Colorectal Cancer with Liver Metastases: A Multidisciplinary Perspective
Panel

- **Surgical Oncology**
  - Dr. Daniel Anaya, Moffitt Cancer Center

- **Medical Oncology**
  - Dr. Craig Lockhart, University of Miami

- **Pathology**
  - Dr. Gregory Lauwers, Moffitt Cancer Center

- **Radiation Oncology**
  - Dr. Kathryn Hitchcock, University of Florida

- **Interventional Radiology**
  - Dr. Beau Toskich, Mayo Clinic
Learning Objectives

*Metastatic disease is resectable until proven otherwise*

- Understand how multidisciplinary evaluation at first contact contributes to treatment planning, sequencing and identifying curable disease
- Recognize when surgery is indicated and what steps lead to surgical candidacy
- Outline the role of chemotherapy
  - Regimen
  - Timeline
  - Toxicity management
- Outline the role of radiation therapy
  - High dose treatment for local control
  - SBRT
  - Palliation of symptoms

- Outline the role of Interventional Radiology
  - Surgical optimization techniques
  - Palliative interventions for nonsurgical patients

- Understand the role of pathology review after surgery
  - Post chemotherapy response
  - Quality of liver after chemotherapy
Multidisciplinary team approach for GI malignancies has become routine over the past two decades
  - NCCN Guidelines

Impacts staging decisions
  - MDT rectify 20% of the referral diagnoses

Impacts treatment and adherence to guidelines
  - Pretreatment plan certainty is high, but changes are made in up to 1/3 of patients after MDT review

More timely implementation of the treatment plan
  - Median number of days from first visit to treatment initiation changes from 24 days to 17 days

Potential impact on outcomes
  - 3-year survival rate increasing from 25.6 to 38.2 % ($P < 0.001$) due to increase in surgical referral

Ehab et al. AHBPA 2019
Case 1: Dr. Sofia Palacio

Hematology/Medical Oncology Fellow, University of Miami

Courtesy of Dr. Daniel Anaya
A 54 year old woman presented with progressive abdominal pain

- **Initial evaluation**
  - CT revealed ‘colitis’

- **Readmitted within 2 weeks with worsening pain**
  - Repeat CT abdomen/pelvis
    - Multiple liver lesions, likely hemangiomas
    - Inflammatory bowel disease at terminal ileum but cannot exclude tumor at IC valve
    - Distended proximal bowel
    - Worsening ascites
  - Unable to tolerate bowel prep for colonoscopy
  - Taken to OR for laparoscopic right hemicolectomy
    - CBC, CMP normal
    - CEA post operatively - 22.1
Surgical pathology

• Right colon, appendix, ileum
  – Low grade colonic adenocarcinoma, 6.5 cm
  – LVI, PNI present
  – 8/14 LN positive
  – T3N2Mx

• MLH1, PMS2, MSH2 and MSH6 intact

• KRAS mutated (p.G13R)
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• Panel: what would you consider next:

  – Are these lesions worrisome for metastatic disease?

  – Is there a role for more imaging?
- PET
• Panel, can you comment on the role of biopsy at this point?
  – Second primary in ovaries?
  – Residual disease at surgical site?
  – Liver biopsy?

• Are these areas important to biopsy for surgical assessment?
• Patient had colonoscopy with biopsy
  – Enteric mucosa with erosion, no dysplasia or tumor

• Ovarian FNA
  – Adenocarcinoma, favor colorectal primary (PAX-8 negative)

• Liver biopsy
  – Metastatic adenocarcinoma
• Patient presented for MDT discussion

• Options
  – Systemic chemotherapy with palliative intent
  – Multi-step treatment with onco-surgical strategies with curative intent
MEDICAL ONCOLOGY PERSPECTIVE

CRAIG LOCKHART, M.D.M.H.S

Professor of Medicine
Chief, Division of Medical Oncology
Sylvester Comprehensive Cancer Center
Miller School of Medicine
University of Miami
Approach to a New Patient

• Resectable metastatic disease - **Curative potential**
  • Oligometastatic liver or lung mets

• “Borderline” resectable disease - **Curative potential**
  • Usually only refers to conversion of unresectable liver mets to resectability
  • ORR is critical in these cases

• Unresectable disease - **Palliative therapy**
  • Multiple lung mets
  • Extensive bilobar liver mets
  • Extensive lymph node disease
  • Bone, subcutaneous mets
EORTC 40983

- Primary endpoint: PFS
- Secondary endpoints: OS, complete resection

• 5-yr OS rate was not significantly different (51.2% vs 47.8%; P = 0.34)

