rectal cancer: primary tumor circular growth, exophytic; no stenosis uT3 uN1; M1 (hep)
- Resectable liver metastases

1. liver resection (bisegmentectomy)
2. CRT of the rectum
3. two-stage: resection of rectal cancer
Summary

Change of paradigm CRC Stadium IV

- **old strategy** (monomodal-sequential, unidirectional)
  
  - Resection of primary tumor
  - Resection of liver metastases
  - Additional treatment

- **new strategy** (multimodal multidirectional)
  (surgery not necessarily first treatment)

  - Liver resection
  - Resection of primary tumor
  - Neoadjuvant (palliative) therapy
  - CTx / RCTx