State of the art management of Colorectal Liver Metastasis: an interplay of Chemotherapy and Surgical options

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• No relevant financial disclosures
Outline

• Introduction
• Definition of metastatic disease to the liver
• NCCN guidelines
• Timing of Chemotherapy
• When to operate?
• What type of operation / procedure?
• Clinical examples
Colorectal Cancer incidence

• In the U.S., Colorectal cancer is:
  • 4th most frequently diagnosed malignancy
  • 2nd leading cause of cancer death

• 100,000 new cases of colon cancer per year
• 40,000 new cases of rectal cancer per year
• An estimated 50,000 deaths
Metastatic Colorectal Cancer

• 50% to 60% of patients will develop colorectal metastasis metachronously

• 20% to 34% of patients with colorectal cancer present with synchronous metastatic disease.
Metastatic disease to the liver
Metastatic disease to the liver: Bilobar disease
Metastatic disease to the liver –
Right lobe dominant
Metastatic disease to the liver – Left lobe dominant
NCCN Guidelines Version 3.2015
Colon Cancer

CLINICAL PRESENTATION

Suspected or proven metastatic synchronous adenocarcinoma (Any T, any N, M1)

WORKUP

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF
- Needle biopsy, if clinically indicated
- Consider PET-CT scan if potentially surgically curable M1 disease in selected cases
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

FINDINGS

- Synchronous liver only and/or lung only metastases
- Resectable
- Unresectable (potentially convertible or unconvertible)

- Synchronous abdominal/peritoneal metastases

- Synchronous unresectable metastases of other sites

See Treatment and Adjuvant Therapy (COL-6)
See Treatment and Adjuvant Therapy (COL-7)
See Primary Treatment (COL-8)
See Chemotherapy for Advanced or Metastatic Disease (COL-C 1 of 9)
NCCN Guidelines Version 3.2015
Colon Cancer

**TREATMENT**
Resectable synchronous liver and/or lung metastases only

Synchronous or staged colectomy with liver or lung resection or

Neoadjuvant therapy (for 2–3 months)
FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or cetuximab (KRAS/NRAS wild-type [WT] gene only) followed by synchronous or staged colectomy and resection of metastatic disease

Colectomy, followed by chemotherapy (for 2–3 months)
FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or cetuximab (KRAS/NRAS WT gene only) and staged resection of metastatic disease

**ADJUVANT THERAPY**
(resected metastatic disease)
(6 MO PERIOPERATIVE TREATMENT PREFERRED)

FOLFOX/CapeOx preferred

Consider observation or shortened course of chemotherapy

Surveillance

If patient stage IV, NET

- History and physical every 2 y, then every 6 mo
- CEA every 3–6 mo x 2 y, then every 1 mo x 3–5 y
- Chest/abdominal/pelvic CT every 3–6 mo x 2 y, then every year x a total of 5 y
- Colonoscopy in 1 y, then 3 y, then every 5 y
Chemotherapy for metastatic colorectal cancer
Resectable OR potentially resectable

• 5-FU + Leucovorin + Oxaliplatin
• 5-FU + Leucovorin + Irinotecan

+ biologic agent:
  • Bevacizumab
  • Cetuximab
  • Panitumumab

• + newer agents, immunotherapy

One major risk: hepatotoxicity!
The most important thing to remember when contemplating induction chemotherapy for metastatic colorectal cancer:
The most important thing to remember when contemplating induction chemotherapy for metastatic colorectal cancer:

Involve a surgeon early!
Simultaneous resection or Staged?

• Simultaneous resection:
  • all disease is cleared in one operation, either preceded or followed by chemotherapy
  • In collaboration with a medical oncologist
Simultaneous resection or Staged?

- **Staged:**
  - The disease usually cannot be resected in one operation
  - A plan needs to be set forth (in collaboration with a medical oncologist) regarding resection of the primary and resection of metastatic burden, in two, or potentially three operations.
  - Sequence of operations (liver first vs. primary first) has no bearing in prognosis
Before we consider the approach to resection, we should consider:

when is it reasonable to aggressively resect colorectal liver metastasis?