Progress with Treatment

Treatment of Advanced CRC


5-FU cornerstone of therapy

5-FU based therapy superior to BSC

5-FU + oxaliplatin or irinotecan

Targeted therapies
- 2004 Bevacizumab & Cetuximab
- 2006 Panitumumab
- 2012 ziv-Aflibercept
- 2012 Regorafenib
- 2015 Ramucirumab
- 2015 Trifluridine/tipiracil

IMMUNOTHERAPY

Median Survival

Months

0 3 6 14 24 30

1960s 1980s 1990s 2000s Current
## ORR with Common Regimens

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>REGIMEN</th>
<th>N</th>
<th>ORR (%)</th>
<th>PFS (mo.)</th>
<th>OS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BICC-C</td>
<td>FOLFIRI + Bev</td>
<td>57</td>
<td>57.9</td>
<td>11.2</td>
<td>28.0</td>
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<tr>
<td>TREE 1/2</td>
<td>FOLFOX + Bev</td>
<td>71</td>
<td>52</td>
<td>9.9</td>
<td>26.1</td>
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<tr>
<td>TRIBE</td>
<td>FOLFOXIRI + Bev</td>
<td>252</td>
<td>65.1</td>
<td>12.1</td>
<td>31.0</td>
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<tr>
<td>CRYSTAL</td>
<td>FOLFIRI + Cetux</td>
<td>599</td>
<td>46.9</td>
<td>8.9</td>
<td>19.9</td>
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<tr>
<td>OPUS</td>
<td>FOLFOX + Cetux</td>
<td>344</td>
<td>46</td>
<td>9.0</td>
<td>_</td>
</tr>
<tr>
<td>CAIRO-2</td>
<td>CAPOX + Bev + Cetux</td>
<td>755</td>
<td>52.7</td>
<td>9.4</td>
<td>19.4</td>
</tr>
</tbody>
</table>
Sidedness Matters?

- Left-sided primary tumors are associated with longer OS
- Location may help to make therapeutic decisions

Venook A et al. ASCO 2016. Abstract 3504
Conclusions

• We need to consider eventual surgical resectability when evaluating a new patient with metastatic CRC – **Multidisciplinary Tumor Board**
• Targeted therapies in CRC combine well with and improve chemotherapy outcomes
• Toxicities of targeted therapy are mostly predictable
• Develop comfort with management and mitigation of common, non-serious, AEs
Case 1

- MDT discussion recommended neoadjuvant chemotherapy
• Completed 7 cycles of treatment
  – Oxaliplatin removed at cycle 5

• Restaging CT TAP
  – Interval decrease in size and enhancement of hepatic metastases
  – No new metastatic disease
• In preparation for surgery, the patient underwent right portal vein embolization
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Next day

- Exploratory laparotomy, IOUS
- Partial liver resection segment 2, wedge resection segment 2, wedge resection segment 3, microwave ablation of caudate
- Linear hepatotomy
- TAH-BSO, left ureterolysis
Liver Volumetry / Hypertrophy – Report Form
- Moffitt Liver Group -

Name: [Redacted]
Age: [Redacted]

Diagnosis:
Metastasogenic CRC LM bilobar > 10 + ovary w/ good response to chemo (4-Kydrax)

1. Baseline information

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Weight (Kg)</th>
<th>BMI</th>
<th>BSA</th>
<th>sILV</th>
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</thead>
<tbody>
<tr>
<td>175</td>
<td>65</td>
<td>24</td>
<td>1.77</td>
<td>1440</td>
</tr>
</tbody>
</table>

2. Embolization procedure

<table>
<thead>
<tr>
<th>Strategy used</th>
<th>Date</th>
<th>Approach</th>
<th>Embolized target</th>
<th>Embolization material</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVE (mini-ALPS)</td>
<td>6/7</td>
<td>Percutaneous</td>
<td>Right</td>
<td></td>
</tr>
</tbody>
</table>

3. Hypertrophy of sILV

<table>
<thead>
<tr>
<th>FLR</th>
<th>Baseline sILV</th>
<th>Baseline sILV</th>
<th>Post-embolization sILV</th>
<th>Post-embolization sILV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(4/04/16 - CT)</td>
<td>(4/04/16 - CT)</td>
<td>(6/15/16 - CT)</td>
<td>(6/15/16 - CT)</td>
</tr>
<tr>
<td></td>
<td>Volume sILV</td>
<td>Volume sILV</td>
<td>sILV DH %</td>
<td>sILV DH %</td>
</tr>
<tr>
<td>414</td>
<td>44.3%</td>
<td>44.3%</td>
<td>16 54%</td>
<td>16 54%</td>
</tr>
</tbody>
</table>

