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

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AAPM 2017 JUL 30–AUG 3

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Disclosures

- Research Grant Support
  - SCK: BTG Biocompatibles Ltd, GE Healthcare

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

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

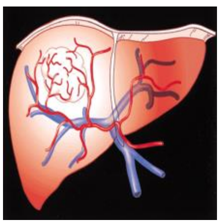
- Ablation
  - Radiofrequency Ablation (RFA)
  - Microwave Ablation
  - Irreversible Electroporation (IRE)
- Chemoinfusion
  - Ports
  - HAI
- Trans-arterial Therapies
  - TAE / Bland Embolization
  - TACE
    - Conventional
    - Drug Eluting Bead
  - Radioembolization/SIRT
  - Percutaneous Hepatic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

Trans-Arterial Therapy Options

TAE	TACE	TACE	SIRT
Bland Embolization	Conventional	Drug-Eluding Beads	Radioactive microspheres
Embolization of arterial vessels feeding tumors	Embolization of art. vessels + Chemotherapy	Embolization of art. vessels + Chemotherapy	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

^{90}Y-microsphere Therapy

- Trans-arterial delivery of radioactive ^{90}Y-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

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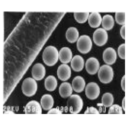

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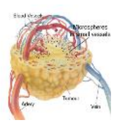
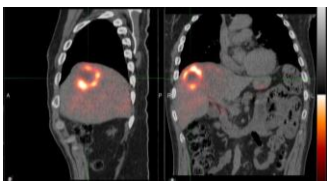


- β emissions from trapped ^{90}Y-microspheres are capable of delivering lethal radiation doses to (proximal) neoplastic tissue while sparing (more distal) surrounding normal tissue

- Post-therapy dosimetry

^{99m}Tc-MAA SPECT/CT

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

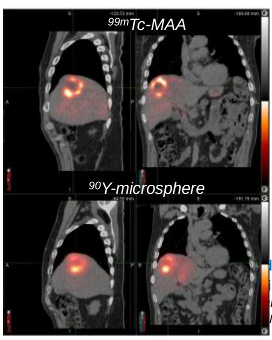


Detection of Extra-Hepatic MAA Shunting

	Sensitivity	Specificity
Planar	32	98
SPECT	41	98
SPECT/CT	100	93

(Ahmadzadehfar et al, JNM, 2010)

Does ^{99m}Tc-MAA represent the distribution of ^{90}Y-microspheres after therapy?



☑ MAA uptake shown to predict tumor response and survival in HCC

(Ho et al., EJNM 23, 1997)
(Garin et al., JNM 53, 2012)

☒ Δ uptake between ^{99m}Tc-MAA & ^{90}Y >20% in 43% (97/225) cases

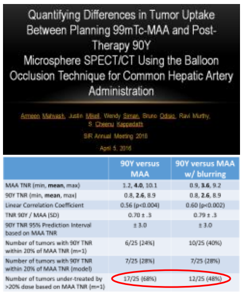
(Wondergem et al., JNM 54, 2013)

☒ Differences in catheter location, embolic load, flow dynamics, etc. contribute to differences in MAA & ^{90}Y

d on post-therapy ^{90}Y SPECT/CT and ^{90}Y
ingful for dosimetry

l., JNM 51, 2010; Kappadath et al., SNMMI, 2014)
Med Comm 33, 2013; Kao et al., EJNMMI 3, 2013)

^{99m}Tc-MAA versus ^{90}Y caveats



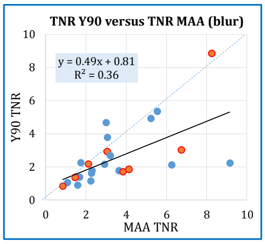
Quantifying Differences in Tumor Uptake Between Planning 99mTc-MAA and Post-Therapy 90Y Microsphere SPECT/CT Using the Balloon Occlusion Technique for Common Hepatic Artery Administration

Armeen Mahvash, Justin Mikell, Wendy Siman, Bruno Odisio, Ravi Murthy, S. Cheenu Kappadath

