Joint AAPM/SNMMI Symposium

Nuclear Medicine Theranostics and Functional Image-Guided Radiation Therapy for Precision Oncology

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

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- Research grants: BTG International, GE Healthcare
- Consultant: BTG International, Terumo Medical Systems, ABK Biomedical

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

- 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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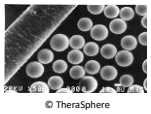

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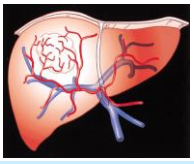
- β emissions from trapped ^{90}Y-microspheres deliver radiation dose to proximal tissue (tumors) while sparing distal (normal liver) tissue → max range of 10 mm

(Murthy et al, Sem IR, 2008; Sarfaraz et al, Med Phys, 2004)

Rationale for liver-directed therapy

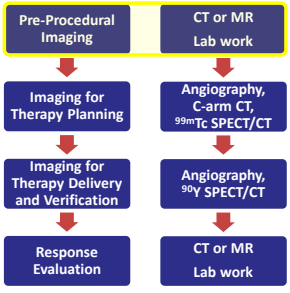
- Normal liver blood flow
  - 75% portal vein
  - 25% hepatic artery
- Hepatic neoplasm, >3mm metastases
  - 80- 100% supply from hepatic artery
  - Greater vascular density in neoplasm
- Primary site of disease in HCC and ICC
- Dominant organ of metastases in CRC and NET
- Resection improves survival HCC, CRC, NET
  - Control of liver disease should increase survival

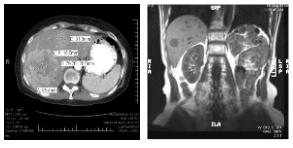


Indications

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

90Y-SIRT Workflow

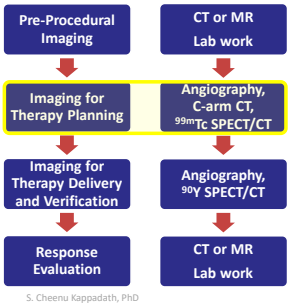


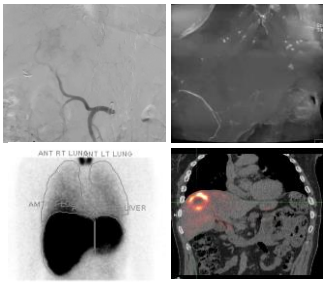


- Tumors fed by hepatic artery

SIR-Spheres, Sirtex
TheraSphere, BTG
QuiremSpheres, Terumo*
Eye90, ABK Biomed*
**not FDA-approved*

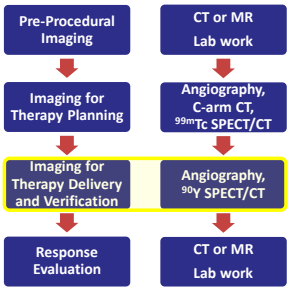
90Y-SIRT Workflow

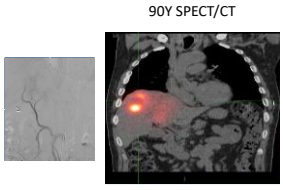




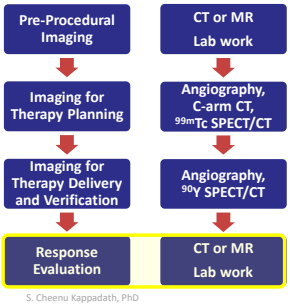
99mTc-MAA

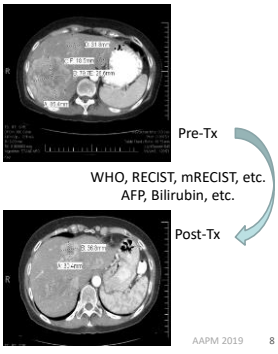
90Y-SIRT Workflow





90Y-SIRT Workflow



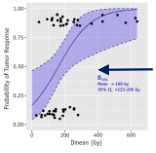


SIRT is "IGRT" but focused on Safety

- 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 to 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