PVE 6/7
1st stage hematectomy, ovariectomy 6/8
2nd stage hematectomy (right hematectomy) pending
• POD 9
• Return to OR
  – Right hepatectomy and cholecystectomy
• All lesions - CRCLM, negative margins
  – Segment 2, partial resection
    • Metastatic adenocarcinoma; TRG 5
  – Segment 2, wedge resection
    • Metastatic adenocarcinoma; TRG 5
  – Segment 3, wedge resection
    • Metastatic adenocarcinoma; TRG 5
  – Ovary and fallopian tube R and L
    • Ovary with metastatic adenocarcinoma
    • Fallopian tube with no evidence of malignancy
• **Right hepatectomy**
  – Metastatic adenocarcinoma; TRG 4
  – Negative margins

• **Gallbladder, cholecystectomy**
  – Mild chronic cholecystitis
PATHOLOGY OF COLORECTAL LIVER METASTASES

Gregory Y. Lauwers, M.D.

Senior Member & Director GI Pathology Service
H. Lee Moffitt Cancer Center & Research Institute
Departments of Pathology & Cell Biology and Oncologic Sciences
University of South Florida
Pathologic evaluation of Colorectal Liver Metastases [CRLM]:

1. Identification of the tumor.
2. Status of the resection margin.
3. Response to therapy.
4. Chemotherapy adverse effect.
Resection margins of CRLM

• A margin is *positive* if a tumor is microscopically present at the margin.
• Dictate a worse outcome.
• Clearance to be recorded.
  – Significance is not entirely clear.
  – Surgical / anatomic limitation
Response to Neo-adjuvant therapy

- Complete pathologic response is associated with improved survival.
  - 76% 5-year overall survival vs. 45% for those with residual tumor
  - Achieved only in 4% of the cases (n=767)
    - Regimens were non uniform.
    - Newer regimens may increase the response rate.

Adam R. J Clin Oncol 2008;26;1635-1641
NO NECROSIS

NECROSIS
Tumor regression grade (TRG) scoring system

- TRG1, absence of residual cancer;
- TRG2, rare residual cancer cells scattered throughout the fibrosis;

Rubbia-Brandt L.  Annals Oncology 2007;18;299-304
• TRG3, more residual tumor cells but fibrosis predominates;
• TRG4, residual cancer cells predominate over fibrosis;
• TRG5, no signs of regression.
<table>
<thead>
<tr>
<th>FEATURES</th>
<th>CONSEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein invasion</td>
<td>Decreased survival</td>
</tr>
<tr>
<td>Bile duct invasion</td>
<td>Not definitive</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Not definitive</td>
</tr>
<tr>
<td>Hepatic vein invasion</td>
<td>Not definitive</td>
</tr>
</tbody>
</table>
Thickness of the fibrous capsule improves survival
Sinusoidal Obstruction Syndrome
Chemotherapy related toxicity

- **Sinusoidal distention [sinusoidal obstruction syndrome]**
  - Oxaliplatin
    - Increased risk of major morbidity
- **Nodular Regenerative Hyperplasia**
  - 5FU
- **Steatosis**
  - Irinotican, 5-FU and others
    - Increased risk of liver surgery specific complications
- **Hepatitis**
  - Regorafenib
    - Idiosyncratic hepatitis - rarely fatal (0.33%)

Zhao J. BJS 2017, 104:990-1002
Uetake H. Clinical Colorectal Cancer 2018;e49-58
Chemotherapy Related Toxicity

- Chemotherapy-related injury should be reported.
- However, liver injury does not appear to affect long-term outcomes.
- Yet, treatment response is decreased in patients with more severe sinusoidal lesions.

Vigano L. Ann Surg. 2013:258;731-740
Case 2: Dr. Bilal Farooqi

Hematology/Medical Oncology Fellow, University of Florida

Courtesy of Dr. Daniel Anaya
A 53 year old man presented to his primary care physician with rectal bleeding. No prior colonoscopies.

PCP did not palpate any masses on exam and referred to Gastroenterology for evaluation.

Colonoscopy identified fungating, non-obstructive mass located 14-18 cm from anal verge.

Biopsied as adenocarcinoma, moderately differentiated.

CBC, CMP normal. CEA elevated at 16.1
• Dr. Anaya, this patient resectable?

• Dr. Lockhart, is systemic treatment first line treatment reasonable? Does bleeding tumor concern your decisions?

• Dr. Hitchcock, is there a role for radiation treatment in this bleeding patient?
RADIATION ONCOLOGY PERSPECTIVE

Kathryn Hitchcock, M.D.

