Current Trends in Yttrium-90 Microsphere Therapy Planning and Dosimetry

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Educational Objectives

▪ To become familiar with the clinical indications and devices for $^{90}$Y-microsphere therapy
▪ To become familiar with the clinical imaging sequence for $^{90}$Y-microsphere therapy
▪ To become familiar with some recent advances
  – $^{90}$Y SPECT/CT and $^{90}$Y PET/CT imaging
  – Voxel-based dosimetry and radiobiological modeling
  – Tumor dose response studies

TRANS-ARTERIAL LIVER-DIRECTED THERAPIES
Rational of Liver Directed Therapy

- Primary site of disease in hepatocellular carcinoma (HCC) and cholangiocarcinoma
- Dominant organ of metastases in colorectal and neuroendocrine tumors
- Resection improves survival in HCC, colorectal and neuroendocrine tumors
- Colorectal cancer - 50% with liver metastases, dominant cause of death
- Control of liver disease should increase survival

Liver Directed Therapies

- Ablation
  - Radiofrequency Ablation (RFA)
  - Microwave Ablation
  - Irreversible Electroporation (IRE)
- Chemoinfusion
  - Ports
  - HAI
- Transarterial Therapies
  - TAE / Bland Embolization
  - TACE
    - Conventional
    - Drug Eluting Bead
  - Radioembolization/SIRT
  - Percutaneous Hepatic Perfusion

Rational For Trans-Arterial Therapy

- Normal liver blood flow
  - 75% portal vein
  - 25% hepatic artery
- Hepatic neoplasm, >3mm metastases
  - 80-100% supply from hepatic artery
- Greater vascular density in neoplasm

Indications

- Non surgical candidate
- Not amenable to ablative therapy
- Bridge to transplant or operative resection
- Palliative for liver only or liver dominant disease
Trans-Arterial Therapy Options

<table>
<thead>
<tr>
<th>TAE</th>
<th>TACE</th>
<th>TACE</th>
<th>SIRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bland Embolization</td>
<td>Conventional</td>
<td>Drug-Eluding Beads</td>
<td>Radioactive Microspheres</td>
</tr>
<tr>
<td>Embolization of arterial vessels feeding tumors</td>
<td>Embolization of art. vessels + Chemotherapy</td>
<td>Embolization of art. vessels + Chemotherapy</td>
<td>Non-embolic Brachytherapy</td>
</tr>
</tbody>
</table>

Transarterial (Bland) Embolization – TAE

- Treatment of tumor with permanent or temporary occlusion of the feeding vessels (arteries)
  - Coil
  - Particles
  - Glue
  - Gelfoam
- Embolization as distal as possible to avoid collateral formation
  - Particle sizes 40 – 900 micron

Transarterial Therapy - TACE

- TACE – Conventional/Oily 1980s
- A combination of a chemotherapeutic agent with an embolic agent to slow arterial blood flow and increase chemotherapy concentration in the liver
- Combination of ischemia and chemotherapy effect
- Chemotherapy regimens are not standardized
- No standard protocol has been adopted
- 2 Randomized Phase III trials for HCC published in 2002
  - TACE vs Supportive Care – Survival benefit
  - TACE is SOC for non operative HCC
Transarterial Therapy – DEB TACE
- Drug Eluting Bead TACE – 2005
- LC (US) / DC (non US) Beads
- Quadrasphere (US) / Hepasphere (non US)
- Oncozene (US) / Tandem (non US)
- US approval for embolization of hypervascular tumors or AVMs
- Not approved for drug elution (off label use)
- IDE for prospective clinical trials
- DEBDOX (doxorubicin)
- DEBIRI (irinotecan)

90Y MICROSPHERE DEVICES

90Y-microsphere Therapy
- Trans-arterial delivery of radioactive 90Y-labeled microspheres via a catheter directly at disease sites (targeted infusion)
- Microspheres (20-30 μm) trapped in tumor capillary vessels due to their embolic size and targeted delivery
- β emissions from trapped 90Y-microspheres are capable of delivering lethal radiation doses to (proximal) neoplastic tissue while sparing (more distal) surrounding normal tissue
Properties of Yttrium-90