Tumor biology (behavior) is King!
Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer: Analysis of 1001 Consecutive Cases

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Abstract

Objective: There is a need for clearly defined and widely applicable clinical criteria for the selection of patients who may benefit from hepatic resection for metastatic colorectal cancer. Such criteria would also be useful for stratification of patients in clinical trials for this disease.

Methods: Clinical, pathologic, and outcome data for 1001 consecutive patients undergoing liver resection for metastatic colorectal cancer between July 1985 and October 1998 were examined. These resections included 237 trisegmentectomies, 394 lobectomies, and 370 resections encompassing less than a lobe. The surgical mortality rate was 2.8%.

Results: The 5-year survival rate was 37%, and the 10-year survival rate was 22%. Seven factors were found to be significant and independent predictors of poor long-term outcome by multivariate analysis: positive margin (p = 0.004), extrahepatic disease (p = 0.003), node-positive primary (p = 0.02), disease-free interval from primary to metastases <12 months (p = 0.03), number of hepatic tumors >1 (p = 0.0004), largest hepatic tumor >5 cm (p = 0.01), and carcinoembryonic antigen level >200 ng/ml (p = 0.01). When the last five of these criteria were used in a preoperative scoring system, assigning one point for each criterion, the total score was highly predictive of outcome (p < 0.0001). No patient with a score of 5 was a long-term survivor.

Conclusion: Resection of hepatic colorectal metastases may produce long-term survival and cure. Long-term outcome can be predicted from five criteria that are readily available for all patients considered for resection. Patients with up to two criteria can have a favorable outcome. Patients with three, four, or five criteria should be considered for experimental adjuvant trials. Studies of preoperative staging techniques or of adjuvant therapies should consider using such a score for stratification of patients.
Fong Criteria: Predictors of recurrence

• Nodal status of primary
• Disease-free interval from the primary to discovery of the liver metastases of >12 months
• Number of metastatic lesions >1
• Preoperative CEA level >200 ng/ml
• Size of the largest metastatic lesions >5 cm
Fong Criteria

• N+
• DFS > 12m
• >1 CLM
• Preop CEA > 200 ng/ml,
• Largest CLM > 5 cm

Median survival score 5 = Median survival of best chemotherapy-alone RCT
Outline

• Introduction
• Definition of metastatic disease to the liver
• NCCN guidelines
• **Timing of Chemotherapy**
• When to operate?
• What type of operation?
• Clinical examples
Chemotherapy:

• Resection alone (inferior)

• Resection + multi-agent Chemotherapy (FOLFOX/FOLFIRI + biologic agent)

• Multi-agent Chemotherapy (FOLFOX/FOLFIRI + biologic agent) + Resection +/- additional Chemotherapy

CONTROVERSIAL topic (more art than science)
Timing of Chemotherapy:

• Benefit of chemotherapy addition to treatment plan is the same regardless of sequence of treatment

• Two reasons to favor Neoadjuvant chemotherapy:
  • Need to prove that biology of tumor is slow & responsive to multimodality treatment before we subject patients to large & potentially morbid operation(s)
  • Post-operative complications may preclude chemotherapy administration
Staged or Simultaneous resection?

Safety of liver and primary resection
Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis

Skye C Mayo, MD, MPH, Carlo Pulitano, MD, Hugo Marques, MD, Jorge Lamelas, MD, Christopher L Wolfgang, MD, PhD, FACS, Wassila de Saussure, MD, Michael A Choti, MD, MBA, Isabelle Gindre, MD, Luca Aldrighetti, MD, Eduardo Barroso, MD, Gilles Mentha, MD, Timothy M Pawlik, MD, MPH, PhD, FACS

BACKGROUND: The goal of this study was to investigate the surgical management and outcomes of patients with primary colorectal cancer (CRC) and synchronous liver metastasis (sCRLM).

