Radioembolization of the Liver

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Brachytherapy Principle

- Radiation is accepted as a standard treatment option for liver cancer
  - Radiation will break nucleic strands and cause cellular death
  - Delivered in high concentrations to tumor with few complications

- External beam radiation (conventional or intensity modulated)
  - Must be fractionated over multiple sessions
  - Nontarget radiation to skin lung and bowel a potential concern
  - Limited to small area of liver to prevent liver injury

- With the advent of radioembolization using Yttrium-90 microspheres (Y90) radiation is delivered into the hepatic arteries providing the tumor.
  - Capitalizes on the tumor hypervascularity
  - Concentrates radiation within that tumor rather than liver
  - Minimal risk of bowel radiation with careful planning
Yttrium

- Yttrium is a rare earth metal with AW 89
- Discovered in 18\textsuperscript{th} century Switzerland
- Yttrium has the highest thermo-dynamic affinity for oxygen
  - used in ceramics for crucibles for molten reactive metals, in florescent screen phosphors, LCD computer displays and automotive fuel sensors.
- It is alpha irradiated to make it radioactive
  - Yttrium 90 decays to stable zirconium 90
Y-90

• Y-90 is a pure β emitter
  – Emits β rays with an average energy of 935 keV
  – Half-life of 64.2 hours (2.67 days)
  – Mean penetration 2.5 mm (Maximum penetration 11 mm)
  – Y-90 does not emit γ rays which is not optimal for imaging purposes

• Y-90 can be embedded in glass or insoluble resin microspheres (mean diameters of 25 µm to 35 µm)

• Administration of the Y-90 microspheres via the hepatic artery results in the deposition of the glass or resin microspheres in the tumor vessels.

Yttrium 90 Delivery

• One gigabecquerel (one billion nuclear decays per second) (27 mCi) delivers a total absorbed radiation dose of 50 Gy/kg (absorbed dose)
• 94% of the radiation is delivered in 11 days.
• Two Y90 microsphere products are commercially available
  – TheraSpheres® (MDS Nordion, Ottawa, Canada)
  – SIR-Spheres® (SIRTTEX Medical, Sydney, Australia)

$1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq}$
Yttrium 90 Agents

Sir Sphere resin bead

Therasphere glass bead
Hepatocellular Carcinoma

• Incidence 2.99 per 100,000 (~10,000 cases per year)
• Most cases associated with cirrhosis
• Accounts for 65% of liver cancer in the U.S
• Between 1976 and 2000, incidence increased by >90%
  – Young white men had an increase of 432%

Therapy Options

• Surgery
  – Resection
  – Transplantation
  – Best therapy but < 30 % are candidates
• Systemic chemotherapy
  – Sorafenib (oral multikinase inhibitor)
• External Beam Radiation
• Regional therapy
  – Percutaneous tumor ablation
  – Trans-arterial chemoembolization (TACE)
  – Trans-arterial radioembolization
HCC Tumor Physiology

• Dual blood supply
  – Normal liver
    • 75% portal vein
    • 25% hepatic artery
  – HCC
    • > 95% hepatic artery
    • Hypervascular

• Y-90
  – Local concentrations of radiation
  – Little liver parenchyma injury
  – No extra-hepatic injury
Hepatocellular Carcinoma
Pre-treatment CT

Typical findings of hepatocellular carcinoma (HCC)

Non-contrast CT

Contrast-enhanced CT
Celiac Arteriogram In 55 y/o Male With Cirrhosis
Selective Injection

Super-selective Injection
Y90 for HCC

- HCCs have a greater arteriolar density than normal liver
- HCCs are predominantly supplied by the hepatic artery rather than the portal venous system
- Three-fold or greater radiation dose in the tumor relative to the normal liver
- Y-90 microspheres can be safely administered via intra-arterial injection to patients with underlying cirrhosis at a dose of 100 Gy to the liver
Workup Prior to Y90

- ECOG Performance Status score of less than or equal to 2
- Bone marrow reserve (granulocytes >1500/µl, platelets >60,000/µl)
- Hepatic function (total bilirubin <2.0 mg/dl, ALT/AST, or Alkaline Phostphatase less than 5 times the upper limit of normal)
- Three-phase liver CT (non-contrast, arterial, portal) or MRI with gadolinium for the assessment of liver disease and the evaluation of extrahepatic metastatic disease.
- Disease-specific tumor markers (CEA for CRC patients, AFP for HCC patients, Serotonin, chromogranin-A, 5HIAA levels for Carcinoid patients)
- FDG-PET imaging performed as clinically indicated (consider CT chest and bone scan)
Technique

