Sequence of treatment in colorectal cancer with synchronous metastases

Gunnar Folprecht · Bernard Nordlinger
Disclosures

• Gunnar Folprecht:
  – Honoraria for lectures or advisory boards: Merck KGaA, Roche, Sanofi-Aventis, Lilly, Celgene
  – Study grant: Meck KGaA

• Bernard Nordlinger:
  – Honoraria for lectures: Merck, Roche, Amgen
Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)
Liver metastases

CEA: 812
CA19-9: 8040

Co-morbidity:
Arterial hypertension
Tumorboards
Questions?

1. Are all findings resectable:
   a. Technically?
Criteria for resectability

Complete resection (± ablation) of tumour
Free resection clearance
Preservation of at least 1 of 3 hepatic veins
Homolateral portal pedicle
Future remnant liver parenchyma ≥25%

Resectability does not depend on the number of metastases
Right lobectomy
Multiple wedge resections
Questions?

1. Are all findings resectable:
   a. Technically?
   b. Would you consider prognostic factors/scores in daily decision making? Which?
Remaining functional liver tissue
Invaded structures/segments

Resectability
- Disease free interval
- Number / size of metastases
- Tumor markers
- Nodal status
Prognostic factors

- Disease free interval
- Number / size of metastases
- Tumor markers
- Nodal status

Technical Resectability

Remaining functional liver tissue
Invaded structures/segments
Prognostic factors

- Disease free interval
- Number / size of metastases
- Tumor markers
- Nodal status

Comorbidity/ Frailty

- "Medical" risk of resection
- Feasibility of chemotherapy
- To be studied
- (but has to be measured first…)

Technical Resectability

Remaining functional liver tissue
Invaded structures/segments
Prognostic factors

Molecular markers?

Probability of:
- recurrences
- overlooked metastases

- Conversion chemotherapy („adjuvant“)

Technical Resectability

- Staged resections
- Portal vein embolisation
- Combination with ablation
- Conversion chemotherapy (tumour shrinkage)

Mobidity
Risk of complications
No of resections
Questions?

1. Are all findings resectable:
   a. Technically?
   b. Would you consider prognostic factors/scores in daily decision making? Which?
   c. We proposed „intensive“ chemotherapy. Will the metastases become resectable?
Initially unresectable metastases

Before

After chemotherapy
Initially unresectable metastases

Before

After chemotherapy
66 LM disappeared on imaging after chemotherapy

\[ \text{Surgery: Macroscopic cancer: 20 LM} \]
\[ \text{No lesion: 46 LM} \]

\[ \begin{align*}
15 \text{ sites resected} & \quad & 31 \text{ sites left in place} \\
\text{Viable tumor cells: 12} & \quad & \text{In situ recurrence: 23}
\end{align*} \]

\[ 55/66 (83\%) \text{ of metastases were not "cured"} \]

Benoist, Nordlinger et al, JCO 2006
Response and resection rates within the trials

Jones, Folprecht Eur J Cancer 2014
Questions?

1. Are all findings resectable:
   a. Technically?
   b. Would you consider prognostic factors/scores in daily decision making? Which?
   c. We propose „intensive“ chemotherapy. Will we achieve resectability?

2. When metastases are unresectable, should the primary be resected (first)?
Treatment options for synchronous initially *unresectable* CRC liver metastases

- Up-front treatment is controversial
- Chemotherapy: which timing? before or after surgery
- Surgery of the primary tumor +/- radiation or chemoradiation
- Surgery of the metastases if they become resectable
Up-front primary tumor resection in *symptomatic* patients

- In symptomatic patients (bleeding, obstruction, perforation) the primary tumor should be resected first.

- Alternatively: stoma, bypass, stent…
Up-front primary tumor resection: *non symptomatic* patients

Goals:

- avoid complications related to the primary tumor in place (bleeding, obstruction, tumor perforation) during chemotherapy particularly with bevacizumab
- cure (if metastases become resectable)

The majority of patients in the US used to undergo primary tumor resection

Chang et al, JCO 2012
Hapani et al, Lancet Oncol, 2009
Up-front primary tumor resection

- Up-front primary tumor resection delays administration of chemotherapy for several weeks.

- Complications of surgery can further delay or even preclude administration of chemotherapy.

