Joint EANM/AAPM Multi-disciplinary Scientific Symposium

Quantitative SPECT for Radionuclide and External Beam Treatment Planning:

SPECT in Radionuclide and External Beam Treatment Planning

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THE UNIVERSITY OF TEXAS MD Anderson ~~Cancer~~ Center Making Cancer History®

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Disclosures

- Research Grants
  - Sirtex Medical, Boston Scientific, GE Healthcare, ABK Biomedical
- Consultant
  - Sirtex Medical, Boston Scientific, Varian, ABK Biomedical, Terumo
- Contact Info
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Outline

- Introduction to Radiopharmaceutical therapy
- SPECT in Radiopharmaceutical therapy
  - ^{177}Lu DOTATATE
  - ^{90}Y SIRT
- SPECT in EBRT/PBR
  - Lung Tx
  - Liver Tx

What is Radiopharmaceutical Therapy?

- Radiopharmaceutical uptake
  - Disease sites (Target)
  - Non-target organs (Organs at Risk)
- Tracer radiopharmaceutical administered to plan therapy dose/activity

  SAFETY
  - Dose constraints on Organs at Risk (e.g., red marrow, lungs, liver, kidneys)

  EFFICACY
  - Dose constraints on tumors (e.g., planned mean dose > threshold dose for response)

Targeted Radionuclide Therapy

Radionuclide Imaging | **Radionuclide Therapy**

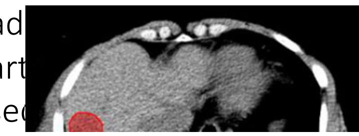
Both involves a radiopharmaceutical (radioactive drug) that targets (binds or uptake) cancer cells via specific biological processes

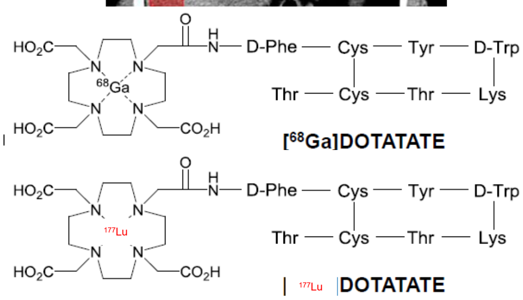
- Rad… …ission use… bioc… …ve asses treatment response

D-glucose

2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)

- Rad… part… …ger e^-) use… …f tissue … d





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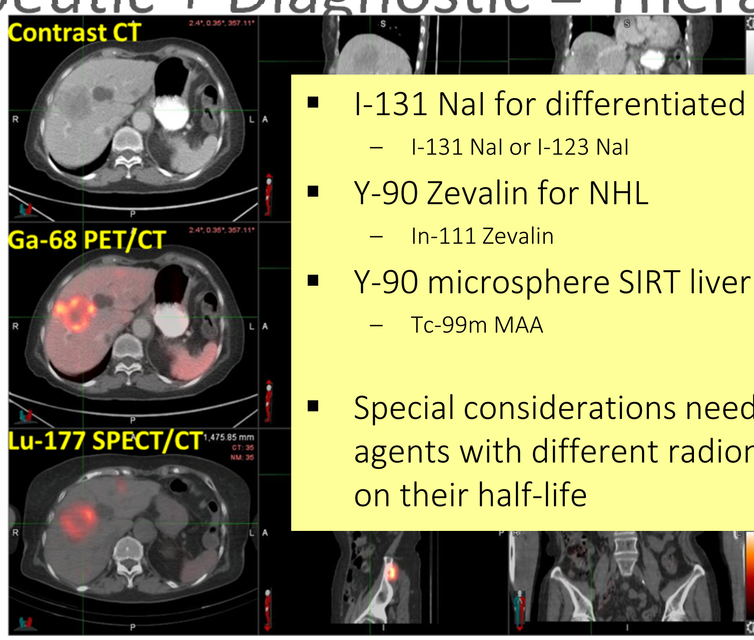
Therapeutic + Diagnostic = Theranostic



Diagnostic
5 mCi

Therapeutic
200 mCi

- I-131 NaI for differentiated thyroid cancers
  - I-131 NaI or I-123 NaI
- Y-90 Zevalin for NHL
  - In-111 Zevalin
- Y-90 microsphere SIRT liver cancers
  - Tc-99m MAA
- Special considerations needed for planning agents with different radionuclide based on their half-life

