Unresectable or borderline resectable disease

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Learning objectives

- All patients with liver limited or oligometastatic disease have a potential chance for cure
- A multidisciplinary approach is essential
- The clinical presentation may be considered as
  - Resectable, borderline resectable, potentially resectable after chemotherapy
- In resectable disease surgery alone or following chemotherapy are options
- In borderline and unresectable disease the most effective and still tolerable chemotherapy according to the molecular profile should be used within a multidisciplinary context
- Even if surgery might not be curative it extends overall survival and can be considered as a further line of „chemotherapy“ or a form of „maintenance“ chemotherapy
ESMO Guidelines for resectable (liver) metastases

Oncological criteria (prognostic)

- Bad
  - Preoperative FOLFOX

- Good
  - Perioperative FOLFOX

- Excellent
  - No preoperative therapy (adjuvant?)

Surgical criteria (technical)

- Easy
- Difficult

Conversion with ‘best systemic therapy’
Liver limited disease: Patient groups

- Clearly resectable
- Borderline resectable
- Definitely NOT resectable
Resectable LLD but high risk of recurrence

**Fong Score**
- Primary tumor N+
- DFI < 12 Monate
- > 1 Metastasis
- Ø > 5 cm
- CEA > 200 ng/ml

**Age 51y**
**Rectal Adeno-Ca: cT3, N+**
**Synchronous LLD, Ø 12 cm**
**CEA 568 ng/ml**

**High Fong Score**
**Estimated survival @ 5y < 10%**
Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure


- Primary tumor N +
- DFI < 12 Monate
- > 1 Metastasis
- Ø > 5 cm
- CEA > 200 ng/ml

Disease specific survival (DSS)

Fong score > 2
Adjuvant systemic chemotherapy of CLM:

Overall survival

Combined analysis

FFCD / EORTC trial 5-FU/FA

Mitri et al. JCO 2008

Overall survival

FOLFIRI

Ychou et al. ASCO 2008
Resectable Colorectal Liver Metastases

ctDNA at the end of all treatment (surgery +/- chemotherapy)

HR: 13 (95% CI: 19–325), p < 0.001

Abstract # e15131

Presented By Jeanne Tie at 2016 ASCO Annual Meeting
Neoadjuvant (perioperative) Chemotherapy in resectable CRC Liver metastases
EORTC 40983 (EPOC)

RFS

OS

Nordlinger et al. Lancet Oncol 2013
Progression-free survival in eligible patients

MOST LIKELY BENEFIT
Borderline resectable pts? High proliferative tumors?

MOST LIKELY NO BENEFIT
Easily resectable? Fong score 0-2?

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>N</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>125</td>
<td>171</td>
<td>1 year</td>
<td>83</td>
<td>57</td>
<td>37</td>
<td>22</td>
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<tr>
<td>1</td>
<td>115</td>
<td>171</td>
<td>2 years</td>
<td>115</td>
<td>74</td>
<td>43</td>
<td>21</td>
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<tr>
<td>2</td>
<td></td>
<td></td>
<td>3 years</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
<td>4 years</td>
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<tr>
<td>4</td>
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<td></td>
<td>5 years</td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td>6 years</td>
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</tbody>
</table>

New EPOC study
Neoadjuvant FOLFOX +/- Cetuximab in LLD

Primrose et al. Lancet Oncol 2014
Neoadjuvant (perioperative) Chemotherapy in resectable CRC Liver metastases
EORTC 40983 (EPOC) and new EPOC

Nordlinger et al. Lancet Oncol 2013
Primrose et al. Lancet Oncol 2014
## Liver limited disease: Patient selection

<table>
<thead>
<tr>
<th></th>
<th>EPOC</th>
<th>New EPOC</th>
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</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Surgery</td>
<td>Chemo</td>
</tr>
<tr>
<td></td>
<td>Definitely resectable</td>
<td>Definitely and „suboptimal“ resectable</td>
</tr>
<tr>
<td><strong>N Lesions</strong></td>
<td>Maximum 4</td>
<td>unlimited</td>
</tr>
<tr>
<td>unresectable</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>12-19%</td>
<td></td>
</tr>
</tbody>
</table>

