Techniques to Improve Resectability of Colorectal Liver Metastases

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Metastatic Colorectal Cancer (CRC)

<table>
<thead>
<tr>
<th>Percent of Cases by Stage</th>
<th>5-Year Relative Survival</th>
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<tbody>
<tr>
<td>Localized (40%) Confined to Primary Site</td>
<td>90.3%</td>
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<tr>
<td>Regional (36%) Spread to Regional Lymph Nodes</td>
<td>70.4%</td>
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<tr>
<td>Distant (20%) Cancer Has Metastasized</td>
<td>12.5%</td>
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<tr>
<td>Unknown (5%) Unstaged</td>
<td>33.6%</td>
</tr>
</tbody>
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SEER 18 2003–2009, All Races, Both Sexes by SEER Summary Stage 2000

- ~50% CRC metastatic at some point
- ~20% colorectal liver mets resectable
Colorectal Liver Mets (CLM): Baseline Understanding

- **1990’s:** CLM a surgical disease
  - 37% 5yr OS in 1,001 (well-selected) resected pts from MSKCC\(^1\)
  - Median OS 42mo
- **2000’s:** more use of chemo (5FU then FOLFOX and FOLFIRI)
  - Median OS better
    - Unresected 2 yrs (chemo alone at MDACC/Mayo) or 1 yr (nationally in SEER)\(^2\)
    - Resected 5yrs with 50% 5-yr OS\(^2\)

1. Fong Ann Surg 1999
2. Kopetz JCO 2009
Improved Survival From Better Chemo For CRC Since Mid-2000’s

Kopetz, JCO 2009
Since 2000’s, More CLM Resections
Resection Better OS vs. Chemo Alone

Kopetz, JCO 2009
Improving Resectability of Colorectal Liver Mets (CLM)

- Role of perioperative chemotherapy
- PVE before major/extended hepatectomy
- Two-stage hepatectomy
- Reverse approach sequencing
Improving Resectability of Colorectal Liver Mets (CLM)

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Potential Advantages of Preoperative Chemotherapy

- Downsize and decrease extent of resection (save parenchyma)
- Margin control (R1=R0 resection in chemo responders)
- Assess tumor response morphologically
- Predict outcomes with pathologic response
- Convert initially unresectable
- Guarantees at least some chemo for the pt
Morphologic Response After Chemo

Chun YS, JAMA 2009
Morphologic Response Predicts OS

A) Morphologic response criteria

- Residual Tumor, %
- None
- Incomplete
- Optimal

P < .001

B) Survival analysis

- Log-rank P = .03
- Optimal response
- Incomplete or no response

No. at risk
- Responder: 22, 20, 12, 4, 2
- Nonresponder: 23, 18, 9, 3, 0

Chun YS, JAMA 2009
More Patients Receiving Preoperative Chemotherapy

MDACC 1995-2011

- 84.9%
- 23.0%

Chemotherapy 1-3 months
Chemotherapy >3 months

MDACC 1995-2011
Potential Disadvantages of Preoperative Chemotherapy

- Chemotherapy-associated liver injury (CALI)
  - Usually from extended duration (>6 cycles)
  - FOLFOX – blue
- Vascular injury
- Increased postop morbidity
  - FOLFIRI – yellow
  - Steatohepatitis with obesity/diabetes
  - Increased postop mortality
- Disease progression is not a “downside”
Perioperative Chemotherapy with Oxaliplatin EORTC 40983 in Eligible Patients: PFS

- > 50% had only one liver metastasis
- Median size of CLM < 5 cm
- 2/3 were metachronous

Nordlinger, Lancet Oncology 2013
Diagnosis of Borderline and Initially Unresectable CLM

Borderline Resectable
- Preoperative Chemotherapy
  4-6 cycles (2-3 mo)
- Hepatectomy
  (One-stage or Two-stage) ± PVE*
- Finish Postoperative Chemotherapy
  3-4 months

Resectable
- First-Line Chemotherapy
  Re-evaluate 2-3 mo
- Second-Line Chemotherapy
- Third-Line Chemotherapy

Unresectable
- Finish Postoperative Chemotherapy 3-4 months
- Adapted from Kopetz and Vauthey, Lancet 2008
Improving Resectability of CLM

- Role of perioperative chemotherapy
- PVE before major/extended hepatectomy
- Two-stage hepatectomy
- Reverse approach sequencing
Portal Vein Embolization (PVE)

Pre-PVE FLR (seg 1-3) 10% vs. Total Liver Volume

Post-PVE FLR (seg 1-3) 33% vs. Total Liver Volume
Indications for PVE?

- Duration of chemo?
- High BMI/fatty liver?
- CALI?

Normal Liver $\leq 20\%$
Extensive Chemotherapy $\leq 30\%$
Cirrhosis $\leq 40\%$

3. Shindoh J Gastrointest Surg 2013

Standardized Future Liver Remnant (sFLR)
Baseline FLR Volume Before Major Hepatectomy

- **Right Liver % of TLV**
  - 10% in Right Hemihepatectomy
  - FLR (Left Hemiliver) ≤ 20%

- **Left Liver % of TLV**
  - 75% in Extended Right Hepatectomy
  - FLR (Segment 2+3) ≤ 20%

- **Bisegment II/III % of TLV**

Abdalla et al, Surgery 2004
Case 1: 55 yo male with metastatic rectal cancer. PS 0. Small FLR.