- Decay scheme: Y-90 (β–, 64.1 hr) Zr-90 with βMax of 2.28 MeV
- Y-90 also emits β+ at low yields (~32 ppm) via internal pair production
- β energy: 0.937 MeV (mean) and 2.28 MeV (max)
- Tissue penetration depth: 2-4 mm (mean) and 11 mm (max)
- 90Y deposits >90% of its energy <5 mm of tissue and <11 days
- Uniformly implanted 1 GBq 90Y in 1 kg of tissue can deliver radiation absorbed doses of ~50 Gy

![Graphs showing Y-90 decay scheme and tissue penetration depth]

Commercial 90Y-microsphere Products

SIR-Spheres®
- Sirtex Medical Pvt Ltd, Australia
- Insoluble, biocompatible resin matrix
- 30–35 μm glass spheres
- 3 GBq (81 mCi) activity = 30–60 x 10^6 spheres
- Maximum activity available: 3 GBq (81 mCi)

TheraSphere®
- BTG, UK
- Insoluble, biocompatible glass matrix
- 20–30 μm glass spheres
- 3 GBq (81 mCi) activity = ~1.2 x 10^6 spheres
- Maximum activity available: 20 GBq (540 mCi)

90Y-microsphere Therapy Preparation
CLINICAL INDICATIONS FOR 90Y THERAPY

Indications

**SIR-Spheres®**
- Indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant chemotherapy (FUDR)
- Guidelines for use established
- Off-label use allowed for patient care under AU
- Liver is common site of metastases from a variety of neoplasms: mCRC, mNET, mBC

**TheraSphere®**
- Indicated for radiation treatment or as a neoadjuvant for surgery or transplantation in patients with unresectable HCC or in patients with partial or branch portal vein thrombosis
- Use under HDE meaning under a specific protocol and requires IRB oversight
- No deviation from protocol allowed

Patient Selection

- ECOG ≤ 2
- Life expectancy > 3 months
- Total bilirubin <2.0 mg/dl
- AST and ALT <5 x ULN
- Less than 70% tumor volume
- Adequate liver function (Child-Pugh ≤ B7)
- Adequate renal function (GFR>30)
Contraindications

- **Absolute**
  - Deposition of MAA into gastrointestinal tract
  - Elevated shunting with lung dose > 30Gy

- **Relative**
  - Complete occlusion of the main portal vein
  - Compromise of the Ampulla of Vater (contamination of biliary ducts) due to prior surgery or biliary stent

SIRFLOX – Phase III RCT in CRC

**Progression-Free Survival in the Liver**

- Median PFS 12.6 months
- HR: 0.69 (95% CI: 0.55-0.83), p<0.002
- 7.9 month improvement in median PFS in the liver
- 31% reduction in risk of disease progression in the liver

ROLE OF CLINICAL IMAGING
Pre-Procedural Imaging

- Cross sectional imaging
  - Contrast enhanced CT or MRI
    - Evaluation of arterial anatomy and variants
    - Evaluation for extrahepatic arterial supply

- Functional Imaging
  - F18 FDG PET

Review of PreProcedure CT to Evaluate Tumor Burden and Vascular Anatomy and Variants
Selective Angiography of Right Phrenic Artery

Day of Procedure - Outpatient
- Catheter angiography
  - Mapping of hepatic and extrahepatic vessels
- Embolization of hepatopancreatic collaterals to ensure safe delivery
- Embolization of extrahepatic arterial supply
- 99mTc-MAA administration at location of planned delivery of 90Y-microspheres
- Nuclear Medicine imaging
  - Lung Shunt evaluation
  - Assess perfusion of tumors
  - Assess extra-hepatic deposition of MAA/90Y
  - Dosimetry

Catheter Angiography
- Avoidance of complications
  - Misadministration of microspheres that lead to gastrointestinal ulceration
  - Review of Literature, 26 studies
  - 1765 patients
  - Ulcer Rate: 0.7 to 28.6%, mean 4.8%
  - 2.6% of 270 patients at reporting institution
  - Determination of lung shunt
- DSA Imaging
- Cone Beam CT
DSA and Cone Beam Imaging

- Non-selective angiography or superior mesenteric and celiac arteries
- Selective angiography of lobar and segmental arteries
- Determination of extrahepatic tumor supply
- Consider embolization of hepatointeretic collaterals
- Incorporating Cone-beam CT into the Treatment Planning for Yttrium-90 Radioembolization, Louie, JVIR, 2009

  - CBCT affected 52% of cases demonstrating extrahepatic enhancement, incomplete liver perfusion or both
  - Change of treatment in 33%
  - One gastrointestinal ulcer due to CBCT finding missed by operator