^{90}Y-SIRT should be based on dosimetry

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

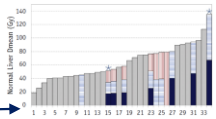


HCC with TheraSphere

(Kappadath et al, IJROBP 2018)

Tumor mean dose of 160 Gy gives 50% probability of response

No significant CTCAE grade complications observed at Dmean below 50 Gy

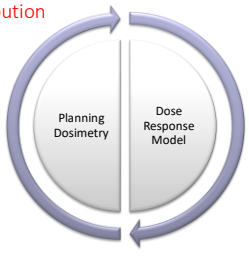


The SIRT Dosimetry Conundrum

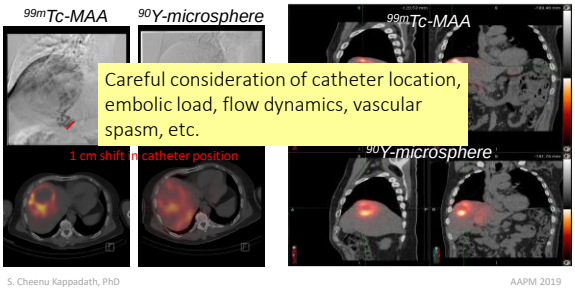
Efficacy is predicated by good match between planned and actual radiation dose distribution

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



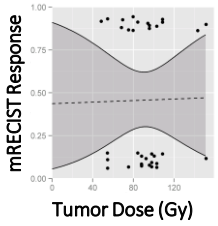
Careful consideration of catheter location, embolic load, flow dynamics, vascular spasm, etc.

Package Insert: Tumor Dose Response

HCC

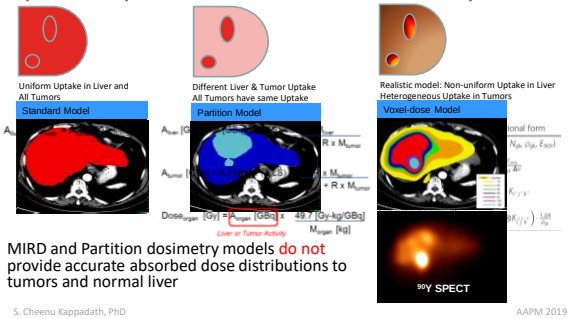
TheraSphere Package Insert

1-compartment MIRD Model



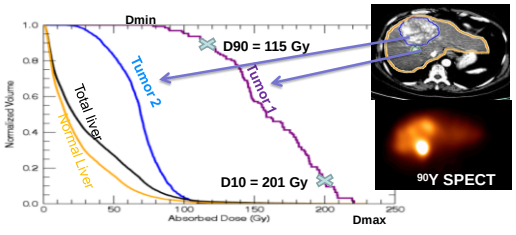
Package Insert dosimetry used in therapy planning cannot predict HCC tumor response

Spatial Representation of SIRT Dosimetry Models



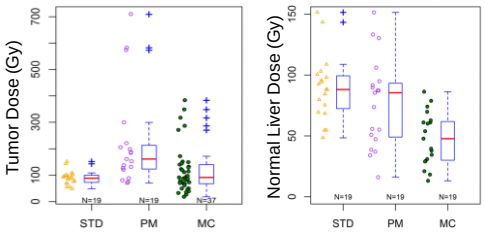
MIRD and Partition dosimetry models do not provide accurate absorbed dose distributions to tumors and normal liver

Voxel Dosimetry: Cumulative DVH



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

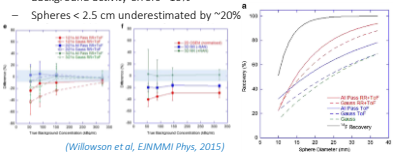
37 HCC tumors from 20 TheraSphere treatments



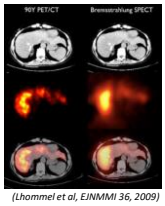
(Mikell et al, Int J Rad Onc Phys Bio, 2016)

