What is the Standard of Care for Metastatic Colorectal Cancer to the Liver: Chemotherapy, Biotherapy, Surgery?

Marwan Fakih, MD
Professor, Medical Oncology
Section Head, Gastrointestinal Oncology
Department of Medical Oncology, City of Hope
Marwan Fakiha, M.D.

- **Speakers Bureau:** Sirtex
- **Consultant/Advisory Board:** Sirtex/Amgen
Patient Stratification Based on Metastatic Disease

Metastatic Colorectal Cancer

- Resectable
- Non-Resectable & Potentially Resectable
- Never Curatively Resectable
Resectable Metastatic Colorectal Cancer: SOC is SURGERY
Hepatectomy for Liver-Only MCRC (N ≥ 100)

<table>
<thead>
<tr>
<th>N. of patients</th>
<th>Operative Mortality</th>
<th>5-ys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adson, 1984</td>
<td>141</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hughes, 1988</td>
<td>859</td>
<td>-</td>
</tr>
<tr>
<td>Doci, 1991</td>
<td>100</td>
<td>5%</td>
</tr>
<tr>
<td>Scheele, 1991</td>
<td>219</td>
<td>6%</td>
</tr>
<tr>
<td>Rosen, 1992</td>
<td>280</td>
<td>4%</td>
</tr>
<tr>
<td>Nordlinger, 1992</td>
<td>1818</td>
<td>2.4%</td>
</tr>
<tr>
<td>Gayowski, 1994</td>
<td>204</td>
<td>0%</td>
</tr>
<tr>
<td>Rees, 1997</td>
<td>114</td>
<td>1%</td>
</tr>
<tr>
<td>Jamison, 1997</td>
<td>280</td>
<td>4%</td>
</tr>
<tr>
<td>Fong, 1999</td>
<td>1001</td>
<td>2%</td>
</tr>
<tr>
<td>Iwatsuki, 1999</td>
<td>305</td>
<td>1%</td>
</tr>
<tr>
<td>Choti, 2002</td>
<td>226</td>
<td>-</td>
</tr>
<tr>
<td>Abdalla, 2004</td>
<td>190</td>
<td>-</td>
</tr>
<tr>
<td>Fernandez, 2004</td>
<td>100</td>
<td>1%</td>
</tr>
<tr>
<td>Pawlic, 2005</td>
<td>557</td>
<td>-</td>
</tr>
</tbody>
</table>
**Resectable MCRC: ECOG 40983**

**RANDOMIZE 364 Pts**

- **FOLFOX4**
  - 6 cycles

- Surgery

- **FOLFOX4**
  - 6 cycles

**Potentially resectable liver metastases of colorectal origin**
- Up to 4 deposits on CT at randomization
- No extrahepatic disease
- ECOG 0-2
- No prior oxaliplatin

**3 Year DFS**

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>FOLFOX + Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eligible</td>
<td>28.1%</td>
<td>36.2%</td>
</tr>
<tr>
<td>All resectable</td>
<td>33.2%</td>
<td>42.4%</td>
</tr>
</tbody>
</table>

5-year OS 51.2% vs. 47.8% (non-significant)

*Nordlinger B. Lancet, 2008: 1007-1016; Nordlinger B. Lancet Oncol 2013: 1208-15*
Regional Therapy in the Adjuvant Treatment of MCRC

156 patients with liver-limited mCRC with hepatectomy

Stratify by: prior 5-FU, hepatic lesions (1; 2-4; > 4)

Hepatic PFS: median hepatic PFS is 42 m vs. unreached for chemo/HAI

PFS: is 17.2 m for chemo vs. 37.4 m for chemo/HAI


76 Fluorouracil + HAI FUDR x 6 cycles

82 Fluorouracil x 6 cycles
Regional Therapy in the Adjuvant Treatment of MCRC

- Median F/U 10.3 years (minimum 6 years)
  - PFS 31.3 m vs. 17.2 m (p = 0.02)
  - LPFS not-reached vs. 32.5 m (p < 0.001)
  - OS 68.4m vs. 58.8 (p = 0.1)
  - 10-year OS 41.1% vs. 27.2%