SIR Annual Meeting 2016

April 5, 2016

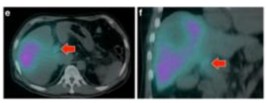
	90Y versus MAA	90Y versus MAA w/ blurring
MAA TNR (min, **mean**, max)	1.2, **4.0**, 10.1	0.9, **3.6**, 9.2
90Y TNR (min, **mean**, max)	0.8, **2.6**, 8.9	0.8, **2.6**, 8.9
Linear Correlation Coefficient	0.56 (p<0.004)	0.60 (p<0.002)
TNR 90Y / MAA (SD)	0.70 ± .3	0.79 ± .3
90Y TNR 95% Prediction Interval based on MAA TNR	± 3.0	± 3.0
Number of tumors with 90Y TNR within 20% of MAA TNR (m=1)	6/25 (24%)	10/25 (40%)
Number of tumors with 90Y TNR within 20% of MAA TNR (model)	7/25 (28%)	7/25 (28%)
Number of tumors under-treated by >20% dose based on MAA TNR (m=1)	17/25 (68%)	12/25 (48%)



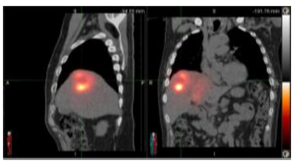
(Mahvash et al, JVIR 2015)

Post-therapy: ^{90}Y-SPECT/CT

- ^{90}Y-bremsstrahlung SPECT/CT imaging
  - Evaluate delivery and in vivo distribution of ^{90}Y-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



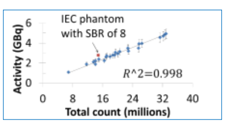
(Kao et al, EJNMMI 2013)



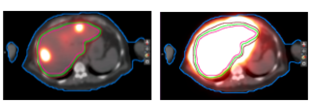
MDACC 90Y-SPECT/CT

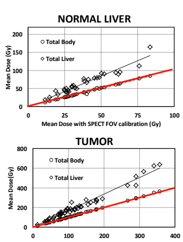
^{90}Y-SPECT/CT Quantitative Accuracy

- Self-calibration approach may introduce systematic bias
  - IEC Phantom calibration errors ~25%
  - Signal outside liver from scatter
- Quantitative ^{90}Y SPECT/CT
  - statistical error < 10% but systematic biases exist



(Siman et al, Med Phys 2017)

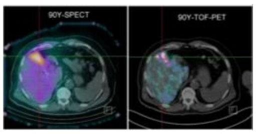




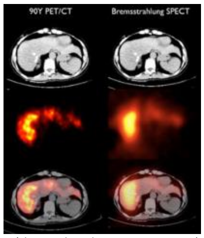
(Balagopal et al, Med Phys 2017 submitted)

Post-therapy ^{90}Y-PET/CT

- ^{90}Y 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 ^{90}Y PET image published in 2009 (30 min/bed)
- PET/CT provides "quantitative ^{90}Y" images with superior spatial resolution
  - Recent papers focus on acquisition parameters and quantitative accuracy



(Carlier et al., EJNMMI Res. 3, 2013)

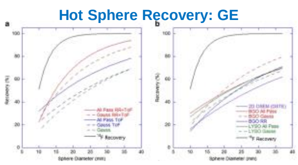


(Lhommel et al, EJNMMI 36, 2009)

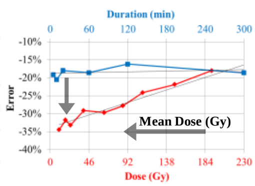
^{90}Y-PET/CT Quantitative Accuracy

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 90Y dose or count rate
- independent of total counts

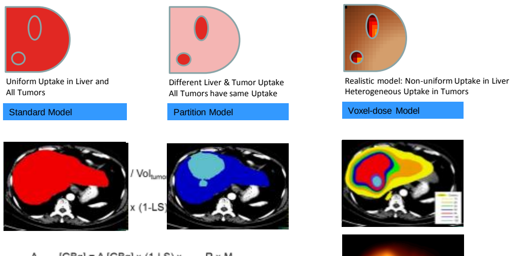


(Willowson et al, EJNMMI Physics, 2015)

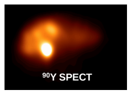


- Compare different dosimetry models

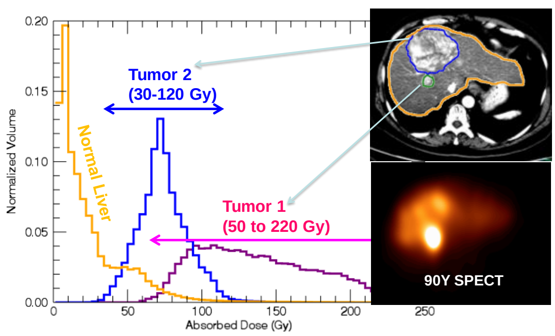
Spatial Representation of Dosimetry Models