STUDY DESIGN: Using a multi-institutional database, we identified 1,004 patients treated for sCRLM between 1982 and 2011. Clinicopathologic and outcomes data were evaluated with uni- and multivariable analyses.

RESULTS: A simultaneous CRC and liver operation was performed in 329 (33%) patients; 675 (67%) underwent a staged approach (“classic” staged approach, n = 647; liver-first strategy, n = 28). Patients managed with the liver-first approach had more hepatic lesions and were more likely to have bilateral disease than those in the other 2 groups (p < 0.05). The use of staged operative strategies increased over the time of the study from 58% to 75% (p < 0.001). Liver-directed therapy included hepatectomy (90%) or combined resection + ablation (10%). A major resection (>3 segments) was more common with a staged approach (39% vs 24%; p < 0.001). Overall, 509 patients (50%) received chemotherapy in either the preoperative (22%) or adjuvant (28%) settings, with 11% of patients having both. There were 197 patients (20%) who had a complication in the postoperative period, with no difference in morbidity between staged and simultaneous groups or major vs minor hepatectomies (p > 0.05). Ninety-day postoperative mortality was 3.0%, with no difference between simultaneous and staged approaches (p = 0.94). The overall median and 5-year survivals were 50.9 months and 44%, respectively; long-term survival was the same regardless of the operative approach (p > 0.05).

CONCLUSIONS: Simultaneous and staged resections for sCRLM can be performed with comparable morbidity, mortality, and long-term oncologic outcomes. (J Am Coll Surg 2013;216: 707–718. © 2013 by the American College of Surgeons)
## Safety of liver + primary resection

**Mayo et al., JHH**

### Table 2. Outcomes after Liver-Directed Management in 1,004 Patients Undergoing Simultaneous, Reverse Strategy (Liver First), and Colorectal Primary First Resections of Colorectal Liver Metastasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 1,004)</th>
<th>Colorectal first (n = 647)</th>
<th>Liver first (n = 28)</th>
<th>Simultaneous (n = 329)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic resection margins*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>732 (72.9)</td>
<td>465 (71.9)</td>
<td>8 (28.6)</td>
<td>259 (78.7)</td>
<td>0.019</td>
</tr>
<tr>
<td>R1</td>
<td>113 (11.5)</td>
<td>75 (11.7)</td>
<td>3 (10.7)</td>
<td>35 (10.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>R2</td>
<td>2 (0.2)</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Missing</td>
<td>157 (15.6)</td>
<td>106 (16.4)</td>
<td>17 (60.7)</td>
<td>34 (10.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any complication after liver-directed therapy†</td>
<td>197 (19.6)</td>
<td>128 (19.8)</td>
<td>6 (21.4)</td>
<td>63 (19.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Clavien Grade of complications within 90 d†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications</td>
<td>743 (74.0)</td>
<td>486 (75.1)</td>
<td>17 (60.7)</td>
<td>240 (72.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade I</td>
<td>13 (1.3)</td>
<td>7 (1.1)</td>
<td>0 (0)</td>
<td>6 (1.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade II</td>
<td>78 (7.8)</td>
<td>43 (6.6)</td>
<td>2 (7.1)</td>
<td>33 (10.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>45 (4.5)</td>
<td>29 (4.5)</td>
<td>0 (0)</td>
<td>16 (4.9)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>19 (1.9)</td>
<td>10 (1.5)</td>
<td>0 (0)</td>
<td>9 (2.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>18 (1.8)</td>
<td>14 (2.2)</td>
<td>0 (0)</td>
<td>4 (1.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Grade V‡</td>
<td>30 (3.0)</td>
<td>21 (3.2)</td>
<td>0 (0)</td>
<td>9 (2.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Unknown</td>
<td>57 (5.7)</td>
<td>37 (5.7)</td>
<td>9 (32.1)</td>
<td>11 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe complications (Clavien Grade ≥ IIIa)</td>
<td>113 (11.2)</td>
<td>74 (11.4)</td>
<td>0 (0)</td>
<td>39 (11.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>90-d mortality†</td>
<td>30 (3.0)</td>
<td>21 (3.2)</td>
<td>0 (0)</td>
<td>9 (2.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Recurrence of CRLM at last follow-up‡</td>
<td>556 (57.0)</td>
<td>373 (59.6)</td>
<td>12 (42.9)</td>
<td>171 (53.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Variable</td>
<td>Staged (n = 598)</td>
<td>Simultaneous (n = 299)</td>
<td>p Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td>------------------------</td>
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<td></td>
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</tr>
<tr>
<td><strong>Major hepatectomy (≥3 segments)</strong>, n = 329, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications</td>
<td>192 (75.9)</td>
<td>51 (67.1)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall complications after liver-directed therapy</td>
<td>60 (23.7)</td>
<td>19 (25.0)</td>
<td>0.818</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor complication (Clavien Grade I or II)</td>
<td>26 (10.3)</td>
<td>13 (17.1)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe complication (Clavien Grade ≥ IIIa)</td>
<td>35 (13.8)</td>
<td>12 (15.8)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality within 90 d (Clavien Grade V)</td>
<td>8 (3.2)</td>
<td>35 (6.6)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>253</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minor hepatectomy (&lt;3 segments)</strong>, n = 568, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications</td>
<td>282 (81.7)</td>
<td>170 (76.2)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall complications after liver-directed therapy</td>
<td>57 (16.5)</td>
<td>43 (19.3)</td>
<td>0.399</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor complication (Clavien Grade I or II)</td>
<td>26 (7.5)</td>
<td>26 (11.7)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe complications (Clavien Grade ≥ IIIa)</td>
<td>37 (10.7)</td>
<td>27 (12.1)</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality within 90 days (Clavien Grade V)</td>
<td>13 (3.8)</td>
<td>4 (1.8)</td>
<td>0.214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, n</td>
<td>345</td>
<td>223</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety of liver + primary resection
Mayo et al., JHH