Non-Resectable and Non-Potentially Resectable mCRC
Which liver mCRC patient should be considered **NOT** potentially resectable

- Multi-organ involvement (beyond liver and lung)
- Diffuse retroperitoneal and/or mediastinal involvement
- Extensive liver and peritoneal disease
- Bony and CNS involvement
- Extensive hepatic metastases (too numerous to count hepatic metastases)
- Patient performance status will not allow for surgical intervention
Each of these agents has been associated with an improvement in Overall Survival
CRC: *RAS* and *BRAF* Status

- **44%**: RAS WT and BRAF WT
- **40%**: RAS MT (*KRAS* exon 2)
- **11%**: RAS MT (*KRAS* non-exon 2 and *NRAS*)
- **5%**: BRAF MT

Status of Biological Therapy in CRC

Colorectal Cancer

- RAS-MT
  - Anti-angiogenic Rx

- BRAF-MT
  - Anti-angiogenic Rx

- RAS-WT/BRAF-WT
  - Anti-angiogenic Rx
  - Anti-EGFR Rx
Overall Survival Time: Cytotoxics + Biologicals

The Future of Targeted Therapies in CRC

- MSI-H (Immunotherapy)
- BRAF (combination of BRAF/anti-EGFR/MEK targeting)
- HER-2 amplifications (trastuzumab + pertuzumab; trastuzumab + lapatenib)
- HER-2 mutations (afatinib + trastuzumab; lapatenib + trastuzumab)
- Many others: ARAF, AKT, ALK, ROS, NTRK, MAPK, FGFR, etc...
- Right vs. Left colon (for anti-EGFR)
Can we improve outcome of unresectable CRC liver metastases with regional therapy?

Radioembolization
HAI
Chemoembolization
SIRFLOX Study Design

Prospective open-label RCT

**Primary endpoint:** Progression-Free Survival

**Eligible patients**
- Non-resectable liver-only or liver-dominant mCRC
- No prior chemo for advanced disease
- WHO performance status 0–1

**Stratified by**
- Presence of extra-hepatic metastases
- Degree of liver involvement
- Intended use of bevacizumab
- Institution

Randomized
1:1
n = 530

- ANZ: 280 (53%)
- EME: 191 (36%)
- US: 59 (11%)

- mFOLFOX6 (+ bevacizumab) (1)
- SIRT

n = 263 enrolled

n = 267 enrolled

1. Bevacizumab allowed at investigator’s discretion, per institutional practice

ANZ: Australia, New Zealand; AP: Asia Pacific; EME: Europe & Middle East; US: United States

PFS in the Liver: Cumulative Incidence of Liver Progression Stratified by Presence or Absence of Extra-Hepatic Metastases

Liver-only metastases

<table>
<thead>
<tr>
<th>N</th>
<th>Median</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>159</td>
<td>12.4 months</td>
<td>p=0.003</td>
<td>0.64 (0.48–0.86)</td>
</tr>
</tbody>
</table>

Liver + extra-hepatic metastases

<table>
<thead>
<tr>
<th>N</th>
<th>Median</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>12.6 months</td>
<td>p=0.147</td>
<td>0.77 (0.54–1.09)</td>
</tr>
</tbody>
</table>

CALGB 9481: Systemic vs. HAI Fluoropyrimidines

Metastatic CRC to Liver

Mayo Clinic FU/LV (67 pts)

HAI FUDR (68 pts)

<table>
<thead>
<tr>
<th></th>
<th>HAI (FUDR)</th>
<th>FU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>9.8 m</td>
<td>7.3 m</td>
</tr>
<tr>
<td>TEHF</td>
<td>7.7 m</td>
<td>14.8 m</td>
</tr>
<tr>
<td>OS</td>
<td>24.4 m</td>
<td>20 m</td>
</tr>
</tbody>
</table>

