Selective Internal Radiation Therapy (SIRT) & Metastatic Liver Disease

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Objectives

- Provide brief overview of current treatment options available for metastatic liver disease
- Discuss SIRT (Selective Internal Radiation Therapy)
  - Y-90 isotope
  - Mode of action
- Review clinical data supporting use of SIRT
- Identify patients eligible for SIRT
- Review contraindications to treatment

Facts About Metastatic Disease

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Main Sites of Metastasis</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>Bone, Brain, Liver</td>
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<tr>
<td>Breast</td>
<td>Bone, Brain, Liver</td>
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<tr>
<td>Pancreas</td>
<td>Liver, Lung, Peritoneum</td>
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<tr>
<td>Colorectal</td>
<td>Liver, Lung, Peritoneum</td>
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<tr>
<td>Ovary</td>
<td>Liver, Lung, Peritoneum</td>
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<tr>
<td>Prostate</td>
<td>Adrenals, Bone, Liver</td>
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<tr>
<td>Stomach</td>
<td>Liver, Lung, Peritoneum</td>
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<tr>
<td>Thyroid</td>
<td>Bone, Liver</td>
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<tr>
<td>Uterus</td>
<td>Bone, Liver</td>
</tr>
<tr>
<td>Bladder</td>
<td>Bone, Liver</td>
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</table>

After the lymph nodes, the liver is the most common site of metastatic disease. Most liver metastases originate from the colon, rectum, pancreas, stomach, esophagus, breast, lung, melanoma and some less common sites.

www.cancer.gov/about-cancer/what-is-cancer/metastatic-fact-sheet
Colorectal Cancer & Metastatic Liver Disease…

Liver metastases from colorectal cancers (mCRC) is very common & associated with a poor prognosis

- Colorectal cancer (CRC) is the 2nd leading cause of cancer-related deaths in the U.S.\(^3\)
- American Cancer Society estimates CRC will be the cause of 49,190 deaths in 2016\(^3\)
- Data suggests 50% of patients with CRC will develop liver metastases; <20% of patients are candidates for surgical resection initially\(^4,5\)
- Up to 90% of mCRC patients die of liver failure due to the local effects of tumors\(^4,12\)

Treatment Options for Metastatic Liver Disease

- Surgical Resection
  - Gold Standard of Treatment
- Portal Vein Embolization
- Systemic Chemotherapy
- Biologic Therapies
  - Nexavar
  - Sutent
- Hepatic arterial infusion therapy (HAC)
- Ablation
  - Microwave
  - Radiofrequency
- Chemoembolization (TACE)
- Selective Internal Radiation Therapy (SIRT)

Selective Internal Radiation Therapy… Y90

Method of delivering radiation to liver tumors while preventing radiation exposure to the normal liver parenchyma

- Not an entirely new technology -- studies date back to the 1960s
- Study by Ariel & Pack in 1967 – standard chemotherapy vs. treatment with Y90 spheres vs. combination therapy\(^6\)
  - Concluded that addition of Y90 extended the average duration of life
    - Chemo alone 3.9 months
    - Y90 alone 4.6 months
    - Combination therapy 5.6 months
- Research continued ... advances in microsphere technology, standardization of Y90 dose, etc
- Collective data from multiple studies supports the use of Y90 for hepatic malignancies
- FDA approved use of Y-90 microspheres in 2002 as a brachytherapy device \(^7\)

SIRT Treatment Goals

I. Decrease tumor burden in the liver\(^8\)
II. Increase the time to progression\(^8\)
III. Potential downsizing to liver resection or ablation\(^8\)
IV. Provide palliation of symptoms\(^8\)
Y-90 Isotope

- Y-90 (yttrium) is a high energy, beta-emitting isotope. This form of ionizing radiation allows for very localized delivery of high-dose radiation.
- Limited tissue penetration - 2.5mm average and 11mm max.
- Yttrium half-life 64 hrs or approx 2.7 days.
- SIR-Spheres Microspheres: Biocompatible polymer microspheres, average diameter 32 microns.

Y-90 ... Mode of Action

Delivery system capitalizes on the anatomic differences in liver perfusion.

Portal Vein & Hepatic Artery:
- 75% of total liver blood flows through the portal vein.
- Hepatic artery supplies the remaining 25%.

Hepatic tumors obtain 90% of their blood supply from the hepatic artery.

Y-90 ... Mode of Action

Microcatheter advanced via femoral artery to right or left hepatic artery.

Y-90 microspheres administered, travel to the tumor and lodge in the arterioles.
- Liver tumor vessel diameter 25-75 µm.
- End arteriole diameter 8 µm.
- Average diameter of microsphere 32 µm.