- Staged vs. Simultaneous approach is “biologically” equivalent
  - Median survival
  - Recurrence free survival
- Operative (90d) mortality for staged resection group vs. simultaneous resection group (major hepatectomy):
  - 3.2% vs. 6.6% (not significant)
Simultaneous Liver and Colorectal Resections Are Safe for Synchronous Colorectal Liver Metastasis

Robert Martin, MD, Philip Paty, MD, Yuman Fong, MD, FACS, Andrew Grace, MD, Alfred Cohen, MD, FACS, Ronald DeMatteo, MD, FACS, William Jarnagin, MD, FACS, Leslie Blumgart, MD, FACS

BACKGROUND: The optimal surgical strategy for the treatment of synchronous resectable colorectal liver metastasis has not been defined. The aims of this study were to review our experience with synchronous colorectal metastasis and to define the safety of simultaneous versus staged resection of the colon and liver.

STUDY DESIGN: From September 1984 through November 2001, 240 patients were treated surgically for primary adenocarcinoma of the large bowel and synchronous hepatic metastasis. Clinicopathologic, operative, and perioperative data were reviewed to evaluate selection criteria, operative methods, and perioperative outcomes.

RESULTS: One hundred thirty-four patients underwent simultaneous resection of a colorectal primary and hepatic metastasis in a single operation (Group I), and 106 patients underwent staged operations (Group II). Simultaneous resections tend to be performed for right colon primaries (p < 0.001), smaller (p < 0.01) and fewer (p < 0.001) liver metastases, and less extensive liver resection (p < 0.001). Complications were less common in the simultaneous resection group, with 65 patients (49%) sustaining 142 complications, compared with 71 patients (67%) sustaining 197 complications for both hospitalizations in the staged resection group (p < 0.003). Patients having simultaneous resection required fewer days in the hospital (median 10 days versus 18 days, p = 0.001). Perioperative mortality was similar (simultaneous, n = 3; staged, n = 3).