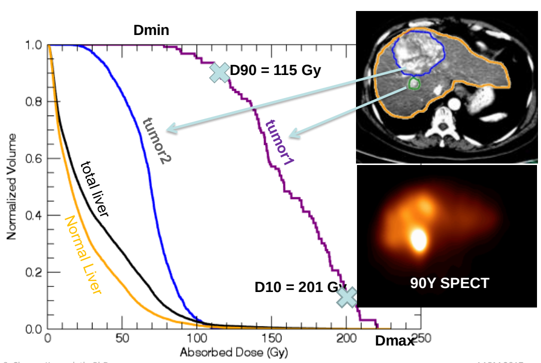
MIRD and Partition dosimetry models do not provide accurate absorbed dose distributions to tumors and normal liver



Differential DVH: voxel-level doses



Cumulative DVH: voxel-level doses

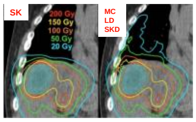


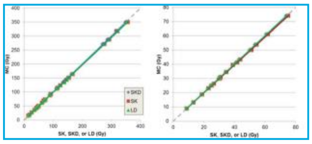
Voxel Dosimetry: Model Comparison

Table 1 Characteristics of the different VBD

VBDM	Functional form
Monte Carlo (MC)	$F(M_{ijk}, N_{ijk}, \rho_{ijk}, E_{90Y})$
Local deposition (LD)	$N_{ijk} \cdot \frac{E_{avg}}{\rho_{ijk} \cdot \delta V}$
Soft-tissue kernel (SK)	$N_{ijk} \otimes K_{i'j'k'}$
Soft-tissue kernel with density correction (SKD)	$\left(N_{ijk} \otimes K_{i'j'k'}\right) \cdot \frac{1.04}{\rho_{ijk}}$

⊗ denotes convolution





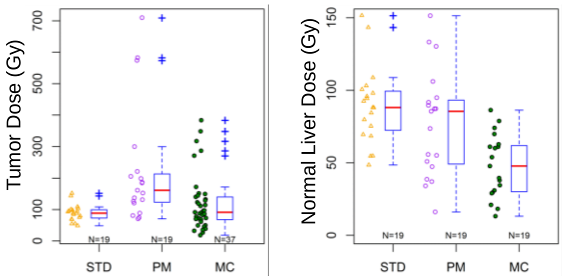
Voxel dosimetry methods for calculating liver and tumor doses:

MC = LD = SK = SKD

Mikell JK, et al. Int J Rad Onc Phys Bio, 96, 2016

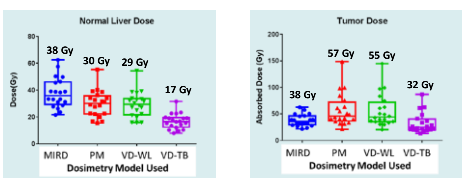
^{90}Y-SIRT for HCC

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

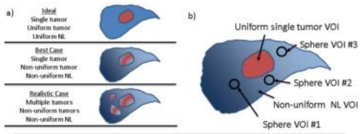


(Mikell JK, et al. Int J Rad Onc Phys Bio, 96, 2016)

^{90}Y-SIRT for mNET



TNR variability effects accuracy of PM dosimetry



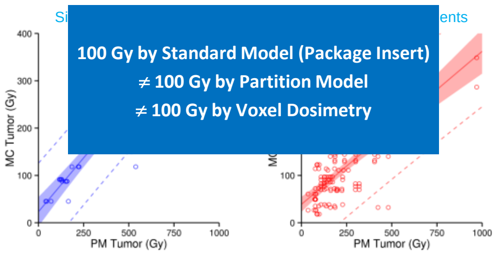
Calculation demonstrating PM variability using different estimates for NL activity concentration

VOI used to estimate NL activity concentration	TNR	Tumor PM (Gy)	NL PM (Gy)
entire NL	4	369	92
sphere #1	8	568	71
sphere #2	4	369	92
sphere #3	1	120	120

Mikell JK, et al. Int J Rad Onc Phys Bio, 96, 2016

Partition model prediction of voxel-level doses have large biases and errors

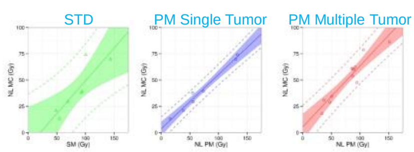
Mean biases are typically ~ 200%
95% Prediction Interval ~ 130-140 Gy



