SAM Imaging Education Course
90Y-Microsphere Therapy: Emerging Trends and Future Directions

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Outline
- Rationale for 90Y-microsphere therapies – SCK
- 90Y-microsphere devices – MV
- Imaging for treatment planning – VG
- Planning dosimetry – MV
- Post-therapy dosimetry – SCK
- Compare dosimetry models – SCK
- Treatment efficacy and dose response – VG, SCK
- Closing remarks – ALL
Rationale for 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 patients: ~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
- Trans-arterial Therapies
  - TAE / Bland Embolization
  - TACE
    - Conventional
    - Drug Eluting Bead
  - Radioembolization/SIRT
  - Percutaneous Hepatic Perfusion
Trans-Arterial Therapy Options

- **TAE**
  - Bland Embolization
  - Embolization of arterial vessels feeding tumors

- **TACE**
  - Conventional Embolization of art. vessels + Chemotherapy

- **TACE**
  - Drug-Eluding Beads
  - Embolization of art. vessels + Chemotherapy

- **SIRT**
  - Radioactive microspheres
  - Non-embolic Brachytherapy

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

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
• Post-therapy dosimetry

99mTc-MAA SPECT/CT
• Extra-hepatic deposition of MAA is evaluated most frequently by SPECT/CT imaging
• SPECT based distribution of 99mTc-MAA with liver (normal liver and tumors) is also being used to evaluate (predict) the distribution of 90Y microspheres

<table>
<thead>
<tr>
<th>Detection of Extra-Hepatic MAA Shunting</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<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)

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, 289T)
• Δ uptake between 99mTc-MAA & 90Y >20% in 45% (97/225) cases (Wondergem et al., JNM 54, 2013)
• Differences in catheter location, embolic load, flow dynamics, etc. contribute to differences in MAA & 90Y on post-therapy 99mTc SPECT/CT and 90Y useful for dosimetry (Strigari et al., JNM 51, 2010; Kappadath et at, EJNM 2014; Med Care Comm 33, 2015; Reo et al., EMMO 3, 2013)
99mTc-MAA versus 90Y caveats

Post-therapy: 90Y-SPECT/CT

- 90Y-bremsstrahlung SPECT/CT imaging
  - Evaluate delivery and in vivo distribution of 90Y-microspheres
  - No standardized SPECT acquisition & reconstruction established
  - Monte Carlo reconstruction – good accuracy but difficult implementation

- Practical 90Y-SPECT/CT reconstruction with quantification
  - CT-AC, Scatter, Collimator-response, optimized iterative recon/filtration
  - Total 90Y activity inside liver can be determined with high accuracy (<10%)
  - Post-therapy 90Y-SPECT/CT images can quantified via self-calibration

90Y-SPECT/CT Quantitative Accuracy

- Self-calibration approach may introduce systematic bias
  - IEC Phantom calibration errors ~25%
  - Signal outside liver from scatter

- Quantitative 90Y SPECT/CT
  - Statistical error < 10% but systematic biases exist
Post-therapy $^{90}\text{Y}$-PET/CT

- $^{90}\text{Y}$ also emits $\beta^+$ ($E_{\text{max}} \sim 800$ keV) with BR = $32 \times 10^{-6}$
  - Internal pair-production in the $0^+\rightarrow0^+$ transition of $^{90}\text{Zr}$ from $^{90}\text{Y}$ decay
    (first works circa 1955; Selwyn et al, App Rad 60, 2007)
- First clinical $^{90}\text{Y}$ PET image published in 2009 (30 min/bed)
- PET/CT provides “quantitative $^{90}\text{Y}$” images with superior spatial resolution
  - Recent papers focus on acquisition parameters and quantitative accuracy

$^{90}\text{Y}$-PET/CT Quantitative Accuracy

QUEST Study (69 scanners):
- Background activity within 10%
- Spheres > 2cm underestimated by 20%
- TOF superior to non-TOF PET systems

GE D690 PET/CT:
- 10%-35% bias in mean dose as function of $^{90}\text{Y}$ dose or count rate
- Independent of total counts

- Compare different dosimetry models
Spatial Representation of Dosimetry Models

- **Standard Model**: Uniform uptake in liver and all tumors.
- **Partition Model**: Different liver and tumor uptake.
- **Voxel-dose Model**: Realistic model: non-uniform uptake in liver and heterogeneous uptake in tumors.