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

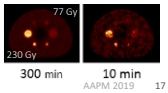
- ^{90}Y also emits β+ (E_{max} ~ 800 keV) with BR = 32 x 10^{-6}
  - Internal pair-production in the 0^+–0^+ transition of ^{90}Zr from ^{90}Y decay (first works circa 1955; Selwyn et al, App Rad Iso 65, 2007)
- First clinical ^{90}Y PET image published in 2009 (30 min/bed)
- Quantitative accuracy depends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



(Willowson et al, EJNMMI Phys, 2015)

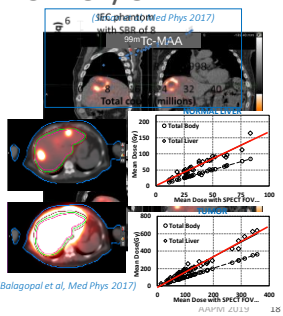


(Lhommel et al, EJNMMI 36, 2009)



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

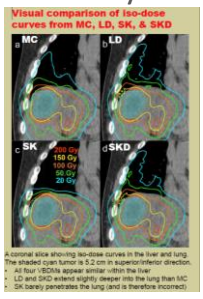
- Standardized acquisition & reconstruction yet to be established
  - Monte-Carlo based techniques excellent image quality
  - Practical approaches can also provides clinically meaningful evaluation of in vivo 90Y distribution
  - Partial volume errors for tumors < 3-4 cm
- Quantitative 90Y SPECT/CT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



(Balagopal et al, Med Phys 2017)

^{90}Y-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)



(Mikell et al, EJNMMI Physics 2, 2015)

Tumor Dose Response Study

- Single-institutional retrospective study (n=34) *(Kappadath et al, Int J Rad Onc Phys Bio, 2018)*
  - 53 HCC tumors from 34 ^{90}Y glass-microsphere treatments
- Tumors and liver lobes segmented by Interventional Radiologist
  - Diagnostic CT or MR images co-registered with ^{90}Y 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 ^{90}Y SPECT/CT
  - Local dose deposition
- Association of tumor response with AD and BED evaluated

$$BED_{ijk} = D_{ijk} + \frac{D_{ijk}^{\,2}}{\left(\frac{\alpha}{\beta}\right)_{ijk}}\left(\frac{\lambda}{\mu_{ijk}+\lambda}\right)$$

(Dale et al. Can Bio Radiopharm 20, 2005)

	HCC tumor	normal liver
λ eff. decay rate (h^{-1})	0.0108	0.0108
α/β radiosensitivity (Gy)	15	2.5
$T_{1/2}$ repair (h)	1.5	2.5

(Tai et al., IJROBP 70, 2008)

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

WHO	• No Correlation
RECIST	• No Correlation
mRECIST	• Significant Correlation (p<0.01) • Most Significant: AD20-70 & BED30-70

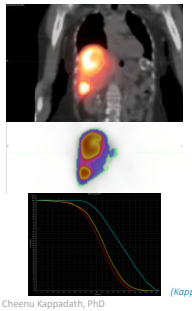
mRECIST

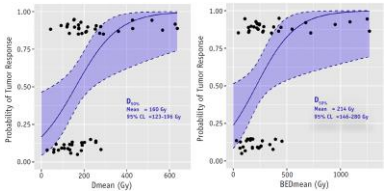
ORR = 57%

DCR = 96%

(Kappadath et al, Int J Rad Onc Phys Bio, 2018)

TCP curves for HCC following SIRT





Dose Metric	Responder (median)	Non-Respond (median)	Threshold Dose (D50)	p-value
Dmean (Gy)	209	138	160 (123-196)	0.002
BEDmean (Gy)	259	178	214 (146-280)	0.006

(Kappadath et al, Int J Rad Onc Phys Bio, 2018)