100 Gy by Standard Model (Package Insert)
≠ 100 Gy by Partition Model
≠ 100 Gy by Voxel Dosimetry

(Mikell JK, et al. Int J Rad Onc Phys Bio, 96, 2016)

Normal Liver Dose Correlations



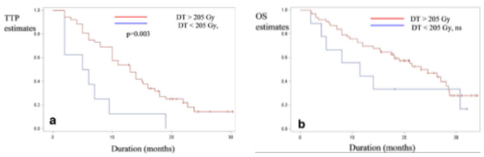
- Differences for mean absorbed doses to normal liver are less sensitive to dosimetry model compared to tumor dosimetry
- Dose prediction intervals larger for STD and PM multiple tumor cases

(Mikell JK, et al. Int J Rad Onc Phys Bio, 96, 2016)

- Treatment efficacy and dose response

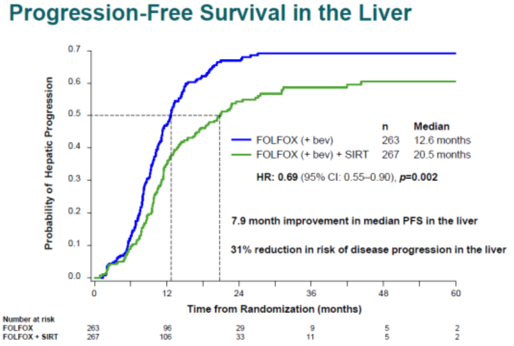
HCC Response Studies

- 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 Gy, Sensitivity=100%, Accuracy=90%
  - Increase in TTP (7.7 months) and OS (11.7 months)

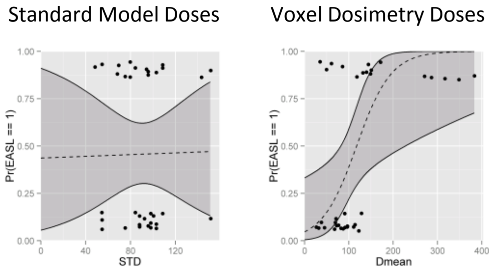


Partition Model based on MAA uptake

SIRFLOX – Phase III RCT in CRC

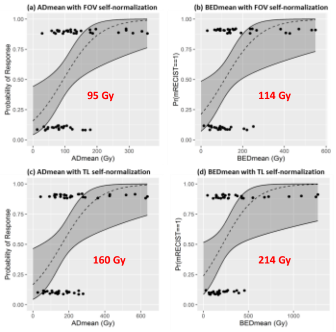


HCC Tumor Dose Response



Standard model dosimetry used in therapy planning cannot predict tumor response

90Y-SIRT HCC Tumor Dose 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**

Kappadath S, et al. J Nucl Med. 2015;56(suppl 3): Abstract 572.

Response Summary: HCC with mRECIST

Study	Patients Tumors	Device Used	Voxel Dose Image	Dosimetry Model	Threshold Dose
Strigari 2010[1]	73 Patients >73 Tumors	SIR-Spheres®	^{90}Y SPECT	Voxel	AD50 >97 Gy
Kao 2013[2]	6 Patients 9 Tumors	SIR-Spheres®	^{90}Y PET/CT	Voxel	AD70 >100 Gy
Kappadath 2017[3]	**34 Patients 53 Tumors**	**TheraSphere®**	**^{90}Y SPECT/CT**	**Voxel**	**AD50 >94 Gy (AD50 >154 Gy)**
Garin 2013[4]	71 Patients >71 Tumors	TheraSphere®	^{99m}Tc-MAA SPECT/CT	Partition	AD50 >205 Gy
Chiesa 2015[5]	52 Patients 60 Tumors	TheraSphere®	^{99m}Tc-MAA SPECT	Voxel	AD50 >390 Gy

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

1. Strigari L, et al. J Nucl Med. 2010;51:1377-1385. 2. Kao Y-H, et al. J Nucl Med Mol Imaging Res. 2013;3(56):1-13. 3. Kappadath S, et al. J Nucl Med. 2015;56(suppl 3). Abstract 572. 4. Garin E, et al. Eur J Nucl Med Mol Imaging. 2013;40:1057-1068. 5. Chiesa C, et al. Eur J Nucl Med Mol Imaging. 2015;42(11):1758.

- 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 ^{90}Y-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