Assistant Professor
Division of Radiation Oncology
Shands Hospital
College Of Medicine
University of Florida
Roles of RT in metastatic colorectal ca:
1. Stereotactic RT to liver to obliterate one/few mets

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases
Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Scheffer

JCO 2009

Local Control

100% LC for tumors < 3 cm

Toxicity:
- 0 RILD
- 0 G4-5
- Before modern computing, used few beams, hard on skin
Roles of RT in metastatic colorectal ca:

2. In rectal cancer, neoadjuvant to resection of primary if considered after strong chemo response

3. To palliate, especially primary tumor

27 studies

Pooled . . . positive responses were reported for pain (78%), bleeding and discharge (81%), mass effect (71%) and other pelvic symptoms (72%).
Case 2

- Short-course stereotactic radiation - 5 Gray per fraction x 5 days

- Systemic chemotherapy
  - FOLFOX x 8 cycles
  - 5-FU/leucovorin and bevacizumab x 2 cycles
  - 5-FU/leucovorin x 8 cycles

- CEA decline to 3.7
• Exlap

• Right hepatectomy

• Wedge resection segment 3
Pathology

- 6 lesions
  - Fibrosis
  - No viable cells - complete pathologic response
  - Tumor Response Grade 1

- Margin - 1.5cm

- Mild steatosis
• Adjuvant therapy
  – 3 cycles of 5-FU/leucovorin

• Restaging with no evidence of disease
• **Panel:** Primary is still in place, what is the next step?
• 6 weeks after completion of adjuvant therapy - hand-assisted laparoscopic low anterior resection with diverting loop ileostomy

• Pathology report
  – Scar tissue with no viable cancer cells (Tumor Response Grade 1)
  – Complete pathologic response
  – Intact mesorectum - 4 lymph nodes, all negative
SURGICAL ONCOLOGY PERSPECTIVE

Daniel Anaya, M.D.

Senior Member and Chief of GI Surgery
Head of Hepatobiliary Section
Department of Gastrointestinal Oncology
Moffitt Cancer Center
## CRCLM - Treatment & Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>6-9 months</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Historic reports (1960-1990)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (5FU/LV)</td>
<td>12-14 months</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Liver resection</td>
<td>35 months</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Current reports (2000-2016)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (FOLFOX/FOLFIRI +/- Bio)</td>
<td>24+ months</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Ablation</td>
<td>30 months</td>
<td>20%</td>
</tr>
<tr>
<td>Chemotherapy + ablation</td>
<td>35-40 months</td>
<td>?</td>
</tr>
<tr>
<td>Liver resection</td>
<td>74 months</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% (10-year OS = cure)</td>
</tr>
</tbody>
</table>
CRCLM - Liver Resection

16%

Orcutt & Anaya et al. ASO 2017

Kopetz S et al. JCO 2009
CRCLM - Presentation

Incidence
Liver metastasis
30-50%

Leporrier J et al. BJS 2006

Resectable
5-20%

Unresectable
80-95%
CRCLM - Treatment Goals

- Complete - R0 resection
- Adequate residual liver
  - 2 contiguous segments with adequate inflow/outflow and biliary drainage
- Functional liver remnant (volume/function)
CRCLM - Treatment Goals

- Complete - R0 resection
- Adequate residual liver
  - 2 contiguous segments with adequate inflow/outflow and biliary drainage
- Functional liver remnant (volume/function)

*Surgery/resection = oncologic benefit*
CRCLM - Presentation

- Multiple lesions
- Larger lesions
- Bilobar tumors
- Synchronous disease

Geriatric population

<table>
<thead>
<tr>
<th>Resectable</th>
<th>Unresectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30%</td>
<td>70-85%</td>
</tr>
<tr>
<td>Resectable</td>
<td>Borderline</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>15-30%</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

**Technically unresectable**
- Close margins
- Vein involvement
- Small liver remnant

**High burden disease**
- Multiple-bilobar disease
  - (liver)
- Extrahepatic disease
- Recurrent CRCLM
- Biologic markers
- Other scores
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- **Technically unresectable**
  - Close margins
  - Vein involvement
  - Small liver remnant

- **High burden disease**
  - Multiple-bilobar disease (liver)

- **Borderline**
  - Extrahepatic disease
  - Recurrent CRCLM
  - Biologic markers

- **Unresectable**
  - All other
  - Progressive disease
  - Poor biology
  - No surgical candidates

- **Resectable**
  - Multiple lesions
  - Larger lesions
  - Bilobar tumors
  - Synchronous disease
  - Geriatric population

- **15-30%**

- **10-20%**

- **50-75%**
Liver Resection for CRCLM

• Good surgery – results
  • Postoperative morbidity/mortality
  • Negative margins