- Complication rates for primary resection in patients with unresectable distant metastases was 11.8% (major complications) and 20.6% (minor complications)

Up-front systemic chemotherapy

• Median survival of patients with unresectable metastases increased to more than 24 months with modern treatments.

• Systemic chemotherapy is active on liver metastases but also on the primary tumor and can even induce complete response in some cases.

Karoui et al. DCR, 2011; Schrag et al. JCO 2010; Grothey et al. JCO 2008; FOxTROT collaboration Group et al. Lancet 2012
Up-front systemic chemotherapy

- Retrospective studies have observed low rates of primary tumor–related complications during treatment in patients with initially asymptomatic disease.

Poultsides et al, JCO, 2009
NSABP C-10:
Ph. II prospective study primary CT ( mFOLFOX6 + bev) for patients (n=86) with asymptomatic primary intact unresectable stage IV colon cancer

The majority of patients could be managed without primary tumor (PT) intervention
• 86% of patients - no major morbidity due to PT
• Median overall survival : 19.9 months

The investigators conclude that avoiding resection of the asymptomatic PT did not result in an unacceptable rate of PT-related complications and did not compromise survival

73.3% of the patients had not required PT resection at the time of death or last follow-up.

McCahill LE, et al. JCO. 2012
Can primary tumor resection improve survival?

- Survival benefit suggested with prior resection of primary
  - Multi-institutional retrospective analysis
  - Population based studies
  - Retrospective analysis of randomized trials

- Analysis are retrospective and potentially biased
  (Patients selected for resection being better fit and with more limited metastatic disease)

- New prospective trials:
  - CLIMAT-PRODIGE 30 (France),
  - CAIRO 4 (The Netherlands),
  - SYNCHRONOUS (Germany)

Karoui et al. DCR, 2011
Temple et al. JCO 2004
Ferrand F et al, Eur J Cancer 2013
Resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV) -

A randomized controlled multicenter trial (SYNCHRONOUS-Trial)

SYNC-03/2011

Metastatic CRC
No curative resection

Resection → Systemic therapy

800 pts (180 pts recruited)
Primary endpoint: Overall survival

Trials with similar design:
CAIRO4 (NL), CLIMAT-PRODIGE (F)
Need for resection of the intact primary after chemotherapy for synchronous metastases?

- Progression of metastases and asymptomatic primary: NO

- Tumor response: YES in particular if resection of metastases is considered

- Complete tumor response on primary tumor: discuss in MDM
Patient, 57 years old

**Sigmoid cancer (adenocarcinoma G2)**

Liver metastases

**CEA:** 812  
**CA19-9:** 8040  
**KRAS/NRAS/B-RAF:** wild type
## FOLFOXIRI combinations in first line therapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>n</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>FOLFOXIRI/Bev</td>
<td>252</td>
<td>65%</td>
<td>12.1</td>
<td>31.0</td>
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<tr>
<td>FOLFIRI/Bev</td>
<td>256</td>
<td>53%</td>
<td>9.7</td>
<td>25.8</td>
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<tr>
<td>Falcone, ASCO 2013</td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>HR 0.77 p&lt;0.01</td>
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<tr>
<td>FOLFOXIRI</td>
<td>122</td>
<td>60%</td>
<td>9.8</td>
<td>22.6</td>
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<tr>
<td>FOLFIRI</td>
<td>122</td>
<td>34%</td>
<td>6.9</td>
<td>16.7</td>
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<tr>
<td>Falcone, JCO 2007</td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td>HR 0.63; p&lt;0.01 HR 0.80;p=0.032</td>
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<tr>
<td>FOLFOXIRI/Bev</td>
<td>41</td>
<td>81%</td>
<td>18.8</td>
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<tr>
<td>FOLFOX/Bev</td>
<td>39</td>
<td>62%</td>
<td>12.0</td>
<td></td>
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<tr>
<td>Bridgewater, ECC 2013</td>
<td></td>
<td></td>
<td>p=0.061</td>
<td>p&lt;0.01</td>
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</table>
### EGFR vs. VEGF plus chemo

k-ras exon 2 wt (not approved)