CONCLUSIONS: Simultaneous colon and liver resection is safe and efficient in the treatment of patients with colorectal cancer and synchronous liver metastasis. By avoiding a second laparotomy, the overall complication rate is reduced, with no change in operative mortality. Given its reduced morbidity, shorter treatment time, and similar cancer outcomes, simultaneous resection should be considered a safe option in patients with resectable synchronous colorectal metastasis. (J Am Coll Surg 2003;197:233–242. © 2003 by the American College of Surgeons)
Table 6. Outcomes and Complications after Staged or Simultaneous Resection Involving Major Liver Resections (Lobectomy or More)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Staged (n = 76)</th>
<th>Simultaneous (n = 45)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time, min (range)</td>
<td>423 (195–793)</td>
<td>290 (203–445)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total blood loss, mL (range)</td>
<td>1100 (250–4,950)</td>
<td>800 (100–4,000)</td>
<td>0.004</td>
</tr>
<tr>
<td>Length of stay, d (range)</td>
<td>18 (7–58)</td>
<td>12 (0–31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total no. of complications</td>
<td>149</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Total patients with complications</td>
<td>53 (70%)</td>
<td>27 (60%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total patients with Grade 3 or 4 complications</td>
<td>19 (25%)</td>
<td>12 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (4%)</td>
<td>2 (4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Operative time, blood loss, and length of stay are median values.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Staged (n = 106)</th>
<th>Simultaneous (n = 134)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of liver lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42 (40%)</td>
<td>81 (60%)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;1</td>
<td>64 (60%)</td>
<td>53 (40%)</td>
<td></td>
</tr>
<tr>
<td>Size of lesions (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>65 (61%)</td>
<td>103 (77%)</td>
<td>0.009</td>
</tr>
<tr>
<td>&gt;5</td>
<td>41 (39%)</td>
<td>31 (23%)</td>
<td></td>
</tr>
<tr>
<td>CEA (median, range)</td>
<td>21 (0.7–2,327)</td>
<td>9.9 (1–6,870)</td>
<td>NS</td>
</tr>
<tr>
<td>Primary resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colectomy</td>
<td>15 (14%)</td>
<td>53 (40%)</td>
<td></td>
</tr>
<tr>
<td>Left colectomy</td>
<td>31 (29%)</td>
<td>30 (22%)</td>
<td>0.001</td>
</tr>
<tr>
<td>LAR</td>
<td>49 (46%)</td>
<td>46 (33%)</td>
<td></td>
</tr>
<tr>
<td>APR</td>
<td>11 (10%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>Liver resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>9 (8%)</td>
<td>49 (37%)</td>
<td></td>
</tr>
<tr>
<td>Segmental</td>
<td>21 (20%)</td>
<td>40 (30%)</td>
<td></td>
</tr>
<tr>
<td>≥Lobe</td>
<td>76 (72%)</td>
<td>45 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>CRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (12%)</td>
<td>29 (21%)</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>34 (32%)</td>
<td>52 (39%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35 (33%)</td>
<td>41 (31%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22 (21%)</td>
<td>7 (5%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
</tbody>
</table>
Safety of liver + primary resection
Martin et al. MSKCC

- Staged vs. Simultaneous approach is “biologically” equivalent
  - Median survival
  - Recurrence free survival
- Reported operative morbidity and mortality similar
Safety of liver + primary resection
Martin et al. MSKCC

• Operative characteristics were different!
• Left colectomy:
  • 85% of staged resection group had left-side colon resection vs. 55% in simultaneous resection group (significant)
• Major hepatectomy (lobectomy):
  • 72% in staged resection group vs. 34% in simultaneous group (significant)
Two-Stage Hepatectomy vs One-Stage Major Hepatectomy with Contralateral Resection or Ablation for Advanced Bilobar Colorectal Liver Metastases