• Surgical strategy – long-term
  • Parenchyma-sparing* / Combined resection

• Multimodality treatment (chemo)
  • Sequence / # cycles

• Oncosurgical strategies***
Liver Resection for CRCLM

• Oncosurgical strategies
  1. Conversion chemotherapy
  2. Preoperative portal vein embolization
  3. Staged hepatectomies
  4. ALPPS

  5. Oncologic considerations

  6. Future: immunotherapy, chemo delivery
1. Conversion Chemotherapy

- Unresectable (mixed)
- Large burden - liver
- EH disease (38%)
- Small liver remnant

- Chemotherapy
  - Median 10 cycles

- Other therapies (30%)
  - PVE
  - Staged hepatectomy
  - +/- RFA

- Outcomes
  - 7% CR
  - Survival

1. Conversion Chemotherapy

- Pooled analysis - phase II/III studies / unresectable
- Median cycles 11 - RR 70% - CR 11% (resected)
- Outcomes: higher resection / OS

1. Conversion Chemotherapy

- Differential benefit in long-term survivors
- Liver toxicity: SOS, steatosis, steatohepatitis

1. Conversion Chemotherapy

• Which chemotherapy / regimen to use
  • Efficacy - Survival outcomes
  • RR / “downstaging”
  • Curative-intent surgery
  • Liver toxicity

• Tumor features - location / biomarkers
1. Conversion Chemotherapy

- Liver Toxicity - CALI
  - Steatosis
  - Sinusoidal Obstructive Syndrome (SOS)
  - Steatohepatitis
## 1. Conversion Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR</th>
<th>Conversion / Resection</th>
<th>5-year OS (median)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>5FU/LV</td>
<td>~40%</td>
<td>11%</td>
<td></td>
<td></td>
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<tr>
<td>FOLFIRI</td>
<td>~40-50%</td>
<td>3-12</td>
<td>33%</td>
<td>-9 cycles -Steatohepatitis</td>
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<tr>
<td>FOLFOX</td>
<td>~50-60%</td>
<td>4-40%</td>
<td>33% (26-42m)</td>
<td>-10 cycles -SOS</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>~70%</td>
<td>19 (34%*)</td>
<td>42% (40-60m*)</td>
<td>-11 Cycles -More toxic</td>
</tr>
<tr>
<td>+ Bevacizumab</td>
<td>~10%</td>
<td>49-60%*</td>
<td></td>
<td>-FOLFOXIRI &gt; FOLFOX / FOLFIRI</td>
</tr>
<tr>
<td>+ Cetuximab</td>
<td>~10-20%</td>
<td>16-34%</td>
<td>(54m)</td>
<td>-RAS wt -FOLFOX / FOLFIRI</td>
</tr>
</tbody>
</table>

* Liver-only metastatic disease
2. Portal Vein Embolization

- Small - future liver remnant (FLR)
  - Common cause of unresectability
  - Multifocal/bilateral, large, poorly located
    - Major resection
    - Small FLR
  - Extensive chemotherapy
2. Portal Vein Embolization

- Primary goal - Hypertrophy FLR
  - Allows for (safe) operation - outcomes
  - “Sufficient” residual liver - FLR

2. Portal Vein Embolization

- FLR volume - Indications

<table>
<thead>
<tr>
<th>Normal Liver</th>
<th>Steatohepatitis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20%</td>
<td>≤ 30%</td>
<td>≤ 40%</td>
</tr>
</tbody>
</table>

Anaya DA et al. Semin Intervent Radiol 2008
Segments 1-3 = 420 cm³ = 25%
Segments 1-3 = 549 cm³ = 33%
2. Portal Vein Embolization

- Outcomes - Efficacy of PVE

2. Portal Vein Embolization

- Outcomes - short-term outcomes / OS

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Non-PVE group (n = 66)</th>
<th>PVE group (n = 49)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Morbidity</td>
<td>16 (25.0 %)</td>
<td>17 (34.7 %)</td>
<td>0.263</td>
</tr>
<tr>
<td>General complication</td>
<td>11 (17.2 %)</td>
<td>2 (4.1 %)</td>
<td>0.022</td>
</tr>
<tr>
<td>Biliary leakage</td>
<td>1 (1.6 %)</td>
<td>7 (14.3 %)</td>
<td>0.007</td>
</tr>
<tr>
<td>Accumulation of pleural or ascitic fluid</td>
<td>4 (6.3 %)</td>
<td>9 (18.4 %)</td>
<td>0.045</td>
</tr>
<tr>
<td>Relaparotomy</td>
<td>1 (1.6 %)</td>
<td>1 (2.0 %)</td>
<td>0.849</td>
</tr>
</tbody>
</table>

