Radioembolization in the Treatment of mCRC Liver Metastasis

David S. Kirsch, MD
Co-section Head Interventional Radiology
Ochsner Clinic Foundation

Disclosures

• none
Goals and Objectives

• Discuss Colorectal Cancer and the need to control metastasis to the liver.
• Discuss outcomes related to catheter directed Y90.
• Present data supporting earlier use of SIRT in delaying disease progression when used concomitantly with systemic treatment.

Secondary Liver Cancer Management Requires a Multidisciplinary Team

- Hepatobiliary Surgery
- Hepatology
- Oncology
- Pathology
- Interventional Radiology
- Radiology
Colorectal cancer

- Colorectal cancer is the third most commonly diagnosed cancer
  - The American Cancer Society estimated that about 143,000 people were diagnosed with colorectal cancer in 2012.
- Second leading cause of cancer-related deaths in both men and women living in the United States.
- Steady decrease in age-adjusted incidence and death rates of colorectal cancer over the last 20 years

<table>
<thead>
<tr>
<th>Races, %</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All races</td>
<td>19.6</td>
<td>13.9</td>
</tr>
<tr>
<td>White</td>
<td>19.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Black</td>
<td>28.7</td>
<td>19.0</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>13.1</td>
<td>9.7</td>
</tr>
<tr>
<td>American Indian/ Alaska Native</td>
<td>18.7</td>
<td>15.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.1</td>
<td>14.1</td>
</tr>
</tbody>
</table>

76% present with early-stage disease.
- 40% localized disease
- 36% regional disease

Only 20% present with distant metastatic disease
- However, over 50% will develop liver metastases at some point.
- It is estimated that 2/3 of patients with colorectal liver metastases will die from their liver disease.
- 5 year survival rate for patients diagnosed with distant mets is 11%

Complete surgical resection offers the best long-term survival but only 10-15% of pts with CRLM are candidates at initial dx.
mCRC: Liver Metastases

- Liver is the most common site of distant mets
- Liver failure due to hepatic tumor burden is the most common cause of death in patients with mCRC
- Hepatic induced parenchymal damage also significantly contributes to liver failure

Protecting healthy parenchyma, while effectively treating liver metastases is a key goal when treating patients with liver dominant metastases

Colorectal metastasis

- MRI more sensitive and specific
- Imaging appearance generally nonspecific
- Generally hypovascular with slight peripheral enhancement with hypoattenuating center
- PET CT controversial but useful in detecting extrahepatic disease
mCRC with Liver Metastases: Goals of Therapy

- Protecting liver parenchyma
- Maximizing survival
- Prolonging progression-free intervals
- Downsize tumors in resection
- Decrease tumor burden
- Maintain quality of life
- Palliating tumor-related symptoms

mCRC with Liver Metastases: Treatment Options

- Surgery
  - 5-year survival > 50% for resectable but < 10% for unresectable
  - Only 10-15% present with resectable disease
- Chemotherapy +/- Targeted Therapy
- Laparoscopic or percutaneous ablation
- Hyperfractionation / External Beam
- Liver-directed Therapy
Ablative Technologies

- Options include radiofrequency, microwave, IRE (irreversible electroporation), SBRT and cryoablation
- Best outcomes in limited number and size of lesions (< 3 cm)
- Favored over resection in patients who are poor surgical candidates
  - Resection considered gold standard
  - Only 5 – 15% of patients are candidates for Rx

Radiofrequency Ablation

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCRC</td>
<td>79 – 98%</td>
<td>38 - 69%</td>
<td>19-25%</td>
</tr>
</tbody>
</table>
Intra-arterial Therapies

Hepatic Artery Infusion

• Direct, pump-administered infusion of chemotherapeutic agents into the hepatic artery to achieve a high concentration of the agent in the tumor.