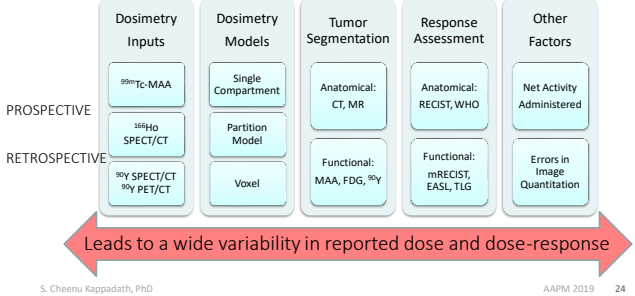
HCC Tumor Response Dose Thresholds

Study	No. of Patients, Tumors	Device Used	Voxel Dose Image	Dosimetry Model	Threshold Dose
Strigari 2010[1]	73 Patients >73 Tumors	SIR-Spheres	^{90}Y SPECT	Voxel	Dmean > 97 Gy TCP 50%
Chan 2018[2]	27 Patients 38 Tumors	TheraSphere	^{90}Y PET/CT	Voxel	Dmean > 200 Gy
Kappadath 2018[3]	34 Patients 53 Tumors	TheraSphere	^{90}Y SPECT/CT	Voxel	Dmean > 160 Gy TCP 50%
Garin 2013[4]	71 Patients >71 Tumors	TheraSphere	^{99m}Tc-MAA SPECT/CT	Partition	Dmean > 205 Gy
Chiesa 2015[5]	52 Patients 60 Tumors	TheraSphere	^{99m}Tc-MAA SPECT	Voxel	Dmean > 390 Gy TCP 50%

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

1. Strigari et al. JNM 51, 2010; 2. Chan et al. IJROBP 101, 2018; 3. Kappadath et al. IJROBP 102, 2018; 4. Garin et al. EJNMMI 40, 2013; 5. Chiesa et al. EJNMMI 42, 2015.

Many Confounding Factors for Dosimetry



Reporting of dose and dose-response

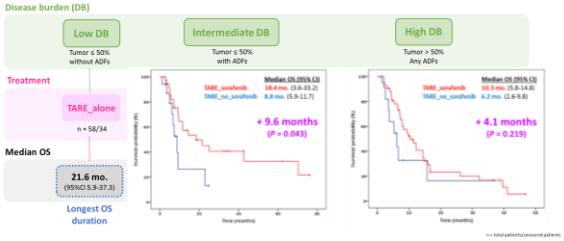
- Radioembolization community needs to be more specific when reporting dosimetry
  - Dose (e.g., 160 Gy, 60 Gy)
  - Methodology (e.g., Voxel dosimetry, Partition model)
  - Device (SIR-Spheres, TheraSphere)
  - Disease (e.g., HCC, mCRC, mNET)
- Estimate of dose deposited depends on model used

  100 Gy MIRD ≠ 100 Gy Partition ≠ 100 Gy Voxel
- Biological effect of dose depends on device properties

  100 Gy SIR-Spheres ≠ 100 Gy TheraSphere

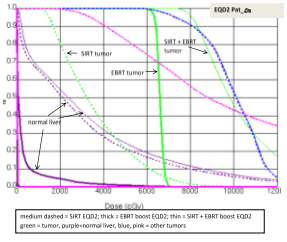
MDACC HCC OS Study (n=181)

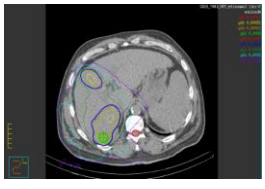
- Median OS: 13.4 months (95% CI 9.7-17.2)
- Stratification: Tumor burden (<50% or >50%) & Aggressive disease features (Y or N)



(Teyateeti et al, SNMMI 2019)

90Y-SIRT + SBRT





Looking Forward

- Time is right to focus on the personalized treatment pla
  - Better knowledge on tumor dose and dose response
  - Better understanding of errors in dose quantificat
- Opportunities for improvements in SIRT
  1. Need for standardization and consistency in practice
  2. Need to be more descriptive when reporting dosim
  3. Improved dose response models for OAR are nee
- Improve understanding on how to incorporate SIRT as pa combination treatments
  - SBRT, proton therapy, systemic, immunotherapy

Growing Value

Cultivating Safety

Building Bridges