*Köhne JCO 2015*
Potential disadvantage of effective neoadjuvant chemotherapy in resectable liver metastases

CT/MRI prior chemo

CT/MRI after chemo

prior surgery

● Non - visible on CT/MRI, potentially visible during operation

○ Visible on CT/MRI

Köhne JCO 2015
Conclusions resectable & boarderline resectable disease

Resectable: Perioperative Chemotherapy questionable

Boarderline: no restrictions in Chemo regimens including use of EGFR
Guidelines CRC unresectable (LLD)

Fit

GOAL

OMD
See figure 2

Cytoreduction (Shrinkage)**

MOLECULAR PROFILE

RAS wt
CT doublet + anti-EGFR

RAS mut
Combination CT + bevacizumab

BRAF mut
CT+ bevacizumab

Re-evaluation/assessment of response every 2 months*
Case: Male 44 y, sigmoid adenocarcinoma

well until 4 months ago, PS 2
weight loss ~ 5 Kg within last 3 months
grossly enlarged palpable liver

abdominal US:
diffuse hypodensic liver lesions

CT scans:
Synchronous diffuse liver metastases

LDH elevated, WBC 12.000 /dl
Bilirubin normal, LFT < 4x ULN
Case: Male 44 y,

05/06
Base line

05/06-11/06
FOLFIRI + Cetux

11/06-03/07
FOLFOX + Cetux

PS 2

PS 0

+ 5 kg
mets not operable

liver mets operable
primary tumor pCR

Patient died 02/15
Response and resection rates within trials

Trials with neoadjuvant focus

Trials with palliative focus CRC

Give the most active (RR) regimen still tolerable by the patient

CELIM: Blinded surgical review

Baseline

Follow-up

32%

60%, p<0.01

Folprecht G….Köhne CH et al. Lancet Oncol 2010
ESMO acknowledges response parameters like early tumor shrinkage (ETS) or depth of response (DpR) for conversion therapy.

**Fire-3 data**

- **Lethal tumor load**
- **ΔOS**
- **ETS**
- **Tumor nadir**
- **PFS**

**Time since start of treatment**

**Tumor load at Baseline**

**Morbidity**

- No CT
- <=5 cycles
- 6-9 cycles
- >=10 cycles


Steatohepatitis

Sinusoidal distention

Vauthey et al. JCO 2006
### FOLFIRI vs. FOFOXIRI

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>122</td>
<td>41%</td>
<td>Falcone</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>122</td>
<td>66%</td>
<td>JCO 2007</td>
</tr>
<tr>
<td>FOLFIRI+Bev</td>
<td>256</td>
<td>53%</td>
<td>Falcone</td>
</tr>
<tr>
<td>FOLFOXIRI+Bev</td>
<td>252</td>
<td>65%</td>
<td>NEJM 2015</td>
</tr>
</tbody>
</table>

- FOLFOXIRI more effective than FOLFIRI
- Unproven role of bevacizumab
## Randomised trials of EGFR antibodies – 1st line k-ras exon 2 wt only European & Asian experience

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infusional 5FU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRYSTAL (n=666)</td>
<td>FOLFIRI +/- Cetux</td>
<td>40% vs. 57%</td>
</tr>
<tr>
<td>Chinese* (n=138)</td>
<td>FOLFIRI or FOLFOX +/- Cetux</td>
<td>40% vs. 57%</td>
</tr>
<tr>
<td>PRIME (n=656)</td>
<td>FOLFOX +/- Pani</td>
<td>48% vs. 57%</td>
</tr>
<tr>
<td>OPUS (n=197)</td>
<td>FOLFOX +/- Cetux</td>
<td>34% vs. 57%</td>
</tr>
<tr>
<td>Tailor (n=380)</td>
<td>FOLFOX +/- Cetux</td>
<td>34% vs. 56%</td>
</tr>
<tr>
<td><strong>Bolus 5FU Cape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COIN (n=729)</td>
<td>XELOX/FOLFOX +/- Cetux</td>
<td>57% vs. 64%</td>
</tr>
<tr>
<td>NORDIC (n=194)</td>
<td>FLOX +/- Cetux</td>
<td>47 vs. 46%</td>
</tr>
</tbody>
</table>

sig. diff; (clinically relevant not statist. Sig); no sig. diff

* LLD only
Chinese randomized trial in patients with non resectable k-ras exon 2 wt CRC LLD
Chemotherapy +/- Cetuximab