• (FUDR dose = \((0.18 \text{ mg} \cdot \text{kg} \cdot 30 \text{ mL}) ÷ (\text{pump flow rate} \text{ mL/d})\); LV dose = \((4 \text{ mg} \cdot \text{m}^2 \cdot 30 \text{ mL}) ÷ (\text{pump flow rate} \text{ mL/d})\); and Dex 25 mg.)
HAI - meta analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>log(HR)</th>
<th>(SE)</th>
<th>HR random</th>
<th>95% CI</th>
<th>Weight %</th>
<th>HR random</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al., 1997</td>
<td>0.1106</td>
<td>0.0073</td>
<td>1.12</td>
<td>0.96 to 1.30</td>
<td>11.45</td>
<td>1.12</td>
<td>0.96 to 1.30</td>
</tr>
<tr>
<td>Kanemura et al., 1997</td>
<td>-0.3966</td>
<td>0.1080</td>
<td>0.66</td>
<td>0.53 to 1.00</td>
<td>7.82</td>
<td>0.66</td>
<td>0.53 to 1.00</td>
</tr>
<tr>
<td>Hider et al., 1999</td>
<td>0.1076</td>
<td>0.0081</td>
<td>1.11</td>
<td>0.95 to 1.30</td>
<td>11.34</td>
<td>1.11</td>
<td>0.95 to 1.30</td>
</tr>
<tr>
<td>Martin et al., 1990</td>
<td>0.1217</td>
<td>0.1204</td>
<td>1.13</td>
<td>0.99 to 1.37</td>
<td>10.03</td>
<td>1.13</td>
<td>0.99 to 1.37</td>
</tr>
<tr>
<td>Wagner et al., 1992</td>
<td>0.1179</td>
<td>0.1082</td>
<td>1.13</td>
<td>0.99 to 1.37</td>
<td>10.18</td>
<td>1.13</td>
<td>0.99 to 1.37</td>
</tr>
<tr>
<td>Roulier et al., 1992</td>
<td>-0.4064</td>
<td>0.1520</td>
<td>0.69</td>
<td>0.56 to 0.86</td>
<td>9.09</td>
<td>0.69</td>
<td>0.56 to 0.86</td>
</tr>
<tr>
<td>Albert et al., 1994</td>
<td>-0.5289</td>
<td>0.0979</td>
<td>0.59</td>
<td>0.49 to 0.72</td>
<td>11.03</td>
<td>0.59</td>
<td>0.49 to 0.72</td>
</tr>
<tr>
<td>Lencioni et al., 2000</td>
<td>-0.0391</td>
<td>0.2170</td>
<td>0.97</td>
<td>0.85 to 1.12</td>
<td>7.02</td>
<td>0.97</td>
<td>0.85 to 1.12</td>
</tr>
<tr>
<td>Kemeny et al., 2003</td>
<td>0.1126</td>
<td>0.0418</td>
<td>1.14</td>
<td>0.99 to 1.28</td>
<td>11.54</td>
<td>1.14</td>
<td>0.99 to 1.28</td>
</tr>
<tr>
<td>Kemeny et al., 2006</td>
<td>-0.3966</td>
<td>0.1360</td>
<td>0.69</td>
<td>0.53 to 0.89</td>
<td>9.99</td>
<td>0.69</td>
<td>0.53 to 0.89</td>
</tr>
</tbody>
</table>

Total (95% CI)

Test for heterogeneity: \( \chi^2 = 60.83 \) (\( P < 0.0001 \)), \( I^2 = 85.2\%

Test for overall effect: \( z = 1.17 \) (\( P = 0.24 \))

Conclusion

Currently available evidence does not support the clinical or investigational use of fluoropyrimidine-based HAI alone for the treatment of patients with unresectable CRC liver metastases, at least as a first-line therapy.
Percutaneous Hepatic Perfusion

Current Status of Percutaneous Hepatic Perfusion as Regional Treatment for Patients with Unresectable Hepatic Metastases: A Review

Reutner A. Lifeson and R. Richard Alexander, Jr.

The Division of General and Oncologic Surgery, Department of Surgery and The Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland

Disclosure: The authors have declared that no conflict of interest exists.

Citation for this article: Am Oncology and Hematolog Rev. 2014: 15-23

Correspondence: R. Richard Alexander, Jr., M.D., Department of Surgery, University of Maryland School of Medicine, 22 S. Greene Street, Baltimore, Maryland 21201. E-Mail: PRAlexander@uomaryland.edu

Acknowledgments: The publication of this article was supported by an educational grant from Delnath Systems. The views and opinions expressed are those of the authors and not necessarily those of Delnath Systems.
The median hPFS for the PHP group was 7.03 months (or 245 days) and for the BAC group, 1.64 months (49 days, P<0.001).
Intra-arterial Therapies

• **RESULTS:** A total of 245 treatments were performed over 141 cycles on 121 patients. Ninety-five of 141 treatment cycles were evaluable for response:
  - 2 (2%) partial response, 39 (41%) stable disease, and 54 (57%) progression.
  - Median time to disease progression (TTP) in the treated liver was 5 months, and median TTP anywhere was 3 months.
  - Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization.
  - Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11-12 months) than after third- to fifth-line therapies (6 months) \( (P = .03) \).
  - Presence of extrahepatic metastases did not adversely affect survival \( (P = .48) \).