Yamashita s et al. W J Surg 2013
3. Staged Hepatectomy

- 2-stage liver resection
- Bilateral liver metastasis
- Not amenable to one-stage approach
  - 1\textsuperscript{st} stage - resect one side disease +/- primary
  - +/- PVE contralateral tumor-bearing liver
- Adequate recovery
- Re-image: hypertrophy + no progression
- 2\textsuperscript{nd} stage - resect tumor-bearing liver (larger)
69 y/o F - rectal cancer and CRCLM

- Bilobar - unresectable CRCLM
- Small FLR
- Biologic behavior?
3. Staged Hepatectomy

- Combined strategies
  - Preoperative chemotherapy - 88%
  - PVE 76%
- Success rate - 77% complete 2-stage
- Major hepatectomy - 84%
  - Morbidity - 17% & 40%
  - Mortality - 0.5% & 3%

Lam VWT et al. HPB 2012
3. Staged Hepatectomy

- Outcomes - Overall survival

Brouquet A, et al. JCO 2011
2008

4. ALPPS

- “Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy”
  - Two-stages within 1-2 weeks
  - First stage with PV ligation and hepatotomoty
    - Faster and Higher hypertrophy

**ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis**

*Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial)*

**N= 100 (49 vs. 48)**

<table>
<thead>
<tr>
<th></th>
<th>ALPSS</th>
<th>TSH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median # lesions</td>
<td>8+/-4</td>
<td>8+/-5</td>
<td>0.48</td>
</tr>
<tr>
<td>% FLR growth reached</td>
<td>92%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resections rate</td>
<td>92%</td>
<td>57%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5. Oncologic Considerations

- Predictive and prognostic factors
  - Anatomic and tumor-burden (CRS - other)
- Molecular markers
  - Extent / site of EH disease
  - Kras/BRAF/MMR, other
- Novel markers - biology

***RESPONSE TO CHEMOTHERAPY***
Response to chemotherapy and survival


Chun YS, et al. JAMA 2009
6. Future (examples)

- Multimodality therapies - immunotherapy
  - Preoperative vaccine injection CRCLM
    - Direct kill effect
    - Abscopal effect
- Chemotherapy modeling
  - Tumor-site chemotherapy concentration
6. Future (examples)

- Chemotherapy modeling

\[ f_{k_{\text{III}}} = 2 \cdot f_{k_{\text{III}}^2} \cdot \text{BVFW}^{1/2} \cdot K_1(r_b/L) - K_2(\text{BVFW}^{1/2} \cdot r_b/L) - K_3(\text{BVFW}^{1/2} \cdot r_b/L) \cdot (1 - \text{BVFW}) \]

- Predict response
- Guides regimen/dose
- Alternative models of delivery

Summary and Conclusions

• Liver surgery and systemic treatment of CRCLM have improved outcomes

• Goal = multimodal treatment
  • Includes surgery
    • Outcomes critical but not sufficient
  • Appropriate use of combined therapies is essential
Summary and Conclusions

• Borderline - Conversion to resectable

• Oncosurgical strategies
  • Understanding of biologic behavior
  • Chemotherapy / PVE
  • Surgical approaches

• Evolving / novel approaches
  • Molecular profiling
  • Immunotherapy / chemotherapy modeling
Case 3: Sonikpreet Aulakh

Hematology/Medical Oncology Fellow, Mayo Clinic
• A 49 year old woman presented to local ER with severe abdominal pain and distention

• CT abdomen/ pelvis:
  1. obstructing rectosigmoid mass
  2. multiple presumed liver metastases

• Underwent palliative resection rectosigmoid colon with end colostomy
Pathology

- 5.5 X 4.5 cm low grade colonic adenocarcinoma with serosal penetration
- Lymphovascular invasion present
- Perineural invasion indeterminate
- 5/12 nodes involved
- Margins clear

Mutational analysis:
- BRAF WT
- KRAS WT
- NRAS WT
- Microsatellite instability negative by PCR
• CT Chest: Tiny pulmonary nodules

• PET: Hypermetabolic abdominal adenopathy

• 3 phase Liver CT: Multiple bilobar liver metastases occupying approximately 2/3 hepatic parenchyma
INTERVENTIONAL RADIOLOGY PERSPECTIVE

Beau Toskitch, M.D.