THF = time to hepatic failure; TEHF: time to extra-hepatic failure

Time to Liver progression

Median: 9.8 vs. 7.3 m

Overall survival

Median: 24.4 vs. 20 m

Chemoembolization: Randomized Phase II Trial of FOLFOX +/- DEBIRI

MCRC with Liver Metastases

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX-Bev</th>
<th>FOLFOX-Bev DEBIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>12 m</td>
<td>15 m (p = 0.18)</td>
</tr>
<tr>
<td>Liver PFS</td>
<td>12 m</td>
<td>17 m (p = 0.05)</td>
</tr>
</tbody>
</table>

RR 76%; Resection Rate = 35%
RR 60%; Resection rate = 16%

High rate of procedure related complications
OS not mature and outcome of hepatic resection not mature

Martin, R. Cancer; 2015. 121: 3649-3658
Conversion Therapy: Role of Biologicals
**Conversion Therapy: The more response the better!**

### Non-resectable liver mets (KRAS WT)
- **N = 80**

1. **1st endpoint: overall resection rate**
   - **FOLFOX**
   - **FOLFOX + BV**
   - **FOLFOXIRI + BV**

### Unresectable liver mets (KRAS WT)
- **N = 138**

1. **FOLFOX + Cetuximab**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX + Cmab</th>
<th>FOLFOX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resection Rate</strong></td>
<td>29% 26% (R0)</td>
<td>13% 7% (R0)</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>HR = 0.6 (p = 0.04)</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>HR = 0.54 (p = 0.013)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FOLFOXIRI + BV</th>
<th>FOLFOX + BV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resection Rare</strong></td>
<td>61% 49% (R0)</td>
<td>49% 23% (R0)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>18.6 m</td>
<td>11.5 m</td>
</tr>
</tbody>
</table>

---

**1st Line MCRC Stratify by FOLFOX/FOLFIRI**
- **N = 1137**
  - **Treating Physician Choice:** FOLFOX or FOLFIRI
  - **Chemo + Cmab**
  - **Chemo + Bev**

**CALGB 80405**
- 1137 enrolled
- 132 resected with NED
- 82 cmab 50 bev

---

Integrating Regional Therapy in Achieving Hepatic Resection

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Systemic Treatment</th>
<th>HAI Treatment</th>
<th>Resection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTILIV N = 64</td>
<td>Pre-treated and unresectable</td>
<td>IV cmab</td>
<td>Oxaliplatin Irinotecan 5-FU</td>
<td>29.7%</td>
</tr>
<tr>
<td>MSKCC N = 49</td>
<td>Pretreated and unresectable</td>
<td>FOLFIRI or IROX</td>
<td>FUDR</td>
<td>47%</td>
</tr>
<tr>
<td>MSKCC N =39</td>
<td>Heavily pretreated and unresectable</td>
<td>Irinotecan</td>
<td>FUDR</td>
<td>18%</td>
</tr>
<tr>
<td>MSKCC N = 36</td>
<td>Pretreated And unresectable</td>
<td>IROX or FOLFOX</td>
<td>FUDR</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

Summary

- Systemic therapy has improved the OS of mCRC over the last 3 decades with expected median OS neighboring 30 months.
- Both bevacizumab and anti-EGFR (RAS-WT) have improved survival in unresectable disease but do not add any benefits in the adjuvant setting.
- Resection +/- RFA is the only established modality associated with cure.
- Regional therapy needs to be individualized around the goad of therapy: disease control or neoadjuvant or adjuvant therapy?
- Conversion therapy should focus on intensive combination chemotherapy. Combinations of systemic and HAI chemotherapy can be considered in select centers in the event of inadequate response to initial treatment.