• Conventional Angiography
  – Confirms diagnosis (if no biopsy performed or biopsy non-diagnostic)
  – Map arteries for embolization

• After initial angiography a shunt test with Tc-99m macroaggregated albumin is required to test for the presence of significant porto-systemic shunting
  – Y-90 microspheres are generally not given when the lung uptake is >15%
  – Extrahepatic shunting is the main limitation to this therapy
Lung and Bowel Shunt of MAA

No shunt                   Lung shunt               GI and lung shunt

\[ \text{LSF} = \frac{\text{Lung counts}}{\text{Lung counts} + \text{liver counts}} \]
Segment V-VIII HCC on MRI

56 y/o with Hepatitis C, cirrhosis and new hypervascular mass
Replaced Right Hepatic Angiogram Demonstrates Tumor Blush
Dyna CT

- Cone beam CT (CBCT) (Dyna CT, Siemens Medical Solutions) improves tumor visualization during diagnostic phase of study.
- CBCT helps the operator identify which vessels are supplying a tumor.
- CBCT improves liver volume calculations in variant anatomy.
Segment V Artery Dyna CT
Segment VI Artery Dyna CT
50 y/o with HCC in Segment IV

Gadolinium enhanced T1W axial image
Pre-radioembolization Angiography

- Celiac arteriogram
- Common hepatic angiogram in three views
- Selective right and left hepatic angiography (3 views or Dyna Vision)
- DynaCT of right or left hepatic artery
- Super-selective angiography
- Repeat Dyna CT of segmental arteries as needed
Selective Angiography

Left gastric angiogram demonstrates lesion
Lesion identified on LV Dyna-CT

LV Dyna-CT confirms entire lesion fed by replaced hepatic artery arising from the left gastric artery
Intra-Arterial Brachytherapy Planning

- Confirm no blush in gallbladder and potential mis-embolizations to mesenteric arteries
- Embolize bowel arteries at time of initial angiogram
  - Right gastric
  - Accessory left gastric from left hepatic
  - Create a bare hepatic artery tree
Comparison Of Standard Intra-Procedural Dyna-CT With Large Volume Dyna-CT

Standard Dyna-CT

Large Volume Dyna-CT
Hepatic Arteriogram with LV Dyna-CT

- Duodenum
- Gallbladder wall
Right Gastric Filling

Angiogram and planar MAA scan showing right gastric

SPECT showing left lobe and stomach
Safety

• Dose escalation studies using intra-arterial Y-90 microspheres with estimated whole liver absorbed doses ranging from 50 Gy to 150 Gy
  – No haematologic, hepatic, or pulmonary toxicity during a mean follow-up period of up to 53 months.
  – Reversible gastritis and duodenitis were encountered in four patients.
  – Reported side effects associated with this form of treatment included fever, elevation of liver enzymes and bilirubin,
  – There was one reported case of death resulting from radiation pneumonitis. This patient, however, had 39% pulmonary shunting, and it is questionable whether the patient should have been eligible for treatment

Therasphere Calculation

- In this equation:
  - $A$ is the activity required at time of deliver,
  - $D$ is the target dose (usu 100 Gy)
  - $M$ is the mass of the treated liver tissue (1cc liver=1.03 gm)

- Correct for shunt fraction using $1/((1-LSF)(1-\text{Residual}))$

- Lung dose (Gy) = $50*A*LSF*(1-R)$
Outcomes for HCC

• Reduction of serum α-fetoprotein levels in 80%
• Other authors have reported an objective response rate of 20% in terms of radiological regression of tumor
• Median survival of 9.4 months to 54 weeks has been achieved with the use of Y-90 microspheres

Colorectal Metastasis

- 437,000 annual worldwide deaths from colorectal cancer
  - Third most important cause of cancer mortality
  - Hepatocellular cancer is the fourth most common cause of death from cancer and rapidly increasing in incidence in the United States
- Surgical resection for colorectal cancer offers survival rates of 30-58% at five years
  - Recurrent, most often unresectable disease in the hepatic remnant contributes significantly to our inability to achieve long term cure rates for colorectal cancer patients
  - Over 50% of colorectal patients will develop liver metastasis

