LIVER DIRECTED THERAPIES FOR PATIENTS WITH UNRESECTABLE COLORECTAL CANCER LIVER METASTASES

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CRC as worldwide health problem

- **CRC Global Statistics:**
  - 3rd highest incidence rate (~1,200,000/yr)
  - 4th highest mortality rate (~608,000/yr)

- **CRC US Statistics:**
  - 3rd highest incidence rate (~143,000/yr)
  - 2nd highest mortality rate (~51,500/yr)
Scope of the Problem

- Nearly 25% of patients present with synchronous metastatic disease at first diagnosis
  - An additional 40-50% develop metastases during the course of their disease
  - Liver involvement is a major source of organ failure, morbidity and mortality in the majority of patients

- Surgical resection is the standard treatment in pts with resectable liver metastases
  - 5-year survival after resection is ~ 25-35%
  - 40-60% of patients who undergo surgery have recurrent disease

- Despite new, active chemotherapy regimens, the majority of MCRC patients have progressive disease

- Ablative techniques or locoregional drug delivery may allow localized minimally invasive therapy and low systemic toxicity

Liver directed therapy options for unresectable CRC liver metastases to be discussed

- **Regional Therapies**
  - Trans-arterial chemoembolization (TACE)
  - Selective Internal Radiation Therapy (SIRT)

- **Local Ablation techniques**
  - Radiofrequency ablation (RFA)
  - Irreversible electroporation (Nanoknife)
Rationale for regional/intraarterial therapies

- Tumors receive 80-100% of their blood supply from hepatic artery
- Normal liver receives > 75% of its blood supply from portal vein
Hepatic Intra-arterial Chemotherapy

- Regional chemotherapy through the hepatic artery
  - Hepatic intra-arterial chemotherapy
    - FUDR via implantable pump
    - Better than FU/LV\(^1\)
    - Historical Interest (not commonly used)
  - Transarterial embolization with chemotherapy (TACE)
    - Embolic particles mixed with chemotherapeutic drugs, producing a shutdown of blood flow and simultaneous release of high dose of drug
    - Approved for intermediate stage HCC without portal invasion\(^2\)
    - Drug Eluting Beads (irinotecan) currently studied in MCRC

Drug Eluting Beads

- Soft deformable microspheres loaded with a chemotherapeutic agent, slowly degradable
- Reduce blood flow to tumor
- Slowly release of drug, enhancing local anti-tumor effect and decreased systemic exposure

[Graphs showing comparison between DEB-TACE and conventional TACE]
TACE with DEBIRI

- Procedure is performed under conscious sedation, antibiotic prophylaxis, and antiemetic drugs
- Demonstrate liver arterial anatomy and the feeding vessels of the tumor
- Injection of loaded beads into the feeding vessels using 3 French micro-catheter
- COMPLICATIONS*
  - Most common: Post-embolization syndrome (abdominal pain, nausea, vomiting, fever (40-63%))
  - Liver enzyme elevation (all patients; > 3x ULN: 58%)
  - Bilirubin elevation: 18%
  - Hypertension transient (may be related to pain)

DEBIRI vs. FOLFIRI

- 74 pts
- Liver only metastases, occupying less than 50% of parenchyma
- Prior chemotherapy (2-3 lines) allowed
- 36 pts (DEBIRI); 38 pts (FOLFIRI)
- Number of cycles: Debiri: 2; FOLFIRI: 8

- Median survival: 22 (95% CI 21-23) vs. 15 months (95% CI 12-18); p 0.031
- PFS: 7 (CI 3-11) vs. 4 months (3-5) p 0.006
- Time to extrahepatic progression: 13 (CI 10-16) vs. 9 (CI 5-13) months (NS)

Systemic Chemotherapy + DEBIRI

- Randomized controlled trial of irinotecan drug eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis
- N: 70 patients
  - 40 pts randomized to FOLFOX-Bev/DEBIRI (alternate weeks)
  - 30 pts randomized to FOLFOX/Bev
- ORR: 78% vs. 54% (2 months), 76 vs. 60% (6 months)
- Greater downsizing to resection (35% vs 16%)
- Improved mPFS (15.3 vs. 7.6 months)
- Grade 3/4 AEs: 54% vs. 46%

Martin RC, et al. ASCO GI Symposium, 2014
Selective Internal Radiation Therapy

To selectively target a radiation dose high enough to kill tumors cells within the liver, while maintaining a low radiation dose to normal parenchyma.