Takashi Mizuno, MD, PhD, Jordan M Cloyd, MD, Kiyohiko Omichi, MD, PhD, Yun Shin Chun, MD, FACS, Claudius Conrad, MD, PhD, FACS, Ching-Wei D Tzeng, MD, FACS, Steven H Wei, PA-C, Thomas A Aloia, MD, FACS, Jean-Nicolas Vauthey, MD, FACS

BACKGROUND: Both 2-stage hepatectomy (TSH) and 1-stage hepatectomy (OSH) represent feasible strategies for resection of advanced bilobar colorectal liver metastases (CLM). However, the influence of the surgical approach on postoperative outcomes and overall survival (OS) is unknown. To define the optimal surgical approach for advanced bilobar CLM requiring right hemihepatectomy, we compared short-term and long-term outcomes after TSH and OSH with contralateral resection or radiofrequency ablation (RFA).

STUDY DESIGN: We retrospectively reviewed 227 patients with bilobar CLM, who underwent right or extended right hepatectomy with treatment of synchronous CLM in segments I, II, and/or III, between 1998 and 2015. Postoperative outcomes and OS were compared between patients who underwent TSH and those who underwent OSH.

RESULTS: Of the 227 patients, 126 (56%) underwent at least the first stage of TSH, and 101 (44%) underwent OSH, 29 (13%) without RFA and 72 (32%) with RFA. Two-stage hepatectomy was associated with a lower incidence of postoperative major complications (14% vs 26%, p = 0.03) and postoperative hepatic insufficiency (6% vs 20%, p = 0.001) than OSH. The 5-year OS rate was higher for patients assigned to TSH than for those who underwent OSH (35% vs 24%, p = 0.016). Patients who completed both stages of TSH had a higher 5-year OS rate than patients who underwent OSH without RFA (50% vs 20%, p = 0.023) or OSH with RFA (50% vs 24%, p < 0.0001).

CONCLUSIONS: In patients with advanced bilobar CLM, TSH is associated with fewer complications than OSH. Both TSH in intention-to-treat analysis and completed TSH in as-treated analysis were associated with better OS than OSH. (J Am Coll Surg 2018;226:825–834. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
Doing too much surgery at one time: Morbidity & Mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All patients (n = 227)</th>
<th>One-stage hepatectomy (n = 101)</th>
<th>One-stage hepatectomy without RFA (n = 29)</th>
<th>One-stage hepatectomy with RFA (n = 72)</th>
<th>Two-stage hepatectomy (n = 126)</th>
<th>p Value* (2-stage hepatectomy vs 1-stage hepatectomy without RFA)</th>
<th>p Value* (2-stage hepatectomy vs 1-stage hepatectomy with RFA)</th>
<th>p Value* (2-stage hepatectomy vs 1-stage hepatectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
<td>n = 88</td>
<td>n = 44</td>
<td>n = 4</td>
<td>n = 40</td>
<td>n = 44</td>
<td>0.03</td>
<td>0.005</td>
<td>0.2</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>n = 44</td>
<td>n = 26</td>
<td>n = 3</td>
<td>n = 23</td>
<td>n = 18</td>
<td>0.6</td>
<td>0.003</td>
<td>0.03</td>
</tr>
<tr>
<td>Bile leak</td>
<td>n = 12</td>
<td>n = 4</td>
<td>n = 1</td>
<td>n = 3</td>
<td>n = 8</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Postoperative hepatic insufficiency†</td>
<td>n = 27</td>
<td>n = 20</td>
<td>n = 0</td>
<td>n = 20</td>
<td>n = 7</td>
<td>0.2</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>Readmission &lt;45 d</td>
<td>n = 26</td>
<td>n = 14</td>
<td>n = 2</td>
<td>n = 12</td>
<td>n = 12</td>
<td>0.7</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Death &lt;90 d</td>
<td>n = 13</td>
<td>n = 8</td>
<td>n = 0</td>
<td>n = 8</td>
<td>n = 5</td>
<td>0.3</td>
<td>0.05</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Chi-squared test.
†According to the criteria of Mullen et al. OSH, 1-stage hepatectomy; RFA, radiofrequency ablation.
Doing too much surgery at one time: Morbidity & Mortality