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<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td><strong>FOLFIRI/Cetux</strong></td>
<td>295</td>
<td>62%</td>
<td>10.0</td>
<td>28.7</td>
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<tr>
<td><strong>FOLFIRI/Beva</strong></td>
<td>297</td>
<td>58%</td>
<td>10.3</td>
<td>25.0</td>
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<tr>
<td>Heinemann, Lancet Oncol 2014</td>
<td></td>
<td></td>
<td></td>
<td><strong>HR 1.06</strong></td>
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<tr>
<td><strong>FOLFOX/Pani</strong></td>
<td>142</td>
<td>58%</td>
<td>10.9</td>
<td>34.2</td>
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<tr>
<td><strong>FOLFOX/Beva</strong></td>
<td>143</td>
<td>54%</td>
<td>10.1</td>
<td>24.3</td>
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<tr>
<td>Schwartzberg, JCO 2014</td>
<td></td>
<td></td>
<td><strong>HR 0.84</strong></td>
<td><strong>HR 0.62 p=0.009</strong></td>
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<tr>
<td><strong>Chemo/Cetux</strong></td>
<td>578</td>
<td>64%</td>
<td>10.4</td>
<td>29.9</td>
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<tr>
<td><strong>Chemo/Beva</strong></td>
<td>559</td>
<td>58%</td>
<td>10.8</td>
<td>29.0</td>
</tr>
<tr>
<td>Venook, ASCO 2014</td>
<td></td>
<td></td>
<td><strong>HR 1.04</strong></td>
<td><strong>HR 0.93</strong></td>
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See discussion in room Madrid after this session
Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)
Liver metastases

CEA: 812
CA19-9: 8040
KRAS/NRAS/B-RAF: wild type

Treatment:
6 cycles
FOLFOXIRI / Cetuximab
Questions?

1. Are all findings resectable:
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2. If unresectable: Should we resect the primary (first)?

3. Did the metastases become resectable?
Questions?

1. Are all findings resectable:
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   c. We propose „intensive“ chemotherapy. Will we achieve resectability?
2. If unresectable: Should we resect the primary (first)?
3. Did the metastases become the resectable?
   a. Which order for resection of primary and metastases?
Surgical options if synchronous metastases become resectable after response to chemotherapy

- Resection of the primary tumor
  (+/- radiation or CRT for rectal cancer)
- Surgery of the liver
- Which order?
  - “Classical” primary tumor first?
  - Combined?
  - Reverse: liver first?
Surgical strategy: the primary first

- Resection of primary tumor $\rightarrow$ Resection of metastases
- No risk of primary related complications
- Risk of progression of CLM which may become unresectable during the treatment of primary
Surgical strategy:
Simultaneous resections of primary and metastases

Advantages:
- Only one operation
- Resection of metastases not delayed by the treatment of the primary

Limitations
- Increased morbidity (major liver resection + major colorectal surgery)
- Requires double surgical expertise
- Depends on surgical access (open +/- laparoscopy)

Fujita et al, Jpn J Clin Oncol 2000
Tocchi et al, Int J Colorectal Dis 2004
Adam et al. Br J Surg 2010
Surgical Strategy: the combined approach

<table>
<thead>
<tr>
<th></th>
<th>Combined resection</th>
<th>Staged resection</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Major Hepatectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (8.3%)</td>
<td>0</td>
<td>0.07</td>
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<tr>
<td>Severe morbidity</td>
<td>13 (36.1%)</td>
<td>9 (17.6%)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Minor Hepatectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>99</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1%)</td>
<td>0</td>
<td>0.83</td>
</tr>
<tr>
<td>Severe morbidity</td>
<td>14 (14.1%)</td>
<td>2 (10.5%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

## Surgical Strategy: the combined approach

<table>
<thead>
<tr>
<th></th>
<th>Combined resection</th>
<th>Staged resection</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Hepatectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>6.1%</td>
<td>2.4%</td>
<td>0.009</td>
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<tr>
<td><strong>Minor Hepatectomy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>2.2%</td>
<td>0.5%</td>
<td>0.11</td>
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</tbody>
</table>
Surgical Strategy: the reverse approach - liver surgery first

Preoperative chemotherapy → Resection of metastases → Resection of the Primary Tumor

Rationale:

– Survival depends on progression of metastases rather than of the primary tumor
– Prevents the risk of progression of CLM which could become unresectable during treatment of primary
– Primary related complications during treatment of CLM are rare

Surgery for synchronous colorectal liver metastases and primary: experience of M. D. Anderson

<table>
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<tr>
<th>Approach</th>
<th>No Pts</th>
<th>Tumors No.</th>
<th>Mortality %</th>
<th>Cumulative Morbidity %</th>
<th>5y OS</th>
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<tr>
<td>Classic</td>
<td>72</td>
<td>3</td>
<td>3</td>
<td>51</td>
<td>48%</td>
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<tr>
<td>Combined</td>
<td>43</td>
<td>1</td>
<td>5</td>
<td>47</td>
<td>55%</td>
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<td>Reverse</td>
<td>27</td>
<td>4</td>
<td>0</td>
<td>31</td>
<td>39%</td>
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<tr>
<td>P value</td>
<td>0.01, 0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Provided adequate patient selection, the different approaches appear similar for postoperative morbidity and control of cancer.
Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)
Liver metastases

CEA: 812
CA19-9: 8040
KRAS/NRAS/B-RAF: wild type

Treatment:
6 cycles
FOLFOXIRI / Cetuximab

Would it influence your decision?
Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)
Liver metastases

CEA: 812
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Treatment:
6 cycles
FOLFOXIRI / Cetuximab

Would you resect it? ...or follow up?
Patient, 57 years old

**Sigmoid cancer (adenocarcinoma G2)**
Liver metastases

CEA: 812
CA19-9: 8040
KRAS/NRAS/B-RAF: wild type

**Treatment:**
6 cycles FOLFOXIRI / Cetuximab
Extended left hemihepatectomy, atypical resection
Histology: Good regression, TRG II (Rubbia-Brandt 2007)
Margin: ≥ 3 mm margin
No CASH, no SOS
Questions?

1. Are all findings resectable:
   a. Technically?
   b. Would you consider prognostic factors/scores in daily decision making? Which?
   c. We propose „intensive“ chemotherapy. Will we achieve resectability?

2. If unresectable: Should we resect the primary (first)?
   a. Which order for resection of primary and metastases?

3. Did the metastases become the resectable?

4. Do you think the patient will be cured?
## Prognostic factors

<table>
<thead>
<tr>
<th></th>
<th>Rees</th>
<th>Malik</th>
<th>Minagawa</th>
<th>Konopke</th>
<th>Nordlinger</th>
<th>Fong</th>
<th>Zakaria</th>
<th>Yamaguchi</th>
<th>Iwatsuki</th>
<th>Tan</th>
<th>Schindl</th>
<th>Tanaka</th>
<th>Lise</th>
<th>Ueno</th>
<th>Nagashima</th>
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<tbody>
<tr>
<td>Number of met’s</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>Nodal status</td>
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<td>Max. size of met’s</td>
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<td>Interval primary-met’s</td>
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<td>CEA at resection: 2.6</td>
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<tr>
<td>Extrahep. spread</td>
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<td>Positive margins</td>
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<td>Poorly diff. tumour</td>
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<td>Serosal invasion</td>
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<td>Hepat. lymph nodes</td>
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   What do you communicate?
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   What do you communicate?

5. Do you think the patient benefited from the combined approach?
Survival according to metastasectomy

**Progression free survival**

**Overall survival**

**R0 resected patients**

**R1 resection / ablation**

**Not resected patients**

**OS**

R0 resected: 53.9 mo. [95% CI: 35.9-71.9]

Not resected: 21.9 mo. [95% CI: 17.1-26.7]

HR 0.29 [0.17-0.50], p < 0.001

**PFS**

R0 resected: 15.4 mo. [95% CI: 11.4-19.5]

Not resected: 6.9 mo. [95% CI: 5.9-8.0]

HR 0.31 [0.19-0.50], p < 0.001

Folprecht et al, Ann Oncol 2014
DFS after R0 resection

Disease free survival after resection

All patients

< 5 metastases
5-10 metastases
> 10 metastases

DFS 9.9 [95% CI: 5.8-14.0] months

Comparison between groups:

\( p < 0.001 \)

Folprecht et al, Ann Oncol 2014
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   What do you communicate?