- **SIR-Spheres**
- **Y-90 bound to microspheres**
- **Biocompatible resin**
- **20-60 (32) micron diameter**
- **50 Bq/sphere**
- **40-80 x 10(6) per 3 GBq vial**

- **Y-90: Beta emitter**
- **Physical half life: 64.1 hours**
- **Maximum energy: 2.28 MeV / Mean energy: 938 keV**
- **Mean tissue penetration: 2.5 mm**
- **Tumor vessels 25μm -75μm diameter**
- **End arterioles 8μm diameter**
- **SIR-Spheres® microspheres mean diameter 32.5μm**
Who are candidates for Y-90 treatment?

- Patients with liver metastasis from GI, Breast or other tumor primary
  - Bilirubin < 2 mg/dl
  - Albumin above 3
  - No history of ascites or hepatic encephalopathy
  - Well controlled primary cancer
  - Performance status, ECOG 0-2
  - Life expectancy >3 months
SIRT: Planning Procedures

- Angiographic evaluation of hepatic vasculature
- Evaluation of lung shunting/ TcMAA
- Treatment Planning
SIR-Spheres microspheres + 5FU in mCRC Salvage Therapy: Design

Eligible Patients
Liver-only mCRC, PS 0–2, refractory to chemotherapy

Stratify
• Institution
• Interval to progression on chemotherapy

Random Assignment

Arm A:
- 5FU protracted IV infusion (300 mg/m\(^2\) D1–14 q3w)

Arm B:
- \(^{90}\)Y resin microspheres on Day 1 (D1) Cycle 1 (C1)
- 5FU protracted IV infusion (225 mg/m\(^2\) D1–14 C1 and 300 mg/m\(^2\) D1–14 q3w thereafter)

until progression

Eligible Patients
Liver-dominant mCRC, PS 0–2

\(^{90}\)Y resin microspheres

until progression

SIR-Spheres microspheres + 5FU in mCRC Salvage Therapy: Primary Endpoint – Time to Liver Progression

Time to Progression at: Any Site Liver

5FU

5FU + radioembolization (censored)

HR: 0.51 0.38
95%CI: 0.28–0.94 0.20–0.72

P = 0.03 0.003

**SIR-Spheres microspheres + 5FU in mCRC**

**Salvage Therapy:** Time to Progression & Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>5FU alone</th>
<th>5FU + SIR-Spheres</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median Time to Liver Progression:</strong></td>
<td>2.1 months</td>
<td>5.5 months</td>
<td><strong>0.38 (0.20–0.72)</strong></td>
<td><strong>p=0.003</strong></td>
</tr>
<tr>
<td><strong>TTLP censored to change of Tx plan:</strong></td>
<td>2.1 months</td>
<td>5.6 months</td>
<td><strong>0.35 (0.18–0.69)</strong></td>
<td><strong>p=0.002</strong></td>
</tr>
<tr>
<td><strong>Median Time to Progression:</strong></td>
<td>2.1 months</td>
<td>4.5 months</td>
<td><strong>0.51 (0.28–0.94)</strong></td>
<td><strong>p=0.03</strong></td>
</tr>
<tr>
<td><strong>Median Overall Survival:</strong></td>
<td>7.3 months*</td>
<td>10.0 months</td>
<td><strong>0.92 (0.47–1.78)</strong></td>
<td><strong>p=0.80</strong></td>
</tr>
</tbody>
</table>

8.8 months

*note: 10 patients in the 5FU arm received SIR-Spheres as salvage therapy after disease progression*
### SIR-Spheres microspheres + 5FU in mCRC

**Salvage Therapy: Results – Best Overall Hepatic Response**

<table>
<thead>
<tr>
<th></th>
<th>5FU alone</th>
<th>5FU + SIR-Spheres</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 23</strong></td>
<td><strong>n = 21</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Response, n (%):</td>
<td>0</td>
<td>2 (10%)</td>
<td>p=0.22</td>
</tr>
<tr>
<td>Stable Disease, n (%):</td>
<td>8 (35%)</td>
<td>16 (76%)</td>
<td></td>
</tr>
<tr>
<td>Disease Control Rate, n (%):</td>
<td>8 (35%)</td>
<td>18 (85%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Progressive Disease, n (%):</td>
<td>14 (61%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Not Evaluable, n (%):</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Surgical Resection, n (%):</td>
<td>0</td>
<td>1 (5%) (¥)</td>
<td></td>
</tr>
</tbody>
</table>

*¥ One patient in Arm B was sufficiently down-sized to enable an R0 resection to be performed successfully.

