Image-guided 90Y-radionuclide treatment planning, delivery, and verification for hepatic cancers

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▪ Consultant: BTG International, Terumo Medical Systems, ABK Biomedical

90Y-microsphere Radioembolization, or Selective Internal Radiation Therapy (SIRT)

▪ 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 deliver radiation dose to proximal tissue (tumors) while sparing distal (normal liver) tissue \( \rightarrow \) max range of 10 mm
Rationale for liver-directed 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
- Primary site of disease in HCC and ICC
- Dominant organ of metastases in CRC and NET
- Resection improves survival HCC, CRC, NET
  - Control of liver disease should increase survival

Indications
Non surgical candidate
Not amenable to ablative therapy
Bridge to transplant or resection
Palliative for liver-only or liver-dominant disease

90Y-SIRT Workflow

Pre-Procedural Imaging
CT or MR
Lab work

Imaging for Therapy Planning
Angiography, C-arm CT, 99mTc SPECT/CT

Imaging for Therapy Delivery and Verification
Angiography, 90Y SPECT/CT

Response Evaluation
CT or MR
Lab work

Tumors fed by hepatic artery
SIR-Spheres, Sirtex
TheraSphere, BTG
QuiremSpheres, Terumo*
Eye90, ABK Biomed*
*not FDA-approved

99mTc-MAA
90Y-SIRT Workflow

Pre-Procedural Imaging
CT or MR Lab work

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Response Evaluation
CT or MR Lab work

90Y SPECT/CT

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SIRT is “IGRT” but focused on Safety

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

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

- Major Challenge for SIRT: Current therapy planning not designed to deliver specific dose to target lesions
  - Accurate dosimetry models not routinely used
  - Tumor dose-response and toxicities not well established
**90Y-SIRT should be based on dosimetry**

- Radiation is the actuator of therapeutic effect not embolization
- Intent: Curative vs Palliative \( \rightarrow \) disease stage, prior treatments
- Organs at Risk (OAR) in SIRT: Lung and Normal Liver
- Aim to increase therapeutic ratio \( \rightarrow \) max tumor dose yet acceptable OAR dose

**The SIRT Dosimetry Conundrum**

Efficacy is predicated by good match between planned and actual radiation dose distribution

**PROSPECTIVE**
- PLANNING: MAA is not a consistently reliably predictor of microsphere distribution (dose)
- TARGET: Doses necessary for tumor response not fully established (recent results are promising)

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

Careful consideration of catheter location, embolic load, flow dynamics, vascular spasm, etc.
Spatial Representation of SIRT Dosimetry Models

MIRD and Partition dosimetry models do not provide accurate absorbed dose distributions to tumors and normal liver.

Voxel Dosimetry: Cumulative DVH

D90 = 115 Gy
D10 = 201 Gy

Dmin
Dmax

90Y SPECT
Different Dosimetry Models On the Same Patients With Matched VOIs Result in Large Differences in Absorbed Dose Estimates

- 37 HCC tumors from 20 TheraSphere treatments

**Post-therapy ⁹⁰Y-PET/CT**

- ⁹⁰Y also emits β⁺ (E_max ~ 800 keV) with BR = 32 × 10⁻⁶
  - Internal pair-production in the ⁰⁺⁻⁰⁺ transition of ⁹⁰Zr from ⁹⁰Y decay (first works circa 1955; Selwyn et al, App Rad Isot 65, 2007)
- First clinical ⁹⁰Y PET image published in 2009 (30 min/bed)
- Quantitative accuracy depends on coincidence counts, system hardware, acquisition & reconstruction parameters
  - Background activity errors ~10%
  - Spheres < 2.5 cm underestimated by ~20%

**Post-therapy ⁹⁰Y-SPECT/CT**

- Standardized acquisition & reconstruction yet to be established
  - Monte-Carlo based techniques excellent image quality
  - Practical approaches can also provides clinically meaningful evaluation of in vivo ⁹⁰Y distribution
  - Partial volume errors for tumors < 3-4 cm
- Quantitative ⁹⁰Y SPECT/CT
  - Self-calibration but VOI choice is critical
  - Calibration errors vary 25%-70%, therefore consistent acquisition & reconstruction parameters is paramount
**90Y-SIRT Voxel Dosimetry**

- Start with quantitative 90Y SPECT/CT or 90Y PET/CT
- Voxel dosimetry calculations
  - Monte Carlo transport = Local Deposition = Soft-tissue kernel (liver only)

**Tumor Dose Response Study**

- Single-institutional retrospective study (n=34)
  - 53 HCC tumors from 34 90Y glass microsphere treatments
- Tumors and liver lobes segmented by Interventional Radiologist
  - Diagnostic CT or MR images co-registered with 90Y SPECT/CT
  - Tumors diameters ≥ 2.5 cm; Maximum of 3 tumors per patient
- Calculate voxel-level absorbed dose (AD) and biological effective dose (BED)
  - Activity & Tissue distributions from quantitative 90Y SPECT/CT
  - Local dose deposition
- Association of tumor response with AD and BED evaluated

\[
\text{BED}_{ijk} = D_{ijk} + D_{ijk}^{2} \frac{\alpha}{\beta}_{ijk} \lambda_{ijk} + \lambda_{ijk} \mu_{ijk}
\]