Assistant Professor
Division of Interventional Radiology
The Mayo Clinic, Jacksonville
Ablation for mCRC
Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomised phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOC"

T. Ruers¹, C.J.A. Punt², F. van Coevorden¹, J.-P. Perie³, I. Borel Rinkes⁴, J. Ledermann⁵, G. Poston⁶, W. Bechstein⁷, M.-A. Lentz⁸, M. Mauer⁸, E. Van Cutsem⁹, M. Lutz¹⁰, B. Nordlinger¹¹

• Phase II study, only of its kind:

• 119 Patients randomized to CT (FOLFOX plus Avastin from 2005) vs CT + RFA for up to 9 lesions

• Conversion to resection 11% vs 45%

• Median OS was mos 40.5 vs 45.6 mos (p .010)

• 8 year OS was 8.9% vs 35.9% (p .010)

• 8 year PFS was 2% vs 22% (p .005)

• ...likely never to be repeated
Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983.

Tanis E¹, Nordlinger B², Mauer M³, Sorbye H⁴, van Coevorden F⁵, Gruenberger T⁶, Schlag PM⁷, Punt CJ⁸, Ledermann J⁹, Ruers TJ⁵

Abstract

AIM: The aim of this study is to describe local tumour control after radiofrequency ablation (RFA) and surgical resection (RES) of colorectal liver metastases (CLM) in two independent European Organisations for Research and Treatment of Cancer (EORTC) studies.

BACKGROUND: Only 10-20% of patients with newly diagnosed CLM are eligible for curative RES. RFA has found a place in daily practice for unresectable CLM. There are no prospective trials comparing RFA to RES for resectable CLM.

METHODS: The CLOCC trial randomised 119 patients with unresectable CLM between RFA (±RES)+adjuvant FOLFOX (±bevacizumab) versus FOLFOX (±bevacizumab) alone. The EPOC trial randomised 364 patients with resectable CLM between RES±perioperative FOLFOX. We describe the local control of resected patients with lesions ≤4 cm in the perioperative chemotherapy arm of the EPOC trial (N=81) and the RFA arm of the CLOCC trial (N=55).

RESULTS: Local recurrence (LR) rate for RES was 7.4% per patient and 5.5% per lesion. LR rate for RFA was 14.5% per patient and 6.0% per lesion. When lesion size was limited to 30 mm, LR rate for RFA lesions was 2.9% per lesion. Non-local hepatic recurrences were more often observed in RFA patients than in RES patients, 30.9% and 22.3% respectively. Patients receiving RFA had a more advanced disease.

CONCLUSIONS: LR rate after RFA for lesions with a limited size is low. The local control per lesion does not appear to differ greatly between RFA and surgical resection. This study supports the local control of RFA in patients with limited liver metastases. Future studies should evaluate in which patients RFA could be an equal alternative to liver resection.
Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases.

Shady W¹, Petre EN¹, Vakiani E², Ziv E¹, Gonen M³, Brown KT¹, Kemeny NE⁴, Solomon SB¹, Solit DB⁴, Sofocles CT¹.

NCCN Guidelines Version 1.2019
Colon Cancer

**Resectable Metachronous Metastases**

- **Primary Treatment**
  - Resection (preferred)\(^v\) and/or local therapy\(^w\)
  - Neoadjuvant chemotherapy (2–3 mo)
    - FOLFOX (preferred) or CAPEOX (preferred) or (Capecitabine or 5-FU/leucovorin) (category 2B)

- **Adjuvant Treatment**\(^b\)
  - FOLFOX or CAPEOX (preferred) or Capecitabine or 5-FU/leucovorin
  - Reinitiate neoadjuvant therapy or FOLFOX or Observation
  - No growth on neoadjuvant chemotherapy
  - Systemic therapy ± biologic therapy (COL-D) (category 2B for biologic therapy) or Observation

- **Observation** (preferred for previous oxaliplatin-based therapy)
  - Systemic therapy ± biologic therapy (COL-D) (category 2B for biologic therapy)
  - Reinitiate neoadjuvant therapy or FOLFOX or Observation
  - No growth on neoadjuvant chemotherapy
  - Systemic therapy ± biologic therapy (COL-D) (category 2B for biologic therapy)
  - Observation

- **Previous chemotherapy**
  - Resection (preferred)\(^v\) and/or local therapy\(^w\)
  - Neoadjuvant chemotherapy (2–3 mo)
    - FOLFOX (preferred) or CAPEOX (preferred) or Capecitabine or 5-FU/leucovorin

- **See Surveillance (COL-8)**

---

\(^b\)See Principles of Imaging (COL-A).