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RNT is Image-Guided Radiation Therapy

- Assessment of disease for treatment selection →
- Evaluate patient-specific bio-distribution of radiopharmaceutical for RNT treatment planning →
- Develop patient-specific treatment plans: dose limits to targets & OAR ↓
- Treat and Image based verification of RNT delivery →
- Assessment of response

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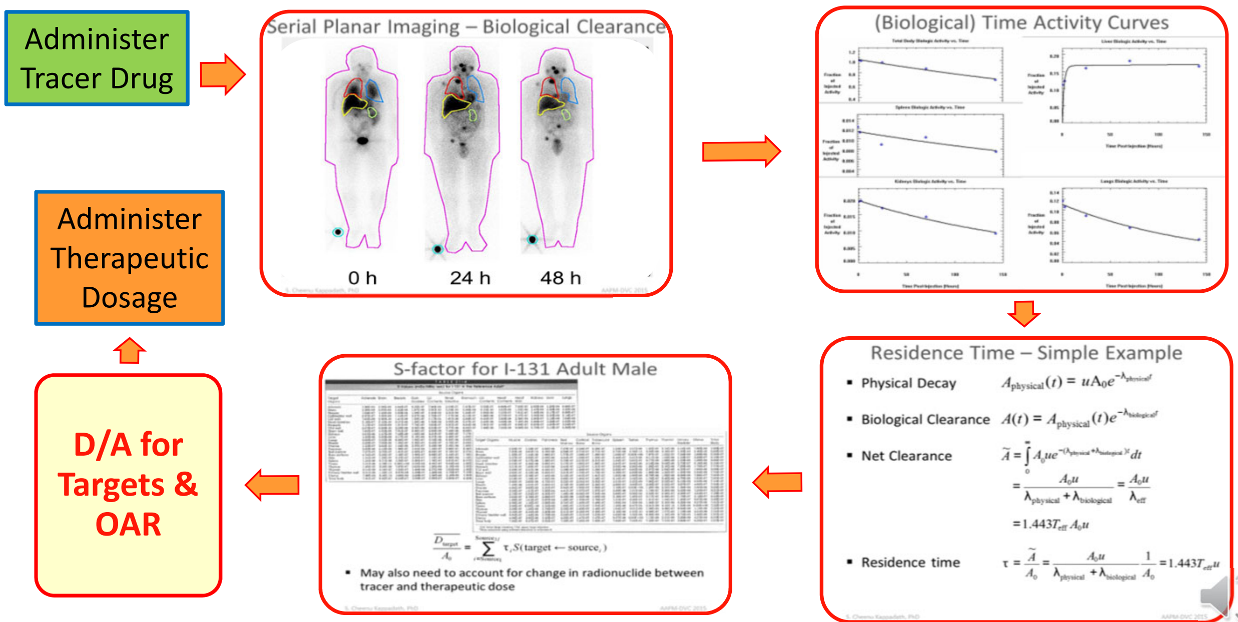
Targeted Radionuclide Therapy



RNT treatment schemas

Fixed Activity Treatment	Patient-specific Activity Treatment

- Almost all investigational trials and clinical approved RNT are based on either Fixed Activity or Maximum Dose to OAR
- Y90-SIRT is one of the exceptions where minimum dose to tumor and maximum dose to OAR is part of dosimetry schema
  - a recent development

Serial Quantitative SPECT/CT scans

Advantages

- More accurate assessment of TAC
- Patient-specific organ masses
- Patient-specific S-factors via Monte Carlo or GBBS
- More accurate tumor dosimetry
- Facilitates Voxel dosimetry

Disadvantages

- Increased patient time on the scanner (factor of 2 or more)
- Higher use of resources for clinical operation
- Increased complexity in data processing

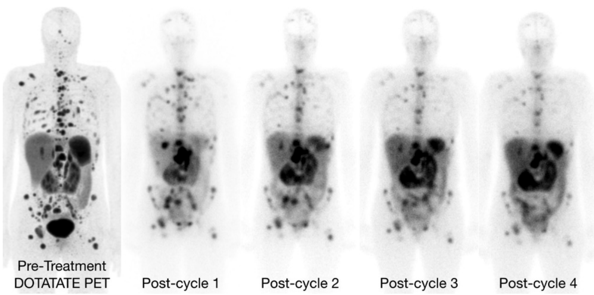
Practical Approaches

- Integrate a single quantitative SPECT/CT scan within the sequence of serial whole-body planar imaging –2.5D dosimetry
- Modified serial quantitative SPECT/CT scans
- Single-time point SPECT/CT