Before PVE with 17% FLR (segments I, II, III)

After PVE with 33% FLR.
Both Degree of Hypertrophy >5% AND sFLR >20% = Less Liver Failure

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<tr>
<th></th>
<th>sFLR or DH</th>
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<tbody>
<tr>
<td></td>
<td>≤ 20% or</td>
<td>&gt; 20%</td>
<td>P†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤ 5%</td>
<td>and &gt; 5%</td>
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<td></td>
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<tr>
<td>(n = 15)</td>
<td>(n = 51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>12 (80)</td>
<td>19 (37)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Major complication</td>
<td>7 (47)</td>
<td>7 (14)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Liver-related</td>
<td>12 (80)</td>
<td>10 (20)</td>
<td>&lt; 0.001</td>
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<tr>
<td>complication</td>
<td></td>
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</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>12 (80)</td>
<td>3 (6)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>3 (20)</td>
<td>1 (2)</td>
<td>0.034</td>
<td></td>
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<tr>
<td>Death within 90 days</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td>0.049</td>
<td></td>
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<tr>
<td>Duration of hospital stay (days)*</td>
<td>8 (6–53)</td>
<td>7 (5–28)</td>
<td>0.119‡</td>
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Ribero D Br J Surg 2007
PVE: Preop Liver Stress Test

- Degree of hypertrophy >5%
- Absolute FLR >20% (30% for extended chemo)
- Kinetic growth rate >2%/week
- If it doesn’t grow, then you save the patient from dying postop from postop liver failure (incurable and irreversible)
- If tumor burden progresses rapidly in post-PVE break of just 5 weeks, then biology has declared itself. Surgery won’t help.
- Having enough FLR with proven regenerative capacity decrease liver-failure-related postop mortality to close to 0%
Improving Resectability of CLM

• Role of perioperative chemotherapy

• PVE before major/extended hepatectomy

• Two-stage hepatectomy

• Reverse approach sequencing
Case 2: 51 yo male with synchronous liver metastases and low rectal cancer

- 13 synchronous CLM, involving 7 of 8 liver segments
After FOLFOX Bevacizumab x4

Type I Morph Response (sharp margin, no enhancement)
After first stage partial left hepatectomy + proctectomy

FLR% (I, II, III) = 17%

After PVE extended to segment IV

FLR% (I, II, III) = 27%
• Second Stage: Extended Right Hepatectomy

• Finished last 8 cycles of chemo

• Alive NED 5 years later
Improving Resectability of CLM

• Role of perioperative chemotherapy
• PVE before major/extended hepatectomy
• Two-stage hepatectomy
• Reverse approach sequencing
Case 3: 36 year old man with synchronous non-obstructing primary CRC

- Two Metastases: Seg 4/8 (encasing MVH) + Seg 6
Synchronous Liver Metastases and Rectal Cancer

**Traditional Approach**

- **Assessment**
- **Chemoradiation**
  - 5 weeks
  - 6 weeks
- **Proctectomy**
  - 1 week
  - 4 weeks
- **Systemic Chemotherapy**
- **Liver Resection**

**Reverse Approach**

- **Assessment**
- **Periop Systemic Chemotherapy**
- **Liver Resection**
- **Chemotherapy + Chemoradiation**
- **Proctectomy**

>15 weeks without effective systemic chemo (only 5-FU or Xeloda)

Synchronous CLM and Non-Obstructing Sigmoid Primary

After FOLFOX-6 + Bevacizumab Type I Morph Response (sharp margin, no enhancement)
- Pre-PVE FLR (seg 1-3) = 10% of Total Liver Volume ("initially unresectable")
- Post-PVE FLR (seg 1-3) = 33% of Total Liver Volume

- Extended R hep
- Path: < 5% viable tumor; neg margin (4 mm from mucin pools)
- Sigmoid colectomy 6-8 weeks later
Minor hepatectomy

Major Hepatectomy

Multifocal/Bilateral

1st Stage: Combined Colorectal with Partial Left Hepatectomy

2nd Stage: Extended or Right Hepatectomy ("Two-Stage Hepatectomy")

"Reverse Approach" Perioperative Chemotherapy

+/−PVE

1st: Major Hepatectomy

2nd: Colorectal Resection ("Reverse Approach")

Standard Colorectal

Extensive Colorectal

Simultaneous Colorectal + Minor Liver ("Combined Approach")

1st: Colorectal

2nd: Minor Liver ("Classic or Traditional Approach")

"Reverse Approach"
Summary

- **Perioperative chemotherapy** downsizes, improves PFS [and likely OS], and guarantees chemo delivery to every pt with CLM.
- **PVE** increases FLR, converting unresectable.
- **Two-stage hepatectomy** spreads the risk of extended hepatectomy and uses PVE.
- **Reverse approach sequencing** addresses CLM when CLM are the more life-limiting issue.
Conclusions

- Multimodality treatment strategies improve resectability of patients with CLM.
- They increase the number of patients with a chance for potentially curative resection.