Table 2. Morbidity and Mortality after Resection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All patients (n = 227)</th>
<th>One-stage hepatectomy (n = 101)</th>
<th>One-stage hepatectomy without RFA (n = 29)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>44</td>
<td>19</td>
<td>26</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Bile leak</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative hepatic insufficiency†</td>
<td>27</td>
<td>12</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Readmission (&lt;45 d)</td>
<td>26</td>
<td>11</td>
<td>14</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Death (&lt;90 d)</td>
<td>13</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

*Chi-squared test.
†According to the criteria of Mullen et al.²⁵
OSH, 1-stage hepatectomy; RFA, radiofrequency ablation.
Outcomes, outcomes, outcomes!

CONCLUSIONS: In patients with advanced bilobar CLM, TSH is associated with fewer complications than OSH. Both TSH in intention-to-treat analysis and completed TSH in as-treated analysis were associated with better OS than OSH. (J Am Coll Surg 2018;226:825—834. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Two stage hepatectomy >>
one stage hepatectomy
Greed, is NOT good!
A (quick) word on ablative techniques:

- Thermal (microwave / radio frequency) vs. cryoablation

- What we *(think we)* know so far:
  - RFA = MWA, but MWA is better near major vascular structures (heat sync effect)
  - Less than 2cm: ablation is safe and efficacious, compared to resection
  - More than 3cm: LESS efficacious, compared to resection
Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases (LAVA): study protocol for a randomised controlled trial


NYU Langone Medical Center
Population: adult patients with resectable colorectal liver metastases

**Inclusion criteria:** Suitable for liver resection or thermal ablation, completed or planned curative radical treatment of the primary colorectal cancer, considered high risk for surgery due to at least one of the following criteria: age, major comorbidities (such as previous history of myocardial infarction, severe chronic airway disease, major cerebrovascular accidents (CVA), recurrent pulmonary embolism (PE)), liver metastases with poor prognosis, or high risk surgery due to tumour burden.

**Patient identification through MDT**

**Consent**

**Baseline**
- Demographics,
- Pre-op staging (as per local protocol but will involve at least a CT scan of the chest, abdomen, and pelvis)
- Tumour markers

**Randomisation (1:1)**
Minimisation incorporating a random element, stratified by:
- Research site,
- Synchronous/metachronous disease,
- Primary cancer in situ,
- Largest size of tumour,
- Prognostic factors for inclusion,
- Planned surgical resection,
- Planned ablative treatment.

**Liver resection N=165**

**Thermal ablation N=165**

3, 6, 12, 18 and 24 month FU post-randomisation staging (as per local protocol; CT scan chest, abdomen & pelvis minimum) complications, survival, disease status, tumour markers, use of subsequent therapies, health economics (HE)

3, 6, 12, 18 and 24 month FU post-randomisation EQ-5D-5L, EORTC QLQC30, EORTC LMC-21 & Resource Use

5 year post date of last participant recruited:
Survival data obtained from Office National Statistics (ONS)

**Fig. 1** Trial schema. The figure shows the pathway that participants who are potentially eligible for the trial follow.
RANDOMISATION (1:1)
Minimisation incorporating a random element, stratified by: research site, synchronous/metachronous disease, primary cancer in situ, largest size of tumour, prognostic factors for inclusion, planned surgical resection, planned ablative treatment.

Liver resection  N=165

Thermal ablation  N=165

3, 6, 12, 18 and 24 month FU post-randomisation staging (as per local protocol; CT scan chest, abdomen & pelvis minimum) complications, survival, disease status, tumour markers, use of subsequent therapies, health economics (HE)

5 year post date of last participant recruited:
Survival data obtained from Office National Statistics (ONS)
One last thing...
RESISTANCE!
What is Resistance?

• Failure to control / progression of disease after first line chemotherapy (FOLFOX)?