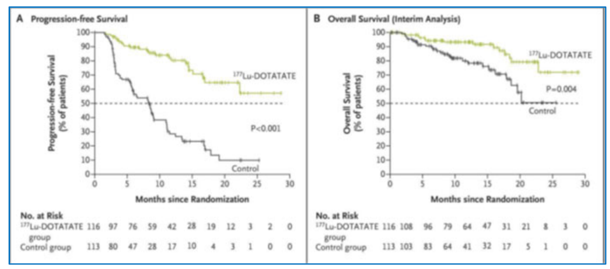
- ^{177}Lu-DOTATATE/DOTATOC

^{177}Lu-DOTATATE (Lutathera)

- Recent FDA-approval for use in GEP-NET tumors (NETTER-1 trial)
  - Expanding to use in all NET expressing SSR2
- Fractionated Schema: 4 cycles of 7.4 GBq (200 mCi) with 8 week interval
  - ^{68}Ga-DOTATATE PET/CT scans to establish the patients disease expresses SSR2 and ensure adequate uptake (theranostic)



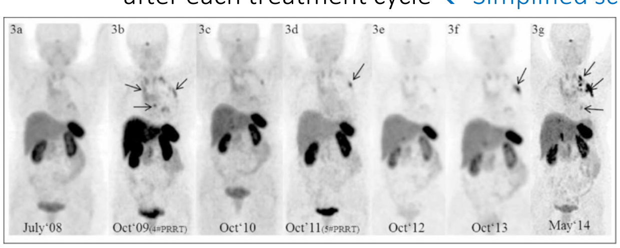
(Hope et al, JNM 60, 2019)



Strosberg, J, et al., 2017. Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med, 376: 125-135.

^{177}Lu-DOTATATE/DOTATOC

- Dosimetry for approval based on planar multi-time point dosimetry
- NO patient specific dosimetry calculations for SOC treatment plans
  - Netter-1 Trial Objective Response Rates ~18%
- Need to develop practical schema for patient specific dosimetry to answer:
  - How do we safely prescribe more than 4 cycles of Tx? ← Track dose to OAR
  - Can we improve the objective response rates (NETTER-1 ~18%)? ← Track dose to tumors
  - Very challenging to perform multi-timepoint imaging for dosimetry spanning 0 to 168 h after each treatment cycle ← Simplified schema needed



Case Report: ^{68}Ga DOTATOC PET/CT scans of patient that underwent 7 cycles of Lu177 treatment in 5 year span illustrating the "waxing and waning" pattern of disease

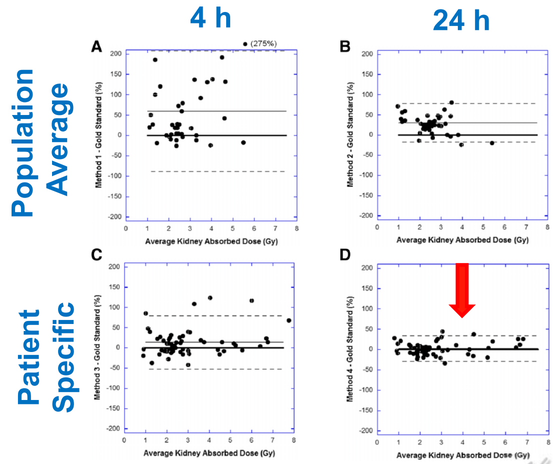
(Puranik et al, Case Reports 1, 2015)

^{177}Lu-DOTATATE/DOTATOC dosimetry

- 20 patients, 4 cycles → 80 Tx
- 3 time-point SPECT/CT (4, 24, 96-120 h) after each Tx were acquired

Recommendations:

- 1st cycle multi-time point SPECT/CT for patient-specific <u>kinetics</u>
- Use single time-point SPECT/CT @ 24 h for <u>uptake</u> in subsequent cycles
- Error in residence times ~16%



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^{177}Lu-DOTATATE/DOTATOC dosimetry

- 29 treatments, 4 cycles → 116 Tx
- 6 time-point SPECT/CT (24, 48, 72, 96, 120, and 144 h) after each Tx were acquired

Recommendations:

- Population-based S-values can be used (<u>kinetics</u>)
- Single SPECT/CT at 4 d (96 h) P.I. to measure the <u>uptake</u>
- Error in residence times < 10%-20%

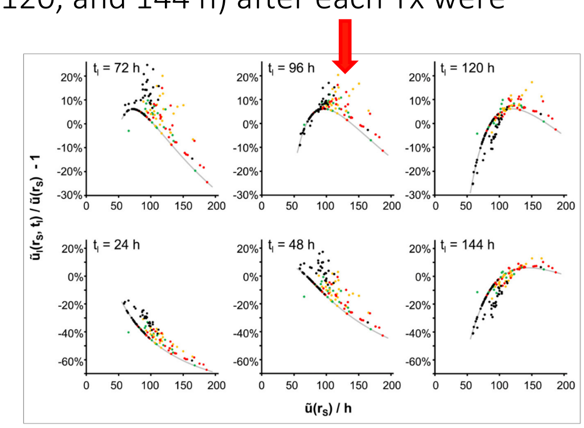

FIGURE 3. Percentage deviation of approximation $\tilde{u}_l(r_S, t_l) = u(r_S, t_l) \times 2 \times t_l/\ln(2)$ from $\tilde{u}(r_S)$ vs. actual time integral $\tilde{u}(r_S)$ for single measurements after t_l = 72, 96, and 120 h (top; scale, −30% to 25%) and t_l = 24, 48, and 144 h (bottom; scale, −70% to 25%). Deviations are positive for overestimations and negative for underestimations of actually absorbed doses. Each point represents kidney (black), liver (green), spleen (yellow), or NET lesion (red). Gray line shows deviation expected for monoexponential decay functions.

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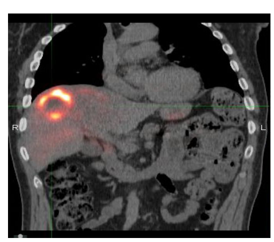
- ^{90}Y-radioembolization or SIRT

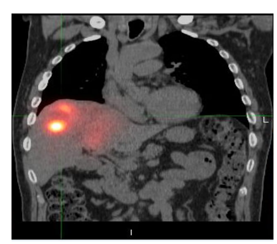
^{90}Y-radioembolization or SIRT

Pre-Procedural Imaging	**CT or MR Lab work**
Imaging for Therapy Planning	**Angiography, C-arm CT, ^{99m}Tc SPECT/CT**
Imaging for Therapy Delivery and Verification	**Angiography, ^{90}Y SPECT/CT**
Response Evaluation	**CT or MR Lab work**

SIRT treatment planning uses ^{99m}Tc-MAA as a surrogate for ^{90}Y-microspheres
- Access extra-hepatic shunting
- Lung dose from arterio-venous shunting
- Tumor & Normal Liver dosimetry