Beta radiation is released killing tumor cells.

Spheres are too large to pass through capillaries and into the venous system:
- No systemic exposure.
- Permanently implant in the tumor bed > embolic effect (cell death).

Tumor death results from:
1) Release of internal beta radiation
2) Embolic effect of microspheres.
Clinical Studies of SIR-Spheres

- Gray & van Hazel both conducted randomized controlled trials suggesting benefits greater if used earlier & in combination with systemic chemotherapy.
- Gray et al was pivotal study that led to FDA approval of Y90 in U.S.
SIRFLOX Study

The first large phase III randomized, multicenter controlled trial to assess efficacy & safety of adding SIRT to FOLFOX chemotherapy for first-line combination therapy. Preliminary data reveals no statistically significant improvement in overall Progression-Free Survival. Does show a statistically significant improvement in Progression-Free Survival in the liver by 7.9 months (31% risk reduction).

Safety Profile

In comparison to other treatment options (i.e. HAC, TACE, RFA), Y-90 is associated with less adverse effects.

- **Most Common Reported Adverse Effects:**
  - Fatigue (grade 1-2)
  - Fever
  - Abdominal pain
  - Nausea
  - Elevated LFTs
  - Mild gastritis/duodenitis

Radiation-induced hepatic failure

With appropriate patient selection & standardized dosing is <1%.

SIRLFOX Study

The final analysis of the study will be submitted to the American Society of Clinical Oncology (ASCO) Annual Meeting, 29th May – 2nd June 2015 in Chicago, Illinois.

Patient Eligibility

- Stable labs (CBC with differential, BUN, serum creatinine, electrolytes, LFTs, albumin, LDH, PT/PTT).
- Imaging (CT and/or MRI) with assessment of portal vein patency.
- Liver involvement <60%.
- Successful Arterial Mapping - arteriography and macroaggregated albumin (MAA) lung shunting study.
  - Assess anatomy of vessels, patency of portal vein.
  - Assess gastroduodenal flow to identify collateral vessels and avoid infusion of radioactive spheres into areas that can cause toxicity.
  - Assess for lung shunt: Lung tumors can have arteriovenous connections which create shunting from the liver to the lungs.

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**ECOG**

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<th>Characteristics</th>
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<tbody>
<tr>
<td>0</td>
<td>Asymptomatic and fully active</td>
</tr>
<tr>
<td>1</td>
<td>Symptomatic; fully ambulatory; restricted in physical strenuous activity</td>
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<tr>
<td>2</td>
<td>Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed</td>
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<tr>
<td>3</td>
<td>Symptomatic; limited self-care; spends more than 50% of time in bed</td>
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<tr>
<td>4</td>
<td>Completely disabled; no self-care; bedridden</td>
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Eastern Cooperative Oncology Group: Numerical score reflecting functional status. The higher the ECOG score, the more risk for morbidity with treatment. Recommended ECOG score 0-2.

**Contraindications**

- Decompensated liver function
- Elevated bilirubin (>2mg/dl)
- Poor performance status (ECOG>2)
- Greater than 20% lung shunting of the hepatic artery blood flow (determined in pre-procedure mapping)
- Abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel
- Disseminated extra-hepatic malignant disease
- Portal vein thrombosis

**Dollars & Cents**

- Most insurance companies cover the cost of the SIR-Spheres.
- Many private payors also have provided coverage including Aetna, Anthem, Cigna, HealthNet, Humana, and United Healthcare.
- SIRT available at 700 centers worldwide, 300 centers in the United States alone.

[Full text in PDF format](http://www.sirtex.com/media/70435/2016-sirtex-coding-sheet-updated032116-final.pdf)
Questions …

References

2. University of California San Francisco. Liver metastases. Retrieved from http://surgery.ucsf.edu/conditions-procedures/liver-metastases-
detailedguide/colorectal-cancer-key-statistics
4. Fakih M. SIR-Spheres radioembolization in the management of metastatic colorectal cancer: a medical oncology perspective. Colorectal
Cancer, 2014; 3(4):331-343
5. Lewandowski R, Salem, R. Yttrium-90 radioembolization of hepatocellular carcinoma and metastatic disease to the liver Sem Inter Radiol
2006; 23(1): 64-72.
6. Arel I, Padg G. Treatment of inoperable cancer of the liver by intra-arterial radioactive isotopes and chemotherapy Cancer 1967;
10. Van Hazel, G, Heinemann, V, Sharma, N, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (plus or minus
bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic
from colorectal cancer (J Vasc Interv Radiol. 2011; 22(S):780-786.
with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy (J Clin Oncol. 2007;25(9):1099-1106