• **CONCLUSIONS:**
  - Chemoembolization provided local disease control of hepatic metastases after 43% of treatment cycles. Median survival was 27 months overall, and 11 months when initiated for salvage after failure of second-line systemic therapy.

Multicenter study, 74 patients were randomly assigned to receive DEBIRI (36) versus systemic irinotecan, fluorouracil and leucovorin (FOLFIRI, 38). Following failure of at least 2 lines of chemotherapy.
• **Conclusion:** This study showed a statistically significant difference between DEBIRI and FOLFIRI for overall survival (7 months), progression-free survival (3+ months) and quality of life (5 months).
Y90 vs TACE

- $^{90}$Yttrium does not occlude the vessels at the arteriolar level
  - Option for repeat embolic treatment
  - Less ischemic damage
- Response rates seem to be similar (limited head-to-head comparisons)
- Equivalent side effect profile:
  
  cTACE > HAE > debTACE > SIRT
Radioembolization Y90

- Transarterial delivery of resin or glass microspheres bound with Yttrium-90
- Delivers β radiation to the tumor cells
- Direct and indirect cell death

Red Blood Cell = 6.2-8.2 µm
Selective internal radiation therapy (SIRT) with Yttrium-90 Rationale

• **Preferential blood supply to the tumor**
  – Parenchyma is 30% arterial and 70% portal venous
  – **Metastases are nearly 100% arterial**
  – Tumor microvasculature is 3-200x as dense as surrounding tissue

• **CRC cells are radiosensitive**
  – Radiation works **synergistically** with radiation-sensitizing chemotherapy drugs

• **Targeted to the tumor**
  – Treatment of multiple and large tumors not amenable to external beam radiation tx

Benefits of SIRT

• Localized radiation therapy delivering a dose of internal radiation 40x higher than conventional external beam therapy

• Healthy liver tissue relatively unaffected
  – 90% experience < Grade 3 adverse events

• **Outpatient procedure**
  – Generally two treatments over 4-6 weeks
  – Patients discharged 2-4 hours after treatment
Integration of SIRT

Original article

Randomised trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer


<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>TTP</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y90 + FUDR HAC</td>
<td>44%</td>
<td>15.9 mo</td>
<td>39% @ 2 years</td>
</tr>
<tr>
<td>FUDR HAC</td>
<td>18%</td>
<td>9.7 mo</td>
<td>29% @ 2 years</td>
</tr>
</tbody>
</table>

Conclusion: The combination of a single injection of SIR-Spheres® plus HAC is substantially more effective in increasing tumor responses and progression free survival than the same regimen of HAC alone.

CONCLUSION: This small phase 2 randomised trial demonstrated that the addition of a single administration of SIR-Spheres to a regimen of systemic fluorouracil/leucovorin chemotherapy significantly increased both treatment related response, time to PD, and survival with acceptable toxicity.
**SIRFLOX trial**

Multi-center, international study*

**Primary endpoint**
- Progression-free survival

**Secondary endpoints**
- Progression-free survival in the liver
- Overall survival
- Liver resection rate
- Tumor response rate
- Hepatic and extra-hepatic recurrence rate
- Health-related quality of life
- Toxicity and safety

SIR-Spheres microspheres
FOLFOX6m1a bevacizumab

Enrollment completed April 2013

---

**Eligibility Criteria**

**Inclusion**
- Aged ≥18 years
- Adenocarcinoma of the colon or rectum with or without primary tumor in situ
- Liver metastases not surgically resectable or suitable for ablation
- WHO Performance Status 0–1
- Limited extra-hepatic metastases
- Life expectancy ≥3 months
- Chemotherapy-naïve for mCRC, but previous adjuvant systemic chemotherapy for primary CRC or neoadjuvant chemotherapy to the pelvis >6 months before recruitment are permitted
- Adequate hematological, renal, and hepatic function