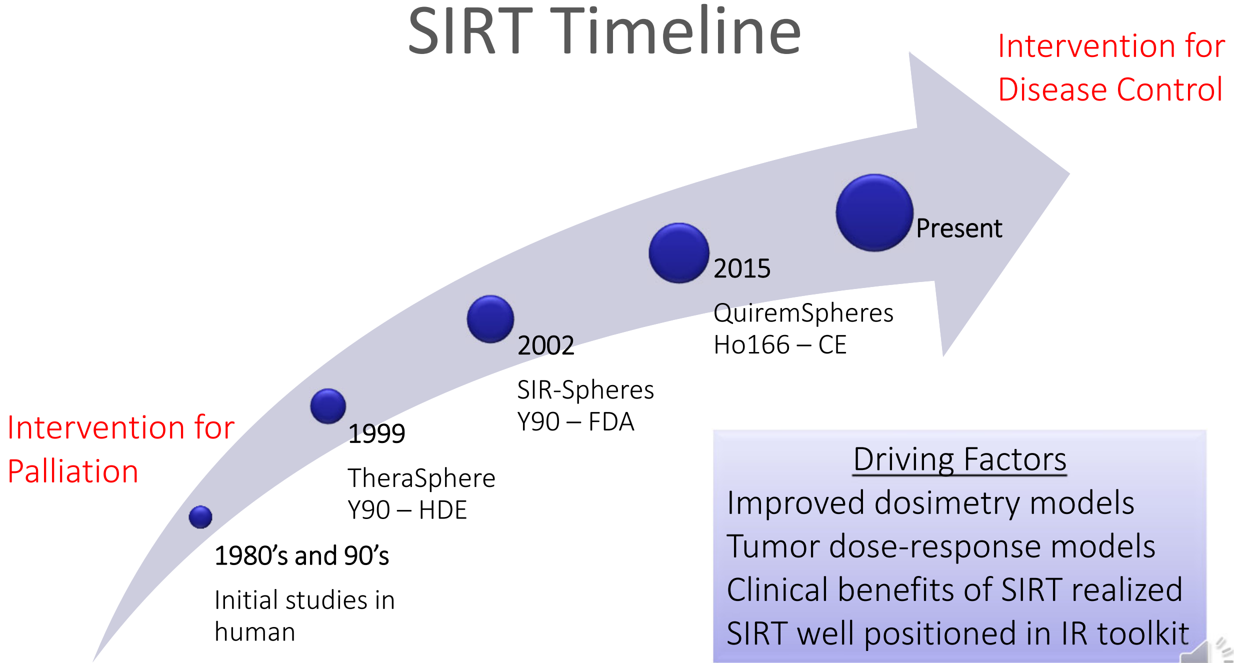


^{99m}Tc-MAA SPECT/CT
For
Planning Dosimetry



^{90}Y SPECT/CT
For
Verification Dosimetry

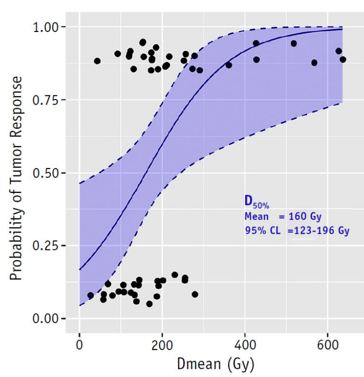
SIRT Timeline

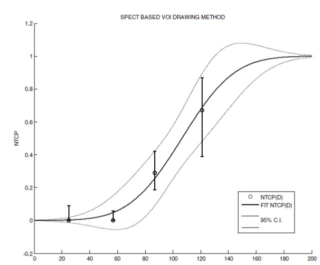


Driving Factors

- Improved dosimetry models
- Tumor dose-response models
- Clinical benefits of SIRT realized
- SIRT well positioned in IR toolkit

^{90}Y-SIRT TCP for HCC with ^{90}Y SPECT/CT





(Chiesa et al, EJNMMI 42, 2015)

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 102, 2018)

Role of SPECT in EBRT

- Use functional NM imaging to assess normal organ function and its spatial distribution during EBRT/PBRT treatment planning dosimetry
  - Goal is to preserve organ function after intervention

Assessment & Dosimetry Planning Phase

- Radiopharmaceutical imaging
  - FDA approved tracer
  - SOC imaging
  - Assess normal tissue function and distribution
- Functional considerations included for Planning Dosimetry

Treatment & Verification Dosimetry

- SBRT/PBRT/IMRT
- Image processing; fusion; dosimetry; etc.
- Voxel dosimetry; DVH; D, BED, other metrics

Follow-up Imaging & Labs

- Toxicity assessments
- Response assessments
- Follow-Up duration

- Lung EBRT/PBRT

- ^{99m}Tc-MAA to assess perfused lung tissue for RT planning of lung cancer patients

Functional Lung Perfusion Imaging

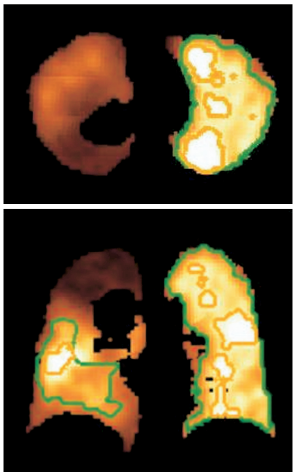


Fig. 1. The percentile single-photon-emission computed tomography (SPECT) images (upon applying histogram equalization on the original SPECT images) in a single case. The increase of the perfusion is represented by the intensity of the images. The F50 and F90 lung are highlighted in green and orange colors, respectively.