5. Do you think the patient benefited from the combined approach?
Female Patient, 54 years

Rectal Cancer

Distance to sphincter: 3 cm
Female Patient, 54 years

Rectal Cancer
Distance to sphincter: 3 cm
Question: treatment options?

Cancer of the low rectum, T3 N+; resectable with multiple resectable liver metastases

• Which treatment strategy?
• Would you recommend radiation:
  - 5x5 → Chemo?
  - Chemo → 5x5?
  - Long course RT (which regimen)?
• Would you recommend chemotherapy?
• Would you recommend chemo-radiation?
• Would you recommend surgery?
If there were isolated/metachronous liver metastases:

EORTC 40983: Lebermet. +/- periop. FOLFOX

**Progression free survival**

- Surgery only vs Perioperative chemotherapy
- Overall log-rank test: $p=0.068$

**Overall survival**

- Surgery only vs Perioperative chemotherapy
- Overall log-rank test: $p=0.34$

Nordlinger Lancet Oncol 2013
If there was isolated rectal cancer

Cape vs 5-FU NSABP-R04
Allegra #3603, O’Conell JCO 2014,
5-FU CI STAR-01
Aschele JCO 2011
Cape ACCORD 12/0405 Prodigie 2
Gerard JCO 2012

Patients: cT ≥ 3 or N ≥ 1, < 12 cm
### Disease free survival

<table>
<thead>
<tr>
<th>Study name</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Hazard ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO/ARO/CAO04</td>
<td>FP +/- Oxal</td>
<td>DFS</td>
<td>0.790</td>
<td>0.638</td>
<td>0.978</td>
<td>-2.169</td>
<td>0.030</td>
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<tr>
<td>PETACC6</td>
<td>FP +/- Oxal</td>
<td>DFS</td>
<td>1.040</td>
<td>0.812</td>
<td>1.333</td>
<td>0.310</td>
<td>0.757</td>
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### Overall survival

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<tr>
<th>Study name</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Hazard ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO/ARO/CAO04</td>
<td>FP +/- Oxal</td>
<td>OS</td>
<td>0.960</td>
<td>0.726</td>
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<td>0.775</td>
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<tr>
<td>PETACC6</td>
<td>FP +/- Oxal</td>
<td>OS</td>
<td>1.310</td>
<td>0.890</td>
<td>1.929</td>
<td>1.367</td>
<td>0.171</td>
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<td>34.33</td>
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</tbody>
</table>
Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer

T. H. van Dijk¹, K. Tamas², J. C. Beukema³, G. L. Beets⁴, A. J. Gelderblom⁵, K. P. de Jong⁶, I. D. Nagtegaal⁷, H. J. Rutten⁸, C. J. van de Velde⁹, T. Wiggers¹, G. A. Hospers² & K. Havenga¹

- **Primary stage IV rectal cancer**
- **Week 1**: Radiotherapy 5x5 Gy
- **Week 3–8**: 2 Cycles of 3 weeks
  - Bevacizumab 7.5 mg/kg IV d1
  - Oxaliplatin 130 mg/m² IV d1
  - Capecitabine 1000 mg/m² bid d1-14
- **Week 9–20**: Another 4 cycles of 3 weeks after evaluation
- **Week 26**: Surgery for primary rectal cancer and metastases

*Abbreviations: bid, twice daily, d, day, IV, intravenous.*
Cancer of the rectum and synchronous metastases

No randomized trials
Only retrospective series
  - A minority of patients with rectal cancer
  - Patients undergoing simultaneous resections had limited metastatic disease
Treatment options depend on site and extent of primary tumor
Upper third or T2 rectal cancer

No need for radiation

Treatment strategy similar to colon cancer
Locally advanced or low rectal cancer

Objectives:
1. Control of rectal primary: integration of RT or CRT in the treatment strategy.
2. Control of liver metastases and avoid progression during treatment of primary.

Limitations:
Chemoradiation
   - Provides suboptimal control of metastases during the 5 weeks of treatment.
   - Determines the date of surgery, 6 to 8 weeks after the end of radiation.
   - 5X5 Gy an alternative.

– Chemotherapy alone: suboptimal control of rectal primary.
Sequence of treatment in colorectal cancer with synchronous metastases

Gunnar Folprecht · Bernard Nordlinger