**Exclusion**
- Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumor involvement, or main portal venous thrombosis
- Previous radiotherapy delivered to the upper abdomen
- Nonmalignant disease that renders patients unsuitable for the study treatment
- Peripheral neuropathy > grade 1 (NCI-CTCv3)
- Previous dose-limiting toxicity associated with adjuvant 5-FU or oxaliplatin chemotherapy
- Allergy to non-ionic contrast

---

*Ochsner Medical Center, New Orleans, LA, USA. CTC, Common Toxicity Criteria; WHO, World Health Organization; mCRC, metastatic colorectal cancer.
**Primary Endpoint**
- PFS at any site

**Secondary Endpoints**
- PFS in the liver
- ORR in the liver
- ORR at any site
- Safety and toxicity
- Liver resection rate
- Health-related quality of life
- Overall survival
### Patient Characteristics in the ITT Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FOLFOX (+ bev) (n = 263)</th>
<th>FOLFOX (+ bev) + SIRT (n = 267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>63 (23 – 89)</td>
<td>63 (28 – 81)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88 (34%)</td>
<td>85 (32%)</td>
</tr>
<tr>
<td>Male</td>
<td>174 (66%)</td>
<td>182 (68%)</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>175 (67%)</td>
<td>176 (66%)</td>
</tr>
<tr>
<td>1</td>
<td>87 (33%)</td>
<td>90 (34%)</td>
</tr>
<tr>
<td>Extra-hepatic metastases</td>
<td>104 (40%)</td>
<td>108 (40%)</td>
</tr>
<tr>
<td>Primary tumor not removed</td>
<td>121 (46%)</td>
<td>119 (45%)</td>
</tr>
<tr>
<td>Synchronous metastases</td>
<td>233 (89%)</td>
<td>241 (90%)</td>
</tr>
</tbody>
</table>

### Progression-Free Survival at Any Site

- **FOLFOX (+ bev)**: 10.2 months (95% CI: 8.57–11.82, *P* = .43)
- **FOLFOX (+ bev) + SIRT**: 10.7 months (95% CI: 9.77–11.67, *P* = .43)

**HR: 0.93**

SIR-Spheres Y-90 resin microspheres are a liver-directed therapy that demonstrated no effect on disease outside of the liver.
Progression-Free Survival in the Liver

SIR-Spheres Y-90 resin microspheres significantly extend PFS in the liver, with a 31% reduction in risk of progression in the liver.

PFS in the Liver: Patients with Liver-only and Liver + Extra-hepatic Mets

Liver-Only Metastases
- Median PFS: 12.4 months
- HR: 0.64 (95% CI: 0.48-0.86)
- P = .003

Liver + Extrahepatic Metastases
- Median PFS: 16.7 months
- HR: 0.77 (95% CI: 0.54-1.09)
- P = .147

<8 months + 8.7 months
Liver metastases are the dominant site of disease in mCRC and the dominant cause of death

No impact on duration of systemic therapy

Results were irrespective of the use of bevacizumab, baseline tumor burden and performance status

Significantly increased ORR vs chemo alone
**SIRFLOX Conclusions**

- The addition of SIRT, using Y-90 resin microspheres, to FOLFOX-based first-line chemotherapy in patients with liver-dominant metastases:
  - Did not improve overall PFS, but...
  - **Achieved a 7.9 month improvement in median PFS in the liver**, representing a 31% reduction in risk of disease progression in the liver [HR: 0.69; *p*=0.002]
  - 3 fold increase in complete responses vs chemotherapy alone
  - Overall survival available 2017

**Y90 Case Study - mCRC**
Conclusions

• ~50% of patients will develop liver metastases at some point during their disease
• Transarterial treatment of mCRC to liver offers significant survival benefits over systemic chemotherapy alone including:
  – First line
  – Second line
  – Third line/Salvage
Conclusions

• The longest survival benefits are achieved if transarterial treatment is employed along with the 1st line of chemotherapy, regardless of method employed.

• Intra-arterial locoregional therapies are evolving tools in the treatment of metastatic liver disease becoming earlier therapeutic options to increase the rate of curative surgical resection and improve survival in combination with systemic therapies.

Thank you!