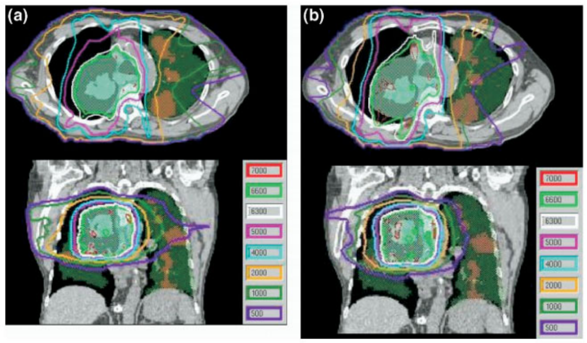
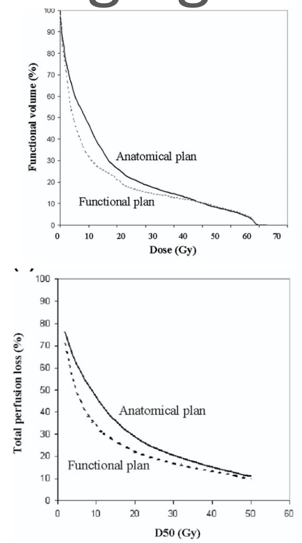


Fig. 3. Comparison of the isodose distributions between the anatomic plan (a) and functional plan (b) in the same case as that of Fig. 1.

Parameter	Anatomic plan	Functional plan	Differences	p
Mean dose (Gy)				
Total lung	21.3 (7.8–24.0)	17.8 (7.8–23.9)	1.1 (0.1–1.8)	0.001
F50 lung	17.6 (4.6–24.5)	14.5 (4.3–23.2)	2.2 (0.3–3.1)	0.000
F90 lung	16.0 (1.6–40.0)	11.8 (1.2–31.1)	4.2 (0.3–9.0)	0.000



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(Shioyama et al, Int J Rad Onc Phys Bio 68, 2007)

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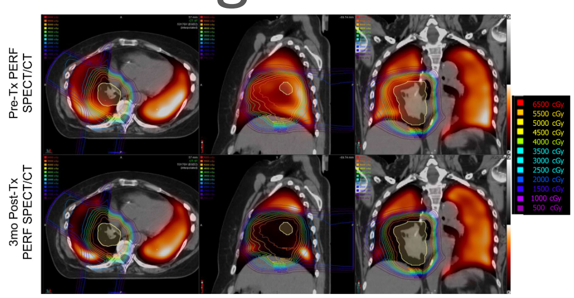
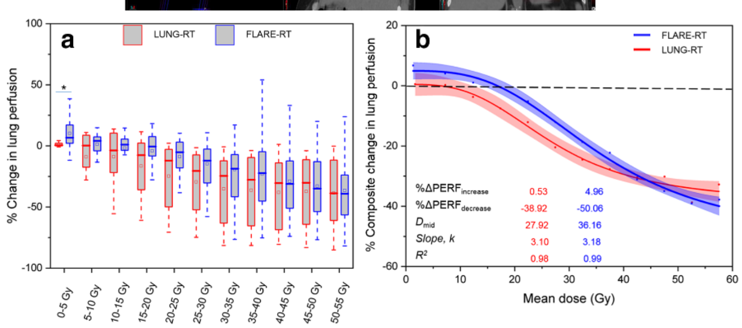
Functional Lung Perfusion Imaging





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(Thomas et al, BJR, 2019)

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- Liver EBRT/PBRT

- ^{99m}Tc-Sulfur Colloid and ^{99m}Tc-mebrofenin to assess functioning normal liver tissue for RT planning of liver cancer patients

Functional Liver in RT Plans

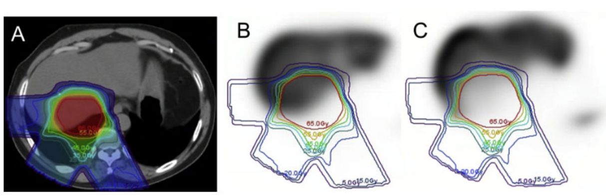
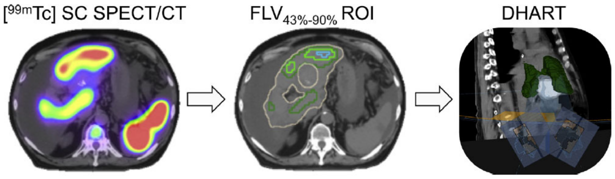


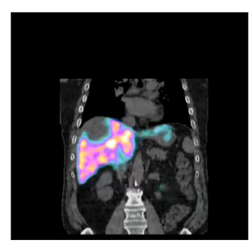
Fig. 1. Observed radiation dose-response on longitudinal SC SPECT/CT for a patient with Child-Pugh A5 hepatocellular carcinoma. (A) Three-field proton radiation therapy planning CT and dose color scale overlay; (B) pretreatment SC SPECT coregistered to isodose overlay; and (C) 1-month posttreatment SC SPECT coregistered to isodose overlay. SC SPECT window/level normalized to out-of-field integral uptake. Regions within the treatment field show reductions in uptake that are correlated with radiation dose magnitude and spatial distribution. *Abbreviations:* CT = computed tomography; SC = sulfur colloid; SPECT = single-photon emission tomography.