(Tai et al., IJROBP 70, 2008)

\[
\text{WHO = 0, DCR = 96%}
\]

**Response Metric?**

- Tumor response evaluated by IR on follow-up CT or MR at 3 and 6 months using WHO, RECIST, and mRECIST
  - Appropriate choice of response metric is essential

<table>
<thead>
<tr>
<th>WHO</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Correlation</td>
<td>Significant Correlation (p&lt;0.01)</td>
</tr>
<tr>
<td>No Correlation</td>
<td>Most Significant: AD20-70 &amp; BED30-70</td>
</tr>
</tbody>
</table>

**mRECIST**

- ORR = 57%
- DCR = 96%
TCP curves for HCC following SIRT

<table>
<thead>
<tr>
<th>Device Used</th>
<th>Dosimetry Model</th>
<th>Threshold Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR-Spheres</td>
<td>Voxel Dmean</td>
<td>&gt; 97 Gy TCP 50%</td>
</tr>
<tr>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>&gt; 200 Gy TCP 50%</td>
</tr>
<tr>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>&gt; 160 Gy TCP 50%</td>
</tr>
<tr>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>&gt; 205 Gy TCP 50%</td>
</tr>
<tr>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>&gt; 390 Gy TCP 50%</td>
</tr>
</tbody>
</table>

Many Confounding Factors for Dosimetry

- Dosimetry Inputs
- Device Used: 99mTc-MAA, 99mTc-MAA SPECT/CT
- Response Assessment: Anatomical CT MRI, Functional mRECIST, WHO
- Tumor Segmentation: Single Compartment, Partition Model, Voxel
- Other Factors: Net Activity Administered, Errors in Image Quantitation

Leads to a wide variability in reported dose and dose-response

HCC Tumor Response Dose Thresholds

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients, Tumors</th>
<th>Device Used</th>
<th>Voxel Dose Image</th>
<th>Dosimetry Model</th>
<th>Threshold Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strigari 2010</td>
<td>73 Patients &gt;73 Tumors</td>
<td>SIR Spheres</td>
<td>Voxel Dmean</td>
<td>Voxel</td>
<td>Dmean &gt; 97 Gy TCP 50%</td>
</tr>
<tr>
<td>Chan 2018</td>
<td>27 Patients 38 Tumors</td>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>Voxel PET/CT</td>
<td>Dmean &gt; 200 Gy TCP 50%</td>
</tr>
<tr>
<td>Kappadath 2018</td>
<td>54 Patients 53 Tumors</td>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>Voxel SPECT/CT</td>
<td>Dmean &gt; 160 Gy TCP 50%</td>
</tr>
<tr>
<td>Garin 2013</td>
<td>71 Patients &gt;71 Tumors</td>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>TheraSphere SPECT/CT</td>
<td>Dmean &gt; 205 Gy TCP 50%</td>
</tr>
<tr>
<td>Chiesa 2015</td>
<td>52 Patients 60 Tumors</td>
<td>TheraSphere</td>
<td>Voxel Dmean</td>
<td>TheraSphere SPECT</td>
<td>Dmean &gt; 390 Gy TCP 50%</td>
</tr>
</tbody>
</table>

Patient selection (BCLC stage), treatment volume (whole liver vs lobar vs segmental) have large effects on patient response


Many Confounding Factors for Dosimetry

- Dosimetry Models
- Tumor Segmentation
- Response Assessment
- Other Factors

Leads to a wide variability in reported dose and dose-response

Patient selection (BCLC stage), treatment volume (whole liver vs lobar vs segmental) have large effects on patient response

Reporting of dose and dose-response

- Radioembolization community needs to be more specific when reporting dosimetry
  - Dose (e.g., 160 Gy, 60 Gy)
  - Methodology (e.g., Voxel dosimetry, Partition model)
  - Device (SIR-Spheres, TheraSphere)
  - Disease (e.g., HCC, mCRC, mNET)

- Estimate of dose deposited depends on model used
  - 100 Gy MIRD ≠ 100 Gy Partition ≠ 100 Gy Voxel

- Biological effect of dose depends on device properties
  - 100 Gy SIR-Spheres ≠ 100 Gy TheraSphere

MDACC HCC OS Study (n=181)

- Median OS: 13.4 months (95% CI 9.7-17.2)
- Stratification: Tumor burden (<50% or >50%) & Aggressive disease features (Y or N)

90Y-SIRT + SBRT
Looking Forward

- Time is right to focus on the personalized treatment plan:
  - Better knowledge on tumor dose and dose response
  - Better understanding of errors in dose quantification

- Opportunities for improvements in SIRT:
  1. Need for standardization and consistency in practice
  2. Need to be more descriptive when reporting dosimetry
  3. Improved dose response models for OAR are needed

- Improve understanding on how to incorporate SIRT as part of combination treatments:
  - SBRT, proton therapy, systemic, immunotherapy