Sir Sphere Calculations

- **Body Surface Area Method**
  \[ \text{Activity (GBq)} = (\text{BSA} - 0.2) + \frac{\text{Volume of Tumour} \times 100}{\text{Liver Volume}} \]

- **Empiric Method**
  - Activity calculated for whole liver delivery based on tumor replacement seen on CT
  \[ \text{Tumour Volume} \leq 25\% = 2\text{GBq} \]
  \[ > 25\% \& \leq 50\% = 2.5\text{GBq} \]
  \[ > 50\% = 3\text{GBq} \]
Sir Sphere Calculation

- Resin microspheres are received in a vial as a 3 GBq dose, and the labs draw up the prescribed activity.
  - This process differs from that for glass microspheres where a predetermined dose is delivered to the facility.
- Due to the higher specific activity with glass microspheres and therefore the relative low volume of the spheres per dose, embolic occlusion of the parent artery has not been observed arteriographically.
  - The prescribed activity of resin spheres cannot always be delivered completely [15] due to embolic arterial occlusion.
  - The residual activity in the delivery vial is measured and the delivered dose is the difference between the prescribed and the residual dose
- The manufacturer recommends one of the two methods for activity determination for the resin microsphere; the Body Surface Area method (BSA) and the Empiric Method (EM). However, most experienced practicing physicians recommend the use of the BSA for resin microsphere dose calculation since the delivered dose more closely resembles the activity calculated by the BSA methodology.
Colorectal Results

- Phase II randomized trial and two phase I trials that combined systemic 5 FU/LV and the 5 FU based regimens of oxaliplatin and irinotecan respectively, were performed in Australia and Europe.
- In the randomized phase II trial, responses were significantly augmented with the addition of the Y90 microspheres (8 PR versus 0 PR).
Follow-up Using PET

- 19 patients with metastatic disease to liver
- Significant decrease in total liver SUV after treatment
  - Baseline, $71,134 \pm 38,055$;
  - SIR-Sphere treatment, $59,941 \pm 26,509; P = .028$)
  - Visual estimates placed 15 patients (79%) in response categories and four patients (21%) in nonresponse categories
- Three patients had major complications related to hyperbilirubinemia (transient, $n = 1$; permanent, $n = 2$).

Bremsstrahlung

• Secondary gamma emission: Bremsstrahlung scans
  – due to the interaction of the high energy Beta emission interacting with matter
  – Bremsstrahlung emissions represent a broad spectrum of energy emissions rendering relatively poor point to point discrimination

• Currently the planar and/or SPECT images are qualitative
  – Extrahepatic activity may warn clinicians of impending gastrointestinal complications and serve as a quality assurance tool
Bremsstrahlung Radiation Image
Post Y-90 treatment
Disadvantages of Y90

- Patients with poor hepatic reserve, advanced tumor stage, portal vein thrombosis, or biliary dilation are high risk for complications after Y90 (like TACE)
- High cost
- Need two-three hepatic angiograms
Contraindications

- >20% hepatopulmonary can lead to fatal radiation pneumonitis when over 30 Gy
- Demonstrable gastrointestinal shunting causes gastric ulceration
- These complications can be predicted by 5 mCi of Tc99m MAA that mimics the distribution of the Y90 microspheres
Post-Treatment

- Most common side effect is mild to moderate fatigue and abdominal pain lasting less than 2 weeks
- Nausea and vomiting are less common
  - if severe may be a harbinger for a more gastrointestinal deposition
- Patients are usually seen in clinic at 2-4 weeks
- At the time of clinic visits complete blood count, serum tumor markers and liver function tests are assayed.
- Cross sectional imaging with CT/MRI is performed between 60-90 days following treatment to avoid radiation therapy tumor edema as erroneously being interpreted as progression.
  - These decrease attenuation changes in the hepatic parenchyma may be noted on CT and are largely reversible
  - 18F-fluorodeoxyglucose Positron Emission Tomography (PET) scans may be of use in cases of discordance where tumor markers are not elevated but CT scans suggest progression or to distinguish the site of progression in the presence of extra-hepatic disease
Conclusions

• Yttrium therapy is a promising tool
• Role still unclear
  – Early or late
  – Alone or adjunct
  – Optimal dose