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Cone Beam CT to Delineate Tumor Supply

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CLINICAL DOSIMETRY
Dosimetry: Standard Model

- **Dose**_{tissue} [Gy] = \( A_{tissue} \text{[GBq]} \times 49.7 \text{[Gy-kg/GBq]} \div M_{tissue} \text{[kg]} \)
  - Self dose from \( \beta \) emission: >90% energy deposit in <5mm
  - 49.7 [Gy-kg/GBq] = equilibrium accumulated dose constant
  - Bremsstrahlung dose \(< \beta \) dose

Liver Activity

\[ \text{Liver Dose [Gy]} = A \times (1 - \text{LS}) \times 49.7 \text{[Gy-kg/GBq]} \div M_{liver} \text{[kg]} \]

Lung Activity

\[ \text{Lung Dose [Gy]} = A \times \text{LS} \times 49.7 \text{[Gy-kg/GBq]} \div M_{lung} \text{[kg]} \]

- Error in mass propagates into dose calculation
- Model estimates average dose to target volume assuming uniform microsphere uptake within volume

Scope of Dosimetry is Radiation Safety

- **Lung Doses:**
  - Arterio-venous shunting in neoplastic vasculature
  - Prevention of radiation pneumonitis
  - Mean lung dose < 25-30 Gy per treatment

- **Liver Doses:**
  - Maintain upper limit to mean to dose total liver
  - SirSpheres < 80 Gy & TheraSphere < 120-150 Gy
  - Assume uniform uptake in tumor and normal liver

- Major Challenge: Accurate dosimetry model or tumor dose-response curves not well developed

90Y-Therapy Planning: SIR-Spheres

- Sir-Spheres therapy doses are based on activity (not target radiation dose) – maximum activity of 81 mCi
- Average liver dose < 80 Gy and lung dose < 25 Gy
- Dosimetry Models: Empirical or BSA
  - Lung Shunt modification: No treatment for LS > 20%

<table>
<thead>
<tr>
<th>BSA Model:</th>
<th>Activity Required [GBq] = (BSA-0.2) x (Tumor_volume/Liver_volume)</th>
</tr>
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<tbody>
<tr>
<td><strong>Empirical Dosimetry Model</strong></td>
<td><strong>Lung-Shunt Fraction Modification</strong></td>
</tr>
<tr>
<td>Tumor fraction in liver</td>
<td>Recommended 90Y-activity</td>
</tr>
<tr>
<td>&gt; 50 %</td>
<td>3.0 GBq (81 mCi)</td>
</tr>
<tr>
<td>25 - 50 %</td>
<td>2.5 GBq (67.5 mCi)</td>
</tr>
<tr>
<td>&lt; 25 %</td>
<td>2.0 GBq (54 mCi)</td>
</tr>
</tbody>
</table>

Lung dose per treatment < 25 Gy
**90Y-Therapy Planning: TheraSphere**

- TheraSphere therapy doses are based on desired radiation dose to target mass; typically 120 to 150 Gy

\[
\text{Activity Required (GBq)} = \frac{\text{Desired Dose [Gy] \times Target Mass [kg]}}{50 \text{ [Gy/kg GBq]}}
\]

- Target mass = whole liver or liver lobe or liver segment
  - Patient-specific vasculature and catheter approach (common or left or right hepatic artery) to target mass defines target mass
- Therapy must maintain lung dose lower than 30 Gy
  - Maximum activity depends on the Lung Shunt fraction

<table>
<thead>
<tr>
<th>TheraSphere</th>
<th>Lung Dose Limit [Gy]</th>
</tr>
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<tbody>
<tr>
<td>Per Treatment</td>
<td>30</td>
</tr>
<tr>
<td>Cumulative</td>
<td>50</td>
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</table>

**NUCLEAR MEDICINE IMAGING**

**Lung Shunt Fraction (~15 min)**

- 2-4 mCi of \(^{99m}\text{Tc}\) MAA delivered trans-arterially in IR suite
- Planar scintigraphy of Thorax and Abdomen
- AP and PA images with LEHR @ 7 min/view

\[
\text{LungShunt(%) = } \frac{\text{LungCounts}}{\text{LungCounts + Liver Counts}} \times 100
\]

\[
\text{GM counts} = \sqrt{\text{ANTcounts} \times \text{POSTcounts}}
\]