\(^v\)Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

\(^w\)Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).
Ablation is a well tolerated, curative intent, therapy when applied to the correct candidate for many malignancies.
Neoadjuvant Ablative Radioembolization
Neoadjuvant “Radiation Lobectomy”
Synchronous mCRC
Neoadjuvant RL with doses ranging from 50-392 Gy (3 glass, 1 resin)
No systemic therapy toxicity or > G1 CTCAE AW
Right hepatectomy from 2.5 to 9 months post RL
50% CPN
No postoperative liver failure in cohort
Synchronous presentation:
51 y/o female with sigmoid junction primary and 10 cm hepatic mass
Right hepatic lobe radiation lobectomy with concurrent FOLFOX / dBev

May 16 CEA = 154.4
Path report:
“Extended right lobectomy:
- Liver with necrotic nodules, 5.2cm and 2.4cm.
- No viable tumor is seen.
- Background liver with no significant steatosis or fibrosis.”

July 7 CEA = 1.8
Palliative radioembolization for mCRC
SIRFLOX, FOXFIRE, and FOXFIRE-Global Combined Analysis: Response (Per Protocol Population)

- **n**: 549, 554
- **Median Events**: 411, 433
- **Overall survival**: 1103
- **Time from Randomisation (months)**: 549, 411 months
- **HR**: 1.04 (95% CI: 0.90–1.19)
- **P-value**: 0.609
- **Proportion Alive**

No. at Risk
- **Chemo**: 549, 419, 242, 88, 33, 12
- **Chemo+SIRT**: 554, 417, 247, 91, 35, 17
Liver
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.\textsuperscript{6}
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.\textsuperscript{7}
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.\textsuperscript{6-11} Having a plan for a debulking resection (less than an R0 resection) is not recommended.\textsuperscript{7}
- Patients with resectable metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.\textsuperscript{12}
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization\textsuperscript{13} or staged liver resection\textsuperscript{14} can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to
  - Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/refractory disease and with predominant hepatic metastases.
  - Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
  - Re-resection can be considered in selected patients.\textsuperscript{15}

Lung
- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.\textsuperscript{16-19}
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.\textsuperscript{20-23}
- Re-resection can be considered in selected patients.\textsuperscript{24}
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can also be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

Evaluation for Conversion to Resectable Disease
- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.\textsuperscript{25-28}
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.\textsuperscript{29}
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.\textsuperscript{30}
# SIRT Salvage Options

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>ORR, %</th>
<th>SD%</th>
<th>‡TTP or †PFS, mo</th>
<th>Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hendlisz</strong>¹</td>
<td>44</td>
<td>Resin microspheres* + 5-FU (Resin microspheres* @PD)</td>
<td>10</td>
<td>76</td>
<td>5.5‡/4.5</td>
<td>10</td>
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<tr>
<td>Level 1</td>
<td></td>
<td>0</td>
<td>(P=.22)</td>
<td>35</td>
<td>2.1</td>
<td>7.3</td>
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<tr>
<td><strong>Seidensticker</strong>²</td>
<td>29</td>
<td>Resin microspheres* BSC (matched-pairs)</td>
<td>41</td>
<td>17</td>
<td>5.5†</td>
<td>8.3</td>
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<tr>
<td>Level 3</td>
<td></td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>2.1†</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Cosimelli</strong>³</td>
<td>50</td>
<td>Resin microspheres*</td>
<td>24</td>
<td>24</td>
<td>4†</td>
<td>12.6</td>
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</table>

## Systematic Salvage Options

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<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
<th>ORR, %</th>
<th>SD%</th>
<th>‡TTP or †PFS, mo</th>
<th>Survival, mo</th>
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<tbody>
<tr>
<td><strong>Grothey</strong>⁴</td>
<td>505</td>
<td>Regorafenib</td>
<td>1</td>
<td>41</td>
<td>1.9</td>
<td>6.4</td>
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<tr>
<td>Level 1</td>
<td>255</td>
<td>BSC</td>
<td>0.4</td>
<td>15</td>
<td>1.7</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR: 0.49, P&lt;0.001)</td>
<td>(HR: 0.77, 0.0052)</td>
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<tr>
<td><strong>Mayer</strong>⁵</td>
<td>534</td>
<td>TAS-102</td>
<td>1.6</td>
<td>44</td>
<td>2.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Level 1</td>
<td>266</td>
<td>BSC</td>
<td>0.4</td>
<td>16</td>
<td>1.7</td>
<td>5.3</td>
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<tr>
<td></td>
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<td>(HR: 0.48, P&lt;0.001)</td>
<td>(HR: 0.77, 0.0052)</td>
</tr>
</tbody>
</table>

*Y-90 resin microspheres cross-over was allowed upon progression; †PFS, Progression free survival; ‡TTP liver; §retrospective data.

Thank You