• Failure to control / progression of disease after second line chemotherapy (FOLFIRI)?
RESISTANCE = BAD BIOLOGY
Resistance / Bad Biology

• How can we quantify resistance?
  • Biologic markers?
  • Inflammatory markers?
  • Genomic markers?
What drives Resistance / Bad biology?

• De-differentiation?
  • Primary clone may be different than metastatic clone

Pathway to metastatic colorectal cancer

- Inactivation of APC tumor suppressor gene
- Activation of K-ras oncogene
- Inactivation of tumor suppressor gene on 18q
- Inactivation of TP53 tumor suppressor gene
- Inactivation of other tumor suppressor genes

Resistance / Bad Biology

• What is third line treatment?
  • Clinical trial?
  • Hepatic artery pump?
  • Y-90 chemo-embolization?

• What about extrahepatic disease?
  • Cytoreduction & HIPEC? + Hepatectomy?

• When is too much surgery, too much, for disease that most definitely will recur?
Greed, is NOT good!
Conclusion

• Metastatic colorectal cancer is a common disease.

• 20-30% of initially unresectable disease will convert to resectable after “induction” or “neo-adjuvant” chemotherapy.

• Aggressive staged or simultaneous resection is indicated in patients with good performance status (who have shown to harbor favorable disease).
Recommendations:

• Consider PET CT for staging, at initial presentation
• (Always) use multi-agent chemotherapy (plus biologic agent) neoadjuvant chemotherapy diagnostically, to ferret out patients with best biology, most likely to benefit from large operation(s)
• Do not over-treat with chemotherapy to avoid steatosis
Recommendations:

• Consider Portal vein Embolization / Ligation of lobe of liver with dominant disease, and re-evaluate (+/- Volumetrics) FLR after 4-5 weeks.

• Consider Ablation of ipsilateral lobe lesions, before PVE/L to prevent growth of ipsilateral lesions.
Recommendations:

• Operative approach:
  • Lobectomy + liver wedge resection
  • Lobectomy + liver lesion(s) ablation
  • Wedge / Ablation + primary resection
  • Lobectomy + primary in carefully selected patients.
Recommendations:

• These patients with complex pathology, should be referred to centers of excellence with an experienced multi-disciplinary tumor board.
• The role of the expert Medical Oncologist is central in a center of excellence, in order to achieve superior outcomes & promote patient long term survival.
• The Medical Oncologist is, in fact, the Liver surgeon’s most trusted partner.
“I think it’s the beginning of a beautiful friendship”
State of the art management of Colorectal Liver Metastasis: an interplay of Chemotherapy and Surgical options

Ioannis S. Hatzaras, MD, MPH, FACS
Assistant Professor of Surgery
Division of Surgical Oncology
New York University
NCCN Guidelines Version 3.2015
Colon Cancer

**TREATMENT**
Unresectable^g synchronous liver and/or lung metastases only

- Systemic therapy (FOLFIRI or FOLFOX or CapeOXd ± bevacizumab^ee or FOLFIRI or FOLFOX ± panitumumab or cetuximab^ff [KRAS/NRAS WT gene only])^g,gg or FOLFOXIRI ± bevacizumab
- Consider colon resection^g only if imminent risk of obstruction or significant bleeding

- Re-evaluate for conversion to resectable^g every 2 mo if conversion to resectability is a reasonable goal
- Converted to resectable
- Synchronized or staged resection^g of colon and metastatic cancer
- Remains unresectable

See Chemotherapy for Advanced or Metastatic Disease (COL-C)

**ADJUVANT THERAPY**
(6 MO PERIOPERATIVE TREATMENT PREFERRED)^hh

**SURVEILLANCE**

If patient stage IV, no evidence of disease (NED):
- History and physical every 3–6 mo x 2 y, then every 6 mo for a total of 5 y
- CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y
- Chest/abdominal/pelvic CT^h scan every 3–6 mo x 2 y, then every 6–12 mo up to a total of 5 y
- Colonoscopy^b in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,^u repeat in 3 y, then every 5 y^v