- SIR-Spheres: geometric-mean images
- TheraSphere: not specified
99mTc-MAA SPECT/CT (~20 min)

- **SPECT**: Photopeak 140/15% keV, LE scatter window 15%, LEHR, 360 deg, 128 views, 16 s/view, SSM, non-circular orbit
- **CT**: 130 kVp, CareDose4D (90 mAs), 0.6 s, pitch 1.2, B31s, 2.5 mm images, 2 mm step
- **Recon**: CT-AC, DEW-SC, 2D OS-EM, 16 subset, 8 iterations, 5 mm Gaussian filter, re-sample SPECT to CT

Detection of Extra-Hepatic MAA Shunting

<table>
<thead>
<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Planar</td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td>SPECT</td>
<td>41</td>
<td>98</td>
</tr>
<tr>
<td>SPECT/CT</td>
<td>100</td>
<td>93</td>
</tr>
</tbody>
</table>

(Ahmadzadehfar et al, JNM, 2010)

MAA SPECT Optimization Study

- Original 34 s/view List-mode SPECT
- 28 s/view
- 24 s/view
- 20 s/view
- 16 s/view

(Gonzalez et al, JNM 53, 2012)

MAA SPECT: Pixel Overflow Artifact

- 34 s/view
- 16 s/view

(Gonzalez et al, JNM 53, 2012)
90Y SPECT/CT (~35 min)

- AP and PA images with MELP @ 10 min/view
- SPECT: Photopak 95-125 keV, Scatter window 250-310 keV, MELP, 360 deg, 128 views, 28 s/view, SSM, non-circular orbit
- CT: 130 kVp, CareDose4D (90 mAs), 0.6 s, pitch 1.2, 831s, 2.5 mm images, 2 mm step
- Recon: CT-AC, EW-SC, 3D OS-EM, 16 subset, 8 iterations, 5 mm Gaussian filter, re-sample SPECT to CT
- Quantitative 90Y SPECT/CT: average absolute error < 4%

90Y PET/CT

- 90Y also emits β+ (E_{max} ~ 800 keV) with BR = 32 x 10^{-6}
  - Internal pair-production in the 0^+→0^+ transition of ^{90}Zr from ^{90}Y decay
    (first works circa 1955; Selwyn et al, App Rad Iso 65, 2007)
- First clinical 90Y PET image published in 2009 – 30 min/bed
- PET/CT provides “quantitative 90Y” images with superior spatial resolution
  - Recent papers focus on acquisition parameters and quantitative accuracy

90Y PET/CT – QUEST Study

- Investigate quantitative accuracy of 90Y PET/CT for dosimetry after radioembolization
  - Looked at a large number of PET/CT scanners (N=69)
  - IEC body phantom
- Background activity within 10%
- Hot spheres > 2cm in size underestimated by 20%
- TOF PET superior to non-TOF PET systems
CLINICAL RELEVANCE OF SPECT/CT IMAGING IN PLANNING & DELIVERY

SPECT MAA for Liver Perfusion

Extrahepatic Perfusion – Missed on Planar
Extrahepatic Supply on SPECT MAA

Extrahepatic Supply – CBCT vs SPECT MAA

Tumor Coverage – CBCT, SPECT MAA/Y90
NEW CONCEPTS IN DOSIMETRY AND RESPONSE

Dosimetry: Partition model

(1) Estimation of fractional Tumor Involvement (TI)
   \[ M_{\text{total}} = M_{\text{tumor}} + M_{\text{tumor}} ; M_{\text{tumor}} = TI \times M_{\text{total}} \]
   \[ M_{\text{liver}} = (1 - TI) \times M_{\text{total}} \]

(2) Estimation of Tumor Mean-Uptake Ratio (R)
   \[ A_{\text{liver}} [\text{mCi}] = A [\text{mCi}] \times (1 - LS) \times M_{\text{liver}} / (M_{\text{liver}} + R \times M_{\text{tumor}}) \]
   \[ A_{\text{tumor}} [\text{mCi}] = A [\text{mCi}] \times (1 - LS) \times R \times M_{\text{tumor}} / (M_{\text{liver}} + R \times M_{\text{tumor}}) \]
   \[ \text{Dose}_{\text{organ}} [\text{Gy}] = \text{Activity}_{\text{organ}} [\text{GBq}] \times 49.7 [\text{Gy-kg/GBq}] / M_{\text{organ}} [\text{kg}] \]