# SIR-Spheres microspheres + 5FU in mCRC Salvage Therapy: Toxicity Assessments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5FU alone n = 23</th>
<th>5FU + SIR-Spheres n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Grades 1–2</td>
<td>Grades 3–4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Constipation</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Gastrointestinal</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Pain</strong></td>
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<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>-</td>
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<tr>
<td>Myalgia</td>
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<td>-</td>
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<tr>
<td>Pain other</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

**SIR-Spheres microspheres + 5FU in mCRC Salvage Therapy: Toxicity Assessments**

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<tr>
<td></td>
<td>Grades 1–2</td>
<td>Grade 3–4</td>
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<tr>
<td><strong>Constitutional</strong></td>
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<tr>
<td>Fatigue</td>
<td>6</td>
<td>5</td>
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<tr>
<td>Fever</td>
<td>3</td>
<td>-</td>
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<tr>
<td>Dermatological/Skin</td>
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<tr>
<td>Skin2</td>
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<td>-</td>
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<tr>
<td>Hand-foot syndrome</td>
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<td>-</td>
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<tr>
<td><strong>Pulmonary</strong></td>
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<td></td>
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<tr>
<td>Dyspnea</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Pulmonary</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td>Neurosensorial</td>
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<tr>
<td>Cognitive disturbance</td>
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<tr>
<td>Cardiac arrhythmia</td>
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<td>-</td>
</tr>
<tr>
<td>Allergy</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Other Toxicity</td>
<td>1†</td>
<td>-</td>
</tr>
</tbody>
</table>

† ascites; ‡ 1 with thrombocytopenia, 1 with stomach ulcer, ascites

Radiofrequency Thermal Ablation (RFA)

HIGH FREQUENCY ALTERNATING CURRENT DELIVERED TO TUMOR VIA AN ELECTRODE. THE CURRENT AGITATES THE TISSUE AROUND THE TIP, CAUSING CHARGED MOLECULES, MAINLY H2O TO RAPIDLY OSCILLATE ALONG A 180º AXIS
Radiofrequency Ablation

- Approach: Open, laparoscopic, percutaneous
- Success depends on tumor size, location, physician experience
- Retrospective series suggest that local recurrence rates are lower in tumors < 3 cm.

- Complications (uncommon): hemorrhage, hepatic abscess, infarction, pleural effusion, bronchobiliary fistula, bowel perforation, thrombosis, skin burn.
- RFA is inferior to resection (higher local recurrence rates)
- No prospective studies comparing RFA vs. other liver directed therapies
RFA in combination with systemic chemotherapy

- EORTC 40004: RFA + systemic therapy vs. systemic therapy alone in pts with non-resectable colorectal liver metastases

Systemic therapy*: 59 pts
Systemic therapy* + RFA: 60 pts
PFS rate at 3 years: 27.6% vs. 10.6%
Median PFS: 16.8 (11.7-22.1) vs. 9.9 mos
*oxaliplatin based

Role of RFA in the management of unresectable CRC liver metastases

- No prospective data to demonstrate better OS over chemotherapy alone.
- Potential option in patients with potentially resectable isolated liver metastases who are not surgical candidates
  - Best results with RFA in patients with ≤ 3 lesions, ≤ 3.5 cm in diameter that are not located near major vascular structures.
- It is sometimes used intraoperatively following incomplete resection in patients with isolated liver metastases
Irreversible Electroporation (IRE)

- A focal “non thermal” ablation therapy that uses high voltage low energy DC electrical pulses to permanently open pores in the cell membranes causing cells to die.
IRREVERSIBLE ELECTROPORATION

DSync device (e.g. AccuSync 72) senses the rising slope of the R-wave, and sends a signal to the NanoKnife. The NanoKnife waits 50 milliseconds (.05 sec) and delivers 1 energy pulse. The energy pulse is delivered during (or just before) the ventricular refractory period. Delivering an IRE Pulse during the vulnerable period could induce an arrhythmia.
IRE: Potential Advantages

3.5 cm hypodense lesion immediately adjacent to IVC, with mass effect on the adjacent hepatic veins.

• Short ablation time (usually under 5 minutes)
• Preservation of vital structures (vessels, bile ducts) within IRE ablated zone
• IRE induces cell death by apoptosis, without significant inflammatory reaction (and scarring), compared to other ablative techniques.
• Avoids heat/cold sink effect (which may cause incomplete ablation in perivascular tumor cells)
• IRE induces complete ablation with well demarcated margin

This is a relatively new technique, used in liver and extrahepatic (i.e. pancreas) tumors
Early experience indicates that procedure is well tolerated, and postprocedure pain is not different compared to RFA*

Conclusions

- An increasing number of local/regional treatment options exist for patients with unresectable colorectal liver metastases.
- Decisions on indication, strategies, and timing requires multidisciplinary evaluation (medical oncologist, surgeon, radiation therapist, interventional radiologist).
- There is increasing prospective clinical trial data on the safe and effective use of radioembolization and TACE with irinotecan drug eluting beads.
- The role of local ablative techniques (RFA, IRE) is evolving.
  - They should not replace resection as the standard in the appropriate settings.
  - IRE may play a role in lesions not amenable by RFA.
OBRIGADO!

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