Ye et al. JCO 2013
CEILM: R0 Resection as a surgical „maintenance therapy“ in the continuum of care

Progression free survival

**R0 resected:** 15.4  
95%CI: 11.3-19.5

**Not R0 res.:** 8.9  
95%CI: 6.7-11.0

HR 2.10 [1.37-3.20]  
p<0.001

Overall survival

**R0 resected:** 53.9  
95%CI: 35.9-71.9

**Not R0 res.:** 27.3  
95%CI: 21.1-33.4

HR 2.25 [1.34-3.78],  
p=0.002

5y-OS: 45.8%

Update CELIM 12/2012, ASCO 2013

few patients without relapse
## Randomized trials in patients with non resectable k-ras exon 2 wt CRC LLD

Chemotherapy +/- Cetuximab

<table>
<thead>
<tr>
<th></th>
<th>METHEP</th>
<th>Chinese study</th>
<th>CELIM</th>
<th>OLIVIA</th>
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<tbody>
<tr>
<td></td>
<td>FOLFIRI/FOLFOX</td>
<td>FOLFIRI/FOLFOLFOX</td>
<td>FOLFIRI/FOLFOLFOX</td>
<td>FOLFIRI/FOLFOLFOX</td>
</tr>
<tr>
<td>N=30</td>
<td>N=30</td>
<td>N=68</td>
<td>N=70</td>
<td>N=39</td>
</tr>
<tr>
<td></td>
<td>FOLFOXIRI</td>
<td>CT + Cet</td>
<td>FOLFOX + Cet + Bev</td>
<td>FOLFOX + Bev</td>
</tr>
<tr>
<td>N=68</td>
<td>N=67</td>
<td>N=70</td>
<td>N=39</td>
<td>N=41</td>
</tr>
<tr>
<td>RR</td>
<td>~60</td>
<td>73%</td>
<td>40%</td>
<td>57%</td>
</tr>
<tr>
<td>R0 resection</td>
<td>~23</td>
<td>30%</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>OS all pts (mo)</td>
<td>~29</td>
<td>48.8</td>
<td>21.0</td>
<td>30.9</td>
</tr>
<tr>
<td>OS resected pts (mo)</td>
<td>-</td>
<td>-</td>
<td>36.0</td>
<td>46.4</td>
</tr>
</tbody>
</table>

Response and resection rates within trials

Trials with palliative focus CRC

Jones, Folprecht Eur J Cancer 2014
2016 - FIRE3: Blinded review for resectability

Evaluations of surgical interventions at baseline

Votes of reviewers in per cent

Resectable vs. non-resectable

Patient

Neumann et al, ESMO 2016
2016 - FIRE3: Blinded review for resectability

Neumann et al, ESMO 2016
2016 - FIRE3: Blinded review for resectability

![Graph: Treatment context and secondary resection rate]

- **Recommended resection at best response (%):**
  - University hospital (n=78): 48.7%
  - Non-university hospital (n=207): 55.6%
  - Medical practice oncology (n=163): 52.1%

- **Resection of metastases (%):**
  - University hospital (n=78): 25.6%
  - Non-university hospital (n=207): 16.9%
  - Medical practice oncology (n=163): 10.4%

Neumann et al, ESMO 2016
Patients treated with palliative chemo at a regional oncology centre