(Ho et al., EJNM 23, 947-52, 1996)
90Y-microsphere Dosimetry Models

PM vs. STD

Liver Doses

Tumor Doses

90Y vs. 99mTc-MAA

Liver Doses

Tumor Doses

Response Studies – PM

- Ho et al, EJNM 1997 (SIRspheres for HCC)
  - Partition Model based on MAA uptake
  - Threshold tumor dose > 225 Gy
  - Increase in OS (4.4 months) with >300 Gy
- Garin et al, EJNMMI 2013 (Therasphere for HCC)
  - Partition Model based on MAA uptake
  - Threshold tumor dose > 205 Gy, Sensitivity=100%, Accuracy=90%
  - Increase in TTP (7.7 months) and OS (11.7 months)

Does 99mTc-MAA represent the distribution of 90Y microspheres after therapy?

- MAA uptake shown to predict tumor response and survival in HCC
  (Ho et al., EJNM 23, 1997)
- Δ uptake between 99mTc-MAA & 90Y >20% in 43% (97/225) cases
  (Garin et al., JNM 53, 2012)
- Differences in catheter location, embolic load, flow dynamics, etc.
  contribute to differences in MAA & 90Y

99mTc-MAA 90Y-SIRSpheres 99mTc-MAA 90Y-microsphere
Spatial Representation of Dosimetry Models

**Standard Model**
Uniform uptake in Liver and All Tumors

**Partition Model**
Different uptake of Liver 
and Tumors

**Voxel-dose Model**
Non-uniform uptake in Liver and Heterogeneous Uptake in Tumors

**DVH:** voxel-based 3Ddose

**HCC Tumor Response and ROC Curves**

Knowledge of the tumor response probability will be useful in planning target tumor dose prior to therapy

(Kappadath et al., JNM 56, 2015)

Knowledge of the ROC will be useful in prediction of response status after therapy

(AAPM 2015)
HCC Response Threshold Dose

- Comparison of HCC response based on mRECIST from various groups using voxel dosimetry
  - Good levels of agreement observed!

<table>
<thead>
<tr>
<th>Study</th>
<th>HCC Patients, Tumors</th>
<th>Device</th>
<th>Voxel Dose Image</th>
<th>Thresh. Dose mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strigari 2010</td>
<td>73 Patients, Tumors</td>
<td>SIRSpheres</td>
<td>^90Y SPECT</td>
<td>AD50 &gt;97 Gy</td>
</tr>
<tr>
<td>Kao 2013</td>
<td>6 Patients, 9 Tumors</td>
<td>SIRSpheres</td>
<td>^90Y PET/CT</td>
<td>AD70 &gt;100 Gy</td>
</tr>
<tr>
<td>Kappadath 2015</td>
<td>30 Patients, 35 Tumors</td>
<td>TheraSphere</td>
<td>^90Y SPECT/CT</td>
<td>AD50 &gt;100 Gy</td>
</tr>
</tbody>
</table>

Some Challenges for ^90Y-Therapy

- ROIs on 2D Planar images introduce uncertainties
  - Estimates of lung shunt fraction and lung dose

- MAA is a sub-optimal surrogate for microspheres
  - Frequent differences between ^99mTc-MAA & ^90Y distributions observed
  - Biological degradation in vivo 1–3 hours; non-spherical shape

- Post-therapy assessment of ^90Y distribution is critical
  - Quantitative ^90Y SPECT/CT and ^90Y PET/CT

- Voxel-based doses and radiobiological models (AD and BED)
  are providing new valuable insights
  - Increase confidence in response models
  - Accurate segmentation of tumors and normal liver
  - Disease-specific assessment of response necessary
Summary

- **90Y-microsphere therapy** is a promising and an increasingly popular treatment option for management of patients with metastatic liver disease and unresectable HCC
- Decreased tumor volumes and increased time to tumor progression have been reported
  - Initial assessment of tumor dose-response and toxicities reported
- Advanced imaging modalities play a critical role in management of these patients
  - CT/MR, C-arm CT, 99mTc-MAA SPECT/CT, 90Y-SPECT/CT, PET/CT
- Quantitative post-therapy 90Y SPECT/CT and 90Y PET/CT imaging provides improved tumor and liver dose estimates
  - SIRT transitioning from the palliative to frontline therapy