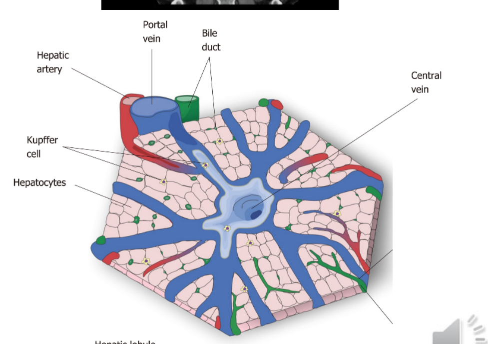
(Price et al, Radiotherapy & Oncol 115, 2015)



(Bowen et al, Radiotherapy & Oncol 115, 2015)

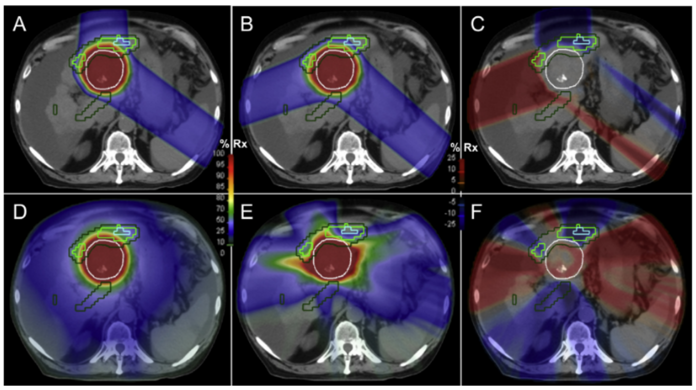
HIDA Pre-TX





doi: 10.3748/wjg.v25.i44.6483

Functional Liver in RT Plans



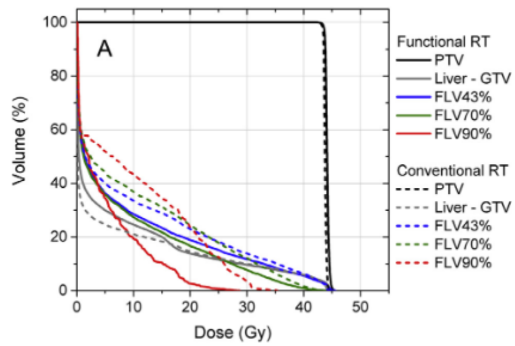


Fig. 2. Conventional radiotherapy vs. DHART for an example HCC patient. Proton PBS dose distributions in an axial plane (A–C) that met either anatomic liver objectives (A) or functional liver objectives (B), with the resulting dose difference distribution (C). Photon VMAT dose distributions in the same axial plane (D–F) that met anatomic liver objectives (D) or functional liver objectives (E), with resulting dose difference distribution (F). Contours are shown for PTV (white), $FLV_{43\%}$ (forest green), $FLV_{70\%}$ (light green) and $FLV_{90\%}$ (cyan). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Bowen et al, Radiotherapy & Oncol 115, 2015)

Summary

Quantitative SPECT/CT has come to maturity

<u>Role of SPECT/CT in RNT</u>

- Central to the development and advancement of new and existing RNT
- Time to focus on the personalized treatment planning based on patient-specific physiology and tumor characteristics
- Need to demonstrate improvement in treatment efficacy with patient-specific dosimetry
  - Prospective clinical studies that incorporate dosimetry measurements
- Need for standardization and consistency in practice

Summary

Quantitative SPECT/CT has come to maturity

Role of SPECT/CT in Radiation Therapy

- Adjust treatment plan based on spatial information of normal tissue function to decrease OAR dose and improve therapeutic ratio
- Need to characterize the quantitative changes in normal tissue function based on dose delivered
- Need to demonstrate mitigation of risk associate with toxicity when treatment plans include functional information