Jones et al, BJS 2012
### Overall response rate left & right

<table>
<thead>
<tr>
<th>Trial</th>
<th>Odds ratio</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYSTAL - Left</td>
<td></td>
<td>4.0 [ 2.4, 6.6 ]</td>
</tr>
<tr>
<td>CRYSTAL - Right</td>
<td>1.5 [ 0.6, 3.6 ]</td>
<td></td>
</tr>
<tr>
<td>FIRE3 - Left</td>
<td>1.4 [ 0.9, 2.2 ]</td>
<td></td>
</tr>
<tr>
<td>FIRE3 - Right</td>
<td>1.1 [ 0.5, 2.6 ]</td>
<td></td>
</tr>
<tr>
<td>PEAK - Left</td>
<td>1.3 [ 0.7, 2.5 ]</td>
<td></td>
</tr>
<tr>
<td>PEAK - Right</td>
<td>1.8 [ 0.6, 5.4 ]</td>
<td></td>
</tr>
<tr>
<td>PRIME - Left</td>
<td>1.9 [ 1.3, 2.7 ]</td>
<td></td>
</tr>
<tr>
<td>PRIME - Right</td>
<td>1.4 [ 0.6, 3.1 ]</td>
<td></td>
</tr>
<tr>
<td>181 - Left</td>
<td>6.5 [ 3.7, 11.3 ]</td>
<td></td>
</tr>
<tr>
<td>181 - Right</td>
<td>5.7 [ 0.6, 53.6 ]</td>
<td></td>
</tr>
<tr>
<td>CALGB80405 - Left</td>
<td>1.6 [ 1.2, 2.3 ]</td>
<td></td>
</tr>
<tr>
<td>CALGB80405 - Right</td>
<td>1.1 [ 0.6, 2.0 ]</td>
<td></td>
</tr>
<tr>
<td>Total Left</td>
<td>2.12 [ 1.77, 2.55 ]</td>
<td></td>
</tr>
<tr>
<td>Total Right</td>
<td>1.47 [ 0.94, 2.29 ]</td>
<td></td>
</tr>
</tbody>
</table>

JY Douillard & JP Pignon ESMO 2016
### Duration of response

- **1st line**: in most arms duration of response appears to be longer in left-sided disease

<table>
<thead>
<tr>
<th>Actual treatment</th>
<th>Left, n</th>
<th>Right, n</th>
<th>Median DoR (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIME</strong> 1st line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pmab + FOLFOX</td>
<td>114</td>
<td>16</td>
<td>11.8 (9.6–14.8)</td>
</tr>
<tr>
<td>FOLFOX alone</td>
<td>82</td>
<td>16</td>
<td>9.3 (7.7–11.0)</td>
</tr>
<tr>
<td><strong>PEAK</strong> 1st line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pmab + FOLFOX</td>
<td>34</td>
<td>14</td>
<td>16.1 (11.1–20.9)</td>
</tr>
<tr>
<td>Beva + FOLFOX</td>
<td>31</td>
<td>7</td>
<td>9.5 (7.9–13.8)</td>
</tr>
</tbody>
</table>

- **2nd line**: not enough responses in right-sided disease to calculate duration of response

<table>
<thead>
<tr>
<th>Actual treatment</th>
<th>Left, n</th>
<th>Right, n</th>
<th>Median DoR (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>181</strong> 2nd line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pmab + FOLFIRI</td>
<td>73</td>
<td>4</td>
<td>7.7 (6.1–9.5)</td>
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<tr>
<td>FOLFIRI alone</td>
<td>19</td>
<td>1</td>
<td>9.3 (5.7–12.3)</td>
</tr>
</tbody>
</table>

Beva, bevacizumab; CI, confidence interval; DoR, duration of response; NE, not evaluable; Pmab, panitumumab
Liver limited / dominant disease

- Clearly resectable
- Borderline resectable
- Definitely NOT resectable

Chemotherapy?
- Adjuvant to surgery

Surgery!
- Adjuvant to chemotherapy
- Maintenance or an additional line of chemotherapy to chemotherapy
Learning objectives

- All patients with liver limited or oligometastatic disease have a curative chance
- A multidisciplinary approach is essential
- Clinical presentation may be considered as
  - Resectable, borderline resectable, potentially resectable after chemotherapy
- In resectable disease surgery alone or following chemotherapy are options
- In borderline and unresectable disease the most effective and still tolerable chemotherapy according to the molecular profile should be used within a multidisciplinary context
- Even if surgery is not curative it extends overall survival and can be considered as a line of „chemotherapy“ or a form of „maintenance“ chemotherapy
Thank you for your attention!