Colon cancers and new developments in treatment of liver metastases

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Worldwide range of colorectal cancer incidence for males (world age standardised rates per 100 000 males)

Liver metastases from colorectal cancer

- No metastases: 50%
- Synchronous: 25%
- Metachronous: 25%
Topics

• Introduction
• Liver metastases (LM)
  1. Resectable
  2. Unresectable, but potentially resectable
  3. Permanently unresectable
• Organisation
• Conclusion
Resectable liver metastases

- R0 for all tumors
  - Width in mm does not count
  - 8-10 LM high recurrence rate

- Sufficient future liver
  - 30% initial liver volume
  - 40% after chemotherapy
  - At least two segments
Liver resections

- (extended) Right
- (extended) Left
- Segment resections
- Wedge resections
- Major resection is > 3 segments
Complications liver resection

- Mortality ranges 0% - 3.7%
- Postoperative morbidity ranges 15% - 46%
  - bloodloss
  - bile leakage
  - sepsis
  - insufficient remaining liver
Synchronous LM

• Surgical approaches:
  – simultaneous
  – primary CRC tumor first
  – liver resection first
Extra Hepatic Disease
Poor prognostic factors

1. EHD other than lung
2. Concomitant CLM recurrence
3. CEA at least 10 ng/ml
4. At least 6 CLM
5. Right colon cancer

5-year survival:
0 factors 64%
> 3 factors 0%

Recurrence and reresection

- Up to 70%
- 50% relapse within 18 months
- Reresection comparable morbidity, mortality and OS
Predicting factors survival after recurrence

• Curative nature of 1st and 2nd liver resections
• Interval > 1 year
• Number of recurrent tumors
• CEA levels
• Presence of EHD

Post-operative chemotherapy for resectable LM?

• Postoperative chemotherapy (adjuvant)
  – prospective studies prematurely stopped
  – better 5-year DFS
  – trend better OS

• Postoperative chemotherapy standard
Pre–operative chemotherapy for resectable LM?

EORTC 40983 Intergroup trial:

6x Folfox4  $\rightarrow$ resection  $\rightarrow$ 6x Folfox4 vs. resection

Unresectable (R0)

- Pre-operative therapy for downstaging
- Increases 12.5% resectable patients
Systemic therapy

• **Chemotherapy:**
  – 5-FU / leucovorin
  – capecitabine
  – oxaliplatin
  – irinotecan

• **Monoclonal antibodies:**
  – EGFR inhibitor; cetuximab for K-RAS wild type
  – VEGF inhibitor; bevacizumab
Crystal trial

Folfiri + cetuximab vs. Folfiri

Improving:

- response rates 59% vs. 43%
- R0 resection rates 4.8% vs. 1.7%

## Pre-operative CapoxB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Day</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>1000 mg/m² bid</td>
<td>1 - 14</td>
<td>Oral</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>1</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>7.5 mg/kg</td>
<td>1</td>
<td>Intravenous</td>
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One cycle, 21 days

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|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| O| B|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| C| C| C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C |
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Oncologisch centrum Isala
Benefits and risks of pre-operative chemotherapy

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Potential negative impacts</th>
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<tbody>
<tr>
<td>Improved PFS</td>
<td>Delayed surgery</td>
</tr>
<tr>
<td>Evaluation chemo response</td>
<td>More reversible surgical complications</td>
</tr>
<tr>
<td>Selection for surgery</td>
<td>Chemo associated liver injuries</td>
</tr>
<tr>
<td>Fewer “open and close”</td>
<td>Complete response</td>
</tr>
<tr>
<td>Low operative mortality</td>
<td>Cost</td>
</tr>
</tbody>
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Steatosis

• 5-FU, oxaliplatin, irinotecan
• Incidence rate 30 - 40%
• Increased postoperative morbidity
Steatohepatitis

- Irinotecan
- Incidence rate 3.6 - 8%
- 90-Day mortality rate 15% vs. 2%
- Caution irinotecan
  - Obese; BMI > 25
  - Diabetes mellitus
  - Hypertension
Sinusoidal Obstruction Syndrome (SOS)

- Oxaliplatin
- Incidence rate 10 - 52%
- No increase morbidity and mortality after resection
Targeted therapies

• Cetuximab; no interference with surgery
• Bevacizumab;
  – impair wound healing and liver regeneration
  – administration stop 4-8 weeks before surgery
  – decrease risk of SOS from oxaliplatin
Unresectable; insufficient remaining liver

- Portal vein embolization (PVE)
- Staged liver resection
- Ablative therapies
- Combination resection and RFA
PVE

- Induce hyperthrophy
- Increase 30% in few weeks
- Before extended right hepatectomy
- PVE + staged resection
Radio Frequency Ablation (RFA)

- Generally LM < 3cm
- Recurrence increase by size LM
- Complication rate is low
- Resection + RFA
Permanently unresectable LM

• 70% remains unresectable
• Palliative systemic therapy
• Resecting primary tumor?
  – Study CAIRO 4; systemic therapy vs. surgery followed by systemic therapy

- 30% resectable
- 70% unresectable
Organization

• Concentration
  – hospital volume of 20 a year
• Nurse specialist
  – single point of coordination
  – overview whole treatment proces
• Multidisciplinary team discussion
• Follow up
Future and conclusion

• Worldwide registry
• Future developments
  – Minimal invasive surgery
  – Flourescente markers
  – HIFU
  – HAI
  – TACE
  – Yttrium -90