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

Differential DVH: voxel-level doses

Cumulative DVH: voxel-level doses

90Y SPECT

90Y SPECT

D90 = 115 Gy

D10 = 201 Gy

Dmin

Dmax
Voxel Dosimetry: Model Comparison

Voxel dosimetry methods for calculating liver and tumor doses:

\[ MC = LD = SK = SKD \]


90Y-SIRT for HCC

Different dosimetry models on the same patients with matched VOIs result in large differences for absorbed dose estimates

90Y-SIRT for mNET

Different dosimetry models on the same patients with matched VOIs result in large differences for absorbed dose estimates.
Partition model prediction of voxel-level doses have large biases and errors

Mean biases are typically ~ 200%
95% Prediction Interval ~ 130-140 Gy

Differences for mean absorbed doses to normal liver are less sensitive to dosimetry model compared to tumor dosimetry
Dose prediction intervals larger for STD and PM multiple tumor cases
- Treatment efficacy and dose response

HCC Response Studies
- Ho et al, EJNM 1997 (SIR-Spheres for HCC)
  - Threshold tumor dose > 225 Gy
  - Increase in OS (4.4 months) with >300 Gy
- Garin et al, EJNMMI 2013 (TheraSphere for HCC)
  - Threshold tumor dose > 205 Gv, Sensitivity=100%, Accuracy=90%
  - Increase in TTP (7.7 months) and OS (11.7 months)

Partition Model based on MAA uptake

SIRFLOX – Phase III RCT in CRC
- Progression-Free Survival in the Liver
  - 7.8-month improvement in median PFS in the liver
  - 31% reduction in risk of disease progression in the liver
Standard model dosimetry used in therapy planning cannot predict tumor response.

Knowledge of the tumor dose response will be useful in planning treatment prior to therapy.

Knowledge of the tumor dose will be useful in prediction of response status after therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>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/73 Tumors</td>
<td>SIR-Spheres®</td>
<td>SPECT</td>
<td>Voxel</td>
<td>AD50 &gt;97 Gy</td>
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<tr>
<td>Kao 2013</td>
<td>6 Patients/9 Tumors</td>
<td>SIR-Spheres®</td>
<td>SPECT</td>
<td>Voxel AD70 &gt;100 Gy</td>
<td></td>
</tr>
<tr>
<td>Kappadath 2017</td>
<td>54 Patients/53 Tumors</td>
<td>Therasphere®</td>
<td>SPECT/CT</td>
<td>Voxel</td>
<td>AD50 &gt;94 Gy (AD50 &gt;154 Gy)</td>
</tr>
<tr>
<td>Garin 2013</td>
<td>71 Patients/73 Tumors</td>
<td>Therasphere®</td>
<td>PET/CT/CT</td>
<td>Remissio</td>
<td>AD50 &gt;205 Gy</td>
</tr>
<tr>
<td>Chiesa 2015</td>
<td>52 Patients/60 Tumors</td>
<td>Therasphere®</td>
<td>SPECT/CT</td>
<td>Voxel</td>
<td>AD50 &gt;130 Gy</td>
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</tbody>
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Response Summary: HCC with mRECIST

Patient selection (BCLC stage) and treatment volume (whole liver vs lobar vs segmental) have large affects on patient response.


S. Cheenu Kappadath, PhD
• Closing Remarks

Discussion

• Lung Shunt Estimates with Planar imaging has bias and errors
• MAA is the approved surrogate but it is not a consistently reliable indicator of microsphere distribution
• MIRD (package insert) and partition models for dosimetry are rudimentary
• Current therapy planning not designed to deliver specific dose to target lesions
• Post-therapy imaging is not routine clinical practice.
• Improvements in emission image quality desired.
• Image segmentation and dosimetry models used has a profound influence on estimated dose values

Summary

• Dosimetry models have different levels of bias/uncertainty — 100 Gy with STD ≠ 100 Gy with PM ≠ 100 Gy with VD
• Caution is warranted when comparing 90Y-SIRT dosimetry between different clinical studies
• Quantitative post-therapy 90Y-imaging can provide tumor and normal liver DHVs
• The radioembolization community needs standardization to aid in interpretation and translation of dose-response relationship between institutions